G. Secondary Prevention of Stroke Educational Supplement

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G1. Transient Ischemic Attack
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G1.1 Case Study: TIA

Case Study

A 32 year old female patient presents to the Emergency Room and tells you that something strange happened one hour ago: She couldn’t see out of her left eye for 50 minutes. Although she can see fine now, she and her family want to know what might have caused this temporary blindness.

Q1. What do you think happened and what is your recommendation?

Answers
1. TIA
2. Immediate workup (preferably by neurologist) for stroke risk.

Discussion

TIA is a syndrome defined as the sudden onset of focal neurological loss of presumed vascular origin lasting less than 24 hours with full recovery commonly occurring within 2 hours. One of the possible symptoms of a TIA is retinal ischemia (transient monocular blindness). The following definition of TIA has recently been proposed: a “brief episode of neurological dysfunction caused by a focal disturbance of brain or retinal ischemia, with clinical symptoms typically lasting less than 1 hour, and without evidence of infarction” (Albers et al. 2002).

The patient should receive a medical examination (by a neurologist if possible) as soon as possible and undergo a full risk evaluation for stroke because TIA is a risk factor for stroke.

Q2. The patient and her family want to know more about the role of TIA as a possible risk factor for Stroke. What information can you give them?

Answer
1. TIA is a significant risk factor for stroke

Discussion

A TIA is considered a very significant risk factor for a stroke. 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), Lisabeth et al. (2004), and Gladstone et al (2004) all concluded that approximately one half of strokes following TIA will take place within the first 48 hours. Van Wijk et al. (2005) reported the 10-year risk for vascular events following TIA to be 35.8%.

With this knowledge, the National Stroke Association (2006) emphasized the importance of urgent assessment and intervention following TIA because intervention can reduce the 90 day risk for stroke.

Q3. Which clinical features are predictive of greater stroke risk with a TIA?

**Answers:**
1. Age (older)
2. High blood pressure
3. Unilateral weakness
4. Speech impairment
5. Length of symptoms
6. Diabetes

**Discussion**
Johnston et al. (2007) validated the use the unified ABCD2 score for the prediction of 2 day risk of stroke after a TIA.

| 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            | 2           |
| • Speech impairment without weakness | 1           |
| Duration of symptoms in minutes  |             |
| • ≥ 60                           | 2           |
| • 10 – 59                        | 1           |
| Diabetes                         | 1           |

The 2 day risk for stroke following TIA was reported to be 1% for those with a score of 0-3 (low risk), 4.1% for those with a score of 4-5 (moderate risk), and 8.1% for those with a score of 6-7 (high risk) (Johnson et al. 2007). This score was also able to predict the risk of stroke from 7 to 90 days following the TIA event.

The risk of stroke following TIA is also influenced by the vascular territory in which the initial event occurred. Vertebrabasilar territory risk for subsequent stroke is higher than the carotid territory (OR= 1.70, 95% CI 1.3 - 2.2) (Flossman and Rothwell 2003).
References


G2. Hypertension
G2. Hypertension

Canadian Best Practice Recommendations (2008): Recommendation 2.2 - Management of High Blood Pressure

Hypertension is the single most important modifiable risk factor for stroke. Blood pressure should be monitored in all persons at risk for stroke.

2.2a. Blood pressure assessment

i. All persons at risk of stroke should have their blood pressure measured at each health care encounter, but no less than once annually [Evidence Level C] (CHEP, NICE, RCP).

ii. Proper standardized techniques, as described by the Canadian Hypertension Education Program, should be followed for blood pressure measurement (CHEP).

iii. Patients found to have elevated blood pressure should undergo thorough assessment for the diagnosis of hypertension following the current guidelines of the Canadian Hypertension Education Program [Evidence Level A] (ASA, CHEP, RCP).

iv. Patients with hypertension or at risk for hypertension should be advised on lifestyle modifications. [Evidence Level C]. Refer to recommendation 2.1, "Lifestyle and risk factor management," for details on lifestyle modifications.

2.2b. Blood pressure management

i. The Canadian Stroke Strategy recommends target blood pressure levels as defined by the Canadian Hypertension Education Program (CHEP) guidelines for prevention of first stroke, recurrent stroke, and other vascular events. CHEP 2008 Recommendations for Management of Blood Pressure (excerpts used with permission; see www.hypertension.ca/chep for detailed information (Khan et al. 2008):

   • For the prevention of first stroke in the general population the systolic blood pressure treatment goal is a pressure level of less than 140 mm Hg [Evidence Level C]. The diastolic blood pressure treatment goal is a pressure level of less than 90mm Hg [Evidence Level A].
   • Blood pressure lowering treatment is recommended for patients who have had a stroke or transient ischemic attack to a target of less than 140/90 mm Hg [Evidence Level C].
   • In patients who have had a stroke, treatment with an angiotensin-converting enzyme (ACE) inhibitor or diuretic is preferred [Evidence LevelB].
   • Blood pressure lowering treatment is recommended for the prevention of first or recurrent stroke in patients with diabetes to attain systolic blood pressures of less than 130 mm Hg [Evidence Level C] and diastolic blood pressures of less than 80 mm Hg [Evidence Level A].
   • Blood pressure lowering treatment is recommended for the prevention of first or recurrent stroke in patients with nondiabetic chronic kidney disease to attain a blood pressure of less than 130/80 mm Hg [Evidence Level C].

ii. Randomized controlled trials have not defined the optimal time to initiate blood pressure lowering therapy after stroke or transient ischemic attack. It is recommended that blood pressure lowering treatment be initiated (or modified) prior to discharge from hospital. For patients with
nondisabling stroke or transient ischemic attack not requiring hospitalization, it is recommended that blood pressure lowering treatment be initiated (or modified) at the time of the first medical assessment [Evidence Level B] (EXPRESS, PROGRESS).

iii. For recommendations on specific agents and sequence of agents, please refer to the current Canadian Hypertension Education Program guidelines (Khan et al. 2008).

G2.1 Case Study: Hypertension

Case Study

A 55 year old woman is admitted to the inpatient rehabilitation unit with a lacunar infarct in the right thalamic/subcortical area. Her past medical records state that she has a history of hypertension which is not well controlled. The nurse notes that the patient’s blood pressure (BP) is 145/90 mmHg and that she is not currently taking any antihypertensive medication.

Q1. What are the risk factors for this patient having a new stroke?

Answers
1. Stroke
2. Hypertension

Discussion

Stroke: Having had a stroke is a significant risk for the development of further strokes. Goldberg and Berger (1988) reported that one in four hospital admissions for stroke are due to recurrence and patients who have had a stroke are five times as likely to experience a reoccurrence when compared to those who have not had a stroke. Coull and 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. Cardioembolic strokes had the greatest risk for recurrence while lacunar stroke had the lowest risk (Kaplan et al 2005).

Hypertension: Hypertension is the most significant risk factor for stroke. However, despite its high prevalence and modifiable nature, as few as 1 in 4 stroke patients receive adequate blood pressure control (Amar et al 2004). Hypertension is a risk factor for both the first stroke and the recurrence (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, this would translate into a
reduction in relative risk of 13% for each 9 mmHg drop in systolic BP and 11% for a 4 mmHg drop in diastolic BP).

**Q2. What BP level is considered normal?**

**Answer**
1. Less than 120/80 mmHg

**Discussion**
Normal BP levels have been defined as <120/80 mm Hg by the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (Chobanian et al. 2003).

