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Secondary Prevention of Stroke

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Abstract

The Heart and Stroke Foundation of Canada has estimated that there are approximately 400,000 individuals living with the effects of stroke (Statistics Canada, 2011). While there is disagreement among studies assessing the relative cost associated with secondary compared to first-ever stroke, recurrent strokes appear to contribute a disproportionate share to the overall national burden of stroke, principally due to costs associated with long-term disability (e.g. nursing home care and re-hospitalization). The secondary prevention of stroke includes strategies used to reduce the risk of stroke recurrence among patients who had previously presented with a stroke or TIA. Management strategies, which should be specific to the underlying etiology, include risk factor modification, the use of antithrombotic or anticoagulant drugs, carotid surgery, endovascular treatments. The present review provides information on risk factor management programs, management of hypertension, diabetes, hyperlipidemia, the role of infection, lifestyle modification (diet, smoking, use of alcohol, physical activity) as well as treatment for atherosclerosis and cardiac abnormalities (e.g. atrial fibrillation) and reperfusion techniques. The review may be downloaded in a single document or in single sections corresponding to the topic areas listed above.

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Introduction and Risk Factor Management

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Key Points

- Urgent assessment and initiation of treatment following TIA is associated with reduced hospital costs and lengths of stay however, the effect of these accelerated programs on stroke risk is unclear. Further research with higher methodological quality is required.
- Cultural differences may exist among the preferred routes of patients seeking medical attention. Future research should account for these discrepancies and caution should be taken when drawing conclusions from the current literature as cultural bias may skew applicability.
- The majority of individuals experiencing symptoms seek their primary care physician versus using a more direct form of care. Proposed solutions should focus on increasing awareness of the importance of seeking urgent medical attention for TIA/stroke symptoms.
- The risk of recurrent stroke is determined by the timing of TIA onset and the presenting symptoms. The highest risk of stroke recurrence exists in patients presenting within 24 hour of TIA onset with transient, fluctuating or persistent unilateral weakness, or speech disturbance. The patients with the lowest risk of stroke recurrence are those presenting with more than two-weeks following a suspected TIA or ischemic stroke and those experiencing atypical sensory symptoms.
- Patient adherence to, as well as success of risk management strategies may be enhanced by early, in-hospital initiation and ongoing advice and support to both the patient and general practitioner.
- Further research is required to assess the impact of risk management programs on risk for recurrent stroke.

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8.1 The Importance of Preventing Recurrent Strokes

An analysis of data from the Framingham Study (n=4897) determined that lifetime risk for first-ever stroke in individuals from age 55 to 75 is approximately 1 in 6 and is slightly higher in women than men (1 in 5 vs. 1 in 6), given longer female life expectancies (Seshadri et al., 2006). While incidence of stroke increases with age, this is offset by lower life expectancy. Among individuals 85 years of age and older, lifetime risk for stroke was reported to be significantly less ($p<0.05$) than for younger groups (Seshadri et al., 2006). The estimates provided by Seshadri and colleagues (2006) are based on overt stroke only and do not include TIA or "silent stroke".

According to the Global Burden of Disease Study, stroke is the second most common cause of death (Murray & Lopez, 1997). The average age of individuals who experience a stroke is 70 years in men and 75 in women and in excess of one half of all strokes occur in adults over the age of 75 (Feigin et al., 2003). In people aged 65 and over, the age standardized prevalence rate ranges from 46 to 72 per 1000 population. While stroke is perceived primarily as a disease of the elderly, even among people aged 15 – 44 years, stroke is still reported to be a significant cause of death (Murray & Lopez, 1997). Strokes are also being identified more frequently in individuals < 55 years of age (Smaijlovic 2015). This is turn poses a higher risk of accruing a life of potential long term disability with increasing cost to the health care system and loss of productive working years (Smaijlovic 2015).

However, given that the majority of strokes are not fatal, focusing on mortality alone underestimates the burden of disease associated with stroke. It has been estimated that of those individuals who survive a stroke, only 65% may be functionally independent one year following the stroke event (Wolfe, 2000). In Canada, 62,000 strokes occur each year and hundreds of thousands of Canadians are living with the effects of stroke stroke (Heart and Stroke Foundation of Canada 2015). While there is disagreement among studies assessing the relative cost associated with secondary compared to first-ever stroke (Samsa et al., 1999; Spieler et al., 2003; Yoneda et al., 2005), recurrent strokes appear to contribute a disproportionate share to the overall national burden of stroke, principally due to costs associated with long-term disability (e.g. nursing home care and re-hospitalization) (Samsa et al., 1999).

Secondary prevention should be regarded as an integral part of stroke rehabilitation, as important as walking, functional skills or swallowing disorders. Goldberg and Berger (1988) have identified the importance of secondary stroke prevention in patients with an atherothrombotic brain infarction and the related problem of reducing the risk of other major vascular events such as a myocardial infarction. Both men and women who have experienced a stroke have a significantly greater risk for MI than individuals with no history of stroke (RR= 1.6 and 1.9, respectively) (Appelros et al., 2011). This may be exacerbated by the presence of other CHD or peripheral artery disease prior to the index stroke event. There is an important practice issue in the long-term rehabilitation of stroke patients since such adverse events as MI may precipitate major setbacks in the process of functional recovery and offset the gains accomplished through comprehensive stroke rehabilitation. Alternatively, successful, long-term secondary prevention helps to maintain regained function by reducing inpatient recidivism (Goldberg & Berger, 1988).

The secondary prevention of stroke includes strategies used to reduce the risk of recurrence among patients who had previously presented with a stroke or TIA. Management strategies, which should be specific to the underlying etiology, include risk factor modification, the use of antithrombotic or anticoagulant drugs, surgery and endovascular treatments.

8.2 Stroke Risk Factors and Risk Factor Management

In the WHO MORGAM project (Monica Risk, Genetics, Archiving and Monograph), 93,695 persons living in 8 European countries and having no history of cardiovascular disease at baseline were followed for approximately 13 years (Asplund et al., 2009). In that time, a total of 3,142 strokes were recorded; 1,851 were in men and 1,291 in women. In both men and women, increased risk for stroke was associated with increased age, elevated blood pressure, and smoking. An increase one unit in body mass index represented an increased risk for stroke of 2%, but in men only. Total serum cholesterol was not predictive of stroke; however, higher levels of HDL cholesterol were associated with a reduction in risk.

The majority of people may be aware of cardiovascular risk factors even when they lack knowledge regarding the signs and symptoms of stroke specifically (Maasland et al., 2007). In a large survey (n=28,090), 68% of respondents were able to name at least one risk factor for stroke (Muller-Nordhorn et al., 2006). Most frequently named risk factors included hypertension, smoking and obesity. Knowledge of more risk factors was associated with higher levels of education, family history of stroke or recent receipt of information about stroke. Individuals at greater risk for stroke (older people or those with low socio-economic status) demonstrated lower levels of knowledge about stroke risk.

In the phase one of the INTERSTROKE study, investigators assessed multiple risk factors in 3000 individuals with stroke and 3000 age and sex-matched controls (O'Donnell et al., 2010a). The following risk factors accounted for approximately 90% of population-attributable risk for all stroke; i) **hypertension**, ii) **current smoking**, iii) **abdominal obesity** (waist-to-hip ratio >0.96 in men and >0.93 in women), iv) **elevated dietary risk**, v) **physical inactivity**, vi) diabetes mellitus, vii) elevated alcohol intake (>30 drinks/month or binge drinking), viii) psychosocial stress (permanent or several periods of stress in the workplace and/or home), ix) depression (feeling sad or depressed for ≥2 weeks over the past year), x) cardiac causes (atrial fibrillation or flutter, previous MI, rheumatic valve disease or prosthetic heart valve), and xi) ratio of apolipoproteins B to A1. The first five of these risk factors accounted for 80% of global risk for all stroke (ischaemic and intracerebral haemorrhagic), while the single, strongest risk factor for stroke was self-reported history of hypertension.

Wilson et al. (2001) noted that 75% of Canadian adults have at least one life-style related risk factor for stroke. Similarly, data from the South London Stroke Register (UK) demonstrated that 87.5% of patients with first stroke had at least one modifiable risk factor (Redfern et al., 2002). Modifiable risk factors are listed in Table 8.2.1.

The Canadian Stroke Best Practice Recommendations (2014) noted that stroke prevention involves adopting a healthy lifestyle that includes smoking cessation, maintaining a healthy body weight, and maintaining a physically active life. It is important to manage key risk factors such as hypertension, diabetes mellitus, hypercholesterolemia and atrial fibrillation which have been associated with an increased risk of developing a stroke (Canadian Best Practice Recommendations 2014). This chapter focuses on interventions that target and reduce various risk factors such as hypertension, smoking, abdominal obesity, diet and physical activity, which could significantly decrease the global burden of stroke (O'Donnell et al., 2010a).

8.2.1 Stroke and TIA as Risk Factors

Stroke is a significant risk factor for the development of further strokes. Coull & Rothwell (2004) suggested that recurrent events account for up to 30% of the strokes reported in population-based studies and are more likely to be fatal or disabling than first strokes. In that report, the documented 3-month risk of recurrent stroke was 14.8% and 18.3% based on data from the Oxfordshire Community Stroke Project and Oxford Vascular Study, respectively. However, reported risk varies with the definition used for recurrent stroke. The above rates are based upon the following definition: any recurrent stroke occurring > 24 hours after onset of index event irrespective of vascular territory and confined to sudden neurological deteriorations having a low probability of being caused by edema, brain swelling, drugs or other potential complications OR evidence of recurrent stroke on imaging (Coull & Rothwell, 2004).

Table 8.2.1.1 Studies Included in Meta-analyses of Early Stroke Risk Following TIA

Wu et al. (2007):	
Whisnant et al. 1973	Correia et al. 2006
Calandre and Molina 1985	Hill et al. 2004
Lovett et al. 2003	Lisabeth et al. 2004
Kleindorfer et al. 2005	Gladstone et al. 2004
Johnston et al. 2000	Wu (unpublished data)
	Coull et al. 2004
Giles and Rothwell (2007):	
Johnston et al. 2000	Cucchiara et al. 2006
Lovett et al.2004	Tsivjoulis et al. 2006
Hill et al. 2004	Johnston et al. 2007 (ED &
Lisabeth et al. 2004	clinic cohorts)
Whitehead et al. 2005	Bray et al. 2007
Kleindorfer et al. 2005	Purroy et al. 2007
Rothwell et al. 2005	Calvet et al. 2007
Correia et al. 2006	Rothwell et al. 2007
	Lavallee et al. 2007

A report from the Northern Manhattan Study (Dhamoon et al., 2006) reported that the age and sex-adjusted 5-year risk for fatal stroke was 3.7% while for nonfatal stroke the risk was 14.8%. During the first year following an index event, the risk for fatal stroke was 1.1% and 6.6% for nonfatal stroke (Dhamoon et al., 2006). This was substantially lower than reported by the Oxfordshire Community Stroke Project. A recently-published study based on 2002 data from stroke patients admitted to hospitals in South Carolina, USA (n=10,399) identified the greatest cumulative risk for recurrent stroke in the first year (5.0% at 6 months, 8.0% at 1 year). Kaplan-Meier estimates of cumulative risk were 8.0% at 1 year, 12.1% at 2 years, 15.2% at 3 years and 18.1% at 4 years (Feng et al., 2010). Risk increased with age and was greater for patients who were African American (vs. Caucasian) and with greater comorbidity.

Kaplan et al. (2005) suggested that the type of stroke might influence the risk of recurrence. In that study, individuals who had experienced a cardioembolic stroke had the greatest risk for recurrence while individuals with lacunar stroke had the lowest risk (Hazard Ratio = 2.01 comparing cardioembolic to lacunar stroke). Feng et al. (2010) also demonstrated that individuals with intracranial or subarachnoid haemorrhage have a smaller risk for recurrent stroke (HR=0.79, 95% CI 0.65-0.94), but noted that the mortality rate was higher following ICH or SAH and death may have occurred before recurrent stroke.

History of TIA has also been identified as a significant long-term predictor of recurrent stroke. In a long-term study of individuals with minor stroke or TIA (Life Long after Cerebral Ischaemia or LiLAC), van Wijk et al. (2005) reported 10-year risk for vascular events following minor stroke or TIA to be 47.8% and 35.8%, respectively. Cumulative risk for recurrent stroke events was 4.7% at one year, 12.0% at 5 years and 18.4% at 10 years. Stroke risk was greatest shortly after the baseline event and fell to its lowest point at approximately 3 years post TIA after which it continued to rise gradually for the duration of follow-up (van Wijk et al., 2005).

Early Stroke Risk. Based on data from two population-based studies and two randomised controlled trials, Rothwell and Warlow (2005) reported that 23% of individuals presenting with stroke had a history of TIA

and, in 43% of these patients the TIA event preceded the stroke event by less than 7 days. Johnston et al. (2000) collected data on a cohort of patients seen in an emergency department and diagnosed with TIA. Of 1,707 TIA patients identified, 10.5% experienced a stroke within 90 days of the index visit. Approximately one-half of these stroke events occurred within 2 days. A similar pattern of events was also reported by Lisabeth et al. (2004) and Gladstone et al. (2004). In contrast, a recent study by Amerenco et al. (2016) that evaluated the risk of stroke after a TIA or minor stroke, demonstrated a lower risk of cardiovascular events after TIA than previously reported. The study included 4789 patients recruited at 61 sites in 21 countries between 2009 and 2011. The rate of stroke at 2, 7, 30, 90, and 365 days after a TIA/minor stroke was found to be 1.5%, 2.1%, 2.8%, 3.7%, and 5.1% respectively.

Two meta-analyses (Table 8.2.1.1) have attempted to provide estimates of early risk for stroke following TIA (Giles & Rothwell, 2007; Rothwell et al., 2007; Wu et al., 2007) Wu et al. (2007) included 11 studies from 1973 through 2006 reporting risk of stroke following TIA from 2 to 90 days post stroke. Pooled estimates of risk were 2.5%, 8.0% and 9.2% at 2, 30 and 90 days, respectively. However, significant heterogeneity associated with method of outcome ascertainment was identified. For studies using administrative data only, estimates of risk were considerably lower than for those using face-to-face data collection methods at follow-up. Pooled estimates of risk at 2, 30 and 90 days were 9.9%, 13.4% and 17.3%, respectively, in studies using face-to-face data collection (Wu et al., 2007).

Giles and Rothwell (2007) included 17 studies (18 cohorts) from 2000 through 2007 that reported 7-day risk of stroke. Pooled estimates for 2- and 7-day risk of stroke were 3.1% and 5.2%, respectively. As in the Wu et al. (2007) study, significant heterogeneity was identified across studies for both estimates. The authors attributed this to differences in study method, setting and treatment. In population-based studies, using face-to-face follow-up methods, pooled estimates of risk for stroke were 6.7% and 10.4% at 2 and 7 days, respectively. These results are to be interpreted with caution as more recent data reveal lower rates of stroke at various time points after a TIA (Amerenco et al. 2016).

8.2.1.1 Urgent Assessment and Intervention Post-TIA

The National Stroke Association (2006) and the Canadian Stroke Best Practice Recommendations: Stroke Recognition and Response (2015) emphasize the importance of urgent assessment and intervention following TIA. Recommendations for initial management include development of policy regarding hospitalization and/or referrals following TIA, availability of specialized TIA clinics for rapid assessment (within 24 to 48 hours) and access to urgent investigations including same-day imaging (CT, MRI and vascular imaging including ultrasound).

However, access to investigation may not always be provided within recommended timeframes. In Gladstone et al. (2004) reported that, in a group of 371 patients with TIA presenting to participating emergency departments in Ontario, Canada, 271 were discharged and by the time of discharge only 31% had obtained neuro-imaging (either CT or MRI). Only 18% had received neurology consultations while in the emergency department; 58% were referred back to their family physician and only 35% were referred to either a neurologist or specialized stroke clinic. Although UK guidelines urge investigation of all TIA patients within 7 days of the index event, Selvarajah et al. (2008) reported a median time from event to clinic assessment of 15 days (range; 0 – 42). In that report, risk of stroke was low; however, strokes occurring within the first few days of the index TIA were not captured. Similarly, Fallon et al. (2006) reported that only 61% of patients referred to a weekly, specialized TIA clinic were seen within one week of referral from an emergency department and only 53% of these were both seen and assessed at that visit. Birns et al. (2006) reported that while the median interval between the TIA event and assessment

in a UK TIA clinic was 28 days, it was significantly shorter than the median interval from TIA event to neurology clinic assessment (129 days).

Studies that have examined the impact of specialized, urgent assessment and intervention following TIA in a variety of settings are summarized in Table 8.2.1.1.1.

Table 8.2.1.1.1 Summary of Urgent Assessment and Management of TIA

Author, Year Study Design (PEDro Score) Sample Size	Intervention	Main Outcome(s) Result
Admission to Hospital		
Wu et al. (2009) Case Series N=189	E1: Rapid evaluation unit E2: High risk standard care cohort C: Standard care cohort	• Incidence of stroke within 90d: E1 vs. E2, E2 (+) • Incidence of early stroke: E1 vs. C, E1 (+) • Costs: E1 vs. C, E1 (+)
Emergency Department (ED) protocols, observation and/or assessment		
Ross et al. (2007) RCT (7) N=149	E: TIA-accelerated protocol + antiplatelet therapy C: Inpatient admission + antiplatelet therapy	• Index length of stay (+) • 90d total costs (+) • Incidence of stroke within 90d (-)
Nahab et al. (2012) PCT N=142	E: Accelerated diagnostic program C: No program	• Length of stay (+) • Costs (+) • 90d incidence of stroke (-)
Kim et al. (2011) Case Series N=1707	E: Neurology consultation in the ED C: No consultation	• Incidence of stroke (+) • 90d incidence of stroke (-)
Expedited/rapid access TIA clinic		
Rothwell et al.(2007) Cohort N=591	E1: EXPRESS Phase 2 – Immediate initiation of treatment with diagnosis C: EXPRESS Phase 1 – No treatment in the clinic	• 90d incidence of stroke (+)
Luengo-Fernandez et al. (2009) Cohort N=591	E1: EXPRESS Phase 2 – Immediate initiation of treatment with diagnosis C: EXPRESS Phase 1 – No treatment in the clinic	• Hospital bed days (+) • Hospital costs (+) • Incidence of recurrent fatal strokes (+) • Incidence of disabling strokes (+) • Progression to disability or death (+)

+ Indicates statistically significant differences between treatment groups
- Indicates non-statistically significant differences between treatment groups

Discussion

90-day risk for stroke following TIA has been estimated to be as high as 17.3% in studies using face-to-face data ascertainment strategies on follow-up (Wu et al., 2007). In the collection of studies identified here, in which assessment and/or intervention was provided most often within 24 hours of symptom onset, reported estimates of 90-day risk following urgent intervention were substantially lower, whether provided as an inpatient, while in the emergency department setting or as part of a rapid access TIA/stroke clinic.

Routine hospital admission results in favourable early outcomes in terms of risk for recurrent events, most likely due to the rapid access to comprehensive investigations and management strategies, including vascular procedures such as carotid endarterectomy (Kehdi et al., 2008). While resource intensive urgent or rapid access TIA clinics seem able to offer similarly favourable outcomes, they are not available in many locations outside of large centers offering specialized stroke care (Kehdi et al., 2008; Nahab et al., 2012)

Although hospital admission may be more expensive, the costs associated with inpatient treatment may be offset by the costs associated with the chronic disability resulting from a preventable stroke (Wu et al., 2009).

Given the expense associated with routine admission, selected admission based on a TIA-protocol for observation and assessment in the emergency department may provide a more resource-friendly alternative to routine hospitalization. The primary objective of emergency department (ED) based observation units is to offer diagnostic assessments as well as initiation of treatments not routinely provided within the ED. Patients can be triaged for admission or referral for outpatient follow-up as required based on the imaging and assessments performed in the emergency department, but expedited assessment and treatment is not dependent upon the availability of a rapid access TIA clinic (Nahab et al., 2012). ED observation or short stay units have been associated with reductions in lengths of hospital stay and total direct costs while producing patient outcomes similar to those reported for routine hospitalization post-TIA (Nahab et al., 2012; Ross et al., 2007; Stead et al., 2009). It may be important to note that, although reduced stroke risk may be achieved using rapid access stroke clinics, it is unclear to what degree this outcome is influenced by the ED-based management protocols that may have been in place (Wasserman et al., 2010).

The impact of early intervention following TIA or minor stroke also depends partly upon the rapid identification of individuals who have experienced an event. A national survey of 10,112 individuals, conducted by the National Stroke Association in the United States, determined that 2.3% of participants had received a diagnosis of TIA from a physician (Johnston et al., 2003). An additional 3.2% recalled experiencing symptoms consistent with TIA, but did not seek medical attention. Among individuals with diagnosed TIA, 64% had seen a physician within 24 hours of the event. In addition, relatively few individuals surveyed could provide a definition of TIA (8.2%) or identify typical symptoms associated with TIA (8.6%).

Proper diagnosis and treatment of TIA can therefore be initiated if access to a clinic or a stroke facility occurs within the first 24 hours of the event. In Lavallee et al. (2007), a SOS-TIA clinic was set up to provide 24 hour access for rapid assessments of patients with TIA (i.e. within 4 hours of admission). A total of 1085 patients were admitted to the SOS-TIA clinic between 2003 and 2005, 53% of which were seen within 24 hours of symptom onset. TIA or minor stroke was confirmed in 701 patients, of which 44 were treated with anticoagulants for atrial fibrillation, 43 had carotid revascularisation, and all were started on a stroke prevention programme. 74% of all patients were assessed and sent home on the same day. Such programs have the potential to reduce the risk of stroke and the length of hospital stay if 24 hour access and rapid assessments and treatments are provided.

Conclusions Regarding Urgent Assessment and Management Post-TIA

There is level 2 and level 4 evidence that urgent assessment and initiation of treatment following transient ischemic attack is associated with reduced hospital costs, length of stay and risk for early stroke.

There is conflicting level 1b evidence that treatment of patients using an accelerated protocol in an emergency department observation unit results in shorter lengths of stay and reduced costs, but does not result in an improved risk for stroke when compared to inpatient admission for transient ischemic attack.

Urgent assessment and initiation of treatment following TIA is associated with reduced hospital costs and lengths of stay however, the effect of these accelerated programs on stroke risk is unclear. Further research with higher methodological quality is required.

8.2.1.1.1 Pre-Hospital Delay in Pursuit of Care

A recent analysis of data from the Oxford Vascular Study (Giles et al., 2006) revealed that, in a population of individuals with a high prevalence of vascular risk factors, only 44.4% responded to the symptoms of TIA as though it were an emergency and more than one-quarter of participants delayed seeking medical attention for more than 2 days. Of those individuals seeking medical attention, 42.4% correctly identified the cause of their symptoms. The decision to seek emergency medical attention was associated with type and duration of symptoms. Individuals experiencing motor symptoms or symptoms of more than one hour duration were more likely to seek immediate medical attention (HR = 2.1 95% CI = 1.4 – 3.2; (Giles et al., 2006).

Sprigg et al. (2009) conducted a systematic review to examine factors associated with delay in seeking appropriate medical attention following TIA and concluded that the majority of delay may be attributable to lack of response on the part of the patient. Further public education, stressing the nature of TIA as well as the importance of seeking medical attention for stroke symptoms even if they resolve, has been suggested (Giles et al., 2006; Johnston et al., 2003; Sprigg et al., 2009). However, education for the service provider and availability of urgent access to medical services may also play a role in reducing delays (Goldstein, 2008; Sprigg et al., 2009).

Relatively few studies have examined the impact of stroke education or knowledge on delays in seeking help for TIA or stroke directly. In a recent review, Teuschl and Brainin (2010), identified 9 population-based studies out of 182 studies included in their review that examined the effect of public education programs on either pre-hospital time or rate of thrombolysis. Education campaigns were conducted for 6 months – 1 year and, in general, were associated with lower pre-hospital times. The authors note that this may be attributable, in part, to improvements in hospital organisation, better coordination with emergency services and heightened knowledge/awareness among medical personnel. However, individuals with the best knowledge may not be the individuals with the shortest delays in seeking treatment and better knowledge was not necessarily associated with delays in contacting emergency medical services (EMS) (Teuschl & Brainin, 2010). In fact, there may be a discrepancy between the theoretical knowledge of symptoms and the recognition of these symptoms in real life situations. While most participants in stroke knowledge studies identified by Teuschl and Brainin (2010) were able to agree that stroke is an emergency and should receive immediate medical attention, descriptions of stroke signs did not trigger a similar response. The most common reasons provided for delays in seeking help were not recognising symptoms as stroke, not realising the urgency and taking a "wait and see" attitude to determine if the symptoms would resolve spontaneously. The decision to seek help is more influenced by perceived severity of the symptoms than by "stroke knowledge". Overall, older age, female sex, higher education and income, not living along and knowing someone with stroke were all factors that were associated with shorter delays in seeking appropriate medical attention.

In an analysis of data from 1000 patients enrolled in the Oxford Vascular Study (OXVASC), 67% of individuals with TIA and 74% with minor stroke sought medical attention within 24 hours of symptom onset (Chandratheva et al., 2010). Fewer than half of those (47% and 46% with TIA & minor stroke respectively) sought help within the first 3 hours. Shorter delays were associated with greater predicted risk for stroke, presence of motor or speech symptoms, longer duration of event (≥60 min.) and older age. When adjusted for clinical characteristics, correct recognition of symptoms was not significantly

associated with delay in seeking medical help for either TIA or minor stroke. The majority of patients contacted their general practitioner rather than emergency medical services and, not surprisingly, the greatest delays were associated with events occurring on the weekend.

The impulse to contact a primary care physician first may, in part, be cultural. In the UK, there has been an emphasis on primary care services that may not exist to the same extent elsewhere (Chandratheva et al., 2010). Manawadu et al. (2010) studied patient behaviour in seeking medical attention in 469 patients in the UK and 197 patients in Canada who were referred to stroke prevention clinics following TIA. Overall 38% of UK patients and 54% of Canadian patients sought medical attention on the same day as the initial TIA event. However, 65% of Canadian patients presented via emergency medical services vs. 40% of the UK patients. 77% of patients reporting to an emergency department did so on the same day as the TIA vs. only 11% of individuals who contacted their primary care physician. For those patients who consulted primary care physicians, greater delays were associated with TIA events occurring on weekends. Indeed, Kerr et al. (2010) reported that most calls received from general practitioners were recorded on weekdays (mean = 5.3/day vs. 1.1/day on weekends). Overall, 80% of calls to the hotline service were made between the hours of 9:00 a.m. and 5:00 p.m. Monday through Friday.

As part of the OXVASC study, Lasserson et al. (2008) examined the role of accessibility to general practice on healthcare seeking behaviours in individuals experiencing TIA or minor stroke (Lasserson et al., 2008). Most (73%) individuals sought medical attention from a primary care physician first. For patients who called their physician first, approximately one-half experienced events outside of regular office hours. Of these, 72% waited to call their own physician during office hours rather than use an on-call physician service or emergency room. Median time to call a physician for events experienced outside of office hours was 24.8 hours for patients waiting to speak to their own physician, while those who used an emergency service had a median delay of only 1.0 hour. To examine the impact of greater accessibility to primary care services, the authors examined the possible impact of extending regular care office hours to 12 hours per day, 7 days per week. If this had been available for the duration of data collection, 30% of individuals who had delayed seeking medical attention until regular office hours would have experienced events within the proposed time frame. Within this subgroup, delay in seeking medical attention was 50 hours, with 34% calling within 24 hours of symptom onset. If greater accessibility prompted them to behave similarly to those who did experience an event during regular office hours, the delay in seeking medical advice could be reduced to 4 hours and 68% would contact a physician within 24 hours. Of course, as the authors point out, increased hours for primary practice would also necessitate increased capacity in terms of access to the investigations and specialist care required for prompt initiation of secondary prevention strategies (Lasserson et al., 2008). Kerr et al. (2010) demonstrated that, for a region with a population of approximately 800,000, implementation of a hotline that represented approximately 40 minutes/day of increased workload per consultant each week day, could facilitate improved access to specialized services and support the triage of patients for urgently-required treatments.

Conclusions Regarding Pre-Hospital Delay in Pursuit of Care

Cultural differences may exist among the preferred routes of patients seeking medical attention. Future research should account for these discrepancies and caution should be taken when drawing conclusions from the current literature as cultural bias may skew applicability.

The majority of individuals experiencing symptoms seek their primary care physician versus using a more direct form of care. Proposed solutions should focus on increasing awareness of the importance of seeking urgent medical attention for TIA/stroke symptoms.

8.2.1.2 Prediction of Risk for Recurrent Stroke Following TIA

In order to identify high-risk patients most in need of urgent evaluation and specific interventions for secondary prevention, strategies for the identification and prediction of stroke risk following TIA have been developed. Johnston et al. (2000) identified five significant predictors of stroke following TIA. These included age (>60 years), diabetes mellitus, duration of episode (>10 minutes), weakness with the episode and speech impairment with the episode. The authors created a simple index (the California score) by assigning a one-point value to each factor. They were able to demonstrate that the presence of none of these factors was associated with 0% risk while the presence of all 5 factors resulted in a risk for stroke of 34%.

Table 8.2.1.2.1 Studies Included in Meta-analyses of Prognostic Value of the ABCD² Score

Galvin et al. 2011	
Johnston et al. 2000	Cucchiara et al. 2009
Tsivgoulis et al. 2007	Fothergill et al. 2009
Coutts et al. 2008	Song et al. 2009
Asimos et al. 2010	Weimar et al. 2009
Ay et al. 2009	Ong et al. 2010
Calvet et al. 2009	Tsivgoulis et al. 2010
	Harrison et al. 2010

Rothwell et al. (2005) created the ABCD score to predict 7-day risk of stroke following TIA using data from the Oxfordshire Community Stroke Project (OCSP) and similar cohorts within the Oxford Vascular Study and a non-Oxford Vascular Study TIA clinic. The ABCD reflects 4 factors found to be predictive of stroke; age, blood pressure, clinical features and duration. In a recent validation study, Tsivgoulis et al. (2006) demonstrated that the ABCD score was a significant predictor of both 7- and 30-day risk for stroke following TIA and that risk significantly increased with increasing ABCD score levels (p=0.0003 and p<0.00001, respectively). Using a cut-off score of ≥5 to define individuals as high risk resulted in 100% sensitivity and 53% specificity for prediction of stroke (Bray et al., 2007).

Table 8.2.1.2.2 ABCD2 Score for the Prediction of 2-day Risk of Stroke (Johnston et al., 2007)

Risk Factor	Points
Age ≥ 60 years	1
Raised blood pressure *(Systolic ≥140 mmHg and/or diastolic ≥ 90 mmHg)*	1
Clinical Features: Unilateral weakness Speech impairment without weakness	 2 1
Duration of symptoms in minutes: ≥ 60 10 – 59	 2 1
Diabetes	1

Johnston et al. (2007) combined elements of the California score and the ABCD score to form a unified index called the ABCD² (Table 8.2.1.2.2). As for the original ABCD, points are assigned for the presence of known risk factors and then summed to provide a total risk score. In 4 independent validation groups, the unified ABCD² score was found to be a more accurate predictor of stroke than scores from either of the two parent indices. Using data from the combined validation groups (n=4,799), 2-day risk for stroke following TIA was reported to be 1.0% for a score of 0 – 3 (low risk), 4.1% for a score of 4 – 5 (moderate risk) and 8.1% for a score of 6 – 7 (high risk) (Johnston et al., 2007). The ABCD² score also predicted stroke risk at time points from 7 – 90 days following the TIA event. Use of a simple tool such as the ABCD² would allow frontline healthcare workers to quickly and reliably assess risk and determine the urgency required in making appropriate referrals for specialist assessment and potential implementation of prevention strategies (Johnston et al., 2007; Lovett et al., 2003; Nguyen-Huynh & Johnston, 2007; Rothwell & Warlow, 2005).

Giles et al. (2010) undertook a pooled analysis of AUC data derived from validation studies examining the use of the ABCD or ABCD² tool for prediction of stroke at 7 days (20 studies) and 90 days (15 studies) post-TIA event. Overall, pooled AUC for prediction of stroke at 7 days was 0.72 (95% CI 0.67 to 0.77) and 0.72 (95% CI 0.63 to 0.80) for the ABCD and ABCD², respectively. Meta-analysis of data from 15 studies that reported risk from 0-7 days and 8 – 90 days post TIA, resulted in a pooled AUC of 0.71 for 0-7 days and

0.63 for 8 – 90 days, suggesting that the reported AUCs of the ABCD score at 90 days may be driven by greater predictive power in the first few days following TIA (Giles et al., 2010). It should be noted that there was significant heterogeneity identified for the pooled estimates produced in Giles et al. (2010). The authors identify the means by which scores were calculated as the primary source of variance (75%). Pooled AUC for studies that used face-to-face evaluation was 0.74 vs. 0.68 for studies that used retrospective calculation based on emergency department records. It should also be noted that the authors could not identify any studies that used face-to-face evaluation by an emergency department physician to calculate risk scores (Giles et al., 2010).

Galvin et al. (2011) also conducted a systematic review and meta-analysis of studies examining the validity of the $ABCD^2$ tool. Rather than focus on the discriminative validity of the $ABCD^2$ using pooled AUC data, the authors compared observed strokes pooled from identified validation studies to predicted strokes across three risk strata (low 0-3, medium 4-5 and high 6-7) based on the probability of stroke calculated in the original $ABCD^2$ derivation study (Johnston et al., 2007). Based on data from 16 studies, use of the $ABCD^2$ tool was associated with accurate prediction of observed stroke at 7 days across all three risk groups. At 90 days, however, there was a trend identified toward over-prediction (Galvin et al., 2011).

In 2007, Lavallee compared the risk of stroke at 90 days estimated using the Kaplain-Meier method with the expected risk of stroke estimated by the $ABCD^2$ score. The findings indicate that the expected risk of stroke was higher than the risk of stroke (measured via the Kaplan-Meier method) in all 1052 patients, as well as in those with TIA without lesion, TIA with new lesion, and in patients with possible TIA (See table 8.2.1.2.3). Similarly, for the patients seen within 24 hours of event onset, the 90-day risk of stroke was 1.63% (95% CI 0.85-3.12) while the expected risk was 6.49% (Lavallee et al. 2007).

Table 8.2.1.2.3 Risk of strokes (adapted from Lavallee et al. 2007)

Patients	% risk of strokes (95% CI) (via Kaplan-Meier method)	% expected risk (via $ABCD^2$ score)
All patients (N=1052)	1.24 (0.72-2.12)	5.96
TIA, no new lesion (N=524)	1.34 (0.64-2.78)	6.13
TIA, new lesion (N=105)	4.76 (2.01-11.06)	7.76
Possible TIA (N=141)	0.71 (0.10-4.93)	4.00

More recently, Warldlaw et al. (2015) conducted a systematic review and meta-analysis to evaluate the ability of the $ABCD^2$ score to discriminate between high and low risk of recurrent stroke by dichotomizing the $ABCD^2$ score into values < 4 indicating low risk, and values ≥4 indicating moderate-to-high risk. A total of 29 studies were included in the analyses, amounting to 13,766 patients with TIA. The findings of the meta-analysis suggests that an $ABCD^2$ score ≥ 4 was sensitive but not specific for estimating recurrent stroke within 7 days of event onset. Most studies using the $ABCD^2$ score were found to include only patients with a definite TIA, while patients with a possible TIA were excluded prior to using the $ABCD^2$ score. Interestingly, almost half of the referrals constitute of patients with undefined TIA (Warldlaw et al. 2015). When these patients were included in the analyses, roughly 1/3 of patients with possible TIA obtained an $ABCD^2$ score ≥ 4, while 1/3 of patients with definite TIA had an $ABCD^2$ score < 4. Due to these conflicting findings, the study suggests that the $ABCD^2$ score may not be an appropriate tool for assessing the recurrent risk of stroke.

For this reason, The 2015 Canadian Stroke Best Practice Guidelines (Coutts et al. 2015) removed the recommendation to use the $ABCD^2$ score for evaluating the risk of recurrent stroke since "*the score has not validated well in real-world practice".* Instead, factors such as the timing and the type of symptoms are emphasized in order to better identify the risk of recurrent stroke. The new stroke recommendations

characterize patient as having the highest risk, a high risk, an increased risk, or the lowest risk of recurrent stroke based on the presented symptoms and the timing of the event. A description of each level is provided below:

Timing of initial assessment (Coutts et al. 2015):

- **The HIGHEST risk for stroke recurrence** exists in patients who present within 48 hours of a suspected TIA or ischemic stroke with transient, fluctuating or persistent unilateral weakness (face, arm, and/or leg), or speech disturbance.
- **Considered at HIGH risk for stroke recurrence** are patients who present within 48 hours of a suspected TIA or ischemic stroke with transient, fluctuating or persistent symptoms without motor weakness or speech disturbance (with symptoms such as hemi-body sensory loss, or acute monocular vision loss, or binocular diplopia or hemi-visual loss or dysmetria).
- **Considered at INCREASED risk for stroke recurrence** are patients that present between 48 hours and two weeks from onset with symptoms of transient fluctuating or persistent unilateral weakness (face, arm and/or leg), or speech disturbance symptoms ***OR*** patients that present between 48 hours and two weeks of a suspected TIA of ischemic stroke with transient, fluctuating, or persistent symptoms without motor weakness or speech disturbance (with symptoms such as hemi-body sensory loss, or acute monocular vision loss, or binocular diplopia or hemi-visual loss or dysmetria).
- **The LOWEST risk for stroke recurrence** are patients presenting more than two-weeks following a suspected TIA or ischemic stroke, whom may be considered as being less urgent, and should be seen by a neurologist or stroke specialist for evaluation as soon as possible, generally within one-month of symptoms onset. Similarly, patients experiencing atypical sensory symptoms (such as patchy numbness and/or tingling) may also be considered as less urgent and should be seen by a neurologist or stroke specialist for evaluation.

Conclusions Regarding Prediction of Risk for Recurrent Stroke Following Transient Ischemic Attack

The risk of recurrent stroke is determined by the timing of TIA onset and the presenting symptoms. The highest risk of stroke recurrence exists in patients presenting within 24 hour of TIA onset with transient, fluctuating or persistent unilateral weakness, or speech disturbance. The patients with the lowest risk of stroke recurrence are those presenting with more than two-weeks following a suspected TIA or ischemic stroke and those experiencing atypical sensory symptoms.

8.2.2 Risk Factor Management

A recent systematic review of secondary prevention trials demonstrated that the annual event rates for recurrent stroke within the research literature have declined by 0.996% (p=0.001) per decade over the 5-decade period from 1960 – 2009 (Hong et al., 2011). Where annual rates of recurrent stroke were 8.71% for studies originating in the 1960s, those in the 2000s reported annual rates of 4.98%. Multiple regression analysis revealed a positive association between rate of recurrent stroke and proportion of study participants with hypertension as well as a negative association with the use of antithrombotic agents. Similarly, in community-based studies, there has been a reported reduction in risk for stroke that has been associated with the implementation of risk factor management strategies including reductions in smoking, cholesterol levels, and blood pressure as well as increasing treatment with antiplatelet, lipid-lowering and blood pressure-lowering medications (Hardie et al., 2005; Rothwell et al., 2004a). In the Second National Health and Nutrition Survey (NHANES II; Qureshi et al. 2004; n=9252), the risk for

cardiovascular death was demonstrated to be dependent upon control of risk factors in those individuals who had a previous history of stroke or myocardial infarction.

The relative risk of cardiovascular death was reported to be 2.6 in adults with adequately controlled risk factors. This relative risk rose to 4.3 in adults having one inadequately controlled risk factor and to 5.7 in adults having 2 or more risk factors that were not adequately controlled (Qureshi et al., 2004).

Despite the benefits associated with risk factor management in secondary prevention, reports suggest that appropriate secondary prevention strategies are not being effectively implemented (Amar et al., 2004a; Brenner et al., 2010; Fan et al., 2010; Girot et al., 2004; Kaplan et al., 2005; Lichtman et al., 2011; Mouradian et al., 2002; Rother et al., 2008; Rudd et al., 2004; Saposnik et al., 2009a; Tapson et al., 2005; Yusuf et al., 2011) While use of some secondary prevention measures, such as antiplatelet and antihypertensive drugs, appears relatively widespread, rates of use are much lower for other measures such as anti-coagulants or lifestyle modification programs. In a cohort of stroke patients from the Swedish Stroke Register (n=14,529), antiplatelet drugs were prescribed to more than 80% of patients and 87% of patients with atrial fibrillation. This is similar to rates of antiplatelet use described elsewhere (Kaplan et al., 2005; Lichtman et al., 2011; Rother et al., 2008) Rates of use for antihypertensives such as ACE inhibitors also tend to be quite high; both Rother et al. (2008) and Kaplan et al. (2005) reported rates in excess of 80%. Although reported antihypertensive treatment is substantially lower in the Swedish Stroke Registry (32.8% or 45.6% of individuals with hypertension; (Asberg et al., 2010), one should note that reported use was limited to ACE-inhibitors only.

Lipid-lowering and anti-coagulant therapies are reportedly used less consistently following stroke. Whereas Lichtman et al. (2011) reported 82.8% of patients with stroke received anticoagulants for atrial fibrillation; Asberg et al. (2010) reported that 31.7% of patients with atrial fibrillation were treated with an oral anti-coagulant. In addition, opportunities for the initiation of appropriate secondary prevention that extend beyond the use of pharmacotherapy are also being missed. Rudd et al. (2004) reported that information regarding lifestyle change was provided in only 37% of cases.

A number of variables have been identified which may influence provision of secondary prevention interventions. Several studies have noted that increasing age, for instance, is associated with treatment, such that older individuals may be less likely to receive treatment focussed on secondary prevention (Rudd et al., 2004) such as prescription of ACE-inhibitors (Asberg et al., 2010), statins (Asberg et al., 2010; Kaplan et al., 2005) and anti-coagulants (Asberg et al., 2010; Lichtman et al., 2011). Patients with higher levels of disability and those patients not treated on a stroke unit were also less likely to receive secondary prevention interventions (Rudd et al., 2004). Based on data from the REGARDS study (n=2,830 patients with stroke, 24, 886 individuals with no TIA/stroke), Brenner et al. (2010) reported that, individuals with stroke may be more likely to have unrecognized and untreated hypertension and diabetes than individuals with no previous history of TIA or stroke. Predictors of unrecognized and untreated risk factors for recurrent stroke included increasing body mass index, black race and lower levels of education.

The Prospective Urban Rural Epidemiological (PURE) study examined the use of drugs prescribed for the secondary prevention of cardiovascular events in 628 communities located in low (153 communities), lower middle (n=193), upper middle (n=166) and high (n=166) income countries. Data was collected for a total of 153, 996 individuals of whom 7,519 reported a history of coronary heart disease or stroke (stroke n=2292). Use of secondary prevention medications by individuals with history of stroke was low overall (ranging from 9.0% for statins to 40% for blood pressure lowering medications); however, country-level factors such as economic status influenced the rate of medication use. Use of secondary prevention medications was highest in high income countries (70.7%) and lowest in the low income countries (46.4%).

In addition, use of secondary prevention medications was greater among urban dwelling participants than for rural participants, particularly within lower income countries (Yusuf et al., 2011).

Even when specific regimens to address secondary prevention are prescribed, success in achieving treatment objectives may be limited. In the international Reduction of Atherothrombosis for Continued Health Registry (REACH), investigators demonstrated that, although the rate at which secondary prevention drugs were used was relatively high, treatment goals were not often achieved (Rother et al., 2008). Alvarez-Sabin et al. (2009) demonstrated that more than 90% of enrolled 5458 study participants with ischemic stroke (IS) and coronary artery disease (CAD) had secondary prevention measures in place to address hypertension, diabetes and/or dyslipidemia. Of these, approximately 25% achieved the recommended goal for the targeted risk factor. Factors associated with success in risk reduction strategies were presence of CAD rather than IS, older age and having fewer than 3 identified risk factors.

An examination of the Vascular Protection and Guidelines-oriented Approach to Lipid-Lowering registries in Canada (Saposnik et al., 2009a) provided similar insight. Management of hypertension and hyperlipidaemia in individuals with existing cerebrovascular disease (CVD; n=647) was suboptimal in the majority of cases with only 40.5% and 46% of patients reaching guideline recommended targets for LDL-C levels and blood pressure, respectively. When compared to individuals with coronary artery disease, individuals with CVD were significantly less likely to receive antihypertensive or lipid-lowering therapy (Saposnik et al., 2009a).

8.2.2.1 Programs for Risk Management Following Stroke

Using data from the Swedish Stroke Registry, Glader et al. (2010) reported that, over a 2-year period following discharge from hospital, rates of adherence to prescribed secondary prevention drug regimens declined steadily. Rates of adherence ranged from 74.2% for antihypertensives to 45% for warfarin. Based on analysis using multiple logistic regression, the authors demonstrated that persistence was associated with a number of factors that varied with the type of drug prescribed. However, institutional living was the variable most strongly and consistently associated with adherence. In addition, individuals treated in a stroke unit, those with diabetes or atrial fibrillation (and therefore, requiring more regular medication attention) and those having family support were more likely continue with prescribed regimens. The authors suggest that this pattern of association between adherence and access to more structured intervention and support highlights the need for structured programs to promote implementation of and adherence to secondary prevention measures.

Studies that have examined the effectiveness of programs to support the systematic implementation of and adherence to secondary prevention interventions following stroke are summarized in Table 8.2.2.1.1.

Table 8.2.2.1.1 Summary of Risk Management Programs in Secondary Prevention

Author, Year Study Design (PEDro Score) Sample Size	Intervention	Main Outcome(s) Result
Nornnes et al. (2011) RCT (9) N=349	E: Four nurse home visits (individually tailored counselling) + usual care C: Usual care	• Change in SBP/DBP from baseline (-)
Kronish et al. (2014) RCT (8) N_{Start}=600 N_{End}=600	E: Peer-led, community-based stroke prevention self-management group workshop C: Workshop waitlist	• Proportion of patients attaining controlled BP (<140/90mmHg), LDL cholesterol (<100mg/dL) and use of antithrombotic medications (-) • Proportion of patients attaining controlled BP (+)

McAlister et al. (2014b) RCT (8) N_{Start}=279 N_{End} =279	E: Pharmacist-led care management (independent prescription of medication) + usual care C: Nurse-led care management (communicated results to primary care physician) + usual care	• SBP and LDL cholesterol (+) • Mortality (-) • Self-reported adherence (-) • Body mass index (-) • Smoking status (-)
McAlister et al. (2014a) Secondary analysis for McAlister et al. (2010) RCT (8) N_{Start}=275 N_{End}=275/164	E: Pharmacist-led care management (independent prescription of medication) + usual care C: Nurse-led care management (communicated results to primary care physician) + usual care	• Framingham Risk Score (-) • Cardiovascular Disease Life Expectancy Model (-)
Ellis et al. (2005) RCT (7) N=205	E: Individualized intensive care C: Usual care	• Control of risk factors (-)
Goessens et al. (2006) RCT (7) N_{Start}=236 N_{End}=175	E: Risk factor management clinic (personalized action plan) C: Usual care	• Change in risk factors (SBP, total cholesterol, LDL-cholesterol, BMI) (+)
Wolfe et al. (2010) RCT (7) N=523 from 136 general practices	E: Individually tailored prevention program C: Usual care	• Risk factor management (-)
Allen et al. (2002) RCT (6) N=96	E: Post-discharge care management program (personalized care plan) + management of risk factors C: Usual post-discharge care	• Management of risk (+) • Knowledge of stroke (+)
Brotons et al. (2011) RCT (6) N=1224 from 42 health centres	E: Specialized secondary prevention care (individually tailored interventions) C: Usual care	• SF-36 (-) • Depression (+) • Anxiety (+) • Health outcomes (-) • Hospital admission (-) • Mortality (+)
Johnston et al. (2010) RCT (6) N=12 hospitals	E: Standardized discharge orders C: Usual discharge care	• Secondary Prevention at the patient level: within E (+), within C (-) • Composite secondary prevention at the hospital level (-)
Ogedegbe et al. (2012) RCT (6) N=256	E: Positive-affect induction and self-affirmation program + patient education C: Patient education	• Medication adherence (+) • SBP/DBP (-)
Dregan et al. (2014) RCT (5) N_{Start}=106 N_{End}=104	E: DXS Point-of-Care system (electronic decision support tool to report stroke-related events) C: Self reporting	• SBP (-) • Total cholesterol (-) • Types of antihypertensive drugs prescribed (-)
Chiu et al. (2008) RCT (4) N=160	E: Pharmacist led risk factor management C: Usual care	• BP (+) • Fasting Blood glucose (-) • Total cholesterol and LDL cholesterol (+) • BP control: E vs C (+) • Lipid level: E (+)
Jonsson et al. (2014) RCT (4) N_{Start}=549	E: 3mo specialist nurse follow-up C: Usual care	• Incidence of health problems (+)

N_{End}=391		
Joubert et al. (2009) PCT N=186	E: Integrated care + shared care through GPs C: Usual care	• SBP (+) • Cholesterol (-) • Smoking (-) • Alcohol intake (-) • BMI (+) • Physical activity (+) • Recollection of risk management advice (+)
Rahiman et al. (2008) PCT N_{Start}=322 N_{End}=143	E: PROTECT (Preventing Recurrence Of Thromboembolic Events through Coordinated Treatment) program C: Non-PROTECT program	• Vascular event frequency: Myocardial infarction (+)
Hohmann et al. (2013) Prospective 2-phase study N_{Start}=310 N_{End}=281	E: Detailed history of medication C: Record of medication at discharge	• Adherence to discharge regimen at 30mo: antithrombotic drugs and statin therapy (+)

+ Indicates statistically significant differences between treatment groups
- Indicates non-statistically significant differences between treatment groups

Discussion

In a recent study, Touze et al. (2008) demonstrated that in-hospital initiation or reinforcement of appropriate risk management interventions was a significant factor associated with maintaining target blood pressure (OR = 2.44, 95% CI 1.20, 4.97) and LDL (OR=3.66, 95% CI 1.27, 8.89) levels 6 months post stroke. The PROTECT program (Ovbiagele et al., 2004) involved the initiation of 8 specific medication and behavioural interventions or goals during the acute admission following stroke or TIA. Strategies were reinforced via bedside teaching, patient logs, information brochures and letters provided to primary care physicians. Study results suggest substantial patient adherence to medication interventions, in particular, over periods of time ranging from 3 months to one year (Ovbiagele et al., 2005; Ovbiagele et al., 2004; Rahiman et al., 2008). Rates of adherence to behavioural interventions were somewhat lower, although, counselling provided while in-hospital may have helped to create a direct link between stroke and lifestyle choice, particularly with regard to tobacco use. Rates of smoking cessation, for instance, were reported to be 97% at 3 months and 94% at one year (Ovbiagele et al., 2005; Ovbiagele et al., 2004).

Unlike the PROTECT program, the GWTG-stroke initiative examined the rate of adherence to guidelines by hospital teams on the basis of seven performance indicators. For all indicators, participation in GWTG-stroke was associated with improved quality of care for each of the pre-defined performance measures including provision of discharge antithrombotics, anticoagulation for AF, lipid-lowering for LDL>100mg/dL and smoking cessation counselling or medication. In the AVAIL follow-up study, overall rates of persistence and adherence at one-year post discharge from a SWTG-Stroke facility were 65.9% and 86.6%, respectively (where adherence was defined as continuation of prescribed medications except for those discontinued by a healthcare professional (Bushnell et al., 2011). Rates of persistence at one year ranged from 87.9% for antihypertensives to 68.2% for anticoagulants (i.e. warfarin).

In outpatient settings, the majority of studies have examined the effectiveness of an individualised risk management program with varying degrees of information and support provided by healthcare professionals such as nurses, nurse practitioners, GPs or pharmacists. Results of these studies have been mixed. Allen et al. (2002) reported improvements in risk factor management defined specifically as adequacy of blood pressure control, appearance of depressive symptomatology, number of falls and medication appropriateness. The authors did not address specific risk management interventions, patient adherence to care plan recommendations or impact of adherence on stroke risk. While Joubert et al.

(2009) demonstrated significant improvements associated with a program of integrated care management and support in the areas of hypertension, body mass index and physical activity, Ellis et al. (2005), Wolfe et al. (2010) and Brotons et al. (2011) demonstrated no benefit associated with specialized care management interventions when compared to conditions of routine care. Additional evidence presented by Nornnes et al. (2011) suggested that follow-up nurse home visits including the administration of individually tailored care programs had no effect on blood pressure control when compared to usual care. Inconsistently, significant improvements on health outcome and risk factor management were observed with specialist nurse follow-up at three months post-stroke (Jonsson et al., 2014).

The success of risk factor management at the patient level may depend on the intensity of care programs as well as the quality of administering professionals. However, proper support of primary care physicians may prove to be an important aspect of this process. Hohmann et al. (2013) investigated adherence to medication of patients discharged from hospital before and after a physician support system put in place by the clinical pharmacist. To study the communication between hospitals and primary care physicians, a basic medication list at discharge versus a detailed account of medication at admission, discharge and any changes during hospital stay were compared and subsequent adherence to medication was observed. Overall, adherence to discharge regimen was improved among patients with the more detailed discharge letter. This study presents a need for further research investigating support protocols for primary care physicians that may improve the administration and success of treatment.

A massive observational study found that ethnicity may be related to recurrence rate of hemorrhagic and ischemic events (Estol et al., 2014). Results described a heightened risk of myocardial infarction among European-Caucasian and Black African groups and of symptomatic intracerebral hemorrhage among Latin Hispanics and Asians. While one current study investigates an intervention for the reduction of recurrent stroke among minority populations (Kronish et al., 2014), the findings by Estol et al. highlight the necessity of further research targeting specific populations in order to develop a proper understanding of care management techniques across racial-ethnic and cultural backgrounds.

Conclusions Regarding Risk Management Programs

There is level 1a evidence that personalized secondary preventative care management programs may not improve risk factor management.

There is level 1b evidence that the addition of a positive affirmation intervention to educational materials focussed on self-management and level 2 evidence that a detailed history of medication provided to the GP versus only a basic record of medication at discharge may improve adherence to statins, antihypertensive and antithrombotic medications.

There is level 1b and level 2 evidence that a pharmacist-led educational intervention, a stroke prevention group workshop or post-discharge management of risk factors conducted using a model of shared care may improve long-term benefits in terms of blood pressure reduction, reduced lipid levels, reduced body mass and increased physical activity.

There is level 1b evidence that recording stroke-related events with an electronic support tool or pharmacist-led care management with direct prescription of medication (versus nurse-led management) may not improve stroke or cardiovascular risk management.

There is level 2 evidence that specialist nurse follow-up three months post-stroke or administration of the PROTECT program may improve health outcomes and short-term risk of myocardial infarction, respectively.

There is level 1b evidence that standardized discharge orders are not associated with improved secondary prevention treatment at six months' post-discharge.

Patient adherence to, as well as success of risk management strategies may be enhanced by early, in-hospital initiation and ongoing advice and support to both the patient and general practitioner.

Further research is required to assess the impact of risk management programs on risk for recurrent stroke.

Summary

1. ***There is level 2 and level 4 evidence that urgent assessment and initiation of treatment following transient ischemic attack is associated with reduced hospital costs, length of stay and risk for early stroke.***
2. ***There is conflicting level 1b evidence that treatment of patients using an accelerated protocol in an emergency department observation unit results in shorter lengths of stay and reduced costs, but does not result in an improved risk for stroke when compared to inpatient admission for transient ischemic attack.***
3. ***There is level 1a evidence that personalized secondary preventative care management programs may not improve risk factor management.***
4. ***There is level 1b evidence that the addition of a positive affirmation intervention to educational materials focussed on self-management and level 2 evidence that a detailed history of medication provided to the GP versus only a basic record of medication at discharge may improve adherence to statins, antihypertensive and antithrombotic medications.***
5. ***There is level 1b and level 2 evidence that a pharmacist-led educational intervention, a stroke prevention group workshop or post-discharge management of risk factors conducted using a model of shared care may improve long-term benefits in terms of blood pressure reduction, reduced lipid levels, reduced body mass and increased physical activity.***
6. ***There is level 1b evidence that recording stroke-related events with an electronic support tool or pharmacist-led care management with direct prescription of medication (versus nurse-led management) may not improve stroke or cardiovascular risk management.***
7. ***There is level 2 evidence that specialist nurse follow-up three months post-stroke or administration of the PROTECT program may improve health outcomes and short-term risk of myocardial infarction, respectively.***
8. ***There is level 1b evidence that standardized discharge orders are not associated with improved secondary prevention treatment at six months' post-discharge.***

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8.3

Hypertension

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Key Points

- The risk of stroke and composite outcomes that include stroke + coronary heart disease +/- and heart failure can be reduced with the use of diuretics at high and low doses, beta-blockers, calcium antagonists, ACE inhibitors, angiotensin receptor blockers, and centrally acting drugs.
- Only Chlorthalidone at low doses and ACE inhibitors were effective at reducing the occurrence of coronary heart disease, while beta-blockers, angiotensin receptor blockers, and centrally acting drugs were also effective at lowering the risk of heart failure.
- The risk of cardiovascular mortality can be reduced by the use of low dose Thiazide, calcium antagonist, and centrally acting drugs. Furthermore, calcium antagonists were also effective at reducing all-cause death along with low dose indapamide.
- Canadian Hypertension Education Program guidelines recommend blood pressures be maintained below 140/90mmHg for individuals with a history of stroke or TIA, and nondiabetic chronic kidney disease, and below 130/80mmHg in patients with diabetes mellitus. Combined treatment with an ACE inhibitor and diuretic is preferred.

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8.3 Hypertension

8.3.1 Significance of Hypertension

Hypertension is the most significant risk factor for stroke, given its high prevalence and modifiable nature. Declining stroke mortality has been largely attributed to better management of hypertension (Garraway et al., 1979). However, incidence and prevalence of hypertension, in the general population are increasing. Tu et al. (2008) reported that between 1995 and 2005, age and sex-adjusted prevalence in Ontario, Canada increased by 60% and incidence by 25.7%.

In Dahlof et al. (2002), 9,193 participants aged 55 – 80 with essential hypertension and left ventricular hypertrophy (LVH) were randomly assigned to receive either Losartan-based or Atenolol-based antihypertensive treatment. The study was undertaken to determine whether benefits of blood pressure-reducing Losartan include reductions in cardiovascular morbidity and death, and if treatment with Losartan is more effective in achieving these effects than Atenolol. The primary endpoint consisted of a composite of death, MI and stroke. Mean duration of follow-up was 4.8 years. BP of less than 140/90 mmHg was achieved in 48% of patients assigned to receive Losartan. In addition, Losartan prevented more cardiovascular morbidity and death than Atenolol. Losartan appears to be better tolerated than Atenolol (significantly fewer drug-related adverse effects, $p<0.0001$).

Risk of stroke increases proportionately as both systolic blood pressure (SBP) and diastolic blood pressure (DBP) increase. A recent analysis of data from the Framingham Study demonstrated a graded increase in stroke risk with increase in blood pressure (Seshadri et al., 2006). Among individuals aged 65, normal blood pressure (SBP <120 and DBP <80mmHg) was associated with a significantly lower ($p<0.01$) lifetime risk of stroke than high blood pressure (SBP ≥140 or DBP ≥90 mmHg). Risks associated with these two strata of blood pressures were 15% vs. 26% among women, and 10% vs. 21% among men. Graded risks were also demonstrated in both younger and older study participants, though actual lifetime risk figures, stratified for blood pressure, were not reported for either of these groups (Seshadri et al., 2006). Similarly, reported results of the Cardiovascular Health Study demonstrated a significantly higher risk of recurrent stroke associated with elevated blood pressure (measured approximately 8 months post incident stroke event) (Kaplan et al., 2006). On multivariate analyses, the hazard ratio for recurrent stroke was 1.42 per standard deviation of systolic blood pressure and 1.39 per standard deviation of diastolic pressure. According to Kaplan et al. (2006), this would translate into a reduction in relative risk of 13% for each 9 mmHg drop in SBP and 11% for a 4 mmHg drop in DBP.

8.3.2 Treatment of Hypertension

Although past reports have demonstrated that hypertension following stroke may be under-recognized and under-treated (Amar et al., 2004b; Feldman et al., 1999; Li et al., 2008; Mouradian et al., 2005; Mouradian et al., 2002), more recent studies suggest that identification and treatment rates may have increased over time. In a review and analysis that included results of 59 RCTs over a 5-decade period, Hong et al. (2011) reported that annual event rates for recurrent stroke declined by 0.996% ($p=0.001$), fatal stroke by 0.282% ($p=0.003$) and major vascular events by 1.331% ($p=0.001$). Multiple regression analysis revealed that both the use of antithrombotic medications and reductions in SBP/DBP were significant factors in the declining annual rates of recurrent stroke over time (Hong et al., 2011).

Toschke et al. (2011) analysed data available in the General Practitioner Research Database (GPRD) in the United Kingdom to examine the proportion of individuals with stroke and hypertension who were

receiving treatment according to accepted guidelines, as well as the association between guideline-standard treatment and outcome (mortality and recurrent stroke). From the GPRD, the authors identified 48,239 individuals who experienced first stroke in the years 1997 – 2006; 44,244 of whom could be assigned age, sex and practice matched controls. Fifty-four percent of individuals with stroke had been diagnosed with hypertension prior to the stroke event, 58% were diagnosed within 90 days, and 65% during the study period. This is significantly greater ($p<0.001$) than in the group of matched controls, 52% of whom were diagnosed with hypertension at some time during the entire study period. The proportion of stroke patients who were diagnosed within 90 days of stroke increased from 54% in 1997 to 62% in 2006 (p for trend <0.001). Seventy-five percent of individuals with stroke were prescribed one or more antihypertensive medications within 3 months of stroke, overall. Over time, the proportion of individuals with stroke and hypertension who received antihypertensives increased from 66% in 1997 to 83% in 2006 (p for trend <0.001). However, the rates of prescription to individuals with stroke who were not treated for hypertension prior to the event were much lower (31% overall). Treatment of hypertension post stroke according to recommended guidelines was associated with a reduced risk for recurrent stroke (HR=0.82, 95% CI 0.71-0.96) and mortality (HR=0.63, 95% CI 0.53-0.75) at 1 year (Toschke et al., 2011).

For patients to benefit from antihypertensive treatment, medication adherence is important. A study by Ji et al. (2013) analyzed data of 9,998 patients (9,028 with acute ischemic stroke and 970 of TIA) taken from the China national Stroke Registry. This study found that at 3-months 63.6% of patients were still taking their medication for secondary prevention purposes; specifically, adherence to anti-hypertensive medications was 79.2%. Patients who were persistent with their secondary prevention medications, compared to those who were not, had significantly lower rates of recurrent stroke (6.6% vs. 8.2%, p=0.003) and were more likely to be functionally independent, mRS ≤2 (OR=1.14, 95% CI; 1.03-1.25, p=0.01). Using the same database Xu et al. (2013) studied 8,409 ischemic stroke patients with hypertension. Approximately one-third of patients had high persistence (≥75%) with anti-hypertensives during the first year post-stroke onset. More patients in the low persistence group had been discharged with traditional anti-hypertensives (e.g., Beta-blockers and diuretics) and were prescribed more than one class of these medications. High persistence patients had a decreased risk of recurrent stroke, combined vascular events, and death compared to the others (Xu et al., 2013). Leistner et al. (2012) found that the implementation of a stepwise modeled support program which incorporated educational and behavioural strategies for secondary prevention, including blood pressure, was beneficial. The support program, compared to usual care, resulted in a greater proportion of patients meeting blood pressure guideline targets (77% vs. 50%, $p<0.01$) and improved risk factor control and medical compliance (Leistner et al., 2012).

Achieving blood pressure targets was also explored in the SPS3 study by Graves et al. (2012) which examined predictors of lowering SBP in 1041 subjects with a recent, within 6 months, lacunar stroke. Subjects were randomized into an 'intensive' (SBP <130mmHg) or 'usual' (SBP 130-149mmHg) target group and also a daily antiplatelet (325mg aspirin or 325mg aspirin and 75mg clopidogrel). At 12-months, targets were met for 64.8% in the 'intensive' group (mean 128.2 ± 14.2 mmHg) and 78.2% in 'usual' group (142.8 ± 15.0 mmHg). Being within the target blood pressure range at 12 months was influenced by having treated hypertension at baseline, reaching targets by the 6-month mark, and adhering to antihypertensive medications; while individuals on an antihypertensive at baseline were less likely to reach target levels.

In a more recent study by the SPRINT group (2015), 9361 patients with systolic blood pressure of 130mmHg or higher were randomized to an intensive treatment (SBP <120mmHg) or to a standard treatment (SBP <140mmHg), with the primary composite outcome being the first occurrence of stroke, myocardial infarction, heart failure, acute coronary syndrome, or death from CV causes. The planned follow-up time was 5 years however, the trial was terminated earlier since the occurrence of a primary

outcome event was significantly lower in the intensive group (1.65%) compared to that in the standard group (2.19%). Similarly, all-cause mortality in the intensive treatment was significantly reduced by 27% compared to the standard treatment. The study also found a lower incidence of stroke in the intensive treatment group (11%) however, the difference was not significant between the two treatment groups.

Numerous randomized controlled trials have examined the effectiveness of antihypertensive treatments in the reduction of blood pressure and the primary and secondary prevention of stroke. Agents assessed for use in antihypertensive therapy for prevention of stroke include β-blockers or β-receptor agonists, diuretics, ACE-inhibitors, calcium channel blockers, α-adrenergic blockers, angiotensin receptor (AT1 or ARB) blockers and α-blockers. Of these, ACE-inhibitors are the most frequently assessed antihypertensive agent. Studies examining the efficacy of blood-pressure reducing agents in stroke prevention, alone and in combination with one another, are summarized in Table 8.3.2.1 and Table 8.3.2.2.

Table 8.3.2.1 Summary of Comparative Studies Evaluating Relative Efficacy of Anti-Hypertensive therapy and Stroke Risk

Author, Year Study Design (PEDro Score) Sample Size	Intervention	Main Outcome(s) Result
CONVINCE (2003) RCT (10) N=16602	E: Verapamil (180mg) C: Atenolol (50mg) or hydrochlorothiazide (12.5mg)	• Incidence of fatal/nonfatal stroke (-)
ACCOMPLISH (2008) RCT (10) N=11506	E1: Benazepril (20mg/d) + amlodipine (5mg/d) E2: Benazepril (20mg/d) + hydrochlorothiazide (12.5mg/d)	• Incidence of fatal/nonfatal stroke (-) • Incidence of fatal/nonfatal myocardial infarction: E1 vs E2 (+) • Composite outcomes of cardiovascular disease: E1 vs E2 (+) • BP (-)
ONTARGET (2008) RCT (10) N=25620	E1: Ramipril (10mg/d) E2: Telmisartan (80mg/d) E3: Combination of both (E1 + E2)	• Mortality (-) • Rate of angio-edema: E2 vs E1 (+) • Hypotensive sypmtoms E1 vs. E3 (+) • Syncope: E1 vs. E3 (+) • Renal dysfunction: E1 vs. E3 (+)
TRANSCEND (2008b) RCT (10) N=5926	E: Telmisartan (80mg/d) C: Placebo	• Incidence of stroke (-) • Composite outcomes of cardiovascular disease (-) • Cardiovascular mortality (-)
PRoFESS (2009; 2008a) RCT (10) N=20332	E: Telmisartan (80mg/d) C: Placebo	• Incidence of recurrent stroke (-)
ALLHAT Collaborative Research Group (2000) RCT (9) N=24335	E1: Chlorthalidone (12.5-25mg/d) E2: Doxazosin (2-8mg/d)	• Incidence of stroke: E1 vs E2 (+) • Combined cardiovascular disease: E1 vs E2 (+)
ALLHAT Collaborative Research Group (2002) RCT (9) N=33357	E1: Chlorthalidone (12.5-25mg/d) E2: Amlodipine (2.5-10mg/d) E3: Lisinopril (10-40mg/d)	• Incidence of stroke: E1 vs. E3 (+); E1 vs. E2 (-) • Combined fatal coronary heart disease (-) • Combined cardiovascular disease: E1 vs. E3 (+) • Heart failure: E1 vs. E3 (+) • 5yr SBP E1 vs E2(+) • 5yr DBP E2 vs E1 (+)
VALUE trial group (2004)	E1: Valsartan	• Incidence of stroke E2 vs E1 (+)

RCT (9) N=15245	E2: Amlodipine	• BP: E2 vs E1 (+)
Systolic Hypertension in Europe (Syst-Eur) Trial Investigators (1997) RCT (8) N=4695	E: Nitrendipine (10-40mg/d) C: Placebo	• Incidence of stroke (+) • Cardiac/cardiovascular risk (+)
Syst-Eur Investigators (1999) RCT (8) N=4695	E: Nitrendipine (10-40mg/d) C: Placebo	• Incidence of stroke (+) • Mortality (+) diabetic subgroup
HOPE Study Investigators (2000) RCT (8) N=1808	E: Ramipril (10mg) + Vitamin E (400 IU) C: Placebo	• Combined primary outcome (MI, stroke or cardiovascular death) (+)
LIFE study (2002) RCT (8) N=9163	E1: Losartan E2: Atenolol	• Cardiovascular event (death, MI or stroke) (+) E1
PROGRESS Collaborative Group (2005; 2004; 2001) RCT (8) N=6105	E: Perindopril (4mg/d) + indapamide C: Placebo	• Incidence of stroke (+)
SCOPE study group (2004) RCT (8) N=1518	E: Candesartan (8mg/d) C: Placebo	• Fatal/nonfatal stroke (+)
ASCOT-BPLA (2005) RCT (8) N=19257	E1: Amlodipine (5-10mg) + perindopril (4-8mg) as required E2: Atenolol (50-100mg) + bendroflumethiazide and potassium (1.25-2.5mg) as required	• Fatal/nonfatal stroke: E1 vs E2 (+) • Total cardiovascular events: E1 vs E2 (+) • Mortality: E1 vs E2 (+)
MOSES study (2005) RCT (8) N=1352	E1:Nitrendipine (10mg/d) E2: Eprosartan (600mg/d)	• Fatal/nonfatal events: E2 vs E1 (+) • Cerebrovascular events: E2 vs E1 (+) • Mortality (-)
Hypertension Optimal Treatment (HOT) Trial (1998) RCT (7) N=18790	E: Acetylsalicylic acid (ASA) (75mg/d) C: Placebo Note: Patient sample was divided into target groups according to DBP (≤90mmHg, ≤85mmHg, ≤80mmHg)	• Incidence of stroke (-) between target groups • Incidence of stroke (+) ≤80mmHg group with pre-existing ischaemic heart disease
CAPPP Study Group (1999) RCT (7) N=10985	E: Captopril (50mg/d) C: Conventional therapy (β-blockers and/or diuretics)	• Incidence of stroke (+) • Combined outcomes of cardiovascular disease (-)
NORDIL Study Group (2000) RCT (7) N=10881	E1: Diltizazam E2: β-blockers and/or diuretics	• Incidence of stroke: E1 vs E2 (+)
ACCESS Study Group (2003) RCT (7) N=342	E: Candesartan cilexetil (4mg/d) C: Placebo	• BP (-) • Mortality (-) • Incidence of vascular events (+)
Second Australian National Blood Pressure Study (2003) RCT (7) N=6083	E1: ACE-inhibitor E2: Diuretic	• Incidence of stroke (-) • Incidence of fatal stroke: E1 vs E2 (+) • Cardiovascular events/deaths: E1 male vs E2 male (+) • BP (-)
Nazir et al. (2005)	E: Perindopril (2-4mg/d)	• Additional cardiovascular outcomes (-)

RCT (7) N=25	C: Placebo	• 1-10hr Mean arterial blood pressure (+)
ALLHAT Extension Study (2012) RCT (7) N=32804	E1: Amlodipine E2: Lisinopril E3: Chlorthalidone	• Stroke mortality: E2 vs. E3 (+) • Cardiovascular mortality (-) • Heart failure: E1 vs. E3 (+)
Kerry et al. (2013) RCT (7) N_{Start}=381 N_{End}=338	E: Personal blood pressure monitor (Omron M6) C: No monitor	• SBP (-)
Morrow et al. (2013) RCT (7) N_{Start}=4883 N_{End}=4883	E: Vorapaxar (2.5mg/d) C: Placebo	• Recurrent ischemic stroke (-) • 3yr incidence of cardiovascular death, MI or stroke (-)
ALLHAT Study Results by Sex (2013) RCT (7) N=32804	E1: Amlodipine E2: Lisinopril E3: Chlorthalidone	• Incidence of fatal/nonfatal stroke: E2 vs. E3 (+) • Combined cardiovascular disease: E2 vs. E3 (+) • All-cause mortality (-)
UK Prospective Diabetes Study (1998) RCT (6) N=1148	E: Captopril (25-50mg, 2/d) or atenolol (50-100mg/d) C: Neither drug	• Incidence of stroke (-) captopril vs. atenolol • Diabetes (+) • Mortality (-) • Weight gain (+)
COPE (2011) RCT (6) N_{Start}=3501 N_{End}=3293	E1: Angiotensin receptor blocker (ARB) + benidipine E2: β-blocker + benidipine E3: Thiazide diuretic + benidipine	• Incidence of fatal/nonfatal stroke: E2 vs. E3 (+) • Composite primary endpoint (cardiovascular events, BP) (-) • Target BP (-)

+ Indicates statistically significant differences between treatment groups
- Indicates non-statistically significant differences between treatment groups

Table 8.3.2.2 Summary of Pharmacological Treatment of Hypertension and Reduction of Stroke Risk

Study	Agent(s) Assessed	Effect on Stroke Risk
ACE-Inhibitors		
UKPDS	Captopril vs. Atenolol	Increased risk (Captopril)
CAPPP	Captopril vs. β-blocker + diuretic	Increased risk (Captopril)
HOPE	Ramipril vs. placebo	Reduced risk
PROGRESS	Perindopril + diuretic vs. placebo	Reduced risk
Australian BP Study	Various ACE-inhibitors vs. various diuretics	Similar risk for nonfatal stroke, increased for fatal (ACE-inhibitor)
ALLHAT* (2002)	Lisinopril vs. diuretic	Increased risk (Lisinopril)
ACCOMPLISH*	Benazepril + Amlodipine vs. Benazepril + diuretic	No difference in risk for stroke.
β-blockers/β-RA		
SHEP	Atenolol + diuretic vs. placebo	Reduced risk
Note: The results of UKPDS, CAPPP, LIFE and ASCOT-BPLA also consider the use of β-blockers.		
Ca-channel blockers/Ca antagonists		
NORDIL*	Diltiazam + regimen vs. regimen alone	Reduced risk
Syst-Eur 1*	Nitrendipene vs. placebo	Reduced risk

Syst-Eur 2* (diabetes)	Nitrendipene vs. placebo	Reduced risk
HOT*	Felodipene + regimen vs. Felodipene + regimen + ASA	Reduced risk with reduced BP. ASA no added effect.
ALLHAT* (2002)	Amlodipine vs. diuretic	No significant difference between treatments.
ASCOT-BPLA*	Amlodipine-based vs. Atenolol-based	Reduced risk (Amlodipine)
CONVINCE*	COER-verapamil vs. atenolol or HCTZ	No significant difference between treatments.
COPE*	Benidipine + ARB vs. benidipine + β-blocker vs. benidipine + thiazide anti-diuretic	No significant difference between treatments in terms of achieving target BP. Trend toward reduction in risk for cardiovascular events including fatal/non-fatal stroke.
α-adrenergic blockers		
ALLHAT* (2000)	Doxazosin vs. diuretic	Increased risk (Doxazosin)
Angiotensin Receptor Blockers (ARBs)		
LIFE*	Losartan-based regimen vs. Atenolol-based regimen	Reduced risk (Losartan)
ACCESS	Candesartan Cilextil at day one post-stroke vs. control of HTN commencing on day 7	Reduced risk with immediate treatment
VALUE	Valsartan-based regimen vs. Amlodipine-based regimen	No significant difference in risk reduction -- trend favouring Amlodipine.
SCOPE	Candesartan-based regimen vs. regimen not including ARB or ACE inhibitors	Reduced risk
MOSES*	Eprosartan vs. Nitrendipine	Reduced rate of events (Eprosartan)
ONTARGET	Ramipril vs. Telmisartan vs. Ramipril + Telmisartan	No significant between group differences in stroke risk.
PRoFESS*	Telmisartan vs. placebo	No significant between group differences in stroke risk.
TRANSCEND*	Telmisartan vs. placebo	No significant between group differences in stroke risk.
**** therapy administered included additions of open-label therapies (ACE-inhibitors or α-blockers or β-blockers,or ARBs, and/or diuretics) as part of a treatment regimen designed to reduce BP as required.***		

Discussion

Many different types of pharmacological therapies have been assessed both on their own and in combination with each other. Based on the results reported in Table 8.3.2.1, blood pressure reduction by pharmacologic intervention seems to be associated with a significant reduction in the risk for stroke. These results include high-risk patients, such as those who have a history of stroke (HOPE and PROGRESS trials) and patients with diabetes (HOPE and Syst-Eur 2).

The PROGRESS trial studied the use of a long-acting ACE inhibitor (perindopril) in conjunction with a thiazide diuretic (indapamide). To determine the effectiveness of a blood-pressure-lowering regimen in hypertensive & nonhypertensive patients with history of ischaemic stroke or TIA, 6105 individuals were randomized to receive either active treatment or placebo. Active treatment consisted of either perindopril 4mg/day + indapamide at the physician's discretion (n=1,770) or perindopril alone (n=1,281). Placebo groups were similarly divided into those receiving double (n=1,774) vs. single placebo (n=1,280) to match treatment conditions. Primary outcome in all conditions was total stroke. This combination, used in the prevention of hypertension, led to a relative risk reduction of 48% for recurrent stroke. 727 strokes were reported during follow-up – 307 in the treatment group, 420 in the placebo group (relative overall risk reduction = 28%). Combination therapy with perindopril & indapamide produced larger risk

reductions for total stroke than treatment with perindopril alone. Hypertensive and non-hypertensive patients with history of ischaemic stroke or TIA both benefited from combined therapy. Further analysis of data obtained from the PROGRESS trial has demonstrated that, for stroke patients with atrial fibrillation, blood pressure reduction was associated with a greater protective effect for major vascular events than for stroke patients without atrial fibrillation (Arima et al., 2005; Chapman et al., 2004). In addition, comparable benefits of blood pressure reduction were demonstrated for patients that were and were not receiving anti-coagulation therapy. The authors suggest that the benefits of blood pressure reduction are in addition to benefits associated with anti-coagulation in patients with atrial fibrillation (Arima et al., 2005).

The HOPE trial (2000) examined the effect of the ACE inhibitor, ramipril and vitamin E on the outcomes of myocardial infarction, stroke or death from cardiovascular causes. While no significant effect was found associated with vitamin E, participants receiving ramipril showed a significant reduction in risk of stroke (33%, $p<0.001$). In both the HOPE and PROGRESS trials, even non-hypertensive patients demonstrated a significant decline in stroke risk while on the ACE inhibitor. One should note, however, that the use of the ACE-inhibitor captopril has been associated with a trend toward an increased number of stroke events (Hansson et al., 1999; UK Prospective Diabetes Study (UKPDS) Group, 1998).

Overall, use of angiotensin receptor blockers (ARBs), either alone or as part of a blood-pressure-lowering regimen, has been associated with reductions in stroke risk. Results from the MOSES study suggested that the ARB, eprosartan, may be more effective than the calcium-channel blocker, nitrendipine (Schrader et al., 2005). Results from the ONTARGET trial demonstrated that the ARB, telmisartan, is not inferior to ramipril (an ACE-inhibitor) in terms of impact on blood pressure levels and risk for stroke. Treatment with telmisartan was associated with fewer reported episodes of cough or angio-edema, but more frequent symptoms of hypotension. However, adherence to therapy with either drug was high. Use of both therapies in combination was not associated with increased benefit but was associated with increased risk for symptoms of hypotension, syncope and renal dysfunction (ONTARGET Investigators et al., 2008). Similarly, results from the PRoFESS study demonstrated that treatment with telmisartan soon after stroke was not associated with any additional benefit in terms of risk for recurrent stroke events when compared to open-label treatment for hypertension. However, there was some indication on *post hoc* analysis that the effect of telmisartan may be time-dependent requiring at least 6 months of use to have an impact on risk for recurrent stroke (Bath et al., 2009; Yusuf et al., 2008a). TRANSCEND investigators examined the combined outcomes of the PRoFESS and TRANSCEND trials stratified by time and reported that, while there was no effect on the combined outcome of cardiovascular death, myocardial infarction and stroke at 6 months, there was a clear benefit associated with use of telmisartan after 6 months. The investigators propose that the benefit of treatment with an angiotensin-receptor blocker may require at least 6 – 12 months to manifest (Yusuf et al., 2008b).

In the Cardiovascular Health Study (ref), it was estimated that reduction of SBP by 9mmHg and DBP by 4 mmHg was associated with a 13% and 11% reduction in the relative risk for recurrent stroke, based on data describing post stroke blood pressure in a population of older adults (mean age = 78.6). These population-based estimates of risk reduction are considerably lower than those provided in the published results of antihypertensive treatment trials. The authors offered several suggestions to explain the discrepancy in estimates. First, participants in clinical trials tend to be younger than the participants in the Cardiovascular Health Study and magnitude of benefit may be influenced by age. In addition, the use of specific regimens of antihypertensive therapy may produce variations in results. For instance, while the combination of an ACE-inhibitor and low-dose diuretic have been associated with significant reduction in risk for recurrent stroke, only 33% and 27% of patients in the present study were receiving diuretics and ACE inhibitors, respectively (Kaplan et al., 2006).

In a systematic review and meta-analysis of 7 clinical trials that examined the effects of lowering blood pressure in patients with previous stroke, Rashid et al. (2003) found that results varied with the drug classes used in the trials selected for their analysis. Alone, β-receptor agonists appeared to have little or no effect on stroke rates, while diuretics reduced stroke by 32%. Though ACE-inhibitors alone were not shown to be as effective in this analysis, the most powerful treatment effect was found in the combination of an ACE-inhibitor and a diuretic. The use of this combination effectively reduced stroke, myocardial infarction and all vascular event outcomes by 40 – 45% (Rashid et al., 2003).

Turnbull et al. (2003) conducted several meta-analyses using data from 29 placebo-controlled randomized trials examining the effectiveness of various blood-pressure lowering regimens. The authors concluded that all commonly used anti-hypertensive therapies were effective in reducing risk for cardiovascular events, including stroke; however, larger reductions in blood pressure were associated with larger reductions in risk (Turnbull & Blood Pressure Lowering Treatment Trialists, 2003). Rashid et al. (2003) demonstrated that, overall, antihypertensive therapy (β-blockers, diuretics, ACE-inhibitors) was associated with a reduction in stroke events of up to 25% (OR=0.76) and that this reduction in risk for stroke events was related primarily to the magnitude of blood pressure reduction rather than the agent used. Further meta-analysis has supported this finding and has identified a dose-response relationship between blood pressure reduction and the reduction of stroke risk such that a 10-mmHg reduction in systolic pressure is associated with a 31% reduction in stroke risk (Lawes et al., 2004). In addition, it has been suggested that the benefits of blood pressure lowering may not be confined to hypertensive patients, but may also extend to patients who are normotensive and at risk for stroke (Lawes et al., 2004; Mancia, 2004). In the past, caution has been urged with regard to the use of antihypertensive therapy among normotensive or hypotensive patients in light of a possible J-shaped relationship between blood pressure and risk for stroke (Lawes et al., 2004; Mancia, 2004; Mason et al., 2004). However, a study of data from the ongoing Women's antioxidant cardiovascular study (WACS) demonstrated a linear relationship between systolic blood pressure and the risk of cardiovascular disease (CVD) in a population of women with a history of CVD or ≥3 cardiovascular risk factors (Mason et al., 2004). Additionally, a secondary analysis of the PROGRESS trial investigated this J-curve phenomenon and found that large reductions in BP among patients with cerebrovascular disease did not result in an increased risk of recurrent stroke (Arima et al., 2014).

In a systematic review and meta-analysis, data from 25 trials were included to evaluate the effect of antihypertensive therapy on recurrent CVD events and mortality in individuals without clinically diagnosable hypertension (Thompson et al., 2011). Overall, treatment of hypertension was associated with reduced risk of fatal or nonfatal stroke (RR=0.77, 95% CI 0.61-0.98), mortality from cardiovascular causes (RR=0.82, 95% CI 0.69-0.99) and all-cause mortality (RR=0.87, 95% CI 0.80-0.95). It should be noted that study participants were included with history of stroke or TIA in only 6 of 25 identified studies.

A more recent meta-analysis evaluated the effectiveness of various blood pressure lowering drug-cases on reducing cardiovascular outcomes pertaining to stroke, coronary heart disease (CHD), heart failure, composite of stroke and CHD, composite of stroke and CHD and heart failure, cardiovascular death, and all cause death in a total of 55 RCTs (Thomopoulos et al. 2015). Results revealed that diuretics significantly reduced all seven cardiovascular outcomes at low doses however at high doses, only the occurrence of stroke and stroke composite outcomes were significantly lowered compared to the control. At low doses, Thiazide was not significantly different than the control at reducing CHD, heart failure, and all-cause death, while Chlorthalidone showed no treatment effect over the control for cardiovascular death events and all-cause death. Both drugs were found to be effective at lowering the occurrence of the remaining outcomes. Indapamide was only effective at reducing the relative risk of stroke, composite of stroke and

CHD, and all-cause death. Primary and secondary analyses revealed no significant effect of beta-blockers over the control therapy at reducing CHD, cardiovascular death, and all-cause death, but were found to be effective at lowering the risk of stroke, heart failure, and stroke composite outcomes. Calcium antagonist drugs were significantly more effective at lowering the risk of stroke, CHD, stroke composite outcomes, cardiovascular death, and all-cause death. While primary analyses showed that ACE inhibitor drugs significantly lowered the relative risk of the majority of outcomes with the exception of cardiovascular death and all-cause death, secondary analyses demonstrated a reduced risk across all outcomes compared to the control treatment. Similar results were also found for angiotensin receptor blocker drugs, showing a risk reduction for all outcomes but not for CHD and death. Lastly, centrally acting drugs fared significantly better than the control at decreasing the risk of stroke, heart failure, stroke composite outcomes, and cardiovascular death. A comprehensive summary of the drug effects is presented in table 8.3.2.3 below.

Table 8.3.2.3 Hypertension Drug Classes and Cardiovascular Outcomes (adapted from Thomopoulos et al. 2015)

Cardiovascular Outcomes	Drug class effective* at reducing outcome	Drug class NOT effective* at reducing outcome
Stroke	• Diuretics (High dose) • Diuretics (Low dose): Thiazides, Chlorthalidone, Indapamide • Beta-blockers • Calcium antagonists • ACE inhibitors • Angiotensin receptor blockers • Centrally acting drugs	
Coronary Heart Disease	• Diuretics (Low dose): Chlorthalidone • ACE inhibitors	• Diuretics (High dose) • Diuretics (Low dose): Thiazides, Indapamide • Beta-blockers • Calcium antagonists • Angiotensin receptor blockers • Centrally acting drugs
Heart Failure	• Diuretics (Low dose): Chlorthalidone • Beta-blockers • ACE inhibitors • Angiotensin receptor blockers • Centrally acting drugs	• Diuretics (Low dose): Thiazides • Calcium antagonists
Stroke + Coronary Heart Disease	• Diuretics (High dose) • Diuretics (Low dose): Thiazides, Chlorthalidone, Indapamide • Beta-blockers • Calcium antagonists • ACE inhibitors • Angiotensin receptor blockers • Centrally acting drugs	
Stroke + Coronary Heart Disease + Heart Failure	• Diuretics (High dose) • Diuretics (Low dose): Thiazides, Chlorthalidone • Beta-blockers • Calcium antagonists • ACE inhibitors	

	• Angiotensin receptor blockers • Centrally acting drugs	
Cardiovascular Death	• Diuretics (Low dose): Thiazides • Calcium antagonists • Centrally acting drugs	• Diuretics (High dose) • Diuretics (Low dose): Chlorthalidone, Indapamide • Beta-blockers • ACE inhibitors • Angiotensin receptor blockers
All-cause Death	• Diuretics (Low dose): Indapamide • Calcium antagonists	• Diuretics (High dose) • Diuretics (Low dose): Thiazides, Chlorthalidone • Beta-blockers • ACE inhibitors • Angiotensin receptor blockers • Centrally acting drugs

*****_Statistically significant difference relative to control therapy._

A summary of studies examining the role of antihypertensive therapy in secondary prevention concluded that therapy with a diuretic alone or in combination with an ACE inhibitor could be recommended based on available data (Hilleman & Lucas, 2004). However, individual cases of hypertension may not all respond equally to the same treatment and reduction and control of blood pressure may require the use of multiple anti-hypertensive agents (Spence, 2003). The TRANSCEND trial examined the use of the angiotensin-receptor blocker telmisartan in a group of high-risk patients unable to tolerate ACE-inhibitors. Although telmisartan was not associated with significant additional benefit when compared to open-label treatment of hypertension, it was well-tolerated and could be considered a potential alternative for those individuals unable to tolerate ACE inhibitors (Yusuf et al., 2008b). In difficult, or resistant, cases of hypertension having eliminated the possibilities of noncompliance or consumption of substances that aggravate hypertension, it is necessary to understand/identify the underlying physiology of elevated blood pressure in the individual and to tailor the therapy accordingly (Spence, 1999, 2002, 2003, 2004).

Conclusions Regarding the Effectiveness of Antihypertensive Therapy and Stroke Risk

There is level 1a evidence that incidence of cardiovascular events, fatal or nonfatal stroke and mortality were reduced by commonly used antihypertensive agents. Furthermore, larger reductions of BP were associated with greater reductions in risk.

There is level 1b evidence that a reduction in blood pressure is associated with a decreased risk of stroke particularly among patients with a previous history of intracerebral haemorrhage.

There is level 1a evidence that the use of an ACE-I and diuretic together may result in the greatest reductions of stroke, myocardial infarction and all vascular events compared to ACE-Is, diuretics and β-receptor agonists used alone.

There is level 1a evidence that diuretics at high doses, diuretics at low doses (i.e. Thiazides, Chlorthalidone, and Indapamide), beta-blockers, calcium antagonists, ACE inhibitors, angiotensin receptor blockers, and centrally acting drugs are more effective than the control therapy at reducing the relative risk of stroke.

There is level 1a evidence that only Chlorthalidone at low doses and ACE inhibitors are superior to the control therapy at lowering the relative risk of coronary heart disease.

There is level 1a evidence that Chlorthalidone at low doses, beta-blockers, ACE inhibitors, angiotensin receptor blockers, and centrally acting drugs are more effective than the control at reducing the occurrence of heart failure.

There is level 1a evidence that a composite of stroke and coronary heart disease can be significantly lowered by diuretics delivered at high and low doses (i.e. Thiazides, Chlorthalidone, and Indapamide), beta-blockers, calcium antagonists, ACE inhibitors, angiotensin receptor blockers, and centrally acting drugs, relative to control therapy.

There is level 1a evidence that a composite of stroke, coronary heart disease, and heart failure can be significantly lowered by diuretics delivered at high and low doses (i.e. Thiazides, and Chlorthalidone), beta-blockers, calcium antagonists, ACE inhibitors, angiotensin receptor blockers, and centrally acting drugs, relative to control therapy.

There is level 1a evidence that cardiovascular death can be significantly reduce by Thiazides at low doses, calcium antagonists, and centrally acting drugs, while all-cause mortality can only be significantly reduced by the use of low dose Indapamide and calcium antagonist, when compared to control therapy.

There is level 1b evidence that combination therapy with telmisartan (angiotensin receptor blocker) and Ramipril (ACE inhibitor) is associated with increased symptoms of hypotension, syncope and renal dysfunction.

Versus placebo, there is level 1b evidence that ramipril (ACE inhibitor) and nitrendipine may reduce the incidence of cardiovascular and stroke events as well as subsequent mortality (particularly among diabetics). Additional level 1b evidence suggests that aspirin may improve odds of stroke among patients with pre-existing ischemic heart disease and BP ≤80mmHg while vorapaxar (PAR-1 receptor inhibitor) may not improve stroke or cardiovascular risk.

There is level 1b evidence that chlorthalidone (diuretic) may be superior to both doxazosin (α-adrenergic blocker) for stroke and cardiovascular risk management.

There is level 1b evidence suggesting that captopril (ACE-inhibitor) may reduce the incidence of stroke when compared to beta-blockers and/or diuretics. Additional level 1b evidence suggests that perindopril (ACE-I) may significantly improve blood pressure while also reducing risk of stroke however, this drug may have no effect on cardiovascular endpoints.

The risk of stroke and composite outcomes that include stroke + coronary heart disease +/- and heart failure can be reduced with the use of diuretics at high and low doses, beta-blockers, calcium antagonists, ACE inhibitors, angiotensin receptor blockers, and centrally acting drugs.

Only Chlorthalidone at low doses and ACE inhibitors were effective at reducing the occurrence of coronary heart disease, while beta-blockers, angiotensin receptor blockers, and centrally acting drugs were also effective at lowering the risk of heart failure.

The risk of cardiovascular mortality can be reduced by the use of low dose Thiazide, calcium antagonist, and centrally acting drugs. Furthermore, calcium antagonists were also effective at reducing all-cause death along with low dose indapamide.

8.3.3 Treatment Recommendations

Randomized controlled trials (RCTs) have established that lowering blood pressure in hypertensive individuals is effective in the primary prevention of haemorrhagic and ischaemic stroke. The optimal level to which elevated blood pressure should be reduced for stroke prevention remains unknown; however, benefit has been associated with reductions of approximately 10/5mmHg and normal blood pressure levels are defined as <120/80mmHg (Furie et al., 2011b). The Hypertension Optimal Treatment (HOT) trial (1998) reported the lowest risk of stroke was associated with a diastolic blood pressure of less than 80mmHg. Li et al. (2008) reported, over a mean follow-up period of 7.5 years, rates of cardiovascular events were small for individuals whose systolic pressure was less than 120 mmHg. Similarly, Vasan et al. (2001), reporting on the results from the Framingham Heart Study, concluded that subjects with blood pressure <120 mmHg had fewer vascular events compared to those with blood pressures between 120-130 mmHg. High normal blood pressure (systolic blood pressure 130-139, diastolic pressure of 85-89) was associated with an increased risk of cardiovascular disease. High normal blood pressure and normal blood pressure frequently progress to hypertension over four years, most commonly among older adults, compared to those with optimal blood pressure.

Currently, the Canadian Hypertension Education Program Recommendations for Blood Pressure Management 2015 guidelines (Daskalopoulou et al. 2015), the 2014 Canadian Stroke Best Practice Guidelines (Coutts et al. 2014), and the European Society of Hypertension (ESH)/European Society of Cardiology (ESC) 2013 guidelines for the management of arterial hypertension (Mancia et al. 2013) recommend achieving and maintain a systolic blood pressure of 140/90mmHg or lower in patients with a previous stroke or TIA. These recommendations are supported by various trials that have demonstrated benefits to reducing blood pressure across age groups typically between 55 and 80. Aggressive treatment in elderly patients over 80 however, has become the topic of recent discussion as some have authors suggested a risk rather than a benefit of reaching a target of 140/90mmHg. Warwick et al. (2015) demonstrated a benefit of aggressive treatment in a sample group consisting of patients over 80. Although Bejan-Angoulvant et al. (2010) demonstrated in a meta-analysis that antihypertensive therapy in patients aged 80 and older was associated with significant reductions in risk for stroke (35%, $p<0.001$), it was not associated with reductions in risk for mortality (RR= 1.06, 95% CI 0.89-1.25, $p=0.54$, $I^2=45.7\%$). Furthermore, an exploratory meta-regression demonstrated a possible association between higher intensity treatment and increased risk for mortality (Bejan-Angoulvant et al., 2010). Therefore, it is currently unclear whether aggressive hypertensive lowering therapy is beneficial or harmful in elderly patients, and more research is warranted to inform practice guidelines.

A recent position statement from the American Society of Hypertension noted that, most patients with hypertension will require two or three drugs to achieve blood pressure control. Preferred combinations include ACE inhibitor/diuretic, ARB/diuretic, ACE inhibitor/CCB and ARB/CCB (Gradman et al., 2010). Of course, the choice of regimen will be dictated by specific patient considerations and may require adjustment on an individual basis if the initial choice is ineffective (European Stroke Organisation Executive & Committee, 2008; Furie et al., 2011b; Gradman et al., 2010; Sacco et al., 2006b). An alternative first-line agent can be used if there are adverse effects or if patients become intolerant. In cases of resistant hypertension, one should identify the underlying physiology of elevated blood pressure in the individual and tailor the therapy accordingly (Spence, 1999, 2002, 2003, 2004).

In addition to pharmacotherapy, several lifestyle modifications (e.g. physical exercise, weight reduction, limited alcohol consumption, a diet rich in fruits, vegetables and low-fat dairy products, restricted sodium intake) have been associated with blood pressure reductions and should be included as part of a comprehensive approach to antihypertensive therapy (Furie et al., 2011b; Khan et al., 2009; P. Lindsay et al., 2008; Sacco et al., 2006b).

Recommendations for the blood pressure management in association with secondary prevention of stroke by the Canadian Stroke Best Practice Guidelines (Coutts et al. 2014) are presented in Table 8.3.3.1

Table 8.3.3.1 Treatment of Hypertension – Canadian Stroke Best Practice Guidelines (Coutts et al. 2014).

Blood pressure should be managed in all patients to reach optimal control as follow: 1. For patients who have had a stroke or TIA, blood pressure lowering treatment is recommended to achieve a target of consistently lower than 140/90mmHg. 2. In patients with diabetes, blood pressure-lowering treatment is recommended for the prevention of first or recurrent stroke to attain systolic blood pressure targets consistently lower than 130mmHg and diastolic blood pressure targets consistently lower than 80mmHg. 3. In patients with nondiabetic chronic kidney disease, blood pressure lowering treatment is recommended for the prevention of first or recurrent stroke to attain a blood pressure consistently lower than 140/90mmHg. 4. For recommendations on specific agents and sequence of agents for the secondary prevention of ischemic stroke, refer to the Canadian Hypertension Education Program treatment guidelines (Daskalopoulou et al. 2015). 5. Randomized controlled trials have not defined the optimal time to initiate blood pressure-lowering therapy after stroke or TIA. Blood pressure-lowering treatment should be initiated or modified before discharge from hospital. 6. Patients who are not started on hypertensive therapy in acute care should have arrangements made for follow-up with primary care for ongoing evaluation and management. 7. For children, blood pressure should be targeted below the 95 percentile for age, height, and gender.

Conclusions Regarding Canadian Hypertension Education Program Recommendations for the Treatment of Hypertension

Canadian Hypertension Education Program guidelines recommend blood pressures be maintained below 140/90mmHg for individuals with a history of stroke or TIA, and nondiabetic chronic kidney disease, and below 130/80mmHg in patients with diabetes mellitus. Combined treatment with an ACE inhibitor and diuretic is preferred.

Summary

1. ***There is level 1a evidence that incidence of cardiovascular events, fatal or nonfatal stroke and mortality were reduced by commonly used antihypertensive agents. Furthermore, larger reductions of BP were associated with greater reductions in risk.***
2. ***There is level 1b evidence that a reduction in blood pressure is associated with a decreased risk of stroke particularly among patients with a previous history of intracerebral haemorrhage.***
3. ***There is level 1a evidence that the use of an ACE-I and diuretic together may result in the greatest reductions of stroke, myocardial infarction and all vascular events compared to ACE-Is, diuretics and β-receptor agonists used alone.***
4. ***There is level 1a evidence that diuretics at high doses, diuretics at low doses (i.e. Thiazides, Chlorthalidone, and Indapamide), beta-blockers, calcium antagonists, ACE inhibitors, angiotensin receptor blockers, and centrally acting drugs are more effective than the control therapy at reducing the relative risk of stroke.***
5. ***There is level 1a evidence that only Chlorthalidone at low doses and ACE inhibitors are superior to the control therapy at lowering the relative risk of coronary heart disease.***
6. ***There is level 1a evidence that Chlorthalidone at low doses, beta-blockers, ACE inhibitors, angiotensin receptor blockers, and centrally acting drugs are more effective than the control at reducing the occurrence of heart failure.***
7. ***There is level 1a evidence that a composite of stroke and coronary heart disease can be significantly lowered by diuretics delivered at high and low doses (i.e. Thiazides, Chlorthalidone, and Indapamide), beta-blockers, calcium antagonists, ACE inhibitors, angiotensin receptor blockers, and centrally acting drugs, relative to control therapy.***
8. ***There is level 1a evidence that a composite of stroke, coronary heart disease, and heart failure can be significantly lowered by diuretics deliveredd at high and low doses (i.e. Thiazides, and Chlorthalidone), beta-blockers, calcium antagonists, ACE inhibitors, angiotensin receptor blockers, and centrally acting drugs, relative to control therapy.***
9. ***There is level 1a evidence that cardiovascular death can be significantly reduce by Thiazides at low doses, calcium antagonists, and centrally acting drugs, while all-cause mortality can only be significantly reduced by the use of low dose Indapamide and calcium antagonist, when compared to control therapy.***
10. ***There is level 1b evidence that combination therapy with telmisartan (angiotensin receptor blocker) and Ramipril (ACE inhibitor) is associated with increased symptoms of hypotension, syncope and renal dysfunction.***
11. ***Versus placebo, there is level 1b evidence that ramipril (ACE inhibitor) and nitrendipine may reduce the incidence of cardiovascular and stroke events as well as subsequent mortality (particularly among diabetics). Additional level 1b evidence suggests that aspirin may improve odds of stroke among patients with pre-existing ischemic heart disease and BP ≤80mmHg while vorapaxar (PAR-1 receptor inhibitor) may not improve stroke or cardiovascular risk.***
12. ***There is level 1b evidence that chlorthalidone (diuretic) may be superior to both doxazosin (α-adrenergic blocker) for stroke and cardiovascular risk management.***
13. ***There is level 1b evidence suggesting that captopril (ACE-inhibitor) may reduce the incidence of stroke when compared to beta-blockers and/or diuretics. Additional level 1b evidence suggests***

that perindopril (ACE-I) may significantly improve blood pressure while also reducing risk of stroke however, this drug may have no effect on cardiovascular endpoints.

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8.4

Managing Diabetes

Last Updated: September 2016

Key Points

- Pioglitazone may not be effective at reducing the risk of stroke in patients without a history of stroke however, it may reduce the risk of recurrent stroke in those with a history of a previous stroke. The composite risk of stroke, myocardial infarction, and death may be reduced with the use of pioglitazone.
- Intensive glucose therapy is superior to standard therapy for the treatment of type 2 diabetes and in patients with a history of macrovascular events but not for the reduction of stroke risk.
- Metformin does not appear to have any additional beneficial actions on cardiovascular events other than reducing blood glucose levels for type 2 diabetes.
- With the recent approval of Empagliflozin for the treatment of diabetes, more studies are needed to determine the potential benefits, harms, and the mechanism of action on cardiovascular health.
- Treatment of hypertension reduces the risk for stroke especially in patient with diabetes. Tighter BP control leads to a greater reduction in risk of stroke, however it may also be associated with an increased risk of adverse events. All hypertensive medications are found to reduce the risk of stroke.
- Although statins may prevent recurrent coronary events in individuals with diabetes, it is not clear whether this drug is associated with reduced risk for recurrent stroke. Further research is required.
- Fibrate therapy may not reduce the risk of stroke however, benefits may be observed for the lowering of lipid levels in diabetic patients. Fibrates may be most effective when used in patients who cannot achieve desirable lipid levels with statin therapy.
- Canadian Best Practice Recommendations for diabetes suggest blood pressure maintenance <130/80mmHg to avoid first or recurrent stroke, HbA_{1C} level ≤7.0% to lower the risk of micro and macrovascular issues, LDL cholesterol ≤2.0mmol/L using statins among adults at risk of a vascular event, and 80 to 325mg per day acetylsalicylic acid among individuals with diabetes and atherosclerotic risk factors and/or cardiovascular disease.

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8.4 Managing Diabetes

8.4.1 Significance of Diabetes

Individuals with diabetes have an increased susceptibility to atherosclerosis, hypertension, obesity and hyperlipidemia. A recent meta-analysis of individual patient data (n=698,782 with no previous stroke or MI) from 102 prospective studies, demonstrated a 2-fold risk for stroke associated with the presence of diabetes (HR=2.27 for ischemic stroke, 1.56 for haemorrhagic stroke and 1.84 for unclassified stroke; adjusted for age, smoking status, body-mass index and systolic blood pressure) (Emerging Risk Factors Collaboration et al., 2010). The risk of recurrent stroke was also found to be significantly higher among patients with diabetes compared to those without diabetes with a hazard ratio of 1.45 according to a meta-analysis by Shou et al. (2015). Risk for stroke was significantly greater in women, individuals aged 40–59 and those with a body mass index (BMI) ≥27 kg/m^2. Piernik-Yoder & Ketchum (2013) found that among stroke patients admitted to rehabilitation, diabetics were admitted at younger ages than non-diabetics.

As noted in reviews undertaken by Stern (1998) and Sacco (2001), conflicting information exists regarding the relative risk of stroke in diabetic women (i.e. vs. non-diabetic women) when compared to the relative risk for men with diabetes. Stern (1998) provided a summary of 16 studies on mortality and diabetes in which only half reported an increased risk for cardiovascular disease in women as opposed to men. A recent analysis of data pooled from nine large epidemiological studies (n=27,269) revealed that diabetic women had a 3.37-fold increased risk of fatal stroke (J. E. Ho et al., 2003). After adjusting for additional factors (total cholesterol, BMI, systolic and diastolic blood pressure, blood pressure medication use, smoking, educational status, age and race) diabetic women had a similar risk for fatal stroke as non-diabetic women who had suffered a previous stroke (hazard ratio = 3.07 vs. 4.67; p=0.43). Subjects with both diabetes and a history of stroke were found to be 7.95 times more likely to experience a fatal stroke than women with no history of diabetes or stroke. Ho et al. (2003) recommended that, given their analysis, women with diabetes should be considered a high-risk group for fatal stroke and be treated as aggressively as patients with a history of previous stroke. However, a recent study by Nomura et al. (2015) reported that stroke patients with diabetes were not significantly more likely to experience further vascular events, including recurrent stroke, compared to non-diabetic patients.

Death from cerebrovascular disease is greatly increased among subjects with elevated blood glucose concentrations (Balkau et al., 1998). The FINNSTROKE study found that the presence of diabetes mellitus was associated with a higher risk for death and disability by day 28 following stroke (OR = 1.20 and 1.51, respectively) (Kaarisalo et al., 2005). Similarly, Reeves et al. (2010) reported that individuals with diabetes may be less likely to be discharged home from acute care, less able to ambulate independently at the time of discharge, and have a greater risk for in-patient mortality following stroke.

8.4.2 Management of Diabetes and Associated Macrovascular Complications

8.4.2.1 Glycemic Control

By definition, macrovascular complications of diabetes are stroke, myocardial infarction (MI) and peripheral arterial disease. Sacco (2001) noted "*Intensive treatment of both type I and type II diabetes, aimed at maintaining near normal levels of blood glucose can substantially reduce the risk of microvascular complications such as retinopathy, nephropathy and neuropathy, but it has not been conclusively shown*

to reduce macrovascular complications including stroke […] (p.25)". There is therefore strong evidence that maintaining tight glycemic control reduces microvascular complications.

Impaired fasting glucose is identified as plasma glucose levels of 100–125 mg/dL (5.6-6.9mmol/L) while a fasting plasma glucose level of ≥126 mg/dL (> 7mmol/L) is associated with the diagnosis of diabetes (The Expert Committee on the Diagnosis Classification of Diabetes Mellitus et al., 2003). A large prospective study of patients (n=13,999) with pre-existing atherosclerotic disease reported a J-shaped relationship between fasting plasma glucose levels and the risk of first ischaemic stroke or TIA (Tanne et al., 2004). Patients with low fasting glucose levels of <80 mg/dL (< 4.4mmol/L) demonstrated an increased risk for stroke (OR=1.47) as did patients with levels >100 mg/dL (> 5.6mmol/L) (OR ranged from 1.27 for patients with glucose of 100–109 mg/dL to 2.82 (5.6-6.1mmol/L) for patients with fasting glucose >140 mg/dL (> 7.8mmol/L)). Comparisons were made with the majority of participants whose glucose levels measured 90–99 mg/dL (5-5.6mmol/L) and who exhibited the lowest risk of ischaemic cerebrovascular disease (Tanne et al., 2004).

In the Northern Manhattan Study (NOMAS), 572 participants reported a diagnosis of diabetes (Boden-Albala et al., 2008). Of these, 338 had fasting blood glucose (FBG) levels ≥126 mg/dL. Of the documented 62 ischemic stroke events, 48 occurred in patients with uncontrolled diabetes. On analysis, elevated FBG was significantly associated with increased risk for stroke (HR=2.7, 95% CI 1.9-3.8) while FBG at the target level (<126 mg/dL) was not significantly associated with increased risk, after adjusting for age, race, sex, insurance status, education, hypertension, coronary artery disease, lipid levels, obesity, physical inactivity, alcohol intake and smoking (Boden-Albala et al., 2008).

A report from the UK Prospective Diabetes Study (UKPDS 33) demonstrated that the use of intensive blood glucose measures (sulphonylurea or insulin) was associated with a 12% reduction of risk for any diabetes-related endpoint when compared to conventional treatment (Turner, 1998b). However, most of this effect could be attributed to a significant reduction in microvascular events. When examining specifically risk for stroke, there was no significant risk reduction associated with intensive glycemic control (RR = 1.11 95% CI 0.81, 1.51). A secondary analysis of 342 obese patients treated with metformin (UKPDS 34) revealed significant decreases in diabetes-related endpoints (p=0.0034), mortality (p=0.021) and stroke (p=0.032) when compared to conventional intensive interventions for blood glucose control including chlorpropamide, glibenclamide and insulin (Turner, 1998a).

In a systematic review and meta-analysis, Stettler et al. (2006) examined the reported findings of eight randomized controlled trials assessing the effects of improved glycemic control in individuals with Type 1 and Type 2 diabetes mellitus (DM). Treatments included sulphonylurea, metformin, insulin, multiple insulin injection therapy, continuous subcutaneous insulin infusion (Type I only) and intensive self-monitoring of blood glucose. The authors determined that improved glycemic control was associated with reduced risk for macrovascular complications (IRR = 0.38 for Type 1 and 0.81 for Type 2 DM). For individuals with Type 1 DM, benefits were most evident in the reduction of cardiac and peripheral vascular events, while for Type 2 DM there were reductions in peripheral vascular disease and stroke. In addition, improved glycemic control was most beneficial in younger patients who had a short duration of DM. In a 10-year period, the number of patients one would need to treat with enhanced glycemic control measures in order to prevent a single macrovascular event is 16 for Type 1, 14 for low-risk Type 2, and 7 for high-risk Type 2 DM (Stettler et al., 2006). Studies examining interventions for glycemic control and risk for stroke in high-risk individuals are summarized in Table 8.4.2.1.1.

Table 8.4.2.1.1 Summary of Interventions for Glycemic Control and Risk of Stroke

Author, Year	Intervention	Main Outcome(s)

Study Design (PEDro Score) Sample Size		Result
PROactive (Dormandy et al., 2005) International RCT (10) N=5238	E: Pioglitazone (15-45mg) C: Placebo	• Primary composite endpoint (mortality, nonfatal MI, stroke, acute coronary syndrome, endovascular or surgical intervention, amputation above the ankle) (-) • Secondary composite endpoint (mortality, nonfatal MI, stroke) (+) • Incidence of stroke (-)
PROactive subgroup analysis (2007); Dormandy et al. (2005) RCT (10) N=5238	E: Pioglitazone (15-45mg) C: Placebo Note: Further analysis of above study with patients grouped by history of previous stroke	Patients with previous stroke • Secondary composite endpoint (mortality, nonfatal MI, stroke) (+) • Incidence of stroke (+) Patients without previous stroke • Incidence of fatal or nonfatal stroke (-)
ADVANCE Collaborative Group (2008) RCT (10) N=11140	E: Intensive glucose control (gliclazide + other drugs to $HbA_{1C} \leq 6.5\%$) C: Standard glucose control	• Microvascular events (+) • Macrovascular events (-) • Severe hypoglycaemia (+) C • Incidence of nonfatal stroke (-) • Cerebrovascular events (-)
ACCORD Study Group (2008) RCT (8) N=10251	E: Intensive glucose-lowering treatment strategies (HbA_{1c} to <6.0%) C: Standard glucose-lowering treatment strategies (HbA_{1c} to 7.0–7.9%)	• Composite primary outcome (nonfatal MI, nonfatal stroke, CV mortality) (-) • Incidence of fatal/nonfatal stroke (-) • All-cause mortality (+) C • Mortality (+) aspirin vs. no aspirin • Hypoglycaemia (+) C • Weight gain (+) C • Fluid retention (+) C
VADT (2009) RCT (8) N=1791	E: Intensive therapy (maximum dose) C: Standard therapy (half maximum dose) Note: BMI ≥27=metformin + rosiglitazone; BMI <27=glimepiride + rosiglitazone	• Time to first cardiovascular event (-); stroke (-) • Adverse events (+) C
Zinman et al. (2015) RCT (6) N_{Start}=7028 N_{End}=7020	E: Empagliflozin 10 or 25mg/d C: Placebo	• Mortality due to cardiovascular causes (+) • Mortality due to all causes (+) • Incidence of stroke (-) • Incidence of non-fatal stroke (-)

+ Indicates statistically significant differences between treatment groups

- Indicates non-statistically significant differences between treatment groups

Discussion

A meta-analysis consisting of 19 trials examining the use of pioglitazone in both high and low-risk individuals with Type 2 DM demonstrated a significantly reduced risk for the composite outcome of death, myocardial infarction and stroke (HR= 0.82, 95% CI 0.72-0.94, p=0.005) (Lincoff et al., 2007). However, when elements of the composite outcome were examined individually, treatment with pioglitazone was not associated with a significant reduction in risk of stroke (HR=0.80, 95% CI 0.62–1.04). It should be noted that treatment was associated with a significantly higher risk for serious heart failure (HR = 1.41, %95 CI 1.14-1.76) however, incidence of heart failure was not associated with increased mortality (Lincoff et al., 2007).

The PROactive study, which focused on high-risk individuals with established macrovascular disease, also demonstrated a significant reduction in risk for the secondary composite endpoint of all-cause mortality, MI and stroke (HR = 0.84, 95% CI 0.72-0.98, p=0.027), but no significant reduction in risk for stroke alone was found (Dormandy et al., 2005). Reduction in risk was associated with treatment given in addition to existing care which included antiplatelets, anti-hypertensives, lipid-lowering agents and glucose-lowering medications. Over a 3-year period, one would need to treat 48 patients in order to avoid a single major cardiovascular event. Treatment with pioglitazone was not associated with increased mortality or liver toxicity, but was associated with increased rates of edema and heart failure (Dormandy et al., 2005).

Almost one-half of the patients included in the PROactive study had a previous history of myocardial infarction, whereas only 19% had previous stroke. An analysis of this subgroup revealed a significant reduction in risk for stroke by 47%. In individuals with no history of stroke, the addition of pioglitazone had no significant effect on risk for any composite outcome, stroke or all-cause mortality. Among individuals with previous stroke, rates of serious adverse events were similar across treatment conditions (pioglitazone vs. placebo). Although there were more hospitalizations for heart failure in the pioglitazone group, this difference was not significant (p=0.09) (Wilcox et al., 2007). Based on the results of the PROactive trial, the European Stroke Organization has recommended treatment with pioglitazone in patients with type 2 DM who do not need insulin (Ringleb et al., 2008a).

Since that time, however, several more studies (Duckworth et al., 2009; Gerstein et al., 2008; Patel et al., 2008) examining the impact of intensive vs. standard glucose-lowering therapies have been published. Each of these has included a significant proportion (32% - 40%) of patients with history of previous macrovascular disease (including stroke). In a meta-analysis examining the effect of intensive control of glucose on cardiovascular outcomes in individuals with Type 2 DM, which included all of the studies summarized here, Ray et al. (2009) demonstrated that intensive treatment was not associated with reduced risk for stroke when compared with standard therapy. In addition, both the ACCORD and ADVANCE studies included subgroup analyses that demonstrated no advantage associated with intensive treatment in terms of risk for macrovascular events (Gerstein et al., 2008; Patel et al., 2008).

In an extended analysis of data from the ACCORD trial that included a mean of 3.7 years of intensive therapy followed by 1.2 years of standard glucose lowering therapy, the researchers reported that intensive therapy was not associated with reductions in the rate of nonfatal MI, non-fatal stroke or death due to cardiovascular causes when compared to standard therapy (Gerstein et al., 2011). Resumption of standard therapy was associated with increases in median glycated haemoglobin level in the intensive therapy group. At 5-year follow-up, the group who had received intensive glucose-lowering therapy had a reduced risk of nonfatal MI (HR=0.82, 95% CI 0.70-0.96) and an increased risk for death from cardiovascular causes (HR=1.29 (95% CI 1.04-1.60). There were no significant between group differences reported for risk of nonfatal or fatal stroke at 5 years (Gerstein et al., 2011).

A recent study as part of the EMPA-REG Outcome Trial by Zinman et al. (2015) revealed that the use of empagliflozin, a selective inhibitor of sodium glucose cotransporter 2 reduced hemoglobin levels and the risk of mortality. However, no significant differences between emplagliflozin and placebo was reported regarding the incidence of stroke, both fatal and non-fatal (HR 1.18, 95% CI 0.89-1.56, p=0.26), and non-fatal alone (HR 1.24, 95% CI 0.92-1.67, p=0.16). Glycemic levels were lower for patients treated with empagliflozin compared to placebo but no significant difference was noted between patients taking 10mg of empagliflozin and those taking higher doses (i.e., 25mg). Empagliflozin has only recently been approved (November 30, 2015) for use as an adjunct drug to exercise and diet in adults with type 2 diabetes. Thus far, the mechanism of action for reducing the risk of stroke, myocardial infarction and cardiovascular events is purely speculative, hence further research is required.

Intensive glucose lowering therapies, however, may be most effective only in specific subgroups of high risk individuals with Type 2 diabetes and previous history of macrovascular events. For example, based on data from the FRENA registry (n=974), Camafort et al. (2011) demonstrated that rates of recurrent ischemic events (MI, stroke or critical limb ischemia) were significantly lower in individuals with lower levels of blood glucose (HbA_{1c} <7.0%) vs. higher levels (>7.0%) among patients with a history of coronary artery disease but not cerebrovascular disease or peripheral artery disease.

Metformin is often the first line of treatment for type 2 diabetes among targeting other medical complications. Its mechanism of action involves the reduction of LDLs and tryglicerides thus lowering blood glucose levels. Some studies have linked the use of metformin to changes in cardiovascular health suggesting some benefits to its use. A meta-analysis by Lamanna et al. (2011) evaluated the effect of metformin on cardiovascular events (i.e., MI, stroke, and peripheral artery disease or other cardiovascular death) and mortality by synthesizing the evidence from 35 clinical trials which compared metformin to placebo. Overall, no significant benefit or harm was found with the use of metformin on cardiovascular events. Further, when the trials included an active control, no significant difference between treatments (i.e., metformin versus active control) was found to indicate a benefit. Metformin was favoured only when the trials compared the therapy against a placebo or a no-therapy control, showing a significant benefit in reducing cardiovascular events.

Conclusions Regarding Interventions for Glycemic Control and Risk for Stroke

There is level 1a and level 1b evidence that pioglitazone may not be associated with a relative reduction in the risk of stroke; however, it may be effective at lowering the composite risk of stroke, myocardial infarction, and death.

There is level 1b evidence that in patients with no history of previous stroke, pioglitazone was not effective at reducing the risk of stroke however, in patients with a history of stroke, the use of pioglitazone was associated with a reduction in the risk of a recurrent stroke.

There is level 1a evidence that intense glucose lowering therapy is not significantly different than standard therapy for reducing the risk of stroke. Intensive glucose lowering therapy may only be an effective treatment for type 2 diabetes and for patients with a history of macrovascular events.

There is level 1b evidence that empagliflozin was not significantly different than placebo therapy at reducing the relative risk of stroke; however, more research is needed to identify the mechanism of action of metformin and potential benefits on cardiovascular health.

There is level 1a evidence that metformin has no additional benefits on cardiovascular health other than reducing blood glucose levels for the treatment of type 2 diabetes.

Pioglitazone may not be effective at reducing the risk of stroke in patients without a history of stroke however, it may reduce the risk of recurrent stroke in those with a history of a previous stroke. The composite risk of stroke, myocardial infarction, and death may be reduced with the use of pioglitazone.

Intensive glucose therapy is superior to standard therapy for the treatment of type 2 diabetes and in patients with a history of macrovascular events but not for the reduction of stroke risk.

Metformin does not appear to have any additional beneficial actions on cardiovascular events other than reducing blood glucose levels for type 2 diabetes.

With the recent approval of Empagliflozin for the treatment of diabetes, more studies are needed to determine the potential benefits, harms, and the mechanism of action on cardiovascular health.

8.4.2.2 Hypertension Control

There is evidence that stroke patients with diabetes are at significantly increased risk of disability and mortality (Ho et al., 2003; Otiniano et al., 2003). Despite the lack of conclusive evidence proving a causal link between tight glycemic control and stroke risk reduction, there is evidence that aggressive treatment of blood pressure (<150/85 mm Hg) among patients with type 2 diabetes significantly reduces the risk of stroke by 44% (UK Prospective Diabetes Study Group, 1998b). The Syst-Eur trial (Tuomilehto et al., 1999) and HOPE Study (Heart Outcomes Prevention Evaluation Study Investigators, 2000) found substantial reductions in stroke risk with anti-hypertensive therapies (73% and 33%, respectively). Details of individual studies are summarized in Table 8.2.2.1.

Table 8.2.2.1 Summary of Studies Assessing Control of Blood Pressure and Stroke Risk in Diabetic Patients

Author, Year Study Design (Pedro Score) Sample Size	Intervention	Main Outcome(s) Result
ADVANCE trial (2007) RCT (10) N=11140	E: Perindopril (2mg) + indapamide (0.625mg) C: Placebo	• Incidence of macrovascular events (-) • Incidence of cerebrovascular events (-)
ALLHAT Collaborative Research Group (2000) RCT (9) N=31512	E1: Chlorthalidone (2.5-10mg/d) E2: Amlodipine Besylate (2.5-10mg/d) E3: Lisinopril (10-40mg/d) Note: Participants stratified into groups based on presence of diabetes mellitus (DM), impaired fasting glucose (IFG) or normoglycemia (NG)	• Cardiovascular mortality and nonfatal MI: E2/E3 vs. E1 (-) DM and NG • Incidence of cardiovascular mortality or nonfatal MI: E2 vs. E1 (+) IFG
ABCD (1998) RCT (8) N=470	E1: Nisoldipine E2: Enalapril	• BP (-) • Incidence of fatal and nonfatal myocardial infarction E2 vs E1 (+)
Syst-Eur Investigators (1999) RCT (8) N=4695	E: Nitrendipine (10-40mg/d) C: Placebo	• Overall mortality (+) • Cardiovascular disease mortality (+) • All cardiovascular events (+)
HOPE Study (2000) RCT (8) N=3577	E: Ramipril (10mg/d) C: Placebo	• Combined primary outcome (MI, stroke, CV mortality) (+)
ACCORD trial (2010) RCT (8) N=4733	E: Intensive therapy (SBP<120mmHg) C: Standard therapy (SBP=140mmHg)	• Composite primary outcome (first nonfatal MI, nonfatal stroke, CV death) (-) • Incidence of adverse events (+) C
UK Prospective Diabetes Study Group (UKPDS 39) (1998a) RCT (7) N=1148	E: Tight BP control (captopril or atenolol) C: Less tight BP control (no ACE-inhibitor or β-blocker)	• BP (-) captopril vs. atenolol • Incidence of stroke (-) captopril vs. atenolol

UK Prospective Diabetes Study Group (UKPDS 38) (1998b) RCT (7) N=1148	E: Tight BP control (captopril or atenolol) C: Less tight BP control (no ACE-inhibitor or β-blocker)	• Mean BP (+) • Incidence of stroke (+) • Diabetes related events (+) • Diabetes mortality (+)
FACET (1998) RCT (7) N=380	E1: Fosinopril (20mg/d) E2: Amlodipine (10mg/d)	• SBP E2 vs E1 (+) • Combined major vascular events (stroke, MI, hospitalized angina) E1 vs E2 (+) • Incidence of fatal and nonfatal stroke (-)
STOP-2 (2000) RCT (7) N=719	E1: ACE-inhibitor E2: Calcium antagonist C: Conventional therapy (β-blockers or diuretics)	• BP (-) • Cardiovascular mortality (-) • Incidence of fatal and nonfatal stroke (-) • Incidence of myocardial infarction: E1 vs. E2 (+)
NAGOYA HEART Study (2012) RCT (7) N=1150	E1: Valsartan (80mg/d) E2: Amlodipine (5mg/d)	• Composite primary outcome (MI, stroke, heart failure, coronary revascularization, sudden cardiac death) (-) • Incidence of heart failure E1 vs E2(+)

+ Indicates statistically significant differences between treatment groups
- Indicates non-statistically significant differences between treatment groups

Discussion

There is strong evidence supporting the effectiveness of blood pressure control in dramatically reducing the risk for both fatal and nonfatal stroke in individuals with diabetes. Agents assessed for use with diabetic populations include ACE-inhibitors (captopril, enalapril, fosinopril, perindopril, lisinopril and ramipril), β-blockers (atenolol), angiotensin receptor blockers (valsartan), diuretics (indapamide and chlorthalidone) and calcium channel blockers (nitrendipine, nisoldipine and amlodipine). Given the relative effectiveness of the agents tested, and the reported benefits of a tightly controlled blood pressure (UK Prospective Diabetes Study Group, 1998b), it has been suggested that the choice of medication may be less important than reaching and maintaining an optimal targeted blood pressure (Vinik & Flemmer, 2002). A 10-year follow-up of the UKDPS trial demonstrated that, as the between group difference in blood pressure disappeared in the years following the trial, so too did the reduction in risk for stroke associated with tight blood pressure control (Holman et al., 2008).

A meta-analysis of twenty-seven trials examined the effectiveness of blood pressure reduction on major cardiovascular events in adults with diabetes (Turnbull et al., 2005). The authors found that for the outcome of stroke, there was no difference in the effects of treatment regimens based on the use of ACE-inhibitors, calcium antagonists, angiotensin receptor blockers, beta-blockers and diuretics between individuals with and without diabetes. All regimens appeared comparable in their ability to reduce the short to medium-term risks of macrovascular complications. Lower target blood pressures resulted in fewer major cardiovascular events and cardiovascular deaths in patients with diabetes compared to those without (p=0.03 and 0.02, respectively) (Turnbull et al., 2005).

Similarly, a meta-analysis of 31 intervention trials demonstrated that antihypertensive therapy aimed at tighter control of blood pressure, in individuals with diabetes, was associated with greater reduction in risk for stroke than "less tight" control (RR=0.61, 95% CI 0.48-0.79) (Reboldi et al., 2011). It should be noted, however, that very tight control may carry other risks. The ACCORD BP study demonstrated that intensive therapy targeting SBP at <120 mmHg was associated with a significantly reduced risk for stroke; however, intensive therapy was also associated with significantly more serious adverse events associated with treatment (Calles-Escandon et al., 2010).

Conclusions Regarding Diabetes and the Treatment of Hypertension

There is level 1a evidence that treatment of hypertension in diabetic patients reduces the risk of stroke. Furthermore, tighter control of blood pressure is associated with greater reduction of risk for stroke compared to "less tight" therapy; however, greater risk of adverse events may be associated with aggressive therapy.

There is level 1b evidence that perindopril (angiotensin converting enzyme inhibitor, ACE-I) administered with indapamide (diuretic) may not be superior to placebo therapy at reducing the incidence of macrovascular or cerebrovascular events.

There is level 1b evidence that nitrendipine (ca-channel blocker, CCB) improves risk of cardiovascular events and mortality compared to placebo.

There is level 1b evidence that ramipril (ACE-I) alone improves a combined outcome of myocardial infarction, stroke and cardiovascular mortality.

There is level 1a evidence suggesting that ACE-Is may improve the incidence of major vascular events, especially myocardial infarction, when compared to CCBs.

There is level 1b evidence that amlodipine besylate (CCB) or lisinopril (ACE-I) may not reduce the risk of cardiovascular mortality or nonfatal myocardial infarction when compared to chlorthalidone (diuretic) among patients with diabetes.

There is level 1b evidence that treatments with CCB and ACE-I provide no additional benefit over conventional therapy in terms of preventing the occurrence of macrovascular events including stroke in individuals with Type 2 diabetes.

There is level 1b evidence that valsartan (angiotensin receptor blocker) is as effective as amlodipine (CCB) at reduction of risk for macrovascular events or cardiac complications. Use of this amlodipine may be associated with increased risk for hospitalization due to heart failure.

There is level 1a evidence that all hypertensive medications reduce the risk of stroke, especially among patients with diabetes.

Treatment of hypertension reduces the risk for stroke especially in patient with diabetes. Tighter BP control leads to a greater reduction in risk of stroke, however it may also be associated with an increased risk of adverse events. All hypertensive medications are found to reduce the risk of stroke.

8.4.2.3 Treatment of Dyslipidemia

In many cases, Type 2 diabetes is associated with plasma lipid and lipid protein abnormalities that include low concentrations of HDL cholesterol, increases in small, dense, atherogenic LDL particles and elevated triglycerides (Krauss, 2004). Each of these abnormalities is associated with increased cardiovascular risk. Lehto et al. (1996) demonstrated that HDL cholesterol levels less than 0.9 mmol/L were associated with a 1.9 fold increase in risk for stroke in diabetic patients and triglyceride levels of >2.3 mmol/L with a 2.1 fold increase in risk. However, in a study of stroke risk factors from the United Kingdom Prospective Diabetes

Study, dyslipidemia was not identified as a significant risk factor. Significant risk factors included age, male sex, hypertension and atrial fibrillation (Davis et al., 1999).

Although behavioural or lifestyle interventions such as diet, weight loss and physical activity may improve features of diabetic dyslipidemia to some extent, pharmacological treatment may be required. In a recent meta-analysis of cholesterol-lowering therapy with statins, using data from 14 randomized controlled trials, it was demonstrated that significant reductions in major vascular events, including major coronary events (RR = 0.78, 99% CI 0.69-0.87), coronary revascularizations (RR=0.75, 99% CI 0.64-0.88) and stroke (RR=0.79, 0.67-0.93) were associated with statin treatment (Kearney et al., 2008). Among patients with diabetes and a history of vascular disease (including cerebrovascular and peripheral vascular disease but not CHD), risk for major vascular events was also reduced (RR=0.80, 99% CI 0.61-1.03). For patients with known vascular disease at baseline, treatment with statins over a 5-year period resulted in 57 fewer events per 1000 per mmol/L LDL cholesterol reduction. It should be noted that, while 37% of patients with diabetes included in the analysis had known vascular disease at baseline, only 5% had a history of previous stroke (Kearney et al., 2008).

Individual studies examining the use of statins and the prevention of stroke in patients with diabetes and previous history of vascular disease are summarized in Table 8.4.2.3.1.

8.4.2.3.1 Summary of Studies Assessing Use of Statins for Secondary Prevention in Individuals with Diabetes

Author, Year Study Design (Pedro Score) Sample Size	Intervention	Main Outcome(s) Result
LIPID Trial (2003; 2000) RCT (9) N=9014	E: Pravastatin (40mg) C: Placebo	• Coronary artery disease mortality (+) • Incidence of stroke (+)
ASPEN Study (2006) RCT (9) N=2410	E: Atorvastatin (10mg/d) C: Placebo	• Composite primary endpoint (various complications of cardiovascular disease) (-) • Incidence of fatal or nonfatal stroke (-)
Callahan et al. (2011) *Post hoc analysis* Of SPARCL trial (2006a) RCT (9) N=4731	E: Atorvastatin (80mg/d) C: Placebo	• Incidence of ischemic stroke (+)
Scandinavian Simvastatin Survival Study (4S) (1997) RCT (8) N=202	E: Simvastatin (20mg/d) C: Placebo	• All-cause mortality (-) • Incidence of cerebrovascular events (-) • Incidence of major coronary heart disease events (+) • Incidence of atherosclerotic events (+)
CARE trial (1998) RCT (8) N=586	E: Prevastatin C: Placebo	• Composite primary endpoint (coronary heart disease mortality, nonfatal MI) (-) • Incidence of stroke (-) • Incidence of coronary events (+)
PROSPER Study Group (2002) RCT (8) N=5804	E: Prevastatin (40mg/d) C: Placebo	• Composite primary endpoint (coronary mortality, nonfatal myocardial infarction, fatal and nonfatal stroke) (+) • Incidence of stroke (-)
MRC/BHF Heart Protection Study (2003)	E: Simvastatin (40mg/d) C: Placebo	• Incidence of first nonfatal or fatal stroke (+)

RCT (8) N=5963		
ASCOT–LLA (2005) RCT (8) N=2532	E: Atorvastatin (10mg/d) C: Placebo	• Incidence of cardiovascular events and procedures (+) • Incidence of fatal and nonfatal stroke (-)
GREACE (2003) RCT (6) N=313	E: Structured care for dyslipidemia (atorvastatin, 80mg/d) C: Usual care for dyslipidemia (physician's standard)	• All-cause mortality (+) • Coronary mortality (+) • Incidence of coronary morbidity (+) • Incidence of stroke (+)

+ Indicates statistically significant differences between treatment groups
- Indicates non-statistically significant differences between treatment groups

Discussion

The majority of studies summarized above provided subgroup analyses of individuals with Type 2 diabetes mellitus. Only two, the MRC/BHF Heart Protection Study and the ASPEN trial, exclusively examined the effect of statins within individuals with Type 2 DM. The MRC/BHF Heart Protection Study reported that 18% of all diabetic participants had a history of "occlusive arterial disease" (vs. 33% with previous MI or other CHD) and within this subgroup, statin use was associated with a significant reduction in risk for stroke by 18.4% (Collins et al., 2003). However, in the ASPEN trial, treatment with atorvastatin was not associated with a significant reduction in risk for stroke for the secondary prevention subgroup (Knopp et al., 2006).

Based on all of the available analyses included in Table 8.4.2.3.1, studies examining the impact of treatment with statins on risk for recurrent stroke in individuals with diabetes and a history of vascular disease have provided mixed results. Moreover, although the benefit of statin treatment for patients with diabetes and existing coronary heart disease seems clear in terms of reduced risk for subsequent coronary events, the benefit for secondary prevention of stroke is less apparent. The CARE, PROSPER, ASCOT-LLA and ASPEN studies reported no significant reduction in risk for stroke among individuals with diabetes and history of previous vascular disease (Goldberg et al., 1998; Knopp et al., 2006; Sever et al., 2005; Shepherd et al., 2002), while the remaining trials reported significant reductions in risk for stroke. However, the majority of patients with existing vascular disease in most of the identified studies reported a history of previous MI, angina or other coronary disease, while relatively few had previous stroke. The LIPID trial, for instance, reported significant reductions for risk of stroke but only 6% of the 1,077 patients with diabetes in that trial also had a history of previous stroke (Keech et al., 2003).

In the *post hoc* analysis of the secondary prevention trial, SPARCL, treatment with atorvastatin was associated with a significant reduction in risk for ischemic stroke when compared with placebo for the subgroup of study participants classified with Type 2 diabetes mellitus at baseline (p=0.04) (Callahan et al., 2011). However, the authors reported no significant difference in treatment effectiveness between subgroups of individuals with Type 2 diabetes or metabolic syndrome and those without diabetes or metabolic syndrome (Callahan et al., 2011).

Conclusions Regarding Statins for Secondary Prevention in Individuals with Diabetes

There is conflicting level 1b evidence regarding the effectiveness of pravastatin for the prevention of stroke and composite endpoints of coronary and cardiac complications.

There is conflicting level 1b evidence regarding the efficacy of atorvastatin in secondary prevention of stroke and cardiovascular complications.

There is level 1b evidence that simvastatin may reduce the odds of stroke as well as the incidence of major coronary and atherosclerotic events when compared to placebo.

There is level 1b evidence that a structured care intervention for hyperlipidemia using atorvastatin and strict implementation of guidelines may decrease mortality, coronary morbidity and incidence of stroke versus usual care.

There is level 1a evidence that statin treatment in patients with diabetes may reduce the risk of stroke; however, in patients with diabetes and existing coronary heart disease, statin treatments only reduced the risk of subsequent coronary heart disease but not stroke.

Although statins may prevent recurrent coronary events in individuals with diabetes, it is not clear whether this drug is associated with reduced risk for recurrent stroke. Further research is required.

8.4.2.4 Fibrates and Stroke Prevention in Patients with Diabetes

Fibrates are PPARα agonists that decrease plasma triglycerides and increase HDL levels and, therefore, may provide different protective effects in terms of cardiovascular risk than statins (Saha et al., 2007). A 1998 meta-analysis of 28 studies examining the effects of interventions on risk for non-haemorrhagic stroke demonstrated that treatment with statins reduced the risk for fatal and nonfatal stroke (OR=0.76) while fibrates, resins and dietary interventions to lower cholesterol did not reduce stroke risk (OR=1.02) (Bucher et al., 1998). However, the results of several large clinical trials, all of which included patients with diabetes mellitus, have been published subsequent to that analysis and are summarized in Table 8.4.2.4.1.

Table 8.4.2.4.1 Summary of Use of Fibrates in Hyperlipidemia and Stroke Prevention in Diabetic Patients

Author, Year Study Design (PEDro Score) Sample Size	Intervention	Main Outcome(s) Results
ACCORD Lipid Study (2010) RCT (10) N=5518	E: Fenofibrate (160mg/d) + simvastatin C: Placebo + simvastatin	• Composite major cardiovascular events (nonfatal myocardial infarction, nonfatal stroke, cardiovascular mortality) (-) • Incidence of fatal/nonfatal stroke (-) • Annual mortality (-)
VA-HIT Study Group (1999) RCT (9) N=2531	E: Gemfibrozil (1200mg/d) C: Placebo	• Incidence of nonfatal myocardial infarction or death from coronary causes (+) • Incidence of stroke (-) • Incidence of transient ischemic attack (+)
VA-HIT Study Group (2001) RCT (9) N=2531	E: Gemfibrozil (1200mg/d) C: Placebo	• HDL cholesterol (+) • LDL cholesterol (-) • Triglycerides (+) • Coronary heart disease events (+)
FIELD Study (2005) RCT (9) N=9795	E: Fenofibrate (200mg/d) C: Placebo	• Incidence of coronary events (-) • Incidence of nonfatal myocardial infarction (+) • Incidence of coronary heart disease mortality (-) • Total cardiovascular disease events (+) • Incidence of stroke (-)
BIP Study Group (2000) RCT (7) N=3090	E: Bezafibrate (400mg/d) C: Placebo	• Incidence of fatal/nonfatal myocardial infarction or sudden death (-) • Incidence of stroke (-)

+ Indicates statistically significant differences between treatment groups

- Indicates non-statistically significant differences between treatment groups

Discussion

In the VA-HIT trial, use of gemfibrozil was not associated with any major adverse effects and was generally well tolerated. The most common complaint was abdominal discomfort (Robins et al., 2001). Within a population of patients with low levels of HDL cholesterol, the magnitude of benefit derived from gemfibrozil therapy appears similar to that reported for pravastatin therapy in populations with average to moderately high levels of LDL cholesterol (Rubins et al., 1999). While 5 year needed to treat calculations are provided for myocardial infarctions and deaths from CHD and are similar to those provided for pravastatin (Rubins et al., 1999), no analysis is provided for the secondary outcomes of stroke and/or TIA. It should be noted that, in the VA-HIT study, benefits of treatment were not apparent until approximately 2 years after commencement of the trial and, although the reduction in stroke events associated with treatment appears large, it did not reach statistical significance (Robins et al., 2001). However, studies examining the effectiveness of treatment with fibrates have not considered stroke events among their primary study outcomes. To this point, studies may not have been adequately powered to adequately detect change in these event rates.

Unlike the VA-HIT trial, the more recent FIELD trial recruited only patients with Type 2 DM. No significant benefit associated with treatment was reported for either the primary study outcome or for stroke events. However, during the study, 36% of patients in the placebo group began treatment with non-study lipid lowering therapies (vs. 19% in the treatment group). When the analysis was adjusted for this factor, treatment was associated with a 15% reduction in risk for cardiovascular events (p=0.004) (Keech et al., 2005). No results of this revised analysis were provided for stroke events alone.

A meta-analysis examining the use of fibrates in patients with Type 2 DM included 8 trials, four of which were considered secondary prevention trials, in that they recruited patients with known coronary heart disease (Allemann et al., 2006). Pooled analysis demonstrated a non-significant reduction in stroke associated with fibrate treatment (Incidence Rate Ratio = 0.87, 95% CI 0.73-1.05). Similar to statin trials, the four secondary prevention trials of fenofibrate included relatively few individuals with both diabetes and history of previous stroke, ranging from none (Bezafibrate Infarction Prevention (BIP) study, 2000) to 12% of diabetic patients in the VA-HIT trial (Robins et al., 2001). In the VA-HIT trial, treatment with gemfibrozil was associated with a non-significant reduction in risk for stroke among participants with diabetes (HR=0.60, p=0.46) (Robins et al., 2001).

A similar meta-analysis confirmed those findings (Saha & Arora, 2010). Based on data from the DAIS, BIP, VA-HIT and FIELD studies, longer term (> 1 year) use of fibrates was associated with a non-significant reduction in the risk for stroke (RR = 0.88, 95% CI 0.73 – 1.05). However, fibrate therapy was associated with a significant reduction in the risk for nonfatal myocardial infarction (RR=0.79, 95% CI 0.67-0.93, p=0.006). The authors suggest that statins should be considered first line therapy for dyslipidemia in individuals with Type 2 DM; although, fibrates may be of use for treatment of individuals who are unable to achieve desired lipid levels via statin therapy.