**Q3. The patient tells you that her current BP (145/90 mmHg) is normal for her and that she questions whether it needs to be treated because she doesn’t want to have to take any “pills”. What can you tell her?**

**Answer**
1. Her BP is considered to be elevated.
2. Hypertension is a modifiable risk factor for stroke.
3. Treatment of hypertension will reduce her risk of stroke.
4. Medications are often needed as nonpharmacological methods are often unsuccessful.

**Discussion**
It is important to inform the patient that high BP is a modifiable risk factor for having a new stroke; in other words, her chances of having a second stroke will decrease if her hypertension is treated.

Based on The Ontario Heart and Stroke Foundation’s (2003) recommendations, this patient’s BP should be less than 140/90. The British Hypertension Society guidelines state that for non-diabetic patients with hypertension the optimal blood pressure treatment goals are systolic blood pressure <140 mmHg and diastolic blood pressure <85 mmHg.

A combination of antihypertensive medication and lifestyle modifications will help this patient lower her BP and, consequently, her risk of stroke. Lifestyle modifications are associated with BP reductions and should be included as part of a comprehensive antihypertensive therapy.

**Q4. After the patient agrees to be treated, the resident asks what pharmacological treatments are available for hypertension and which treatment would be most appropriate for this patient. What would be your initial treatment?**
Answer
1. Diuretic alone or in combination with an ACE inhibitor

Discussion
Therapy with a diuretic, alone or in combination with ACE inhibitor, could be recommended based on available data (Hilleman and Lucas 2004). However, individual cases may not respond equally to the same treatment and reduction and control of BP may require the use of multiple antihypertensive agents (Spence 2003). The use of combination treatment has been found to effectively reduce stroke, myocardial infarction, and all vascular events outcomes by 40-45% (Rashid et al. 2003). An example of the benefit of combined therapy over single therapy is the PROGRESS trial (2001) which was a randomized controlled trial in which 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. Combination therapy with perindopril & indapamide produced larger risk reductions for total stroke than treatment with perindapril alone. Hypertensive and non-hypertensive patients with history of ischaemic stroke or TIA both benefited from combined therapy.

Many agents have been assessed for use as antihypertensive treatments in the reduction of BP in the primary and secondary prevention of stroke. The research studies supporting or not supporting different pharmacological options are presented in the table below.

Summary of Pharmacological Treatment of Hypertension and Reduction of Risk of Stroke:

<table>
<thead>
<tr>
<th>Study</th>
<th>Agent(s) Assessed</th>
<th>Effect on Stroke Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE-Inhibitors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>UKPDS</td>
<td>Captopril vs. Atenolol</td>
<td>Increased risk (Captopril)</td>
</tr>
<tr>
<td>CAPPP</td>
<td>Captopril vs. β-blocker + diuretic</td>
<td>Increased risk (Captopril)</td>
</tr>
<tr>
<td>HOPE</td>
<td>Ramipril vs. placebo</td>
<td>Reduced risk</td>
</tr>
<tr>
<td>PROGRESS</td>
<td>Perindopril + diuretic vs. placebo</td>
<td>Reduced risk</td>
</tr>
<tr>
<td>Australian BP Study</td>
<td>Various ACE-inhibitors vs. various diuretics</td>
<td>Similar risk for nonfatal stroke, increased for fatal (ACE-inhibitor)</td>
</tr>
<tr>
<td>ALLHAT</td>
<td>Lisinopril vs. diuretic</td>
<td>Increased risk (Lisinopril)</td>
</tr>
<tr>
<td>β-blockers/β-RA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SHEP</td>
<td>Atenolol + diuretic vs. placebo</td>
<td>Reduced risk</td>
</tr>
</tbody>
</table>

Note: The results of UKPDS, CAPPP, LIFE and ASCOT-BPLA also consider the use of β-blockers.

Ca-channel blockers/Ca antagonists

<table>
<thead>
<tr>
<th>Study</th>
<th>Agent(s) Assessed</th>
<th>Effect on Stroke Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>NORDIL*</td>
<td>Diltiazam + regimen vs. regimen alone</td>
<td>Reduced risk</td>
</tr>
<tr>
<td>Syst-Eur 1*</td>
<td>Nitrendipene vs. placebo</td>
<td>Reduced risk</td>
</tr>
<tr>
<td>Syst-Eur 2*</td>
<td>Nitrendipene vs. placebo</td>
<td>Reduced risk</td>
</tr>
</tbody>
</table>
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)

**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. Atenolol-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.

* therapy administered included the possible additions of ACE-inhibitors (or α-blockers or β-blockers), and/or diuretics as part of a treatment regimen designed to reduce BP to meet target.

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**Q5. List the reasons why it is important to treat hypertension in stroke survivors?**

**Answers:**
1. Most important treatable risk factor
2. High prevalence
3. Easily modifiable
4. Proportional risk
5. Reduction associated with decreased risk.

**Discussion**
- Hypertension is the most powerful treatable risk factor.
- It has a high prevalence and is easily modifiable.
- Declining stroke incidence and mortality over the last 4 decades has been attributed to better management of hypertension.
- Risk of stroke rises proportionally with increasing systolic and diastolic blood pressure.
- Kaplan et al. (2006) reported a 9 mmHg drop in systolic blood pressure reduced the relative risk of recurrent stroke by 13% while a 4mmHg drop in diastolic blood pressure results in an 11% drop in relative risk.
- Treatment of systolic hypertension in the elderly decreases the risk of stroke by 36%.
There is strong evidence that a reduction in blood pressure is associated with a decreased risk of stroke.

**Q6. Two important studies looking at the treatment of hypertension post-stroke were the PROGRESS and HOPE trials. Describe both of these trials.**

**Answers:**
1. The PROGRESS trial randomized 6105 patients (both HBP and non-HBP) with a history of ischemic stroke or TIA to either perindopril 4mg/day + indapamide versus perindopril alone versus placebo. The researchers found a 28% reduction in relative risk was associated with the combined treatment of perindopril + indapamide, as compared to perindopril alone.
2. The HOPE trial randomized 3577 diabetic patients (age 55+ and history of cardiovascular disease) to 10 mg Ramipril/day versus placebo. Ramipril lowered the risk of myocardial infarction by 22%, stroke by 33%, cardiovascular disease by 37%, and total mortality by 24%.

**G2.2 Case Study: Intracerebral Hemorrhage and Hypertension**

**Case Study**
34 year old obese male presented to hospital emergency room with aphasia, right hemiparesis and decreased level of consciousness. CT scan showed a large left intracerebral hemorrhage. BP was 236/124. Patient was admitted to the ICU.

Past medical history was a 2 year history of malignant hypertension complicated by two hypertensive crisis in the month before his stroke for which he was treated but he failed to follow through with his prescriptions. At the time of admission and in the ICU his BP proved extremely difficult to control and he was discharged from the ICU with a BP of 170/95.

**Q7. What treatment options are available?**

**Answers**
1. Thiazide diuretic (i.e. hydrochlorothiazide)
2. ACE inhibitor (i.e. Ramipril – HOPE trial; Perindopril – PROGRESS; Captopril not to be used)
3. ARB (angiotensin receptor blocker) (i.e. Losartan – LIFE trial; Candesartan; Eprosartan – MOSES trial)
4. Calcium channel blocker (i.e. Diltiazem – NORDIL; Amlodipine)
5. Beta-blocker
6. Salt restrictions
* These medications can be used in combination for resistant hypertension

Case Study (continued)
He was admitted to rehabilitation and during his rehabilitation stay his blood pressure was generally running between 120-140 systolic and 70-90 diastolic with occasional BPs of 150-160 systolic and 90-100 diastolic.