Jun et al. (2010) conducted a systematic review and meta-analysis of all trials (n=18) evaluating the effects of fibrates on cardiovascular outcomes. Overall, use of fibrates had no effect on risk for stroke (RR=1.03, 95%CI 0.91-1.16), but was associated with a significant 13% reduction in risk for coronary events. Subgroup analyses were conducted for coronary events. When trials enrolling only individuals with diabetes mellitus were considered as part of these analyses, there was no significant reduction in risk for coronary events associated with the use of fibrates (RR=0.887, 95% CI 0.775-1.016) (Jun et al., 2010). Most recently, a systematic review found that treatment with fibrates was not associated with a

significant reduction on the risk of stroke (Zhou et al., 2013). In a subgroup analysis, the authors reported that gemfibrozil therapy showed a beneficial effect on stroke risk and they concluded that fibrate therapy may play a role in fatal stroke for patients with previous diabetes, cardiovascular disease or stroke (Zhou et al., 2013).

Conclusions Regarding Fibrates in Hyperlipidemia and Stroke Prevention in Diabetic Patients

There is level 1a evidence that fibrate treatment may not reduce the risk of stroke or coronary events.

There is conflicting level 1b evidence regarding the effect of gemfibrozil on lowering the risk of stroke in patients with diabetes.

There is level 1a evidence that fenofibrate and simvastatin combination therapy or fenofibrate treatment alone may not be more efficacious in the prevention of stroke and cardiovascular events when compared to simvastatin monotherapy or placebo. Additional level 1b evidence suggests that unaccompanied fenofibrate administration may decrease the risk of nonfatal myocardial infarction.

There is level 1b evidence that bezafibrate may not improve incidence of myocardial infarction or stroke.

Fibrate therapy may not reduce the risk of stroke however, benefits may be observed for the lowering of lipid levels in diabetic patients. Fibrates may be most effective when used in patients who cannot achieve desirable lipid levels with statin therapy.

8.4.3 Treatment Recommendations

Treatment of hypertension and hyperlipidemia in patients with diabetes reduces the incidence of macrovascular complications such as stroke. Early screening for diabetes in individuals with hypertension and/or hyperlipidemia together with prompt intervention to reduce cardiovascular risk has been recommended (Brown et al., 2004; Feig et al., 2005). Current guidelines for the secondary prevention of stroke, from the American Heart Association/ American Stroke Association Council on Stroke (Kernan et al. 2014), recommend the use of existing guidelines from the American Diabetes Association for glycemic control and BP targets in patients with diabetes who have had a stroke or TIA. Canadian Best Practice Recommendations are presented in Table 8.4.3.1.

Table 8.4.3.1 Canadian Best Stroke Practice Recommendations for Diabetes (Coutts et al. 2015)

1. Glycemic targets must be individualized; however, therapy in most patients with type 1 or type 2 diabetes and stroke or TIA should be treated to achieve a glycated hemoglobin (A1C) level ≤7.0% to reduce the risk of microvascular complications and, in individuals with type 1 diabetes, macrovascular complications.
2. To achieve an A1C ≤7.0%, patients with type 1 or type 2 diabetes should aim for a fasting plasma glucose or preprandial plasma glucose target of 4.0 to 7.0 mmol/L. The two-hour postprandial plasma glucose target is 5.0 to 10.0 mmol/L. If A1C targets cannot be achieved with a postprandial target of 5.0 to 10.0 mmol/L, further postprandial blood lowering, to 5.0 to 8.0 mmol/L, can be considered.
3. Adults with diabetes and ischemic stroke are at high risk of further vascular events and should also be treated with a statin to achieve a low-density lipoprotein cholesterol ≤2.0 mmol/L.
4. Unless contraindicted, low-dose acetylsalicylic acid (ASA) therapy (80 to 325 mg/day) is recommended in all patients with diabetes with evidence of stroke or cardiovascular disease.

In a review of target blood pressure in diabetic patients, Shlomai & Grossman (2012) concluded that although intensive BP control is associated with a significant reduction in all-cause mortality and stroke rate, intensive BP control can also lead to an increased risk of serious adverse effects such as hypotension, bradycardia, hyperkalemia and renal deterioration. The authors therefore recommend that target blood pressure in diabetic patients should be carefully determined and that potential cerebrovascular protection should be weighed against the increased risk of serious side effects (Shlomai & Grossman, 2012). For individuals with DM with albuminuria, ACE inhibitors or ARBs are recommended as first line therapy with the addition of thiazide diuretics, cardioselective beta blockers or long-acting CCBs as necessary to achieve target blood pressure. For individuals with DM, but no albuminuria, ACE inhibitors, ARBs, dihydropyridine CCBs or thiazide diuretics are recommended as first-line drugs. Combinations of these drugs may be used as required to achieve appropriate blood pressure levels. It should be noted however, that the combination of an ACE-inhibitor with an ARB is specifically not recommended (Hackam et al., 2010).

Conclusions Regarding Canadian Best Practice Recommendations for Diabetes Management

Canadian Best Practice Recommendations for diabetes suggest blood pressure maintenance <130/80mmHg to avoid first or recurrent stroke, HbA_{1C} level ≤7.0% to lower the risk of micro and macrovascular issues, LDL cholesterol ≤2.0mmol/L using statins among adults at risk of a vascular event, and 80 to 325mg per day acetylsalicylic acid among individuals with diabetes and atherosclerotic risk factors and/or cardiovascular disease.

Summary

1. ***There is level 1a and level 1b evidence that pioglitazone may not be associated with a relative reduction in the risk of stroke; however, it may be effective at lowering the composite risk of stroke, myocardial infarction, and death.***
2. ***There is level 1b evidence that in patients with no history of previous stroke, pioglitazone was not effective at reducing the risk of stroke however, in patients with a history of stroke, the use of pioglitazone was associated with a reduction in the risk of a recurrent stroke.***
3. ***There is level 1a evidence that intense glucose lowering therapy is not significantly different than standard therapy for reducing the risk of stroke. Intensive glucose lowering therapy may only be an effective treatment for type 2 diabetes and for patients with a history of macrovascular events.***
4. ***There is level 1b evidence that empagliflozin was not significantly different than placebo therapy at reducing the relative risk of stroke; however, more research is needed to identify the mechanism of action of metformin and potential benefits on cardiovascular health.***
5. ***There is level 1a evidence that metformin has no additional benefits on cardiovascular health other than reducing blood glucose levels for the treatment of type 2 diabetes.***
6. ***There is level 1a evidence that treatment of hypertension in diabetic patients reduces the risk of stroke. Furthermore, tighter control of blood pressure is associated with greater reduction of risk for stroke compared to "less tight" therapy; however, greater risk of adverse events may be associated with aggressive therapy.***
7. ***There is level 1b evidence that perindopril (angiotensin converting enzyme inhibitor, ACE-I) administered with indapamide (diuretic) may not be superior to placebo therapy at reducing the incidence of macrovascular or cerebrovascular events.***
8. ***There is level 1b evidence that nitrendipine (ca-channel blocker, CCB) improves risk of cardiovascular events and mortality compared to placebo.***
9. ***There is level 1b evidence that ramipril (ACE-I) alone improves a combined outcome of myocardial infarction, stroke and cardiovascular mortality.***
10. ***There is level 1a evidence suggesting that ACE-Is may improve the incidence of major vascular events, especially myocardial infarction, when compared to CCBs.***
11. ***There is level 1b evidence that amlodipine besylate (CCB) or lisinopril (ACE-I) may not reduce the risk of cardiovascular mortality or nonfatal myocardial infarction when compared to chlorthalidone (diuretic) among patients with diabetes.***
12. ***There is level 1b evidence that treatments with CCB and ACE-I provide no additional benefit over conventional therapy in terms of preventing the occurrence of macrovascular events including stroke in individuals with Type 2 diabetes.***
13. ***There is level 1b evidence that valsartan (angiotensin receptor blocker) is as effective as amlodipine (CCB) at reduction of risk for macrovascular events or cardiac complications. Use of this amlodipine may be associated with increased risk for hospitalization due to heart failure.***
14. ***There is level 1a evidence that all hypertensive medications reduce the risk of stroke, especially among patients with diabetes.***
15. ***There is conflicting level 1b evidence regarding the effectiveness of pravastatin for the prevention of stroke and composite endpoints of coronary and cardiac complications.***

16. ***There is conflicting level 1b evidence regarding the efficacy of atorvastatin in the secondary prevention of stroke and cardiovascular complications.***

17. ***There is level 1b evidence that simvastatin may reduce the odds of stroke as well as the incidence of major coronary and atherosclerotic events when compared to placebo.***

18. ***There is level 1b evidence that a structured care intervention for hyperlipidemia using atorvastatin and strict implementation of guidelines may decrease mortality, coronary morbidity and incidence of stroke versus usual care.***

19. ***There is level 1a evidence that statin treatment in patients with diabetes may reduce the risk of stroke; however, in patients with diabetes and existing coronary heart disease, statin treatments only reduced the risk of subsequent coronary heart disease but not stroke.***

20. ***There is level 1a evidence that fibrate treatment may not reduce the risk of stroke or coronary events.***

21. ***There is conflicting level 1b evidence regarding the effect of gemfibrozil on lowering the risk of stroke in patients with diabetes.***

22. ***There is level 1a evidence that fenofibrate and simvastatin combination therapy or fenofibrate treatment alone may not be more efficacious in the prevention of stroke and cardiovascular events when compared to simvastatin monotherapy or placebo. Additional level 1b evidence suggests that unaccompanied fenofibrate administration may decrease the risk of nonfatal myocardial infarction.***

23. ***There is level 1b evidence that bezafibrate may not improve incidence of myocardial infarction or stroke.***

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8.5

Hyperlipidemia

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Key Points

- Treatment with statins following stroke reduces the risk for recurrent ischemic stroke however, it may not lower the risk of haemorrhagic stroke occurrence. More research is needed to determine the effect of statins on the risk of mortality.
- Withdrawal of statin treatment at the time of acute stroke may result in poorer outcomes. More studies are required to conclude the effect of statin treatments on functional outcomes/disability and stroke severity.
- Statin therapy with intensive lipid-lowering effects in addition to lifestyle modification is recommended for individuals with previous ischemic stroke or TIA. A target reduction of at least 50% or to a level of ≤2.0mmol/L in LDL-C is considered reasonable to achieve maximum benefit of therapy. Statin therapy is not indicated for the prevention of intracerebral hemorrhage.

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8.5 Hyperlipidemia

8.5.1 The Significance of Elevated Cholesterol Levels

Data from several large cohort studies demonstrated a significant positive association between serum cholesterol level and death from non-haemorrhagic stroke (Iso et al., 1989; Lindenstrom et al., 1994). However, it has not been clearly established that elevated serum cholesterol is an independent, predictive risk factor for stroke and the relationship between cholesterol and stroke has remained unclear (Amarenco, 2001; Blauw et al., 1997; Lewington et al., 2007; Nago et al., 2011; Plehn et al., 1999; Prospective Studies Collaboration, 1995; Stegmayr et al., 1997).

In 2007, the Prospective Studies Collaboration undertook a pooled analysis of 61 prospective, observational, cohort studies conducted primarily in Western Europe or North America and involving a total of 892,337 adult subjects (aged 40-89) with no previous vascular disease (Lewington et al., 2007). In approximately 13 years of follow-up (11.6 million person years), there were 33,744 deaths from ischemic heart disease (IHD), 11,663 due to stroke and 9,855 from other vascular causes. The authors reported a significant association between total cholesterol and risk for mortality attributable to IHD for both men and women such that 1mmol/L lower cholesterol was associated with reductions in risk of 56% for individuals aged 40-49 (HR=0.44, 95% CI 0.42-0.48), 34% for those aged 50 – 69 (HR=0.66, 95% CI 0.65-0.68) and 17% for those aged 70-89 (HR=0.83, 95% CI 0.81-0.85). In addition, the relationship between cholesterol and risk for IHD mortality was modified by blood pressure such that reductions in risk associated with lower cholesterol became smaller as blood pressure increased (Lewington et al., 2007).

However, in the case of stroke mortality, there was no clear association between risk for mortality from total stroke (ischemic, haemorrhagic and undefined) and 1mmol/L lower usual cholesterol in any age group from 60 – 89. There was an association between total cholesterol and both total stroke (HR=0.90, 95% CI 0.84-0.97) and ischemic stroke (HR=0.73, 95% CI 0.61-0.87) in the group of individuals aged 40-49; however, this could be attributable, at least in part, to the relationship between cholesterol and blood pressure level. There was a significant reduction in risk for total stroke associated with 1 mmol/L cholesterol in individuals with baseline systolic blood pressure, SBP<125 (HR=0.84 95% CI 0.78-0.91) and 125-144 (HR=0.94, 95% CI 0.90-0.99). There was a negative association between total cholesterol and total stroke in individuals with baseline SBP>185mmHg. Overall, the positive association between lower cholesterol and risk for stroke mortality appeared to be limited to participants aged 40 – 49 with baseline blood pressure <145mmHg. In older age groups, total cholesterol appeared to be negatively related to haemorrhagic or total stroke mortality, particularly for individuals with SBP≥145 mmHg (Lewington et al., 2007). A more recent study of 1,895 individuals with first-ever ischemic stroke, reported that patients with low cholesterol (≤155 mg/dl) compared to those with higher levels, at baseline, presented with more severe strokes (p<0.0001), higher rates of in-hospital mortality (p=0.0007) and poor functional outcomes (p<0.0001). The mortality rates were greater in the low cholesterol group compared to those with higher levels at 3-years (35% vs. 20.5%; p=0.003), regardless of pre-stroke statin use (Koton et al., 2012).

It has been suggested that the inability of studies to demonstrate a clear relationship between cholesterol and stroke may be due, in part, to the inclusion of thromboembolic stroke together with haemorrhagic stroke in an overall assessment of stroke mortality. In the Prospective Studies Collaboration report, there was a positive association between total cholesterol and ischemic stroke only for middle-aged individuals; in the older age groups, there was little relationship demonstrated between total cholesterol and ischemic stroke and a negative association between cholesterol and haemorrhagic stroke (Lewington et al., 2007).

Similarly, in a meta-analysis of nine cohort studies, Law et al. (2003) reported that for a standard 1.0 mmol/L decrease in LDL cholesterol there was an associated 15% decrease in thromboembolic stroke and a 19% increase in haemorrhagic stroke.

8.5.2 Treatment of Hyperlipidemia and the Risk of Stroke

HMG-CoA reductase inhibitors generically classified as "statins" are often the first line of treatment for the management of dyslipidemia (i.e., abnormal levels of LDL cholesterol) and hyperlipidemia (i.e., abnormally high levels of LDL cholesterol). They function by regulating LDL receptor activity and reduce the entry of LDL cholesterol into circulation. Recent research suggests that a LDL-C/HDL-C ratio ≤2 may represent a viable cut off point for statin treatment in stroke patients to prevent the reoccurrence of a secondary stroke (Igase et al., 2012).

There are two kinds of statins available; natural or fermentation-derived statins (lovastatin, pravastatin and simvastatin) and synthetic statins (atorvastatin, cerivastatin and fluvastatin) (Gorelick, 2002). Statins are generally well tolerated. The most common adverse effects associated with statin therapy are gastrointestinal upset, muscle aches and hepatitis or hepatotoxicity (<1%) (Gorelick, 2002).

The strength of association between treatment of hyperlipidemia with statins and reduction in stroke risk seems to support the association between elevated serum cholesterol and stroke risk (Amarenco, 2001; Blauw et al., 1997; Bucher et al., 1998). However, it may be that statin agents have other treatment effects (including anti-inflammatory effects) apart from lowering serum cholesterol, which could contribute to their success in reducing the risk of stroke (Amarenco, 2001; Blauw et al., 1997; Gorelick, 2002; Plehn et al., 1999). Individual studies examining the effectiveness of statins in the treatment of hyperlipidemia and prevention of stroke are summarized in Table 8.5.2.1.

Table 8.5.2.1 Summary of Treatment of Hyperlipidemia with Statins and Risk of Stroke

Author, Year Study Design (PEDro Score) Sample Size	Intervention	Main Outcome(s) Result
GISSI-HF Investigators (2008) RCT (10) N=4574	E: Rosuvastatin (10mg/d) C: Placebo	• Incidence of fatal/nonfatal myocardial infarction (-) • LDL-C concentration (+)
LIPID Trial (2000; 2003) RCT (9) N=9014	E: Pravastatin (40mg) C: Placebo	• Primary end-points: Incidence of major coronary events, stroke and mortality (+) patients with low LDL and HDL-C • Secondary end-points: Incidence of stroke (+); Incidence of non-hemorrhagic stroke (+)
SPARCL Study Investigators (2006b) RCT (9) N=4732	E: Atorvastatin (80mg/d) C: Placebo	• Incidence of fatal/nonfatal stroke (+) • Incidence of stroke or transient ischemic attack (+) • Incidence of serious adverse events (-)
CORONA Study Investigators (2007) RCT (9) N=5011	E: Rosuvastatin (10mg/d) C: Placebo	• Composite primary outcome (cardiovascular mortality, nonfatal myocardial infarction, nonfatal stroke) (-) • Cardiovascular mortality (-) • Incidence of fatal/nonfatal myocardial infarction or stroke (+)
CARE Study (1999; 1996)	E: Pravastatin (40mg/d)	• Incidence of fatal coronary event or nonfatal

RCT (8) N=4159	C: Placebo	myocardial infarction (+) • Incidence of stroke (+) • Incidence of transient ischemic attack and nonfatal stroke (+)
MRC/BHF Heart Protection Study (2002) RCT (8) N=20536	E: Simvastatin (40mg/d) C: Placebo	• Incidence of fatal/nonfatal stroke (+)
PROSPER Study Group (2002) RCT (8) N=5804	E: Pravastatin (40mg/d) C: Placebo	• Composite primary outcome (coronary disease mortality, nonfatal myocardial infarction, fatal/nonfatal stroke) (+) • Coronary disease mortality (+) • Incidence of nonfatal myocardial infarction (+) • Incidence of stroke (-)
CARDS(2004) RCT (8) N=2838	E: Atorvastatin (10mg/d) C: Placebo	• Incidence of major cardiovascular events (+) • Overall incidence of adverse events (-)
ASCOT–LLA (2005) RCT (8) N=10305	E: Atorvastatin (10mg/d) C: Placebo	• Incidence of nonfatal myocardial infarction and fatal coronary heart disease (+) • Incidence of fatal/nonfatal stroke (+)
GREACE (2002) RCT (6) N=1600	E: Structured care for hyperlipidemia (atorvastatin, 10-80mg/d) C: Usual care for hyperlipidemia (physician's standard)	• All-cause mortality (+) • Incidence of stroke (+) • All-cause and coronary mortality (+)

+ Indicates statistically significant differences between treatment groups
- Indicates non-statistically significant differences between treatment groups

Discussion

Numerous studies have examined the impact of statin use on the risk for mortality and for various cardio- and cerebrovascular outcomes. We have attempted to limit the studies appearing in Table 8.5.2.1 to those that i) included only high-risk adults with some history of vascular disease and ii) reported the impact of intervention on fatal or nonfatal stroke, either alone or as part of a composite study endpoint. Several meta-analyses examining the effect of statin treatment on mortality and vascular event outcomes have been conducted that include a more comprehensive selection of studies that include a wider range of participant populations. These analyses are summarized in Table 8.5.2.2.

Table 8.5.2.2 Meta-Analyses Examining the Effectiveness of Statin Therapy in the Prevention of Stroke

Study	Meta-Analysis Description and Results
Law et al. (2003)	As part of a trio of meta-analyses, the authors conducted an analysis of 9 cohort studies and 58 randomized studies of cholesterol lowering therapies that reported both reductions in serum cholesterol and stroke events. Based on data from the identified cohort studies, there was a significant overall decrease in risk for thromboembolic stroke (RR=0.85, 95% CI 0.79-0.94) for 1.0 mmol/l decrease in LDL cholesterol concentration. However, there was also a significant increase in risk for haemorrhagic (SAH and ICH) stroke (RR=1.19, 95%CI 1.1-1.29). From the 58 RCTs, there was a reported, significant, reduction in risk for all stroke of 20% (95%CI -14 to -26, p<0.001); however, in high risk individuals with known vascular disease, this risk reduction was 6% (95% CI, -22 to 14, p=ns). As for the cohort studies, significant reduction in risk was also seen only in thromboembolic stroke (-29%, 95%CI -35 to -20, p<0.001) and not haemorrhagic stroke (-3, -35 to 47, p=ns).

Amarenco et al. (2004)	A meta-analysis and systematic review was performed on all randomized trials testing the effects of statin therapy on stroke prevention. A total of 26 trials were analyzed. Statin treatment was found to reduce the relative odds ratio of all strokes compared to control (p<0.0001). The pooled data from 15 trails demonstrated no significant effect of statin therapy in reducing death cause by a stroke (p=0.37). Similarly, the incidence of a hemorrhagic stroke was not significant following treatment with statins.
Cholesterol Treatment Trialists' Collaborators Baigent et al. (2005)	Utilized data obtained from 14 randomized controlled trials for a total of 90,056 participants 15% of whom had a history of intracerebral haemorrhage, transient ischaemic attack, ischaemic stroke, or peripheral artery disease. Overall, statin therapy was associated with a 12% proportional reduction in mortality from any cause per mmol/L reduction in LDL cholesterol (p<0.0001). Most of this decrease was attributable to a decrease in deaths from coronary heart disease. Reduction in fatal stroke was not significant (RR=0.91, p=0.2). In trials that sought information about stroke and stroke subtype, there was a 17% proportional reduction in first stroke for each mmol/L of LDL reduction (p<0.0001). A significant trend toward greater reductions in stroke events associated with greater mean LDL reductions was also noted (p=0.009). Proportional reductions in vascular events per mmol/L reductions in LDL cholesterol were not associated with initial LDL levels. Rather, lowering LDL by one mmol/L was associated with the same benefit regardless of the starting point. Overall, the reduction in stroke events was attributable to a reduction in ischaemic rather than haemorrhagic stroke (RR=0.81, p<0.0001 vs. RR=1.05, p=0.7). With statin therapy, incidence of major vascular events, including stroke, was reduced for all subgroups examined. While this included individuals with previous MI or coronary heart disease, diabetes and hypertension, it did not include individuals with a previous history of stroke or TIA.
Cannon et al. (2006)	Conducted a meta-analysis to examine the effect of intensive vs. standard dose statin therapy. 4 RCTs were included; patient participants (n=27,548) had a history of either stable coronary heart disease or acute coronary syndromes. 3 of 4 trials included stroke as a primary trial endpoint. Pooled analysis demonstrated a reduction of 16% in the odds for the combined outcome of coronary death or any cardiovascular event, including stroke (OR=0.84, 95% CI 0.8-0.89) associated with more intensive therapy. In addition, high intensity therapy was associated with a reduction in the odds of stroke (OR=0.82, 95% CI, 0.71-0.96, p=0.012). There was no significant difference between therapy intensity for risk of cardiovascular death, non-cardiovascular mortality or overall mortality.
O'Regan et al. (2008)	Included data on the primary outcome of "all strokes" from a total of 42 studies assessing the impact of statin therapy (n=121,000) and reported a pooled relative risk of 0.84 (95% CI 0.79-0.91). In addition, data from 11 studies were pooled to demonstrate a significant decrease in risk for non-hemorrhagic stroke (RR=0.81, 95% CI 0.74-0.94), and no significant increase in haemorrhagic events (RR=0.94, 95% CI 0.68-1.30). Although the authors were able to demonstrate a relationship between absolute LDL change and all-cause mortality, such that each unit increase in LDL was associated with an increase in mortality risk of 0.3% (p=0.02), they were not able to demonstrate a similar relationship for stroke outcomes. The authors suggested that the role of pleiotropic effects of statins such as anti-inflammatory or plaque stabilization effects may make greater contributions to decreasing stroke risk than reduction of LDL cholesterol. It should be noted that the majority of data used in this meta-analysis was not gathered from trials that could be considered secondary prevention trials. The sole trial to provide data related to the prevention of recurrent stroke was SPARCL.
Cholesterol Treatment Trialists Collaboration Baigent et al. (2010)	Individual patient data from RCTs 1) evaluating intensive vs. less intensive regimens of statin therapy (5 trials) and 2) evaluating the effectiveness of statin therapy vs. control condition (21 trials). Intensive therapy was associated with a decreased rate for any major vascular event (RR=0.86, 95%CI 0.77-0.96) when compared with less intense therapy. In addition, intensive therapy was associated with reduced risk for ischemic (RR=0.84, 95% CI 0.71-0.99) and total stroke (RR= 0.86-0.77-0.96), though not haemorrhagic stroke (RR=1.21, 95% CI 0.76-1.91). Rate ratios per 1 mmol/L in LDL-C was 0.74 (95% CI 0.59-0.92) and 0.69 (95% CI 0.50-0.95) for total stroke and ischemic stroke, respectively. Similarly, in trials comparing statin therapy to a control condition, there was a significant reduction in rate of events identified for any stroke (RR=0.85, 95% CI 0.80-0.91) and ischemic stroke (RR=0.80, 95% CI 0.72-0.89) associated with statin therapy. Treatment was associated with a non-significant

	increase in rate of events for haemorrhagic stroke (RR=1.15, 95% CI 0.87-1.51). RR (rate ratio) per 1mmol/L in LDL-C associated with statin therapy vs. control was reported to be 0.85 (95% CI 0.80-0.90) and 0.80 (95% CI 0.73-0.88) for any and ischemic stroke, respectively. In patients with previous, non-CHD vascular disease, statin therapy or more intense statin therapy was associated with a reduction in rate of major vascular events (RR per 1 mmol/L reduction in LDL-C = 0.81, 95%CI 0.71-0.92). There was no significant reduction in risk for stroke mortality associated with statin therapy (RR=0.96, 95% CI = 0.84-1.09).
McKinney & Kostis (2012)	A total of 31 RCTs on statin therapy, that included a hemorrhagic stroke rate, were analyzed. High-dose vs. low-dose statin use was compared in 6 studies; statin therapy vs. a placebo or usual care was compared in the remainder. Using 30 studies, it was found that active therapy was not associated with an increase in ICH (OR, 1.08; 95% CI, 0.88-1.32; P=0.47). Further, no relationship was found between active and control therapy effects on measures of LDL cholesterol. The all-cause mortality rate was significantly lower in the active therapy vs. control (10.67% vs. 11.43%; OR, 0.92; 95% CI, 0.87-0/96; P=0.0007). Active therapy also had a significant reduction in total stroke compared to the control group (OR, 0.84; 95% CI, 0.78-0.91; P<0.0001). To prevent a stroke or a single death, the number needed to treat with statin therapy was 200 and 167, respectively.
Thomopoulos et al. (2015)	A total of 5 RCTs (2 evaluating ezetimibe/simvastatin vs placebo, and 3 evaluating a simvastatin to less intense LDL-lowering treatment) were analyzed. Risk ratios were calculated for 5 primary outcomes (stroke, coronary heart disease, a composite of stroke + coronary heart disease, cardiovascular death, and all-cause death), and 4 secondary outcomes (non-cardiovascular death, cancer, hepatopathy, and myopathy). Only results pertaining to primary outcomes are discussed. The results suggest that the use of ezetimibe/simvastatin was favoured over the control therapy for lowering the risk of stroke (RR=5, 95% CI, 1-8), coronary heart disease (RR=10, 95% CI, 4-16), and a composite of stroke and coronary heart disease (RR=16, 95% CI, 9-23). The relative risk reduction of stroke, coronary heart disease, and a composite of stroke and coronary heart disease were 13%, 12%, and 14% respectively. Conversely, the risk of mortality was not significantly associated with more intensive LDL-lowering therapy with ezetimibe/simvastatin therapy. The meta-analysis also calculated the residual risk, a measure of "*inadequate or suboptimal treatment*" and found that suboptimal treatment with ezetimibe/simvastatin over the course of 5 years compared to placebo or less active treatment was roughly 7 times higher relative to the treatment benefit. These findings suggest the need to undertake more effective treatment strategies.
Jung et al. (2015)	Sixteen studies were analyzed to determine the association between the use of statins and the occurrence of intracerebral hemorrhage. Statin use prior to the occurrence of an intracerebral hemisphere was not associated with an increased risk of mortality however, it was associated with a decreased risk of death at 3 months post-stroke. Similarly, in-hospital use of statins significantly reduced the risk of death regardless of preadmission statin use.

The SPARCL study was designed to evaluate the use of statin therapy to prevent stroke within a population of individuals with a recent history of stroke or TIA (Amarenco et al., 2006b; Amarenco et al., 2003). In that study, treatment with high dose atorvastatin was associated with a significant reduction in LDL cholesterol levels and a 16% reduction in risk for fatal or nonfatal stroke when compared to placebo. It should also be noted that the benefit of statin therapy appeared to increase over time becoming notably different from the placebo condition during the third year of treatment (Amarenco et al., 2006b; Ovbiagele & Saver, 2007). Although treatment with atorvastatin was generally well tolerated and there were no differences in reported serious adverse effects between study conditions, lipid therapy was associated with a higher incidence of haemorrhagic strokes (2.3% vs. 1.6%, HR = 1.66)-future analyses showed this to be in the hemorrhagic stroke group. It should be noted that the SPARCL trial sample was comprised of patients who, although they had experienced a stroke or TIA within 1-6 months prior to randomization, did not have a known history of coronary artery disease. These high-risk patients were excluded from the trial despite evidence that those with a history of coronary artery disease are among the patients at the highest risk of MI and stroke. The SPARCL trial may also have underestimated the magnitude of the true treatment effect due to relatively high rates of discontinuation of the assigned

statin therapy (15.4%) and placebo group crossovers to open-label, non-study statin therapy (7.5%) (Ovbiagele & Saver, 2007). Concurrent treatment with anti-thrombotic and anti-hypertensive treatment may also have contributed to an underestimation of treatment outcome by effectively lowering the stroke event rate (2.7%) in the placebo group, thereby limiting the investigators' ability to detect the full benefit of statin therapy.

A number of *post hoc* analyses of SPARCL data have been undertaken. Given that these analyses may lack statistical power, results should not be regarded as conclusive; rather they may be viewed as exploratory or hypothesis-generating (Table 8.5.2.3). Overall, reduction of LDL-C of 50% or more is associated with greater reductions in stroke when compared to no change. In addition, treatment with atorvastatin for the secondary prevention of stroke appears similarly effective in all of the subgroups evaluated thus far (Amarenco & Labreuche, 2009; Welch, 2009).

Table 8.5.2.3 Post hoc Analyses from SPARCL

Study	Comparison	Results
Amarenco et al. (2007)	≥ 50% vs. < 50% reduction in LDL-C from baseline	Decrease in LDL of at least 50% was associated with a 31% decrease in risk (HR= 0.69, 95% CI 0.55-0.87) for fatal or non-fatal stroke, a 33% decrease for ischemic stroke (HR=0.67, 95% CI 0.52-0.86) and a non-significant increase in hemorrhagic stroke vs. no change or increased LDL. Reduction of LDL ≥50% was associated with the highest rates of persistent elevations of liver enzymes (5.7 per 1000 patient-years), although there were no increased risks reported for either myalgias or rhabdomyolysis.
Goldstein et al. (2008b)	Risk for hemorrhagic stroke based on patient characteristics, recent BP and LDL	Regression analysis demonstrated that risk for hemorrhagic stroke was increased by atorvastatin treatment (HR=1.68, 95% CI 1.09-2.59), having hemorrhagic stroke as the entry event (HR 5.65, 95% CI 2.82-11.30), being male (HR=1.79, 95% CI 1.13-2.84) and increasing age (in 10-year increments, HR=1.42, 95% CI 1.16-1.74).
Goldstein et al. (2008a)	Men vs. women	Men and women experienced similar benefits from treatment. There were no significant sex X treatment interactions for outcomes of combined risk for fatal/nonfatal stroke, fatal stroke or TIA, major cardiac events, major cardiovascular events, revascularization procedures or CHD events.
Sillesen et al. (2008)	Patients with vs. without carotid artery stenosis	In the subgroup with carotid artery stenosis, use of atorvastatin was associated with a 33% risk reduction for any stroke (HR=0.67, 95% CI 0.47-0.94). However, there was no heterogeneity identified between groups (with vs. without carotid artery stenosis) for treatment effect for the primary endpoints of fatal or nonfatal stroke.
Amarenco et al. (2009a)	Benefit of treatment associated with index ischemic stroke subtype	There was no difference in treatment effect for the primary study outcome based on subtype of ischemic stroke at baseline. Similar event rates were reported for individuals with index events classified as large vs. small vessel.
Amarenco et al. (2009b)	Impact of baseline systolic and diastolic BP & baseline lipid levels on treatment outcome	There was no significant association between level of BP or LDL-C (by tertiles) at baseline and risk of outcome stroke. However, there was a positive relationship between baseline LDL-HDL ratio and stroke, as well as an inverse relationship between HDL-C and risk for ischemic stroke.
Chaturvedi et al. (2009)	Older (≥65 years of age) vs. younger patients	Primary endpoints were reduced by 26% in younger patients (HR=0.74, 95% CI 0.57-0.96) and 10% in older patients (HR = 0.90,

		95% CI 0.73-1.11); however, assessment for heterogeneity of effect (treatment X age interaction) was not significant.

Conclusions Regarding the Treatment of Hyperlipidemia with Statins and Risk of Stroke

There is level 1a evidence that statin therapy is effective at lowering the risk of further strokes however, it may not reduce the risk of intracerebral hemorrhage.

There is level 1a evidence that intensive statin therapy may be more effective than less intense therapy in reducing risk for ischemic stroke events.

There is level 1a evidence that statin therapy may not reduce stroke-related mortality, however the evidence is unclear regarding its effects on all-cause mortality.

Treatment with statins following stroke reduces the risk for recurrent ischemic stroke however, it may not lower the risk of haemorrhagic stroke occurrence. More research is needed to determine the effect of statins on the risk of mortality.

8.5.2.1 Statins and Functional Outcome

Through a variety of pleiotropic actions, statins exhibit neuroprotective properties which may reduce the severity of ischemic events and improve potential for neuro-recovery (Chen et al., 2003; Vaughan & Delanty, 1999). While a number of observational studies have examined the impact of statin use on stroke severity and functional disability, function has not been included as an outcome in most randomized controlled trials.

In a recent longitudinal analysis of a cohort study of 114 individuals with stroke, it was demonstrated that total serum cholesterol was a significant independent predictor for motor recovery following stroke (Lai et al., 2012). When participants were grouped according to high total cholesterol (TC≥200 mg/dl) vs. low total cholesterol (TC < 200 mg/dl), those with high total serum cholesterol had higher levels of motor recovery assessed using the motor score of the Fugl Meyer Assessment at 2 weeks, 1, 3, 6 and 12 months post stroke (Lai et al., 2012). The authors suggested that higher levels of total serum cholesterol, particularly in the acute stage post-stroke, may be protective for brain damage and neuroplasticity and that statin therapy initiated later for the purposes of secondary prevention should have no effect on the association between motor recovery and high total serum cholesterol during the acute phase (Lai et al., 2012). Studies examining the effect of statin therapy initiated prior to stroke on post-stroke functional outcome are summarized in Table 8.5.2.1.1.

Table 8.5.2.1.1 Summary of Pre-Stroke Statin Treatment and Stroke Outcome

Author, Year Study Design (PEDro Score) Sample Size	Intervention	Main Outcome(s) Result
Goldstein et al. (2009) from the SPARCL study (Amarenco et al., 2006b) RCT (9) N=576	E: Atorvastatin (80mg/d) pre-treatment C: Placebo pre-treatment	• Ischemic stroke outcome severity (Modified Rankin Scale, National Institutes of Health Stroke Scale, Barthel Index) (-) • Haemorrhagic stroke outcome severity (-) • Incidence of stroke (+)
Blanco et al. (2007) RCT (6)	E1: Pre-treatment with statins followed by atorvastatin (20mg/d) post-stroke	• Modified Rankin Scale (+) E1 • Incidence of death and dependency (+) E1

N=89	E2: Pre-treatment with statins followed by withdrawal of statin use post-stroke for 3d followed by restart at 4d (with atorvastatin, 20mg/d)	• Early neurologic deterioration (+) E1 • Infarct volume (+) E1
Marti-Fabregas et al. (2004) Cohort N=167	E: Statins pre-treatment C: No statins	• National Institutes of Health Stroke scale (-) • Barthel Index (+) • Modified Rankin Scale (-)
Yoon et al. (2004) Cohort N_{Start}=436 N_{End}=433	E: Statin pre-treatment C: No statins	• Modified Rankin Scale (+)
Reeves et al. (2008) Cohort N=1360	E: Statin pre-treatment C: No statins	• Modified Rankin Scale (-): Whites (+); Blacks (-)
Elkind et al. (2005) Case Control N=650	E: Lipid-lowering agents (90.0% taking statins) C: No lipid-lowering agents	• Barthel Index (+) • National Institutes of Health Stroke Scale (-) • 90d mortality (+)
Moonis et al. (2005) Case Control N=852	E1: Statin pre-treatment E2: Statins within 4wk post-stroke C: No statins	• National Institutes of Health Stroke Scale (≤2) and Modified Rankin Scale (≤2): E2 vs. E1/C, E2 (+)
Yu et al. (2009) Case control N=553	E: Statin pre-stroke C: No statins	• Modified Rankin Scale (+)
Dowlatshahi et al. (2012) Case Control N=2466	E: Statins pre-stroke C: No statins	• Canadian Neurological Scale (+) • Modified Rankin Score (-) • 30d mortality (-) • 6mo mortality (-)
Hjalmarrson et al. (2012) Case Control N=799	E: Statin pre-stroke C: No statins	• National Institutes of Health Stroke Scale (-) • 30d mortality (-)
Phipps et al. (2013) Case Control N=804	E: Statins pre-stroke C: No statins	• National Institutes of Health Stroke Scale (-) • In-hospital mortality (-) • Discharge to hospice (-)

+ Indicates statistically significant differences between treatment groups
- Indicates non-statistically significant differences between treatment groups

Discussion

The majority of studies examining the impact of pre-treatment with statins on stroke outcomes are observational, and often retrospective studies. Observed effects may be compromised by concerns such as selection bias, lack of controlled comparisons, unblinded assessments and inadequate sample sizes. Certainly, the observational studies identified provide inconsistent results with regard to the impact of pre-stroke treatment with statins on the functional outcome of either first or recurrent stroke. In a prospective, population-based study, Ni Chroinin et al. (2011) reported a significant association between pre-stroke or acutely prescribed statin therapy and improved survival at 7 days, 90 days and 1 year following the index ischemic stroke event. Although the association was not as clear, a similar trend was identified for good functional outcome, defined as a score of 0-2 on the Modified Rankin Scale (mRS) (Ni Chroinin et al., 2011). Analyses from the randomised, controlled SPARCL trial suggest a similar trend toward less severe outcomes in terms of function, assessed on the modified Rankin Scale, for individuals experiencing an ischemic stroke (Goldstein et al., 2009). In an alternative study, Blanco et al. (2007) found

an increased risk of death and dependency post-stroke due to withdrawal of statin use versus continuous atorvastatin among acute ischemic stroke patients.

As mentioned earlier, statins have also been studied for their improved outcome through pleiotropic non-cholesterol-dependent effects in stroke patients. Many positive outcomes have been found for stroke patients who receive statin therapy during their acute treatment phase, including: discharge disposition, functional outcome, neurologic deterioration, stroke recurrence, and survival rate (Cappellari et al., 2013; Flint et al., 2012a; Flint et al., 2012b; Sicras-Mainar et al., 2012; Tapia-Perez et al., 2013). More specifically, research has shown that statin users (individuals taking statins before and/or during hospitalization for stroke) are more likely to be discharged home and less likely to die in-hospital compared to their non-statin-user counterparts (Flint et al., 2012a; Flint et al., 2012b). In one study, statin treatment within four weeks' post-stroke was associated with improved stroke severity and functional independence when compared to no statins or pre-stroke statin use (Moonis et al., 2005). However, similar to the trials examining the impact of pre-treatment statin and stroke outcome, these are primarily observational and often retrospective. More RCTs are warranted to fully understand the beneficial outcomes of pre-stroke statin intervention among stroke patients.

Conclusions Regarding Pre-Stroke Statin Treatment and Stroke Outcome

There is level 1b evidence that withdrawal of statin treatment at the time of acute stroke is associated with increased risk for death and dependency when compared to continuous statin use.

There is level 1b evidence that pre-treatment with atorvastatin may not improve ischemic or haemorrhagic stroke outcome when compared to placebo.

There is level 2 and level 3 evidence that pre-stroke treatment with statins may improve functional disability on the Barthel Index but may not improve stroke severity on the National Institutes of Health Stroke Scale when compared to no statin pre-treatment. Conflicting level 2 and level 3 evidence suggests no consistent data for functional independence on the Modified Rankin Scale or mortality up to 6 months.

Withdrawal of statin treatment at the time of acute stroke may result in poorer outcomes. More studies are required to conclude the effect of statin treatments on functional outcomes/disability and stroke severity.

8.5.3 Treatment Recommendations

Current Canadian Best Practice Recommendations for stroke care suggest that individuals with previous stroke or TIA should have their serum cholesterol levels assessed and lipid levels managed aggressively (Coutts et al. 2015). Specific recommendations for management are summarized in Table 8.5.3.1.

Table 8.5.3.1 Canadian Best Practice Recommendations for Lipid Management (Coutts et al. 2015)

- Patients with ischemic stroke or TIA should be managed with aggressive therapeutic lifestyle changes to lower lipid levels, including dietary modifications, as part of a comprehensive approach to lower risk of first or recurrent stroke.
- A statin should be prescribed as *secondary prevention* to most patients who have had an ischemic stroke or TIA in order to achieve an LDL cholesterol of less than 2.0mmol/L, or a 50% reduction in LDL cholesterol from baseline.

- Statin therapy is not indicated for prevention of intracerebral hemorrhage.

Conclusions Regarding Treatment Recommendations for Lipid Management

Statin therapy with intensive lipid-lowering effects in addition to lifestyle modification is recommended for individuals with previous ischemic stroke or TIA. A target reduction of at least 50% or to a level of ≤2.0mmol/L in LDL-C is considered reasonable to achieve maximum benefit of therapy. Statin therapy is not indicated for the prevention of intracerebral hemorrhage.

Summary

1. ***There is level 1a evidence that statin therapy is effective at lowering the risk of further strokes however, it may not reduce the risk of intracerebral hemorrhage.***
2. ***There is level 1a evidence that intensive statin therapy may be more effective than less intense therapy in reducing risk for ischemic stroke events.***
3. ***There is level 1a evidence that statin therapy may not reduce stroke-related mortality, however the evidence is unclear regarding its effects on all-cause mortality.***
4. ***There is level 1b evidence that withdrawal of statin treatment at the time of acute stroke is associated with increased risk for death and dependency when compared to continuous statin use.***
5. ***There is level 1b evidence that pre-treatment with atorvastatin may not improve ischemic or haemorrhagic stroke outcome when compared to placebo.***
6. ***There is level 2 and level 3 evidence that pre-stroke treatment with statins may improve functional disability on the Barthel Index but may not improve stroke severity on the National Institutes of Health Stroke Scale when compared to no statin pre-treatment. Conflicting level 2 and level 3 evidence suggests no consistent data for functional independence on the Modified Rankin Scale or mortality up to 6 months.***

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8.6
Infection

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Key Points

- Chlamydia pneumoniae infection may be associated with increased stroke risk, particularly among younger stroke patients. Further research is required to define the association between macrolide antibiotics and cardiovascular events among patients with a history of stroke or transient ischemic attack, and among those without arterial disease.
- More studies are needed to determine whether an association exists between the presence of the hepatitis C virus or the human immunodeficiency virus and the incidence of stroke.

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8.6 Infection

The ongoing exploration of the role of infection in atherosclerosis has generated considerable interest in the possible association between infection and the risk of stroke. Both recent and chronic infections have been linked to stroke, as have recent inflammatory syndromes (Gorelick, 2002). A number of case control studies have demonstrated a significant association between infection and stroke such that acute infection (within one week prior to stroke onset) can be viewed as an independent risk factor for stroke in individuals aged 18 – 80 years (Bova et al., 1996; Grau et al., 1998; Grau et al., 1995). Stronger associations have been noted among younger patients; however, these groups tend to be very small and analyses may lack power (Grau et al., 1998; Grau et al., 1995). Respiratory infections are most commonly cited within these studies. Chronic Hepatitis C Virus (HCV) infection has also been shown to increase the risk of stroke, and is an important independent risk factor (Adinolfi et al., 2013).

8.6.1 Pneumonia

Community-acquired pneumonia (CAP) is the most frequent infectious cause of death in western countries (Singanayagam et al., 2012). Clinical studies in multiple care settings have identified an increase in both short- and long-term risks of cardiovascular events and death, following acute respiratory infection and vascular events. A review by Signanayagam (2012) studied the link between CAP and increased risk of cardiovascular events. Many hospital-based, short-term studies have found a frequent reporting of respiratory infection symptoms preceding admission. Specifically, Staphylococcus aureus, S. pneumonia, Mycoplasma pneuomoniae and C. pneuomoniae were five times more likely in patients presenting with ischaemic stroke than in controls. Additionally, two prospective multicentre long-term studies found that one third of deaths following a CAP event were from cardiovascular causes (Johnstone et al., 2008; Yende et al., 2007).

Chlamydia pneumoniae (c. pneumoniae) has been investigated as one of the most likely microbial agents linked to stroke. It is a common bacterial cause of respiratory infections, including bronchitis and pneumonia, and has been identified as being involved in the atherosclerotic process (Fagerberg et al., 1999; Gorelick, 2002; Muhlestein et al., 2000). Erdur et al. (2015) reported that post-stroke pneumonia was significantly associated with the recurrence of minor stroke and TIAs (HR 4.73, 95% CI 1.34-16.70, p=0.02). Studies of the presence of antibodies specific to c. pneumoniae suggest that c. pneumoniae infection represents an independent risk factor for stroke taking into consideration the effect of other risk factors such as age, diabetes, hypertension, smoking, previous cardiovascular disease, migraine, serum cholesterol and obesity (Cook et al., 1998; Elkind et al., 2000; Fagerberg et al., 1999; Wimmer et al., 1996). In a review, Gorelick (2002) concluded that the weight of evidence supports the notion that acute and chronic infection with c. pneumoniae may increase the risk of stroke.

A recent case-control study reported a greater proportion of seropositivity against c. pneumonia among patients with subarachnoid haemorrhage (SAH) than among matched controls (Yoneda et al., 2005). A univariate analysis found hypertension, current smoking, seropositivity (indicative of chronic infection), and strong seropositivity against c. pneumoniae (indicative of acute infection) were all associated with SAH. After adjusting for risk factors, both hypertension and strong seropositivity (acute infection with c. pneumoniae) demonstrated significant associations with SAH.

A higher seroprevalence of c. pneumoniae among elderly stroke patients has been confirmed, although a significant relationship between seroprevalence and cerebrovascular events in this population has not been demonstrated (Ngeh et al., 2003). However, a case-control study demonstrated a significant association between stroke and the presence of c. pneumoniae-specific antibodies in a group of young

stroke patients aged 18 – 46 (Anzini et al., 2004). A subgroup analysis based on stroke etiology revealed a significant association between the presence of c. pneumonia IgA and large vessel atherosclerosis, suggesting that c. pneumoniae infection may be a risk factor for atherosclerotic stroke in young adults (Anzini et al., 2004). The relative importance of c. pneumoniae as a risk factor for stroke may be dependent upon age.

Several studies have attempted to establish an association between exposure to antibiotics and a reduction in stroke risk. Luchsinger et al. (2001) examined exposure to antibiotics with activity against c. pneumoniae and first ischaemic stroke using health insurance claims. There was no evidence to support the hypothesis that short courses of antibiotic treatment are associated with decreased risk of stroke (Luchsinger et al., 2001). A similar study by Brassard et al. (2003) focusing on a group of elderly patients being treated for hypertension concluded that while any antibiotic use showed a "protective trend" in association with stroke, there was no clear, consistent effect.

While there may be preliminary evidence for an association between infection and stroke, the nature of the relationship has not yet been defined. Secondary prevention trials assessing the effects of treatment of c. pneumoniae infection with antibiotics on rates of stroke are needed. These trials would help to clarify the association between infection and stroke and also provide important information regarding the nature of that relationship (Grayston, 1999).

To date, few randomized controlled trials have been undertaken to examine the effects of treatment with macrolide antibiotics on cardiovascular events including nonfatal stroke (Table 8.6.1.1).

Table 8.6.1.1 Summary of Macrolide Antibiotics in the Prevention of Cardiovascular Events and Infection

Author, Year Study Design (PEDro Score) Sample Size	Intervention	Main Outcome(s) Result
ACES (2005) RCT (9) N=4012	E: Azithromycin (600mg/wk) C: Placebo	• Composite primary outcome (coronary artery disease mortality, nonfatal myocardial infarction, revascularization procedure, unstable angina hospitalization) (-) • Incidence of stroke (-)
ACADEMIC trial (1999; 2000) RCT (8) N=302	E: Azithromycin (500mg/d) for 3d followed by 300mg/wk for 3mo C: Placebo	• 6mo global inflammatory marker score (+) • Composite cardiovascular events (-) • Composite primary outcome (cardiovascular mortality, resuscitated cardiac arrest, nonfatal myocardial infarction or stroke, unstable angina to hospitalization, unplanned coronary interventions) (-)
SPACE (2005) Netherlands RCT (8) N=509	E: 3d course of azithromycin (500mg/d) C: Placebo	• Composite primary outcome (coronary, cerebral peripheral events, mortality) (-) • Incidence of cerebral events (-) • Incidence of coronary events (-) • Incidence of peripheral arterial events (-) • Mean seropositivity (-) • Mean IgA-titre (+) subjects who reached cardiovascular or peripheral arterial endpoint
Joensen et al. (2008) RCT (8) N=507	E: Roxithromycin (300mg/d) C: Placebo	• Peripheral revascularization (-) • Mortality (-) • Major lower limb amputation (-)

		• Incidence of myocardial infarction, stroke or thrombosis (-)
Dogra (2012) PCT N=40	E: Positive IgG titre (500mg/d azithromycin added to standard care) C: Negative IgG titre (no azithromycin added to standard care)	• Risk of coronary artery disease (+)

+ Indicates statistically significant differences between treatment groups
- Indicates non-statistically significant differences between treatment groups

Discussion
In their study of 302 patients with coronary artery disease (CAD) who were seropositive for c. pneumoniae, the ACADEMIC study did not find a 3-month course of azithromycin to be associated with a reduction in cardiovascular events when compared to a matched placebo group (Anderson et al., 1999; Muhlestein et al., 2000). Similar findings have been reported among patients with peripheral arterial disease following a course of Azithromycin (Joensen et al., 2008; Vainas et al., 2005) and among patients with stable CAD treated once weekly for a longer duration (Grayston et al., 2005). At present, there are no trials specific to patients with a history of stroke or TIA. All trials were conducted with patients having established arterial disease; however, no trials have examined the effectiveness of treatment at an earlier stage, prior to the presence of established arterial disease.

Conclusion Regarding Macrolide Antibiotics the Prevention of Cardiovascular Events

There is level 1a and level 1b evidence that azithromycin or roxithromycin (macrolide antibiotic) may not decrease the incidence of cardiovascular events

Chlamydia pneumoniae infection may be associated with increased stroke risk, particularly among younger stroke patients. Further research is required to define the association between macrolide antibiotics and cardiovascular events among subjects with a history of stroke or transient ischemic attack, and among those without arterial disease.

8.6.2 Other Conditions

Hepatitis C Virus (HCV) infection increases the risk of stroke and should be considered an important and independent risk factor. In a population-based cohort study, Liao et al. (2012) found that chronic HCV infection was associated with increased risk of stroke after controlling for conventional stroke risk factors. Previous findings have also shown an association between HCV infection and carotid atherosclerosis and acute myocardial infarction (Liao et al., 2012). Similarly, a case-control study looking at the prevalence of HCV infection in patients with ischemic stroke and the independent association of HCV with stroke found a higher prevalence of HCV infection in patients with stroke than in controls (Adinolfi et al., 2013). Also, stroke patients with HCV infection were younger, had lower serum levels of cholesterol, triglycerides, and higher serum levels of inflammation markers (Adinolfi et al., 2013). The authors concluded that HCV infected patients have a higher and earlier risk of stroke.

Human Immunodeficiency Virus (HIV) infection is strongly associated with ischemic stroke in the young (15-44 years of age) and in women (Chow et al., 2012; Cruse et al., 2012; Sen et al., 2012). However, the mechanism by which HIV infection leads to an increase in stroke risk is still unclear (Sen et al., 2012). Highly active antiretroviral therapy has been associated with metabolic syndrome and accelerated atherosclerosis which may lead to an increased stroke risk (Cruse et al., 2012; Sen et al., 2012). In a recent

study, the incidence of ischemic stroke was not significantly different between HIV-positive and HIV-negative adults (Marcus et al. 2014). However, the results did reveal a significantly greater incidence of stroke in HIV-positive patients with a CD4 cell count of 200-499 cells/ul or <200 cells/ul compared to HIV-negative patients (Marcus et al. 2014).

Conclusions Regarding Other Conditions and the Risk of Stroke

More studies are needed to determine whether an association exists between the presence of the hepatitis C virus or the human immunodeficiency virus and the incidence of stroke.

Summary

1. ***There is level 1a and level 1b evidence that azithromycin or roxithromycin (macrolide antibiotic) may not decrease the incidence of cardiovascular events.***

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8.7
Lifestyle Modification

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Key Points

- Exercise is associated with significant reductions in risk for stroke and cardiovascular disease. Modest to high levels of activity performed regularly (once/week for at least 30 minutes) may be optimally beneficial for reducing stroke risk.
- Individuals engaging in moderate to high levels of physical activity prior to stroke may be more likely to experience less severe stroke and improved short-term functional outcome. Further research is required.
- Individuals who engage in pre-stroke physical activity may reduce their risk of post-stroke mortality however, more research is needed to determine a conclusive association.
- Periodic instruction and encouragement may not be sufficient to improve level of physical activity in individuals with stroke. Further research is required to identify effective interventions.
- Post-stroke patients are encouraged to start a regular exercise program and achieve roughly 150 minutes per week of moderate activity. Supervision is encouraged for patients with additional medical complications.
- Low-fat, low-cholesterol diets rich in fruits, vegetables, whole grains, legumes, nuts and omega-3 fatty acids may be effective in reducing blood pressure and risk of cardiovascular complications.
- Antioxidant vitamins may affect the progress of atherosclerosis; most effectively when used as a combination therapy (vitamin C and E). However, further research is required to understand the mechanism by which these supplements provide benefits against stroke.
- Antioxidant vitamins used individually may not be protective for cardiovascular risk including stroke and mortality. Combination of different antioxidants and simvastatin + niacin have been shown to effectively reduce the risk of these clinical outcomes.
- More research is needed to determine the potential benefits of vitamin B supplementation on atherosclerotic progression.
- While treatment with folic acid and/or vitamins B_6 & B_{12} reduces plasma homocysteine levels, subsequent cardiovascular outcomes and stroke risk may not be improved.
- Concurrent antiplatelet use may alter the action of vitamin therapy however, there is conflicting evidence supporting this association. Further research is required.
- Vitamin therapy to lower homocysteine may not affect functional ability post-stroke however, it seems to improve risk of secondary complications among older patients.
- The ideal diet in stroke care is low in saturated fat and consists of fresh fruits, vegetables, dietary and soluble fibre, whole grains and protein from plant sources, and low-fat dairy products. Recommended daily sodium intake from all sources should total no more than 2000mg per day.
- Smoking and exposure to tobacco smoke has consistently been associated with an increased risk of stroke (ischemic and haemorrhagic) while smoking cessation reduces this risk.
- Older age is the only reliable predictor of smoking termination. Information regarding the importance of quitting should be provided to all smokers, including pharmacological (nicotine replacement therapy, bupropion, varenicline) and behavioural therapy. Further research is required to investigate and develop effective smoking cessation interventions.

- Heavy alcohol consumption and binge drinking increases the risk of stroke. Light to moderate consumption (<2 drinks per day) may be beneficial, especially when drinking wine (versus beer or liquor).
- Women are encouraged to restrict intake of alcohol to 10 drinks per week (with ≤2 drinks per day) and men to no more than 15 drinks per week (with ≤3 drinks per day.
- Behavioural intervention may be an effective means to reduce stroke risk and prognostic factors involved in secondary prevention. Further research is required to gain an understanding of how behavioural change occurs for the optimal promotion of healthy lifestyles.
- Knowledge transfer among clinicians for the application of updated behavioural strategies is essential for optimal alteration of maladaptive habits. Personally designed cognitive behavioural programs targeting the individual and a specific maladaptive behaviour may be most beneficial. Self-reports of change should be prohibited.

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8.7 Lifestyle Modification

8.7.1 Physical Activity

In lieu of a lack of data on post-stroke physical activity and secondary stroke prevention, the following section, for the most part, relates to pre-stroke physical activity. Despite this research gap, physical activity remains a cornerstone in the armamentarium for risk factor management regarding the prevention and treatment of stroke and cardiovascular disease (Gordon, 2004). Please see Chapters 9 and 10, Mobility and Lower Extremity and Upper Extremity Interventions, respectively, regarding specific types of aerobic and resistance training exercises used in stroke rehabilitation.

Post-stroke disability can alter (or reduce) activity level and behaviour, highlighting the importance for physical activity interventions post-stroke. One study that measured daily physical activity (intensity, duration, and frequency) in stroke survivors with mild disability one- year post stroke, found that individuals spent most of their activity time (81%) in very light intensity activity (Baert et al., 2012). On average, survivors spent a mean duration of 149 (±107) and 44 (±39) minutes in light and moderate intensity activity, respectively. Based on steps/day data, most participants were considered inactive (44%; 5 000 steps/day) or normally active (38%; 5 000-10 000 steps/day), however a moderate to high association was found between assessment of functional mobility and steps/day.

8.7.1.1 Stroke Risk

In the past, no clear relationship had been established between level of physical activity and risk of stroke. However, pre-existing conditions such as coronary heart disease, hypertension, diabetes mellitus, and obesity are also risk factors for stroke hence, a strong rationale exists for encouraging an active lifestyle to reduce the risk of stroke.

The international, INTERSTROKE case-control study (O'Donnell et al., 2010b) demonstrated that, in the first 3000 cases (and 3000 controls), regular physical activity was associated with a significant reduction in risk for all stroke (OR=0.69 95% CI 0.53-0.90). Physical activity was defined as regular involvement in moderate or strenuous activity for 4 hours or more per week. Cases were patients with first-ever stroke while controls had no history of stroke and were age and sex-matched.

Meta-analyses that have examined the association between physical activity and stroke risk are summarized in Table 8.7.1.1.1.

Table 8.7.1.1.1 Meta-Analyses Examining Physical Activity and Stroke Risk

Study	Meta-Analysis Description and Results
Lee et al. (2003)	Included 23 studies (18 cohort studies, 5 case-control) published between 1983 and 2002. In the cohort studies, individuals classified as highly active had a reduced risk of stroke/mortality than individuals considered "low-active" (RR=0.75, 95% CI 0.69-0.82). In case control studies, the risk reduction was even greater (RR=0.36, 95% CI 0.25-0.52). Combined estimate of risk associated with high levels of activity was 0.73 (95% CI 0.67-0.79). A similar pattern of result was noted for the comparison of moderately active to low-active individuals in the cohort, case control and combination of both types of studies (RR=0.83 95%CI 0.76 = 0.89, 0.52 95% CI 0.40-0.69 and 0.80 95% CI 0.74-0.86, respectively). Reduction of risk was greater for haemorrhagic stroke than for ischemic stroke for both highly active (34% vs. 21%) and moderately active individuals (15%vs 9%).

Wendel-Vos et al. (2004)	Included 31 publications (24 cohort studies, 7 case-control) prior to 2001. Lowest level of activity from included studies was classified as inactive, the highest level of active and all levels in between were collapsed to form a moderately active category for the purposes of this meta-analysis. Further, type of activity was stratified (leisure vs. occupational). Being active or moderately active at work was associated with significantly reduced risk for stroke vs. inactivity (RR=0.57, 95% CI 0.43-0.77 and RR=0.64, 95% CI 0.48-0.87, respectively). When compared to physical inactivity, high level of leisure activity was also associated with reduced risk for total stroke (RR=0.78, 95% CI 0.71-0.85), haemorrhagic stroke (RR=0.76, 95% CI 0.57-0.96) and ischemic stroke (RR=0.79, 95%CI 0.69-0.91). Moderate leisure activity was also associated with reduced risk for total stroke (RR=0.85, 95% CI 0.78-0.93).
Reimers et al. (2009)	43 studies were identified for inclusion (33 cohort studies, 10 case-control). Of 33 cohort studies identified, 28 were included for meta-analysis (complete reporting of effect estimates and CIs). Cohort and case-control studies were analysed separately. For the purpose of this meta-analysis, the physically active group with the lowest risk of stroke compared to physically inactive persons in the source document was included in the pooled analysis. Overall, there was a reduction in risk for ischemic stroke (RR=0.75, 95% CI 0.67-0.84), haemorrhagic stroke (RR=0.67, 95% CI 0.52-0.86) and "stroke of undifferentiated type" (RR=0.71, 95% CI 0.64-0.80) associated with physical activity vs. inactivity. In case control studies, greater risk reductions for ischemic stroke were noted (RR=0.32, 95% CI 0.17-0.59). Based on data from the cohort studies, risks for men and women were calculated separately. There were no significant differences in risk for ischemic or haemorrhagic stroke for physically active vs. inactive women, whereas for men, regular physical activity was associated with significant reductions in stroke risk (27% for ischemic stroke and 40% for haemorrhagic stroke).
Li & Siegrist (2012)	21 prospective cohort studies (a sample size of more than 650, 000 adults) that obtained objective measures of physical activity (PA) were included for meta-analysis. Distinctions were made between men and women, occupational and leisure time PA, coronary heart disease (CHD), and stroke, respectively. Among men who engaged in moderate levels of occupational PA, the pooled relative risk (RR) for cardiovascular disease (CVD) was 0.89 (95% CI 0.82-0.97, p = 0.008). A similar effect was observed in the case of both CHD and stroke. Results for women were in line with those reported for men. High levels of occupational PA did not have a more protective effect. With respect to leisure time PA, among men, a high level of leisure time (opposed to moderate or low level) demonstrated the highest protective effect against overall CVD (RR=0.76, 95% CI 0.70-0.82, p<0.001). A similar effect was observed in case of both CHD and stroke. Among women, a similar pattern was found.

Discussion

The results of the 4 identified meta-analyses demonstrate a clear association between engaging in physical activity and reduced risk for stroke in excess of 25%. There have been contrasting findings regarding risk reduction and gender (men versus women). One meta-analysis observed significant differences in risk reduction for stroke for men versus women (Reimers et al., 2009), whereas another (Li & Siegrist, 2012) found similar risk reductions for both genders. Furthermore, there have been differences found for the level of risk reduction dependent on stroke type (ischemic versus haemorrhagic stroke) (Lee et al., 2003; Reimers et al., 2009; Wendel-Vos et al., 2004) and significant reductions for haemorrhagic stroke risk reported for regularly active men (Reimers et al., 2009)

Physical activity may have a positive effect on a number of important risk factors for stroke (e.g. obesity, arterial blood pressure, glucose metabolism, platelet aggregation). These were accounted for within the multivariate analysis in most of the individual papers included in the identified meta-analysis. Reimers et al. (2009) suggested that there may be a "gross" effect of exercise on stroke risk that exceeds this controlled "net" effect. Calling et al. (2006) demonstrated a clear association between elevated body fat percentage (BFI%) and stroke risk, particularly in women. When compared to women with a low BFI%, those with high BFI% were more than three times as likely to experience stroke (RR=3.83 CI=2.28-6.46).

However, in both men and women with high BFI%, increased physical activity was associated with reduced risk for stroke (RR=0.67 & 0.68, respectively) (Calling et al., 2006).

While there is a substantial benefit in terms of reduced risk for stroke associated with physical activity, the type, amount and intensity of activity required to realize these benefits is not yet clear. While the analyses provided by Lee et al. (2003) and Wendel-Vos et al. (2004) both suggest a dose-response relationship between physical activity and stroke risk, Reimers et al. (2009) notes that a saturation effect or even increased risk may exist with very frequent and very intense activity. The tools used to assess physical activity and the definitions of high, moderate and low levels of physical activity vary substantially between the individual studies included in these analyses. Reimers et al. (2009) suggest that the types of activity reported most often are aerobic leisure time pursuits such as jogging, swimming, cycling or walking. But there exists no single, uniform definition of what constitutes each level of activity or how these types of activity and the frequency with which they are conducted fit into these categories.

Frequency of Physical Activity. McDonnell et al. (2013) examined the association between physical activity frequency and incidence of stroke/transient ischemic attack (TIA). Engaging in physical activity ≥4x per week provided improved protection for stroke/TIA compared to no physical activity. A trend effect was also detected, where engaging in activity 1-3x per week provided less protective benefit compared to activity ≥4x per week. In an earlier study (Fossum et al., 2007), researchers categorized patients with existing hypertension and left ventricle hypertrophy based on self-reported amount of physical activity: i) never exercise, ii) ≤ 30 minutes twice per week and iii) >30 minutes twice per week. All forms of exercise, such as walking or "more strenuous" forms, were considered applicable. Risk of stroke was not significantly different between the groups that reported no exercise versus exercising 30 minutes or less per week. For individuals who exercised in excess of 30 minutes, there was a significant reduction in stroke risk (adj. HR = 0.77, 95% CI 0.62-0.96, p=0.019) compared to the no exercise group. When the analysis was performed for women and men separately, there were moderate, non-significant reductions in risk reported for both groups (adj. HR= 0.83 95% CI 0.61-1.12, p=0.22 and adj. HR=0.76 95% CI 0.56-1.05, p=0.09, respectively). In addition, a very modest level of activity appeared to be associated with reductions in risk for stroke in older individuals with existing cardiovascular disease (see also Wisloff et al. 2006 in Table 8.7.1.1.2).

Type and Intensity of Activity. There have been several large, prospective cohort studies and a meta-analysis that have examined the type and intensity of activity associated with reduced risk for stroke or stroke-related mortality (Table 8.7.1.1.2).

Table 8.7.1.1.2 Type and Intensity of Physical Activity and Stroke Risk

Study	Study Description and Results
Manson et al. (2002)	As part of the Women's Health Initiative Observational Study, total physical activity, walking, vigorous exercise and sedentary hours were examined as predictors of cardiovascular events (including stroke) in a group of 73,743 post-menopausal women. Weekly energy expenditures (MET scores) were calculated for each participant for walking and for total reported activity. Overall, multivariate adjusted relative risk for cardiovascular disease decreased across increasing quintiles of MET score (p<0.001) when compared to the lowest quintile (RR= 0.89, 0.81, 0.78, 0.72 for quintiles 2, 3, 4 and 5). When walking was considered alone, a similar significant trend was demonstrated (RR=0.91, 0.82, 0.75, 0.68, p<0.001 for trend) vs. the lowest quintile. Vigorous activity (e.g. jogging, aerobics, swimming laps, tennis) was similarly protective for stroke; multivariate adjusted relative risk was 0.91, 0.81, 0.85 and 0.76 for quintiles 2 through 5, respectively when compared to the lowest quintile (p for trend = 0.01). Brisker walking pace was also associated with decreased risk such that 2-3 mph, 3-4 mph and >4mph were associated with relative risks of 0.86, 0.76, 0.58, respectively (p for trend = 0.002). Sedentary behaviour was

	associated with increased risk; 12 to 15 hours per day spent lying down or sleeping was associated with an increased risk for stroke (RR = 1.38, 95% CI 1.01 – 1.87).
Wisloff et al. (2006)	Examined the relationship between amount and intensity of exercise and risk for cardiovascular (including stroke-related) death in 27, 143 men and 28, 929 women free from cardiovascular disease at study entry. Exercise intensity was defined as low (no sweat) and high (sweat and exhausted). Amount of exercise was described in terms of minutes per session (none, ≤30 or >30) and sessions per week (1, 2-3 and ≥4). Among men, a single session of low intensity exercise was associated with a significant reduction in risk (RR=0.61, 95% CI 0.40-0.95) as was a single session of high intensity exercise performed with the same frequency and lasting at least 30 minutes (RR=0.51, 95% CI 0.31-0.91) compared with men reporting no activity. In women, a single weekly session of low intensity exercise was associated with a significant reduction in risk for stroke death (RR=0.63 95% CI 0.42-0.94) vs. no activity. In both cases, increasing the number of exercise sessions did not result in additional benefit.
Willey et al. (2009)	As part of the Northern Manhattan Study, 3,298 older, stroke-free individuals were followed for a median of 9.1 years. In that time, there were 238 incident ischemic strokes. Physical activity was assessed via a questionnaire that recorded the frequency and duration of various leisure or recreational activities. Light intensity physical activity included activities such as golf, walking for exercise and dancing while moderate to heavy exercise included hiking, tennis, swimming, cycling, jogging or racquetball. Intensity was based on the sum of METs for each activity for each individual. Further energy expenditure/week was estimated. Light intensity activity was not associated with reduced risk for stroke (adj. HR = 0.94, 95% CO 0.17-1.25); however, moderate to heavy intensity activity was associated with significantly reduced risk compared to both no activity (adj. HR=0.65, 95% CI 0.43 – 0.98) and to light intensity activity (adj. HR = 0.68, 95% CI 0.46 – 0.99). There was an interaction identified between sex and moderate to heavy activity such that this level of activity was associated with a protective effect for ischemic stroke in men only (HR = 0.37, 95% CI 0.18-0.78). Energy expenditure (kcal/week) was not associated with risk for ischemic stroke.
Sattelmair et al. (2010)	39,315 healthy participants from the Women's Health Study were asked to report the average time spent/week participating in 8 different categories of physical activity (walking or hiking, jogging, running, bicycling, aerobic exercise, aerobic dance, use of exercise machines, racquet sports, lap swimming and lower intensity exercise such as yoga, stretching or toning). Usual walking pace was also recorded. MET scores were assigned to each group of activities based on energy costs and kcal/week expenditures were estimated. Vigorous activity was defined as requiring ≥6 METS. There was trend toward reduction in stroke risk associated with increasing energy expenditure (p=0.06 for trend, adj. RR = 1.11, 0.86 and 0.89 for 200 – 599, 600 – 1499 and ≥100 vs. <200 kcal/week). There was no decrease in risk for total stroke associated with increases in vigorous activity (p for trend=0.50). This was true for both ischemic and haemorrhagic stroke (p for trend = 0.38 and 0.71, respectively). Time spent walking and walking pace were both inversely associated with total stroke risk (p=0.002 and 0.007, respectively. 2 hours or more spent walking was associated with a 39% and 36% reduction in risk for total stroke and ischemic stroke, respectively. A walking pace of 3.2 – 4.7 km/hour was associated with a significant reduction of risk (RR = 0.72, 95% CI 0.54 – 0.96) as was ≥4.8 km/hour (RR= 0.63 (95% CI 0.44-0.91)
Willey et al. (2011)	As part of the Northern Manhattan Study, 1,238 clinically stroke-free individuals (age ≥55 yrs) and 199 additional household members were followed for a median of 9.1 years. In that time, there were 238 incident ischemic strokes. Physical activity was assessed as described above (Willey et al. 2009). In addition, MRI was performed on all participants to determine 1) presence of subclinical infarcts and 2) white matter hyperintensities volumes. Analyses adjusted for sociodemographic factors and vascular disease risk factors demonstrated that individuals reporting moderate to heavy intensity physical activity were less likely to have evidence of subclinical infarcts on MRI than those who reported no activity (OR =0.60, 95% CI 0.4-0.9). Light intensity activity was not associated with a significant reduction in the odds for subclinical

	infarction. There was no association demonstrated between intensity of physical activity and white matter hyperintensities volume.
Li et al. (2013)	Meta-analysis including 23 prospective cohort studies, published in 2011-2013, examining different types of physical activity (leisure time and occupational) as predictors of cardiovascular disease (CVD, CHD and stroke). The pooled relative risk (RR) for overall CVD indicated a risk reduction of 24% for individual engaging in moderate level of leisure time activity compared to those engaging in low level (RR=0.76, 95% CI 0.71-0.81). This association was even stronger for high level of leisure time versus low level (RR=0.66, 95% CI 0.60-0.72). Similar associations were observed in separate analyses for CHD and stroke. With respect to occupational activity, the pooled RR was statistically significant for overall CVD when comparing individuals engaging in high levels of activity to individual engaging in low levels (RR=1.24, 95% CI 1.05-1.47). A similar relationship was observed in the analyses restricted to CHD, but not in the analyses for stroke.

Overall, it would appear that increasing intensity of activity appears to be associated with decreasing risk of stroke, including subclinical infarcts. However, significant benefits in terms of stroke risk may still be realized with lower intensity activities. Wisloff et al. (2006) demonstrated a significant reduction in risk for stroke associated with low intensity exercise (defined as one that does not cause the participant to sweat while engaging in it) lasting at least 30 minutes once per week for both men and women. This was similar to the amount of exercise found to be beneficial in older individuals with existing cardiovascular disease (Fossum et al., 2007). Although Willey et al. (2009) did not find any benefit associated with lower intensity activity (golfing, walking, dancing), both Manson et al. (2002) and Sattelmair et al. (2010) demonstrated benefits associated with walking and, as might be expected, both time spent walking and walking pace appear to be inversely associated with risk for stroke. Type of physical activity, whether leisure or occupational, is also an important distinction. Some doubt has been cast regarding the role occupational physical activity plays on reducing one's risk for stroke (Li et al., 2013).

Conclusions Regarding Pre-Stroke Physical Activity and Stroke Risk

There is level 1a evidence that engaging in physical activity is associated with substantial benefits in terms of a reduced risk for stroke and cardiovascular disease. A dose-response relationship may exist between exercise and stroke risk. Conflicting level 1a evidence from a meta-analyses of 10 cohort studies suggests that this relationship may only be significant for men.

There is level 1a evidence that moderate to high levels of leisure and occupational activity may be beneficial for a reduced rate of cardiovascular disease compared to low level exercise.

Exercise is associated with significant reductions in risk for stroke and cardiovascular disease. Modest to high levels of activity performed regularly (once/week for at least 30 minutes) may be optimally beneficial for reducing stroke risk.

8.7.1.2 Functional Outcomes

In addition to the prevention of stroke, physical activity may also be associated with milder stroke severity on admission for acute stroke as well as with improved short-term functional outcomes. In a study of 362 patients following ischemic stroke, Deplanque et al. (2006b) determined that greater levels of physical activity (OR = 1.67, 95% CI 1.07 – 2.66) and use of lipid-lowering drugs (OR = 1.76 95% CI 1.06 – 4.87) were associated with less severe clinical deficits on admission and improved short-term outcomes assessed on the Barthel Index and Rankin Scale one week post stroke event. Further analyses demonstrated that any amount of pre-stroke leisure time physical activity was associated with mild rather than more severe

stroke (OR=1.9 for <2 hours/week to 3.63 for >5 hours/week). Weak and moderate intensity of exercise was also found to be protective (Deplanque et al., 2012).

Similarly, interim analyses of data collected at baseline from a subset of patients with first stroke (n=265), enrolled in the ongoing ExStroke Pilot Trial, demonstrated that level of pre-stroke activity was associated with both stroke severity and functional outcome (Boysen et al., 2009; Krarup et al., 2008). Participants reporting higher levels of physical activity (top quartile) were more likely to experience a less severe stroke (OR=2.54, 96% CI 1.30 – 4.95) and less likely to have a poor functional outcome (OR = 0.46, 95% CI 0.22 – 0.96). Overall, the relationship between physical activity and stroke severity or functional outcome was described as linear, suggesting a dose-dependent response.

The benefit associated with moderate levels of pre-stroke physical activity on functional outcome may extend beyond the immediate short term. Stroud et al. (2009) demonstrated that for 673 individuals with first-ever stroke, those with moderate and high levels of pre-stroke leisure activity were more likely to have a good or high level of function, defined as a Barthel Index score ≥95 (OR=1.95 95%CI 1.08 – 2.51 and OR=1.94 95% CI 1.22-3.09, respectively). Three months following stroke, moderate pre-stroke activity was still associated with good functional outcome (OR=2.21 95% CI 1.22-4.01). Although individuals with high levels of pre-stroke activity appeared more likely to experience better outcomes at 3 months, this association was no longer significant (OR=1.64, 95% CI 0.86-3.13).

Conclusions Regarding Pre-Stroke Physical Activity and Functional Outcomes

Individuals engaging in moderate to high levels of physical activity prior to stroke may be more likely to experience less severe stroke and improved short-term functional outcome. Further research is required.

8.7.1.3 Mortality

Beyond the short-term and long-term benefits of pre-stroke physical activity on functional outcomes, its effects on post-stroke mortality have also been examined. Using data from the Women's Health Initiative (WHI), Bell et al. (2013) found that women who engaged in no physical activity had a 39% greater risk of post-stroke mortality compared to women who engaged in 150 min per week of physical activity pre-stroke. Gulsvik et al. (2012) also found that physical activity was inversely associated with post-stroke mortality. Overall, physical activity was found to have a beneficial dose-response relationship with fatal stroke (high level of activity, HR=0.66, 95% CI: 0.47-0.93; moderate level of activity, HR=0.83, 95% CI: 0.67-1.03).

Conclusions Regarding Pre-Stroke Physical Activity and Stroke Mortality

Individuals who engage in pre-stroke physical activity may reduce their risk of post-stroke mortality however, more research is needed to determine a conclusive association.

8.7.1.4 Interventions to Promote Physical Activity Following Stroke

Trials examining interventions to encourage physical activity following stroke are summarized in Table 8.7.1.4.1. Please refer to Section 8.7.5 for physical activity interventions that are a part of multi-behavioural lifestyle interventions.

Table 8.7.1.4.1 Interventions to Promote Physical Activity Following Stroke

Author, Year Study Design (PEDro Score) Sample Size	Intervention	Main Outcome(s) Result
Boysen et al. (2009) RCT (8) N=314	E: Post-discharge individualized training program C: Information regarding physical activity (no training program)	• Physical Activity Scale for the Elderly (-) • Incidence of recurrent events (-) • Number of first falls (-) • Modified Rankin Scale (-)

+ Indicates statistically significant differences between treatment groups
- Indicates non-statistically significant differences between treatment groups

Discussion
Only a single RCT investigated an intervention aimed at promoting long-term physical activity post-stroke. The authors concluded that an individualized training program including recurrent verbal instruction and encouragement was not able to increase long-term physical activity or mortality, incidence of recurrent stroke, myocardial infarction or falls and fractures (Boysen et al. 2009). From the previously discussed studies in this section, there seems to be a connection between physical activity and stroke severity as well as overall post-stroke outcome. Therefore, research of higher methodological quality is required to investigate alternative strategies to promote physical activity for improved functional outcome and secondary prevention.

Conclusions Regarding Interventions to Improve Physical Activity Following Stroke

There is level 1b evidence that a detailed, personalized activity program with regular verbal instruction and encouragement does not effectively increase level of physical activity when compared to the provision of basic information regarding physical activity and no training program.

Periodic instruction and encouragement may not be sufficient to improve level of physical activity in individuals with stroke. Further research is required to identify effective interventions.

8.7.1.5 Physical Activity Recommendations

The Canadian Best Practice guidelines for the secondary prevention of stroke recommend the participation "*in moderate dynamic exercise such as walking (ideally brisk walking), jogging, cycling, swimming or other dynamic exercise 4 to 7 days each week in addition to routine activities of daily living.*" (Coutts et al. 2015). Further recommendations are summarized below:

Table 8.7.1.5.1 Canadian Stroke Best Practice Recommendations Regarding Physical Activity (Coutts et al. 2015)

- Patients should be counseled to achieve an accumulation of 150 mins of moderate to vigorous activity per week, in episodes of 10 mins or more.
- Most stroke patients should be encouraged to start a regular exercise program. Supervision by a health-care professional (such as a physiotherapist) at exercise initiation should be considered in individuals with stroke at risk of falls or injury, or in individuals with other comorbid disease (such as cardiac disease), which may place them at higher risk of medical complications.

Conclusions Regarding Physical Activity Recommendations

Post-stroke patients are encouraged to start a regular exercise program and achieve roughly 150 minutes per week of moderate activity. Supervision is encouraged for patients with additional medical complications.

8.7.2 Diet

Diet may be of significance in the modification of several risk factors for stroke including hypertension and dyslipidemia as well as obesity. While control of hypertension and management of hyperlipidemia can be achieved via pharmacological interventions, dietary changes should be part of a holistic approach to reduce hypertension, hyperlipidemia and hyperglycaemia (Apostolopoulou et al., 2012). Drug treatments and dietary interventions have both additional and independent benefits (de Lorgeril et al., 1999; Genest et al., 2003). Unfortunately, there have been no reported studies of the effect of dietary changes on the secondary prevention of stroke as the primary outcome (Apostolopoulou et al., 2012). Nonetheless, dietary guidelines for secondary prevention do not differ from those for primary prevention.

Fruits and Vegetables. There is substantial evidence that consumption of fruits and vegetables is associated with decreased risk for stroke and other cardiovascular events. Gillman et al. (1995) reported that, based on data collected as part of the Framingham Study, age-adjusted risk for stroke decreased as consumption of fruits and vegetables increased such that RR=0.78 for each increase of 3 servings per day. This effect was independent of BMI, smoking, glucose intolerance, physical activity, blood pressure, serum cholesterol and intake of energy, ethanol and fat. Similarly, analyses of data from the Nurses' Health Study, the Health Professionals' Follow-up Study, the Women's Health Study and the Physician's Health Study supported the association between consumption of fruit and vegetables and reduction of stroke risk in both men and women (Joshipura et al., 1999; Liu et al., 2001; Liu et al., 2000). In an analysis of combined data from the Nurses' Health Study and the Health Professionals' Follow-up Study, Joshipura et al. (1999) found that an increase of 1 serving per day of fruits or vegetables was associated with a reduction of risk of 6% and that cruciferous vegetables, leafy green vegetables and citrus fruit (including juice) were responsible for the majority of this effect.

Results from the international case control study, INTERSTROKE, however, demonstrated that increasing consumption of fruits, but not vegetables was associated with a significant reduction in risk for stroke (OR=0.61, 95% CI 0.50-0.73 vs. OR = 0.91, 95% CI 0.75-1.00) (O'Donnell et al., 2010b). Similarly, a recent Korean study (Park, 2010) demonstrated a significant, inverse association between consumption of vegetables and risk for stroke ($p<0.04$ for trend). Compared with individuals who reported consuming 3 or fewer servings of vegetables per day, participants who reported eating 4-6 servings and more than 6 servings of vegetables per day experienced a significant reduction in stroke risk (OR = 0.69 95% CI 0.60-0.88 and 0.31 95% CI 0.10-0.96, respectively). There was no association demonstrated between intake of fruit and risk for stroke.

Whole grains. In the ARIC study, the intake of whole grains, fruits and vegetables was inversely related to the outcome of total mortality, while the consumption of whole grains was inversely related to the incidence of coronary artery disease (Steffen et al., 2003).

In a recent review and meta-analysis, Anderson et al. (2009) reported that, based on data from 4 studies, individuals with higher levels of consumption of dietary fibre (including whole grains and cereal fibre) have a significantly decreased risk for stroke (RR=0.74, 95% 0.63-0.86) when compared to individuals with the lowest reported intake.

Dairy Products. Many prospective, observational studies have been conducted to examine the associations between risk for cardiovascular disease and stroke and the consumption of dairy products. Individually, results from these studies have been inconclusive and have not demonstrated a consistent association between the consumption of dairy products and increased risk for either coronary heart disease or stroke (Huth & Park, 2012). Elwood et al. (2010) conducted a review and meta-analysis of 38 cohort studies examining the consumption of milk and dairy products. Based on the pooled results of 6 studies, the authors reported that there was a small, significant protective effect for mortality associated with the highest vs. lowest dairy food consumption overall (RR=0.87, 95% CI 0.77,0.98). In addition, based on the results of 11 studies, there was a reduction of risk for ischemic stroke in individuals with the greatest vs. the lowest consumption of milk and dairy foods (RR=0.79, 95% CI 0.68, 0.91). It should be noted that this result was associated with significant heterogeneity and, therefore, should be interpreted with caution (Elwood et al., 2010). Less evidence was available regarding the association between vascular disease and consumption of butter, cheese, and other dairy products. In addition, the authors did not provide an analysis of high-fat vs. low-fat varieties of dairy products.

Soedamah-Muthu et al. (2011) also reported the results of a similar review and meta-analysis of 17 prospective cohort studies. However, these authors included analyses with outcomes associated with consumption of high vs. low-fat dairy products. Overall, the authors demonstrated that, based on the pooled data from 6 studies, consumption of milk was not associated with increased risk for stroke (RR=0.87, 95% CI 0.72, 1.05) or total mortality (RR=0.99/200mL/d; 95% CI 0.95, 1.03). Examination of consumption of high-fat (4 studies), total dairy (4 studies) and low-fat (4 studies) revealed no association between any level of dairy fat and risk for CHD. Similarly, there was no significant association identified between high and low-fat milk and risk for stroke though significant between-study heterogeneity was also identified for these analyses (Soedamah-Muthu et al., 2011).

The Netherlands Cohort Study (n=120,852) was not included in either of the meta-analyses summarized here (Goldbohm et al., 2011). Complete dietary intake information was available for 16,136 individuals who had died at the end of 10 years of follow-up. Consumption was considered in terms of mean daily intake (grams/day) and categorized into quintiles. Overall, there was a small increase in risk for mortality associated with increased consumption of butter (RR per 10g/day = 1.04 95% CI 1.01,1.06) and fat from dairy products (RR per 10g/day = 1.04 95% CI 1.01, 1.06), but this was only found in women. In addition, there was a small protective effect against stroke mortality found associated with the consumption of full fat yogurt in both sexes (RR per 100 mg/d = 0.92 95% CI 0.85, 1.00 for women and 0.91 95% CI 0.86, 0.97 for men). Analyses of risk were adjusted for age, education, cigarette smoking, nonoccupational physical activity, BMI, multivitamin use, alcohol, energy, and vegetable and fruit consumption (Goldbohm et al., 2011).

Unsaturated fats, fish and fish oil. In addition to fruits, vegetables and whole grains, a possible inverse association has been identified between consumption of long-chain Omega-3 polyunsaturated fatty acids (as is present in fish and fish oil) and stroke risk. A meta-analysis by He et al. (2004), based on data from 9 cohort studies examining the effects of fish intake on risk for stroke, demonstrated a significant reduction in stroke events among individuals who consumed fish once per week (RR= 0.87). In addition, there was a non-significant trend toward increasing risk reduction with increasing fish consumption ($p<0.06$). Consumption of fish 5 or more times per week was associated with a stroke risk reduction of 31% (RR=0.69) when compared to individuals who ate fish less than once per month. Of the 9 studies included in the analysis, only 3 large studies examined stroke risk by stroke type. Based on data from these 3 studies, it was determined that consumption of fish at least once per month was associated with relative risk reduction of 0.67 for ischemic stroke and 1.06 for haemorrhagic stroke (K. He et al., 2004). The authors suggested that eating fish as infrequently as 1 to 3 times per month may reduce the risk of ischemic stroke.

Similarly, in a study limited to women, Larsson et al. (2011) reported a significant reduction in risk for stroke associated with consumption of more than 3 servings of fish per week (adj. RR= 0.84, 95% CI 0.71-0.98). In addition, the effect of fish consumption on stroke risk may be most evident for lean fish (Larsson et al., 2011). However, based on the results of a meta-analysis, Bouzan et al. (2005) suggested that overall consumption of fish may reduce stroke risk by 12% when compared to no fish consumption. Further, the authors suggested that reduction of risk for stroke may be incremental such that increased consumption is associated with increased risk reduction (2% risk reduction per serving per week). Similarly, in the INTERSTROKE study, increased fish consumption was associated with reduced stroke risk (OR=0.78, 95% CI 0.66-0.91) (O'Donnell et al., 2010b).

Olive oil consumption is a feature of the Mediterranean diet which is often recommended to reduce risk of stroke and stroke-related mortality. Olive oil is high in monounsaturated fats (80% oleic acid) and also contains polyunsaturated fats as well as several antioxidants. As part of the Three City Study, Samieri et al. (2011) examined the association between consumption of olive oil and risk for incident stroke (n=7,625). On multivariate analysis (adjusted for sociodemographic factors, stroke risk factors, physical activity and dietary patterns including consumption of fruits, vegetables, fish, grains and omega-3 & 6 rich oils), intense use of olive oil (for both cooking and dressing) was associated with a significant reduction in risk for stroke over a 6-year period when compared to individuals who reported no use of olive oil at baseline (HR=0.59, 95% CI 0.37-0.94). A similar reduction in risk was noted when plasma oleic acid was assessed rather than self-reported use. Individuals in the third (highest) tertile of measured plasma oleic acid were at the lowest risk for incident stroke (HR=0.27, 95% CI 0.08 – 0.90). A recent review concluded that strict adherence to the Mediterranean diet significantly reduces the risk of mortality from cardiovascular disease (Apostolopoulou et al., 2012).

Saturated Fats. Based on the results of a recent, large meta-analysis, there may be insufficient evidence to suggest that saturated fat consumption is associated with increased risk of stroke (Siri-Tarino et al. 2010a). The meta-analysis included data from a total of 21 prospective epidemiologic studies (8 of which focused on the association between saturated fat and stroke) and found that intake of saturated fat was not significantly associated with increased risk for stroke (RR=0.81 (95% CI 0.62-1.05), coronary heart disease (RR=1.07, 95% CI 0.96-1.07) or combined cardiovascular disease (RR=1.00, 95% CI 0.89-1.11). The authors indicate that the reported benefits of diets that recommend reduction of saturated fat may depend upon a corresponding increase in polyunsaturated fats. A recent meta-analysis by de Souza et al. (2015) was also unable to find a significant influence of saturated fat consumption on risk of ischemic stroke (RR 1.02, 95% CI 0.90-1.15). The authors note that although there no association was found between ischemic stroke and saturated fat, patients in the highest category of saturated fat intake were found to have an 18% reduction in relative risk of ischemic stroke compared to those in the lowest category. Exchanging saturated fat with carbohydrates, particularly refined carbohydrates, has not been associated with reduced cardiovascular disease risk (Siri-Tarino et al., 2010b). As part of the Japan Public Health Center-based (JHPC) study, Yamagishi et al. (2013) also revealed an inverse relationship between intake of saturated fats and stroke, including both ischemic and hemorrhagic. Further analyses suggest that there is a threshold of 20g per day of saturated fat intake to achieve an inverse relationship with stroke, particularly hemorrhagic stroke (Yamagishi et al. 2013).

Conversely, other studies have reported potential links between consumption of saturated fats and stroke. A case control study across four Australasian cities by Shiue et al. (2011) reported that a diet consisting of low-fat milk was significantly associated with a lower risk of subarachnoid hemorrhage (SAH) whereas a diet with increased consumption of fat/skin on red meat was associated with a higher risk of SAH. Darvishi et al. (2013) observed that intake of saturated fats and monounsaturated fats were both significantly higher among stroke patients compared to controls. Although this could suggest a causal link

between the two, the authors note that the effects of saturated fats can be affected by the consumption of other supplements.

Other studies have reported that consumption of saturated fats is associated with elevated levels of low-density lipoprotein (LDL) cholesterol (Faghihnia et al. 2012) while other studies have shown that a reduction in LDL cholesterol levels results in a lower risk of stroke when saturated fat intake is also reduced (Cholesterol Treatment Trialists Collaborators, 2005). In a recent meta-analysis, lower levels of high-density lipoprotein (HDL) cholesterol was found to be significantly and positively associated with the risk of intracerebral hemorrhage but elevated levels of LDL was found to be associated with a lower risk of hemorrhagic stroke (Wang et al. 2013). HDL cholesterol levels of <40mg/dL (<2.22mmol/L) on admission have also been found to be a significant independent predictor of recurrent ischemic stroke (OR 2.73, 95% CI 1.01-7.38; p=0.048) (Kuwashiro et al. 2012). Previous literature has reported that HDL cholesterol can block inflammation, and reverse oxidative damage by means of paraoxonases and lipid hydroperoxides, hence preventing the risk of stroke. Markaki et al. (2014) revealed that patients with higher total cholesterol levels were at a significantly lower risk of mortality compared to patients with lower total cholesterol levels however, an additional analysis did not yield any association between mortality and LDL cholesterol level. In female stroke patients, cholesterol was found to be significantly associated with risk of stroke and cerebral infarction but saturated fat was not (Larsson et al. 2012). The mechanisms for this finding remain unclear but Markaki et al. (2014) suggest that low BMI and weight loss are both associated with poor outcome post-stroke.

Red Meat. Micha et al. (2010) reported the results of a systematic review and meta-analysis examining the association between the consumption of red and processed meat and the incidence of coronary heart disease, stroke and diabetes. Although the authors identified a total of 17 prospective cohort and 3 case-control studies in total, only 3 studies included data regarding stroke events and part of study outcomes. Unfortunately, no 2 studies examined consumption of the same meats and the same stroke subtypes, making pooling of results more difficult (Micha et al., 2010).

A more recent meta-analysis by Kaluza at al. (2012) identified 5 articles for inclusion in their examination of the association between the consumption of red meat and risk for stroke. Overall, total red meat (fresh and processed) consumption was associated with an increased risk for stroke (RR per 1 serving per day = 1.11, 95% CI 1.06, 1.16). When examined separately, consumption of fresh red meat and processed meat were associated with similar risk (RR per serving = 1.11 and 1.13, respectively). When examined by stroke type, it was noted that risk for ischemic stroke increased with consumption of red or processed meat; however, risk for haemorrhagic stroke did not increase (Kaluza et al., 2012). It should be noted that relative risks are reported per serving, but no standardized definition of serving size was reported by the review authors. It should also be noted that the structure of dietary patterns may have differed between countries of study origin. No attempt was made to control for variations in dietary pattern or consumption of whole or refined grains, fruits or vegetables.

Salt. Of course, hypertension is a major risk factor for stroke. There is substantial evidence that increased salt consumption is associated with elevated blood pressure, thus providing an indirect opportunity to reduce risk for stroke by reducing salt intake (Frisoli et al., 2012). There is relatively little evidence regarding a direct effect of salt consumption on stroke risk (Chandratheva et al., 2010).

In a meta-analysis of 17 trials in individuals with hypertension and 11 trials in normotensive individuals, He and MacGregor (2002) demonstrated that a modest reduction of salt intake (40 – 118 mmol/day) was associated with significant reduction in BP in both normotensive (2.03/0.97 ±0.27/0.21 mmHg, p<0.001 for SBP and DBP) and hypertensive (4.96/2.73 ±0.40/24 mmHg, p<0.001 for SBP and DBP) individuals. The

authors suggest that modest reductions in salt consumption could result in immediate reductions in stroke deaths of approximately 14%.

Diets and Dietary Patterns. Dietary patterns, more than any single nutrient or food, may have cumulative effects on the risk of stroke (Hu et al., 2000). Analyses of the data from the Nurses' Health Study and the Health Professionals Follow-up Study (Fung et al., 2004; Hu et al., 2000) used factor analysis of a food frequency survey to identify two distinct dietary patterns: a prudent pattern associated with greater consumption of vegetables, fruits, whole grains, fish and poultry and a Western pattern associated with greater consumption of refined grains, full fat dairy products, red and processed meat and desserts/sweets. In both studies, an inverse association was identified between the prudent diet and risk of cardiovascular events such that reduced risk was associated with greater levels of consumption of foods associated with the prudent diet. Fung et al. (2004) reported a relative risk of 0.68 for ischemic stroke and 0.70 for total stroke among women in the Nurses' Health Study when comparing the top and bottom quintiles of the prudent diet consumers, after adjusting for age and energy intake. While this trend remained, it was no longer significant when controlling for the effects of lifestyle and other stroke risk factors. In contrast, the Western dietary pattern was positively associated with cardiovascular risk (Fung et al., 2004; Hu et al., 2000). Among women, the relative risk associated with high versus low consumption of the Western diet was 1.58 for total stroke and 1.56 for ischemic stroke after adjusting for age and energy intake as well as lifestyle and other stroke risk factors (Fung et al., 2004).

Several clinical trials have examined the role of dietary interventions. Details of the Lyon Diet Heart Study, the DASH (Dietary Approaches to Stop Hypertension) trial and the Indo-Mediterranean Diet Heart Study are summarized in Table 8.7.2.1.

Table 8.7.2.1 Summary of Dietary Interventions in Secondary Prevention

Author, Year Study Design (PEDro Score) Sample Size	Intervention	Main Outcome(s) Result
Appel et al. (1997) RCT (8) N=456	E1: Diet rich in fruits and vegetables E2: Diet rich in fruits and vegetables and low in saturated fat/dairy products (DASH diet) C: Control diet	• SBP: E1/E2 vs. C (+) • DBP: E1/E2 vs. C (+)
Sacks et al. (2001) RCT (8) N=412	E: DASH diet C: Control diet Note: within assigned diets, subjects ate foods with low, intermediate or high sodium levels	• SBP (+) at each sodium level • DBP (+) intermediate and high sodium levels
Singh et al. (2002) RCT (8) N=1000	E: Indo-Mediterranean diet rich in alpha linolenic acid C: Step I National Cholesterol Education Program prudent diet	• Consumption of vegetables, legumes, walnuts and almonds (+) • Mean intake of α-linolenic acid (+) • Fasting blood glucose (+) • Body mass index (+) • BP (+) • Total cardiac endpoints (+)
De Lorgeril et al. (1999) RCT (7) N=423	E: Low-fat, low cholesterol Mediterranean-type diet C: Prudent western-type diet	• Composite outcome 1 (cardiac mortality, nonfatal myocardial infarction) (+) • Composite outcome 2 (unstable angina, stroke heart failure, pulmonary/peripheral embolism) (+) • Composite outcome 3 (minor hospitalization requiring events) (+)

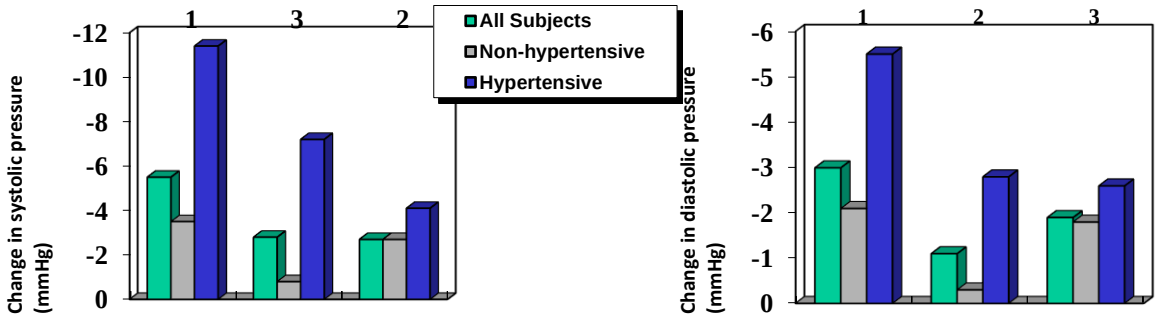
+ Indicates statistically significant differences between treatment groups
- Indicates non-statistically significant differences between treatment groups

Discussion

Diet has been shown to have a role in stroke prevention through either protective cardiovascular effects or influence on modifiable risk factors such as blood pressure or serum cholesterol. Increased consumption of vegetables has been shown to have an inverse association with stroke events. This association has been tested within both the Lyon Diet Heart Study and the DASH diet (See Figure 8.7.2.1 below) with positive results. Additionally, a Mediterranean diet, rich in nuts and Ω-3 fatty acids, has been demonstrated to be superior to conventional "prudent" diets in terms of lowering cholesterol and blood pressure (Apostolopoulou et al., 2012; de Lorgeril et al., 1999; Singh et al., 2002). In addition, consumption of an Indo-Mediterranean diet was associated with decreased body mass index and fasting blood glucose (Singh et al., 2002).

Eating habits may be difficult to alter, but as de Lorgeril et al (1999) pointed out, dietary change must be feasible financially and fit within one's particular lifestyle as well as be appealing to one's tastes in order to be sustained over time. Singh et al. (2002) demonstrated that it is possible to use seasonal, traditional and local produce to create an economically accessible and effective alternative diet even among populations who traditionally consume a low fat diet.

In order to assess the effects of dietary patterns on blood pressure, 459 participants not currently receiving antihypertensive medication and having an average systolic blood pressure (BP) <160 mmHg & a diastolic BP of 80 – 90 mmHg were randomly assigned to 1 of 3 diets: 1) a control diet approximately a typical American diet (n=154), (2) a fruits & vegetables diet featuring additional fruits and vegetables, fewer snacks and sweets than the control diet (n=154) and (3) the combination or DASH diet - rich in fruits, vegetables, low fat dairy products (n=151). The intervention or feeding phase continued for a total of 8 weeks.



Average between-diet differences in mean change in systolic and diastolic blood pressure.
(1) mean change in DASH diet group minus mean change in control group; (2) mean change in fruits/vegetable group minus change in control group; (3) mean change in DASH group minus mean change in fruits/vegetables group.

Greater reductions in blood pressure were seen among subjects with hypertension than those without ($p<0.001$ – systolic; $p=0.03$ – diastolic). Overall, substantial reductions in blood pressure were seen among participants consuming a diet rich in fruits, vegetables, low fat dairy products and reduced saturated and total

Figure 8.7.2.1 Effects of Dietary Patterns on Blood Pressure (Dash Collaborative Research Group)(Appel et al. 1997).

In a prospective, population-based study of 20,993 non-hypertensive women, aged 55 to 69, Folsom et al. (2007) found that 30% of those surveyed met DASH guidelines for consumption of whole grains, vegetables, dairy foods and meats and only 25% met DASH guidelines for total grain, fruits, fats and

sodium. Overall, self-reported concordance with the DASH diet was associated with reduced risk for incident hypertension and stroke; however, these trends were not significant when adjusted for age, education, body mass index, smoking status, estrogen use, alcohol intake and use of multi-vitamins.

Conclusions Regarding Diet in Secondary Prevention

There is level 1a evidence that low-fat, low-cholesterol diets rich in fruits, vegetables and low-fat dairy products are effective in reducing blood pressure when compared to control diets low in fruits and vegetables, and with average fat content.

There is level 1a evidence that Mediterranean type diets (rich in whole grains, fruits, vegetables, legumes, walnuts, almonds and alpha-linolenic acid) may improve blood pressure and reduce risk of cardiovascular events including stroke when compared to a prudent type diet.

Low-fat, low-cholesterol diets rich in fruits, vegetables, whole grains, legumes, nuts and omega-3 fatty acids may be effective in reducing blood pressure and risk of cardiovascular complications.

8.7.2.1 Vitamins/Antioxidants

Dietary intake of antioxidants (vitamin C, vitamin E and β-carotene) has been linked to lower risks of cancer and cardiovascular disease. It has been postulated that antioxidants may play a role in the progression of atherosclerosis by inhibiting the oxidation of LDL cholesterol (Gorelick, 2002).

In a systematic review of research examining antioxidant vitamins and the prevention of cardiovascular disease, Asplund (2002) identified 16 case-control studies and 18 cohort studies. Overall, a general pattern was identified suggesting that higher levels of antioxidant intake, through either diet or supplementation, are associated with a modest reduction of risk for cardiovascular events. This pattern finds support in a more recent study by Voko et al. (2003), which identified a trend toward decreased risk of stroke with increased dietary intake of antioxidants, especially vitamin C. This protective effect was most pronounced among smokers (Voko et al., 2003). However, a recent study by Marniemi et al. (2005) reported no protective association between higher serum concentrations of β-carotene, vitamin C or vitamin E and stroke risk. Only low serum levels of 1.25-OH vitamin D and iron were found to be predictive for stroke (Marniemi et al., 2005).

The association between antioxidant intake and reduced risk of stroke has been demonstrated primarily within observational studies concerned mostly with primary prevention. A meta-analysis of 8 randomized controlled trials (Asplund, 2002) attempting to assess the effects of food supplementation on primary prevention of cardiovascular disease, have produced little or no treatment effect suggesting neither benefit or harm from the use of dietary supplementation of antioxidants.

8.7.2.1.1 Antioxidant Vitamins on Atherosclerotic Progression

The use of antioxidants in secondary prevention has been studied less frequently. However, a number of trials have been undertaken to assess the effects of antioxidant vitamins on atherosclerotic progression (Table 8.7.2.1.1.1). Antioxidants have been assessed either alone or in combination with each other and/or other drugs used in secondary prevention of stroke.

Table 8.7.2.1.1.1 Summary of Effect of Supplementation with Antioxidant Vitamins on Atherosclerotic Progression

Author, Year Study Design (PEDro Score) Sample Size	Intervention	Main Outcome(s) Result
Lonn et al. for the SECURE investigators (2001) RCT (8) N=732	E1: Ramipril (10mg/d) with and without vitamin E (400 IU/d) E2: Ramipril (2.5mg/d) with and without vitamin E (400 IU/d) E3: Vitamin E (400 IU/d) C: Placebo	• Atherosclerotic progression: E1/E2 (ramipril overall) vs. C (+); E1 vs. C (-); E3 vs. C (-)
Salonen et al. (2000; 2003) RCT (6) N_{Start}=520 N_{End}=440	E1: Vitamin E (136 IU, 2/d) E2: Vitamin C (250mg slow-release) E3: Combination of both (CellaVie, 2/d) C: Placebo	• Atherosclerotic progression: E1/E2/E3 vs. C; men, E3 (+); women (-)

+ Indicates statistically significant differences between treatment groups
- Indicates non-statistically significant differences between treatment groups

Discussion

There have been conflicting results with regard to the effect of antioxidants on progression of atherosclerosis. However, given that the ASAP study (Salonen et al., 2003) examined the use of a combination of antioxidants over a long period, it is possible that a combination of vitamins E and C is more effective in retarding atherosclerotic progression than vitamin E alone. However, these results were only present among male study participants, especially smokers. Lonn et al. (Lonn et al., 2001) found a neutral effect of vitamin E on atherosclerotic progression. Additional research is required to investigate antioxidant vitamins as they pertain to atherosclerotic progression when administered independently and to gain further insight into the strength of combination therapy.

Conclusions Regarding Supplementation with Antioxidant Vitamins on Atherosclerotic Progression

There is level 1a evidence that the use of vitamin C and vitamin E together may reduce atherosclerotic progression.

Antioxidant vitamins may affect the progress of atherosclerosis; most effectively when used as a combination therapy (vitamin C and E). However, further research is required to understand the mechanism by which these supplements provide benefits against stroke.

8.7.2.1.2 Antioxidant Vitamins on Clinical Event Rates

A few RCTs have investigated the effect of antioxidant vitamins on clinical event rates (Table 8.7.2.1.2.1). The majority of these trials have used vitamin E as the sole treatment antioxidant.

Table 8.7.2.1.2.1 Summary of Supplementation with Antioxidant Vitamins on Clinical Event Rates

Author, Year Study Design (PEDro Score) Sample Size	Intervention	Main Outcome(s) Result
HOPE & HOPE-TOO Bosch et al. (2005) RCT (9) N=16571	E: Vitamin E (400IU/d) C: Placebo	• Risk for cardiovascular events or death (-) • Incidence of stroke (-) • Incidence of heart failure and hospitalization for heart failure (+) C

WACS Study Cook et al. (2007) RCT (9) N=8171	E1: Ascorbic acid (500mg/d) E2: Vitamin E (600IU every other day) E3: β-carotene (50mg every other day) C: Placebo (for non-active agents)	• Combined cardiovascular disease morbidity and mortality (-) • Incidence of stroke: E1/E2 vs. C (+)
Stephens et al. (1996) RCT (8) N=2002	E: Vitamin E (400 or 800IU/d) C: Placebo	• Cardiovascular mortality and incidence of nonfatal myocardial infarction (+) • Incidence of nonfatal myocardial infarction (+)
Heart Outcomes Prevention Evaluation (HOPE) Study Investigators (2000) RCT (8) N=9541	E: Vitamin E (400IU/d) C: Placebo	• Mortality (-) • Incidence of myocardial infarction (-) • Incidence of stroke (-) • Incidence of cardiovascular events at4-6yr follow-up (-)
Brown et al. (2001) RCT (8) N=160	E1: Simvastatin + niacin E2: Antioxidant vitamins (C, E, β-carotene, selenium) E3: Simvastatin/niacin + antioxidant vitamins C: Placebo	• Stenosis progression: E1 vs C (+), E2 vs C (-), E3 vs C (+) • Composite clinical endpoint (coronary stenosis, first cardiovascular event, mortality): E1 vs C (+), E2 vs C (-), E3 vs C (-)
MRC/BHF Heart Protection Study Heart Protection Study (2002) RCT (8) N=20536	E: Daily antioxidant vitamins (E, 600mg; C, 200mg; β-carotene, 20mg) C: Placebo	• All-cause mortality (+) • Incidence of first nonfatal myocardial infarction or coronary mortality (+) • Incidence of fatal/nonfatal stroke (+) • Coronary or noncoronary revascularisation (+)
GISSI-Prevenzione Investigators (1999) RCT (7) N=11324	E1: n-3 polyunsaturated fatty acid (PUFA, 1g/d) E2: Vitamin E (300mg/d) E3: PUFA + vitamin E C: Nothing	• Composite primary endpoint (mortality, nonfatal myocardial infarction, stroke): E1 vs C (+); E2 vs C (-); E3 vs C (+)
Steiner et al. (1995) RCT (6) N=100	E: Aspirin (325mg/d) + vitamin E (400IU/d) C: Aspirin (325mg/d)	• Incidence of stroke and transient ischemic attack (+) • Reduction of platelet adhesion (+)

+ Indicates statistically significant differences between treatment groups

- Indicates non-statistically significant differences between treatment groups

Discussion

While reports from observational studies suggest an association between greater levels of anti-oxidant intake and modest reduction in risk for cardiovascular events (Asplund, 2002), this trend has not been supported in randomized controlled trials among individuals with existing cardiovascular disease. A meta-analysis of 7 randomized controlled trials of vitamin E and 8 trials of β-carotene conducted among diverse populations with varying risk for the development of vascular disease reported no benefit associated with either treatment in the reduction of all-cause mortality or cardiovascular mortality (Vivekananthan et al., 2003). Pooled analysis from 6 trials (n=131,113) demonstrated a slightly increased risk of all-cause death and cardiovascular death associated with the use of beta-carotene. Additional analysis of vitamin E trials (n=45, 896) demonstrated no reduction in the odds of all-cause stroke associated with treatment (OR=1.02, p=0.71) (Vivekananthan et al., 2003).

The WACS study examined the use of vitamin C, vitamin E and beta-carotene in a sample of 8,171 women with either a history of CVD (including stroke) or at least 3 risk factors for CVD (N. R. Cook et al., 2007). The authors demonstrated no significant protective effects associated with active treatment with any of these agents using intention-to-treat analysis. There was also no significant effect found for any

combination of agents with the exception of vitamin C and vitamin E. Patients receiving both of these experienced fewer strokes than patients receiving placebo for both agents (RR=0.69, 95% CI 0.49-0.98, p=0.04). Further study examining the use of this combination of agents for the secondary prevention of stroke may be warranted; however, the authors note that widespread use of vitamins C, E and beta-carotene individually for cardiovascular protection is not supported.

Conclusions Regarding Supplementation with Antioxidant Vitamins on Clinical Event Rates

There is level 1a evidence that vitamin E may not affect the incidence of cerebrovascular accidents, and all-cause/cardiovascular mortality while use of β-carotene may be associated with an increase in cardiovascular and all-cause mortality when compared to control.

There is conflicting level 1b evidence suggesting variable efficacy of daily antioxidant vitamins (vitamin E, vitamin C and β-carotene) when used alone on clinical cardiovascular endpoints including stroke, and mortality. Additional level 1b evidence suggests a beneficial effect of combinatorial therapy with ascorbic acid (vitamin C) and vitamin E on stroke risk.

Antioxidant vitamins used individually may not be protective for cardiovascular risk including stroke and mortality. Combination of different antioxidants and simvastatin + niacin have been shown to effectively reduce the risk of these clinical outcomes.

8.7.2.2 Homocysteine

Homocysteine is a sulphur-containing amino acid that has been linked to cardiovascular disease and stroke. A normal serum level of plasma homocysteine is from 5 to 15 µmol/L. Mild to moderate elevations are from 16 to 100 µmol/L.Levels in excess of 100 µmol/L are considered to be indicative of severe hyperhomocysteinemia. A 1995 meta-analysis (Boushey & al., 1995) suggested that high levels of homocysteine are associated with increased risk of atherosclerotic vascular disease and that a prolonged reduction of plasma homocysteine of 5 µmol/L would reduce this risk by approximately 33%.

Elevated levels of homocysteine may be attributable to deficiencies in folic acid, vitamin B_6 and vitamin B_{12}, as well as old age (over 70 years), renal insufficiency, drinking more than 4 cups of coffee per day, alcohol use, smoking and physical inactivity (Eikelboom et al., 1999; Gorelick, 2002; Omenn et al., 1998). A recent study Robertson et al. (2005) reported 17% of elderly participants with vascular disease had vitamin B_{12} deficiency and that individuals with levels of B_{12} lower than 253 µmol/L had significantly greater areas of carotid plaque than those participants with higher levels of vitamin B_{12}.

In a review, Eikelboom et al. (1999) concluded that recent studies, including the European Concerted Action Project (Graham et al., 1997; Robinson et al., 1998) and Framingham Study (Bostom et al., 1999) have confirmed an association between atherosclerotic vascular disease and elevated plasma homocysteine levels. In a 1998 report from the European Concerted Action Project (Robinson et al., 1998), plasma levels of red cell folate, vitamin B_{12} and vitamin B_6 were reported to be inversely correlated with homocysteine levels while deficiencies of vitamin B_6 and folic acid were found to be significantly associated with increased relative risk for vascular disease. Vitamin B_{12} deficiencies showed no such association.

8.7.2.2.1 B-Vitamins on Atherosclerotic Progression

Several randomized controlled trials have examined the effect of B-vitamin therapy on atherosclerotic progression in individuals with existing cardio- or cerebrovascular disease. These are summarized in Table 8.7.2.2.1.1.

Table 8.7.2.2.1.1 Summary of Effect of Supplementation with B-Vitamins on Atherosclerotic Progression

Author, Year Study Design (Pedro Score) Sample Size	Intervention	Main Outcome(s) Result
VITATOPS (substudy) Potter et al. (2008) RCT (10) N=162	E: Vitamin supplementation (2mg folic acid, 25 mg vitamin B_6 and 0.5mg vitamin B_{12}) C: Placebo	• Carotid intima-medial thickness (-) • Flow-mediated dilation (-)
Till et al. (2005) Germany RCT (8) N=50	E: Vitamin supplementation (2.5mg folic acid, 25mg vitamin B_6 and 0.5mg vitamin B_{12}) C: Placebo	• Plasma homocysteine (+) • Carotid intima-medial thickness (+)
Fernandez-Miranda et al. (2007) RCT (6) N=137	E: Open-label folic acid (2.5mg/d) C: No treatment	• Carotid intima-medial thickness (CIMT) (-) • CIMT (+) treatment patients with MTHFR 677TT polymorphism vs. no polymorphism

+ Indicates statistically significant differences between treatment groups
- Indicates non-statistically significant differences between treatment groups

Discussion

These RCTs and have provided mixed results regarding the impact of vitamin B supplementation on vascular structure in individuals with existing vascular disease. Neither the Fernandez-Miranda et al. (2007) nor the VITATOPS substudy (Potter et al., 2008) reported a significant impact of therapy on CIMT over time. It should be noted that the CIMT of patients at baseline in both these studies was < 1.0mm, whereas Till et al. (2005) enrolled patients with CIMT > 1.0 mm.

Potter et al. (2008) also conducted a meta-analysis of trials examining CIMT that included the studies summarized above in addition to several trials enrolling only renal failure or renal transplant patients. On pooled analysis, treatment was associated with a significant reduction in CIMT (WMD = -0.10, 95% CI -0.20,-0.01). In addition, meta-analysis revealed a modest increase in flow-mediated dilation (FMD) associated with short-term treatment only. The authors noted that results of the CIMT analysis should be interpreted with caution given that most studies included were quite small with a single exception that dominated the results. Significant heterogeneity and publication bias were identified.

While Till et al. (2005) demonstrated that level of B_{12} and not Hcy concentration was a significant predictor of CIMT, a report based on data from the Northern Sweden Health and Disease Cohort (Van Guelpen et al., 2005) demonstrated that higher levels of dietary intake and plasma concentrations of folate were associated with lower risk of hemorrhagic stroke only. When adjusted for homocysteine, this association was no longer significant. Neither dietary intake nor plasma levels of vitamin B_{12} were associated with risk of either ischemic or haemorrhagic stroke (Van Guelpen et al., 2005). Similarly, a report from the large, population-based Northern Manhattan Study found that total homocysteine levels >15 µmol/L were an independent risk factor for ischemic stroke (HR=2.06), particularly among those of white race-ethnicity (HR=4.04) (Sacco et al., 2004).

Although an elevated level of plasma homocysteine has been identified as a possible risk factor for stroke associated with older age, the effects of elevated plasma homocysteine have not been well documented among younger patients. Bos et al. (2005) demonstrated an elevated risk for secondary cardiovascular events including cerebral infarct and TIA associated with high plasma homocysteine levels (≥13.7 µmol/L vs. ≤10.7 µmol/L) among stroke patients 45 years of age or younger (HR= 1.6; 95% CI 1.0 to 2.5).

Omenn et al. (1998) assigned 1.4 as the best estimate of relative risk for atherosclerotic cardiovascular disease when comparing a plasma homocysteine level of >1.5 µmol/L with one of <10 µmol/L and adjusting for other cardiovascular risk factors. The authors further suggested, given the body of evidence linking folic acid, homocysteine and risk for cardiovascular disease, that one should consume at least 400 µg of folic acid/day.

Conclusions Regarding Supplementation with B-Vitamins on Atherosclerotic Progression

There is level 1a evidence that vitamin B therapy may improve flow-mediated dilation (FMD) in the short-term however, no long-term effects on FMD or carotid intima-media thickness are observed.

More research is needed to determine the potential benefits of vitamin B supplementation on atherosclerotic progression.

8.7.2.2.2 Folic Acid, Vitamin B3, B6 and Vitamin B12 in Secondary Prevention

The results of randomized controlled trials to assess the effect of vitamin therapy to reduce homocysteine levels for secondary stroke prevention are summarized in Table 8.7.2.2.2.1.

Table 8.7.2.2.2.1 Summary of Folic Acid, Vitamin B3, B6 and Vitamin B12 in Secondary Prevention

Author, Year Study Design (PEDro Score) Sample Size	Intervention	Main Outcome(s) Result
VITATOPS (Interim report) Hankey et al. (2005) RCT (10) N=285	E: B-vitamins (2.0mg/d folic acid, 25mg/d pyridoxine, 0.5mg/d cobalamin) C: Placebo	• 6mo homocysteine level (+)
NORVIT Trial Bonaa et al. (2006) RCT (10) N=3749	E1: Folic acid (0.8mg), vitamin B12 (0.4mg) and vitamin B_6 (40mg) E2: Folic acid (0.8mg), vitamin B12 (0.4mg) E3: Vitamin B_6 (40mg) C: Placebo	• Composite primary endpoint (recurrent myocardial infarction, stroke, sudden death due to coronary artery disease): E1 vs. C (+)
Grace et al. (2006) RCT (10) N=443	E: B-vitamins (2.5mg folic acid, 0.5mg vitamin B_{12}, and 25mg vitamin B_6) C: Placebo	• 1yr plasma total homocysteine level (+)
SU.FOL.OM3 Galan et al. (2010) RCT (10) N=2501	E1: B-vitamins (560µg 5-methyltetrahydrofolate, 3 mg B_6, 20µg B_{12}) E2: Omega-3 fatty acids (600 mg) E3: B vitamins + omega-3 fatty acids C: Placebo	• First major cardiovascular event: E1/E2 vs. C (-) • Incidence of stroke: E1 vs C (+), E2 vs C (-)

VITATOPS Hankey et al. (2010) RCT (10) N=8164	E: B-vitamins (2mg folic acid, 25mg vitamin B_6, 0.5mg vitamin B_{12}) C: Placebo	• Composite primary outcome (nonfatal stroke, nonfatal myocardial infarction, vascular cause mortality) (+) • Incidence of fatal/nonfatal stroke (-)
AIM-HIGH Boden et al. (2011) RCT (10) N=3414	E: Extended-release niacin (1500-2000mg/d) + simvastatin (40-80mg/d) C: Placebo + simvastatin (40-80mg/d)	• Composite primary endpoint (first event of coronary heart disease mortality, nonfatal myocardial infarction, ischemic stroke, acute coronary syndrome hospitalization, symptom-driven coronary/cerebral revascularization) (-) • Incidence of stroke (-); ischemic stroke (-)
VITATOPS Hankey et al. (2012a) RCT (10) *Post hoc analysis* N=6609	E: B-vitamins (2mg folic acid, 25mg vitamin B_6, 0.5mg vitamin B_{12}) C: Placebo	• Composite primary outcome (nonfatal stroke, nonfatal myocardial infarction, vascular cause mortality): antiplatelet therapy (-); no antiplatelet therapy (+) • Incidence of fatal/nonfatal stroke (+) no antiplatelet therapy
Lonn et al. (2006) RCT (9) N=5522	E: Daily folic acid (2.5mg), vitamin B_6 (50mg) and vitamin B_{12} (1mg) C: Placebo	• Composite mortality (cardiovascular causes, myocardial infarction, stroke) (-) • Incidence of stroke (+)
WAFACS Trial Albert et al. (2008) RCT (9) N=5442	E: Daily Folic acid (2.5mg), Vitamin B_6 (50mg) and Vitamin B_{12} (1mg) C: Placebo	• Composite of cardiovascular morbidity and mortality (-) • Incidence of stroke: ischemic (-); haemorrhagic (-)
VISP Trial Toole et al. (2004) RCT (8) N=3680	E: Daily high-dose supplementation with folic acid (2.5mg), vitamin B_6 (25mg) and vitamin B_{12} (0.4mg) E: Daily low-dose supplementation (same vitamins; 200µg, 6µg and 20µg, respectively)	• Incidence of recurrent cerebral infarction (-) • Incidence of coronary heart disease (-) • Mortality (-)
Goes Trial Liem et al. (2003, 2005) RCT (6) N=593	E: Open-label folic acid (0.5mg/d) C: Standard care	• Composite primary endpoint (vascular mortality, noncardiovascular mortality, recurrent myocardial infarction, invasive coronary procedures, stroke, transient ischemic attack, other vascular surgery) (-)
Arshi et al. (2015) RCT (6) N_{Start} =3680 N_{End}=3649	E: High dose vitamin therapy (25mg pyridoxine, 0.4mg cobalamin, 2.5mg folic acid) C: Low dose vitamin therapy (200µg pyridoxine, 6µg cobalamin, 20µg folic acid) Note: Patients sugrouped based on concurrent antiplatelet therapy	Concurrent Antiplatelet Use • Incidence of stroke C (+) • Combined outcome (stroke, myocardial infarction, or vascular death) (-) No Antiplatelet Use • Incidence of stroke (-) • Combined outcome (stroke, myocardial infarction, or vascular death) (-)

+ Indicates statistically significant differences between treatment groups
- Indicates non-statistically significant differences between treatment groups

Discussion

Although the VISP trial reported no significant treatment effects, a *post hoc* analysis of VISP data identified a subgroup of participants most likely to benefit from the VISP supplementation (Spence et al., 2005). Participants with vitamin B_{12} levels above the 95th percentile who may have been taking additional, non-study, supplements were eliminated from the analysis, as were participants with vitamin B_{12} levels below

the 25th percentile (suspected B_{12} malabsorption). In addition, subjects with possible renal impairment (glomerular filtration rate <47) were excluded. In the remaining participants, high-dose supplementation was associated with a reduced risk of the combined outcome of ischemic stroke coronary disease or death (adjusted for age, sex, blood pressure, smoking and vitamin B_{12} level HRR=0.79, p=0.056). For stroke events alone, there was no significant reduction in events associated with high dose vitamin therapy (adjusted HRR = 0.92, p=0.56). Groups were further subdivided into high and low baseline B_{12} levels indicative of adequate versus inadequate B_{12} absorption. Participants with adequate absorption assigned to the high-dose condition experienced the best outcome in terms of the combined outcome of stroke or coronary event when compared to participants with inadequate absorption assigned to the low-dose condition (p=0.03). However, comparisons for stroke events alone were not significant (p=0.31).

The international VITATOPS study examined the effect of lowering plasma homocysteine levels via vitamin supplementation (folate, B_6 and B_{12}) on the incidence of vascular sequelae following recent stroke or TIA. Despite documented, significant reductions in plasma homocysteine (Hankey et al., 2005)(G. Y. Ho et al., 2006), treatment with daily supplements of folic acid, vitamin B6 and vitamin B12, was not associated with significant reduction in risk (RR=0.91, 95% CI 0.82 to 1.00 p=0.05; absolute risk reduction for the composite study endpoint = 1.56%; 95% CI -0.01 to 3.16). Examination of stroke events (fatal and nonfatal) revealed no significant benefit in terms of risk reduction associated with B-vitamin supplementation.

In a *post hoc* analysis of data from the VITATOPS trial, study authors postulate an interaction between antiplatelet therapy and homocysteine-lowering therapy whereby the effect of homocysteine lowering therapy is modified by the presence of antiplatelet therapy (Hankey et al., 2012a). More than 6,600 individuals were identified as receiving antiplatelet therapy (see Table 8.7.2.2.2.1) at study baseline. For these individuals, receipt of B-vitamin therapy appeared to have no significant effect on either the composite study outcome or the individual outcome of risk for recurrent stroke when compared to placebo. However, when considering only individuals not receiving any antiplatelet therapy, treatment with B-vitamins was associated with a significant benefit in terms of reduced risk for stroke (Hankey et al., 2012a). Alternatively, in a similar study evaluating the effects of vitamin therapy and antiplatelet use on secondary prevention, Arshi et al. (2015) found that a high dose regimen of vitamins along with antiplatelets resulted in an increased risk of stroke when compared to low dose vitamin therapy. No significant effects were observed among the combined study outcome of stroke, myocardial infarction and vascular death, regardless of strength of dose or antiplatelet use.

Boden et al. (2011) found among patients with atherosclerotic cardiovascular disease and LDL cholesterol levels of less than 70 mg per deciliter (1.81 mmol per liter) there was no clinical benefit from the addition of niacin to statin therapy during a 36-month follow-up period, despite significant improvements in HDL cholesterol and triglyceride levels.

Not all trials have reported entirely negative results. Both the HOPE-2 and SU.FOL.OM3 trials reported significant benefits associated with folic acid supplementation and B-vitamin therapies in terms of reduction in risk for stroke (see Table 8.7.2.2.2.1). In recent years, several meta-analyses have been performed in an attempt to clarify the effect of treatment with folic acid supplementation and B-vitamin therapies on the risk for stroke, cardiovascular disease and vascular death. A summary of these efforts appears in Table 8.7.2.2.2.2.

Table 8.7.2.2.2.2 Meta-Analyses Examining Folic Acid Supplementation and B-vitamin Therapy in Secondary Prevention

Study	Meta-Analysis Description and Results

Wang et al. (2007)	Included data from 8 randomized controlled trials examining folic acid supplementation and the risk of stroke. Overall, folic supplementation was associated with a significantly reduced risk for stroke (RR = 0.82, 95% CI 0.68 – 1.00) and, in addition, longer periods of intervention were associated with greater risk reductions. All eight trials included participants with pre-existing medical conditions; however, only one included individuals with previous stroke (i.e. VISP). When trials were stratified by history of stroke, the relative risk associated with treatment in individuals with stroke was 1.04 (95% CI 0.84-1.29) compared to 0.75 in trials that included individuals with no history of stroke (95% CI 0.62, 0.94; p=0.002). When stratified by fortification status, RR for fortification was 0.89 (95% CI 0.55, 1.42) vs. 0.75 for regions without fortification (95% CI 0.62, 0.91, p=0.003).
Mei et al. (2010)	17 trials examining folic acid supplementation or B-vitamin therapy for homocysteine lowering were identified. All participants had existing cardiovascular or renal disease. Only one trial examined individuals with previous stroke exclusively (VISP). There was no significant protective effect associated with folic acid or B-vitamin therapy in terms of risk for cardiovascular events (RR=1.01 95% CI 0.97, 1.05) or stroke (RR=0.94 95% CI 0.85, 1.04). Exclusion of the 7 trials from countries with grain fortification programs demonstrated no significant reduction in risk for stroke associated with folic acid or B-vitamin therapy (RR=0.96, 95% CI 0.83, 1.12).
Miller et al. (2010)	Identified 14 studies for inclusion in their analysis – 7 studies included stroke as a study endpoint. All trials included individuals with pre-existing disease (only one with prior stroke - VISP). All trials demonstrated a significant reduction in homocysteine levels associated with folic acid supplementation. Overall, there was no significant reduction in risk for clinical cardiovascular end points (RR=1.02, 95% CI 0.98, 1.06) or stroke (RR=0.95 95% CI 0.84, 1.08 – data from 7 studies) associated with folic acid supplementation. Subgroup analysis by fortification status showed no significant differences in homocysteine levels at baseline, net decreases in homocysteine levels over time, or CVD risk.
Zhou et al. (2011)	16 trials were included in this meta-analysis examining the impact of folic acid supplementation on cardiovascular outcomes. All trial participants had pre-existing disease but only one trial included only individuals with prior stroke/TIA (VITATOPS). Overall (12 trials), supplementation was not associated with reduction in risk for major cardiovascular events (RR=0.98 95% 0.93, 1.04). In addition, supplementation was not associated with reduced risk for stroke (12 trials) (RR=0.89, 95% CI 0.78, 1.01; p=0.07) or vascular death (RR=0.94, 95% CI 0.88, 1.02).
Huo et al. (2012)	In a meta-analyses of 15 studies, the authors investigated the effect of folic acid supplementation on stroke risk among populations with varying levels of folic acid fortification. Overall, stroke risk was reduced by 8% with folic acid supplementation (RR=0.92, 95% CI 0.86-1.00; p=0.038). Among the 10 studies with no or partial fortification, stroke risk was reduced by 11% (RR=0.89, 95% CI 0.82-0.97; p=0.010), and there was a larger improvement among trials with lesser use of statins (RR=0.0.77, 95% CI 0.64-0.92; p=0.005). Additionally, a positive dose-response relationship was reported for percent use of statins and log-RR for stroke, relating to folic acid supplementation. Among the 5 studies assessing folic acid supplementation with fortification, no improvement was observed for stroke risk (RR=0.1.03, 95% CI 0.88-1.21; p=0.69).

Three of the five identified meta-analyses reported no significant benefit associated with folic acid supplementation or vitamin-B therapy in terms of risk for stroke. For the most part, although study participants all had some pre-existing disease condition, relatively few were included on the basis of previous stroke or TIA. Only in the most recent analysis (Huo et al., 2012) was there more than a single stroke-based study included in the analysis. In that study, supplementation was associated with a significant reduction in risk for stroke. In the preceding analysis (Zhou et al., 2011), data was included from the VITATOPS trial for the first time and the authors reported the results of an analysis that did demonstrate a trend toward significant benefit associated with supplementation in terms of risk for stroke.

Several authors provided the results of sensitivity analyses examining the impact of grain fortification programs (Huo et al., 2012; Mei et al., 2010; Miller, 2010; Wang et al., 2007). Both generally positive meta-

analyses (Huo et al., 2012; Wang et al., 2007) determined supplementation was associated with significant benefit in terms of reduced risk for stroke based on data obtained from studies originating in countries with no or partial (Huo et al., 2012) grain fortification. Neither Mei et al. (2010) nor Miller et al. (2010) could demonstrate a similar effect associated with the presence of fortification.

It has also been suggested that the effectiveness of supplementation may be modified by the administration of other therapies such as antiplatelet (Hankey et al., 2012a) or statin therapy (Huo et al., 2012). Huo et al. (2012) demonstrated that, in studies where there had been no grain fortification, there was a greater benefit associated with supplementation in studies where fewer participants were taking statins.

Conclusions Regarding Folic Acid, Vitamin B3, B6 and Vitamin B12 in Secondary Prevention

There is conflicting level 1a evidence regarding the effect of B-vitamins (folic acid, vitamin B6 and B12) on cardiovascular outcome or risk of stroke.

There is level 1a evidence that supplementation with folic acid and vitamins B_6 and B_{12} is associated with significant reductions in plasma homocysteine levels (tHcy) up to one year from baseline.

There is level 1b evidence that folic acid alone may have no effect on a combined cardiovascular outcome when compared to standard care.

There is level 1b evidence that high dose vitamin B therapy concurrent with antiplatelets may increase risk of stroke versus low dose therapy. There may be no effect on incidence of stroke or a cardiovascular composite endpoint among patients not supplementing vitamin therapy with antiplatelets.

While treatment with folic acid and/or vitamins B_6 & B_{12} reduces plasma homocysteine levels, subsequent cardiovascular outcomes and stroke risk may not be improved.

Concurrent antiplatelet use may alter the action of vitamin therapy however, there is conflicting evidence supporting this association. Further research is required.

8.7.2.2.3 Homocysteine-Lowering Therapy and Functional Outcome

A possible relationship between plasma homocysteine levels and functional outcome post stroke has also been examined (Mizrahi et al., 2005). Patients with high plasma homocysteine (>15 µmol/L) did not differ from patients with low plasma homocysteine (≤15 µmol/L) by age, gender, presence of diabetes mellitus, ischemic heart disease, atrial fibrillation, hyperlipidemia or by FIM scores, both motor FIM and total FIM, at admission or at discharge. Level of plasma homocysteine was not associated with functional status or with functional gain over the course of rehabilitation. The sole difference identified between groups based on high versus low levels of homocysteine was hypertension. Approximately 80% of patients with high homocysteine levels had hypertension, while only 51.7% of patients in the low plasma homocysteine group were hypertensive (Mizrahi et al., 2005). Results from studies pertaining to functional outcome following stroke are summarized in Table 8.7.2.2.3.1.

Table 8.7.2.2.3.1 Homocysteine-Lowering Therapy and Functional Outcome Post-Stroke

Author, Year Study Design (Pedro Score) Sample Size	Intervention	Main Outcome(s) Result
HOPE-2 Saposnik et al. (2009b) (additional analysis) RCT (9) N=5522	E: B-vitamins (2.5mg folic acid, 50mg vitamin B_6 and 1mg vitamin B_{12} per day) C: Placebo	• Incidence of stroke (+) • Risk of disabling stroke (-) • Recovery by day 7 or hospital discharge (-) • Risk of poor function (mRS 3-6) (-)
Towfighi et al. (2014) Post-hoc analysis of VISP trial RCT (8) N_{Start}=3680 N_{End}=2993	E1: High dose treatment (25mg pyridoxine, 0.4mg cobalamin and 2.5mg folic acid) E2: Low dose treatment (200µg pyridoxine, 6µg cobalamin and 20µg folic acid)	• Risk of stroke, myocardial infarction or death: E1 (+) median age ≥67yr; median age ≤67yr (-)

+ Indicates statistically significant differences between treatment groups
- Indicates non-statistically significant differences between treatment groups

Discussion

While there appeared to be a positive effect on risk for stroke associated with B-vitamin therapy in the HOPE-2 trial, the effect was most pronounced in certain subgroups. The greatest absolute risk reduction was observed in individuals with the highest elevations in homocysteine concentration (>13.8 ч mol/L). Overall, therapy was associated with a modest reduction in stroke risk but had no impact on stroke severity or functional disability post-stroke (Saposnik et al., 2009b). In a post-hoc analysis controlling for factors not considered in the HOPE-2 trial, Towfighi et al. (2014) examined the influence of age on serum homocysteine therapy for the reduction of vascular risk post-stroke. Results indicated that among patients with elevated levels of homocysteine and over the age of 67, high dose therapy was associated with reduced incidence of stroke, myocardial infarction or death. No significant treatment effect was found for subjects under 67 years old.

Conclusions Regarding Homocysteine-lowering Therapy and Functional Outcome Post-Stroke

There is level 1b evidence that homocysteine-lowering therapy with B-vitamins may not improve the risk of recurrent stroke, stroke severity or functional outcome when compared to placebo.

There is level 1b evidence that high dose homocysteine-lowering therapy may improve risk of stroke, myocardial infarction or death in patients ≥67 years old versus low dose treatment.

Vitamin therapy to lower homocysteine may not affect functional ability post-stroke however, it seems to improve risk of secondary complications among older patients.

8.7.2.3 Treatment Recommendations

The British Diabetic Association has written evidence-based dietetic guidelines for secondary prevention in cardiovascular disease (Hooper et al., 2004); however, the paucity of information specific to diet and secondary prevention in stroke populations is highlighted. The following advice is recommended for patients with a history of MI, stroke and others with cardiovascular disease (See Table 8.7.2.4.1).

Table 8.7.2.3.1 Canadian Stroke Best Practice Recommendations for Diet (Coutts et al. 2015)

- Diet - Counsel and educate individuals with stroke to consume:
  - Fresh fruits, vegetables, low-fat dairy products, dietary and soluble fibre, whole grains and protein from plant sources and low in saturated fat (i.e. Mediterranean-type diet)
  - Cholesterol (< 200 mg daily for patients at increased vascular risk)
  - Sodium in accordance with Canada's Food Guide to Healthy Eating
- Sodium - Counsel and educate individuals with stroke and high blood pressure to consume:
  - < 2000mg per day of sodium intake from all sources. A daily upper consumption limit of 2300 mg should not be exceeded by any age group.

Conclusions Regarding Canadian Stroke Best Practice Recommendations for Diet in Stroke Care

The ideal diet in stroke care is low in saturated fat and consists of fresh fruits, vegetables, dietary and soluble fibre, whole grains and protein from plant sources, and low-fat dairy products. Recommended daily sodium intake from all sources should total no more than 2000mg per day.

8.7.3 Smoking

Goldstein et al. (2001) estimated that approximately 18% of strokes may be attributed to active smoking. Early results from the INTERSTROKE study demonstrated that being a current smoker (vs. a non-smoker or former smoker) was associated with increased odds for stroke (OR=2.09, 95% CI 1.75 – 2.51). This effect appeared stronger for ischemic than for haemorrhagic stroke (O'Donnell et al., 2010b). Current smokers who smoke 20 or more cigarettes per day have an associated increase of stroke risk approximately 2 – 4 times that of a non-smoker (Flemming & Brown, 2004; Kawachi et al., 1993; Robbins et al., 1994; Wolf et al., 1988). Not only does smoking increase risk of stroke, but may also be associated with increased risk for death and dependency (assessed on the Rankin Scale, OR = 1.23 p=0.007) and for functional limitations (assessed on the Barthel Index OR = 1.42 p=0.002) following the stroke event (Ovbiagele et al., 2006b). In a study of 660 adults with stroke, Kumagai et al. (2013) reported that lower NIHSS scores at admission, fewer ischemic lesions and non-smoking were significant prognostic factors for favourable outcome (defined as NIHSS score ≤4 90 days post stroke).

Smoking acts as a risk factor in a dose-dependent fashion such that heavy smokers have more risk than light smokers who in turn have more risk than non-smokers (Bonita et al., 1999; Hankey, 1999; O'Donnell et al., 2010b; Robbins et al., 1994; Wolf et al., 1988). Kurth et al. (2003a) demonstrated that the relative risk for ischemic stroke associated with smoking fewer than 20 cigarettes per day was 1.56 and 2.25 when 20 or more cigarettes were smoked per day (vs. non-smokers). Reported relative risks for haemorrhagic stroke among smokers follow a similar pattern. Within a male population, smoking fewer than 20 cigarettes was associated with a 1.6 fold increase for ICH and a 1.8 fold increase for SAH compared to non-smokers (Kurth et al., 2003a). When rate of smoking increased to ≥20 cigarettes, the associated risk increased to 2.1 and 3.2 for ICH and SAH, respectively. Studies conducted within a female subject population have yielded a similar pattern of risk (Kurth et al., 2003a; Lu et al., 2008).

Duration of smoking behaviour also influences risk. The Cardiovascular Study in the Elderly (CASTEL) (Mazza et al., 2001) reported the relative risk associated with current smoking compared to current non-smokers to be 1.60 for fatal stroke. Mortality was particularly high among current smokers who had been smoking for 40 or more years (7.2% vs. 1.8% for non-smokers, p<0.01).

Environmental Exposure. Increased risk of stroke is not confined to active smokers. Exposure to environmental tobacco smoke is associated with an increased risk of stroke among non-smokers and long-

term (>10 years) ex-smokers (OR = 1.82) (Bonita et al., 1999). Iribarren et al. (2004) demonstrated that more than 20 hours per week of exposure within the home to environmental cigarette smoke was associated with a 1.29 fold increase in risk of first ischemic stroke among nonsmoking men and a 1.5 fold increase among nonsmoking women when compared to individuals who were exposed for 1 hour or less per week. Among 60,377 lifelong female non-smokers in China, it was reported that approximately one-half lived with a husband who was a current smoker (Zhang et al., 2005). These women were at a significantly greater risk for stroke (OR=1.47) than women married to men who had never smoked.

Women whose husbands were former smokers were not at an increased risk (OR=1.03). Risk for stroke was related to both the amount smoked by the husband (p for trend = 0.0002) and the duration of smoking by the husband (p for trend=0.0004) in a dose-dependent fashion (Zhang et al., 2005).