Medications for HBP while on the rehabilitation unit included Amlodipine 7.5 mg q12h, Metoprolol 150 mg q12h, Perindopril 2 mg OD, Prazosin 6 mg q6h with the suggestion of adding an additional 12.5 mg of Hydrochlorothiazide to further regulate the patient's blood pressure.

Discussion (from the SREBR 11th Edition; Teasell et al. 2008)
“Many different types of pharmacological therapies have been assessed both on their own and in combination with each other. Most have clearly demonstrated a relationship between the reduction of blood pressure and reduced risk of stroke.

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, alpha-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 et al. 2003). Rashid et al. (2003) demonstrated that, overall, antihypertensive therapy (beta-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; Mason et al. 2004; Mancia, 2004). However, a
study of data from the ongoing WACS trial demonstrated a linear relationship between systolic blood pressure and the risk of cardiovascular disease in a population of women with a history of CVD or ≥3 cardiovascular risk factors (Mason et al. 2004).”

References


Key Study: Hypertension


<table>
<thead>
<tr>
<th>Author, Year Country, Pedro Score</th>
<th>Methods</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROGRESS Collaborative Group 2001, 2003, 2004 International 8 (RCT)</td>
<td>Population studied were hypertensive and non-hypertensive patients with a history of stroke or transient ischaemic attack. A total of 6105 patients were studied. 3501 received active treatment flexible regimen based on ACE inhibitor perindopril (4mg daily) with addition of diuretic indapamide at discretion of the treating physicians while 3054 received a placebo.</td>
<td>During a mean 3.9 yrs of follow-up – active treatment reduced BP by 9/4 mm Hg. 10% of active treatment patients suffered stroke compared to 14% of placebo (28% risk reduction, p&lt;.0001). Active treatment also reduced risk of total major vascular events. With treatment, relative risk reduction for ischaemic stroke was 24% and 50% for intracerebral haemorrhage. Relative risk of any stroke was reduced by 26% in patients with a baseline history of ischaemic stroke and 49% in patients whose history included an intracerebral haemorrhage. Treatment effects were not modified by antiplatelet or antihypertensive therapy or by AF, residual neurological signs or time since historical cerebrovascular event. Additional analysis revealed that BP reduction benefits were seen across all age groups for both men and women and for Asian and Western subjects, although blood pressure differences were greater among Asian subjects than among Western subjects. Reductions in stroke risk were greater in participants &lt; age 65 – each decade of age increase was associated with ¼ less relative risk reduction.</td>
</tr>
</tbody>
</table>
**Importance:** The PROGRESS trial studied the use of a long-acting ACE inhibitor (perindopril) in conjunction with a thiazide diuretic (inda pamide). This combination, used in the prevention of hypertension, led to a relative risk reduction of 48% for recurrent stroke. The number needed to treat to prevent the development of another stroke was 45. Even non-hypertensive stroke
patients demonstrated a significant decline in stroke risk. The PROGRESS trial demonstrated that lowering blood pressure not only reduced risk of stroke but also, not unexpectedly reduced the risk of functional disability and dependency.

**Relevant SREBR Conclusions:** Reduction of blood pressure via antihypertensive therapy is associated with a reduction in stroke events. Control of hypertension post-stroke is associated with a decreased risk of functional disability and dependency.
Key Study: Hypertension


<table>
<thead>
<tr>
<th>Author, Year Country, Pedro Score</th>
<th>Methods</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>HOPE Study Investigators 2000 International 8 (RCT)</td>
<td>Population studied was diabetic stroke patients. 1,808 patients received 10 mg Ramipril and 400 IU vitamin E while 1769 received a placebo daily.</td>
<td>The study stopped 6 months early because of consistent benefit of Ramipril compared to placebo. Ramipril lowered risk of combined primary outcome by 25% (p=.0004), myocardial infarction by 22%, stroke by 33%, cardiovascular death by 37%, total mortality by 24%, revascularization by 17%, overt nephropathy by 24%.</td>
</tr>
</tbody>
</table>

The Relationship between Ramipril and Placebo Treatment for Clinical Outcomes

Importance: This study looked at diabetic stroke patients, some of whom were hypertensive and others who were not. Ramipril reduced the risk of recurrent stroke in both hypertensive and non-hypertensive diabetic stroke patients.

Relevant SREBR Conclusion: There is strong evidence that the addition of a Ca-antagonist to a regimen that may include ACE-inhibitors or beta-blockers and a diuretic decrease the risk of stroke events in both diabetic and non-diabetic stroke patients.
G3. Hyperlipidemia and Hypercholesterolemia
G3. Hyperlipidemia and Hypercholesterolemia

Canadian Best Practice Recommendations (2008): Recommendation 2.3 - Lipid Management

Lipid levels should be monitored in all persons at risk for stroke.

2.3a. Lipid assessment

i. Fasting lipid levels (total cholesterol, total glycerides, low-density-lipoprotein [LDL] cholesterol, high-density-lipoprotein [HDL] cholesterol) should be measured every 1 to 3 years for all men 40 years or older and for women who are postmenopausal and/or 50 years or older [Evidence Level C] (McPherson et al., VA/DoD). More frequent testing should be performed for patients with abnormal values or if treatment is initiated.

ii. Adults at any age should have their blood lipid levels measured if they have a history of diabetes, smoking, hypertension, obesity, ischemic heart disease, renal vascular disease, peripheral vascular disease, ischemic stroke, transient ischemic attack or asymptomatic carotid stenosis [Evidence Level C] (McPherson et al.).

2.3b. Lipid management

i. Ischemic stroke patients with LDL cholesterol of >2.0mmol/L should be managed with lifestyle modification and dietary guidelines [Evidence Level A] (AU, CSQCS, McPherson et al., VA/DoD)

ii. Statin agents should be prescribed for most patients who have had an ischemic stroke or transient ischemic attack to achieve current recommended lipid levels [Evidence Level A] (AU, CSQCS, McPherson et al., VA/DoD).

G3.1 Case Study: Hyperlipidemia

Case Study

A 68 year old man was admitted into the stroke rehabilitation program with an ischemic stroke on the left ACM territory. He has a history of hyperlipidemia and the cholesterol related results from a recent blood test are as follows:

- Total cholesterol 4.1 mmol/L
- Triglycerides 0.74 mmol/L
- LDL 2.83 mmol/L
- HDL cholesterol 0.94 mmol/L
- Total cholesterol to HDL ratio 4.4
Q1. When the patient asks about the cause of his stroke, the resident tells him that high cholesterol is a major risk factor and that it is the likely cause of his stroke. Do you agree with the resident and why?

Answer
1. No
2. It is not possible at this point to say it is the most likely cause of his stroke.

Discussion
Although it is known that a relationship exits between cholesterol plasma levels and cardiovascular risk, the exact nature of this relationship has not yet been established (Gorelick 2002, Amarenco et al. 2004). After adjusting for multiple risk factors, there is a weak association between cholesterol level and risk of ischemic stroke (Shahar et al. 2003). However, it has been demonstrated that the treatment of hypercholesterolemia with HMG-CoA reductasa inhibitors (statins) reduces the risk of cardiovascular events, including stroke (Lewington et al. 2007).

Q2. After your explanation, the resident asks “if hyperlipidemia is not a major risk factor, do you still have to treat it”?

Answer
1. Yes
2. Reducing hyperlipidemia or hypercholesterolemia does reduce stroke incidence.