In a meta-analysis by Lee and Forey (2006) based on 16 studies of risks associated with exposure to environmental tobacco smoke, the pooled estimate of risk for stroke in lifelong non-smokers was 1.25 (95% CI 1.16-1.36, p<0.001) based on 24 sex-specific estimates of relative risk based on current spousal exposure (or closest equivalent) when compared to unexposed non-smokers. In addition, Lee and Forey (2006) reported a significant dose-related relationship (p<0.001) such that highest rates of self-reported exposure were associated with the greatest risk for stroke. For example, based on data from 7 included studies, the relative risk for stroke among the group of individuals whose self-reported exposure was "a lot" was 1.56 (95% CI 1.34-1.82).

Estimates of risks associated with active smoking may have been deflated by including non-smokers who have passive exposure in non-smoking comparison groups. Bonita et al.(1999) reported a four-fold risk of stroke associated with active smoking when active smokers were compared to all non-smokers. However, when non-smokers who had been exposed to environmental smoke were removed from the comparison group, the risk increased to six-fold.

Conclusions Regarding Smoking and Stroke Risk

There is level 1a evidence that smoking or exposure to environmental tobacco smoke may increase risk of stroke in a dose-dependent manner.

Smoking and exposure to tobacco smoke has consistently been associated with an increased risk of stroke (ischemic and haemorrhagic) while smoking cessation reduces this risk.

8.7.3.1 Smoking Cessation Interventions

Cessation of smoking is associated with a rapid decline in the risk of stroke associated with current smoking. Both the Framingham Study (Wolf et al., 1988) and the Nurses' Health Study (Kawachi et al., 1993) reported a substantial decrease in risk 2 to 4 years following smoking cessation. Several recent studies have reported no significant difference in relative stroke risk between former smokers and subjects who have never smoked (Kurth et al., 2003a; Kurth et al., 2003b; Mazza et al., 2001). Similarly, Tse et al. (2012) reported that smoking cessation reduced the risk of ischemic stroke but this was not statistically significant.

In a recent study of 7,764 middle-aged and elderly smokers, those who received a diagnosis of stroke, cancer, lung disease, heart disease or diabetes mellitus were 3.2 times more likely to quit smoking (p<0.001) (Keenan, 2009). Individuals who experienced stroke were more than 4 times as likely to quit (OR = 4.3, p<0.001). It should be noted that the odds of smoking cessation were greater among older

individuals (>70 years) when compared to those aged 50 – 55. Living with a spouse who smokes may also decrease the likelihood of quitting (Keenan, 2009).

Smoking cessation involves a variety of treatments including counselling, nicotine replacement, Zyban (Wellbutrin) and/or formal programs. Jorenby et al. (1999) reported that treatment with sustained release bupropion in combination with a nicotine patch resulted in significantly higher long-term rates of smoking cessation than use of either the nicotine patch alone or placebo. Unfortunately, smoking cessation advice and/or treatment remains an underused strategy. Ambriz et al. (2004), in a study of CAD patients at Veteran Affairs Medical Centers in the United States, reported that only 56% of smokers received appropriate smoking cessation interventions while in hospital. A recent systematic review concluded that there are limited intervention studies that explore this area of secondary stroke prevention (Edjoc et al., 2012). A non-pharmacological smoking cessation intervention is summarized in Table 8.7.3.1.1.

Table 8.7.3.1.1 Summary of Non-Pharmacological Smoking Cessation Interventions

Author, Year Study Design (Pedro Score) Sample Size	Intervention	Main Outcome(s) Result
Frandsen et al. (2012) RCT (7) N=94	E1: Intensive smoking cessation intervention E2: Minimal smoking cessation intervention	• Rate of smoking cessation (-)

+ Indicates statistically significant differences between treatment groups
- Indicates non-statistically significant differences between treatment groups

Discussion

A study based on data from the South London Stroke Register (SLSR) reported smoking cessation over a period of 3 years for a sample of 363 individuals who were smokers at the time of stroke (Ives et al., 2008). The majority of smokers (71%) reported quitting at some point during follow-up. Of these, most (66%) reported quitting by 3 months post-stroke. Unfortunately, of those individuals who quit smoking soon after stroke, only 17% continued to report not smoking at 3 years. Older age was the sole significant predictor of continued abstinence. Patients aged 75 or older were far more likely to continue to report not smoking at both the 1 year and 3 year follow-up assessments (OR = 4.5, 95% CI 1.5-13.5). It has been suggested that, perhaps, provision of intervention and support for smoking cessation would be most effective when provided soon after the stroke event when individuals are most motivated to change and the risk for stroke recurrence is greatest. However, an examination of minimal vs. intensive smoking cessation interventions in the subacute period post-stroke demonstrated no significant between group differences in terms of cessation rates (Brunner Frandsen et al., 2012).

Conclusions Regarding Non-Pharmacological Smoking Cessation Interventions

There is level 1b evidence that an intensive smoking cessation program providing a period of counselling and support may be as effective as a minimal intervention providing a single 30-minute session of counselling only.

8.7.3.2 Treatment Recommendations

Current evidence-based guidelines suggest that every patient with stroke or TIA who is a smoker be advised to quit and, in addition, avoid environmental smoke. Counselling, nicotine replacement and oral smoking cessation medications may also be included in an effective smoking cessation plan. Current Canadian best practice recommendations appear in Table 8.7.3.2.1.

Table 8.7.3.2.1 Canadian Best Practice Recommendations Regarding Smoking (Coutts et al. 2015)

All members of the interdisciplinary team should address smoking cessation and a smoke-free environment at every healthcare encounter for active smokers.

- In all health-care settings along the stroke continuum (inpatient, ambulatory, and community), patient smoking status should be identified, assessed and documented.
- Provide unambiguous, nonjudgmental, and patient-specific advice regarding the importance of cessation to all smokers and others who reside with the patient.
- Offer assistance with the initiation of a smoking cessation attempt – either directly or through referral to appropriate resources.
- People who are not ready to quit should be offered a motivational intervention to help enhance their readiness to quit.
- A combination of pharmacological therapy and behavioral therapy should be considered in all smoking cessation programs and interventions.
- The three classes of pharmacological agents that should be considered as first-line therapy for smoking cessation are nicotine replacement therapy, bupropion, and varenicline.
    - The choice of appropriate pharmacotherapy should take into account the patient's medical stability, clinical needs, other medical factors, and patient preferences.
- For admitted stroke patients who are current smokers, protocols should be in place to manage nicotine withdrawal during hospitalization.
- There is a lack of clear evidence regarding the timing to initiate nicotine withdrawal/replacement therapy in patients following a stroke. Expert opinion suggests this should begin as soon as possible.
- Interdisciplinary team members should counsel patients, family members, and caregivers about the harmful effects of exposure to second-hand smoke

Conclusions Regarding the Canadian Stroke Best Practice Recommendations for Smoking Cessation

Older age is the only reliable predictor of smoking termination. Information regarding the importance of quitting should be provided to all smokers, including pharmacological (nicotine replacement therapy, bupropion, varenicline) and behavioural therapy. Further research is required to investigate and develop effective smoking cessation interventions.

8.7.4 Alcohol

A large meta-analysis of 35 observational studies examining the effects of alcohol consumption on stroke risk revealed a significant (p=0.004), J-shaped relationship between the amounts of alcohol consumed per day on the risk for ischemic stroke (Reynolds et al., 2003). In that analysis, individuals who consumed 1 – 2 drinks per day had the least risk for ischemic stroke (RR=0.72) while those having more than 5 drinks per day had the most risk (RR=1.69) when compared to a group of abstainers. The analysis also confirmed that alcohol consumption has a linear, dose-dependent effect on risk of haemorrhagic stroke. Heavy drinking (more than 5 drinks per day) was associated with a relative risk of haemorrhagic stroke of 2.18. Irregular and binge drinking (more than 5 drinks at one sitting) have also been associated with an increase in risk for haemorrhagic stroke (Mazzaglia et al., 2001). Results of a recent meta-analysis Patra et al. (2010) confirm a J-shaped relationship between alcohol consumed and ischemic stroke in both men and women. For haemorrhagic stroke, the relationship appeared close to linear in men, but remained J-shaped in women. Although the amount of alcohol reported as protective appeared much higher than previously reported (e.g. 1-4 drinks/day were found protective for ischemic stroke in women), the authors recommend that, for cardio-protective benefit, consumption be limited to 2 or fewer drinks per day.

Type of Alcohol. Data from the Copenhagen City Heart Study was used to examine whether the type of alcohol consumed was related to the apparent decreased risk of ischemic stroke with moderate alcohol consumption (Truelsen et al., 1998). The overall beneficial effect of moderate alcohol consumption was confirmed; however, the benefit was seen mostly among those individuals who consumed wine. Wine drinking on a daily, weekly or monthly basis was associated with reduced risk of ischemic stroke (RR=0.68, 0.66, 0.88 respectively, after adjustments for age, sex, smoking, BMI, physical activity, systolic BP, cholesterol, antihypertensive treatment, triglycerides, education and diabetes mellitus). No similar effect was demonstrated among drinkers of beer or spirits. Both Kiechl et al.(1998) and Sacco et al. (1999) reported the greatest risk reduction (RR= 0.41 & 0.40 respectively) among wine drinkers; however, this was not significantly lower than among drinkers of beer, liquor or a combination of types of alcohol.

Various mechanisms for the observed protective effect of alcohol, and particularly wine, have been proposed including actions on the coagulation system and/or processes of atherogenesis including modification of serum cholesterol and antiplatelet effects (Kiechl et al., 1998; Orgogozo & Renaud, 2001; Truelsen et al., 1998). Differences associated with wine, and particularly red wine, may be attributable to the anti-oxidant effects of tannins (Orgogozo & Renaud, 2001).

Patterns of Consumption. It has also been suggested that the pattern of consumption may account for the difference in effect between wine and other alcoholic beverages. Wine is typically consumed in a more regular fashion, with meals, whereas beer and spirits are consumed in a more irregular fashion and may be more often associated with binge drinking. Sundell et al. (2008) conducted an analysis of data from the FINNRISK surveys. A cohort of 3,558 individuals with a pattern of alcohol consumption classified as binge-drinking (≥6 drinks of the same beverage type on a single occasion for men or ≥4 drinks for women) were compared to 12,407 individuals with no binge drinking. Overall, the risk for any type of stroke was significantly greater among binge drinkers (HR=1.85, 95% CI 1.35 – 2.54) when adjusted for average alcohol consumption, gender and age. Among binge drinkers, there was a significant increase in risk for ischemic stroke (adj. HR = 1.99, 95% CI 1.39-2.87) but not haemorrhagic stroke (adj. HR=1.50, 95% CI 0.79-2.83). Lack of association between heavy drinking and hemorrhagic stroke may have been influenced by the relatively few haemorrhagic strokes reported (Sundell et al., 2008).

Conclusions Regarding Alcohol Consumption on Stroke Risk

There is level 1a evidence that light (1-2 drinks per day) alcohol consumption reduces the risk for ischemic stroke while heavy drinking (>5 drinks per day) and binge-drinking increase the risk of haemorrhagic stroke in a linear dose-dependent fashion.

Heavy alcohol consumption and binge drinking increases the risk of stroke. Light to moderate consumption (<2 drinks per day) may be beneficial, especially when drinking wine (versus beer or liquor).

8.7.4.1 Treatment Recommendations

While there is a convincing amount of observational evidence supporting the protective association between moderate alcohol consumption and risk of ischemic stroke, it has not been tested by means of a randomized controlled trial. While moderate drinking seems to provide a protective effect, it would not be prudent to suggest that abstainers begin drinking to reduce risk of stroke. However, individuals who currently consume 1 – 2 drinks per day need not discontinue this practice (Patra et al., 2010). Additionally, Sacco et al. (1999) demonstrated that heavy drinkers who decreased or discontinued their intake of alcohol likewise decreased their risk of ischemic stroke. Current Canadian best practice recommendations

(Coutts et al. 2015) suggest that consumption be limited to 3 or fewer standard drinks per day; ≤15 drinks per week for men and ≤10 for women (See Table 8.7.4.1.1).

Table 8.7.4.1.1 Canadian Stroke Best Practice Recommendations: Alcohol Consumption (Coutts et al. 2015)

- Excessive alcohol intake increases the risk of ischemic stroke and intracranial hemorrhage. Counsel and educate individuals with stroke to avoid heavy alcohol use.
- Following Canada's Low-Risk Alcohol Drinking Guidelines is recommended:
    - For women, no more than 10 drinks per week, with no more than 2 drinks per day most days and no more than 3 drinks on any single occasion.
    - For men, no more than 15 drinks per week, with no more than 3 drinks per day most days and no more than 4 drinks on any single occasion.

Conclusions Regarding Canadian Stroke Best Practice Recommendations for Alcohol Consumption

Women are encouraged to restrict intake of alcohol to 10 drinks per week (with ≤2 drinks per day) and men to no more than 15 drinks per week (with ≤3 drinks per day.

8.7.5 Behavioural Change

People at high risk for stroke often have multiple risk factors, a number of which have the potential to be affected by a change in lifestyle. In a study of the prevalence of behavioural risk factors following stroke based on data in the South London Stroke Register (UK), Redfern et al.(2000) reported that a substantial proportion of patients with behavioural risk factors at the time of the stroke event (smoking, obesity and alcohol consumption greater than the recommended weekly limit) did attempt to modify their lifestyle post-stroke. By one-year post-stroke, 41.4% of smokers had quit smoking, 85% excessive alcohol drinkers had reduced their consumption to below recommended weekly limits and 41.1% of obese patients were no longer obese. Most changes occurred within 3 months of the index event.

Medical treatment of one or more of these risk factors might be supplemented by an effective behavioural intervention strategy. A trial of health promotion strategies among patients with a history of angina demonstrated that personal health education is able to improve exercise and dietary habits (Cupples & McKnight, 1994), though the effects of intervention diminish over time in the absence of ongoing support (Cupples & McKnight, 1999).

Despite the importance of personal health education and its potential impact on behavioural change, the frequency with which lifestyle preventative advice is provided and documented remains low and poor, respectively (Lager et al., 2012). In a study based on the Behavioral Risk Factor Surveillance System of the Centers for Disease Control and Prevention in the United States, Greenlund et al. (2002) reported that persons with stroke were significantly more likely than non-stroke individuals to receive advice regarding diet and exercise from their physicians (OR = 1.7 and 1.5, respectively). However, only 61% of individuals with a history of stroke received advice on diet and 64% received advice regarding exercise. A far greater proportion of patients receiving professional advice reported eating fewer foods high in fat and cholesterol and participating in exercise than patients who received no physician advice (85% vs. 56% and 76.5% vs. 38.5%, respectively). Studies in primary prevention among high-risk populations such as the Risk Factor Intervention Study (see Table 8.7.5.1) suggest that supplementary, non-pharmacological interventions may assist in reducing the risk of stroke among high-risk populations (Fagerberg et al., 1998).

Studies examining behavioural interventions for reduced risk of secondary stroke are summarized in Table 8.7.5.1.

Table 8.7.5.1 Summary of Multi-factorial Behavioural Intervention on Secondary Prevention

Author, Year Study Design (Pedro Score) Sample Size	Intervention	Main Outcome(s) Result
Risk Factor Intervention Study (RIS) Fagerberg et al. (1998) RCT (7) N=508	E: Multifactoral, behavioural intervention to change eating habits + smoking cessation program C: Usual care	• Incidence of cardiovascular events (+) • Serum concentration of total cholesterol (+); LDL cholesterol (+); blood glucose (+) • Smoking cessation rate (+) • Mortality (+)
Nolan et al. (2012) RCT (5) N=387	E : E-counselling protocol C : Waitlisted control group	• SBP (+) • Pulse pressure (+) • Total cholesterol (+)
Evans-Hudnall et al. (2012) RCT (4) N=52	E: Secondary Stroke Prevention (STOP) program C: Usual care	• Stroke knowledge (+) • Tobacco cessation and alcohol use (+)

+ Indicates statistically significant differences between treatment groups
- Indicates non-statistically significant differences between treatment groups

Discussion

All of the behavioural interventions included in Table 8.7.5.1 reported improvements in factors associated with secondary stroke prevention. Among a male population at high cardiovascular risk with treated hypertension, Fagerber et al. (1998) examined the effect of a multi-factorial behavioural intervention including group meetings to discuss smoking cessation and improved eating habits versus usual care according to clinical practice. The treatment led to significantly reduced risk of cardiovascular events, incidence of stroke, smoking rates and lower serum cholesterol concentrations. In another RCT involving hypertensive patients, Nolan et al. (2012) compared a four month e-counselling protocol (encouraging healthy change of diet, exercise and smoke-free living to control blood pressure) to a waitlisted control group provided only general information on heart-healthy living. While no differences were found by intention to treat analysis due to contamination between the two groups, per protocol analysis presented significant improvements in systolic blood pressure and total cholesterol for patients in the treatment group receiving over eight e-counselling messages when compared to the control group.

Three of the studies included in Table 8.7.5.1 involved subjects with previous stroke or transient ischemic attack (TIA). Prior et al. (2011) tested a comprehensive cardiac rehabilitation (CCR) program among a sample of individuals with history of mild disabling stroke or TIA. Group orientation sessions, and smoking cessation, exercise and nutrition programs were all included as part of the CCR program. Overall, significant improvements were observed for a multitude of factors indicative of recurrent stroke, including; aerobic capacity, total cholesterol with/without high-density lipoprotein, triglycerides, waist circumference, body mass index and body weight. Additional, but not significant, improvements included low-density lipoprotein, high-density lipoprotein, and systolic and diastolic blood pressure. However, half of the smoking subjects quit the program before the end of the six month program. Evans-Hudnall et al. (2012) found that a Secondary Stroke Prevention (STOP) program aimed at improving stroke knowledge and modification of behaviour for healthier living increased stroke knowledge, smoking cessation rate and alcohol consumption among a sample of first ever stroke patients when compared to usual care. Finally, among stroke survivors included in a study addressing stroke prevention with the Masterstroke program, successive sessions of exercise training and stroke education over a nine week period improved fat, fibre and salt intake, functional balance, stroke knowledge and quality of life (J. H. White et al., 2013).

Conclusions Regarding Multi-factorial Behavioural Intervention on Secondary Prevention

There is level 1b evidence that a multi-factorial behavioural intervention focussing on eating habits and smoking cessation may substantially improve smoking cessation, mortality, and serum cholesterol and glucose concentrations, and reduce the risk of cardiovascular events.

There is level 1b evidence that a program of e-counselling that promotes self-directed lifestyle change in the area of diet, exercise and smoking cessation may be associated with reductions in systolic blood pressure and total cholesterol.

There is level 2 evidence that the Secondary Stroke Prevention Program (STOP) may improve stroke knowledge, smoking cessation and alcohol use when compared to usual care.

Behavioural intervention may be an effective means to reduce stroke risk and prognostic factors involved in secondary prevention. Further research is required to gain an understanding of how behavioural change occurs for the optimal promotion of healthy lifestyles.

8.7.5.1 Developing Behavioural Change Programs

The Heart and Stroke Ontario Clinical Guidelines (2003) note that psychological factors, such as anxiety and depression, play a well-established role in unhealthy lifestyle choices, which in turn contribute to stroke risk factors. Behavioural change strategies have been well studied in eating disorders and substance abuse as well as in risk factor modification in a variety of disease states but not in stroke. Nevertheless, the potential effectiveness of efforts designed to promote healthy behaviours such as active lifestyles, healthy eating, smoking cessation, moderating alcohol consumption and reducing stress is intuitively apparent.

On the basis of other populations and the lack of data to guide the development of behavioural modification strategies to change unhealthy behaviours, The Heart and Stroke Guidelines (2003) note, "in stroke populations, the following principles are advocated:

- Clinical skills in health education and in psychology and psychiatry, including psychotherapeutic skills, are central to the design and implementation of effective programs. It is therefore crucial to include a psychologist as a member of, or consultant to, the clinical team designing and implementing stroke prevention strategies that target behavioural change. It is also important to maintain a commitment to the continuing education of clinicians working in this area.

- An understanding of the mechanisms mediating maladaptive healthcare choices, the factors hampering behavioural change, and the literature about behavioural change in various populations is critical to developing effective strategies. Interventions should be theoretically driven, but there is insufficient supporting evidence for any specific theory to guide the development of behavioural interventions in stroke prevention.

- Interventions required for behavioural change may differ among subgroups within the stroke prevention population. While some patients may require education, others may also require additional interventions, such as psychotherapeutic strategies. Although knowledge, motivation, and

readiness for change are necessary, they are generally insufficient to create enduring behavioural change. It is therefore important to tailor the behavioural change strategy to the individual.

- Studies of other clinical populations have demonstrated that neurocognitive difficulties, stress, health-related attitudes, readiness for change, and psychopathology can all influence maladaptive choices and the efficacy of any interventions. It is important to use patient assessment information, theoretical frameworks, and the clinical literature on behavioural change to directly guide treatment.

- Factors that promote the initiation of change may not be the same across target behaviours, such as healthy eating, smoking cessation, and increasing activity. They may also differ from factors involved in maintaining behavioural change across different target behaviours.

- It is important that programs provide a prescription for changing behaviour, use goal setting and employ clinical strategies to help the individual move through behavioural change, maintenance and relapse avoidance. Studies in several populations have demonstrated the efficacy of cognitive-behavioural psychotherapeutic strategies.

- Finally, it is important to measure changes in behaviour, not simply self-reports of behavioural change, as self-reported behavioural change may not correlate with actual behavioural change."

Conclusions Regarding the Development of Behavioural Change Programs

Knowledge transfer among clinicians for the application of updated behavioural strategies is essential for optimal alteration of maladaptive habits. Personally designed cognitive behavioural programs targeting the individual and a specific maladaptive behaviour may be most beneficial. Self-reports of change should be prohibited.

Summary

1. ***There is level 1a evidence that engaging in physical activity is associated with substantial benefits in terms of a reduced risk for stroke and cardiovascular disease. A dose-response relationship may exist between exercise and stroke risk. Conflicting level 1a evidence from a meta-analyses of 10 cohort studies suggests that this relationship may only be significant for men.***
2. ***There is level 1a evidence that moderate to high levels of leisure and occupational activity may be beneficial for a reduced rate of cardiovascular disease compared to low level exercise.***
3. ***There is level 1b evidence that a detailed, personalized activity program with regular verbal instruction and encouragement does not effectively increase level of physical activity when compared to the provision of basic information regarding physical activity and no training program.***
4. ***There is level 1a evidence that low-fat, low-cholesterol diets rich in fruits, vegetables and low-fat dairy products are effective in reducing blood pressure when compared to control diets low in fruits and vegetables, and with average fat content.***
5. ***There is level 1a evidence that Mediterranean type diets (rich in whole grains, fruits, vegetables, legumes, walnuts, almonds and alpha-linolenic acid) may improve blood pressure and reduce risk of cardiovascular events including stroke when compared to a prudent type diet.***
6. ***There is level 1a evidence that the use of vitamin C and vitamin E together may reduce atherosclerotic progression.***
7. ***There is level 1a evidence that vitamin E may not affect the incidence of cerebrovascular accidents, and all-cause/cardiovascular mortality while use of β-carotene may be associated with an increase in cardiovascular and all-cause mortality when compared to control.***
8. ***There is conflicting level 1b evidence suggesting variable efficacy of daily antioxidant vitamins (vitamin E, vitamin C and β-carotene) when used alone on clinical cardiovascular endpoints including stroke, and mortality. Additional level 1b evidence suggests a beneficial effect of combinatorial therapy with ascorbic acid (vitamin C) and vitamin E on stroke risk.***
9. ***There is level 1a evidence that vitamin B therapy may improve flow-mediated dilation (FMD) in the short-term however, no long-term effects on FMD or carotid intima-media thickness are observed.***
10. ***There is conflicting level 1a evidence regarding the effect of B-vitamins (folic acid, vitamin B6 and B12) on cardiovascular outcome or risk of stroke.***
11. ***There is level 1a evidence that supplementation with folic acid and vitamins B_6 and B_{12} is associated with significant reductions in plasma homocysteine levels (tHcy) up to one year from baseline.***
12. ***There is level 1b evidence that folic acid alone may have no effect on a combined cardiovascular outcome when compared to standard care.***
13. ***There is level 1b evidence that high dose vitamin B therapy concurrent with antiplatelets may increase risk of stroke versus low dose therapy. There may be no effect on incidence of stroke or a cardiovascular composite endpoint among patients not supplementing vitamin therapy with antiplatelets.***
14. ***There is level 1b evidence that homocysteine-lowering therapy with B-vitamins may not improve the risk of recurrent stroke, stroke severity or functional outcome when compared to placebo.***

15. ***There is level 1b evidence that high dose homocysteine-lowering therapy may improve risk of stroke, myocardial infarction or death in patients ≥67 years old versus low dose treatment.***

16. ***There is level 1a evidence that smoking or exposure to environmental tobacco smoke may increase risk of stroke in a dose-dependent manner.***

17. ***There is level 1b evidence that an intensive smoking cessation program providing a period of counselling and support may be as effective as a minimal intervention providing a single 30-minute session of counselling only.***

18. ***There is level 1a evidence that light (1-2 drinks per day) alcohol consumption reduces the risk for ischemic stroke while heavy drinking (>5 drinks per day) and binge-drinking increase the risk of haemorrhagic stroke in a linear dose-dependent fashion.***

19. ***There is level 1b evidence that a multi-factorial behavioural intervention focussing on eating habits and smoking cessation may substantially improve smoking cessation, mortality, and serum cholesterol and glucose concentrations, and reduce the risk of cardiovascular events.***

20. ***There is level 1b evidence that a program of e-counselling that promotes self-directed lifestyle change in the area of diet, exercise and smoking cessation may be associated with reductions in systolic blood pressure and total cholesterol.***

21. ***There is level 2 evidence that the Secondary Stroke Prevention Program (STOP) may improve stroke knowledge, smoking cessation and alcohol use when compared to usual care.***

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8.8

Atherosclerosis and Non-cardiac Embolism

Last Updated: September 2016

Key Points

- ASA monotherapy may reduce the risk of a second ischaemic stroke.
- Treatment with clopidogrel may be as effective as ticlopidine for prevention of recurrent stroke, but has fewer adverse effects.
- For individuals with previous stroke/TIA, treatment with cilostazol may be more effective than ASA in the prevention of recurrent strokes and haemorrhagic events.
- The use of Lotrafiban (a glycoprotein IIb/IIIa inhibitor) for the secondary prevention of stroke is associated with excessive bleeding incidents.
- In the prevention of recurrent stroke, the combination of clopidogrel and ASA is not more effective than either clopidogrel or ASA alone however it is also significantly associated with an increased incidence of major bleeding events.
- ASA in combination with dipyridamole may be more effective than ASA alone in reducing the risk for recurrent stroke. Reported side effects associated with the use of combination therapy (i.e., dipyridamole with ASA) include headaches and diarrhea.
- ASA + extended release dipyridamole and clopidogrel monotherapy may have a similar effect on rates of recurrent stroke.
- Triple antiplatelet therapy with aspirin, cilostazol and clopidogrel is comparable to dual antiplatelet therapy with aspirin and clopidogrel regarding its effects on mortality, stroke and bleeding.
- The impact of combination antiplatelet therapy on functional outcome is unclear.
- Anti-coagulant therapy is as effective as antiplatelet therapy in preventing the occurrence of death or stroke however, it may increase the risk of bleeding more than antiplatelet therapy.
- Acetylsalicylic acid (80mg to 325mg), combined acetylsalicylic acid (25mg) and extended-release dipyridamole (200mg), or clopidogrel (75mg) are all appropriate options and selection should depend on the clinical circumstances.
- Short-term concurrent use of ASA and clopidogrel (up to 90 days) has not shown an increased risk of bleeding; however, longer-term use is not recommended for secondary stroke prevention, unless there is an alternative indication due to an increased risk of bleeding and mortality.
- The combination of ASA (81mg) and clopidogrel 75mg is still of uncertain benefit in the Canadian setting for early prevention of recurrent stroke when used within 90 days, and should not be routinely used in all patients.
- At the present time, there is not enough evidence to guide management if a patient has a stroke while on a specific antiplatelet agent. In all cases of recurrent stroke while on antiplatelet therapy, all other vascular risk factors should be reassessed and aggressively managed.

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8.8 Atherosclerosis and Non-cardiac Embolism

In addition to treatment of identified, modifiable risk factors, secondary prevention should include treatment or prophylaxis based on the underlying etiology of the primary event. Specific mechanisms of ischemia are associated with corresponding treatments or prophylaxes as illustrated in Table 8.8.1 (Diener & Ringleb, 2002).

Table 8.8.1 Mechanisms of Stroke and Secondary Prevention

Underlying Etiology	Treatment/Prophylaxis
Atherosclerotic plaque/atherothrombosis	Antiplatelet therapy
Cardiac abnormalities (cardiogenic emboli)	Anticoagulation therapy
Internal Carotid Artery (ICA) stenosis (severe occlusion)	Reperfusion techniques

An analysis of data from nine clinical trials, examining the effects of acetylsalicylic acid (ASA; also known as aspirin) post-stroke, revealed that patients with stroke from an arterial, rather than cardiac, origin are more likely to be younger, a smoker and less likely to have a history of hypertension (Ariesen et al., 2004). The vast majority of all strokes are ischaemic and caused by atherothrombotic or thromboembolic occlusion. Common sites for thrombus formation include the extracranial cerebral arteries, the heart, the small penetrating arteries of the brain (as in the case of lacunar infarcts), and aortic arch plaque (Easton, 2001a; Goldszmidt & Caplan, 2003). Blood factors (clotting agents), primarily platelets and fibrin, aggregate on diseased or damaged arteries and promote the formation of thrombi which can occlude the artery at the site of formation or embolize and cause an occlusion at a different location. As such, platelets and the mechanisms of adhesion, activation and aggregation occurring at the site of arterial damage play an important role in thrombus development and progression of atherothrombosis (Easton, 2001a; Goldszmidt & Caplan, 2003; Serebruany et al., 2004). Antiplatelet therapy is used to disrupt platelet mechanisms particularly with regard to non-cardiac thrombosis.

8.8.1 Antiplatelet Therapy

The Antithrombotic Trialists' Collaboration meta-analysis of randomized trials of preventive antiplatelet therapy in high-risk patients reviewed 287 studies available by September 1997 (Antithrombotic Trialists' Collaboration, 2002). More than 77,000 patients were included in trials comparing antiplatelet regimens, and 135,000 patients were included in trials comparing active therapy versus a control. In high-risk patients, antiplatelet therapy reduced nonfatal myocardial infarction (MI) by one-third, nonfatal stroke by one-quarter, and vascular death by one-sixth. In high-risk individuals with a history of previous stroke or TIA, antiplatelet therapy was associated with a decrease in risk of ischaemic stroke (OR=0.75) and a corresponding increase in risk for haemorrhagic stroke (OR=1.2) (Antithrombotic Trialists' Collaboration, 2002).

Antiplatelet therapy is associated with an increased risk for bleeding; however, the benefits of antiplatelet therapy seem to outweigh the risks for the most part. A 25% reduction in risk of stroke carries with it the risk of approximately 1-2 additional major extracranial bleeds per 1000 patients per year (Antithrombotic Trialists' Collaboration, 2002). Given the magnitude of benefit and relatively few risks, antiplatelet therapy has become central to the secondary prevention of stroke (Diener & Ringleb, 2002). Unless there is a definite contraindication, antiplatelet therapy should be considered for anyone who is considered to be at an increased risk for the development of occlusive vascular disease (Antithrombotic Trialists' Collaboration, 2002). Unfortunately, results of the GIFA study demonstrated that a large proportion of patients with TIA and/or stroke are still discharged from hospital without either antiplatelet or

anticoagulant therapy (Volpato et al., 2004). Treatment with antithrombotic therapy was inversely associated with functional disability and cognitive impairment such that patients with increasing levels of cognitive impairment or severe disability were the least likely to receive antithrombotic medication (OR=0.26 and OR=0.27, respectively) (Volpato et al., 2004).

There are several different types of antiplatelet therapy, each using different mechanisms to disrupt platelet processes; these include ASA monotherapy, thienopyridines (which include clopidogrel and ticlopidine), combination therapy (more than one antiplatelet agent) and anticoagulants. The most commonly used agent in antiplatelet therapy is ASA.

8.8.1.1 Monotherapies

8.8.1.1.1 Aspirin (ASA)

ASA is the least expensive, most widely studied and most commonly used antiplatelet agent (Easton, 2001a; Goldszmidt & Caplan, 2003; MacWalter & Shirley, 2002). ASA is a cyclo-oxygenase inhibitor. It blocks the formation of thromboxane A2 (a platelet aggregating prostaglandin) by acetylation of the enzyme cyclo-oxygenase, which reduces the likelihood for thrombus formation by interfering with platelet aggregation. However, for the duration of its presence in the cells, ASA also inhibits the production of prostacyclin, an anti-aggregating prostaglandin produced in endothelial cells. Low dose ASA may effectively block thromboxane A2 formation while not substantially inhibiting the production of prostacyclin (Easton, 2001a). ASA has been shown to significantly reduce the risk for stroke when given after a TIA (Acelajado & Oparil, 2012).

In an extensive meta-analysis, the Antithrombotic Trialists' collaborative (ATTC) (2002) found that treatment with ASA reduced the risk of vascular events in high-risk patients (including recurrent stroke) by 23%. Algra and van Gijn (1999) performed a mini-meta-analysis of 10 trials evaluating the benefit of ASA monotherapy in patients with prior stroke or TIA and found that ASA reduced the odds of stroke, myocardial infarction or vascular death by 16% and the relative risk reduction when compared to placebo was 13%.

An update to the ATTC meta-analysis demonstrated that, based on individual participant data from 16 secondary prevention trials, ASA therapy was associated with a significant reduction in risk for vascular events (RR=0.81, 95% CI 0.75 – 0.81) including ischemic stroke (RR=0.78, 95% CI 0.61-0.99) (Baigent et al., 2009). This represented an absolute reduction in rate of stroke of 0.46% per year. Treatment with ASA was also associated with a non-significant increase in risk for haemorrhagic stroke (HR=1.67, 95% CI 0.81-3.44). Hypothetical calculations regarding absolute effects of allocation to treatment with ASA on 5-year outcomes suggested that the reduction of secondary vascular events would exceed the accompanying increase in bleeding events, regardless of age or sex (Baigent et al., 2009).

Given the established effectiveness of ASA as an antiplatelet therapy, a number of studies have focused on the issue of optimal dosage and timing for the initiation of treatment. Studies investigating dosage and timing of ASA monotherapy are summarized in Table 8.8.1.1.1.1.

Table 8.8.1.1.1.1 Summary of Studies Evaluating of ASA Monotherapy Post-stroke Trials

Author, Year Study Design (PEDro Score) Sample Size	Intervention	Main Outcome(s) Result
SALT	E: Aspirin (75mg/d)	• Risk of stroke or death (+)

Swedish ASA Low-dose Trial (1991) RCT (8) N=1360	C: Placebo	• Self-reported "bleeding episodes" C (+)
CAST Chinese Acute Stroke Trial Collaborative Group (1997) RCT (8) N=21106	E: Aspirin (160mg/d) C: Placebo	• Incidence of death or nonfatal stroke (+) • Incidence of ischaemic stroke (+) • Incidence of haemorrhagic stroke (-)
Dutch TIA Trial Study Group (1991) RCT (7) N=3131	E1: 30mg water-soluble aspirin E2: 283mg water-soluble aspirin	• Minor bleeding reports E1 (+)
IST International Stroke Trial Collaborative Group (1997) RCT (5) N=19435	Heparin groups E_H: Heparin (5000 or 12500IU bd, 2/d) C_H: No heparin Aspirin groups E_C: Aspirin (300mg/d) C_C: No aspirin	• Incidence of death or nonfatal recurrent stroke: Heparin (-); 5000 vs. 12500 IU bd (+); E_C (+) • Transfused or fatal extracranial bleeds: C_H (+); 5000 vs. 12500IU bd (+) • Incidence of haemorrhagic stroke: 5000 vs. 12500 IUbd, (+); Aspirin (-) • Transfused or fatal extracranial bleeds: C_C (+) • Incidence of recurrent ischaemic stroke: E_C (+) • 14d mortality: Aspirin (-)
Brighton et al. (2013) RCT (3) N_{Start}=109 N_{End} =109	E: Aspirin (100mg) C: Placebo	• Recurrence of venous thromboembolism (-) • Incidence of vascular events (myocardial infarction, stroke, cardiovascular death) (+)
Georgiadis et al. (2013) Quasi-experimental *Post hoc analysis of two RCTs* N_{Start}=1899 N_{End} =1899	E: Aspirin treatment failure C: No aspirin	• Incidence of stroke and/or death (-)

+ Indicates statistically significant differences between treatment groups

- Indicates non-statistically significant differences between treatment groups

Discussion

Table 8.8.1.1.1.2 ASA Dose Regimens, Associated Risk Reduction and Proportional Increase in Risk for Major Extracranial Bleed*

ASA Dose/Day	Risk Reduction	Risk of Major Extracranial Bleed *OR ASA versus Control (95% CI)*
<75mg	13%	1.7 (0.8 – 3.3)
75 – 150mg	32%	1.5 (1.0 – 2.3)
160 – 325mg	26%	1.4 (1.0 – 2.0)
500 – 1500mg	19%	N/a
**(Antithrombotic Trialists' Collaboration, 2002)*		

The optimal dose of ASA has still not been established formally. However, it is generally agreed that high doses are not necessary and in fact may be counterproductive. In their 2002 meta-analysis, the Antithrombotic Trialists' Collaboration reported that doses of 75-150mg/day appeared to have the greatest effect reducing the risk for ischaemic stroke by 32% (see Table 8.8.1.1.1.2). It has been reported that risk for major bleeding associated with ASA therapy has not been found to be dose dependent and is similar with all levels of daily dosages under 325mg (Antithrombotic Trialists' Collaboration, 2002; Diener & Ringleb, 2002). A meta-analysis of bleeding complications in antiplatelet therapy reported low-dose ASA (<100mg/day) to be associated with the lowest risk (3.6%) for

haemorrhagic events (including both major and minor events) while doses in excess of 100mg/day were associated with a relatively high risk (9.1%) (Serebruany et al., 2004). Enteric-coated preparations are recommended to reduce the incidence of gastrointestinal side effects (Diener & Ringleb, 2002).

The IST and CAST trials examined the effects of introducing ASA therapy in the acute phase post-stroke. Meta-analyses of the data from these studies revealed a 13% reduction in the risk for recurrent stroke and mortality (Algra & van Gijn, 1999; Diener & Ringleb, 2002). The Antithrombotic Trialists' Collaboration (2002) reported that antiplatelet therapy in acute stroke patients resulted in nine fewer strokes for every 1000 patients treated. With prolonged therapy (mean=29 months), this number increased to 36 per 1000 (Antithrombotic Trialists' Collaboration, 2002). A less reliable study (Brighton et al., 2013) also reported a decrease in incidents of stroke in patients who received 100 mg of ASA compared to the placebo control group, however this study only contained 109 patients. Therefore, ASA therapy should be initiated acutely post-stroke and continued over the long-term for maximum benefit.

Discontinuation of ASA therapy may be associated with increased risk for recurrent stroke. In a recent study of primary care patients with previous cerebrovascular or cardiovascular patients in the UK, discontinuation of ASA therapy prescribed for secondary prevention 31-180 days prior to the recurrent event was associated with increased overall risk (RR=1.4, 95% CI 1.03-1.92) when compared to continuous therapy (Garcia Rodriguez et al., 2011). Increased risk for stroke or TIA was significant only for those individuals who were classified as non-adherent (i.e. discontinuation that could not be explained by physician-initiated therapy change, safety concerns, intolerance, drug interaction, or use of over-the-counter ASA) (Garcia Rodriguez et al., 2011).

ASA monotherapy may not be equally effective in all high-risk groups. In a meta-analysis of data from 21 studies (17 RCTs and 4 cohort) reporting mortality and cardiovascular events in individuals with diabetes, overall pooled relative risk for death was 0.93 (95% CI 0.81-1.07) (Simpson et al., 2011). When stratified by ASA dose (i.e., ≤100mg, 101-325mg, or >325mg), no significant difference in risk was found. Overall, pooled risk for stroke was 0.98 (95% CI 0.81-1.16). Stratification revealed a significant reduction in risk for stroke associated with ASA dose of ≤100mg/day with no significant between-study heterogeneity (RR=0.81, 95% 0.68-0.97, p=0.02). However, when only secondary prevention studies were included in the analysis (n=13), use of ASA monotherapy was associated with lower risk of mortality from all causes (RR=0.82, 95% CI 0.69-0.98, p=0.03). Stratification by dose revealed that this appeared to be associated with doses of ≤325mg/day; however, there was significant heterogeneity associated with this analysis (Simpson et al., 2011).

Conclusions Regarding ASA Monotherapy

There is level 1a and level 2 evidence that ASA therapy effectively reduces the risk for recurrent stroke and should be initiated as soon as it is safe following the onset of the stroke event and maintained over the long-term.

ASA monotherapy may reduce the risk of a second ischaemic stroke.

8.8.1.1.2 Thienopyridines (Ticlopidine and Clopidogrel)

Where ASA therapy is contraindicated, or for those who experience stroke while on ASA therapy, thienopyridines have been investigated as an alternative. Thienopyridines are adenosine diphosphate (ADP) receptor blockers that inhibit platelet activation and aggregation induced by ADP (Easton, 2001a; Goldszmidt & Caplan, 2003; MacWalter & Shirley, 2002).

A recent review of studies examining the effectiveness of therapy with thienopyridines (ticlopidine and clopidogrel) reported that, among patients with previous TIA or stroke, thienopyridine therapy reduced the risk of vascular events and further stroke events more than ASA therapy (OR=0.90 and OR=0.86, respectively). This reduction in stroke risk is equivalent to an absolute reduction in stroke events of 16 strokes per 1000 patients (Hankey et al., 2000). An examination of adverse effects associated with the thienopyridines compared with those associated with ASA, demonstrated no significant difference between the two therapies in terms of risk of intracranial or extracranial haemorrhage. Overall, treatment with thienopyridines was associated with a reduced risk for gastrointestinal haemorrhage (OR=0.71), indigestion/nausea/ vomiting (OR=0.84) and an increased risk for diarrhea (OR=1.34 to 2.27) and skin rashes (OR=1.32 to 2.23). However, the risk profile of ticlopidine differed significantly from clopidogrel especially with regard to diarrhea, skin rashes and adverse haematological effects (Hankey et al., 2000).

8.8.1.1.3 Clopidogrel

Clopidogrel is a thienopyridine derivative that is chemically related to ticlopidine (Diener & Ringleb, 2002; Easton, 2001a; Goldszmidt & Caplan, 2003). It is faster acting than ticlopidine and has a longer duration of effectiveness (Goldszmidt & Caplan, 2003). The benefits of clopidogrel are similar to those of ticlopidine, while its side effects are similar to those observed with ASA therapy (Diener & Ringleb, 2002; Easton, 2001a). It has been argued that clopidogrel should be the antiplatelet of choice in secondary prevention of stroke as it is superior to ASA monotherapy, and has fewer side effects than extended-release dipyridamole (Aw & Sharma, 2012; Montagu et al., 2012).

There is a single, pivotal, large-scale trial assessing the efficacy of clopidogrel in comparison to ASA for patients with a history of recent cardiovascular events. The Clopidogrel versus ASA in Patients at Risk of Ischaemic Stroke (CAPRIE) study was a randomized, multi-centered trial comparing the efficacy of clopidogrel to ASA (325mg/day) in reducing the combined risk of ischaemic stroke, myocardial infarction or vascular death (CAPRIE Steering Committee, 1996). Studies examining the relative effectiveness of clopidogrel monotherapy are summarized in Table 8.8.1.2.1.1.

Table 8.8.1.2.1.1 Summary of Studies Evaluating Clopidogrel Monotherapy

Author, Year Study Design (PEDro Score) Sample Size	Intervention	Main Outcome(s) Result
CAPRIE Steering Committee (1996) RCT (8) N=19099	E1: Clopidogrel (75mg) + aspirin placebo E2: Aspirin (325mg) + clopidogrel placebo	• Incidence of ischaemic stroke, myocardial infarction or vascular mortality (+) E1
Fukuuchi et al. (2008) RCT (7) N_{Start}=1151 N_{End}=1151	E1: Clopidogrel (75mg/d) E2: Ticlopidine (200mg/d)	• Incidence of adverse events (+) E1 • Hepatic dysfunction (+) E1 • Incidence of vascular events (-)
Uchiyama et al. (2009b) RCT (7) N=1862	E1: Clopidogrel (75mg/d) E2: Ticlopidine (200mg/d)	• Clinical safety of treatment (+) E1 • Incidence of hepatic dysfunction (+) E1 • Incidence of vascular events (-)
Davidai et al.(2014) Post-hoc retrospective N_{Start}=11705 N_{End}=11705	PRoFESS trial E1: Aspirin (ASA) + extended-release dipyridamole (ER-DP) E2: Clopidogrel	• Incidence of stroke: E1 discontinued with headache (+); E2 (-); ESPS2 (-) • Mortality: E1 discontinued with headache (+); E4 discontinued with headache (+)

	ESPS2 study E3: ASA+ER-DP E4: ER-DP Note: analysis based on discontinuation due to headache vs. no discontinuation	

+ Indicates statistically significant differences between treatment groups

- *Indicates non-statistically significant differences between treatment groups*

Discussion

To assess the relative efficacy of clopidogrel and aspirin in reducing the risk of ischaemic stroke, MI or vascular death, 19 185 patients with atherosclerotic vascular disease (recent history of MI, ischaemic stroke or symptomatic peripheral artery disease) were divided into subgroups based on their history at baseline and assigned to receive either clopidogrel 325mg/day or ASA 75mg/day: (1) previous stroke patients receiving clopidogrel totaled 3 233, and those receiving ASA therapy totaled 3 198; (2) patients with previous MI receiving clopidogrel totaled 3 143, and those receiving ASA therapy totaled 3 159; and (3) patients with peripheral artery disease (PAD) receiving clopidogrel totaled 3 223 and those receiving ASA therapy totaled 3 229. The CAPRIE study demonstrated that clopidogrel was approximately as effective in reducing the risk of stroke as ticlopidine (8.7% versus approximately 10%) when compared to ASA therapy.

Post hoc analysis demonstrated that CAPRIE patients with pre-existing, symptomatic, atherosclerotic disease had elevated 3-year rates of ischaemic stroke, myocardial infarction or vascular death; this amounted to 20.4% of patients receiving clopidogrel and 23.8% of patients receiving ASA (Ringleb et al., 2004). This represented an absolute risk reduction of 3.4% (relative risk reduction=14.9%, p=0.045) associated with the use of clopidogrel. According to the analysis presented by Ringleb et al. (2004), one would need to treat 29 patients for 3 years with clopidogrel instead of ASA to prevent one ischaemic event.

The clear advantage of clopidogrel over ticlopidine lies in its improved adverse event profile. Contraindications to clopidogrel therapy include “severe liver impairment and haemostatic disorders or pathological bleeding” (Diener & Ringleb, 2002). A meta-analysis of bleeding complications associated with antiplatelet therapy found clopidogrel to be associated with an 8.5% rate of bleeding complications, which is slightly less than that associated with a treatment regimen of 100-325mg ASA/day (Serebruany et al., 2004). Clopidogrel therapy was associated with an increase of approximately 1/3 in the odds for developing a skin rash and/or diarrhea when compared to ASA (Hankey et al., 2000). This is substantially less than the reported risks associated with ticlopidine in the same analysis (p=0.0002 and p=0.00003, respectively). Neutropenia has been reported to occur in 0.1% of patients treated with clopidogrel; this is significantly less than reported for ticlopidine (p=0.003) (Hankey et al., 2000).

Two publications from Japan have reported that the efficacy of treatment with clopidogrel in the prevention of secondary vascular events in individuals with previous stroke may be similar to ticlopidine (Fukuuchi et al., 2008; Uchiyama et al., 2009b). However, treatment with ticlopidine was associated with a significantly greater risk for serious adverse events including hepatic dysfunction.

Clopidogrel is not available in generic form and is an expensive alternative to ASA (Diener & Ringleb, 2002). However, cost effectiveness analyses have proposed that, while expensive, clopidogrel is within accepted limits for cost-effectiveness (Sarasin et al., 2000; Schleinitz et al., 2004).

Conclusions Regarding Clopidogrel

There is level 1a evidence that treatment with clopidogrel may be as effective as ticlopidine in terms of prevention of secondary vascular events, including stroke.

There is level 1b evidence that clopidogrel may be similar to ASA with regard to safety.

There is level 1a evidence that treatment with ticlopidine may be associated with a significantly greater risk for adverse events, including hepatic dysfunction, than clopidogrel.

Treatment with clopidogrel may be as effective as ticlopidine for prevention of recurrent stroke, but has fewer adverse effects.

8.8.1.1.4 Cilostazol

As an antiplatelet agent, Cilostazol inhibits primary and secondary platelet aggregation and has been associated with significantly greater reduction in platelet aggregation than ASA (Gotoh et al., 2000). As such, its effectiveness in the prevention of stroke has been assessed in several randomized controlled trials. Uchiyama et al. (2009a) undertook a systematic review and meta-analysis of randomized controlled trials that included patients with a history of cardiac or cerebrovascular events or peripheral artery disease and evaluated the impact of cilostazol therapy on the outcomes of ischemic or haemorrhagic stroke. Twelve trials were identified for inclusion; however, only two of these focussed on patients with previous stroke. Overall, treatment with cilostazol was associated with a significant reduction in risk for cerebrovascular events (RR=0.58, 95% CI 0.43-0.78) when compared to a placebo condition. In addition, cilostazol therapy was not associated with increased risk of serious bleeding events, overall (RR=1.0, 95% CI 0.66-1.51) (Uchiyama et al., 2009a). Similarly, a recent systematic review studies evaluating the safety and efficacy of cilostazol in the secondary prevention of atherosclerotic ischemic stroke. Three clinical trials were reviewed (one placebo-controlled, two ASA-controlled), all of which were conducted in either Japan or China. It was concluded that cilostazol may be safer and more effective than ASA in the secondary prevention of stroke in Asian patients. These studies examining the use of cilostazol therapy for the prevention of stroke in individuals with previous stroke or TIA are summarized in Table 8.8.1.1.4.1.

Table 8.8.1.1.4.1 Summary of Studies Evaluating Cilostazol and the Prevention of Recurrent Stroke

Author, Year Study Design (PEDro Score) Sample Size	Intervention	Main Outcome(s) Result
CSPS (2000) RCT (9) N_{Start}=1095 N_{End}=1052	E: Cilostazol (100mg, 2/d) C: Placebo	• Incidence of recurrent stroke (+) • Combined outcome (ischemic stroke, intracranial haemorrhage, transient ischemic attack) (+) • Incidence of bleeding events (-)
CASISP Investigators (2008) RCT (9) N=720	E: Cilostazol (200mg, 2/d) C: Aspirin (100mg/d)	• Incidence of any recurrent stroke (-) • Incidence of cerebral bleeding (+)
CSPS-2(2010) RCT (7) N=2757	E: Cilostazol (100mg, 2/d) C: Aspirin (80mg/d)	• Incidence of stroke (+) • Incidence of haemorrhagic events (+) • Combined enpoint (stroke, TIA, angina pectoris, MI, heart failure, any hospitalization requiring haemorrhage) (+)
Shimizu et al. (2013) RCT (5	E: Cilostazol (200mg/d) C: no treatment	• Stroke progression (-) • Cerebrovascular events (-)

N_{Start}=510 N_{End}=476		

+ Indicates statistically significant differences between treatment groups
- Indicates non-statistically significant differences between treatment groups

Discussion

A single randomized controlled trial has investigated the effectiveness of cilostazol therapy when compared to a placebo condition. All other identified trials have compared the use of cilostazol with ASA. The sole trial that examined the impact of cilostazol on the progression of symptomatic stenosis compared the addition of cilostazol to ASA with ASA monotherapy.

In a secondary analysis of the CSPS 2 study, Uchiyama et al. (2014) evaluated the risk of bleeding following cilostazol therapy versus monotherapy with aspirin. The incidence of hemorrhagic stroke in patients with previous lacunar strokes was significantly reduced after therapy with cilostazol relative to aspirin monotherapy (Uchiyama et al. 2014). This effect however, was no observed among patients with prior atherothrombotic strokes, demonstrating no significant difference in the incidence of hemorrhagic strokes between the two treatment groups. Cilostazol monotherapy also resulted in a reduced incidence of hemorrhagic strokes, cerebral hemorrhage, overall hemorrhage requiring hospitalization, and gastrointestinal bleeding requiring hospitalization versus aspirin monotherapy (Uchiyama et al. 2014). Despite the benefits observed with the use of cilostazol, the study has several limitations that prevent the generalizability of these findings. First, the study included only Japanese patients which may have biased the results towards this particular ethnic group. Secondly, the number of male participants (78%) in the experimental group outweighed the number of female participants (22%). This effect was not as pronounced in the control group, as male participants accounted for 54% of the sample, while females made up the remaining 46%. The difference in gender proportions between the two groups may have led to biases in the interpretation of these results given that more males were present in the experimental group than the control group despite a relatively even distribution of sample sizes across the groups (i.e., experimental group N=83; control group N=80).

Another open-label study conducted in Japan evaluated the effects of cilostazol in patients with acute noncardioembolic ischemic stroke over the course of 3 months (Shimizu et al. 2013). The study randomized a total of 510 patients either to an experimental group receiving 200mg/d of cilostazol or to a control group which did not receive treatment. Stroke progression was defined by a change in the modified Rankin Scale (mRS) scores from 0 to 1 and from 0 to 2, as well as changes in the National Institute of Health for Stroke Scale (NIHSS) scores by more than 4 points. The study found no significant difference in the progression of stroke or in the number of cardiovascular events which included cerebral infarction, intracerebral or subarachnoid hemorrhage, and congestive heart failure between the two groups. Overall, no benefit for the use of cilostazol in patients with acute ischemic stroke was found. Results are however, to be interpreted with caution as the study did not use a proper placebo protocol for the control group, and like Uchiyama et al. 2014, all of the participants were of Japanese ethnicity. The lack of blinding may have also biased the results.

A Cochrane meta-analysis examined the effectiveness of cilostazol therapy for the prevention of recurrent stroke events in individuals with previous stroke or TIA when compared to ASA monotherapy (Kamal et al., 2011). Two trials were identified for inclusion: CASISP and CSPS-2 (see Table 8.8.1.1.4.1). The authors reported that, on the basis of data from 3477 participants, treatment with cilostazol was associated with a lower risk for a composite outcome of “vascular events” (pooled RR=0.72, 95% CI 0.57-0.91) as well as for haemorrhagic stroke (pooled RR=0.26, 95% CI 0.13-0.55). In addition, cilostazol was associated with

increased risk for minor adverse effects including headaches, gastrointestinal intolerance, dizziness, palpitations and tachycardia (Kamal et al., 2011).

Cilostazol was compared to ASA monotherapy in another meta-analysis which identified a total of 4 trials, (Dinicolntonio et al. 2013). Results show that compared to ASA, cilostazol reduced the risk of hemorrhagic stroke by 73%. Similarly, the composite endpoint of stroke, myocardial infarction, or vascular death was reduced by 28% after cilostazol monotherapy. Further significant findings were reported in the ability of cilostazol to reduce the risk of total hemorrhagic events by 48% relative to ASA monotherapy. The risk of gastrointestinal bleeds however, was not found to differ between cilostazol monotherapy and ASA monotherapy.

A recent meta-analysis evaluated the benefits and safety of cilostazol in patients with ischemic stroke (Tan et al. 2015). The study included a total of 9 studies, which synthesized results from 6328 participants. In the control group, stroke recurrence occurred in 8.3% of the population, while in the groups receiving cilostazol, the stroke recurrence was significantly lower (5.3%) (Tan et al. 2015). A similar trend was observed for poststroke intracerebral hemorrhage (1.6% vs. 0.5%), and in poststroke extracranial bleeding complications (3.9% vs. 2.4%). The meta-analysis however, found no significant difference between cilostazol and the control monotherapy in nonfatal stroke, intracranial hemorrhage, and transient ischaemic attack (Tan et al. 2015).

Conclusions regarding Cilostazol Therapy

There is level 1a evidence suggesting that cilostazol is superior to aspirin monotherapy in reducing the risk of recurrent stroke and hemorrhagic events however, it is unclear whether its use results in an increased risk of gastrointestinal bleeds.

For individuals with previous stroke/TIA, treatment with cilostazol may be more effective than ASA in the prevention of recurrent strokes and haemorrhagic events.

8.8.1.1.5 Glycoprotein IIb/IIIa Inhibitor

Glycoprotein (GP) IIb/IIIa inhibitors function through a different mechanism involved in platelet aggregation. They block what is termed the “final common pathway of platelet aggregation” by preventing fibrinogen binding to the GP IIb/IIIa receptors (Antithrombotic Trialists' Collaboration, 2002; Harrington et al., 2000). A meta-analysis on fifteen studies up to 1997 demonstrated that short-term treatment with an intravenous GP IIb/IIIa receptor antagonist produced a highly significant reduction in serious vascular events when compared to treatment with ASA alone (19%) (Antithrombotic Trialists' Collaboration, 2002). However, the benefits associated with this treatment must be considered along with an increased risk for bleeding events. The Antithrombotic Trialists’ Collaboration (2002) reported an absolute excess of 23 major extracranial bleeds per 1000 patients while fatal bleeding was rare. In a 2004 analysis of reported bleeding events associated with antiplatelet therapies, Serebruany et al. (2004) reported that the highest rate of bleeding complications were associated with IV GPIIb/IIIa blocker therapy (49%). The rate of bleeding events was reported to be slightly less for oral therapy (44.6%).

Thus far, only one clinical trial examined the effectiveness of Lotrafiban (an oral GP IIb/IIIa inhibitor) in addition to ASA in secondary prevention of stroke. The literature supporting the use of Abciximab (another GP IIb/IIIa inhibitor) in the treatment of acute ischaemic stroke is also limited (Table 8.8.1.5.1.1).

Table 8.8.1.4.3.1 Summary of Studies Evaluating Glycoprotein IIb and IIIa inhibitors

Author, Year Study Design (PEDro Score) Sample Size	Intervention	Main Outcome(s) Result
APLAUD Study Investigators (2000) RCT (7) N=451	E1: Lotrafiban (5mg) E2: Lotrafiban (20mg) E3: Lotrafiban (50mg) E4: Lotrafiban (100mg) C: Placebo Note: all dosing regimens were given 2/d with aspirin (300-325mg)	• Composite endpoint (mortality, myocardial infarction, readmission for cardiac/neurological events) (-)
AbESTT Study Investigators (2005) RCT (7) N_{Start}=400 N_{End}=385	E: Intravenous Abciximab (0.25mg/kg bolus) followed by 0.125mg/kg/min infusion for 12hr C: Intravenous placebo	• Mortality (-) • Symptomatic intracranial hemorrhage at 5d (-) • National Institute of Stroke Scale (-) • Modified Rankin Scale at 3mo (-)

+ Indicates statistically significant differences between treatment groups
- Indicates non-statistically significant differences between treatment groups

Discussion

While GP IIb/IIIc inhibitors are capable of blocking platelet aggregation in a dose-dependent fashion, they also produce major bleeding events in a similar, dose-dependent fashion. Lotrafiban, at its safest dosage, does not inhibit platelet aggregation any more effectively than ASA alone. Given the strong correlation between increased platelet inhibition and increased bleeding, it would not be appropriate to use GP IIb/IIIa inhibitors for long-term secondary prevention of stroke (Diener & Ringleb, 2002). BRAVO was a clinical trial specifically designed to test the effectiveness of Lotrafiban in preventing stroke in patients with a history of recent MI, TIA, stroke or any peripheral vascular disease. The drug's manufacturer stopped the trial in December 2000 when serious safety and efficacy concerns became apparent.

Abciximab is a monoclonal antibody that binds to the GP IIb/IIIa receptor and functions to limit thrombus propagation by reducing the interaction between monocytes and platelets (Kopp et al. 2003). It has previously been tested on a small group of patients and found to introduce a risk of bleeding however, the evidence is still very limited. To obtain a better understanding of the safety of Abciximab, a large multicentre trial was conducted (i.e., the Abciximab in Emergent Stroke Treatment Trial (AbESTT)), in which 400 patients less than 6 hours after stroke onset were randomized either to an intravenous infusion of Abciximab or an intravenous placebo infusion (AbESTT Investigators, 2005). The results suggest that the drug was found to be safe relative to the placebo, given that the mortality rate and intracranial hemorrhage occurrence were not significantly different between the two treatment groups (AbESTT Investigators, 2005). However, the results of this trial are to be interpreted with caution since the study reports on the experimental group being less severely affected than the control group with respect to stroke. Furthermore, the study also does not report on the stroke recurrence rates or on the cause of death. Treatment with abciximab was provided at around 3 hours or later after stroke, and thus far, there are no trials currently that have evaluated the effects of this drug after this time period. More research is needed to understand the benefits and harms of using this drug for the treatment of acute ischemic stroke.

Conclusions Regarding the Use of Glycoprotein IIb/IIIa Inhibitor (Lotrafiban)

There is level 1b evidence that the use of Lotrafiban (a glycoprotein IIb/IIIa inhibitor) in the secondary prevention of stroke may be associated with excessive bleeding incidents.

The use of Lotrafiban (a glycoprotein IIb/IIIa inhibitor) for the secondary prevention of stroke is associated with excessive bleeding incidents.

8.8.1.2 Dual Therapies

Since various antiplatelet drugs work through different mechanisms, it has been theorized that the effects of different drugs may be cumulative. In examining the potential effectiveness of combination or dual-platelet therapy, ASA has been added to thienopyridines as well as to dipyridamole (Antithrombotic Trialists' Collaboration, 2002; Ringleb et al., 2004).

8.8.1.2.1 Clopidogrel plus ASA

The *Clopidogrel in Unstable angina to prevent Recurrent Events* (CURE) study compared the effects of treatment with clopidogrel plus ASA versus ASA monotherapy in patients with unstable angina and non-Q-wave MI (Yusuf et al., 2001). To examine the potential effectiveness in secondary prevention of stroke, the *Management of Atherosclerosis with Clopidogrel in High-Risk Patients with Recent Transient Ischaemic Attack or Ischaemic Stroke* (MATCH) study compared treatment with clopidogrel plus ASA versus clopidogrel monotherapy in high-risk patients with recent ischaemic stroke or TIA. Both studies are summarized in Table 8.8.1.2.1.1 along with other studies evaluating the effects of the combined therapy.

Table 8.8.1.2.1.1 Summary of Studies Assessing ASA in Combination with Clopidogrel

Author, Year Study Design (PEDro Score) Sample Size	Intervention	Main Outcome(s) Result
FASTER Investigators (2007) RCT (10) N=392	E1: Clopidogrel (300mg loading dose followed by 75mg/d) + aspirin (80mg/d) (ASA) E2: Simvastatin (40mg/d) + ASA C: Placebo + ASA	• Incidence of stroke: E1/E2 vs. C (-); E1 vs. E2 (-) • Composite secondary outcome (myocardial infarction, stroke, vascular mortality) E1/E2 vs. C (-); E1 vs. E2 (-)
CHANCE Trial (2013) RCT (10) N=5170	E: Clopidogrel (300mg loading dose followed by 75mg/d) + aspirin (75mg/d) C: Placebo + aspirin (75mg/d)	• Incidence of stroke (+) • Incidence of moderate/severe hemorrhage (-)
CHARISMA Investigators (2006) RCT (9) N=15603	E: Clopidogrel (75mg/d) + aspirin (75-162mg/d) C: Placebo + aspirin (75-162mg/d)	• Composite primary endpoint (myocardial infarction, stroke, cardiovascular mortality) (-); symptomatic patients (+) • Incidence of nonfatal stroke (+) • Incidence of moderate bleeding (+) symptomatic patients
CURE Collaborative Group (2001) RCT (8) N=12562	E: Clopidogrel (75mg/d) + aspirin (75-325mg/d) C: Placebo	• Composite primary outcome (cardiovascular disease mortality, nonfatal myocardial infarction, stroke) (+) • Incidence of major bleeding episodes: C (+)
MATCH Investigators (2004) RCT (8) N=7599	E: Clopidogrel (75mg/d) + aspirin (75mg/d) C: Clopidogrel (75mg/d) + placebo	• Composite primary outcome (ischaemic stroke, myocardial infarction, vascular death, acute ischaemic event hospitalization) (-) • Incidence of fatal/nonfatal ischaemic stroke (-)

		• Incidence of minor/major or life-threatening bleeding: C (+)
Markus et al. (2005) RCT (8) N=107	E: Clopidogrel (300mg on day 1 to 75mg/d for 7d) + aspirin (75mg/d) C: Aspirin (75mg/d) + Placebo	• Day 7 frequency of asymptomatic microembolic signals (+)
CLAIR Study Investigators (2010) RCT (8) N=100	E: Clopidogrel (300mg loading dose followed by 75mg/d) + aspirin (75-160mg/d) C: Aspirin	• Incidence of microembolic signals (day 2 and day 7) (+) • Incidence of new infarctions (-) • Incidence of adverse events (-)
Cote et al. (2014) RCT (6) N_{Start}=838 N_{End} =838	E: Clopidogrel (75mg/d) + aspirin (325mg/d) C: Placebo	• Incidence of recurrent stroke (-) • Incidence of recurrent ischemic stroke, intracranial hemorrhage and other major vascular events (-) • Mortality: C (+)
Serebruany et al. (2005) RCT (5) N=70	E1: Clopidogrel (75mg/d) + aspirin (81mg/d) E2: Aspirin (81mg/d)	• Inhibition of platelet activity/function: E1 (+)
Seadon et al. (2015) RCT (4) N_{Start}=5170 N_{End}=5170	E: Clopidogrel + aspirin C: Aspirin	• Incidence of ischemic/hemorrhagic stroke (+) • Incidence of vascular events (+) • Mortality (-)

+ Indicates statistically significant differences between treatment groups
- Indicates non-statistically significant differences between treatment groups

Discussion

In patients with unstable angina, the CURE trial demonstrated a relative risk reduction of 14% for cardiovascular death, nonfatal MI, nonfatal stroke or refractory ischemia ($p<0.001$). The use of clopidogrel plus ASA demonstrated both early and sustained benefit in the CURE subject population. While these results seemed promising, there was no evidence available specific to the secondary prevention of stroke.

The MATCH trial examined the use of clopidogrel plus ASA specifically in the population of individuals with previous stroke/TIA. However, results from the MATCH trial demonstrated little benefit associated with the use of clopidogrel in combination with ASA in a population of high-risk stroke patients. Furthermore, any beneficial effect attributable to the use of combined therapy in the MATCH study was offset by the significantly higher rates of life-threatening, major and minor bleeding events associated with the use of clopidogrel in combination with ASA (Diener et al., 2004).

Maasland et al. (2009) compared inclusion and exclusion criteria used by large RCTs examining antiplatelet therapy for secondary prevention with a large, population-based sample of individuals with stroke. Of the 972 patients surveyed, only 25% would have been eligible for the MATCH study. Exclusion criteria intended to select only the most high risk patients and eliminate the most severely affected individuals were cited as the most important factors in creating a less representative trial sample (Maasland et al., 2009). A number of commentaries published subsequent to the MATCH study highlighted several issues to consider with regard to the interpretation of the reported results, including the creation of an unrepresentative sample. The MATCH study population contained a disproportionately large number of patients with diabetes (68%) and with small vessel or lacunar strokes (54%) (Amarenco & Donnan, 2004; Caplan, 2004; Rothwell et al., 2005). Only 34% of patients had large artery disease and of these, an

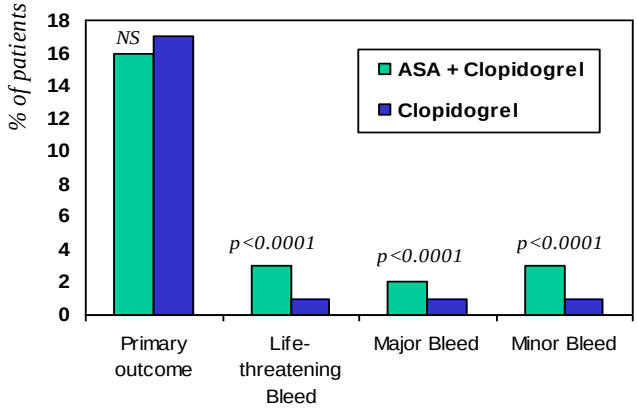
unexpectedly small proportion (5%) reported previous MI (Amarenco & Donnan, 2004). In addition to creating an unrepresentative population sample and reducing generalizability of results, this may have affected specific study outcomes. For instance, antiplatelet therapies may not be particularly efficacious in the prevention of secondary events in diabetic patients (Antithrombotic Trialists' Collaboration, 2002; Caplan, 2004) and patients with diabetic microangiopathy are more prone to bleeding complications (Amarenco & Donnan, 2004). Small vessel or lacunar stroke patients have a much lower risk for recurrent stroke than patients with large artery disease (Amarenco & Donnan, 2004; Caplan, 2004; Rothwell et al., 2005).

In addition to problems with the composition of the study population, it has been noted that the MATCH study did not include an ASA only treatment group for comparison (Amarenco & Donnan, 2004; Caplan, 2004). The comparison between ASA and the combined therapy may have yielded additional information and provided a different perspective with regard to bleeding complications (Amarenco & Donnan, 2004).

Management of Atherosclerosis with Clopidogrel in High-Risk Patients with Recent Transient Ischaemic Attack or Ischaemic Stroke Study (MATCH): Diener et al. 2004.

7,599 patients with previous ischaemic stroke and at least one additional vascular risk factor were assigned at random to receive either ASA (75 mg/day; n=3797) or matching placebo (n=3802). All patients received 75 mg clopidogrel once per day. Treatment continued for 18 months. Primary outcome was the composite of ischaemic stroke, myocardial infarction, vascular death and rehospitalization for an acute ischaemic event.

At the end of 18 months, there were fewer primary outcomes among patients receiving combination therapy than those receiving clopidogrel alone. However, this difference was not significant. In addition, there were significantly more bleeding events associated with the use of combined therapy.



The addition of aspirin to clopidogrel had little benefit in the prevention of the primary study outcome. The small demonstrated benefit was outweighed by the higher rate of bleeding events associated with combined therapy.

The CHARISMA trial provided an opportunity to examine the effectiveness of clopidogrel + ASA combination therapy compared to ASA monotherapy in a broad population of patients with either cardiovascular disease or multiple risk factors (Bhatt et al., 2006). Approximately 12% of patients assigned to each condition reported a previous history of stroke and 42% had diabetes. Results of CHARISMA demonstrated no significant benefit associated with combination therapy when compared to ASA monotherapy, in terms of the composite study endpoint of myocardial infarction, stroke or death from cardiovascular causes. However, for the outcome of non-fatal stroke alone, there was a significant protective effect associated with combination therapy. Unfortunately, treatment with clopidogrel plus ASA was associated with increased episodes of moderate to severe bleeding, particularly among individuals with symptomatic cardiovascular disease (Bhatt et al., 2006). The authors note that while 94 ischemic endpoints were prevented by treatment with combination therapy, it was at the expense of 93 moderate or severe bleeding events.

The CHARISMA investigators speculated that the inclusion of a lower-risk population may have diluted the apparent effect of combination therapy with clopidogrel on risk for stroke and, if the trial had included only higher-risk secondary prevention patients, a greater treatment effect would have been demonstrated (Bhatt et al., 2007). In a subgroup analysis of higher-risk “CAPRIE-like” patients (n=9,478),

Bhatt et al. (2007) demonstrated that treatment with combination therapy was associated with a reduced rate of the combined primary outcome of cardiovascular death, MI or stroke (HR=0.83, 95% CI 0.72-0.96, p=0.01). There was also a significant reduction in risk associated with combination therapy for all strokes (HR=0.80, 95% CI 0.64-0.99, p=0.048), but not for ischemic strokes (HR=0.83, 95% CI 0.65-1.05, p=0.115). When only individuals with previous ischemic strokes were examined, there was also a significant reduction in risk for the combined primary outcome noted (HR=0.78, 95% CI 0.67-0.97, p=0.03); however, risk for recurrent stroke was not reported for this subgroup. In addition, within this higher risk subgroup, the authors reported no significant between-group differences for severe bleeding events, but did note a significantly increased risk for moderate bleeding events associated with dual platelet therapy (HR=1.6, 95% CI 1.16-2.20, p=0.004), where moderate bleeding events were defined as those that require transfusion, but do not cause hemodynamic compromise. Given that this information is based on a *post hoc*, subgroup analysis, further research is required to determine whether some higher risk individuals may benefit from dual antiplatelet therapy despite increased risk bleeding events.

Most recently, the double-blind, placebo controlled CHANCE trial compared patients within 24 hours after the onset of a minor ischemic stroke or high-risk TIA to a combination therapy of clopidogrel plus ASA or to placebo plus ASA (Wang et al., 2013). Results of this study demonstrated that the combination of ASA and clopidogrel given for 21 days with clopidogrel alone continued up to day 90 was more effective than ASA alone in preventing recurrent strokes in Chinese patients who had experienced a minor stroke or TIA. Results showed a 3.5% absolute reduction in the occurrence of stroke at 90 days in the ASA/clopidogrel group, with a similar rate of moderate or severe hemorrhage in both groups. This suggests that treatment with clopidogrel and ASA as soon as possible after symptom onset is likely to produce the greatest absolute benefit for reducing the risk of stroke in the first 90 days without increasing the risk of haemorrhage. However, the CHANCE investigators had to screen more than 40 000 patients to find 5000 subjects appropriate for inclusion. Wang et al. (2013) also discussed a lack of generalizability as a limitation since results may not be generalizable to non-Chinese patients. A follow-up to this study was conducted by Wang et al. (2015) to determine whether the benefits of the combined clopidogrel and ASA treatment were maintained at 1 year beyond the trial termination. Findings indicate that significantly fewer strokes occurred in the patients receiving combination therapy (N=275, 10.6%) compared to those receiving ASA therapy only (N=362, 14.0%) (HR=0.78, 95% CI 0.5-0.93, p=0.006). Conversely, the number of patients experiencing moderate to severe hemorrhage was not significantly different between the two treatment groups (0.3% vs. 0.4%, p=0.44). The studies therefore suggests that the benefits of reducing the risk of stroke with combined clopidogrel and ASA therapy are not only observed in the short term but they are maintained up to 1 year.

To synthesize the benefits and the harms of dual clopidogrel with ASA therapy, several recent meta-analyses have been conducted. Findings from these studies suggest that use of dual therapy reduces the risk of stroke, especially among patients with early brain ischaemia (i.e., <30 days) (Palacio et al. 2015; Zhang et al. 2015). Furthermore, the incidence of ischaemic stroke in particular, was significantly reduced after both a short-term (<90d) and a long-term (>90d) treatment follow-up period (Palacio et al. 2015; Zhang et al. 2015). However, despite these benefits, a significant increase in major bleeding events was found following the use of dual therapy compared to ASA monotherapy in both the short and long term (Zhang et al. 2015). In fact, Palacio et al. (2015) reported a 40% increase in major bleeding outweighing the 19% reduction in stroke risk.

Conclusions Regarding Clopidogrel plus ASA dual therapy

There is level 1a evidence suggesting that administration of clopidogrel and ASA dual therapy is significantly more effective than ASA monotherapy at reducing the risk of stroke, particularly among patients with early (<30d) brain ischaemia.

There is level 1a evidence suggesting that combination clopidogrel and ASA therapy increases the risk of major bleeding relative to ASA therapy alone.

In the prevention of recurrent stroke, the combination of clopidogrel and ASA is not more effective than either clopidogrel or ASA alone however it is also significantly associated with an increased incidence of major bleeding events.

8.8.1.2.2 Dipyridamole plus ASA

Dipyridamole is an antiplatelet agent working through inhibition of "cyclic nucleotide phosphodiesterase and blockade of the uptake of adenosine" (Diener & Ringleb, 2002).

A recent meta-analysis of individual patient data from six randomized controlled trials assessing the effectiveness of the combination therapy (dipyridamole plus ASA) reported that patients randomized to treatment with combination therapy had 22%, 26% and 39% less risk for stroke than patients who had been treated with ASA alone, dipyridamole alone or placebo, respectively (Leonardi-Bee et al., 2005). Of all the trials included in this analysis, only the ESPS-II used the now standard dosage of ASA and dipyridamole (25mg ASA and 200mg extended release dipyridamole twice daily). Dipyridamole is available in a generic preparation and is considerably less expensive than other ASA alternatives. It is also available in a combination drug (Aggrenox©) containing 25mg ASA and 200mg dipyridamole; however, the combination form is not available generically.

The first European Stroke Prevention Study (ESPS Group, 1990) examined the effects of a high dose of ASA plus dipyridamole on the risk for fatal and nonfatal stroke in a subject population that included 2500 patients with previous stroke or TIA. Fatal and nonfatal stroke were reported as reduced by 38.1% when compared to a placebo condition. The second European Stroke Prevention Study (ESPS-2) was undertaken to assess the relative effectiveness of the combination therapy versus ASA monotherapy (Diener et al., 1996). Details of trials assessing combined therapy with dipyridamole and ASA are summarized in Table 8.8.1.2.1.

Table 8.8.1.2.2.1 Summary of Details of Trials Assessing ASA in Combination with Dipyridamole

Author, Year Study Design (PEDro Score) Sample Size	Intervention	Main Outcome(s) Result
JASAP Study (2011) RCT (9) N=1294	E: Dipyridamole (200mg, 2/d) + aspirin (25mg, 2/d) C: Aspirin (81mg/d)	• Incidence of recurrent fatal/nonfatal ischemic stroke (-) • Total adverse events: C (+) • Incidence of bleeding events (-)
ESPS Group (1990) RCT (8) N=2500	E: Dipyridamole (75mg) + aspirin (330mg) C: Placebo	• Incidence of stroke and mortality (+)
ESPS-2 (1996) RCT (8) N=6602	E1: Aspirin (50mg/d) E2: Dipyridamole (400mg/d) E3: Combined drug therapy C: Placebo	• Incidence of stroke: E1/E2/E3 vs. C (+) • Incidence of stroke or death: E1/E2/E3 vs. C (+) • Mortality (-)

		• Incidence of bleeding/gastrointenstinal bleeding: E2/C vs.E1 (+)
AGATE (2004) RCT (6) N=40	E: Aggrenox (2 pills/d) C: Aspirin (81mg/d) + placebo	• Antiplatelet characteristics (+)

+ Indicates statistically significant differences between treatment groups

- Indicates non-statistically significant differences between treatment groups

Discussion

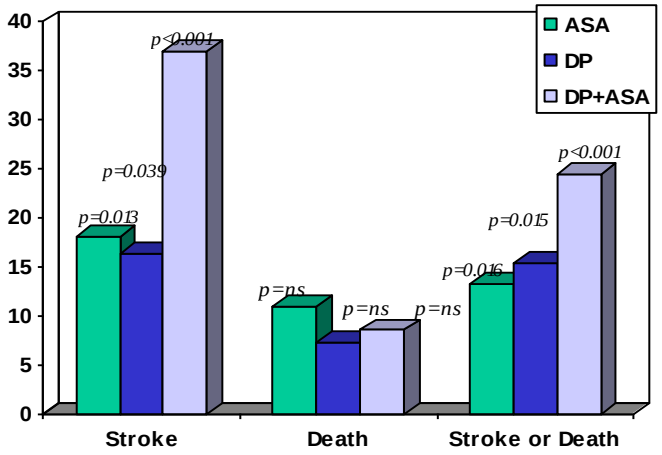
Results from the first ESPS trial demonstrated the effectiveness of combined therapy in reducing recurrent cerebrovascular events and death in patients with a history of TIA, RINDs or stroke (ESPS Group, 1990). The results from the ESPS-2 trial suggest that the benefits of dipyridamole and ASA have an additive effect in the secondary prevention of stroke by including an ASA-only treatment condition. In ESPS-2, the use of the combination therapy was associated with an absolute risk reduction of 5.9% for stroke when compared to placebo; in the ASA-only condition this reduction was 2.9% (Redman & Ryan, 2004). In addition, the AGATE study has demonstrated that, after approximately 2 weeks of treatment, the combination of dipyridamole and ASA in the form of Aggrenox©, exhibits antiplatelet properties superior to ASA alone (Serebruany et al., 2004).

The ESPRIT study was an open-label controlled study intended to be more representative of actual clinical practice. It assessed the effectiveness of combination therapy compared with ASA monotherapy in the prevention of death from vascular causes and non-fatal stroke, MI or bleeding complications in a population of individuals with a history of recent TIA or minor stroke. Patients in the combined therapy condition received a fixed dose of dipyridamole plus a free dose of ASA at the discretion of the treating physician. ASA monotherapy was also provided in a free dose format. The authors reported a significant treatment effect in favour of the combination therapy. Treatment with ASA and dipyridamole resulted in a 20% relative risk reduction for the combined primary outcome (HR=0.80, 95% CI 0.66-0.98). However, for the secondary endpoint of major ischemic events, the relative risk reduction was not significant (HR=0.82, 95% CI 0.65-1.01). Although the authors suggest that this is sufficient evidence to support the combination regimen as the preferred treatment, study limitations should be noted. First, a significant proportion of individuals randomized to receive combination therapy discontinued treatment (34%). Little information is provided about this subgroup and how they may have differed from those individuals who completed the trial. No information is provided regarding ongoing treatment for individuals who discontinued combined therapy (Flaherty et al., 2006). Though the authors acknowledge the difficulties presented by low events rates, there is no information regarding ongoing treatment provided, such as management of hypertension or treatment with statins, which could have had an impact on events. Although a baseline blood pressure is provided, no end study value is given. In addition, while free-dose ASA therapy may serve to better simulate clinical practice, almost half of the patients receiving ASA monotherapy were receiving only 30mg/day. This extremely low dose could have resulted in an increased rate of events in this group (Einhaupl, 2007; von Maxen et al., 2006).

Similarly, the more recent JASAP study demonstrated no clear advantage associated with combination therapy when compared to ASA monotherapy at a fixed dose of 81mg daily in terms of reduction in risk for recurrent ischemic stroke (Uchiyama et al., 2011). The authors suggest that the negative result of the trial may be attributable to a smaller sample size, lower event rates and shorter treatment durations than previous trials.

Dipyridamole & ASA in secondary prevention of stroke: European Stroke Prevention Study (ESPS-II): Diener et al. (1996)

6,602 participants with a recent history of TIA or complete ischaemic stroke were randomly allocated to one of 4 groups: (1) Dipyrimadole 200 mg twice/day, (2) ASA 25 mg twice/day (3) ASA 25 mg and Dipyrimadole 200 mg each twice per day or (4) matched placebo. Primary outcomes used to examine the efficacy of dipyridamole & ASA were stroke (fatal & nonfatal); death (from all other causes) and stroke and/or death (combined outcome). Mean length of follow-up was 2 years.



Relative risk reduction (%) – pairwise comparison of treatment conditions vs. placebo.

While treatment had no significant effect on the primary outcome death, ASA 25 mg and Dipyridamole 200 mg were both effective in the prevention of stroke. When the treatments were combined, the protective effects were additive. The most commonly reported adverse effect was headache, which was reported most frequently among patients in groups receiving dipyridamole ($p<0.001$). Bleeding, as an adverse effect, was reported more frequently among patients assigned to groups receiving ASA ($p<0.001$)

Halkes et al. (2008) performed a meta-analysis of five trials examining the effect of combination therapy with dipyridamole + ASA versus ASA monotherapy in individuals with previous TIA or stroke. Based on data from 7612 patients (3800 of whom received combination therapy), use of combination therapy was associated with a significant reduction in risk for recurrent stroke (HR=0.78, 95% CI 0.68-0.90), as well as an overall reduction in risk for the combined outcome of vascular death, non-fatal MI and non-fatal stroke (HR=0.82, 95%CI 0.72-0.92). Reduction in risk did not differ significantly across a variety of subgroup analyses, including those based on age, gender or baseline risk scores (Halkes et al., 2008).

In the ESPS-2 trial and the more recent JASAP trial significant more patients treated with combination therapy experienced some mild recurring events such as diarrhea or headache. In a meta-analysis it was reported that patients receiving dipyridamole alone or in combination with ASA were more likely to drop out of trials or report significant headache associated with treatment (Leonardi-Bee et al., 2005). However, rate of bleeding complications is less with dipyridamole combination therapy than in clopidogrel combination therapy. In a meta-analysis of reported bleeding events in 13 trials of antithrombotic therapy with follow-up of one year or more, Usman et al. (2009) demonstrated that mean rates of total bleeding events were greater for clopidogrel combination therapy (10.1%) than for ASA + extended release dipyridamole (ERD) (3.6%). Although this rate is lower than for ASA monotherapy (4.8%), it is not lower than for clopidogrel alone (2.9%). In terms of major bleeding events, clopidogrel alone demonstrated a significantly lower rate compared to clopidogrel + ASA ($p<0.0001$), but not significantly lower than for dipyridamole + ASA.

Contraindications to combination therapy with dipyridamole include "active haemostatic disorder or active pathologic bleeding" with a caution regarding patients with hypotension as it has the potential to cause peripheral vasodilation (Diener & Ringleb, 2002). Aggrenox© should be used with caution in patients with severe coronary artery disease as dipyridamole can increase the risk of MI or exacerbate angina (http://www.cp.gsm.com) (Redman & Ryan, 2004). There is also a potential for a hazardous interaction between Aggrenox© and adenosine (e.g., used during stress tests, nuclear perfusion heart

scans or in the termination of supraventricular tachycardia). Dipyridamole increases local adenosine levels and may cause an exaggerated reaction to adenosine, which could result in hypotension and AV block (Bergmann, 2001; Littmann et al., 2002).

Conclusions regarding Dipyridamole plus ASA

There is level 1a evidence that the use of dipyridamole in combination with ASA may be associated with reduced risk for recurrent vascular events including stroke, non-fatal MI, and non-fatal stroke when compared to placebo.

There is level 1a evidence that dipyridamole in combination with ASA may be more effective than ASA monotherapy when used in the prevention of recurrent stroke.

There is level 1a evidence that use of combination therapy of dipyridamole and ASA may be associated with increased occurrence of headaches and diarrhea when compared to ASA alone.

There is level 1a evidence that combination therapy with dipyridamole and ASA is associated with a lower incidence of bleeding events compared to combination therapy with clopidogrel and ASA.

ASA in combination with dipyridamole may be more effective than ASA alone in reducing the risk for recurrent stroke. Reported side effects associated with the use of combination therapy (i.e., dipyridamole with ASA) include headaches and diarrhea.

8.8.1.2.3 Cilostazol plus ASA

Due to its inhibitory action on platelet aggregation, cilostazol may have beneficial effects on reducing the risk of stroke especially when combined with ASA therapy. This effect has been studied in several large trials described below in table 8.8.1.2.3.1.

Table 8.8.1.2.3.1 Summary of Studies Evaluating Cilostazol and ASA Dual Therapy for the Prevention of Recurrent Stroke

Author, Year Study Design (PEDro Score) Sample Size	Intervention	Main Outcome(s) Result
TOSS Trial (2005) RCT (6) N=135	E: Cilostazol (100mg, 2/d) + ASA (100mg/d) C: Placebo + ASA (100mg/d)	• Progression of symptomatic intracranial arterial stenosis (+)
Nakamura et al. (2012) RCT (5) N=76	E: Cilostazol (100mg, 2/d) + ASA (300mg/d) C: ASA (300mg/d)	• Incidence of neurological deterioration or stroke recurrence (+) • Modified Rankin Scale (+)
CATHARSIS Trial (2015) Uchiyama et al. RCT (5) N_{Start}=165 N_{End}=122	E: Cilostazol (200mg/d) + ASA (100mg/d) C: ASA (100mg/d)	• Progression of intracranial arterial stenosis (-) • Stroke recurrence (-) • Ischemic stroke recurrence (-) • New silent brain infarcts (-) • ischemic stroke with new silent brain infarcts (-) • all vascular events with new silent brain infarcts: E vs C (+) • Modified Rankin Scale: E vs C (+)

+ Indicates statistically significant differences between treatment groups

- Indicates non-statistically significant differences between treatment groups

8.8.1.2.4 Clopidogrel Versus Dipyridamole-based Combination Therapies

An indirect comparison between ASA, Aggrenox© (dipyridamole plus ASA) and Plavix© (clopidogrel) suggests that Aggrenox© is the more effective treatment option for the reduction of stroke recurrence (Albers et al., 2001). However, there is relatively little evidence available derived from direct comparison of these two therapies (Table 8.8.1.2.4.1).

Table 8.8.1.2.4.1 Summary of Details of Trials Assessing Clopidogrel versus Dipyridamole-based Combination Therapies

Author, Year Study Design (PEDro Score) Sample Size	Intervention	Main Outcome(s) Result
ProFESS Study Group (2008) RCT (10) N=20332	E1: Dipyridamole (200mg/d) + aspirin (25mg/d) E2: Clopidogrel (75mg/d)	• Incidence of recurrent stroke (-) • Incidence of study discontinuation: E2 (+) • Incidence of major bleeding events: E2 (+)
Caplain (2005) RCT (5) N=26	E1: Aspirin E2: Clopidogrel (75mg) + aspirin (75mg) E3: Dipyridamole (200mg) + aspirin (25mg)	• Inhibition of collagen-induced platelet aggregation: E2 vs. E3 (+); in platelet rich plasma (PRP): E2 (+) • Inhibition of ADP-induced aggregation in whole blood and PRP: E2 (+) • Inhibition of arachidonic acid-induced platelet aggregation in whole blood; E1/E2 vs. E3 (+)
King et al. (2011) RCT (5) N=60	E1: Dipyridamole (200mg, 2/d) + aspirin (75mg/d) E2: Clopidogrel (300mg loading dose then 75mg/d) + aspirin (75mg/d)	• Change in embolic signals (baseline to 48hr) (-) • ADP-aggregation rate reduction: E2 (+)

+ Indicates statistically significant differences between treatment groups
- Indicates non-statistically significant differences between treatment groups

Discussion

Clopidogrel + ASA may provide superior inhibition of platelet aggregation (Caplain, 2005; King et al., 2011). However, the combination of clopidogrel and ASA has been associated with rates of bleeding events significantly greater than those associated with either clopidogrel monotherapy or ASA + extended release dipyridamole (Usman et al., 2009).

The ProFESS trial (PRoFESS-Prevention Regimen for Effectively Avoiding Second Strokes) was originally designed to compare the effectiveness of ASA + extended release dipyridamole versus ASA + clopidogrel (Sacco et al., 2008). However, following the results reported by the MATCH study in which there was an increased incidence of bleeding events associated with ASA + clopiogrel therapy, the study design was modified to include clopidogrel monotherapy rather than combination therapy. Following six protocol amendments to address lower than expected primary outcome events, a non-inferiority test condition was introduced. Although the rates of events were similar in both groups, the non-inferiority condition was not met. Therefore, it cannot be confirmed, based on the reported trial results, that treatment with ASA + extended release dipyridamole is non-inferior to clopidogrel monotherapy, despite no significant difference between groups in terms of risk for recurrent stroke events. From these results, it is not possible to conclude that either therapy is more efficacious in the secondary prevention of stroke. It should be noted, however, that there were more major bleeding events recorded among patients receiving combination therapy with ASA + dipyridamole than clopidogrel alone (HR=1.15, 95%CI 1.0-1.32).

In a meta-analysis of bleeding events that included data from the ProFESS trial, clopidogrel monotherapy had an annual major bleeding rate of 0.85% (Usman et al., 2009). This was significantly lower than the

rate recorded for ASA + clopidogrel (1.76%, p<0.0001), but did not differ significantly from the rate associated with ASA + extended release dipyridamole (0.93%, 95%CI for the comparison 0.81%-1.06%).

In a population-based sample of 503 individuals with stroke in Denmark, followed over a period of approximately 3 years, 97% received prescriptions for antiplatelet therapy (Ostergaard et al., 2012). The most common prescription was for ASA; however, many patients were prescribed a dual antiplatelet therapy with ASA + dipyridamole (n=320). Far fewer participants received treatment with clopidogrel (n=70). Overall, 64% of individuals were described as persistent in their prescribed therapy. Among individuals prescribed ASA+ dipyridamole, 110 (34%) were described as non-persistent, although 64 of these stopped using the ASA component of the therapy only (Ostergaard et al., 2012).

Conclusions Regarding Clopidogrel versus Dipyridamole-based Combination Therapies

There is level 1a evidence that clopidogrel in combination with ASA may provide more effective platelet inhibition than ASA in combination with dipyridamole.

There is level 1b evidence that combined ASA + extended release dipyridamole therapy is less likely to cause major bleeding events.

ASA + extended release dipyridamole and clopidogrel monotherapy may have a similar effect on rates of recurrent stroke.

8.8.1.3 Triple Therapies

Thus far, only a few randomized controlled trials has investigated the effect of therapy using a combination of three antiplatelet agents (Table 8.8.1.3.1).

Table 8.8.1.3.1 Summary of Studies Evaluating Triple Antiplatelet Therapy

Author, Year Study Design (PEDro Score) Sample Size	Intervention	Main Outcome(s) Result
Sprigg et al. (2008) RCT (6) N_{Start}=17 N_{End}=16	E: Open-label aspirin (75mg) + clopidogrel (75mg) + dipyridamole (200mg) C: Aspirin (75mg/d)	• Incidence of bleeding and adverse events: C (+)
Han et al. (2009) RCT (4) N=1212	E: Open-label aspirin (300mg/d for 1mo then 100mg/d + clopidogrel (loading dose 300-600mg/d then 75mg/d for 3 to 12mo) + cilostazol (100mg twice/d) C: Open-label aspirin (300mg/d for 1mo then 100mg/d + clopidogrel (loading dose 300-600mg/d then 75mg/d for 3 to 12mo)	• All-cause death: at 30d E vs C (+) • Cardiovascular death: at 30d E vs. C (+) • Composite of cardiac death + stroke + MI: at 30d and 1yr E vs C (+) • Major adverse cardiac or cerebral event (MACCE): at 30d and 1yr E vs C (+)

+ Indicates statistically significant differences between treatment groups

- Indicates non-statistically significant differences between treatment groups

Discussion

The Sprigg et al. (2008) trial was halted early following the publication of the ESPRIT trial results. The authors stated that they felt it unethical to continue assigning patients to the ASA monotherapy condition

given the demonstrated superiority of ASA + dipyridamole. Therefore, they provided an analysis of data collected from only 17 patients. However, as might be anticipated, bleeding and adverse events were more frequent among patients assigned to triple antiplatelet therapy.

In 2009, a large trial evaluated the vascular effects of a combination therapy consisting of aspirin, clopidogrel and cilostazol to a dual therapy of aspirin and clopidogrel in patients with acute coronary syndromes that had undergone percutaneous coronary intervention (Han et al. 2009). Outcomes at 30 days showed that triple antiplatelet therapy resulted in lower rates of all-cause death, cardiovascular death, a composite outcome of stroke, death, and MI, and major adverse cardiac or cerebral events (MACCE) compared to dual therapy (Han et al. 2009). At 1 year, only the composite outcome and the MACCE were found to be significantly lower in the triple therapy than the dual therapy (Han et al. 2009). It is important to note that the study was an open-label study hence, no blinding of assessors or patients occurred. Despite the large sample size, male participants contributed to 73% of the sample leading to an underrepresentation of females in this study. This imbalance of gender representation may have biased the results towards males and thus limiting the generalizability of the findings.

A recent meta-analysis compared the safety and efficacy of triple antiplatelet therapy consisting of aspirin, clopidogrel and cilostazol to dual antiplatelet therapy which combined aspirin with clopidogrel (Chen et al. 2015). A total of 19 trials involving 7464 patients were selected for analysis. Overall, the results suggested that the incidence of all-cause death, non-fatal myocardial infarction, and ischaemic stroke favoured triple antiplatelet therapy over dual antiplatelet therapy however, the effect was non-significant (Chen et al. 2015). Bleeding events were found to be more common among those using triple antiplatelet therapy however, no significant difference in the incidence of bleeding was found between the two types of therapy modalities (Chen et al. 2015).

Conclusions Regarding Triple Antiplatelet Therapy

There is level 1b evidence that major bleeding events are more common among patients using aspirin monotherapy compared to those using a combination therapy consisting of aspirin, clopidogrel, and dipyridamole.

There is level 1a evidence that triple antiplatelet therapy with aspirin, clopidogrel and cilostazol is comparable to dual therapy consisting of aspirin and clopidogrel regarding its effect on all-cause death, non-fatal MI, ischaemic stroke, and bleeding events.

Triple antiplatelet therapy with aspirin, cilostazol and clopidogrel is comparable to dual antiplatelet therapy with aspirin and clopidogrel regarding its effects on mortality, stroke and bleeding.

8.8.1.4 Combination Therapies and Functional Outcome

Several studies examining the effectiveness of antiplatelet therapy on the risk for recurrent stroke have also included an assessment of functional outcome. Results from these analyses are summarized in Table 8.8.1.4.1.

Table 8.8.1.4.1 Summary of Studies Evaluating Combination Antiplatelet Therapy and Functional Outcome

Author, Year Study Design (PEDro Score) Sample Size	Intervention	Main Outcome(s)

PRoFESS Study (2010) RCT (10) *Post hoc analysis* N=1360	E1: Dipyridamole (200mg, 2/d) + aspirin (25mg, 2/d) E2: Clopidogrel (75mg/d)	• Modified Rankin Scale (-)
CHARISMA Trial (2010) RCT (9) *Post hoc analysis* N=436	E: Clopidogrel + aspirin C: Aspirin + placebo	• Modified Rankin Scale (-)
EARLY Trial (2010) RCT (8) N=543	E: Dipyridamole (200mg, 2/d) + aspirin (25mg, 2/d) C: Aspirin (100mg/d)	• Modified Rankin Scale (-) • Incidence of adverse events (-) • 7d incidence of headache, nausea and vomiting (+)
Lau et al. (2014) RCT (6) N_{Start}=65 N_{End}=39	E: Clopidogrel (300mg starter dose then 75mg/d) + aspirin (75-169mg/d) C: Aspirin (75-160mg/d)	• Proportion of patients with microembolic signals (MES) (day 2 or 7) (-)
CATHARSIS Trial (2015) Uchiyama et al. RCT (5) N_{Start}=165 N_{End}=122	E: Cilostazol (200mg/d) + ASA (100mg/d) C: ASA (100mg/d)	• Modified Rankin Scale: E vs C (+)

+ Indicates statistically significant differences between treatment groups
- Indicates non-statistically significant differences between treatment groups

Discussion
There were no significant between-group differences reported in any of the studies identified that would suggest that any form of combination therapy has a greater impact on functional outcome when compared to either ASA or clopidogrel monotherapy. It is also important to note that none of the previously summarized studies examined the effect of antiplatelet therapy on functional outcome compared to a placebo condition that represents no or usual treatment.

Conclusions Regarding Combination Antiplatelet Therapy and Functional Outcome

There is level 1a evidence that combination therapy of clopidogrel and aspirin or dipyridamole and aspirin has no additional benefit on functional outcomes compared to either ASA or clopidogrel monotherapy.

There is level 1b evidence that early initiation of dipyridamole + ASA therapy has no impact on functional outcome relative to early ASA monotherapy.

The impact of combination antiplatelet therapy on functional outcome is unclear.

8.8.2 Anticoagulants

Anticoagulation therapy has been found to be effective in the primary and secondary prevention of cardioembolic stroke (see Section 8.10). Anticoagulants have also been assessed, alone and in combination with antiplatelet therapy, for effectiveness in the secondary prevention of noncardioembolic stroke. Details of recent studies assessing anticoagulation in noncardioembolic stroke are summarized in Table 8.8.2.1.

Table 8.8.2.1 Summary of Studies Evaluating Anticoagulants in the Prevention of Noncardioembolic Stroke

Author, Year Study Design (PEDro Score) Sample Size	Intervention	Main Outcome(s) Result
WASID Trial (2005) RCT (9) N=569	E: Warfarin (5mg/d) C: Aspirin (650mg, 2/d)	• Composite primary endpoint (ischemic stroke, brain haemorrhage, vascular mortality besides stroke) (-) • Incidence of major cardiac events C (+) • Mortality C (+) • Incidence of major haemorrhages C (+)
WARSS Warfarin- ASA Recurrent Study Stroke Group (2001) RCT (8) N=2206	E: Warfarin (adjusted dose) C: Aspirin (325mg/d)	• Incidence of ischemic stroke or mortality (-)
WARSS Warfarin- ASA Recurrent Study Stroke Group (2006a) RCT (8) N=2206	E: Warfarin (adjusted dose) C: Aspirin (325mg/d)	• Treatment outcome: patients with moderate stroke severity (-)
ESPRIT Study Group (2007) RCT (8) N=1068	E: Oral anticoagulants (Phenprocoumon, acenocoumarol or warfarin) C: Aspirin (30-325mg)	• Composite primary outcome (vascular mortality, nonfatal stroke/myocardial infarction/bleeding complications) (-) • Incidence of major ischemic events (-) • Risk of bleeding complications C (+)

+ Indicates statistically significant differences between treatment groups
- Indicates non-statistically significant differences between treatment groups

Discussion

Ariesen et al. (2004) note that patients who receive anticoagulant therapy following an ischaemic stroke of arterial origin are 19 times more likely to experience an intracerebral haemorrhage (ICH) than patients whose stroke was from a cardiac source. In their meta-analysis of data from nine clinical trials examining the use of ASA therapy, however, they found that ASA-treated patients with a history of arterial origin stroke had a 3.7% incidence per year of ICH while ASA-treated patients with a history stroke from a cardiac source had a 0.39% risk (Ariesen et al., 2004). The authors propose that cerebral ischemia of arterial origin is not in itself associated with an increased risk of ICH but rather that elevated risk exists only in the presence of high-intensity anti-coagulation therapies (INR 3.0-4.5). Certainly, the results of the WARSS study suggests that dose-adjusted therapy at a lower intensity (INR 1.4-2.8) is as effective as ASA in preventing recurrent stroke events while carrying a slightly increased, though non-significant, risk for bleeding events. However, an analysis of WARSS subgroups (Sacco et al., 2006a) demonstrated an increased risk among patients with strokes of moderate severity. Better outcomes were observed among patients with no hypertension and baseline or posterior circulation infarcts. Results of the WASID study demonstrated no benefit associated with warfarin therapy in a population of patients with a history of TIA or stroke attributable to confirmed stenosis of a major intracranial artery (Chimowitz et al., 2005). In addition, treatment with warfarin therapy was associated with a higher rate of adverse events such as death and major haemorrhage (Chimowitz et al., 2005).

A meta-analysis of the use of anticoagulants in the prevention of non-cardioembolic stroke demonstrated that, based on data from seven studies, oral anticoagulation of moderate intensity did not differ significantly from antiplatelet therapy in the prevention of death, recurrent ischemic stroke or myocardial infarction (OR=0.99, 95% CI 0.75-1.30). However, the frequency of total bleeding events (OR=2.18,

p=0.0007) and major bleeding events (OR=2.03, p<0.001) were significantly increased with oral anticoagulant versus antiplatelet therapy (Schachter et al., 2008).

Conclusions Regarding Anticoagulant Therapy in Noncardioembolic Stroke

There is level 1a evidence that treatment with oral anticoagulant therapy of moderate intensity is not superior to antiplatelet therapy in preventing death, recurrent ischemic stroke or myocardial infarction however, it may result in a greater risk for bleeding.

Anti-coagulant therapy is as effective as antiplatelet therapy in preventing the occurrence of death or stroke however, it may increase the risk of bleeding more than antiplatelet therapy.

8.8.3 Treatment Recommendations

The current Canadian best practice recommendations (Coutts et al., 2015) are provided in Table 8.8.3.1.

Table 8.8.3.1 Canadian Best Practice Recommendations (Coutts et al., 2015)

All patients with ischemic stroke or transient ischemic attack should be prescribed antiplatelet therapy for secondary prevention of recurrent stroke unless there is an indication for anticoagulation: 1. Acetylsalicylic acid (80mg to 325mg), combined acetylsalicylic acid (25mg) and extended-release dipyridamole (200mg), or clopidogrel (75mg) are all appropriate options and selection should depend on the clinical circumstances. 2. Short-term concurrent use of ASA and clopidogrel (up to 90 days) has not shown an increased risk of bleeding; however, longer-term use is not recommended for secondary stroke prevention, unless there is an alternative indication (i.e., drug-eluting stent requiring dual antiplatelet therapy), due to an increased risk of bleeding and mortality. 3. The combination of ASA (81mg) and clopidogrel 75mg is still of uncertain benefit in the Canadian setting for early prevention of recurrent stroke when used within 90 days, and should not be routinely used in all patients. 4. At the present time, there is not enough evidence to guide management if a patient has a stroke while on a specific antiplatelet agent. In all cases of recurrent stroke while on antiplatelet therapy, all other vascular risk factors should be reassessed and aggressively managed. 5. In children with stroke the usual maintenance dosage of ASA is 1 to 5mg/kg per day for the prevention of recurrent stroke. The usual maximum dose is 81mg/day. 6. The evidence for clopidogrel use in children is sparse at this time. Clopidogrel may be considered an alternative for adolescents at a dose of 1mg/kg/day up to a maximum of 75mg/day. Younger children may have higher anti-platelet effects of clopidogrel, and the suggested doses should be considered within the range of 0.2-0.5mg/kg/day.

Conclusions Regarding the Canadian Stroke Best Practice Recommendations

Acetylsalicylic acid (80mg to 325mg), combined acetylsalicylic acid (25mg) and extended-release dipyridamole (200mg), or clopidogrel (75mg) are all appropriate options and selection should depend on the clinical circumstances.

Short-term concurrent use of ASA and clopidogrel (up to 90 days) has not shown an increased risk of bleeding; however, longer-term use is not recommended for secondary stroke prevention, unless there is an alternative indication due to an increased risk of bleeding and mortality.

The combination of ASA (81mg) and clopidogrel 75mg is still of uncertain benefit in the Canadian setting for early prevention of recurrent stroke when used within 90 days, and should not be routinely used in all patients.

At the present time, there is not enough evidence to guide management if a patient has a stroke while on a specific antiplatelet agent. In all cases of recurrent stroke while on antiplatelet therapy, all other vascular risk factors should be reassessed and aggressively managed.

Summary

1. ***There is level 1a and level 2 evidence that ASA therapy effectively reduces the risk for recurrent stroke and should be initiated as soon as it is safe following the onset of the stroke event and maintained over the long-term.***
2. ***There is level 1a evidence that treatment with clopidogrel may be as effective as ticlopidine in terms of prevention of secondary vascular events, including stroke.***
3. ***There is level 1b evidence that clopidogrel may be similar to ASA with regard to safety.***
4. ***There is level 1a evidence that treatment with ticlopidine may be associated with a significantly greater risk for adverse events, including hepatic dysfunction, than clopidogrel.***
5. ***There is level 1a evidence suggesting that cilostazol is superior to aspirin monotherapy in reducing the risk of recurrent stroke and hemorrhagic events however, it is unclear whether its use results in an increased risk of gastrointestinal bleeds.***
6. ***There is level 1b evidence that the use of Lotrafiban (a glycoprotein IIb/IIIa inhibitor) in the secondary prevention of stroke may be associated with excessive bleeding incidents.***
7. ***There is level 1a evidence suggesting that administration of clopidogrel and ASA dual therapy is significantly more effective than ASA monotherapy at reducing the risk of stroke, particularly among patients with early (<30d) brain ischaemia.***
8. ***There is level 1a evidence suggesting that combination clopidogrel and ASA therapy increases the risk of major bleeding relative to ASA therapy alone.***
9. ***There is level 1a evidence that the use of dipyridamole in combination with ASA may be associated with reduced risk for recurrent vascular events including stroke, non-fatal MI, and non-fatal stroke when compared to placebo.***
10. ***There is level 1a evidence that dipyridamole in combination with ASA may be more effective than ASA monotherapy when used in the prevention of recurrent stroke.***
11. ***There is level 1a evidence that use of combination therapy of dipyridamole and ASA may be associated with increased occurrence of headaches and diarrhea when compared to ASA alone.***
12. ***There is level 1a evidence that combination therapy with dipyridamole and ASA is associated with a lower incidence of bleeding events compared to combination therapy with clopidogrel and ASA.***
13. ***There is level 1a evidence that clopidogrel in combination with ASA may provide more effective platelet inhibition than ASA in combination with dipyridamole.***
14. ***There is level 1b evidence that combined ASA + extended release dipyridamole therapy is less likely to cause major bleeding events.***
15. ***There is level 1b evidence that major bleeding events are more common among patients using aspirin monotherapy compared to those using a combination therapy consisting of aspirin, clopidogrel, and dipyridamole.***
16. ***There is level 1a evidence that triple antiplatelet therapy with aspirin, clopidogrel and cilostazol is comparable to dual therapy consisting of aspirin and clopidogrel regarding its effect on all-cause death, non-fatal MI, ischaemic stroke, and bleeding events.***
17. ***There is level 1a evidence that combination therapy of clopidogrel and aspirin or dipyridamole and aspirin has no additional benefit on functional outcomes compared to either ASA or clopidogrel monotherapy.***

18. ***There is level 1b evidence that early initiation of dipyridamole + ASA therapy has no impact on functional outcome relative to early ASA monotherapy.***

19. ***There is level 1a evidence that treatment with oral anticoagulant therapy of moderate intensity is not superior to antiplatelet therapy in preventing death, recurrent ischemic stroke or myocardial infarction however, it may result in a greater risk for bleeding.***

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8.9

Cardiac Abnormalities

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Key Points

- Atrial fibrillation may increase the risk of cardioembolic stroke; stroke patients with atrial fibrillation may be at high risk for recurrent stroke and should receive anti-coagulation therapy.
- Treatment with ASA (300 – 325 mg/day) may reduce the risk of stroke in individuals with atrial fibrillation. However, it may not be as effective as therapy with dose-adjusted warfarin.
- Dual antiplatelet therapy with clopidogrel + ASA may not be as effective as oral anticoagulation therapy in the prevention of stroke in patients with atrial fibrillation.
- For individuals in whom oral anticoagulation is contraindicated, dual antiplatelet therapy may result in reduced risk for stroke, but may also result in a significant increase for major bleeding events.
- The antiplatelet Indobufen may be an effective alternative to warfarin. Currently, it is not used in the Canadian clinical practice.
- Ximelagatran may be equally effective as warfarin however, its development has been terminated due to risk of liver injury.
- Dabigatran may be more effective than warfarin therapy at reducing the risk of stroke. A higher dose of dabigatran (150mg b.i.d) appears to be associated with a reduced risk of stroke and an increased risk of major bleeding compared to a lower dose of dabigatran (110mg b.i.d), however; the two doses were found to achieve comparable net clinical benefits observed over a period of 5 years of treatment.
- Rivaroxaban is a Factor Xa inhibitor that may provide an alternative to treatment with dose-adjusted warfarin in high-risk individuals with stroke.
- Apixaban may provide another fixed dose option to dose-adjusted warfarin therapy for the secondary prevention of stroke in individuals with AF. Like rivaroxaban and dabigatran, it requires no laboratory monitoring.
- Patient decision aids may increase patient knowledge, reduce uncertainty regarding treatment options and may result in more realistic expectations regarding therapy.
- Self-testing and self-management programs may be an effective approach to the administration of oral anticoagulation therapy for a select group of patients only.
- Improved adherence to guidelines for oral anti-coagulation therapy may be facilitated by a coordinated, multidisciplinary and goal-driven approach.
- No clear benefit is found as a result of patent foramen ovale closure in patients with cryptogenic strokes.
- Patients with ischemic stroke and atrial fibrillation should receive oral anticoagulation (such as apixaban, bagicatran, or edoxaban) as soon as it is thought to be safe for the patient. The use of heparin for bridging is not recommended, the patient should instead be given antiplatelets until anticoagulated.

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8.9 Cardiac Abnormalities

Various cardiac conditions have been clearly associated with an increased risk of ischaemic stroke (Sacco, 2001) (see Table 8.9.1). Sacco (2001) noted, *"Because certain stroke risk factors, like hypertension, may also be determinants of cardiac disease, some cardiac conditions may be viewed as intervening events in the causal chain for stroke".*

Table 8.9.1 Cardiac Risk Factors for Ischaemic Stroke (Sacco et al. 2001)

Definite Risk Factor	Possible Risk Factor
Atrial Fibrillation	
Myocardial Disease *Coronary artery disease* *Cardiac failure* *Left ventricular failure* *Intracardiac thrombus*	 *Patent foramen ovale* *Atrial septic aneurysm* *Spontaneous echo contrast*
Cardiac Valve Abnormalities *Mitral stenosis* *Prosthetic valves* *Endocarditis*	 *Valve strands*

8.9.1 Atrial Fibrillation

Atrial fibrillation (AF) is a common, pathological tachycardia the prevalence of which increases with age. Under the age of 30, prevalence has been estimated at approximately 0.2% (Thrombosis Interest Group 2002) whereas estimates vary from 5 – 12% over the age of 70 (Hart et al., 2002; Khairy & Nattel, 2002; Snow et al., 2003). During the acute phase following first ischemic stroke, the prevalence of AF may be as high as 24% (Marini et al., 2005). Marini et al. (2005) reported that patients with AF were more likely to be women, over the age of 80 and have coronary heart disease and peripheral artery disease. In a recent study of the very elderly (aged 85 at study inclusion), previous heart failure (OR=4.17, 95% CI 1.9-9.02) and history of stroke (OR=2.43, 95% CI 1.1-5.4) were significantly associated with the diagnosis of permanent atrial fibrillation (Formiga et al., 2012).

Atrial fibrillation has been identified as a powerful, independent risk factor for ischaemic (SPAF III Writing Committee, 1998) increasing the risk of stroke as much as 5-fold for individuals over the age of 70. Sixteen percent (16%) of all ischaemic strokes within this age group are associated with non-valvular AF (Devuyst & Bogousslavasky, 2001; Hart et al., 2002). Approximately two thirds of those can be attributed to left atrial thrombi (Hart et al., 2002). The formation of left atrial thrombi in AF patients is linked to stasis within the fibrillating atrium although the factors that serve to promote stasis have not been well defined (Hart et al., 2002; Khairy & Nattel, 2002).

Following a primary ischaemic event, patients with AF are also at a high risk for recurrent stroke. Within the first 2 weeks following a stroke event, risk has been estimated to be 0.1% - 1.3% per day, while subsequent to this the risk for AF patients with a history of prior stroke or TIA has been estimated to be 12% per annum (Devuyst & Bogousslavasky, 2001). A review of the literature reported that ischaemic stroke associated with AF is more likely to be fatal both in the short-term (within one month of the stroke event) and in the longer term (one year post stroke) (Miller et al., 2005). Among stroke survivors with AF, recurrence rates are at least twice those for non-AF stroke survivors. Strokes in individuals with AF tend to be more severe, require longer periods of hospitalization and are associated with greater levels of disability and dependency (Miller et al., 2005). Marini et al. (2005) reported that the presence of AF in

individuals following first ischaemic stroke was associated with higher 30-day (32.5%) and one-year (49.5%) fatality rates as well as with a higher rate of stroke recurrence (6.9% vs. 4.7% in individuals without AF, p=0.04). At 5 years post stroke, significant predictors of mortality may include increased age, lower preadmission functional independence, greater severity of stroke and the presence of atrial fibrillation (Whiting et al., 2011).

There are a number of treatment options available for the secondary prevention of stroke, most of which fall under the category of antiplatelet drugs and anticoagulants. Warfarin is a commonly prescribed anticoagulant which prevents the formation of blood clots and their migration throughout the vasculature. The magnitude of benefit achieved with warfarin therapy is dependent upon the individual patient's stroke risk (Hart & Halperin, 2001). Patients with atrial fibrillation who are at lower risk have fewer cardioembolic strokes than those at a higher risk (e.g. patients who have had a previous stroke or TIA). ASA (i.e. Aspirin, an antiplatelet), which is more effective in the treatment of noncardioembolic stroke than cardioembolic stroke in AF, may be an appropriate treatment for those patients in low risk categories (Devuyst & Bogousslavasky, 2001; Hart & Halperin, 2001). Warfarin therapy, on the other hand, is approximately twice as effective as aspirin in reducing the risk of cardioembolic stroke among high-risk patients and may be a more appropriate choice in secondary prevention (Hart & Halperin, 2001; Khairy & Nattel, 2002). Therefore, identification of risk is an important component in determining the appropriate prophylactic treatment.

Determining the threshold of risk above which treatment with long-term warfarin therapy is justified has led to the development of numerous risk stratification models (Hughes & Lip, 2008) that are supported within various clinical guideline recommendations (LaPointe et al., 2007). In general, factors associated with high-moderate risk for cardioembolic stroke in AF include prior stroke or TIA, hypertension, poor left ventricular function, age ≥ 75, rheumatic mitral valve disease, prosthetic heart valve, diabetes mellitus and recent congestive heart failure (Albers et al., 2001; Fuster et al., 2006; Snow et al., 2003).

One tool used to evaluate the risk and the benefits associated with a particular type of treatment, is the $CHADS_2$ risk stratification scheme (Gage et al., 2001) (See Table 8.9.3.1). CHADS stands for Congestive heart failure, Hypertension, Age, Diabetes, prior Stroke or transient ischaemic attack. Points are awarded for each risk factor and summed to provide total scores. Based on annual adjusted risk for stroke, total scores of 0-1 are considered low risk, 2-3 moderate risk and ≥4 high risk scores. The validity of the $CHADS_2$ has been demonstrated in the identification of high vs. low risk patients (Gage et al., 2001) and prediction of stroke (Baruch et al., 2007). Other scales have been proposed to risk stratify patients including CHADS-VASC2 and also to estimate risk of bleeding with anticoagulants HASBLED.

Table 8.9.3.1 $CHADS_2$ Risk Stratification (Gage et al., 2001)

Risk Factor	Points
Congestive Heart Failure	1
Hypertension	1
Age >75	1
Diabetes	1
Stroke/TIA	2

Our discussion will focus on the use of anti-coagulant and antiplatelet therapies in stroke prevention.

8.9.2 Anticoagulant Therapy

The study of pharmacologic management of AF through anti-coagulation therapy has been focused primarily on the use of oral vitamin K antagonists (which inhibit vitamin-K dependent clotting factors) and

aspirin either alone or in combination. Various other agents have also been assessed for use when a vitamin K antagonist might be contraindicated.

8.9.2.1 Warfarin (Coumadin)

The most thoroughly studied anticoagulant therapy is the vitamin K antagonist, warfarin. Warfarin inhibits the synthesis of vitamin K-dependent clotting factors (i.e., Factors II, VII, IX or X) leading to the synthesis of inactive clotting proteins. Therapeutic anticoagulation requires inactivation of factor II, which has a half-life of 60 hours, the longest of the clotting proteins. The activity of warfarin is monitored by the International Normalized Ratio (INR). Therapeutic anticoagulation has generally had as its goal an. Because of the prolonged onset of action of Warfarin, the results of dosage adjustments may not be seen until 3 to 5 days later.

Warfarin's greatest advantage is that it is well absorbed by the gastrointestinal system. Side effects of warfarin include bleeding and, uncommonly, skin necrosis, dermatitis and a syndrome of painful blue toes. During pregnancy, warfarin crosses the placenta and must be avoided. Warfarin is highly bound to plasma proteins and medications like salicylates, sulfonamides, and phenytoin may increase the anticoagulant effect by displacing warfarin from these plasma proteins. Drugs such as barbiturates, rifampin and spironolactone may decrease the anticoagulant effect by inducing hepatic microsomal enzymes. Patients with dietary deficiencies of vitamin K are more susceptible to bleeding complications. Vitamin K is an antagonist of warfarin's anticoagulant effect; however, because of the time taken to make clotting proteins there is a delay before it reverses the anticoagulation effect. With significant bleeding, the depleted clotting factors can be replaced with whole blood or fresh frozen plasma or prothrombin concentrate (octaplex). Risk of intracranial bleeding associated with the use of warfarin have been estimated at 0.8% per year, while the risk of major bleeding was found to range between 0.4% and 4.2% per year (Snipelisky & Kusumoto, 2013; Patel et a. 2011).

Anticoagulation therapy using warfarin has been assessed in various adjusted-dose treatment plans alone and in combination with ASA as well as in low intensity and fixed mini-dose regimens. Clinical trials assessing the effectiveness of warfarin and ASA in reducing the risk of cardioembolic stroke among individuals with atrial fibrillation are summarized in Table 8.9.2.1.1.

Table 8.9.2.1.1 Summary of Warfarin and ASA Therapy trials In Atrial Fibrillation

Author, Year Study Design (PEDro Score) Sample Size	Intervention	Main Outcome(s) Result
CAFA (1991) RCT (8) N=378	E: Warfarin (adjusted dose) C: Placebo	• Combined primary outcome (non-lacunar stroke, non-CNS embolism, fatal or intracranial haemorrhage) (-)
Veterans Affairs Stroke Prevention in Nonrheumatic Atrial Fibrillation Investigators (1992) RCT (8) N=571	E: Warfarin (low intensity, adjusted dose) C: Placebo	• Incidence of stroke (+) patients with no history of stroke • Annual event rate among patients ≥70yr (+)
BAFTA(2007) RCT (8) N=973	E1: Warfarin (adjusted dose) E2: Aspirin (75mg/d)	• Incidence of disabling, nonfatal or ischemic stroke: E1 (+)
BAATAF (1990) RCT (7)	E: Warfarin (adjusted dose) C: No warfarin	• Incidence of stroke (+) • Mortality (+)

N=420		
SPAF I (1991) RCT (7) N=1330	E1: Warfarin (adjusted dose) E2: Enteric-coated aspirin (325mg/d) C: Placebo	• Incidence of ischemic stroke and systemic embolism (primary events): E1/E2 vs. C (+) • Primary events or death: E1/E2 vs. C (+)
EAFT (1993) RCT (7) N=1007	E1: Anticoagulants (adjusted dose) E2: Aspirin (300mg/d) C: Placebo	• Incidence of outcome events (death from vascular disease, stroke, myocardial infarction or systemic embolism): E1 vs. E2 (+)
SPAFIII (1996) RCT (7) N=1044	E1: Warfarin (adjusted dose) E2: Warfarin (low intensity, dose to INR 1.2-1.5) + aspirin (325mg/d)	• Incidence of ischemic stroke and systemic embolism (primary events): E1 (+) • Annual rates of disabling stroke and primary event/vascular mortality: E1 (+)
AFASAK I (1989) RCT (6) N=1007	E1: Warfarin (adjusted dose) E2: Aspirin (75mg/d) C: Placebo	• Incidence of thromboembolic complications: E1 vs. E2/C (+) • Vascular mortality: E1 vs. E2/C (+)
SPAF II (1994) RCT (6) $N_{\leq 75yr}$=715 $N_{\geq 75yr}$=385	E1: Warfarin (adjusted dose) E2: Enteric-coated aspirin (325mg/d)	• Incidence of primary events (ischemic stroke and systemic embolism) (-) • Risk of major haemorrhage: ≥75yr (+) E2
Second Copenhagen Atrial Fibrillation, Aspirin & Anticoagulation Study (1998) RCT (6) N=677	E1: Warfarin (1.25mg/d) E2: Warfarin (1.25mg/d) + aspirin (300mg/d) E3: Aspirin (300mg/d) E4: Warfarin (adjusted dose)	• Incidence of combined primary outcome (stroke or systemic embolic event) (-)
Japanese Nonvalvular Atrial Fibrillation-Embolism Prevention Cooperative Study Group (2000) RCT (5) N=115	E1: Warfarin (conventional therapy, INR 2.2-3.5) E2: Warfarin (low-intensity, INR 1.5-2.1)	• Incidence of major haemorrhage: E2 (+) • Annual stroke rate (-)

+ Indicates statistically significant differences between treatment groups

- Indicates non-statistically significant differences between treatment groups

Discussion

A significant amount of research has been conducted to examine the relative efficacy and safety of anticoagulation with warfarin in patients with non-valvular atrial fibrillation. The conclusion that adjusted dose warfarin therapy is substantially more effective than ASA in reducing risk of cardioembolic stroke in individuals with atrial fibrillation is well supported in meta-analyses (Albers et al., 2001; Hart et al., 1999; Perret-Guillaume & Wahl, 2004; Segal et al., 2000) and in the results of individual clinical trials. Hart et al. (2002) reported that, when compared to a placebo group, the occurrence of all stroke is reduced by approximately 60% with adjusted dose warfarin therapy and by approximately 20% with ASA. It is estimated that anticoagulation of 1000 patients with warfarin compared to treatment with ASA would prevent 48 strokes per year at the cost of 2 major extracranial haemorrhages (Hart et al., 1999). A summary of the effects of anticoagulation with warfarin on stroke prevention is provided in Table 8.9.2.1.2.

However, few trials have focussed specifically on secondary stroke prevention in atrial fibrillation. Hart et al. (2004) examined the question of secondary prevention by pooling data from the 2 large clinical trials (Cowburn & Cleland, 1996; European Atrial Fibrillation Trial Study Group, 1993) whose subject populations had a history of stroke or TIA. In pooling the data from these 2 trials, the annualized rate of stroke events while on ASA therapy was 7% for patients with a previous history of TIA versus 11% for those participants with prior stroke. Anticoagulation therapy reduced the rate of stroke in patients with previous TIA by 56% (p=0.09) and by 63% (p<0.001) in patients with a history of stroke (Hart et al., 2004). In addition, a Cochrane review (Saxena & Koudstaal, 2004) reported a reduction in the odds of recurrent stroke of approximately two-thirds (OR = 0.36) based on data from the VA study (1992) and EAFT (1993).

Table 8.9.2.1.2 Summary of Anticoagulation with Adjusted-dose Warfarin in Atrial Fibrillation

Study	INR Range	Reduced Stroke Risk
AFASAK 1	2.8 – 4.2	+
BAATAF	1.5 – 2.7	+
SPAF 1	2.0 – 4.5	+
CAFA	2.0 – 3.0	+ (ns)
VA-Stroke Prevention	1.5 – 2.7	+
EAFT	2.5 – 4.0	+
SPAFII	2.0 – 4.5	+
SPAFIII	2.0 – 3.0	+
Second Copenhagen Study AF	2.0 – 3.0	+
Japanese AF study	2.2 – 3.5 vs. 1.5 – 2.1	+ (both groups)
BAFTA	2.0 - 3.0	+
ns = reduction in stroke risk was non-significant		

A prospective case series analysis of 207 individuals with AF and first-ever stroke over the age of 75 demonstrated a reduced risk of mortality (HR=0.47) and stroke recurrence (HR=0.31) after adjusting for known stroke risk factors (Tsivgoulis et al., 2005). A recent meta-analysis concluded that there has been an increase in the use of warfarin as a stroke prevention agent in patients with AF and a corresponding decrease in the incidence of recurrent stroke (Agarwal et al., 2012). Rate of residual stroke or systemic embolism was estimated to be 1.66% per year and major bleeding rates varied from 1.40% to 3.40% across the studies considered in this analysis (Agarwal et al., 2012).

Table 8.9.2.1.3 Contraindications to Anticoagulant Therapy

Absolute Contraindications
- Subarachnoid or cerebral haemorrhage
- Malignant hypertension
- Serious active bleeding
- Recent brain, eye and spinal cord surgery
- Lack of patient compliance ie. monitoring the PT, PTT.

Relative Contraindications
- Severe hypertension
- Major recent surgical operation
- Recent major trauma
- Active GI bleeding
- Bacterial endocarditis
- Severe renal failure
- Severe hepatic failure
- Haemorrhagic diathesis

Anticoagulation therapy is associated with a risk for both major and minor haemorrhagic events. The risk for bleeding is related to a number of factors including intensity of treatment, patient age, and fluctuation of the INR (International Normalized Ratio) (Devuyst & Bogousslavasky, 2001; MacWalter & Shirley, 2002). The INR must be carefully monitored during warfarin therapy. The most effective range has been identified as between 2.0 and 3.0. INR's below 2.0 have been associated with increasing risk for thromboembolic stroke while INR values of >4.0 are associated with increasing risk for intracerebral haemorrhage (Albers et al., 2001; Hart & Halperin, 2001; Khairy & Nattel, 2002; Oden et al., 2006). In a recent analysis of 6 clinical trials, Hart & Halperin (2001) reported the rate of intracerebral haemorrhage while on an appropriately adjusted dose to be 0.5% per year. However, the risks of long-term anticoagulation are dependent upon the intensity and duration of therapy as well as the patient's age, compliance and medical condition (Anderson, 1987). Contraindications to the use of anticoagulants

include GI bleed, active peptic ulcer disorders, frequent falls, alcohol misuse and a history of intracranial haemorrhage (Table 8.9.2.1.3).

In an attempt to determine the best therapeutic levels with minimum risk, minidose and low-dose warfarin therapies have been assessed. A meta-analysis conducted by Perret-Guillaume and Wahl (2004) concluded that while mini or low-dose warfarin therapy tended to reduce major bleeding events when compared to adjusted dose therapy, it was significantly less effective in reducing the risk of thrombosis (OR for adjusted-dose versus low or minidose therapy = 0.50).

Hart et al. (2002) suggested that ASA followed by early initiation of adjusted dose warfarin therapy for secondary prevention is reasonable for AF patients following a primary stroke event. The authors suggested that anticoagulation could be undertaken as soon as the patient is both medically & neurologically stable. Prior to initiation, it is recommended that a repeat CT scan be undertaken "if there is clinical worsening, the infarct is large or in the presence of undue headache" (Hart et al., 2002).

The use of combined therapy, most often ASA and warfarin, is not uncommon among patients with atrial fibrillation. Shireman et al. (2004) reported that 20% of patients admitted to hospital with atrial fibrillation were discharged on warfarin plus one antiplatelet medication. In 89.5% of the cases, the antiplatelet agent used in combination with warfarin was aspirin, given most frequently in association with the presence of coronary heart disease. However, an increased risk for bleeding events associated with combined warfarin-antiplatelet therapy was also demonstrated. Individuals using combined therapy were found to be 1.53 times more likely to experience a bleeding event and had a 3-fold risk of intracranial haemorrhage than individuals using warfarin alone (Shireman et al., 2004). Similarly, Cairns & McMurty (2013) reported that warfarin alone (INR, 2.8-4.8) or warfarin (INR, 2-2.5) plus aspirin (75-100 mg) are at least as efficacious as aspirin alone in reducing subsequent coronary events. However, the addition of aspirin to warfarin treatment has been found to increase the risk of bleeding (Cairns & McMurtry, 2013). Current Canadian Stroke Best Practice Recommendations for the secondary prevention of stroke advise against the use of ASA and oral anticoagulants (Coutts et al. 2015).

Moreover, studies have shown that relatively few patients for whom warfarin therapy is appropriate receive warfarin (Andersen & Olsen, 2007; Baker et al., 2009; Birman-Deych et al., 2006; Blich & Gross, 2004; Deplanque et al., 2006a; Elkind & Sacco, 2004; Formiga et al., 2012; Nieuwlaat et al., 2007; Pisters et al., 2010; Singer et al., 2009; Somerfield et al., 2006; Sudlow et al., 1998; Tapson et al., 2005; Walker & Bennett, 2008).

Singer et al. (2009) examined the net clinical benefit associated with warfarin use in a large cohort of patients diagnosed with non-valvular atrial fibrillation (n=13,559). At study entry, 53% of the cohort was receiving warfarin therapy. Excluding INR test intervals >8 weeks, patients receiving warfarin were in the therapeutic INR range 65.4% of the time. Overall, the yearly rate of ischemic stroke or systemic embolism was 2.1% in individuals not receiving warfarin vs. 1.27% in those receiving treatment. The annual rate of intracranial haemorrhage was 0.32% in those patients not on warfarin but only 0.58% for those receiving warfarin. Taking the risk for stroke and for bleeding into account, while adjusting for age, sex, risk factors and incorporating a weighting factor for intracranial haemorrhages, the overall adjusted net clinical benefit associated with warfarin use was 0.68 (95% CI 0.34 – 0.87) adverse events prevented per 100 patients per year. The greatest net clinical benefit was demonstrated for individuals with previous ischemic stroke (2.48% per year) and for those over the age of 85 (2.34% per year) (Singer et al., 2009).

In a meta-analysis, Baker et al. (2009) identified 8 studies assessing warfarin anti-coagulation for patients with atrial fibrillation in the United States in order to compare the effect of treatment in specialty clinics

versus usual primary care within the community. Based on data from 5 studies, only 48% of AF patients who were eligible to receive warfarin treatment did so (53% in specialty clinics, 47% in community-based treatment). Overall, patients were maintained within the therapeutic INR range 55% of the time. However, differences by care setting were observed. Patients whose care was managed in specialty clinics spent a mean of 63% of the time within the therapeutic INR range vs. 51% in community-based care. Even within specialized facilities, using newer dosing strategies, patients still spent one-third or more of their time outside of the optimal therapeutic INR range.

Potential causes for underutilization of warfarin therapy have been identified as physician concerns with regard to potential bleeding events, unpredictable dose-response, slow onset of action, potential food and drug interactions, the need to closely monitor INR via blood testing and risk for falls (Blich & Gross, 2004; Donnan et al., 2004; Elkind & Sacco, 2004; Garwood & Corbett, 2008). A study by Choudhry et al. (2006) examined patterns of prescribing for patients with AF before and after physician exposure to an adverse bleeding event in one of their patients receiving warfarin and to thromboembolic stroke in one of their patients with AF not receiving warfarin. Exposure to a serious bleeding event was associated with significantly reduced odds of prescribing warfarin in the 90 days following the event (OR = 0.77, 95% CI 0.61 – 098), whereas exposure to stroke did not change the likelihood that the physician would prescribe warfarin (Choudhry et al., 2006).

Conclusions Regarding Warfarin Therapy

There is level 1a evidence that the use of anti-coagulation therapy, particularly with adjusted dose warfarin, may substantially reduce the risk of primary and secondary stroke in individuals with atrial fibrillation.

Atrial fibrillation may increase the risk of cardioembolic stroke; stroke patients with atrial fibrillation may be at high risk for recurrent stroke and should receive anti-coagulation therapy.

8.9.3 Antiplatelet Therapy

8.9.3.1 ASA Monotherapy

Aspirin has been used in the prevention of stroke for individuals with non-valvular atrial fibrillation both alone and in combination with Warfarin. Several studies have provided the opportunity to evaluate the effectiveness of ASA monotherapy when compared to a placebo condition. These studies are summarized in Table 8.9.3.1.

Table 8.9.3.1 Summary of Studies Evaluating ASA Monotherapy in Patients with AF

Author, Year Study Design (PEDro Score) Sample Size	Intervention	Main Outcome(s) Result
SPAF I (1991) RCT (7) N=1330	E1: Warfarin (adjusted dose) E2: Enteric-coated aspirin (325mg/d) C: Placebo	• Incidence of primary events (ischemic stroke, systemic embolism): E1/E2 vs. C (+) • Incidence of primary event or death: E1/E2 vs. C (+)
EAFT (1993) RCT (7) N=1007	E1: Anticoagulation (INR 2.5-4.0) E2: Aspirin (300mg/d) C: Placebo	• Incidence of stroke: E1 vs. E2 (+)
JAST (2006)	E: Aspirin (150-200mg/d)	• Cardiovascular mortality (-)

RCT (7) N=871	C: No treatment	• Incidence of stroke (-) • Risk of major bleeding (-)

+ Indicates statistically significant differences between treatment groups
- Indicates non-statistically significant differences between treatment groups

Discussion

ASA therapy (300 – 325 mg/day) was associated with reduction of stroke risk in individuals with AF when compared to no treatment. However, doses of 150 – 200 mg/day do not appear to be either safe or effective. Based on the results of the EAFT trial and several meta-analyses (Albers et al., 2001; Hart et al., 1999; Perret-Guillaume & Wahl, 2004; Segal et al., 2000), it is clear that anticoagulant therapy (dose-adjusted warfarin) is more effective in preventing strokes among individuals with atrial fibrillation than antiplatelet therapy (ASA monotherapy).

Conclusions Regarding ASA Monotherapy

There is level 1a evidence that treatment with ASA 300 – 325 mg/day may be associated with reduced risk of stroke when compared to no treatment in individuals with atrial fibrillation. However, anticoagulant therapy (dose-adjusted warfarin) may be more effective in preventing strokes among individuals with atrial fibrillation than antiplatelet therapy (ASA).

Treatment with ASA (300 – 325 mg/day) may reduce the risk of stroke in individuals with atrial fibrillation. However, it may not be as effective as therapy with dose-adjusted warfarin.

8.9.3.2 ASA Combination Therapy

The use of dual antiplatelet therapy has proven effective in the prevention of secondary stroke events in high risk patients. Given the protective effect of aspirin in individuals with atrial fibrillation and the effectiveness of combined antiplatelet therapy in secondary prevention, investigators have examined the use of ASA-based combination therapy for prevention of stroke in AF (Table 8.9.3.2.1).

Table 8.9.3.2.1 Summary of Studies Evaluating ASA + Clopidogrel in Patients with AF

Author, Year Study Design (PEDro Score) Sample Size	Intervention	Main Outcome(s) Result
ACTIVE-A Connolly et al. (2009a) RCT (10) N=7554	E: Clopidogrel (75mg/d) + aspirin (75-100mg/d) C: Placebo + aspirin (75-100mg/d)	• Combined primary outcome (stroke, non-CNS embolism, myocardial infarction, vascular mortality) (+) • Incidence of stroke (+); ischemic stroke (+); haemorrhagic stroke (-) • Incidence of minor/major bleeding events: C (+)
ACTIVE-W Connolly et al. (2006) RCT (8) N=6706	E1: Open-label oral anticoagulation (vitamin K antagonist, INR 2.0-3.0) E2: Dual antiplatelet therapy (75mg clopidogrel + 75-100mg aspirin)	• Incidence of stroke: E1 (+) • Incidence of major bleeding (-) • Incidence of minor bleeding: E1 (+)

+ Indicates statistically significant differences between treatment groups
- Indicates non-statistically significant differences between treatment groups

Discussion

For patients who are eligible for oral anticoagulation therapy (OAC), the risks and benefits associated with OAC vs. dual antiplatelet therapy in the ACTIVE-W trial have been examined by stroke risk using the

$CHADS_2$ classification scheme (also see section 8.9.1) (Healey et al., 2008). For low-risk patients $CHADS_2$=1), risk for stroke was significantly lower in patients receiving OAC (p=0.01). In addition, there was a non-significant trend toward greater risk for bleeding associated with clopidogrel combination therapy (RR=1.55, 95% CI 0.91-2.64, p=0.11). For higher risk patients ($CHADS_2$>1), the risk of stroke was greater for individuals receiving treatment with clopidogrel + ASA (RR=1.58, 95% 1.11-2.24), but the risk for major bleeding events was not significantly different between treatment groups. Regardless of baseline risk, treatment with oral anticoagulants resulted in more effective prevention against stroke events. Treatment with clopidogrel + ASA resulted in neither reduced risk nor few bleeding events when compared to OAC with a vitamin K antagonist.

Unfortunately, not all individuals are eligible for oral anticoagulation therapy with vitamin K antagonists. The ACTIVE-A trial examined the use of antiplatelet therapy in these individuals, but did not provide a clear definition of unsuitability for vitamin K antagonist therapy (Pisters et al., 2009; Richard et al., 2009). While high risk for bleeding complications excluded some patients from treatment, 50% of patients were judged unsuitable based on "physician's judgement" (reasons unspecified) and another 26% on the basis of "patient preference". This does little to describe the sample or define unsuitability (Pisters et al., 2009). However, in those individuals judged unsuitable for vitamin K antagonist therapy, clopidogrel + ASA resulted in a modest reduction in the risk for stroke (0.8%/year) when compared to ASA monotherapy (Connolly et al., 2009b). At the same time, use of dual antiplatelet therapy was also associated with a similar increase in risk for major haemorrhage (0.7%/year). Although intracranial haemorrhage was not considered a major vascular event, use of combination therapy was associated with a substantial increase in the rate of these events (Goldstein, 2009).

A retrospective cohort study using the Taiwan National Health Insurance Research Dataset identified patients with stroke and peripheral artery disease for six years to consider secondary prevention of ischemic stroke in these patients (Lee et al., 2013). Patients were stratified according to their use of ASA, clopidogrel, cilostazol, warfarin or combination therapy. Cilostazol was found to significantly reduce the risk of ischemic stroke with similar safety to aspirin. Clopidogrel significantly reduced the risk of ischemic stroke and was found to be safer than aspirin. Lastly, there were no statistically significantdifferences in the risk of stroke or hemorrhagic events among warfarin, cilostazol-based combination therapy and aspirin.

Conclusions Regarding Dual Antiplatelet Therapy in Atrial Fibrillation

There is level 1b evidence that oral anticoagulation therapy may be more effective than ASA + clopidogrel in the prevention of stroke in individuals with atrial fibrillation. However, for patients not eligible for oral anticoagulation, ASA + clopidogrel may be associated with reduced risk for stroke when compared to ASA monotherapy.

There is level 1b evidence that use of ASA + clopidogrel may be associated with increased risk for bleeding events compared with ASA monotherapy. Risk for major bleeding events with dual therapy may be similar to that reported for oral anticoagulation with vitamin-K antagonists.

Dual antiplatelet therapy with clopidogrel + ASA may not be as effective as oral anticoagulation therapy in the prevention of stroke in patients with atrial fibrillation.

For individuals in whom oral anticoagulation is contraindicated, dual antiplatelet therapy may result in reduced risk for stroke, but may also result in a significant increase for major bleeding events.

8.9.4 Alternate Therapies

Given the significant benefits of anticoagulation therapy following cardioembolic stroke and the risks and contraindications associated with warfarin, alternative therapies have been investigated.

8.9.4.1 Indobufen

Aside from ASA, which has been identified as a less effective alternative to warfarin in terms of reducing the risk of cardioembolic stroke among individuals with AF (Albers et al., 2001; Hart et al., 1999; Perret-Guillaume & Wahl, 2004; Segal et al., 2000), indobufen has been investigated as an alternative therapy. Indobufen is a reversible inhibitor of platelet cyclo-oxygenase activity shown to be effective in preventing thromboembolic events in several patient populations (Fornaro et al., 1993; Morocutti et al., 1997; Saxena & Koudstaal, 2004). Trials assessing the effectiveness of indobufen in the prevention of stroke are summarized in Table 8.9.4.1.