Discussion
Hyperlipidemia should be treated. Meta-analyses of clinical trials examining lipid-lowering therapies have reported significant reductions in overall stroke incidence (both fatal and non-fatal), although research has failed to demonstrate any significant reduction in haemorrhagic stroke (Law et al. 2003, Corvol et al. 2003).

Q3. How would you treat the hyperlipidemia?

Answers
1. Reduce dietary intake of saturated fats and cholesterol.
2. Weight reduction
3. Increase physical activity
4. Use of statins.
Discussion
A review of recent prevention guidelines concerning cholesterol lowering by statin use in stroke prevention (Pearson et al. 2002, Smith et al. 2001) suggests that the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Cholesterol in Adults (Adult Treatment Panel III 2001) is one of the most comprehensive guide for management of lipids in persons who have or are at risk for cerebrovascular disease.

NCEP emphasizes LDL-C lowering and recommends 2 major modalities for LDL-C lowering:
- Therapeutic lifestyle change: Therapeutic lifestyle change stresses a reduction in saturated fats and cholesterol intake, weight reduction, and an increase in physical activity.
- Drug-specific therapy: Drug therapy options and management of metabolic syndrome and other dyslipidemias are addressed in the NCEP guideline (Adult Treatment Panel III 2001, www.nhlbi.nih.gov/guidelines/cholesterol/index.htm). Among treatments, statins are the gold standard treatment. There is strong evidence that statins are effective treatment interventions for lowering cholesterol and reducing the risk of stroke and TIA (CARE and LIPIDS studies, Byington et al. 2001). Atrovastatin will reduce the risk of recurrent stroke in individuals with previous stroke (SPARCL study, Amarenco et al 2003, 2006). The most common adverse effects associated with statin therapy are gastrointestinal upset, muscle aches, and hepatitis or hepatotoxicity (gorelick, 2002).

Q4. What are the target values for treating hyperlipidemia following stroke?

Answer
1. Stroke patients are considered high risk patients
2. For high risk patients aim for values of LDL < 2.5 mmol/L and Total cholesterol to HDL ratio < 4.0.

Discussion
The treatment is individualized for each patient and depends on both the risk factors and the Cholesterol results. Although you can use different tables, we include here the Canadian guidelines for target Serum lipid levels per risk category, and the ATP III Guidelines.

<table>
<thead>
<tr>
<th>Canadian Guidelines for Target Serum Lipid Levels per Risk Category</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High Risk</strong></td>
</tr>
<tr>
<td>• LDL &lt; 2.5 mmol/L AND</td>
</tr>
<tr>
<td>• Total cholesterol to HDL ratio &lt; 4.0</td>
</tr>
</tbody>
</table>
### ATP III LDL-C Goals and Cutpoints for TLC and Drug Therapy in Different Risk Categories and Proposed Modifications Based on Recent Clinical Trial Evidence (Grundy et al. 2004)

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>LDL-C Goal</th>
<th>Initiate TLC</th>
<th>Consider Drug Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>High risk: CHD or CHD risk equivalents (10 yr risk &gt;20%)</td>
<td>&lt;100 mg/dL (optional goal &lt;70 mg/dL)</td>
<td>≥ 100 mg/dL</td>
<td>≥ 100 mg/dL (or &lt;100 mg/dL: consider drug options)</td>
</tr>
<tr>
<td>Moderately high risk: 2 + risk factors (10 yr risk 10%-20%)</td>
<td>≤ 130 mg/dL</td>
<td>≥ 130 mg/dL</td>
<td>≥ 130 mg/dL (100-129 mg/dL: consider drug options)</td>
</tr>
<tr>
<td>Moderate risk: 2 + risk factors (10 yr risk &lt;10%)</td>
<td>≤ 130 mg/dL</td>
<td>≥ 130 mg/dL</td>
<td>≥ 160 mg/dL</td>
</tr>
<tr>
<td>Lower risk: 0-1 risk factors</td>
<td>≤ 160 mg/dL</td>
<td>≥ 160 mg/dL</td>
<td>≥ 190 mg/dL (160-189 mg/dL: LDL-lowering drug optional)</td>
</tr>
</tbody>
</table>

1. CHD includes history of myocardial infarction, unstable angina, stable angina, coronary artery procedures (angioplasty or bypass surgery), or evidence of clinically significant myocardial ischemic.

2. CHD risk equivalents include clinical manifestations of noncoronary forms of atherosclerotic disease (peripheral arterial disease, abdominal aortic aneurysm, and peripheral artery disease (transient ischemic attacks or stroke of carotid origin or >50% obstruction of a carotid artery), diabetes, and 2 + risk factors with 10 year risk for hard CHD >20%.

3. Risk factors include cigarette smoking, hypertension (BP ≥ 140/90 mmHg or an antihypertensive medicine), low HDL cholesterol (<40 mg/dL), family history of premature CHD (CHD in male first-degree relative < 55 years of age; CHD in female first-degree relative < 65 years of age), and age (men ≥ 45 years; women ≥ 55 years).


5. Almost all people with zero or 1 risk factor have a 10 year risk <10% and 10 year risk assessment in people with zero or 1 risk factor is thus not necessary.

6. Very high risk favors the optional LDL-C goal of <70 mg/dL, and in patients with high triglycerides, non-HDL-C <100 mg/dL.

7. Optional LDL-C goal <100 mg/dL.

8. Any person at high risk or moderately high risk who has lifestyle-related risk factors (e.g., obesity, physical inactivity, elevated triglyceride, low HDL-C, or metabolic syndrome) is a candidate for therapeutic lifestyle changes to modify these risk factors regardless of LDL-C level.

9. When LDL-lowering drug therapy is employed, it is advised that intensity of therapy be sufficient to achieve at least a 30% to 40% reduction in LDL-C levels.

10. If baseline LDL-C is <100 mg/dL, institution of an LDL-lowering drug is a therapeutic option on the basis of available clinical trial results. If a high-risk person has high triglycerides or low HDL-C, combining a fibrate or nicotinic acid with LDL-lowering drug can be considered.

11. For moderately high-risk persons, when LDL-C level is 100 to 129 mg/dL, at baseline or on lifestyle therapy, initiation of an LDL-lowering drug to achieve an LDL-C level <100 mg/dL is a therapeutic option on the basis of available clinical trial results.
**Q5. Why is it important to distinguish between LDLs, HDLs and total cholesterol in high risk patients?**

**Answers**
1. Canadian Guidelines note that LDL-C should be < 2.5 mmol/L
2. Total cholesterol to HDL ratio < 4.0.
3. Total cholesterol < 4-5 mmol/L

**Discussion**
- LDL is the bad cholesterol; LDL should be less than 2.5 mmol/L and there is linear correlation between total cholesterol/LDL and stroke mortality.
- HDL is the good cholesterol and total cholesterol to HDL ratio should be <4.0.
- Too much cholesterol is not good - Total cholesterol > 5.50 increases relative risk of stroke by 1.3.
**Q6. Describe the pharmacological treatment of hypercholesterolemia.**

**Answer**

1. Statins, HMG-CoA reductase inhibitors, are considered the first-line treatment for hypercholesterolemia.

**Discussion**

- Statins are now considered first-line treatment.
- Statins are HMG-CoA reductase inhibitors.
- Regulate LDL receptor activity and reduce the entry of LDL cholesterol into circulation.
- Most common adverse effects are GI upset, muscle aches and hepatitis/hepatotoxicity (<1%); rare complication is severe myopathy +/- rhabdomyolysis.
- Statins used post-MI resulted in a 24-34% risk reduction for stroke.