Table 8.9.4.1 Summary of Studies Evaluating Indobufen Therapy in Patients with AF

Author, Year Study Design (PEDro Score) Sample Size	Intervention	Main Outcome(s) Result
Fornaro et al. (1993) RCT (7) N=196	E: Indobufen (100mg, 2/d) C: Placebo	• Incidence of transient ischemic attack and fatal/nonfatal stroke (+)
SIFA Investigators (1997) RCT (7) N=916	E: Indobufen (100 or 200mg/d) C: Warfarin (adjusted dose, INR 2.0-3.5)	• Combined primary outcome (nonfatal stroke/myocardial infarction, systemic embolism, vascular mortality) (-)

+ Indicates statistically significant differences between treatment groups
- Indicates non-statistically significant differences between treatment groups

Discussion

Fornaro et al. (1993) evaluated the pharmacodynamics effects of Indobufen in preventing thromboembolic events in a population with various heart conditions. A total of 196 participants were recruited and randomized to receive either indobufen or placebo therapy. The primary study end points included the occurrence of cerebral ischemic attack including (either stroke or TIA), systemic embolism, pulmonary embolism, and fatal MI. Results suggest that compared to placebo, individuals taking indobufen had a significant reduction in the risk of a primary event. The study however, suffered a substantial loss-to-follow-up, as patients (N=22) discontinued treatment for a number of reasons (i.e., adverse reactions, epistaxis, hematuria, ecchymosis, haemorrhoidal bleeding, GI disturbances etc.). Given the varying inclusion criteria, it is difficult to interpret the outcomes of patients with just atrial fibrillation. When indobufen was compared to warfarin in a later study by the SIFA ingestigators (1997), the findings reported no significant difference between the two drugs with respect to their effect on reducing the incidence of primary outcome events which included nonfatal stroke, systemic or pulmonary embolism, nonfatal MI, and vascular death (SIFA Investigators, 1997).

Currently, there is a lack of literature on the safety and efficacy of indobufen for the secondary prevention of stroke. Due to the limited evidence for its use, indobufen is not used in Canadian clinical practices.

Conclusions Regarding Indobufen

There is level 1b evidence that Indobufen may be as effective as warfarin, but is associated with a reduced risk of bleeding events. It is currently not used in the Canadian clinical practice.

The antiplatelet Indobufen may be an effective alternative to warfarin. Currently, it is not used in the Canadian clinical practice.

8.9.4.2 Ximelagatran

When taken orally, ximelagatran converts rapidly *in vivo* to Melagatran, a reversible, direct thrombin inhibitor (Brighton, 2004; Mohapatra et al., 2005). Melagatran functions to prevent clotting by inhibiting both soluble and clot-bound thrombin, a key enzyme in converting fibrinogen into fibrin (Brighton, 2004; Nutescu et al., 2004).

Melagatran acts rapidly and has a relatively short half-life ranging from 1.5 – 2 hours in young, healthy individuals to approximately 4 hours in the elderly. Unlike warfarin, there are no known significant interactions with food or other drugs (Brighton, 2004; Nutescu et al., 2004) and bioavailability of the drug is not affected by food (Mohapatra et al., 2005). Its short half-life necessitates twice daily administration; however, administration is by fixed dose. The drug is not well metabolised and approximately 80% is excreted renally (Brighton, 2004; Nutescu et al., 2004). The effect of renal impairment on the use of Ximelagatran is not known (Brighton, 2004). Clinical studies have been undertaken to examine the effectiveness of Ximelagatran/ Melagatran as therapy for vein thrombosis, prophylaxis for venous thromboembolism after orthopaedic surgery, in the prevention of recurrent vascular events in patients with acute coronary syndromes and in patients with atrial fibrillation. Studies focusing on the use of Ximelagatran for the prevention of stroke in individuals with AF are summarized in Table 8.9.4.2.1.

Table 8.9.4.2.1 Summary of Studies Evaluating the Use of Ximelagatran for the Prevention of Stroke

Author, Year Study Design (PEDro Score) Sample Size	Intervention	Main Outcome(s) Result
SPORTIF V (2005) RCT (9) N=3922	E: Ximelagatran (36mg, 2/d) C: Warfarin (adjusted dose, INR 2.0-3.0)	• Combined primary endpoint (stroke, systemic embolic events) (-) • Incidence of fatal/nonfatal stroke (-) • Mortality (-) • Incidence of major extracerebral bleeds (-) • Incidence of minor and major bleeding events (+)
SPORTIF III (2003) RCT (7) N=3410	E: Open-label ximelagatran (36mg/d) C: Open-label warfarin (adjusted dose, INR 2.0-3.0)	• Combined primary endpoint (stroke, systemic embolism) (-) • Incidence of minor/major bleeding events (+)

+ Indicates statistically significant differences between treatment groups

- Indicates non-statistically significant differences between treatment groups

Discussion

The results of both the SPORTIF III and SPORTIF V trials have demonstrated the noninferiority of ximelagatran when compared to well-controlled warfarin therapy. In addition, 40% of SPORTIF participants were aged 75 years or older, suggesting that ximelagatran is effective in this high-risk age group in which AF is most prevalent. Ximelagatran may offer a less complicated treatment alternative to warfarin. It is administered by a fixed dose twice daily, requires no routine INR monitoring, has a quick onset and short half-life and has no known food or drug interactions. In clinical practice, it is conceivable

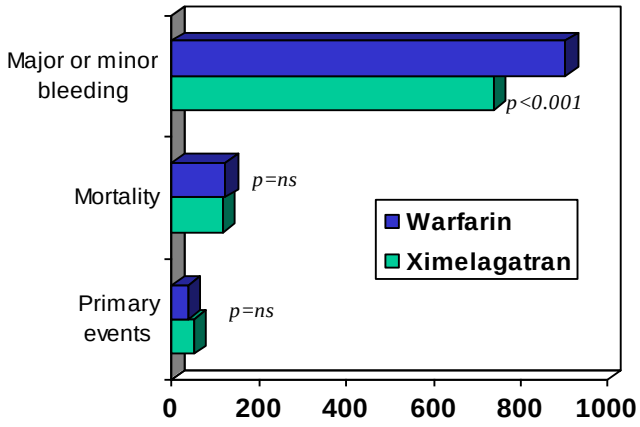
that ximelagatran could produce superior risk reduction for stroke since it overcomes many of the perceived treatment barriers associated with warfarin therapy (Albers, 2004; Elkind & Sacco, 2004).

Pooled analyses of data from the SPORTIF III and SPORTIF V trials have demonstrated no significant difference between treatment with ximelagatran and well-controlled warfarin in the prevention of all stroke or systemic embolic events among individuals with a history of previous stroke or TIA (Akins et al., 2007; Albers, 2004). Albers et al. (2004) reported that the risk of intracranial haemorrhage was 0.11% per year in the ximelagatran group and 0.19% in the warfarin group. Risk of ischaemic stroke was reported to be 1.37% and 1.46% in the ximelagatran and warfarin groups respectively (Albers 2004). Pooled on-treatment analysis revealed a 1% absolute risk reduction and 16% relative risk reduction in favour of treatment with ximelagatran ($p<0.038$) (Albers, 2004).

Rates of major bleeding events appear to be similar between SPORTIF treatment groups (Albers, 2004). However, when combined minor and major bleeding episodes are considered, there is significantly less bleeding associated with ximelagatran therapy (31.7% per year for ximelagatran vs. 38.7% for warfarin, $p<0.0001$). A pooled analysis of SPORTIF III and V (Douketis et al., 2006), reported an 18.2% reduction in risk for any bleeding events associated with ximelagatran when compared to warfarin therapy ($p<0.001$). For major bleeding events, relative risk reduction was 25.1%. Ximegalatran therapy was associated with a 0.67% (NNT = 149) and 7% (NNT = 14) annual absolute risk reduction for major and any bleeding events, respectively. Risk factors for bleeding events when treated with ximelagatran included diabetes mellitus (HR = 1.81 p=0.006), previous stroke or TIA (HR = 1.78 p=0.008), age ≥ 75 years (HR = 1.70 $p<0.001$) and aspirin use (HR = 1.68 p=0.02) (Douketis et al., 2006). Among individuals with history of stroke/TIA, the risk for major bleeding events may be greater than for patients with no prior stroke (p=0.086) (Akins et al., 2007). In addition, in the SPORTIF III and V trials approximately 20% of patients with a previous history of stroke or TIA received low-dose aspirin in addition to treatment with ximelagatran or warfarin on the advice of their physicians. The combination therapy was, in both cases, associated with a significant increase in major bleeding events when compared to anticoagulant treatment alone (2.2 times greater for ximelagatran and 3.3 times greater for warfarin) (Akins et al., 2007). Both Albers (2004) and Akins (2007) reported that approximately 6% of patients in the ximelagatran treatment groups experienced asymptomatic elevations of the liver enzyme alanine aminotransferase (ALT) to more than 3 times above the upper limit of normal.

Ximelagatran vs. Warfarin for stroke prevention in in patients with Nonvalvular Atrial Fibrillation: SPORTIF V (2005)

3922 patients with atrial fibrillation and one or more stroke risk factors were randomly assigned to receive either adjusted dose warfarin therapy (INR 2.0 – 3.0) or ximelagatran (36 mg twice daily). Primary events were stroke and systemic embolism. Mean follow-up time was 20 months.



Primary study events were stroke (ischaemic or haemorrhagic) or systemic embolic events. The primary event rate per year was 1.2% with warfarin therapy and 1.6% with ximelagatran (relative risk reduction in favour of warfarin = 0.45; 95% CI –0.13 to 1.0; p=0.13). Rates of major bleeding were similar between treatment conditions (p=0.15), however, combined major and minor bleeding events were significantly fewer in the group receiving ximelagatran.

In most patients, this resolves either spontaneously or once therapy is withdrawn. In approximately 1% of patients, abnormal liver function has been reported (Brighton, 2004). Reported increases in liver enzyme levels have made it necessary to monitor liver function closely. It is recommended that patients undergo monthly liver function tests for the first 6 months of treatment. Elevated enzymes rarely develop after 6 months. Therapy should be withdrawn if levels exceed 5 times the upper limit of normal at any time (Brighton, 2004). It should be noted that ximelagatran is not currently approved for use in North America.

In February 2006, AstraZeneca International withdrew ximelagatran (ExantaTM) from the market and announced the termination of its development citing concerns with reported risk for severe liver injury under conditions of prolonged use (in excess of 35 days) (AstraZeneca press release, www.astrazeneca.com/pressrelease/5217.aspx, 2006).

Conclusions Regarding Ximelagatran

There is level 1a evidence that treatment with the direct thrombin inhibitor ximelagatran/melagatran may not be inferior to treatment with warfarin. Ximelagatran treatment is associated with risk for liver injury and due to concerns with safety, it has been withdrawn from the market and its development terminated.

Ximelagatran may be equally effective as warfarin however, its development has been terminated due to risk of liver injury.

8.9.4.3 Dabigatran

Dabigatran etexilate is a pro-drug of dabigatran, an oral, reversible direct thrombin inhibitor that has been evaluated for use in prophylaxis of venous thromboembolism following orthopaedic surgery (Schulman & Reilly, 2009). Like melagatran, dabigatran has a rapid onset and offset necessitating twice daily administration (fixed dose). However, no coagulation monitoring is required. Approximately 80% of dabigatran etexilate is excreted, unchanged, by the kidneys and therefore, in individuals with renal insufficiency, plasma concentrations of the drug increase (Khoo & Lip, 2010; Schulman & Reilly, 2009). No commercially available blood test is available to monitor dabigatran blood levels. Thrombin Time is the most accurate form of measurement of clotting level for dabigatran.

Dabigatran has been studied in the acute treatment of venous thromboembolism, secondary prevention of venous thromboembolism, prevention of cardiac events in individuals with acute coronary syndrome and prevention of stroke in individuals with atrial fibrillation. Studies examining prevention of stroke are summarized in Table 8.9.4.3.1.

Table 8.9.2.3.3.1 Summary of Studies Evaluating Dabigatran in AF

Author, Year Study Design (PEDro Score) Sample Size	Intervention	Main Outcome(s) Result
RE-LY Study Connolly et al. (2009a) RCT (9) N=18113	E1: Dabigatran (110mg, 2/d) E2: Dabigatran (150mg, 2/d) C: Warfarin (dose adjusted)	• Combined primary outcome (stroke, systemic embolism) (+) • Incidence of major bleeding: E1 vs. C (+); E2 vs. C (-) • Incidence of haemorrhagic stroke (+) • Mortality (-)

RE-LY Substudy Ezekowitz et al. (2010) RCT (9) N=18113	E1: Dabigatran (110mg, 2/d) E2: Dabigatran (150mg, 2/d) C: Warfarin (dose adjusted) Note: Analysis based on vitamin K antagonist (VKA)-naïve vs. experienced patients	• Combined primary outcome (stroke, systemic embolism) (-) • Incidence of major bleeding events: E2 vs. C (-); VKA-experienced; E1 vs. C (+), VKA-naïve; E1 vs. C (-)
RE-LY Subgroup analysis Diener et al. (2010) RCT (9) N=18113	E1: Dabigatran (110mg, 2/d) E2: Dabigatran (150mg, 2/d) C: Warfarin (dose adjusted) Note: Analysis based on individuals with previous stroke or transient ischemic attack	• Incidence of stroke (-) • Combined primary endpoint (stroke, systemic embolism): individuals with previous stroke, E2 vs. C (+) • Incidence of major bleeding: E1 vs. C (+); E2 vs. C (-) • Vascular mortality and overall mortality: individuals with previous stroke: E1 vs. C (+)
RE-LY Subgroup analysis Ferreira et al. (2013) RCT (9) N=4904	E1: Dabigatran (110mg, 2/d) E2: Dabigatran (150mg, 2/d) C: Warfarin (dose adjusted) Note: Analysis based on individuals with previous symptomatic heart failure	• Vascular death (-) • Hospitalization (-) • Major intracranial bleeding: E1/E2 vs C (+)
RE-LY Subgroup analysis Hori et al. (2013) RCT (9) N_{Asian}=2782 $N_{non\text{-}Asian}$=15331	E1: Dabigatran (110mg, 2/d) E2: Dabigatran (150mg, 2/d) C: Warfarin (dose adjusted) Note: Analysis based on Asian individuals versus non-Asian individuals	• Incidence of stroke or systemic embolism in Asian patients: E1 vs C (-); E2 vs C (+) • Incidence of stroke or systemic embolism in non-Asian patients: E1 vs C (-); E2 vs C (+) • Incidence of stroke, ischemic stroke, haemorrhagic stroke, myocardial infarction, death between Asians and non-Asians (-) • Incidence of major bleeding events in Asians: E1/E2 vs C (+) • Rate of haemorrhagic stroke in warfarin treated Asians vs. non-Asians (+)
PETRO Study Ezekowitz et al. (2007) RCT (5) N=502	E1: Dabigatran (50/150/300mg, 2/d) + aspirin (81/325mg/d) E2: Dabigatran (50/150/300mg, 2/d) C: Warfarin (adjusted dose, INR 2.0-3.0)	• Incidence of clinically relevant and total bleeding events: 300mg; E1 vs. E2 (+) • Incidence of bleeding events: 150mg vs. 300mg(+); 50mg vs. 150mg (+)
RELY-ABLE (Extension of RE-LY trial) Connolly et al. (2013) Observational N_{Start}=5851 N_{End}=2188	E1: Dabigatran (110mg, 2/d) E2: Dabigatran (150mg, 2/d)	• Incidence of stroke (-) • Incidence of mortality (-) • Major bleeding events: E2 vs E1 (+) • Net clinical benefit (composite of stroke, bleeding, and death (-)

+ Indicates statistically significant differences between treatment groups

- Indicates non-statistically significant differences between treatment groups

Discussion

Advantages associated with dabigatran therapy include oral administration, minimal food and drug interactions, a wide therapeutic window and no requirement for regular blood testing, monitoring and dose adjustment (Siddiqui & Qureshi, 2010). However, dabigatran therapy may also be associated with increased risk for gastrointestinal bleeding and myocardial infarction (Connolly et al., 2009b; Diener et al., 2010; Siddiqui & Qureshi, 2010). The inferiority of dabigatran in preventing myocardial infarction was

further supported by Rasmussen et al. (2012) who found that apixaban resulted in statistically significantly fewer cases of myocardial infarction compared to dabigatran (Rasmussen et al., 2012).

In addition to demonstrating non-inferiority to dose-adjusted warfarin therapy, results of the RE-LY trial suggest that there may be a modest net clinical benefit associated with the use of dabigatran 150 mg b.i.d. compared to warfarin in the total participant sample.

A subgroup analysis of the RE-LY trial compared dabigatran with warfarin therapy in patients with both atrial fibrillation and a previous history of stroke or TIA (Diener et al., 2010). In that analysis, neither dose of dabigatran was associated with a statistically significant reduction in risk for the primary study outcomes of stroke or systemic thromboembolism. However, both doses were associated with a significant reduction in risk for haemorrhagic stroke in individuals with and without previous stroke. In addition, dabigatran 110 mg twice daily was associated with a reduction in risk for vascular death and death from any cause when compared to warfarin therapy for individuals with previous stroke (Diener et al., 2010; Lane & Lip, 2010).

Of course, assessment of potential advantages or disadvantages of any anti-coagulant therapy must also include risks for bleeding events (Lane & Lip, 2010). In terms of adverse bleeding events, for individuals with previous stroke and AF, dabigatran 110 mg was associated with significant reductions in major bleeding (RR=0.66, 95% CI 0.48-0.90), life threatening bleeding (RR = 0.57, 95% CI 0.38-0.87) and intracranial bleeding (RR=0.20, 95% CI 0.08-0.47) when compared with warfarin therapy. Although dabigatran 150 mg was associated with a decreased risk for intracranial bleeding (RR=0.41, 95% CI 0.21-0.79), there was no significant advantage over warfarin in terms of risk for major or life-threatening bleeding events. In addition, dabigatran 150mg was associated with a significant increase in risk for gastrointestinal bleeding in individuals with previous stroke (RR=1.67, 95% CI 1.09-2.56) vs. warfarin. When examining the net clinical benefit in the group of individuals, there was a significant net benefit associated with dabigatran 110 mg twice daily compared to warfarin therapy (RR=0.81, 95% CI 0.66-1.00). There was no significant net benefit reported for dabigatran 150 mg for this high risk group (RR=1.01, 95% CI 0.84-1.23) (Diener et al., 2010).

In RE-LY, there were a high percentage of participants who were treated with combined ASA and warfarin (approximately 20%) and this could have contributed significantly to the elevated rates of bleeding events observed among individuals allocated to the warfarin therapy condition (Moia & Mannucci, 2009; Worthington & Gattellari, 2009). There were high rates of discontinuation, particularly within the dabigatran conditions ($p<0.001$ vs. warfarin at both 1 and 2 year follow-up). Patients receiving dabigatran experienced a significantly greater number of serious adverse events and gastrointestinal symptoms (pain, vomiting and diarrhea) than those assigned to treatment with warfarin. Dabigatran therapy at 150 mg b.i.d. was associated with increased risk for gastrointestinal bleeding. Connolly et al. (2009b) suggest that this may, in part, be due to the composition of dabigatran capsules (dabigatran-coated pellets with a tartaric acid core).

More than a quarter of the patients included in the RE-LY trial (i.e., 27%) had a history of symptomatic heart failure (HF). A subgroup analysis revealed that regardless of treatment allocation, a higher rate of stroke or SE (1.75%/yr vs. 1.35%/yr), vascular death (4.69%/yr vs. 1.67%/yr) and hospitalization (22.41%/yr vs. 19.35%/yr) was found among patients with HF compared to those without (Ferreira et al. 2013). The rates of major bleeding events and intracranial hemorrhage were comparable among the two population groups. In patients with HF, warfarin therapy resulted in a higher incidence of stroke or SE (1.92%/yr) compared to patients receiving dabigatran 110mg (1.90%/yr) (HR=0.99, 95% CI 0.69-1.42) and those receiving the higher dose of dabigatran (i.e., 150mg) (1.44%/yr) (HR=0.75, 95% CI 0.51-1.10)

however, the difference was not significant (Ferreira et al. 2013). Similarly, major bleeding events occurred less in the dabigatran treated HF patients (110mg: 3.26%/yr; 150mg: 3.10%/yr) compared to those allocated to warfarin therapy (3.90%/yr) but no significant difference was found. Conversely, intracranial bleeding occurred significantly more in the warfarin-treated patients (0.65%/yr) compared to either those receiving 110mg of dabigatran (0.22%/yr) or those receiving 150mg of dabigatran (0.26%/yr) (Ferreira et al. 2013). A similar trend was found when total bleeding events were analyzed. Overall, the result of this subgroup analysis was consistent with the findings from the RE-LY trial.

Previous studies have noted that patients with atrial fibrillation of Asian ethnicity have a higher risk of hemorrhage while receiving anticoagulation therapy (Shen et al. 2007). In a subgroup analysis of the RE-LY trial, a total of 2780 patients comprising of 15.4% of the RE-LY sample population were of Asian descent. The rates of stroke in Asian patients receiving warfarin (3.06%/yr) were found to be non-significantly higher compared to Asian patients receiving 110mg of dabigatran (2.50%/yr) however, significant differences were found between those taking warfarin and those taking 150mg of dabigatran (1.39%/yr) (HR=0.45, 95% CI 0.28-0.72). In non-Asian patients, lower rates of stroke were found across the treatment conditions (i.e. Warfarin: 1.48%/yr; 110mg dabigatran: 1.37%/yr; 150mg dabigatran: 1.06%/yr) however, no significant interaction between region and treatment was found. For other outcomes such as major bleeding events, analyses evaluating region (i.e., Asian vs non-Asian) and treatment (i.e., dabigatran 150mg vs warfarin) interactions resulted in significant findings but not when the analyses were adjusted for age. In line with previous findings, the rate of hemorrhagic stroke was higher in warfarin treated Asian patients (0.75%/yr) relative to non-Asian patients (0.32%/yr; p=0.007). In fact, all bleeding outcomes (i.e., major, life-threatening, total, intracranial, minor, hemorrhagic, and gastrointestinal) were higher in Asians than in non-Asians receiving warfarin. Despite these differences, it is important to take caution when interpreting these findings. The study noted that the number of Asians (N=2780) was considerably smaller compared to the number of non-Asians (N=15331), and some demographic components were not comparable at baseline. For instance, Asians tended to be younger in age and have higher frequencies of stroke and myocardial infarction than non-Asians.

Patients that had not discontinued the use of dabigatran after the end of the RE-LY study were followed-up for a median of 2.3 years to determine the long-term effects of the dabigatran (Connolly et al. 2013). A total of 5851 patients (150mg dabigatran N=2937; 110mg dabigatran N=2914) were enrolled in the study and only 2188 patients (150mg dabigatran N=1102; 110mg dabigatran N=1086) continued with the RELY-ABLE study beyond the 28-month visit. There was a slight benefit associated with the use of a higher dose of dabigatran over a lower dose for reducing the risk of ischemic stroke (HR=0.92, 95% CI 1.04-1.53), however total mortality (HR=0.97, 95% CI 0.80-1.19), vascular mortality (HR=1.03, 95% CI 0.78-1.35), and a composite of disabling stroke, life-threatening bleed, and death (HR=1.07, 95% CI 0.94-1.22) were comparable among the two doses. Conversely, the higher dose of dabigatran led to an increased risk of minor and major bleeding compared to a lower dose of dabigatran (HR=1.21, 95% CI 1.07-1.36; HR=1.26, 95% CI 1.04-1.53). Overall, no difference in the net clinical benefit as measured by the composite of stroke, death and bleeding, was found between the two doses. Furthermore, compared to the RE-LY trial, the outcomes remained consistent after an additional 2.3 years of treatment.

Results of the PETRO study suggested that dabigatran may have platelet-activating effects (Ezekowitz et al., 2007). Given the role of platelet aggregation in coronary thrombosis, the increased risk for myocardial infarction associated with dabigatran 150 mg b.i.d. vs. warfarin could be a result of this increased platelet aggregation (Tomoda, 2009).

At present, dabigatran is available in over 100 countries, and it has been approved for use in both Canada and the United States. It is also much more expensive than the widely-available warfarin (Gage et al.,

2001). In a cost effectiveness study of Health Canada approved dosing (150 mg b.i.d. for patients <80 years, 110 mg b.i.d. for patients ≥80), the incremental cost effectiveness ratio (ICER) associated with dabigatran was $10,440/QALY vs. warfarin therapy (when it was assumed that warfarin was used as per research or trial conditions) (Sorensen et al., 2011). Of course, creation of the economic model relied heavily upon the information provided by the RE-LY trial, which may not necessarily reflect "real life" prescribing, use and adherence. When dabigatran therapy was compared to "real life" prescribing of warfarin therapy, the ICER of dabigatran was reduced to $3,962/QALY.

An economic evaluation performed in the United Stated based on both low and high dose dabigatran vs. warfarin reported ICERs of $51,229/QALY for dabigatran 110 mg b.i.d. and $45,372/QALY for 150 mg b.i.d. (Freeman et al., 2011); while a more recent American study reported an ICER of $25,000/QALY associated with a dose of 150 mg b.i.d in a population of individuals with prior stroke and aged ≥ 70 years (Kamel et al., 2012). The authors suggested that, for individuals with previous stroke and TIA, dabigatran may be considered a cost-effective alternative therapy to warfarin (Kamel et al., 2012).

An economic study conducted in the UK used a discrete simulation model that takes patient characteristics, experience and clinical events over time into account (Pink et al., 2011). The authors used participants of the RE-LY study as the basis for the population model used in the simulation. Overall, both low and high doses of dabigatran were associated with small benefits measured in quality adjust life years (QALYs: 0.09 and 0.14, for low and high dose respectively). Expressed in Canadian dollars, the reported ICER for low dose dabigatran (vs. warfarin) was estimated to be $68,235 (per QALY gained) and $36,560 for high dose therapy. Sensitivity analysis demonstrated that high dose dabigatran (150 mg b.i.d) was more cost effective in individuals whose risk for stroke was greater (based on a $CHADS_2$ score ≥3) and control of the INR more difficult (Pink et al., 2011).

Conclusions Regarding Dabigatran

There is level 1a evidence that a dabigatran may be more effective in preventing stroke than warfarin. With respect to dabigatran prescription, a higher dose (150mg b.i.d) appears to be more effective than a lower dose (110mg b.i.d) at reducing the risk of ischemic stroke however, it also increases the risk of major bleeding. The risk or mortality is comparable amongst the two doses and based on a composite of major ischemic, hemorrhagic, and fatal events, both doses demonstrate a similar net clinical benefit. This effect is observed up to 5 years of treatment.

Dabigatran may be more effective than warfarin therapy at reducing the risk of stroke. A higher dose of dabigatran (150mg b.i.d) appears to be associated with a reduced risk of stroke and an increased risk of major bleeding compared to a lower dose of dabigatran (110mg b.i.d), however; the two doses were found to achieve comparable net clinical benefits observed over a period of 5 years of treatment.

8.9.4.4 Rivaroxaban

Rivaroxaban is an orally active, direct, Factor Xa (FXa) inhibitor (Kubitza et al., 2008; Kubitza et al., 2005). It has been used in the prevention of venous thromboembolism in individuals undergoing orthopaedic surgery (Kubitza et al., 2008) and evaluated as a treatment alternative for acute deep vein thrombosis or pulmonary embolism (Bauersachs et al., 2010).

Rivaroxaban is a fixed dose alternative to warfarin therapy that, like dabigatran, requires no laboratory monitoring (Bauersachs et al., 2010; Mega, 2011). In healthy older adults, rivaroxaban appears to reach

maximum plasma concentration approximately 4 hours following administration (Kubitza et al., 2008). Treatment at 30 – 50 mg. doses appeared well tolerated and was associated with no major adverse events. Some minor bleeding events were reported; however, these resolved spontaneously. In addition, headache was reported by approximately 22% of participants (Kubitza et al., 2008).

Studies examining the use of rivaroxaban in individuals with AF for the prevention of stroke are summarised in Table 8.9.4.4.1.

Table 8.9.4.4.1 Summary of Studies Evaluating the Use of Rivaroxaban in Atrial Fibrillation

Author, Year Study Design (PEDro Score) Sample Size	Intervention	Main Outcome(s) Result
ROCKET-AF Patel et al. (2011) RCT (10) N=14264	E: Rivaroxaban (20mg/d) C: Warfarin (dose adjusted, INR 2.0-3.0)	• Composite primary outcome (stroke, systemic embolism) (-) • Incidence of major or clinically relevant bleeding events (-) • Incidence of intracranial haemorrhage (+)
ROCKET-AF Hankey et al. (2012b) Patel et al. (2011) RCT (10) Sub-group analysis N=14264	E: Rivaroxaban (20mg/d) C: Warfarin (dose adjusted, INR 2.0-3.0) Note: Analysis based on individuals with previous history of stroke or transient ischemic attack	• Composite primary outcome (stroke, systemic embolism) (-) • Incidence of adverse events (-) • Incidence of major or clinically relevant bleeding events (-)
Mega et al. (2012) RCT (9) N=15526	E1: Rivaroxaban (2.5mg, 2/d) E2: Rivaroxaban (5mg, 2/d) C: Placebo	• Composite primary endpoint (cardiovascular mortality, myocardial infarction, stroke): E1/E2 vs. C (+) • Cardiovascular and overall mortality: E1 vs. C (+) • Incidence of major bleeding events: C vs E1/E2 (+)

+ Indicates statistically significant differences between treatment groups
- Indicates non-statistically significant differences between treatment groups

Discussion

The ROCKET-AF trial demonstrated the non-inferiority of rivaroxaban, a Factor Xa inhibitor, to warfarin for the prevention of stroke and system embolism in high risk individuals with atrial fibrillation (Patel et al., 2011). In addition, *a post hoc* analysis from the ROCKET-AF trial demonstrated no significant difference in treatment effectiveness or risk for adverse events between groups of individuals with or without previous stroke or TIA suggesting that rivaroxaban may be considered as a potential alternative to warfarin in secondary prevention of stroke (Hankey et al., 2012b). A secondary analysis by (Tanahashi et al., 2013) was analyzed to determine the consistency of safety and efficacy profile of rivaroxaban. Results showed no significant interaction in the primary safety outcome or major bleeding of rivaroxaban compared to warfarin between patients in the primary prevention group and those in the secondary prevention group (Tanahashi et al., 2013).

Although there were no overall between group differences in major or clinically relevant bleeding events, the risk for intracerebral haemorrhage appeared to be lower in the group receiving treatment with rivaroxaban compared to dose-adjusted warfarin while bleeding from a gastrointestinal site appeared more common among individuals treated with rivaroxaban (Patel et al., 2011). Rates of bleeding events may have been affected by the addition of concurrent aspirin therapy. The authors report that, at some point during the treatment period, more than one-third of patients in each condition also took aspirin (Patel et al., 2011). Mega et al. (2012) also found that patients with recent acute coronary syndrome receiving rivaroxaban (patients were also taking low dose aspirin) had a reduced risk of the composite end

point of death from cardiovascular causes, myocardial infarction or stroke in comparison to stroke. Additionally, as found in Patel et al. (2011), rivaroxaban increased the risk of major bleeding. Risk of intracranial hemorrhage risk was also increased, but not the risk of fatal bleeding (Mega et al., 2012).

Conclusions Regarding Rivaroxaban

There is level 1b evidence that treatment with fixed dose rivaroxaban (20 mg p.o. o.d.) is not superior to dose-adjusted warfarin for the prevention of stroke in high risk individuals with atrial fibrillation. Treatment with rivaroxaban may also be associated with less risk for intracranial bleeding when compared with dose-adjusted warfarin.

Rivaroxaban is a Factor Xa inhibitor that may provide an alternative to treatment with dose-adjusted warfarin in high-risk individuals with stroke.

8.9.4.5 Apixaban

Like rivaroxaban, apixaban is an oral, direct, Factor Xa inhibitor that has been evaluated as an alternative to the vitamin K antagonist, warfarin, for the prevention of stroke in individuals with atrial fibrillation (Lopes et al., 2010). Clinical trials that have examined the use of apixaban in the prevention of stroke are summarized in Table 8.9.5.5.1.

Table 8.9.4.5.1 Summary of Studies Evaluating the Use of Apixaban in Atrial Fibrillation

Author, Year Study Design (PEDro Score) Sample Size	Intervention	Main Outcome(s) Result
AVERROES Connolly et al. (2011) RCT (10) N=5599	E: Apixaban (5mg, 2/d) C: Aspirin (81-324mg/d)	• Composite primary outcome (stroke, systemic embolism) (+) • Incidence of ischemic stroke (+) • Incidence of haemorrhagic stroke (-) • Mortality (-) • Major bleeding events (-)
ARISTOTLE Granger et al. (2011) RCT (10) N=18201	E: Apixaban (5mg, 2/d) C: Warfarin (dose adjusted, INR 2.0-3.0)	• Composite primary outcome (stroke, systemic embolism) (+) • Incidence of ischemic stroke (-) • Incidence of haemorrhagic stroke (+) • Mortality (+) • Major or intracranial bleeding events (+)

+ Indicates statistically significant differences between treatment groups
- Indicates non-statistically significant differences between treatment groups

Discussion

The AVERROES trial examined the use of apixaban compared to ASA as an alternative to dose-adjusted warfarin in a group of high risk individuals with AF for whom vitamin K antagonist therapy was considered to be inappropriate (Connolly et al., 2011). In that trial, use of apixaban was associated with a significant reduction of risk for stroke or systemic embolism, and no increased risk for major bleeding events, when compared to ASA.

Use of apixaban has been also been compared directly to dose-adjusted warfarin. Results of the ARISTOTLE trial suggest that, in high risk individuals with atrial fibrillation, treatment with apixaban may be superior to dose-adjusted warfarin in terms of reduction of risk for haemorrhagic stroke and all-cause

mortality. In addition, use of apixaban appears to be associated with a reduction in risk for intracranial bleeding events (Granger et al., 2011).

As for rivaroxaban, no significant interaction between treatment assignment and history of previous stroke could be identified in any of the published subgroup analyses, suggesting that treatment with apixaban is an appropriate alternative to dose-adjusted warfarin in the secondary prevention of stroke for individuals with AF (Diener et al., 2012; Easton et al., 2012). Given that the risk for stroke was significantly greater among individuals with previous history of stroke in both of these major trials, absolute benefit from treatment with apixaban may be greater within this patient group (Diener et al., 2012).

Conclusions Regarding Apixaban

There is level 1b evidence that treatment with apixaban may be superior to ASA for the reduction in risk of stroke in individuals with AF and for whom a vitamin K antagonist is considered unsuitable.

There is level 1b evidence that treatment with apixaban may be superior to dose-adjusted warfarin for the prevention of stroke or systemic embolism in high risk individuals with atrial fibrillation.

There is level 1b evidence that treatment with apixaban may be associated with reduced risk for death from any cause and for major bleeding events when compared to treatment with dose-adjusted warfarin.

Apixaban may provide another fixed dose option to dose-adjusted warfarin therapy for the secondary prevention of stroke in individuals with AF. Like rivaroxaban and dabigatran, it requires no laboratory monitoring.

8.9.5 Drug Management

8.9.5.1 Patient Decision Aids

Randomized controlled trials examining the use of decision aids in implementing anti-coagulant therapy are summarized in Table 8.9.5.1.

Table 8.9.5.1 Summary of Patient Decision Aids and Anti-thrombotic Therapy

Author, Year Study Design (PEDro Score) Sample Size	Intervention	Main Outcome(s) Result
McAlister et al. (2005) RCT (8) N=446	E: Self-administered booklet and audiotape decision aid C: Usual care	• Change in proportion of patients taking appropriate anti-thrombotic therapy: 3mo (+); 12mo (-)
Man-Song-Hing et al. (1999) RCT (6) N=287	E: Audiobooklet decision aid C: No decision aid	• Number of patients choosing an anti-thrombotic therapy (+) • Knowledge of aspirin and warfarin (+) • Satisfaction or decisional conflict (-)
Evans-Hudnall et al. (2014) RCT (6) N_{Start}=60 N_{End}=52	E: Secondary stroke prevention (STOP) program C: Usual care	• Improvement in stroke knowledge (+) • Abstinence from smoking (+)

Mazor et al. (2007) RCT (5) N=317	E1: Narrative evidence (patient anecdotes) E2: Statistical evidence E3: Combined therapy (E1 + E2) C: Usual care (no video)	• Knowledge gain: E1/E2/E3 vs. C (+) • Positive beliefs of the importance of testing: E1/E2/E3 vs. C (+) • Positive beliefs of benefits associated with warfarin therapy: E1/E2/E3 vs. C (+) • Attendance for lab testing (-) • Beliefs of importance of lab testing: E1 vs. E2 (+)
Thomson et al. (2007) RCT (5) N=109	E1: Computerized decision aid in shared decision-making clinic E2: Evidence-based paper guidelines/physician recommendations	• Decision conflict: post-intervention E1 (+); at 3mo (-) • Level of knowledge (-)

+ Indicates statistically significant differences between treatment groups
- Indicates non-statistically significant differences between treatment groups

Discussion
The use of decision aids appears to be associated with improved knowledge and a decrease in uncertainty regarding warfarin therapy (Man-Son-Hing et al., 1999; McAlister et al., 2005; Thomson et al., 2007). In addition, the use of anecdotal or narrative information may serve to improve patient belief or recognition of the importance of regular laboratory testing (Mazor et al., 2007). However, improved knowledge and/or reduction of uncertainty does not necessarily improve adherence to guidelines. In both Thomson et al. (2007) and Man-Song-Hing et al. (1999), participants in the decision aid conditions were less likely to choose warfarin therapy despite improvements in decision conflict or increased knowledge.

Conclusions Regarding Patient Decision Aids and Use of Warfarin Therapy.

There is level 1a evidence that the use of patient decision aids may be associated with an increase in patient knowledge and a decrease in uncertainty regarding treatment.

There is level 2 evidence that incorporating narrative information in the form of patient anecdotes may help increase patient knowledge and belief in the importance of laboratory testing.

There is level 1b evidence that, among high risk patients with atrial fibrillation, use of patient aids may be associated with a temporary increase in the use of appropriate warfarin-based therapy.

Patient decision aids may increase patient knowledge, reduce uncertainty regarding treatment options and may result in more realistic expectations regarding therapy.

8.9.5.2 Self-testing and Self-management
Efforts to improve adherence to therapy by minimizing or streamlining the process of testing and dose adjustment have led to the development of outpatient anticoagulation clinics and, more recently, portable devices that may be used to measure INR based on a drop of capillary blood (self-testing). With these devices, patients may relay INR results to their healthcare provider who may suggest dose adjustments or, given the appropriate training, may adjust the dose of their medications on their own (self-management) (Bloomfield et al., 2011). The effectiveness of self-testing and self-management programs for oral anti-coagulation therapy has been the subject of two recent meta-analyses. These studies are summarized in Table 8.9.5.2.1.

Table 8.9.5.2.1 Meta-Analyses Examining Self-testing and Self-management of Anti-coagulation Therapy

Study	Meta-Analysis Description and Results
Garcia-Alamino et al. (2010)	18 randomized trials were included in this Cochrane review and meta-analysis (n=4,723). Trials included both adult and paediatric patients on long-term anticoagulation therapy for a variety of indications (e.g. valve replacement, venous thromboembolism, atrial fibrillation). Pooled analysis of 13 trials demonstrated that self-testing and management was associated with reduced risk for a thromboembolic event (RR = 0.50, 95% CI 0.36-0.69) and for all-cause mortality (RR = 0.64, 95% CI 0.46-0.90), when compared to usual or standard care. While trials that examined only self-management showed similarly significant reductions in risk thromboembolic events and mortality, those that studied self-testing or monitoring did not (RR=0.57, 95% CI 0.32-1.0 for thromboembolism and RR=0.84, 95% CI 0.50-1.41 for mortality). 12/18 trials reported improvement in terms of the percentage of mean INR measurements falling within the therapeutic range.
Bloomfield et al. (2011)	Included 22 randomized controlled trials of long-term, oral anti-coagulation therapy with a vitamin K antagonist for adult outpatients in order to compare therapy using patient self-testing (with or without self-management) with therapy managed by healthcare professionals (in clinical settings). Three major outcomes were evaluated; 1) major thromboembolic complications (stroke, new or recurrent DVT, pulmonary embolism or arterial embolism), 2) all-cause mortality 3) major bleeding events. Overall, the mean participant age was 65 years (range = 42-75). 5 studies examined self-testing only (with dose adjustment made by a clinic) while 14 examined self management interventions (testing and dose adjustment done by the participant). Warfarin was the most commonly used anti-coagulant therapy. Usually, interventions included 2-4 group training sessions of 1-3 hours over a period of several weeks followed by home practice and a test to ensure competency prior to beginning the intervention. Patients often had access to a 24-hour help telephone help line. Control groups (usual care) usually consisted of anticoagulation therapy/management in clinic, physician offices or primary care settings. Pooled analysis demonstrated a significantly reduced odds for major thromboembolic events (OR=0.58, 95% CI 0.45-0.75, p<0.001) and total mortality (OR=0.74, 95% CI 0.63-0.87, p<0.001), but no increased odds for major bleeding events (OR=0.89, 95% CI 0.75-1.05) associated with self-testing/self-management interventions vs. usual care. There was no difference in the percentage of INRs in the therapeutic range between self-testing/self management vs. usual care.

Discussion

Although self-monitoring and self-management interventions are associated with favourable outcomes in terms of thromboembolic events and mortality and have the potential to improve the quality of oral anticoagulation therapy, there are many limitations associated with their use. In both reviews summarized above, relatively few of the potential trial participants were actually included in and completed the study. Bloomfield et al. (2011) reported that, on average fewer than 50% of potentially eligible patients met all inclusion criteria, completed the mandatory intensive training and agreed to be allocated randomly to an intervention. Garcia-Alamino et al. (2010) stated that the average proportion of potential participants who could not or would not participate was 68% (ranging from 31% to 88%) and that, in trials focussing on older individuals, exclusion rates were much higher than average. In addition, approximately one-quarter of individuals who were assigned to a self-monitoring or management condition were unable to complete the study often due to problems with the devices used, physical limitations, lack of confidence in their ability to follow the study protocol and problems in attending the required training sessions.

Patients who met all study inclusion criteria and were willing and able to participate had to have adequate dexterity, visual acuity and cognitive ability to manage adherence to the required study protocol

(Bloomfield et al., 2011). Although some participants may have been unwilling or unable to complete the training sessions, those that did received much more extensive information and education than those individuals allocated to usual care (Bloomfield et al., 2011). Overall, individuals who did persist in the self-testing and self-management conditions reported higher levels of satisfaction and quality of life than those participants assigned to usual care (Bloomfield et al., 2011; Garcia-Alamino et al., 2010). While participation in self-testing may simply not be feasible for a large proportion of individuals with atrial fibrillation, for a carefully selected group of patients, it may represent an opportunity for independence that results in improved satisfaction and quality of life (Garcia-Alamino et al., 2010).

Conclusions Regarding Self-testing and Self-Monitoring of Oral Anticoagulation Therapy

There is level 1a evidence that self-management programs are associated with a reduced risk of thromboembolic events and mortality. However, these programmes are more likely to be feasible for a small, select group of patients only.

There is level 1a evidence that self-testing and self-management programmes may not be associated with increased risk of bleeding events.

Self-testing and self-management programs may be an effective approach to the administration of oral anticoagulation therapy for a select group of patients only.

8.9.5.3 Guideline Adherence and Inpatient Anticoagulation

Indredavik et al. (2005) recorded data on 394 patients over the age of 60 with known atrial fibrillation admitted to a stroke unit for acute treatment. At the time of admission, 29% were being treated with warfarin; however, only 16% of these had an INR≥2.0. The proportion of patients treated with warfarin increased to 68% by discharge. Patients receiving no anticoagulation therapy (OR=2.5), ASA (OR=2.4) or warfarin with an INR less than 2.0 (OR=3.7) were more likely than patients receiving warfarin therapy (INR≥2.0) to experience poor functional outcome at 7 days post stroke. Similarly, optimal anticoagulation was associated with less risk of the combined outcome of death or discharge to a nursing home facility. For the study outcomes of death (alone) or stroke severity, no significant difference was noted between treatment groups (Indredavik et al., 2005).

Hospital-based performance improvement programs to improve adherence to guidelines for anticoagulation therapy for individuals with atrial fibrillation are summarized in Table 8.9.5.3.1.

Table 8.9.5.3.1 Summary of Guideline Adherence and Inpatient Anticoagulation

Author, Year Study Design (PEDro Score) Sample Size	Intervention	Main Outcome(s) Result
Peng et al. (2014) RCT (4) N_{Start}=3821 N_{End}=3821	E: Standard Medical Management in Secondary Prevention of Ischemic Stroke in China (SMART) program C: Usual care	• Adherence to statin treatment (+) • Adherence to other drugs (-)

+ Indicates statistically significant differences between treatment groups
- Indicates non-statistically significant differences between treatment groups

Discussion

It has been demonstrated that, for patients with AF, treatment with appropriate anticoagulation therapy may be associated with improved functional outcome and reduced risk for either discharge to long-term care or death (Indredavik et al., 2005). Indredavik et al. (2005) reported substantial increases in the use of warfarin therapy over the course of hospital admission for stroke. Although not stroke specific, the results presented by Duff and Walker (2010) suggest that a coordinated, multidisciplinary approach may be effective in addressing specific goals in the application of evidence-based practice in the administration of anti-coagulation therapy.

In the recent GTWG-stroke program, patients admitted with stroke or TIA to participating facilities experienced increasing rates of treatment only if there was current ECG documentation to support the diagnosis of AF. Decision aids and supports within this program were directed primarily at the group of individuals with current AF. Although the use of warfarin was indicated for secondary prevention in this high-risk group of patients, only one-half (49.4%) of patients with a history AF (not ECG-documented on the current admission) were prescribed treatment (Lewis et al., 2009).

Conclusion Regarding Guideline Adherence

There is level 2 evidence suggesting that a coordinated, multidisciplinary approach may result in improved adherence to specific targeted guidelines.

Improved adherence to guidelines for oral anti-coagulation therapy may be facilitated by a coordinated, multidisciplinary and goal-driven approach.

8.9.6 Other Cardiac Diseases

The types of cardiac disease that contribute to the risk of cardioembolic stroke include: valvular heart disease (including endocarditis, mitral valve prolapse and prosthetic heart valves), recent myocardial infarction, intracardiac thrombus, dilated cardiomyopathy, sick sinus syndrome, patent foramen ovale, hypokinetic/akinetic left ventricular segment, and calcification of the mitral valve.

Overall, approximately 20% of strokes are cardioembolic. Acute myocardial infarction is infrequently associated with stroke, occurring in only 0.8% of patients. There is a 1-2% per year risk of ischaemic stroke after myocardial infarction with the risk being greatest in the first month after the MI. Perioperative stroke occurs in 1-7% of patients undergoing cardiac surgical procedures (reference). Risk factors include: previous neurological events, atrial fibrillation, diabetes mellitus, increasing age, aortic atherosclerosis and duration of bypass.

The Aspirin & Coumadin after Acute Coronary Syndromes (ASPECT-2) study examined and compared the effectiveness of ASA and moderate intensity anti-coagulation therapy in preventing the occurrence of ischaemic events following myocardial infarction (Van Es et al., 2002). Recent research has suggested that patent foramen ovale (PFO) may lead to higher risk of stroke (Carroll et al., 2013; Hornung et al., 2013) however, in most cases PFO is an incidental finding and not the cause of the patient's stroke. PFO is an incomplete closure of the foramen ovale within the heart that allows for the passage of blood from venous to arterial circulation and occurs in about 25% of adults. Details of the ASPECT-2 study and trials examining the PFO's role in cardiac disease and stroke are summarized in Table 8.9.6.1.

Table 8.9.6.1 Summary of Studies Evaluating Other Cardiac Disease

Author, Year Study Design (PEDro Score) Sample Size	Intervention	Main Outcome(s) Result
ASPECT-2 Research Group Van Es et al. (2002) RCT (7) N=999	E1: High-intensity oral anticoagulation E2: Low-dose aspirin + moderate intensity oral anticoagulation C: Low-dose aspirin	• Composite primary outcome (myocardial infarction, stroke, death): E1/E2 vs. C (+) • Frequency of minor bleeding: E2 vs. C (+) • Rate of major bleeding (-)
Carroll et al. (2013) RCT (6) N_{Start}=980 N_{End}=851	E: Closure of the patent foramen ovale C: Medical therapy	• Incidence of recurrent stroke (+)
Hornung et al. (2013) RCT (6) N_{Start}=660 N_{End}=587	E1: Amplatzer patent foramen ovale (PFO) occluder E2: Helex septal occluder E3: CardioSEAL-STARflex device	• Composite primary outcome (recurrent cerebral ischemia, neurological mortality, any other paradoxical embolism within 5yr of index procedure): E1 vs. E2/E3 (+) • Incidence of stroke, transient ischemic attack or cerebral mortality (-)
Furlan et al. (2012) RCT (6) N_{Start}=909 N_{End}=909	E: STARFlex septal closure device C: Conventional medical therapy (warfarin, aspirin, or both)	• Recurrence of stroke (-) • Recurrence of TIA (-) • Recurrence of stroke and TIA (-)
Meier et al. (2013) RCT (6) N_{Start}=414 N_{End}=341	E: Amplatzer PFO Occluder C: Conventional medical therapy (antiplatelet or anticoagulant)	• Composite of stroke, TIA, or peripheral embolism (-) • Death (-) • Stroke (-) • TIA (-)

+ Indicates statistically significant differences between treatment groups
- Indicates non-statistically significant differences between treatment groups

Discussion

The ASPECT-2 research group examined 999 patients with a previous myocardial infarction and separated them into 3 groups; high-intensity oral anti-coagulation, low-dose asprin plus moderate-intensity oral anti-coagulation, and low-dose asprin. Results suggest that both doses of anti-coagulation therapy were more effective than the low-dose asprin in reducing the risk of stroke (van Es et al., 2002). Furthermore, there was no significant difference between any of the groups in rate of major bleeding (van Es et al., 2002).

The Amplatzer device has been recently investigated to evaluate its benefits on recurrent stroke in patients with patent foramen ovale. In Hornung et al. (2013) the Amplazer was found to be superior over the Helex septal occluder and the CardioSEAL-STARFlex device at reducing the composite of various paradoxical embolism, neurological mortality, and recurrent cerebral ischemia, however all of the devices were comparable at reducing the risk or recurrent stroke. Compared to traditional medical therapy including warfarin and aspiring or a combination of the two drugs, the Amplazer was not found to superior at reducing the risk of stroke, TIA or death in patients with a crytogenic stroke or TIA with a patent foramen ovale (Meier et al., 2013). Furthermore, the STARFlex device also failed to demonstrate superiority over the use of antiplatelets or anticoagulants at reducing the risk of recurrent stroke, death, or TIA. Overall, no clear benefit of patent foramen closure is found.

Conclusions Regarding Cardiac Abnormalities

There is level 1a evidence that patent foramen closure does not reduce the risk of recurrent stroke, death or TIA relative to traditional medical therapy in patients with cryptogenic strokes and patent foramen ovale.

No clear benefit is found as a result of patent foramen ovale closure in patients with cryptogenic strokes.

8.9.7 Treatment Recommendations

The current Canadian Stroke Best Practice Guidelines recommend the following treatment for patients with atrial fibrillation (See table 8.9.7.1):

Table 8.9.7.1 Canadian Stroke Best Practice Recommendations (Coutts et al., 2015)

- Patients with TIA or ischemic stroke AND atrial fibrillation should receive oral anticoagulation. In most patients, direct oral anticoagulation such as apixaban, bagigatran, or edoxaban, should be prescribed in preference over warfarin. When selecting oral anticoagulants, patient-specific criterial should be considered (available at www.strokebestpractice.ca).
- The time to start oral anticoagulation following TIA or ischemic stroke is unclear and therapy should be started as soon as it is through to be safe for the patient.
- For patients with acute ischemic stroke and atrial fibrillation, routine use of bridging with heparin is not recommended. Physicians should use antiplatelet agents until the patient is anticoagulated.

Conclusions Regarding Canadian Stroke Best Practice Recommendations:

Patients with ischemic stroke and atrial fibrillation should receive oral anticoagulation (such as apixaban, bagicatran, or edoxaban) as soon as it is thought to be safe for the patient. The use of heparin for bridging is not recommended, the patient should instead be given antiplatelets until anticoagulated.

Summary

1. ***There is level 1a evidence that the use of anti-coagulation therapy, particularly with adjusted dose warfarin, may substantially reduce the risk of primary and secondary stroke in individuals with atrial fibrillation.***
2. ***There is level 1a evidence that treatment with ASA 300 – 325 mg/day may be associated with reduced risk of stroke when compared to no treatment in individuals with atrial fibrillation. However, anticoagulant therapy (dose-adjusted warfarin) may be more effective in preventing strokes among individuals with atrial fibrillation than antiplatelet therapy (ASA).***
3. ***There is level 1b evidence that oral anticoagulation therapy may be more effective than ASA + clopidogrel in the prevention of stroke in individuals with atrial fibrillation. However, for patients not eligible for oral anticoagulation, ASA + clopidogrel may be associated with reduced risk for stroke when compared to ASA monotherapy.***
4. ***There is level 1b evidence that use of ASA + clopidogrel may be associated with increased risk for bleeding events compared with ASA monotherapy. Risk for major bleeding events with dual therapy may be similar to that reported for oral anticoagulation with vitamin-K antagonists.***
5. ***There is level 1b evidence that Indobufen may be as effective as warfarin, but is associated with a reduced risk of bleeding events. It is currently not used in the Canadian clinical practice.***
6. ***There is level 1a evidence that treatment with the direct thrombin inhibitor ximelagatran/melagatran may not be inferior to treatment with warfarin. Ximelagatran treatment is associated with risk for liver injury and due to concerns with safety, it has been withdrawn from the market and its development terminated.***
7. ***There is level 1a evidence that a dabigatran may be more effective in preventing stroke than warfarin. With respect to dabigatran prescription, a higher dose (150mg b.i.d) appears to be more effective than a lower dose (110mg b.i.d) at reducing the risk of ischemic stroke however, it also increases the risk of major bleeding. The risk or mortality is comparable amongst the two doses and based on a composite of major ischemic, hemorrhagic, and fatal events, both doses demonstrate a similar net clinical benefit. This effect is observed up to 5 years of treatment.***
8. ***There is level 1b evidence that treatment with fixed dose rivaroxaban (20 mg p.o. o.d.) is not superior to dose-adjusted warfarin for the prevention of stroke in high risk individuals with atrial fibrillation. Treatment with rivaroxaban may also be associated with less risk for intracranial bleeding when compared with dose-adjusted warfarin.***
9. ***There is level 1b evidence that treatment with apixaban may be superior to ASA for the reduction in risk of stroke in individuals with AF and for whom a vitamin K antagonist is considered unsuitable.***
10. ***There is level 1b evidence that treatment with apixaban may be superior to dose-adjusted warfarin for the prevention of stroke or systemic embolism in high risk individuals with atrial fibrillation.***
11. ***There is level 1b evidence that treatment with apixaban may be associated with reduced risk for death from any cause and for major bleeding events when compared to treatment with dose-adjusted warfarin.***
12. ***There is level 1a evidence that the use of patient decision aids may be associated with an increase in patient knowledge and a decrease in uncertainty regarding treatment.***

13. ***There is level 2 evidence that incorporating narrative information in the form of patient anecdotes may help increase patient knowledge and belief in the importance of laboratory testing.***
14. ***There is level 1b evidence that, among high risk patients with atrial fibrillation, use of patient aids may be associated with a temporary increase in the use of appropriate warfarin-based therapy.***
15. ***There is level 1a evidence that self-management programs are associated with a reduced risk of thromboembolic events and mortality. However, these programmes are more likely to be feasible for a small, select group of patients only.***
16. ***There is level 1a evidence that self-testing and self-management programmes may not be associated with increased risk of bleeding events.***
17. ***There is level 2 evidence suggesting that a coordinated, multidisciplinary approach may result in improved adherence to specific targeted guidelines.***
18. ***There is level 1a evidence that patent foramen closure does not reduce the risk of recurrent stroke, death or TIA relative to traditional medical therapy in patients with cryptogenic strokes and patent foramen ovale.***

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8.10

Carotid Artery Occlusion and Reperfusion Interventions

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Key Points

- Carotid endarterectomy (CEA) may be an effective surgical intervention in the treatment of symptomatic carotid artery stenosis of 70%-99%. In cases of asymptomatic stenosis ≥ 60%, CEA may be of benefit but only if surgical risk does not exceed 3%.
- Assessment of risk is important in determining overall benefit of carotid endarterectomy, particularly in patients with asymptomatic stenosis.
- To maximize the potential benefits associated with CEA, intervention should take place within 14 days of the index stroke or TIA event for individuals with symptomatic carotid stenosis.
- Coordinated case management post-discharge following CEA may be beneficial in increasing patient knowledge and encouraging lifestyle changes to prevent stroke.
- Carotid angioplasty and stenosis (CAS) may be as effective as CEA in preventing strokes. The rates of restenosis are comparable between the two procedures.
- Carotid Angioplasty and Stenting with protection and without protection are equally effective in decreasing risk of stroke.
- When compared with carotid endarterectomy, use of carotid artery stenting is associated with significantly increased 30-day risk for stroke however, long term outcomes indicate a comparable rate of stroke recurrence between carotid endarterectomy and carotid artery stenting.
- Careful case selection should be exercised for the appropriate use of CAS especially when the patients are of >70 years of age and have symptomatic stenosis.

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8.10 Carotid Artery Disease and Reperfusion Interventions

Carotid artery atherosclerosis is a common condition, which poses a major health threat (Connors et al., 2003). Carotid artery stenosis of greater than 50% is present in 7-10% of men and 5-7% of women over the age of 65 years. In individuals over the age of 80 years, the prevalence has been estimated to be approximately 10%; however, in the majority of cases, the stenosis is asymptomatic (Connors et al., 2003).

The risk for stroke is not determined solely by the degree of stenosis, but also by the pathology of the plaque creating the stenosis. An asymptomatic individual with an 80% stenosis, for example, has a 1-2% risk of stroke per year resulting from the presence of the stenotic lesion, whereas, an individual with 80% stenosis who is symptomatic has a 10-20% risk of stroke per year (Connors et al., 2003). There is evidence suggesting that development of symptoms becomes more likely when there is a rapid increase in size of the lesion at the site of the stenosis (Norris & Zhu, 1990). However, data from the NASCET trials suggest that the average annual rate of increase in stenosis is approximately 4% over the long-term (Barnett & Meldrum, 2001).

8.10.1 Carotid Endarterectomy (CEA)

Carotid endarterectomy (CEA) is a surgical intervention involving the removal of atherosclerotic plaque from the internal carotid artery. Originally established as a surgical procedure to prevent stroke in the 1950's, more than 2 million CEAs had been performed worldwide by 1999 (Barnett & Meldrum, 2001; Biller et al., 1998); as many as one-third of these procedures were conducted prior to any substantial clinical evidence as to the relative efficacy, safety or durability of CEA (Barnett & Meldrum, 2001). More recent statistics from the National Institute of Neurological Disorders and Stroke noted that an estimated 140,000 carotid endarterectomies are performed each year in America based on a National Hospital Discharge survey from 2009 (National Institute of Neurological Disorders and Stroke, 2012).

8.10.1.1 Carotid Endarterectomy (CEA) and Symptomatic Carotid Artery Stenosis

Carotid endarterectomy is a treatment specifically for use in stroke survivors with moderate- to high-grade stenosis of the ICA and history of a "non-disabling stroke" (Barnett et al., 1998; Goldszmidt & Caplan, 2003). In 1991, two large clinical trials published results that have provided the basis for current CEA procedures and have helped define appropriate treatment guidelines and recommendations. In fact, CEA has become the standard treatment for severe symptomatic carotid artery stenosis following ECST and the NASCET trials publication (Martin et al., 2001). The absolute risk reduction for stroke associated with CEA in symptomatic carotid artery stenosis over two years has been reported to be 17% (Barnett, 1991; Bettmann et al., 1998; Hill et al., 2004). Details of the NASCET and ECST trials are summarized in Table 8.10.1.1.1.

Table 8.10.1.1.1 Summary of Studies Evaluating Carotid Endarterectomy and Symptomatic Carotid Artery Stenosis

Author, Year Study Design (PEDro Score) Sample Size	Intervention	Main Outcome(s) Result
NASCET Trial Collaborators (1991) RCT (8) N=659	E: Carotid endarterectomy C: Medical treatment	• Incidence of stroke (any ipsilateral or major) (+)

NASCET Trial Collaborators (1998) RCT (8) N=2226	E: Carotid endarterectomy C: Medical treatment	• Incidence of fatal/nonfatal stroke: 50-69% stenosis (+); <50% stenosis (-)
ECST Trial Collaborative Group (1991) RCT (7) N=2518	E: Carotid endarterectomy C: Aspirin + advice to stop smoking	• Incidence of stroke: mild stenosis (-); severe stenosis (+)
ECST Trial Collaborative Group (2003) RCT (7) N=3018	E: Immediate carotid endarterectomy + medical treatment C: Medical treatment	• Incidence of stroke or surgical death: <30% stenosis (+) C; near occlusion or 30-49% stenosis (-); 50-69% stenosis (+); 70-99% stenosis, without near occlusion (+)

+ Indicates statistically significant differences between treatment groups
- Indicates non-statistically significant differences between treatment groups

Discussion
While measurement protocols used in the ECST trial were different than those employed by NASCET trialists, when the trial data were analyzed to compensate for these differences, the results were consistent. Surgery, in both trials, was most beneficial to patients with 70-99% stenosis (Rothwell et al., 2003). In this group, treatment was found to be both effective and durable based on eight years of follow-up. In patients with moderate stenosis (50-69%), while significant (p=0.045) the benefit was less convincingly so. In symptomatic patients with less than 50% stenosis, no benefit was seen with surgical treatment (Barnett & Meldrum, 2001; Rothwell et al., 2003). CEA significantly increased the 5-year risk of ipsilateral stroke in patients with less than 30% stenosis (Rothwell et al., 2003), while the effectiveness of CEA in patients with near occlusion was uncertain (Barnett & Meldrum, 2001; Rothwell et al., 2003).

CEA is indicated for reducing the risk of recurrent ischaemic stroke in symptomatic patients with moderate- to high- grade stenosis of the ICA (>50%-69%). The number needed to treat (NNT) to prevent one stroke at two years is eight individuals for stenosis severity of 70-99% and 20 individuals for stenosis severity of 50-69% (Goldszmidt & Caplan, 2003). In a report based on data from the Ontario Carotid Endarterectomy Registry, the 30-day post-CEA rate of nonfatal stroke was 5.7% and the rate of death and/or stroke was 7.3% in patients with symptomatic stenosis (Tu et al., 2003).

8.10.1.2 CEA and Asymptomatic Carotid Artery Stenosis
The majority of carotid artery stenoses are asymptomatic (Connors et al., 2003). The short-term risk for stroke associated with asymptomatic internal carotid artery stenosis is approximately 1-3% per year depending on the degree of stenosis (European Carotid Surgery Trialists Collaborative Group, 1995; Norris et al., 1991). In the long-term, the 10-year and 15-year risks for stroke among individuals with less than 50% internal carotid artery stenosis have been reported to be 5.7% and 8.7%, respectively. Among individuals with 50% or greater stenosis the risk for stroke has been reported at 9.3% and 16.6%, respectively (Nadareishvili et al., 2002). These figures are consistent with the low annual rate reported over the short term and suggest that risk remains stable over the long-term (Dodick et al., 2004; Nadareishvili et al., 2002).

As part of the NASCET trial, all strokes in asymptomatic arteries were recorded and causes identified as lacunar, cardioembolic or large artery lesions (Barnett & Meldrum, 2001). Of these, the only types of event that might be prevented by CEA would be those associated with large artery lesions. At all degrees of stenosis, more than 40% of strokes in asymptomatic arteries were attributable to origins other than large artery lesions suggesting that risk needs to be calculated taking into account only those strokes that could be prevented by surgical intervention. Perioperative risks associated with CEA may limit the benefit

derived from the procedure especially when one considers the low risk for large-artery stroke among the asymptomatic population (Barnett et al., 2002).

A meta-analysis confirmed the necessity of determining the cause of stroke in assessing risk (Barr et al., 2003). Barr et al. (2003) determined that approximately 45% of strokes in patients with asymptomatic stenoses are caused by intracranial or cardiovascular sources and are not a direct result of the stenosis itself. The presence and prevalence of these lesions is not a sufficient reason for surgical intervention and, in light of the low risk associated with asymptomatic carotid artery stenosis, the appropriateness of CEA in this patient group has been a controversial subject. The risks and benefits of surgery must be weighed carefully. The use of CEA as a safe and effective intervention in the treatment of asymptomatic carotid artery stenosis has been examined in a number of randomized clinical trials, the results of which are summarized in Table 8.10.1.2.1.

Table 8.10.1.2.1 Summary of Details of Studies Examining CEA and Asymptomatic Carotid Artery Stenosis

Author, Year Study Design (PEDro Score) Sample Size	Intervention	Main Outcome(s) Result
MRC-ACST Trial Collaborative Group (2004) RCT (8) N=3120	E: Immediate carotid endarterectomy C: Deferred carotid endarterectomy	• Incidence of stroke (+) • Incidence of carotid artery territory stroke (+)
ACST Trial Collaborative Group (2010); (2004) RCT (8) N=3120	E: Immediate carotid endarterectomy C: Deferred carotid endarterectomy	• Incidence of stroke (+)
Veterans Affairs Cooperative Study Group (1993) RCT (7) N=444	E: Carotid endarterectomy + medical management including antiplatelet therapy (325-650mg/d aspirin) C: Medical management including antiplatelet therapy (325-650mg/d aspirin)	• Incidence of ipsilateral neurologic events (stroke, transient ischemic attack, transient monocular blindness) (+) • Combined outcome (stroke and death 30d after the procedure) (-)
Asymptomatic Carotid Artery Study (ACAS) Group (1995) RCT (6) N=1662	E: Carotid endarterectomy + medical management (including aspirin) C: Medical management (including aspirin)	• Incidence of ipsilateral stroke and any perioperative stroke or death (+)

+ Indicates statistically significant differences between treatment groups
- Indicates non-statistically significant differences between treatment groups

Discussion

The results of ACAS have been criticized because of methodological problems including relatively low enrolment which lead to poor subgroup analysis due to small numbers, reliance on only Doppler examinations to assess stenosis and use of relative risk reduction rather than absolute risk reduction to report benefits (Barnett & Meldrum, 2001). ASCT was the largest prospective study evaluating the potential efficacy of CEA in asymptomatic carotid artery stenosis. Reported results were similar to those of ACAS and a combined analysis of data from both studies demonstrated a 5-year risk of stroke (including procedural morbidity) of 6.0% versus 11.5% in patients deferred or non-CEA patients (Halliday et al., 2004). This represents a reduction of 5.5% over five years. While ACAS did not report a significant reduction in the absolute risk of fatal or disabling stroke following CEA, ACST did (2.5%; p=0.004). The ACST trial, however, may suffer from its own limitations including no clear control or regulation of medical treatment provided to the deferred group in terms of primary prevention strategies, the failure to

demonstrate differences dependent upon degree of stenosis (perhaps due to imaging technique) and lack of analysis with regard to reduction in ipsilateral carotid territory strokes (Barnett, 2004; Rothwell & Goldstein, 2004). Long-term follow up of ACST patients is ongoing.

To report relative risk reduction associated with CEA in either ACAS or ACST may be misleading due to the low risk of stroke for subjects prior to treatment. In terms of absolute risk reduction for ipsilateral stroke or perioperative stroke or death, the five-year absolute reduction was 5.9% and in the ACST was 5.4%. In annual terms, this represents a risk reduction of approximately 1%. The benefits of surgery will not outweigh the risks unless surgical or perioperative risk is less than 3% (Barnett & Meldrum, 2001; Dodick et al., 2004). In both ACAS and ACST, surgical skill was high and reported perioperative risk was low (2.3% and 3.1% respectively). However, it has been reported that the rate of operative complications outside clinical trials may exceed clinical trial rates by 1-2% (Barnett, 2004; Barnett et al., 2002; Tu et al., 2003) and in so doing would eliminate any benefit associated with CEA in asymptomatic stenosis (Barnett, 2004; Dodick et al., 2004). As the ACST trialists (Halliday et al., 2004) and Barnett (2004) both suggest, independent audits of surgeons' operative records as well as of institutions and departments should be readily available in order to evaluate surgical risk.

A report from the National Surgical Quality Improvement Program (NSQIP) database demonstrated that for more than 5000 CEA procedures conducted for asymptomatic stenoses, the 30-day rate for stroke was 0.96% and 1.4% for the combined outcome of stroke and death (Woo et al., 2010). These rates were generated from results provided from both community and academic or university-based hospitals and suggest that it is possible to achieve results similar to the randomized controlled trials outside of the trial environment. Excluding perioperative stroke and death, the ACST trial reported a 5-year stroke risk of 3.8%. The authors combine the NSQIP perioperative risk with this figure to arrive at a 5-year risk of 4.8% or 1.0% annually. In the Second Manifestations of Arterial Disease Study (SMART), annual stroke risk in individuals whose asymptomatic carotid artery stenosis was managed medically was 0.8% (Goessens et al., 2007; Woo et al., 2010). Further research is required to determine if the outcome associated with surgical intervention provides any benefit when compared to best medical management.

In a recent meta-analysis, Guay and Ochroch (2012) examined the impact of CEA when added to conventional medical management of symptomatic and asymptomatic carotid artery stenosis. In their meta-analysis, they identified a total of eight randomized controlled trials, six of which included individuals with asymptomatic stenoses. Pooled analyses revealed that the addition of CEA to medical management made no significant difference in the long-term risk for stroke/death (2-4 years) when compared to medical management alone (RR=0.93, 95% CI 0.84, 1.02; p=0.14). However, in symptomatic individuals (represented by data from two identified RCTs) with severe stenosis addition of CEA was associated with a reduction in long-term risk for stroke and/or death (RR=0.69, 95% CI 0.59, 0.81; p<0.001) (Guay & Ochroch, 2012).