**Q7. Describe your treatment for each of the following cases.**

<table>
<thead>
<tr>
<th>Patient Description</th>
<th>Lipid Profile</th>
<th>Proposed Treatment and Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case A: Post Stroke -- High Risk</td>
<td>Total cholesterol 4.75 LDL 2.4 mmol/L HDL 1.2 mmol/L</td>
<td>No treatment needed. All cholesterol numbers are at target levels and total cholesterol to HDL &lt;4.0.</td>
</tr>
<tr>
<td>Case B: Post Stroke -- High Risk</td>
<td>Total cholesterol 5.8 LDL 3.3 mmol/L HDL 1.4 mmol/L</td>
<td>Treatment with statin and diet. Total cholesterol and LDL-C is high and total cholesterol to HDL &gt; 4.0.</td>
</tr>
<tr>
<td>Case C: Post Stroke -- High Risk</td>
<td>Total cholesterol 4.72 LDL cholesterol 3.0 mmol/L HDL 1.04 mmol/L</td>
<td>Treatment with statin and diet. LDL-C is high and total cholesterol to HDL &gt; 4.0.</td>
</tr>
<tr>
<td>Case D: Post Stroke -- High Risk</td>
<td>Total cholesterol 5.2 LDL cholesterol 2.6 mmol/L HDL cholesterol 1.2 mmol/L</td>
<td>Treatment with statin and diet. Total cholesterol to HDL &gt; 4.0, LDL &gt; 2.5.</td>
</tr>
</tbody>
</table>

**References**


G4. Diabetes
G4. Diabetes

Canadian Best Practice Recommendations (2008): Recommendation 2.4 - Diabetes Management

2.4a. Diabetes Assessment

i. All individuals in the general population should be evaluated annually for type 2 diabetes risk on the basis of demographic and clinical criteria [Evidence Level C] (CDA).

ii. A fasting plasma glucose should be performed every 3 years in individuals > 40 years of age to screen for diabetes [Evidence Level C] (CDA). More frequent and/or earlier testing with either a fasting plasma glucose or plasma glucose sample drawn 2 hours after a 75-g oral glucose load should be considered in people with additional risk factors for diabetes [Evidence Level C] (CDA). Some of these risk factors include family history, high-risk population, vascular disease, history of gestational diabetes, hypertension, dyslipidemia, overweight, abdominal obesity, polycystic ovary syndrome.

iii. In adults, fasting lipid levels (total cholesterol, HDL cholesterol, total glycerides and calculated LDL cholesterol) should be measured at the time of diagnosis of diabetes and then every 1 to 3 years as clinically indicated. More frequent testing should be performed if treatment for dyslipidemia is initiated [Evidence Level C] (CDA).

iv. Blood pressure should be measured at every diabetes visit [Evidence Level C] (CDA).

2.4b. Diabetes Management

i. Glycemic targets must be individualized; however, therapy in most patients with type 1 or type 2 diabetes should be targeted to achieve a glycated hemoglobin (HbA1c) level ≤7.0% in order to reduce the risk of microvascular complications [Evidence Level A] (CDA) and, for individuals with type 1 diabetes, macrovascular complications. [Evidence Level C] (CDA).

ii. To achieve an HbA1c ≤7.0%, patients with type 1 or type 2 diabetes should aim for a fasting plasma glucose or preprandial plasma glucose targets of 4.0 to 7.0 mmol/L [Evidence Level B] (CDA).

iii. The 2-hour postprandial plasma glucose target is 5.0–10.0 mmol/L [Evidence Level B]. If HbA1c targets cannot be achieved with a postprandial target of 5.0–10.0 mmol/L, further postprandial blood glucose lowering, to 5.0–8.0 mmol/L, can be considered [Evidence Level C] (CDA).

iv. Adults at high risk of a vascular event should be treated with a statin to achieve an LDL cholesterol ≤2.0mmol/L [Evidence Level A] (CDA).

v. Unless contraindicated, low dose acetylsalicylic acid (ASA) therapy (80 to 325 mg/day) is recommended in all patients with diabetes with evidence of cardiovascular disease, as well as for those individuals with atherosclerotic risk factors that increase their likelihood of cardiovascular events [Evidence Level A] (CDA).
G4.1 Case Study: Diabetes

Case Study

A 55 year old man was admitted into the rehabilitation unit with a right MCA ischemic stroke and he has no known history of medical problems or complications.

Q1. The nurse tells you that he has a fasting plasma glucose level of 127 mg/dL or 7.0 mmol/L. Is he diabetic?

Answer

1. Yes. Diagnosis of diabetes according to 2008 CDA Guidelines: Fasting plasma glucose 7.0 mmol/L (fasting = no caloric intake for at least 8 hours) or casual plasma glucose 11.1 mmol/L + symptoms of diabetes.

Discussion

Normal fasting glucose levels are defined as glucose <100 mg/dL (5.6 mmol/L), whereas impaired fasting glucose has been defined at levels between 100 and 126 mg/dL (5.6 and 6.9 mmol/L). A fasting plasma glucose level >126 mg/dL (7.0 mmol/L) or a casual plasma glucose >200 mg/dL (11.1 mmol/L) meets the threshold for the diagnosis of diabetes (American Diabetes Association 2004 and 2008 CDA Guidelines). Casual = any time of the day, without regard to the interval since the last meal. Classic symptoms of diabetes = polyuria, polydipsia and unexplained weight loss or 2 hour plasma glucose with a 75 gm oral glucose tolerance test (11.1 mmol/L).

Q2. His Hemoglobin A1C level is 8.2%. What is its significance?

Answer

Hemoglobin A1c level >7% is defined as inadequate control of hyperglycemia.

Discussion

Glycosylated (or glycated) hemoglobin (hemoglobin A1c, Hb1c, HbA1c, or A1C; sometimes also HgA1c) is a form of hemoglobin used primarily to identify the average plasma glucose concentration over prolonged periods of time. It is formed in a non-enzymatic pathway by hemoglobin's normal exposure to high plasma levels of glucose. Glycosylation of hemoglobin...
has been implicated in nephropathy and retinopathy in diabetes mellitus. Monitoring the HbA1c in type-1 diabetic patients may improve treatment (Larson et al. 1990).

**Q3. Provide a classification for diabetes.**

**Answer**
1. Prediabetes
2. Type 1 diabetes
3. Type 2 diabetes
4. Gestational diabetes
5. Other specific types – eg LADA (latent autoimmune diabetes in adults), prednisone-induced hyperglycemia

**Discussion**
Diabetes is estimated to affect 8% of the adult population.
1. Prediabetes is a practical and convenient term for impaired fasting glucose and impaired glucose tolerance, conditions that place individuals at risk of developing diabetes and its complications.
2. Type 1 diabetes is an early onset failure of the pancreas to produce sufficient insulin.
3. Type 2 diabetes, on the other hand is characterized by insulin resistance and progressive beta-cell failure.

**Q4. How is diabetes related to stroke?**

**Answers**
1. Diabetics have increased susceptibility to atherosclerosis, hypertension, obesity and hyperlipidemia
2. Diabetics, in particular, have elevated levels of triglycerides, reduced levels of HDL cholesterol and increased LDLs when compared to a non-diabetic sample.
3. Glucose intolerance has been shown to double the risk of a stroke
4. Diabetes has an independent effect on stroke risk after controlling for other risk factors with relative risks ranging from 1.5-3.0.
5. Diabetes is present in 15% to 33% of patients with ischemic stroke and its treatment reduces the stroke risk.

**Discussion (from SREBR 11th edition; Teasell et al. 2008)**
Diabetics have an increased susceptibility to atherosclerosis, hypertension, obesity and hyperlipidemia. Elevated levels of triglycerides, reduced levels of HDL cholesterol and increased small, dense LDL particles have been found in individuals with diabetes when compared to a non-diabetic sample (Krauss 2004). The presence of glucose intolerance has been shown to double the risk of a stroke (Sacco 2001). Sacco (2001) notes “Diabetes is a determinant of atherosclerosis and microangiopathy of the coronary, peripheral and cerebral
Death from cerebrovascular disease is greatly increased among subjects with elevated blood glucose values (Balkan et al. 1998). Cohort studies have demonstrated an independent effect of diabetes on stroke risk after controlling for other risk factors with relative risks ranging from 1.5 to 3.0 (Sacco et al. 1997, Wolf et al. 1991, Barrett-Connor et al. 1988, Kuller et al. 1985).” A recent study based on data from the FINNSTROKE study (Kaarisalo et al. 2005) 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). Diabetes is frequently encountered in stroke care, being present in 15% to 33% of patients with ischemic stroke and its treatment reduces the stroke risk (American Diabetes Association 2004, Karapanayiotides et al. 2004, Woo et al. 1999).

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) cited a summary of 16 studies on the 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 9 large epidemiological studies (n=27,269) conducted in the United States, revealed that diabetic women had a 3.37-fold increased risk of fatal stroke (Women's Pooling Project; Ho et al. 2003). After adjustment for additional factors such as 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) recommend that, given their analysis, women with diabetes should be considered a high-risk group for fatal stroke and, therefore, be treated as aggressively as patients with a history of previous stroke.

Q5. Is glycemic control associated with secondary stroke prevention?

Answer
1. The evidence that glycemic control reduces the risk of a second stroke has been slow to come.
2. Glycemic control is often associated more with prevention of microvascular complications (retinopathy, nephropathy, peripheral neuropathy) than macrovascular complications (stroke, myocardial infarction, peripheral vascular disease)
3. Recent data suggests that glycemic control may help prevent strokes in patients with type 2 diabetes (particularly if they are obese) but not in type 1 diabetics

Discussion (from the SREBR 11th edition; Teasell 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 significant (p=0.29), 12% reduction of risk for any diabetes-related endpoint when compared to conventional treatment (UKPDS Study Group, 1998). Most of this effect could be attributed to a significant reduction in microvascular events. Examination of risk for stroke, in particular, revealed no significant risk reduction associated with intensive glycemic control (RR = 1.11 95% CI 0.81, 1.51). However, 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 (UKPDS Study Group, 1998).

In a recent systematic review and meta-analysis, Stettler et al. (2006) examined the reported findings of 8 randomized controlled trials assessing the effects of improved glycemic control in individuals with Type 1 and Type 2 diabetes mellitus (DM). Treatments included sulfonylurea, 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 in Type 2 DM, reductions were observed in peripheral vascular disease and stroke. In addition, improved glycemic control was most beneficial in younger patients who had DM of shorter duration. Overall, 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 were reported to be 16 for Type 1, 14 for low-risk Type 2 and 7 for high-risk Type 2 DM (Stettler et al. 2006).

The majority of studies examining the impact of glycemic control have not been specific to the secondary prevention of macrovascular events. The PROactive study (Charbonnel et al. 2004, Dormandy et al. 2005) examined the impact of treatment with pioglitazone (a peroxisome proliferator activator gamma agonist) for glycemic control on the secondary prevention of macrovascular events in patients with Type 2 DM. In this patient sample, the addition of pioglitazone was associated with reduced risk for the recurrence of stroke.

Q6. List three different groups of treatments recommended for glycemic control.

Answer
1. Diet and exercise.
2. Oral hypoglycemic drugs.
3. Insulin.

Case Study (continued)
The 55 year old man who was admitted into the rehabilitation unit with a right MCA ischemic stroke with no known history of medical problems or complications has now been diagnosed with type 2 diabetes. His fasting blood sugar is 7.0 mmol/L and his hemoglobin A1c is 8.2%. He has no other complications apart from the stroke.

Q7. Describe a glycemic control protocol for his new found Type 2 diabetes.
**Answer**
1. Lifestyle intervention is important (initiation of nutrition therapy and physical activity).

**Discussion**

**Lifestyle Intervention**
1. Nutritional therapy can reduce glycated haemoglobin by 1.0-2.0% and, when used with other components of diabetes care, can further improve clinical and metabolic outcomes. Consistency in carbohydrate intake, and spacing and regularity in meal consumption may help control blood glucose and weight. Replacing high-glycemic index carbohydrates with low-glycemic index carbohydrates in mixed meals has a clinically significant effect on glycemic control in people with type 1 or type 2 diabetes.
2. Structured physical activity counselling by a physician or skilled healthcare personnel or case managers has been very effective in increasing physical activity, improving glycemic control, reducing the need for antihyperglycemic agents and insulin, and producing modest but sustained weight loss. Before beginning a program of physical activity more vigorous than walking, people with diabetes should be assessed for conditions that might be certain contraindications to certain types of exercise, predispose to injury or be associated with increased likelihood of cardiovascular disease.

**Case Study (continued)**
Despite nutritional interventions and a structured physical activity program his Hemoglobin A1C still comes back at 8.3%.

**Q8. What treatment is indicated now?**

**Answer**
1. Because the HA1c remains elevated but <9.0% the treatment of choice is Metformin, an oral hypoglycaemic agent.

**Discussion**
Metformin, an oral hypoglycaemic is considered the first-line treatment for type 2 diabetes.

**Q9. How important is BP control important in this diabetic patient post stroke?**

**Answer**
1. It is even more important than in non-diabetic patients.
Discussion (from the SREBR 11th edition; Teasell et al. 2008)
There is recent evidence that stroke patients with diabetes are at significantly increased risk of disability and mortality (Otiniano et al. 2003; Ho 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 II diabetes significantly reduces the risk of stroke by 44% (UK Prospective Diabetes Study Group 1998). The Syst-Eur Investigators (1999) and HOPE Study investigators (2000) reported substantial reductions in stroke risk with anti-hypertensive therapies (73% and 33% respectively). 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 and ramipril), β-blockers (atenolol) and calcium channel blockers (nitrendipine). Given the relative effectiveness of the agents tested, and the reported benefits of a tightly controlled blood pressure (UKDPS 1998), 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 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 diabetes (p=0.03 and 0.02, respectively).

Conclusions from SREBR Regarding Diabetes and the Treatment of Hypertension

There is strong (Level 1a) evidence that treatment of hypertension in diabetic patients reduces the risk of stroke. There is moderate evidence (Level 1b) evidence that neither calcium channel blockers nor ACE inhibitors are superior to a diuretic in the initial treatment of hypertension in individuals with diabetes mellitus, impaired fasting glucose levels or normoglycemia.