Thus far, there are a number of CEA management strategies available however, it remains unclear as to which treatment option is optimal. Raman et al. (2013) compared various CEA management strategies for patients with symptomatic carotid artery stenosis through a systematic and meta-analyses of RCTs and nonrandomized controlled studies (NRCs). Three RCTs and 10 NRCs evaluated the efficacy of carotid artery stenting (CAS) plus medical therapy compared to CEA plus medical therapy. The meta-analysis of the RCTs demonstrated no significant difference between the two groups with respect to the incidence of stroke (Raman et al. 2013). A total of 3 RCTs and 8 NRCs evaluated CEA with medical therapy versus medical therapy alone and found that patients in the RCTs were not provided with the "optimal" medical therapy at the time, hence the evidence is limited for the use of CEA plus medical therapy compared to medical therapy alone for reducing the risk of stroke (Raman et al. 2013). Of the 3 RCTs, 2 revealed an increased

risk for death, MI and periprocedural death as a result of CEA with medical therapy compared to medical therapy alone at 30 days post-intervention. In the long-term, meta-analyses of the RCTs and NRCs revealed no significant difference between the treatment types for stroke. No RCTs were found that compared CAS plus medial therapy with medial therapy alone. Only 2 NRCs compared these management strategies and the evidence was insufficient to draw conclusions regarding the benefit of adding CEA to medical therapy for the incidence of stroke (Raman et al. 2013).

Conclusions Regarding Carotid Endarterectomy

There is level 1a evidence that carotid endarterectomy may be an effective procedure to reduce the risk of stroke in individuals with symptomatic carotid artery stenosis of 70-99%.

There is level 1a evidence that carotid endarterectomy may be an effective procedure to reduce the risk of stroke in individuals with asymptomatic carotid artery stenosis of ≥60% however, the operative risks associated with the procedure outweigh the benefit if they exceed 3%. Current guidelines do not recommend regular revascularization in asymptomatic patients.

There is level 1a evidence that CEA may be an effective procedure to reduce stroke risk in individuals with 50-69% stenosis if done soon after the event (< 14 days). Risk of procedure needs to be weighed on an individual patient basis.

Carotid endarterectomy may be an effective surgical intervention in the treatment of symptomatic carotid artery stenosis of 70%-99%. In cases of asymptomatic stenosis ≥60%, CEA may be of benefit but only if surgical risk does not exceed 3%.

8.10.1.3 Clinical Risk Assessment and CEA

While some studies have shown that it is possible to attain results similar to those in large clinical trials outside of study centers (Mullenix et al., 2002), others have concluded that current practice has changed substantially from that employed in a RCT (Barnett & Meldrum, 2001). Thirty-day mortality rates were reported to be 0.5% and 0.1% in the NASCET and ACAS trials respectively. However, Feasby et al. (2002) reported an inverse relationship between institution and surgeon case volumes and adverse surgical outcomes such that institutions in which less than 150 procedures are performed annually have higher rates of patient mortality and morbidity. Likewise, surgeons who perform CEAs infrequently (14 or fewer per year) have higher periprocedural rates of stroke or death than surgeons with more experience (Feasby et al., 2002).

In a meta-analysis by Bond et al. (2003) the authors reported the pooled estimate of absolute risk of stroke and/or death resulting from CEA to be 5.1% among symptomatic patients (95 studies) and 2.8% in asymptomatic patients (60 studies). These results supported an earlier analysis undertaken by Rothwell et al. (1996) who reported the rate of stroke and/or death to be 5.64% in symptomatic patients. Both analyses reported significant heterogeneity between studies.

Based on data from the Swedish vascular registry, Kragsterman et al. (2006) examined long-term survival of individuals undergoing CEA for asymptomatic stenosis. In total, the authors identified 6169 procedures performed in 5808 individuals, 10.8% of whom were asymptomatic. Five-year survival was 78.2% for the asymptomatic groups versus 81.1% (p=0.353) for the symptomatic patients while 10-year survival was 45.5% and 53.8%, respectively (p=0.114).

In the Bond et al. (2003) analysis, symptomatic patients were reported to be at a significantly greater risk for stroke and/or death following CEA than asymptomatic patients (OR=1.62; p<0.0001, heterogeneity=0.94). Stratification of risk by classifying patients into asymptomatic and symptomatic is too simplistic and taking clinical indications for CEA into account might assess risk more appropriately. For instance, the lowest risks for complications were associated with surgery undertaken subsequent to ocular events while the highest risks were associated with surgery for stroke in evolution, crescendo TIA, and "urgent" cases (Bond et al., 2003).

Conditions that increase the risk of post-operative outcome complications, but do not necessarily contraindicate the procedure include: hemispheric TIA rather than retinal TIA as qualifying event, left-sided procedure, presence of contralateral carotid occlusion, an ipsilateral ischaemic lesion on the entry CT scan and irregular or ulcerated plaque detected by angiography on the side of surgery, and lack of collateral circulation in the hemisphere beyond severe symptomatic stenosis (Barnett & Meldrum, 2001). It has been shown that the degree of stenosis is directly related to risk for subsequent stroke such that risk is highest among patients with 75-94% stenosis (Barnett & Meldrum, 2001).

Overall, based on data from the NASCET and ACE (ASA and Carotid Endarterectomy trial), female sex was associated with a significantly higher 30-day risk of death and a non-significant, but increased, risk for the composite of stroke and death following CEA (Alamowitch et al., 2005). Despite greater perioperative risk, similar long-term benefits were reported for men and women with ≥70% stenosis in terms of absolute risk reduction. However, among patients with 50-69% stenosis, CEA was of benefit among men only. In this group, the only women who derived benefit from CEA in terms of absolute risk reduction were those at higher risk for stroke by virtue of the presence of multiple risk factors (Alamowitch et al., 2005).

The American Heart Association (Biller et al., 1998) recommend that the combined risk of stroke/death resulting from CEA should be no more than 3% for asymptomatic patients, 5% for TIA patients, 7% for stroke patients and 10% for patients with recurrent stenosis. Ideally, candidates for carotid endarterectomy would have a high risk for stroke combined with a low surgical risk, as high surgical risk patients are at a higher risk of complications from CEA (H. J. Barnett et al., 2002; Barr et al., 2003; Rothwell & Warlow, 1999). Rothwell et al. (1999) proposed a prognostic risk assessment model encompassing both medical stroke risk and surgical risk to assist in determining which patients might benefit most from carotid endarterectomy (Table 8.10.1.3.1). Using data from ECST study, prognostic scores were derived for all study patients. Five-year actuarial risks of ipsilateral carotid territory major ischaemic stroke, surgical major stroke or death in the surgical arm were compared with the medical group at each prognostic score. It was reported that based on the results of the comparison, CEA was only of significant benefit in patients with a score ≥4. In patients with a prognostic score <4, the procedure was of no significant benefit and may have been harmful to patients with prognostic scores of one or less (Rothwell & Warlow, 1999).

Table 8.10.1.3.1 Proposed Risk Assessment Model (Rothwell & Warlow, 1999)

Prognostic Variable	Risk Points
Medical model:	
Cerebral versus ocular events	1
Plaque surface irregularity	1
Any events in past 2 months	1
Carotid Stenosis (pick one): 70-79% 80–89% 90-99%	 0 1 2
Surgical Model:	
Female	1*
Peripheral Vascular disease	1*
Systolic blood pressure>180 mmHg	1*
** if stenosis=70-99%, surgical risk points are subtracted and the value of each is ½ .*	

A more recent report based on data from the Ontario Carotid Endarterectomy Registry cited perioperative patient risk factors which were significantly associated with higher rates of adverse outcomes (death or nonfatal stroke) within 30 days following CEA (Table 8.10.1.3.2). The authors recommended the use of a simple checklist of risk factors based on the preceding list. Each factor present would receive one point. Total scores would reflect increasing levels of risk. A risk score of 4, on this system was associated with a 15.8% risk for death and/or stroke (Tu et al., 2003).

Table 8.10.1.3.2 Proposed Assessment of Risk (Tu et al., 2003)

Prognostic Variable	Risk Points
History of TIA/stroke	1
Atrial fibrillation	1
Contralateral carotid occlusion	1
Congestive heart failure	1
Diabetes	1

Although not included in the risk assessment models proposed by either Rothwell et al. (1999) or Tu et al. (2003), advanced age (≥80 years) has been considered an important factor in determining whether a patient is considered at high risk and, therefore, not a suitable candidate for CEA. However, the impact of risk factors such as older age is not certain. A study of the American College of Surgeons National Surgical Quality Improvement Program reported that the 30-day risk for stroke in high risk patients was not significantly different from those patients not identified as high risk, based on data collected from 3949 procedures conducted over a 2-year period. The high-risk variable of age ≥80 years was not significantly associated with increased risk. In contrast, a report based on data collected from a cohort of 9308 CEA procedures as part of the New York Carotid Artery Surgery Study (NYCAS) demonstrated that, on multivariate analysis, age ≥80 years was a significant predictor of increased risk for 30-day stroke or death (OR=1.30, 95% CI 1.03-1.64) along with being nonwhite, admitted from the emergency department, asymptomatic but with a distant history (>6 months) of TIA/stroke, TIA or stroke as an indication for surgery, crescendo TIA/stroke-in-evolution, contralateral carotid stenosis, severe disability, coronary artery disease and presence of insulin-treated diabetes (Halm et al., 2009).

Given the importance of perioperative risk in determining the overall benefit of surgical intervention for asymptomatic individuals, Calvillo-King et al. (2010) proposed a risk prediction model for use with patients with asymptomatic stenoses (Table 8.10.1.3.3). The proposed CEA-8 comprises a group of eight variables found to be significant, independent predictors of perioperative death and stroke following CEA in a group of 6533 asymptomatic cases drawn from the New York State Medicare database (Calvillo-King et al., 2010). Points are awarded for each of the eight risk factors and a simple summed score used to categorize risk as *low*, *moderate* and *high*. A "patient-friendly" version omits "non-operated stenosis ≥50%" on the assumption that patients or families may be less likely to know the degree of existing stenosis. The resulting summary score of the 7-item version may also be used to stratify risk.

Table 8.10.1.3.3 CEA-8 for Prediction of Risk in Asymptomatic Patients (Calvillo-King et al., 2010)

Prognostic Variable	Risk Points
Female	1
Non-white	1
Distant stroke/TIA	1
Non-operated stenosis≥50%	1
Congestive heart failure	1
Coronary artery disease	1
Valvular heart disease	1
Severe disability	2
Risk categories based on total score: *Low 0-2; Moderate 3; High ≥4*	

Conclusions Regarding Clinical Risk Assessment and CEA

Assessment of risk is important in determining overall benefit of carotid endarterectomy, particularly in patients with asymptomatic stenosis.

8.10.1.4 Timing for Carotid Endarterectomy

While CEA is often delayed for more than four weeks following a symptomatic stroke event, an analysis based on data from the NASCET and ECST trials demonstrated that the time between a symptomatic ischaemic event and CEA has no effect on the 30-day perioperative risk of stroke and death and may result in decreasing benefits (Rothwell & Goldstein, 2004). Early CEA, within two weeks of a symptomatic event (excluding progressive or major disabling stroke), was not associated with increased operative or perioperative risk. However, the benefit associated with CEA in terms of 5-year absolute risk reduction of ischaemic stroke, decreased as the time between symptomatic event and CEA increased ($p<0.001$) (Fairhead et al., 2005; Rothwell & Goldstein, 2004). Early versus delayed CEA has been examined in one randomized controlled trial (Table 8.10.1.4.1).

Table 8.10.1.4.1 Summary of Timing of CEA Following Ischemic Stroke

Author, Year Study Design (PEDro Score) Sample Size	Intervention	Main Outcome(s) Result
Ballotta et al. (2002) RCT (5) N=86	E1: Early carotid endarterectomy (<30d post-ischemic event) E2: Delayed carotid endarterectomy (≥30d post-ischemic event)	• Perioperative stroke (-) • Survival rate (-)

+ Indicates statistically significant differences between treatment groups
- Indicates non-statistically significant differences between treatment groups

Discussion

In the single RCT that examined the impact of timing on the outcomes of stroke and death following CEA, there were no negative consequences associated with procedures conducted within the first 30 days of a minor, non-disabling, ischemic stroke (Ballotta et al. 2002). This confirmed the result of an earlier subgroup analysis from the NASCET trial that identified similar rates of perioperative stroke in individuals undergoing early (<30 days) versus delayed (>30 days) CEA (Gasecki et al., 1994).

In a pooled analysis of data from ECST and NASCET trials, Rothwell et al. (2004b) reported no risk increase for patients who underwent CEA within two weeks of their index ischemic event. Benefit of CEA (in terms of risk for stroke or death) was greatest for patients who were randomized to treatment within two weeks. Increasing delay to treatment was associated with decreasing benefit. In addition, for patients with 50-69%, absolute benefit was observed only for those patients randomized to CEA treatment within two weeks of the initial symptomatic event (median time from randomization to treatment=6 days). However, the decrease in absolute benefits from CEA was associated with patient gender such that treatment benefits declined significantly ($p<0.001$) with increased time from symptomatic event to randomization in women only (Rothwell et al., 2004b). Overall, in patients with>50% stenosis randomized within two weeks, one would have to treat five patients with CEA to prevent one ipsilateral stroke in a 5-year period. The number needed to treat increased to 125 in patients randomized more than 12 weeks following the index ischemic event.

A recent report based on data from the registry of the Canadian Stroke Network suggested that the median time to intervention for a group of patients receiving treatment within six months of the index

event was 30 days and approximately 1/3 of patients for whom CEA was recommended underwent the procedure within two weeks (Gladstone et al., 2009). To maximize the potential benefits associated with CEA, efforts should be made to reduce delays from event to surgical intervention. However, patients with unstable presentations may be at greater risk if CEA is conducted on an urgent basis. In a recent meta-analysis, Patterson et al. (2009) demonstrated that urgent CEA following crescendo TIA or unstable stroke is associated with significantly increased risk for stroke or death when compared to CEA with more usual indications (OR=5.6 and 5.5, respectively).

Conclusions Regarding Timing of CEA

There is level 1b evidence that early CEA may not be associated with increased risk for stroke or death. Pooled analysis suggests that benefits associated with CEA may decrease as time from the qualifying ischemic event increases especially in patients with moderate (50-69%) carotid stenosis.

To maximize the potential benefits associated with CEA, intervention should take place within 14 days of the index stroke or TIA event for individuals with symptomatic carotid stenosis.

8.10.1.5 Coordinated Care Following CEA

Coordinated case management may serve to increase patient knowledge about stroke and stroke risk and improve patient outcomes. A single randomized controlled trial has evaluated the effectiveness of a nursing-led, coordinated case management intervention after discharge following CEA (Table 8.10.1.5.1).

Table 8.10.1.5.1 Summary of Studies Evaluating Coordinated Nursing-Led Care Post CEA

Author, Year Study Design (PEDro Score) Sample Size	Intervention	Main Outcome(s) Result
Middleton et al. (2005) RCT (7) N=133	E: Coordinated care C: Usual care	• Health status (-) • Time spent in physical activity per week (-) • Knowledge/perceived risk of recurrent stroke (-) • Change in BP, cholesterol, smoking behaviour (-) • Lifestyle and dietary changes (+) • Knowledge of the warning signs of stroke (+)

+ Indicates statistically significant differences between treatment groups

- Indicates non-statistically significant differences between treatment groups

Discussion

One RCT involving 133 cases separated patients into either a coordinated care experimental group or a usual care control group (Middleton et al., 2005). The results suggest that the coordinated care group had improved lifestyle and dietary changes (self-reported measures) and increased knowledge of stroke warning signs (Middelton et al., 2005). However, there was no significant difference between the groups for overall health status, physical activity, perceived risk of another stroke, or blood pressure, cholesterol or smoking behaviour (Middleton et al., 2005).

Conclusions Regarding Nursing-led Coordinated Care Post-Discharge

There is level 1b evidence that nursing-led coordinated case management may be associated with short-term improvements in knowledge of stroke warning signs and self-reported lifestyle and dietary changes.

Coordinated case management post-discharge following CEA may be beneficial in increasing patient knowledge and encouraging lifestyle changes to prevent stroke.

8.10.2 Carotid Artery Angioplasty and Stenting (CAS)

Carotid artery angioplasty and stenting (CAS) is a percutaneous, minimally invasive approach to treating carotid artery stenosis. Carotid-artery angioplasty with stenting emerged as an alternative to carotid endarterectomy in patients at high risk for complications for endarterectomy such as contralateral occlusion or severe coronary artery disease (Grotta, 2013). It relies on basic techniques already present in the interventional endovascular community and may fulfill a role in treating carotid artery stenosis in specific subgroups of patients; patients not eligible for CEA under NASCET criteria, patients with contralateral carotid occlusion, post-CEA restenosis, radiation-induced stenosis or surgically inaccessible lesions (Cohen et al., 2003; Connors et al., 2003). Additionally, the percutaneous approach avoids the risks of general anaesthesia and the local complications of neck haematoma, infection, cervical strain and cranial nerve damage associated with endarterectomy and, from the patient's point of view, is a minor procedure with minimal hospital stay and a quicker return to pre-procedural levels of activity (Brown et al., 2001; Cohen et al., 2003; Martin et al., 2001).

Trials assessing the safety and effectiveness of carotid angioplasty and stenting (*without the use of embolic protection devices*) are summarized in Table 8.10.2.1. Cerebral protection will be discussed in the section that follows.

Table 8.10.2.1 Summary of Trials Assessing Carotid Angioplasty and Stenting

Author, Year Study Design (PEDro Score) Sample Size	Intervention	Main Outcome(s) Result
CAVATAS I Investigators (2001) RCT (7) N=504	E1: Carotid balloon angioplasty (with or without stents) E2: Carotid endarterectomy	• 30d mortality (-) • Cranial neuropathy post-treatment (+) • Major groin or neck haematoma: E1 (+) • 1yr ipsilateral carotid stenosis: E2 (+) • Incidence of ipsilateral stroke (-)
CAVATAS III (2007) RCT (7) N=16	E: Endovascular therapy (balloon therapy or stenting) C: Best medical treatment	• 30d risk of cerebrovascular symptoms (-) • Incidence of secondary endpoints (risk of vertebrobasilar transient ischemic attack, fatal/nonfatal carotid territory stroke, fatal myocardial infarction): C (+)
CAVATAS Investigators (2009) RCT (7) N=504	E1: Carotid angioplasty (with or without stents) E2: Carotid endarterectomy	• Incidence of stroke (-)
CAVATAS Investigators (2009) RCT (7) *Subgroup Analysis and long-term follow-up* N=413	E1: Carotid angioplasty (with or without stents) E2 Carotid endarterectomy Note: additional analysis was based on use of stents and re-stenosis	• Re-stenosis of ≥70%: E2 (+);E1 with stent vs E1 without stent (+)
Brooks et al. (2001) RCT (5)	E1: Carotid angioplasty and stenting E2: Carotid endarterectomy	• Perioperative or postoperative complications (-) • Perceptions of related discomfort and pain (-)

N=104		• Return to activity (-) • Length of hospital stay (-) • Associated hospital costs (-)
Brooks et al. (2004) RCT (5) N=85	E1: Carotid angioplasty E2: Carotid endarterectomy	• Perceptions of related discomfort and pain (-) • Return to activity (-) • Length of hospital stay (-) • Associated hospital costs (-)
Steinbauer et al. (2008) RCT (5) N=87	E1: Carotid angioplasty E2: Carotid endarterectomy	• Incidence of ipsilateral stroke: E2 (+) • Incidence of all neurological events (stroke and transient ischemic attack) (-) • Rate of re-stenosis: E2 (+)
CREST Investigators Lal et al. (2012) RCT (4) N_{Start}=2191 N_{End}=385	E1: Carotid artery stenting E2: Carotid endarterectomy	• Restenosis rates (-)

+ Indicates statistically significant differences between treatment groups

- Indicates non-statistically significant differences between treatment groups

Discussion

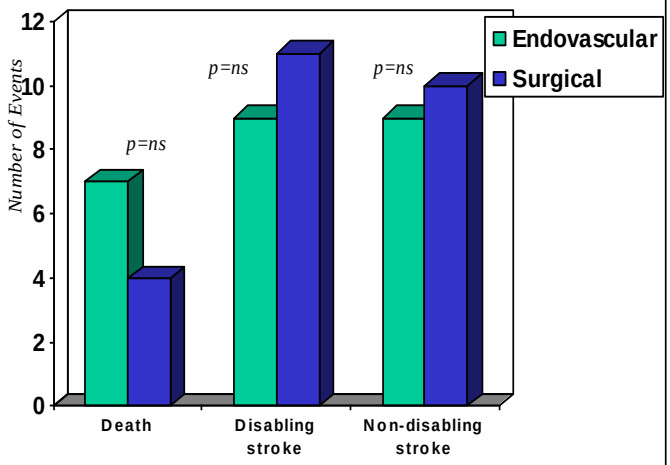
CAVATAS I demonstrated similar results in terms of 30-day adverse events rates following endovascular treatment and CEA in patients with symptomatic internal carotid artery stenosis. Survival curves demonstrated that both treatments were equally effective in preventing strokes over the course of the study. There was no significant difference in stroke event rates, up to three years post-procedure. While there was a higher rate of stroke and/or death reported in the CAVATAS I study versus the ECST study, one should consider that higher risk patients (e.g., patients with ischaemic heart disease) were involved in CAVATAS (Martin et al., 2001). Over the long-term, the incidence of stroke was greater in patients receiving endovascular treatment, but the between-group differences were not significant. Eight-year cumulative incidence for ipsilateral, non-perioperative stroke was 11.3% for endovascular treatment and 8.6% for CEA (HR=1.22, 95% CI 0.59-2.54) (Bonati et al., 2009).

In CAVATAS I, patients receiving endovascular treatment demonstrated a greater likelihood to develop re-stenosis of >70%, although, the re-stenosis was usually asymptomatic. It should be noted, however,

Endovascular versus Surgical Treatment in Patients with Carotid Artery Stenosis: CAVATAS I Investigators (2001)

504 patients with carotid artery stenosis (who were eligible for both procedures) were randomly assigned to endovascular treatment (carotid angioplasty and stenting; n=251) or surgical treatment (carotid endarterectomy; n=253). 97% of randomized patients had experienced ischaemic symptoms.

30-day rates of disabling stroke and death did not differ significantly between the two treatment groups (6.4% vs. 5.9%). There was no significant difference in rate of ipsilateral stroke up to 3 years post-randomization (based on survival analysis; adjusted hazard ratio = 1.04). However, 1 year following treatment, severe restenosis was more frequent among patients who had received endovascular treatment (p<0.001).



Major Events within 30 days of intervention

that only 23% of patients assigned to endovascular treatment received a stent. When, on long-term follow-up, the use of stenting was compared to balloon angioplasty alone, a significant reduction in risk for recurrent stenosis ≥70% was associated with the use of a stent (HR=0.43, 95% CI 0.19-0.97) (Bonati et al., 2009). This, the authors suggest, may provide evidence that stenting may be superior to balloon angioplasty alone for the prevention of re-stenosis. Of course, since the time of the CAVATAS trial, balloon angioplasty has been largely replaced by primary stenting as the favoured technique for carotid stenosis (Bonati et al., 2009).

In a systematic review of 34 studies representing 3814 patients, long-term restenosis rates were reported to be approximately 6% after one year and 7.5% after two years when a threshold of 50% stenosis was used to indicate restenosis (Groschel et al., 2005). Using a restenosis threshold of 70-80%, rates were approximately 4% one and two years following CAS. Almost half of all restenoses occurred within six months of the CAS procedure (Groschel et al., 2005). These figures are substantially larger than those reported by Wholey et al. (2000) as part of a large, global survey involving 36 centers and based on 5210 CAS procedures. Restenosis rates from the survey were reported to be 1.99% after six months and 1.42% after 12 months. Lal et al. (2012) indicated that 6.0% of patients receiving CAS developed restenosis of 70% after 2 years, a non-significant rate compared to patients receiving CES (6.3%).

In addition to restenosis rates, results of the global survey indicated the overall rate of combined minor and major stroke and procedure-related death post CAS was 5.76% when the procedure involved symptomatic patients and 3.38% when involving asymptomatic patients (Wholey et al., 2000). Similar results have been reported in high risk, NASCET ineligible patients (Malek et al., 2000) and in a meta-analysis by Kastrup et al. (2003). In an analysis of series of patients treated by carotid angioplasty and/or stenting, Martin (2001) found that stroke and death rates were comparable to surgery and ranged 2.0-6.9%, although one early study reported much higher rates (9.1%). In a recent study of a series of 672 consecutive patients undergoing CAS, 30-day rates of stroke and death were reported to be 4.5% among symptomatic patients and 2.0% among asymptomatic patients (Fanelli et al., 2012). In a prospective, observational study, Moratto et al. (2012) found that urgent CAS in carefully selected patients with symptomatic carotid stenosis was satisfactory in preventing the recurrence of TIA and stroke. A recent systematic review further supported this conclusion and stated that CAS represents a safe and effective stroke prevention strategy in high surgical risk patients when compared with CEA (Al-Damluji et al., 2013).

Not all reports suggest that CAS outcomes are necessarily comparable to CEA in terms of post-procedural stroke. Mathur et al. (1998) reported the 30-day risk for stroke or death to be 7.7% overall and complication rates were found to be similar in patients with symptomatic and asymptomatic stenoses. In patients under the age of 80 years, the 30-day risk for stroke and/or death was reported to be 5.6% while in patients over 80 years of age it jumped to 19.2%. Advanced age, presence of long or multiple lesions and severe stenosis were all identified as significant predictors of procedural strokes following carotid stenting (Mathur et al., 1998). It should be noted that, in patients who met NASCET criteria, the incidence of stroke and/or death within 30 days of CAS was 2.7%. Kastrup et al. (2005) demonstrated that advanced age (OR=1.06), history of hemispherical TIA (OR=4.7) and history of stroke (OR=8.0) were predictive of 30-day complication rates associated with CAS, while Schluter et al. (2007) reported that age and diabetes both had a significant impact on short-term outcomes such that diabetic patients ≥75 years of age had a risk for major stroke or death that was 12 times greater than their non-diabetic counterparts.

In the treatment of early and late recurrent carotid stenosis post-CEA, CAS resulted in similar anatomic and neurologic outcomes when compared to repeat CEA. At 2-year follow-up, the durability of the procedure (assessed by stenosis-free patency on duplex scanning) was comparable to repeat CEA (66% versus 74%) (Bowser et al., 2003). More recently, Mehta et al. (2007) reported that, based on data from

3070 patients enrolled in a CAS registry, patients undergoing CAS for restenosis following CEA experienced very low periprocedural complication rates, similar to the rates found for patients with no previous CEA intervention. Overall, rates for all nonfatal ipsilateral strokes or death were 1.7% (1.4% in patients with restenosis versus 1.7% in patients with no previous CEA).

Conclusions Regarding Carotid Angioplasty and Stenting

There is level 1b evidence that CAS procedures may result in a decrease incidence of carotid territory stroke.

There is level 1a evidence that both CAS and CEA procedures may be equally effective in preventing strokes. Both procedures generate comparable rates of restenosis.

Carotid angioplasty and stenosis may be as effective as carotid endarterectomy in preventing strokes. The rates of restenosis are comparable between the two procedures.

8.10.2.1 Cerebral Protection

Carotid angioplasty and stenting have been associated with an increased risk for thromboembolic complications due to disruption of plaque during stent placement (Kastrup et al., 2003; Martin et al., 2001). The distal embolization of plaque fragments or debris to the brain generated during the procedure is the most important acute complication of carotid angioplasty and stenting (Barr et al., 2003; Cremonesi et al., 2003; Kastrup et al., 2003). Due to the risks of thromboembolism during CAS patients typically receive a course of antiplatelet therapy before stenting and after the procedure for several months up to 1 year. In addition, the use of protection devices to prevent this severe and common complication is under ongoing investigation. In general, cerebral protection devices take one of two forms. They are based either on a temporary distal balloon occlusion and subsequent aspiration of debris particles or an intravascular filtration device that maintains blood flow while trapping particles which are then removed along with the device (Cohen et al., 2003; Kastrup et al., 2003).

Randomized controlled trials that have evaluated the effects of cerebral protection devices when compared to unprotected CAS are summarized in Table 8.10.2.1.1.

Table 8.10.2.1.1 Summary of Studies Evaluating the Efficacy of Cerebral Protection Therapies

Author, Year Study Design (PEDro Score) Sample Size	Intervention	Main Outcome(s) Result
Barbato et al. (2008) RCT (7) N=35	E: Carotid angioplasty with cerebral protection (distal filters) C: Carotid angioplasty without cerebral protection	• Proportion of patients with new ischemic injury (-) • Incidence of stroke and death (-)
Jansen et al. (2009) RCT (7) Subgroup analysis SPACE trial N=563	E: Carotid angioplasty with protection devices C: Carotid angioplasty without protection devices	• 30d ipsilateral stroke or subsequent mortality (-)
EVA-3S Trial (2004) RCT (5) N=80	E: Carotid angioplasty with cerebral protection	• 30d incidence of stroke (-)

	C: Carotid angioplasty without cerebral protection	

+ Indicates statistically significant differences between treatment groups
- Indicates non-statistically significant differences between treatment groups

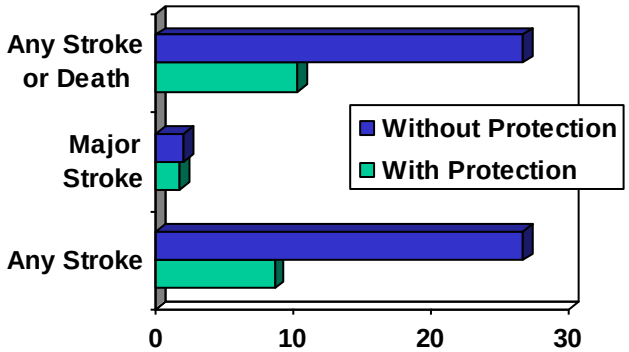
Discussion

There is conflicting evidence provided by randomized controlled trials regarding the impact of embolic protection devices on stroke associated with CAS. Although the safety committee of the EVA-3S committee recommended the suspension of CAS without cerebral protection and a clinical alert was published (RVA-3S Investigators, Mas et al. 2004), these actions have been criticized as premature (Barbato et al., 2008; Brown et al., 2004). Early between-group differences in outcome did not reach statistical significance, while possible differences in indications for treatment, nature of stenosis or difficulty in access were not reported (Brown et al., 2004). The majority of strokes occurred some time after completion of the intervention, and may not be attributable, therefore, to the presence versus absence of an embolic protection device. In addition, at the time of the interim report, patients undergoing protected CAS were significantly younger than those undergoing CAS without protection. As age is a risk factor for complications, this could explain, at least in part, the difference in stroke rates observed between groups (Brown et al., 2004; Naylor, 2006). A subgroup analysis from the SPACE trial provided additional evidence regarding the effectiveness of embolic protection devices in the prevention of early risk for stroke following CAS. In that trial, use of a protective device in CAS was left to the discretion of the interventionists (Ringleb et al., 2006). As a result, a protection device was used in approximately one-quarter of cases randomized to the CAS treatment arm. Further examination of data from 563 of patients allocated to CAS intervention demonstrated no significant difference in 30-day rates of ipsilateral stroke or death in patients treated with versus without embolic protection devices (Jansen et al., 2009).

Much of the support for the effectiveness of cerebral protection devices is based on the reports from other sources, such as registries or reports from observational studies. Garg et al. (2009) conducted a systematic review and meta-analysis of peer-reviewed publications (1995 to mid-2007), including observational studies, that reported 30-day stroke outcomes in individuals undergoing protected or unprotected CAS. Based on pooled analysis of data from 134 studies the relative risk for stroke was significantly lower in patients receiving CAS using embolic protection devices (RR=0.62, 95% CI 0.54-0.72), overall. The pooled 30-day stroke rate was 2.6% in patients undergoing CAS with protection versus 4.2% for unprotected CAS. When examining only those studies that reported results from both protected and unprotected procedures, similar benefits were demonstrated (RR=0.59, 95% CI 0.47-0.73) in

Carotid Angioplasty and Stenting with and without cerebral protection: EVA-3S Investigators (2004)

Within one arm of a larger, ongoing study, 80 patients with severe (70%) and recently symptomatic carotid artery stenosis were randomized to receive carotid angioplasty and stenting (CAS) either with or without the use of a cerebral protection device.



Percentage of patients experiencing adverse outcome events within 30 days of CAS procedure

73 procedures were completed before the trial was suspended. The 30-day rate of stroke for the completed procedures was 3.9 times greater in the group who had undergone unprotected CAS than among those patients who had undergone CAS with the use of a cerebral protection device.

favour of cerebral protection. It should be noted that, while cerebral protection was of significant benefit for both symptomatic and asymptomatic patients, 30-day stroke rates in symptomatic patients were two times higher than for asymptomatic patients regardless of protective device status. Stroke rates for protected versus unprotected CAS were 3.8% versus 5.6% in symptomatic patients and 1.7% versus 2.8% in asymptomatic patients. It should be noted that, for CAS with embolic protection, these rates are within what might be considered acceptable (3.0% and 6.0% for asymptomatic and symptomatic patients, respectively) (Ringleb et al., 2008b).

In light of the large amount of data available and the magnitude of benefit associated with the use of embolic protection devices, Garg et al. (2009) also undertook a cumulative analysis, in which studies are added individually according to date of publication. This process revealed that the use of protection devices reached statistical superiority in 2004, while the relative risk stabilized at approximately 0.6 in 2005. Removal of any single, individual study from the analysis did not influence the result and no publication bias was identified (Garg et al., 2009).

Another meta-analysis (Burton & Lindsay, 2005) included studies published from 2002 to 2005 that reported adverse events (stroke or death) following protected CAS procedures in at least 10 patients. Of the 26 included studies (n=2992), from nine countries, the pooled perioperative rate for the combined outcome of stroke and death was 2.4%. The 30-day pooled rates for minor and major stroke or death individually were 1.1%, 0.6% and 0.9%, respectively (Burton & Lindsay, 2005). Unfortunately, the authors were not able to provide separate rates for groups of patients with symptomatic versus asymptomatic stenosis. The results suggest that selective use of PCAS in those at high surgical risk is appropriate.

Data from the CAPTURE Registry in the United States (Fairman et al., 2007)(n=3500) were not included in the Garg et al. (2009) meta-analysis as the report was published after the selected end point for the literature review. The CAPTURE registry examined stroke events occurring post CAS using a specific stent and embolic protection system produced by a single manufacturer (Abbott Vascular Carotid RX Acculink/Accunet). Fairman et al. (2007) reported a 30-day rate of 2.9% for major stroke and death, and 6.3% for the primary endpoint of death, stroke and myocardial infarction (MI). In all, 4.8% of patients experienced a stroke, with the majority of these events occurring post-procedure, but prior to hospital discharge. It should be noted that in the CAPTURE registry, only 14% of the 3500 patients undergoing CAS were considered symptomatic. As in Garg et al. (2009), the rate of stroke in symptomatic patients was approximately double that of asymptomatic patients; however, in both cases the estimates in the CAPTURE study were far greater (8.9% versus 4.1%).

Risk for early stroke following protected CAS may be lower in individuals undergoing treatment for recurrent stenosis following CEA. AbuRahma et al. (2009) report both perioperative and midterm outcomes for 180 individuals undergoing protected primary CAS and CAS for stenosis following CEA. In primary CAS, 30-day rate for combined stroke and death was 7.4% versus 0.9% for individuals with previous CEA (p=0.029). It should be noted that all perioperative strokes occurred in patients with symptomatic stenoses. Stroke-free rates at years 1-4 were 89% for the primary CAS group versus 98% for post-CEA CAS (p=0.01) (AbuRahma et al., 2009). The majority of patients included in this retrospective study were also part of the CAPTURE study.

Of course, a learning curve is associated with the use of these technologies. Outcomes depend on physician expertise and institutional experience as well as appropriate patient selection. All of these factors contribute to the varying reports of stroke rates in CAS series (Connors et al., 2003). The global survey undertaken by Wholey et al. (2000) reported that centers undertaking fewer than 50 CAS procedures had a significantly higher rate of minor and major strokes and procedure-related deaths (6.8%

compared to 4.63% in centers performing 50-100 cases). The rate did not change significantly in centers performing 200-300 cases (Wholey et al., 2000). Protection devices increase catheter time and technical complexity and some neuroradiologists may hesitate to implement them for these reasons (Eckert & Zeumer, 2003).

The ongoing evolution of CAS technology makes the comparison of outcomes difficult. Factors such as improved stents and guide wire systems along with increasing levels of expertise and improved perioperative medical regimens may have as much or more to do with improving results of CAS than the use of cerebral protection devices. Use of the protection device does not, in any case, eliminate all risk of embolization, even after deployment (Garg et al., 2009). However, it has been acknowledged that, like CEA, carotid angioplasty and stenting will have benefit only if performed with a high degree of technical proficiency, using carefully selected devices on appropriate patients (Connors et al., 2003; Garg et al., 2009).

Conclusions Regarding Cerebral Protection Therapies

There is level 1b and level 2 evidence that carotid angioplasty with cerebral protection may not provide additional benefits relative to CAS without protection.

Carotid Angioplasty and Stenting with protection and without protection are equally effective in decreasing risk of stroke.

8.10.2.2 Carotid Endarterectomy (CEA) Versus Carotid Artery Stenting (CAS)

Carotid endarterectomy has been established as an effective intervention for the prevention of stroke, particularly in symptomatic individuals with severe carotid artery stenosis. However, the relative effectiveness and role of carotid artery stenting (with or without the use of embolic protection devices) remain uncertain. Carotid artery stenting emerged as a less invasive alternative for revascularization (Skerritt et al., 2012). Trials that compare CEA directly with CAS (including the use of protection devices) are summarized in Table 8.10.2.2.1.

Table 8.10.2.2.1 Summary of Carotid Endarterectomy (CEA) Versus Carotid Artery Stenting (CAS)

Author, Year Study Design (PEDro Score) Sample Size	Intervention	Main Outcome(s) Result
ICSS International Carotid Stenting Study Investigators (2010) RCT (9) N=1713	E1: Carotid artery stenting (with or without protection) E2: Carotid endarterectomy	• Combined primary outcome (stroke, death, procedural myocardial infarction): E2 (+) • Incidence of stroke: E2 (+)
CREST Investigators (2010) RCT (8) N=2502	E1: Carotid artery stenting E2: Carotid endarterectomy	• 4yr composite primary outcome (30d stroke, ipsilateral stroke, myocardial infarction, death) (-) • Incidence of periprocedural stroke: E2 (+) • Incidence of periprocedural myocardial infarction: E1 (+) • 30d incidence of ipsilateral stroke (-)
SAPPHIRE Investigators (2004) RCT (7) N=334	E1: Carotid artery stenting with emboli protection device E2: Carotid endarterectomy	• 30d incidence of stroke, myocardial infarction or death (-) • Mean length of hospital stay: E1 (+) • Incidence of adverse events (30d stroke or death,

		ipsilateral stroke or death from neurologic causes, myocardial infarction): E1 (+)
EVA-3S (2006) RCT (7) N=527	E1: Carotid artery stenting with protection E2: Carotid endarterectomy	• 6mo incidence of stroke or death: E2 (+)
SPACE Collaborative Group (2006) RCT (7) N=1200	E1: Carotid artery stenting E2: Carotid endarterectomy	• 30d incidence of ipsilateral stroke or death (-); CAS with or without protection devices (-)
SPACE Collaborative Group (2008) RCT (7) *Long-term follow-up* N=1214	E1: Carotid artery stenting E2: Carotid endarterectomy	• 2yr Incidence of ipsilateral stroke or death (-) • Incidence of re-stenosis (≥70%): E2 (+)
SAPPHIRE Investigators (2008) RCT (7) *Long-term follow-up* N=334	E1: Carotid artery stenting with emboli protection device E2: Carotid endarterectomy	• Composite endpoint between 31-1080d (death, ipsilateral stroke) (-) • 3yr incidence of stroke (-)
EVA-3S (2008) RCT (7) *Long-term follow-up* N=527	E1: Carotid artery stenting with protection E2: Carotid endarterectomy	• 4yr incidence of stroke or death: E2 (+) • Post-30d incidence of ipsilateral stroke (-) • 4yr incidence of nonprocedural stroke (-)
CaRESS Steering Committee (2005) PCT N=397	E1: Carotid artery stenting with protection E2: Carotid endarterectomy	• Combined primary outcome (incidence of stroke or mortality) (-) • Mortality (-) • Incidence of stroke (-) • Incidence of acute myocardial infarction (-) • 1yr quality of life (-)
SPACE-1 collaborative group (2012) PCT N=563	E1: Eversion endarterectomy C: Conventional endarterectomy with patch angioplasty	• 30d incidence of ipsilateral stroke or death post-surgery: C (+) • Incidence of intraoperative ipsilateral stroke: C (+) • 2yr incidence of ipsilateral stroke: E1 (+)
CaRESS Investigators (2009) PCT *Long-term follow-up* N=397	E1: Carotid artery stenting with protection E2: Carotid endarterectomy	• 4yr incidence of stroke (-) • Combined outcome (death, nonfatal stroke) (-)

+ Indicates statistically significant differences between treatment groups

- Indicates non-statistically significant differences between treatment groups

Discussion

Major randomized controlled trials have offered conflicting results regarding the non-inferiority of CAS when compared to CEA in patients with either symptomatic or asymptomatic carotid stenosis. While results of the SAPPHIRE trial (Yadav, 2004) demonstrated that CAS was not inferior to CEA, the more recent SPACE trial failed to confirm the non-inferiority of CAS (Ringleb et al., 2006). It should be noted that the SAPPHIRE trial enrolled a substantial proportion of individuals with asymptomatic stenosis while enrolment in the SPACE trial was confined to individuals with symptomatic stenosis. Similarly, interim results from the ICSS trial (which enrolled only symptomatic patients) suggest a significant increase in risk for early stroke associated with the use of CAS (Ederle et al., 2010). The CREST trial (symptomatic and asymptomatic patients included) reported a significant increase in risk for periprocedural stroke associated with CEA and a similar increase in risk for periprocedural MI associated with CEA (Brott et al.,

2010). However, comparison of 4-year event rates revealed no significant between-group differences and rates of ipsilateral stroke were similarly low, following the initial 30-day periprocedural period. It should be noted that CREST investigators reported that the treatment effect was not modified by symptomatic status. Recently, Rantner et al. (2013) concluded that the increase in risk of CAS compared with CEA appears to be greatest in patients treated within seven days of symptoms and that early surgery might remain most effective in stroke prevention in patients with symptomatic carotid artery stenosis.

Overall, interpretation of the evidence has been made more complicated by factors such as diversity in enrolment criteria, interventionalist training and experience, the ongoing evolution of technique and technology as well as early trial stoppages. Smaller trials that provided interim findings, but were stopped early are not summarized in Table 8.10.2.2.2, but have been included in several meta-analyses. Trials with early stoppages may provide an over-estimation of either the risk or benefit associated with treatment (Naylor, 2006; Ringleb et al., 2008b). We identified nine recent meta-analyses that have compared CAS with CEA in terms of short and longer-term stroke outcomes. Summaries of these analyses are provided in Table 8.10.2.2.2.

Table 8.10.2.2.2 Meta-Analyses Comparing Carotid Endarterectomy (CEA) and Carotid Artery Stenting (CAS)

Study	Meta-Analysis Description and Results
Ringleb et al. (2008b)	Reported pooled estimates based on eight large RCTs that enrolled a total of 2985 patients, 89% of whom were symptomatic. Overall, there was a 38% increase in the odds for 30-day stroke or death associated with CAS when compared to CEA (p=0.024); however, significant heterogeneity was reported for this analysis. Included trials differed substantially in terms of enrolled study population and technical details. When smaller trials and a non-peer reviewed study were eliminated, there was a non-significant increase in risk associated with CAS (OR=1.29, 95% CI 0.94-1.76, p=0.11), and no associated heterogeneity. When the analysis was restricted to only large trials enrolling symptomatic patients, there was a non-significant increase in 30-day risk for stroke or death associated with endovascular treatment (OR=1.33, 95% CI 0.89-1.93, p=0.17) and no significant heterogeneity.
Brahmanandam et al. (2008)	Included data from ten trials enrolling 3580 patients and reported a higher risk of 30-day stroke or death associated with CAS compared with CEA (RR=1.30, 95% CI 1.01-1.67), although there was no significant difference between procedures in terms of stroke risk alone. Sensitivity analysis, including only data from RCTs, demonstrated a similar risk for stroke/death associated with CAS (RR=1.38, 95% CI 1.06-1.79) as well as a significantly increased risk for stroke (RR=1.37, 95% CI 1.02-1.84). Analysis of studies including only symptomatic patients revealed a similar pattern of increased 30-day risk associated with CAS. No evidence of heterogeneity was demonstrated with either the overall or RCT-only analyses. In addition, meta-regression demonstrated that factors such as percentage of males enrolled, mean age, duration of follow-up, type of stent used, completion of trial, inclusion criteria and use of an embolic protection device made no significant contribution to between-trial heterogeneity. The role of the qualifications of the trial interventionalists could not be assessed as a source of heterogeneity given the gross disparity of information provided by various studies.
Ederle et al. (2009)	Ten trials were included in this Cochrane review (representing 3178 patients). Not all studies were used for every analysis. Using a fixed effects model, 30-day odds for the combined outcome of stroke/death was significantly greater following CAS than CEA (OR=1.4, 95% CI=1.04-1.88, p=0.03); however, significant heterogeneity was identified between stopped trials (p=0.03) and the whole group of trials (p=0.02). Use of a random effects model resulted in an insignificant difference in odds for the combined outcome (OR=1.53, 95% CI 0.89-2.62, p=0.12). In terms of stroke or disabling stroke, the use of CAS did not differ significantly from

	surgery (OR=1.37, 95% CI 0.99-1.90 and OR=1.51, 95% CI 0.95-2.41, respectively). The OR for stroke or death at 24 months (two trials) did not favour either group (OR=1.26, 95% CI 0.83-1.90, p=0.28). Odds ratios for any stroke or death at 30 days plus ipsilateral stroke between 31 days and 6 months (3 trials) favoured surgery (OR=1.53, 95% CI 1.14-2.35, p=0.005).
Meier et al. (2010)	Eleven RCTs were included. Interim, per-protocol data from the ICSS trial was used. Weighted average incidence of periprocedural death or stroke was 5.4% for CEA versus 7.3% for CAS (OR=0.67, 95% CI 0.47-0.95, p=0.02) in favour of surgical intervention. Cumulative meta-analysis demonstrated that the inferiority of CAS when compared to CEA has diminished over time. In addition, trials stopped early demonstrated greater superiority in favour of CEA (OR=0.56, p=0.058) than trials completed formally (OR=0.76, p=0.26). Average incidence of periprocedural stroke was 4.2% for CEA versus 5.7% for CAS (OR=0.65, 95% CI 0.43-1.00, p=0.049). There was no significant difference between groups in rates of periprocedural morality. Rate of MI was reported in four trials. Greater 30-day rates of MI were demonstrated for CEA than CAS (OR=2.69, 95% CI 1.06-6.79, p=0.036). 6 studies provided data regarding early cranial facial neuropathy-greater risk was associated with CEA versus CAS (OR=10.25, 95% CI 4.02-26.13, p<0.001). Intermediate outcomes (1-4 years) were reported by nine trials. No between treatment differences were found for the combined outcome of stroke or death (HR=1.11, 95% CI 0.91-1.35, p=0.32). Neither odds of stroke (based on eight trials reporting binary data) (OR=0.78, 95% CI=0.56-1.09, p=0.15) nor odds for morality (seven trials reported binary data) (OR=1.04, 95% CI 0.78-1.38, p=0.86) differed with treatment.
Carotid Stenting Trialists' Collaboration (2010)	Results from three RCTs comparing CAS with CEA were included for analysis (EVA-3S, SPACE and ICSS). Primary outcome of fixed effect analysis was 120-day stroke or death (based on intention to treat). The 30-day risk for stroke and death was also reported based on per-protocol analyses. For 120-day outcomes of any stroke or death, there was a significant increase in risk associated with CAS when compared to CEA for symptomatic patients (RR=1.53, 95% CI 1.2-1.95, p=0.0006). There was no significant statistical heterogeneity identified for this analysis. In addition, per-protocol analysis demonstrated a significant increase in risk for 30-day stroke or death associated with CAS versus CEA (RR=1.74, 95% CI 1.32-2.3). In both cases, advantage in risk associated with CEA was attributed primarily to lower risk for stroke associated with CEA. Analyses of patient subgroups demonstrated a significantly greater 120-day risk for stroke or death in individuals ≥70 years associated with CAS versus CEA (RR=2.04, 95% CI 1.48-2.82). In per-protocol analysis, periprocedural (30-day) risk for stroke or death was 5.1% versus 4.5% for individuals <70 years in the CAS versus CEA groups. For older patients, estimated risk was 10.0% versus 4.4% in the CAS versus CEA groups (RR=2.41, 95% CI 1.65-3.51).
Murad et al. (2011)	Included 13 trials with 7484 patients (60% with symptomatic stenoses). Study outcome used for a random effects meta-analysis was the composite of death, stroke and MI assessed at the longest reported follow-up. Overall, CAS was associated with increased risk of any stroke versus CEA (RR=1.45, 95% CI 1.06-1.99), as well as decreased risk for periprocedural MI (RR=0.43, 95% 0.26-0.71). Analysis of long-term outcomes (from studies reporting ≥12 months follow-up) also demonstrated an increase in risk for stroke associated with CAS versus CEA (RR=1.74, 95% CI 1.14-2.66).
Economopoulos et al. (2011)	Included 13 randomized controlled trials in which 3723 patients were randomized to CEA and 3754 to CAS. 30-day outcomes (death, stroke, MI, death or stroke, death or ipsilateral stroke, death or disabling stroke, death/stroke/MI, and cranial nerve injury) and long-term outcomes (≥1 year post intervention) were abstracted from identified studies. CAS was associated with greater 30-day odds for death or stroke when compared to CEA (OR=1.54, 95% CI 1.25-1.89). This seems primarily driven by increased risk for stroke OR=0.153, 95% CI 1.23-1.91) associated with CAS rather than death (OR=1.49, 95% CI 0.93-2.37, p=0.10). CAS was associated with significantly lower odds for MI (OR=0.48, 95% CI 0.30-0.78) and cranial nerve injury (OR=0.09, 95% CI 0.05-0.16) at 30 days when compared to CEA. In terms of outcomes assessed ≥1 year of follow-up, CAS was associated with an increased risk for stroke (OR=1.37, 95% CI 1.13-1.65)

	but not for the combined outcome of stroke and death (OR=1.25, 95% CI 0.06-1.48) versus CEA.
Guay (2011)	Ten randomized controlled trials (n=6950) were included in the comparison of CAS and CEA in terms of 30-day risk stroke, MI and death in symptomatic and asymptomatic patients. Cerebral protection was used in only 4 of the identified studies. When results from these four studies were pooled, 30-day risk for stroke was significantly lower in individuals assigned to received CEA (OR=0.50, 95% CI 0.38-0.67). Based on data from six trials, there was an increase in 30-day risk for MI associated with CEA versus CAS (RR=2.16, 95% CI 1.32-3.54). There was no significant between-group difference noted for the 30-day outcome of death (seven trials).
Yavin et al. (2011)	Identified 12 RCTs for inclusion. Primary study outcomes identified for pooled analysis were 30-day rates of stroke, death and MI. Secondary outcomes included 30-day disabling stroke, stroke or death, stroke/MI/death, incidence of restenosis, cranial neuropathy and access-related haematoma. On pooled analysis there were increased odds of stroke (OR=1.72, 95% CI 1.2-2.47; 10 trials) associated with CAS as well as decreased odds of MI (OR=0.47, 95% CI 0.29-0.78; 8 trials) when compared with CEA. There was no significant difference between interventions in terms of periprocedural death (OR=1.11, 95% CI 0.56-2.18; 11 trials). Pooled odds of restenosis (seven trials) did not differ between CAS and CEA (OR=1.95, 95% CI 0.63-6.06). There was a significant reduction in odds for cranial neuropathy associated with CAS versus CEA (OR=0.08, 95% CI 0.04-0.16; 10 trials).
Liu et al. (2012)	Identified 13 RCTs for inclusion (n=7501 participants). Primary study endpoints abstracted for pooled analysis included rates of adverse events including <30 day stroke/death, 1-4 year stroke/death, periprocedural death/disabling stroke or nondisabling stroke. CAS was associated with greater 30-day risk for stroke/death than CEA (OR=1.57, 95% CI 1.11-2.22; p=0.01). This was especially notable in individuals with previously symptomatic stenosis (OR=1.89, 95% CI 1.48, 2.41; p<0.01). It was also noted that, while there was no difference between CEA and CAS in terms of 30-day risk for death or disabling stroke, CAS was associated with increased 30-day risk for nondisabling stroke compared with CEA (OR=1.87, 95% CI 1.4, 2.5, p<0.01). There was no difference between procedures in terms of pooled risk for stroke/death at one year. CAS, compared to CEA was associated with a smaller 30-day risk for MI (OR=0.43, 95% CI 0.26, 0.71; p=0.001). It should be noted that analyses of both 30-day and 1-year outcomes were associated with heterogeneity (p=0.04 and p=0.06, respectively). The authors suggest that this may be attributed to factors such as variations in endovascular techniques, development of adjuvant techniques/devices, variations in baseline characteristics of participants, variations in degree of stenoses and time from symptom onset to intervention.

Despite difficulties in interpretation given significant study heterogeneity, both Ederle et al. (2009) and Meier et al. (2010) concluded that, at present, there is insufficient evidence to support a shift in practice away from carotid endarterectomy to CAS as the intervention of choice for carotid artery stenosis.However, in a study looking at trends in CEA and CAS utilization it was found that from 1998 to 2008 there was a statistically significant reduction in the number of CEA procedures performed over time and a statistically significant increase in CAS procedures in this time period (Skerritt et al., 2012).

Carotid endarterectomy appears to be associated with better short-term (30-day) outcomes than carotid artery stenting attributable to a significantly greater early risk for stroke in patients treated with carotid artery stenting (Economopoulos et al., 2011; Guay, 2011; Meier et al., 2010; Yavin et al., 2011).

In the cumulative meta-analysis by Meier et al. (2010), studies added to the analysis individually in chronological order, demonstrated that the outcomes associated with CAS have continued to improve as technology and technique evolve. This is also reflected in the results provided from registry data. For example, investigators presented analyses of provider-reported data from a large on-line database developed by the Outcomes Committee of the Society for Vascular Surgery (SVS) to facilitate real-world comparison between CAS and CEA (Sidawy et al., 2009). Overall, CAS (n=1450) was associated with

significantly higher 30-day event rates for stroke (3.52% vs 1.68%, p=0.003), as well as for the combined outcome of stroke/death/MI (5.72% versus 2.63%, p<0.001), than CEA (n=1368). These rates are all lower than those provided in the report by Meier et al. (2010). In the SVS registry, CAS was provided to more symptomatic patients than CEA. Symptomatic patients receiving CAS experienced a significantly higher rate of stroke (5.27% versus 2.11%, p=0.0014) and of the combined study outcome (7.13% versus 4.6%, p=0.04) than asymptomatic patients. This between group difference was not noted among patients undergoing CEA for whom the 30-day rates of stroke and of combined death/stroke/MI were not significantly different for symptomatic and asymptomatic patients (p=0.133 and 0.055, respectively) (Sidawy et al., 2009).

A study of data collected from 3,179 CAS procedures at 4 European facilities provided information regarding the long-term outcomes of stroke and death. Over 5 years, average annual rates for stroke and death from all causes were 1.9% and 3.43%, respectively. The only significant predictor of neurological complications was the presence of neurological symptoms prior to the procedure (HR=1.38, 95% CI 1.05-1.82, p=0.02). The authors noted that the average annual rate reported for any type of ipsilateral fatal/disabling stroke (1.7%) was similar to complication rates reported previously for CEA (de Donato et al., 2008).

Of course, as the technology and technical expertise associated with both CAS and CEA have improved, medical management has also likely improved over time. None of the trials that address either or both of these interventions include a best medical therapy group for comparison. Since these interventions are specifically intended to prevent stroke, risk of complications (i.e. stroke) and benefits over the longer term must be considered carefully, ideally against the background of improved medical management and aggressive risk factor reduction (Meier et al., 2010).

Conclusions Regarding Carotid Endarterectomy (CEA) Versus Carotid Artery Stenting (CAS)

There is level 1a evidence that CAS may be associated with a greater 30-day and longer term (≥ 12 months) risk for stroke than CEA.

There is level 1a evidence that CEA may be associated with a greater 30-day risk for myocardial infarction and cranial neuropathy however, in the long-term the risk of recurrent stroke is similar between CAS and CEA.

When compared with carotid endarterectomy, use of carotid artery stenting is associated with significantly increased 30-day risk for stroke however, long term outcomes indicate a comparable rate of stroke recurrence between carotid endarterectomy and carotid artery stenting.

8.10.2.3 Age and Symptomatic Status

The number of CAS procedures has continued to increase over time and with it the proportion of octogenarians who undergo this intervention. In a report from the ALKK Carotid Artery Stent Registry, Zahn et al. (2007) reported that the proportion of individuals ≥80 years receiving CAS increased significantly from 1996 to 2007 (5.9% to 13.7%, p=0.002). In addition, among individuals who are 80 years of age or older, symptomatic stenosis may be a more common indication for intervention than in younger individuals (Zahn et al., 2007).

Age has been demonstrated to be a significant predictor of risk for many medical complications, including CEA. However, the evidence regarding the association between advancing age and risk for adverse outcomes following CAS has been mixed. Recently, subgroup analyses of data from both clinical trials and large clinical databases or registries has been examined in order to evaluate the role of age and symptom status in the risk for adverse events such as stroke and death, following CAS (Table 8.10.2.3.1).

Table 8.10.2.3.1 Age and Symptomatic Status

Author, Year, Country	Data Source	Total N	N ≥80 yrs (%)	Results
Roubin et al. (2001) USA	Clinical Database	528	66 (12.5%)	There were significantly more reported occurrences of the combined 30-day outcome (stroke/death) in octogenarians (p<0.001), based mostly on increased incidence of major nonfatal strokes in this group. An age ≥80 year was the best predictor of 30-day stroke/death.
Hobson et al. (2004) USA	CREST trial (lead-in period)	749	99 (13.2%)	There was a significant difference in 30-day event rates associated with increasing age (p=0.0006). Patients were divided in age categories of <60, 60-69, 70-79 and ≥80 years. 30-day event rates (stroke and death) associated with these categories were 1.7%, 1.3%, 5.3% and 12.1%, respectively. Adjustment for symptomatic status, use of embolic protection devices, gender, percentage stenosis or distal arterial tortuosity did not affect the association between age and outcome events.
Gray et al. (2007) USA	CAPTURE Registry	3500	829 (23.7%)	Overall, the 30-day rate for stroke was 4.8%. In individuals over 80 years, 30-day rate for stroke was 7.2%. Combined rate for death/stroke was 8.9% in individuals ≥80 years, 4.7% for younger individuals and 5.7% overall. On multivariate analysis, the presence of symptoms and age were both identified as independent predictors of 30-day death/stroke or stroke (p<0.001, for all).
Zahn et al. (2007) Germany	ALKK Registry	2780	321 (11.2%)	Symptomatic stenosis was more frequent among individuals aged ≥80 years (60.7% versus 48%, p<0.001). The rate for in-hospital stroke/death was 7.1% in symptomatic octogenarians versus 3.4% in those who were asymptomatic. In-hospital rates for stroke/death were also higher than for younger patients (5.5% versus 3.2%, OR=1.79, 95%CI 1.04-3.06). Increasing age was associated with increasing rates of stroke/death (p=0.001 for the trend) as well as of stroke alone (p=0.004).
Henry et al. (2008) France	Clinical Database	870	121 (13.9%)	Among individuals receiving CAS using embolic protection devices, there was no reported deaths/stroke at 30 days. Overall, the 30-day rate of stroke/death was 1.1% in symptomatic patients and 0.8% in asymptomatic patients. Approximately the same proportion of young versus old patients was symptomatic (62% versus 64%).
Stingele et al. (2008) International	SPACE trial sub-group analysis	607	138 (22.7%>75 yrs)	The event (30-day ipsilateral stroke/death) rate was 11.2% in the oldest age group (>75 yrs). There was a significant trend (p=0.0003) for increasing events associated with increasing age. The estimated relative risk increase (OR) was 7.2% per year of age in the CAS group (p=0.001). There was no similar association found in the CEA group. The best cut-off point for separation of high and low risk groups based on age was 68 years. Event rates were 10.8% for individuals above this cut-off point and 2.7% for individuals below it.
deDonato et al. (2008) International	Clinical database	3179	Not reported	Overall, the average annual rate for any stroke was 1.9% and 3.43% for death from any cause. Univariate analysis was used to identify potential risk factors for neurological complications. Age ≥80 years was not a significant risk factor (HR=1.02, p=0.91). The only significant risk factor identified was the presence of pre-procedural neurological symptoms (HR=1.38, 95% CI 1.05-1.82, p=0.02).

Chaturvedi et al. (2010) USA	CAPTURE-2 Ongoing trial subgroup analysis	5297	1166	Overall, the rate of the combined outcome of stroke/death was 2.2% (2.7% for stroke alone). Rates of stroke/death (4.5% versus 3.0%) and for stroke alone (3.8% versus 2.0%) were significantly higher for individuals ≥80 years of age. Logistic regression was undertaken to identify factors associated with stroke following CAS. Age, although it was an overall predictor of outcome, was not significantly associated with stroke following CAS within the subgroup of individuals ≥80 years. Significant predictors of stroke were symptomatic status (yes versus no; OR=3.31, 95% CI 1.62-6.75), EPD dwell time in minutes (OR=1.04, 95% CI 1.01-1.07) and lesion length ≥20 mm (yes versus no; OR=2.34, 95% CI 1.13-4.85).
Mantese et al. (2010)	CREST subgroup analysis	2502	Not reported	Neither status of symptoms (symptomatic versus asymptomatic) nor gender modified the treatment effect demonstrated. Authors reported a significant interaction (p=0.02) between age and treatment such that reported outcomes were more favourable for patients assigned to CAS and who were <70 years (versus CEA for this age category) and CEA resulted in better outcomes (versus CAS) for individuals >70 years.

Discussion

In the majority of studies, older, symptomatic patients experienced significantly greater risk for 30-day stroke or death. Those at least risk following CAS may be those with asymptomatic stenosis who are under the age of 80.

In a meta-analysis, the Carotid Stenting Trialists' Collaboration reported similar risks for 120-day stroke or death in individuals under the age of 70 years with symptomatic stenosis who were treated with CAS when compared to CEA (RR=1.0, 95% CI 0.68-1.47) (Bonati et al., 2010). However, for individuals ≥70 years, risk for 120-day stroke or death associated with CAS was approximately double than that associated with CEA (12% versus 5.9%; RR=2.04, 95% CI 1.48-2.92). Similarly, in a meta-analysis of both symptomatic and asymptomatic patients, Economopoulos et al. (2011) reported more equivalent outcomes following CAS and CEA in younger patient groups (<68 years).

Table 8.10.2.3.2 Case selection (Chiam et al., 2008)

Patients ≥80 years of age with symptomatic stenosis (≥50%) or asymptomatic stenosis (≥70%) were considered in the absence of:

- Decreased cerebral reserve
  (prior large stroke, multiple lacunar infacts, intracranial microantiopathy or dementia); or
- Excessive vessel tortuosity
  (≥2 90 de.g., bends within 5 cm of the lesion); or
- Heavy calcification
  (concentric calcification ≥3 mm wide)

Chiam et al. (2009) examined the long-term outcomes of a group of older individuals (≥80 years of age) who had undergone CAS procedures with embolic protection for either symptomatic stenosis of ≥50% or asymptomatic stenosis ≥70%. By three years, survival was estimated to be 76%. The average annual mortality rate was 8.7% (Chiam et al., 2009). Significant independent predictors of mortality included previous remote stroke/TIA, smoking status and preprocedural creatinine clearance, but not age. However, when asymptomatic patients were analysed separately, increasing age was associated with increasing mortality risk (HR=1.19, 95% CI 1.05-1.35-per year).

Chiam et al. (2008; 2009) have suggested that, given the high proportion of elderly patients who survive more than 2 or 3 years following CAS, this procedure may be considered as a reasonable alternative within this population if periprocedural event rates are within the current recommended guidelines. Careful selection of patients may reduce procedural risk and increase the likelihood for survival over time. Predictors of greater periprocedural risk associated with aging include increased vessel tortuosity, lesion

calcification and decreased cerebral reserve (Roubin et al., 2006). Chiam et al. (2008) proposed a method of case selection based on these previously identified risk factors (Table 8.10.2.3.2).

Ultimately, the decision to treat carotid artery stenosis relies on a risk-benefit analysis taking into account the cumulative risk of stroke in the patient undergoing treatment as well as the procedural risks of stroke and death from revascularization, whether by means of CEA or CAS (Malek et al., 2000).

Conclusions Regarding Indications for CAS

There is level 1a evidence that the risk for death and stroke may be higher in patients over 70 years of age with symptomatic stenosis treated with CAS compared to those treated with CEA.

Careful case selection should be exercised for the appropriate use of CAS especially when the patients are of >70 years of age and have symptomatic stenosis.

8.10.3 Recommendations for the Use of Reperfusion Interventions

The Canadian Stroke Best Practice Guidelines provide several recommendations with respect to the management of extracranial carotid diseases and intracranial atherosclerosis (Coutts et al. 2015). See table 8.10.3.1 for recommendations.

Table 8.10.3.1 Canadian Stroke Best Practice Recommendations for the Management of Carotid Disease and atherosclerosis

Symptomatic Carotid Stenosis

Patients with TIA or nondisabling stroke and ipsilateral 50% to 99% internal carotid artery stenosis should have an evaluation by an individual with stroke expertise and selected patients should be offered carotid endarterectomy as soon as possible.

- Carotid stenosis should be measured by CTA alone or two concordant noninvasive imaging modalities such as MRA and carotid ultrasound or digital subtraction angiography (DSA).
- Individuals with mild stroke or TIA should have carotid endarterectomy performed within 48 hours of symptom onset (NASCET Trial, NNT=3), and within 14 days for patients who are not clinically stable within the first 48 hours. Carotid endarterectomy should be performed by a surgeon with a known perioperative morbidity and mortality of less than 6%.
- Carotid stenting may be considered for patients who are not operative candidates for technical anatomic or medical reasons. Interventionalists should have expertise in carotid procedures and an expected risk of per-procedural morbidity and mortality rate less than 5%.
- Carotid endarterectomy is more appropriate than carotid stenting for patients over age 70 who are otherwise fit for surgery because stenting carries a higher peri-procedural risk of stroke and death.

Asymptomatic and remotely symptomatic carotid stenosis

Carotid endarterectomy may be considered for selected patients with 60% to 99% carotid stenosis who are symptomatic or even remotely symptomatic.

- Stroke patients with asymptomatic carotid stenosis should receive aggressive medical management of risk factors.
- Patients with asymptomatic carotid disease should be evaluated by a physician with expertise in stroke management.
- Patients should be evaluated to determine eligibility for carotid endarterectomy, such as a life expectancy of more than five-years, and an acceptable risk of surgical complications.
- In carefully selected patients, carotid endarterectomy should be performed by a surgeon with a less than 3% risk of perioperative morbidity and mortality.
- Carotid stenting may be considered in patients who are not operative candidates for technical, anatomic or medical reasons provided there is a less than 3% risk of peri-procedural morbidity ad mortality.

Intracranial stenosis

- Intracranial stenting is not recommended for the treatment of recently symptomatic intracranial 70% to 99% stenosis.
- In the SAMMPRIS trial the medical management arm included dual antiplatelet therapy with ASA 325mg and Clopidogrel 75mg started within 30 days of stroke or TIA and treated for up to 90 days. This should be considered for each patient on an individual basis. In addition, there should be aggressive management of all vascular risk factors including blood pressure, lipids, diabetes mellitus, and other at-risk lifestyle patterns.
- In patients who have been managed with maximal medical therapy in the presence of intracranial stenosis and experience a recurrent stroke, there is lack of clear evidence to guide further management decisions; intracranial stenting may be reasonable in carefully selected patients.

8.10.4 Posterior Circulation Ischemic Stroke and TIA

Ischemia in the posterior circulation has long been overshadowed by ischemic events in the carotid artery region. However, several studies on posterior circulation ischemic stroke and TIA have shown that they are associated with a high risk of early recurrent stroke (Markus et al., 2013). Although patients presenting with anterior circulation stroke are easily identified due to a distinct pattern of clinical features, patients with posterior circulation stroke and TIA are often not identified in a timely manner. Diagnosing, in particular, is challenging due to overlap in symptoms with anterior circulation ischemia.

In a large case series study, Searls et al. (2012) found that the most frequent posterior circulation ischemia symptoms were dizziness, unilateral limb weakness, dysarthria, headache, and nausea or vomiting. Frequent signs of posterior circulation ischemia included unilateral limb weakness, gait ataxia, unilateral limb ataxia, dysarthria, and nystagmus. Because identical signs and symptoms can be produced in both anterior and posterior circulation ischemia, identification on the basis of signs and symptoms alone can be difficult or impossible. A confident diagnosis in clinical practice can only be reached after brain imaging (Markus et al., 2013).

The treatment and risk factor management of a patient with posterior circulation stroke or TIA is similar to that for ischemic stroke in general (Markus et al., 2013). However there is no evidence of revascularization therapy of the posterior circulation vessels is safe or beneficial. Future research in the diagnosis and secondary prevention of posterior circulation stroke and TIA is needed.

Summary

1. ***There is level 1a evidence that carotid endarterectomy may be an effective procedure to reduce the risk of stroke in individuals with symptomatic carotid artery stenosis of 70-99%.***
2. ***There is level 1a evidence that carotid endarterectomy may be an effective procedure to reduce the risk of stroke in individuals with asymptomatic carotid artery stenosis of ≥ 60% however, the operative risks associated with the procedure outweigh the benefit if they exceed 3%. Current guidelines do not recommend regular revascularization in asymptomatic patients.***
3. ***There is level 1a evidence that CEA may be an effective procedure to reduce stroke risk in individuals with 50-69% stenosis if done soon after the event (< 14 days). Risk of procedure needs to be weighed on an individual patient basis.***
4. ***There is level 1b evidence that early CEA may not be associated with increased risk for stroke or death. Pooled analysis suggests that benefits associated with CEA may decrease as time from the qualifying ischemic event increases especially in patients with moderate (50-69%) carotid stenosis.***
5. ***There is level 1b evidence that nursing-led coordinated case management may be associated with short-term improvements in knowledge of stroke warning signs and self-reported lifestyle and dietary changes.***
6. ***There is level 1b evidence that CAS procedures may result in a decrease incidence of carotid territory stroke.***
7. ***There is level 1a evidence that both CAS and CEA procedures may be equally effective in preventing strokes. Both procedures generate comparable rates of restenosis.***
8. ***There is level 1b and level 2 evidence that carotid angioplasty with cerebral protection may not provide additional benefits relative to CAS without protection.***
9. ***There is level 1a evidence that CAS may be associated with a greater 30-day and longer term (≥ 12 months) risk for stroke than CEA.***
10. ***There is level 1a evidence that CEA may be associated with a greater 30-day risk for myocardial infarction and cranial neuropathy however, in the long-term the risk of recurrent stroke is similar between CAS and CEA.***
11. ***There is level 1a evidence that the risk for death and stroke may be higher in patients over 70 years of age with symptomatic stenosis treated with CAS compared to those treated with CEA.***

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