AHA/ASA Treatment Recommendations for Diabetes

- More rigorous control of blood pressure and lipids should be considered in patients with diabetes.
- Although all major classes of antihypertensives are suitable for the control of BP, most patients will require more than one agent. ACE inhibitors and ARBs are more effective in reducing the progression of renal disease and are recommended as first-choice medications for patients with diabetes mellitus.
- Glucose control is recommended to near normoglycemic levels among diabetics with ischemic stroke or TIA to reduce microvascular complications.
- The goal for Hb A1c should be ≤7%
Patient has no history of diabetes

Fasting blood glucose in acute care to screen for diabetes

Repeat fasting blood glucose in rehab (twice if not done in acute care)

<5.7 mmol/L
Normal, no further action

5.7 – 6.9 mmol/L (may indicate IFG/IGT)

2hPG in Oral Glucose Tolerance test (75-g OGTT)

IFG – impaired fasting glucose
IGT – impaired glucose tolerance

6.1 – 6.9 (IGF) 7.8 – 11.1 mmol/L (IGT)

Dietary and/or medication interventions for IGT

Patient is a known diabetic

Hb A1C (preferably in acute care) to assesses diabetic control

> 6.9 mmol/L

BG testing ac meals, pc meals, and hs prn

>11 mmol/L (diabetes)

Recommend to repeat HbA1C after discharge every 3-6 months

IFG – impaired fasting glucose
IGT – impaired glucose tolerance
2hPG – 2 hour plasma glucose

References


G5. Lifestyle Modification
G5. Lifestyle Modification

Canadian Best Practice Recommendations (2008): Recommendation 2.1 – Lifestyle and risk factor management

Persons at risk of stroke and patients who have had a stroke should be assessed for vascular disease risk factors and lifestyle management issues (diet, sodium intake, exercise, weight, smoking and alcohol intake). They should receive information and counselling about possible strategies to modify their lifestyle and risk factors [Evidence Level B] (AU, NZ, RCP, VA/DoD). Lifestyle and risk factor interventions should include:

i. **Healthy balanced diet:** High in fresh fruits, vegetables, low-fat dairy products, dietary and soluble fibre, whole grains and protein from plant sources and low in saturated fat, cholesterol and sodium, in accordance with Canada's Food Guide to Healthy Eating [Evidence Level B] (ASA, CHEP, RCP).

ii. **Sodium:** The recommended daily sodium intake from all sources is the Adequate Intake by age. For persons 9–50 years, the Adequate Intake is 1500 mg. Adequate Intake decreases to 1300 mg for persons 50–70 years and to 1200 mg for persons >70 years. A daily upper consumption limit of 2300 mg should not be exceeded by any age group [Evidence Level B]. See [www.sodium101.ca](http://www.sodium101.ca) for sodium intake guidelines.

iii. **Exercise:** Moderate exercise (an accumulation of 30 to 60 minutes) of 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 [Evidence Level A]. Medically supervised exercise programs are recommended for high-risk patients (e.g., those with cardiac disease) (ASA, CHEP, EBRSR, NZ).

iv. **Weight:** Maintain goal of a body mass index (BMI) of 18.5 to 24.9 kg/m² and a waist circumference of <88 cm for women and <102 cm for men [Evidence Level B] (ASA, CHEP, OCCPG).

v. **Smoking:** Smoking cessation and a smoke-free environment; nicotine replacement therapy and behavioural therapy [Evidence Level B] (ASA, CHEP, CSQCS, RCP). For nicotine replacement therapy, nortriptyline therapy, nicotine receptor partial agonist therapy and/or behavioural therapy should be considered [Evidence Level A] (ASA, AU).

vi. **Alcohol consumption:** Two or fewer standard drinks per day; and fewer than 14 drinks per week for men; and fewer than 9 drinks per week for women [Evidence Level C] (ASA, AU, CHEP).

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G5.1 Case Study: Lifestyle Modification

**Case Study**
A 54 year old male patient is admitted to the rehabilitation unit. He has been a lifelong smoker and has a history of alcoholism. As well, he is overweight (with a BMI of 36kg/m2) and acknowledges that he rarely engages in physical activity.

**Q1. What known modifiable risk factors does he have?**

**Answer**
- Smoking
- Alcohol
- Obesity
- Physical activity

**Q2. How can physical activity affect the risk of stroke?**

**Answer**
1. Physical activity reduces the risk of stroke through lowering BP, decreasing weight, improving vasodilatation, improving glucose control and improving cardiovascular health.

**Discussion**
In a meta-analysis, Lee et al. (2003) demonstrated that highly active individuals were reported as having a 27% lower risk of stroke than individuals who were less active. Moderately active individuals also had a significantly reduced risk of stroke when compared with low active individuals (RR=0.8, p<0.001). These benefits were reported for both ischaemic and haemorrhagic strokes. A plausible explanation for these observed reductions is that physical activity tends to lower BP and weight (Thompson et al. 2003, Kokkinos et al. 1995), enhance vasodilation (Endres et al. 2003), improve glucose tolerance (Kohrt et al. 1993, Dylewicz et al. 1999), and promote cardiovascular health (Williams et al. 2002). Through lifestyle modification, exercise can minimize the need for more intensive medical and pharmacological interventions or enhance treatment end points.

For those at risk for recurrent stroke and TIA, sedentary behaviours complicate the recovery process and affect recurrent risk status. Because disability after stroke is substantial and because neurological deficits predispose to activity intolerance and physical deconditioning, the challenge for clinicians is to establish a safe therapeutic exercise regimen that allows the patient to regain pre-stroke levels of activity and then to attain sufficient physical activity and exercise to reduce stroke recurrence (Sacco et al. 2006).

Recommendations from the Heart and Stroke Association (Sacco et al. 2006) include:
- Promote physical activity.
- Moderate intensity exercise for 30 minutes on most days of the week.
Q3. Is the patient obese?

Answer
Yes. Obesity is defined as a body mass index (BMI) of >30 kg/m2.

Discussion
Obesity, (defined as a body mass index (BMI) of >30 kg/m2) is strongly related to several major risk factors, including hypertension, diabetes, dyslipidemia (Mann 1974, Turcato et al. 2000), and poor diet. Clinically, abdominal obesity is defined by a waist circumference >102 cm (40 in) in men and 88 cm (35 in) in women.

Q4. What can you tell the patient regarding obesity and diet in the secondary prevention of stroke?

Answer
1. Abdominal obesity, more than general obesity, is related to stroke risk.
2. Diet is important in treatment of hypertension and hyperlipidemia.

Discussion

Obesity: Several studies have suggested that abdominal obesity, rather than general obesity, is more related to stroke risk (Suk et al. 2003, Dey et al. 2002). For stroke, a significant and independent association between abdominal obesity and ischemic stroke was found in all racial/ethnic groups in the Northern Manhattan Study (Suk et al. 2003). Comparing the first quartile of waist-to-hip ratio with the third and fourth quartiles gave ORs of 2.4 (95% CI, 1.5 to 3.9) and 3.0 (95% CI, 1.8 to 4.8), respectively, after adjustment for other risk factors and BMI.

Diet: Diet may be of significance in the modification of several risk factors for stroke including hypertension and dyslipidemia. Dietary patterns, more than any single nutrient or food, may have cumulative effects on the risk of stroke (Hu 2002).

Recommendations:
- Increased consumption of fruits, legumes, and vegetables.
- Low-fat, low cholesterol, and low sodium diet.
- Diet rich in omega-3 fatty acids, whole grains, and nuts.

In summary, weight reduction should be considered for all overweight ischemic stroke and TIA patients to maintain the goal of a BMI of between 18.5 and 24.9 kg/m2 and a waist circumference of <35 inches for women and <40 inches for men (Sacco et al. 2006).
Q5. The patient does not want to stop smoking. What can you tell him regarding smoke cessation in the secondary prevention of stroke?

Answer
1. Smoking generally doubles the risk of stroke.
2. There is a dose-responsive risk.
3. The risk of stroke is reduced by quitting smoking.

Discussion
Smoking increases the risk of both ischemic and haemorrhagic stroke in a positive dose-response manner at all ages, in both sexes, and among different racial/ethnic groups. Exposure to environmental smoke is also associated with an increased risk of stroke. This means that quitting smoking will act as a secondary preventative measure for him and a primary preventative measure for his family.

Because ethical issues preclude conducting RCTs for smoking after stroke, RCTs of quitting after stroke are not available. However, from observational studies, we know that risk of stroke decreases after quitting and that the elevated risk disappears after 5 years. In addition, smoking cessation is associated with a reduction in stroke-related hospitalizations (Lightwood et al. 1997, Naidoo et al. 2000) and therefore supports secondary prevention efforts.

Q6. The patient tells you that he is going to need help in order to avoid cigarette consumption. What can you suggest to help him?

Answer
1. Counseling, nicotine products, and oral smoking cessation medications have all been found to be effective in helping smokers to quit.

Q7. What can you tell the patient regarding alcohol consumption as a risk factor for stroke?

Answer
1. Light alcohol consumption reduces the risk of ischemic stroke.
2. Heavy drinking increases the risk of stroke.

Discussion
There is limited evidence that light (1-2 drinks per day) alcohol consumption reduces risk for ischemic stroke while heavy drinking (more than 5 drinks per day) increases it. Given this patient is an alcoholic, and in light of their obesity, recommendation of a significant reduction in alcohol consumption would be appropriate.
## Recommendations for Modifiable Behavioural Risk Factors (Sacco et al. 2006)

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Recommendation</th>
<th>Class/Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking</td>
<td>All ischemic stroke or TIA patients who have smoked in the past year should be strongly encouraged not to smoke.</td>
<td>Class I, Level C</td>
</tr>
<tr>
<td></td>
<td>Avoid environmental smoke.</td>
<td>Class IIa, Level C</td>
</tr>
<tr>
<td></td>
<td>Counseling, nicotine products, and oral smoking cessation medications have been found to be effective for smokers.</td>
<td>Class IIa, Level B</td>
</tr>
<tr>
<td>Alcohol</td>
<td>Patients with prior ischemic stroke or TIA who are heavy drinkers should eliminate or reduce their consumption of alcohol.</td>
<td>Class I, Level A</td>
</tr>
<tr>
<td></td>
<td>Light to moderate levels of 2 drinks per day for men and 1 drink per day for nonpregnant women may be considered.</td>
<td>Class IIb, Level C</td>
</tr>
<tr>
<td>Obesity</td>
<td>Weight reduction may be considered for all overweight ischemic stroke or TIA patients to maintain the goal of a BMI of 18.5 to 24.9 kg/m² and a waist circumference of &lt;35 in for women and &lt;40 in for men. Clinicians should encourage weight management through an appropriate balance of caloric intake, physical activity, and behavioral counseling.</td>
<td>Class IIb, Level C</td>
</tr>
<tr>
<td>Physical Activity</td>
<td>For those with ischemic stroke or TIA who are capable of engaging in physical activity, at least 30 minutes of moderate-intensity physical exercise most days may be considered to reduce risk factors and comorbid conditions that increase the likelihood of recurrence of stroke. For those with disability after ischemic stroke, a supervised therapeutic exercise regimen is recommended.</td>
<td>Class IIb, Level C</td>
</tr>
</tbody>
</table>

**Class 1**: Conditions for which there is evidence for and/or general agreement that the procedure or treatment is useful and effective.

**Class 2**: Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment
- Class 2a – Weight of evidence or opinion is in favor of the procedure or treatment
- Class 2b – Usefulness/efficacy is less well established by evidence or opinion.

**Class 3**: Conditions for which there is evidence and/or general agreement that the procedure or treatment is not useful/effective and in some cases may be harmful.

**Level of Evidence A**: Data derived from multiple randomized clinical trials

**Level of Evidence B**: Data derived from a single randomized trial or nonrandomized studies

**Level of Evidence C**: Expert opinion or case studies

### References


Williams MA, Fleg JL, Ades PA, Chaitman BR, Miller NH, Mohiuddin SM, Ockene IS, Taylor CB, Wenger NK, for the American Heart Association Council on Clinical Cardiology Subcommittee on Exercise, Cardiac Rehabilitation, and Prevention. Secondary prevention of coronary heart disease in the elderly
(with emphasis on patients ≥75 years of age): an American Heart Association scientific statement from the Council on Clinical Cardiology Subcommittee on Exercise, Cardiac Rehabilitation, and Prevention. Circulation 2002; 105:1735-43.
Key Study: Alcohol Consumption


<table>
<thead>
<tr>
<th>Author, Year, Country, Pedro Score</th>
<th>Methods</th>
<th>Outcomes</th>
</tr>
</thead>
</table>
| Reynolds et al. 2003 ns           | Meta-analysis  
Included 35 observational studies examining the effects of alcohol consumption on stroke risk. | A significant (p=0.01), J-shaped relationship was found between the amount of alcohol consumed per day and the risk for ischaemic stroke. Individuals who consumed 1-2 drinks per day had the least risk for ischaemic 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. Results also showed a linear, dose-dependent effect, with heavy drinking (> 5 drinks per day) associated with a relative risk of haemorrhagic stroke of 2.18 |

![Relative Risk of Stroke Associated with Varying Levels of Alcohol Consumption](image)

**Importance:** This meta-analysis confirmed that heavy alcohol consumption (> 5 drinks per day) increases risk for stroke and that this relationship is dose-dependent. However, this study also showed that light-to-moderate alcohol consumption (1-2 drinks per day) may be a protective factor.

**Relevant SREBR Conclusion:** Heavy alcohol consumption increases the risk of stroke. Light to moderate alcohol consumption may be beneficial.
Key Study: Smoking


<table>
<thead>
<tr>
<th>Author, Year, Country, Pedro Score</th>
<th>Methods</th>
<th>Outcomes</th>
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<tbody>
<tr>
<td>Bonita et al. 1999 New Zealand</td>
<td><strong>Cohort Study</strong> 521 patients with first-ever acute stroke and 1851 community controls were included in this population-based study. Controls were obtained from a cross-sectional survey of major cardiovascular risk factors measured in the same population. Questionnaires were administered by trained nurse interviewers.</td>
<td>Environmental tobacco smoke exposure was associated with a significantly increased risk of stroke among both non-smokers and long-term ex-smokers (odds ratio (OR) = 1.82; 95% confidence interval (95% CI) = 1.34 to 2.49). Additionally, active smokers had a fourfold risk of stroke compared with those who had never smoked (OR = 4.14; 95% CI = 3.04 to 5.63).</td>
</tr>
</tbody>
</table>

**Importance**: Bonita et al. (1999) demonstrated that 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). The authors also reported that active smoking is associated with a four-fold increase in the risk of stroke when active smokers are compared to all non-smokers and a six-fold increase when they are compared to non-smokers who are not exposed to environmental smoke.

**Relevant SREBR Conclusion**: Smoking increases the risk of stroke while smoking cessation reduces the risk.
Key Study: Physical Activity


<table>
<thead>
<tr>
<th>Author, Year Country, Pedro Score</th>
<th>Methods</th>
<th>Outcomes</th>
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<tbody>
<tr>
<td>Lee et al. 2003 ns</td>
<td>Meta-analysis Included 23 studies (18 cohort studies and 5 case control) published between 1983 and 2002 that examined the association between physical activity and stroke incidence or mortality.</td>
<td>Highly active individuals were reported as having a 27% lower risk of stroke than individuals who were designated as “low active”. Individuals who were designated as moderately active also had a significantly reduced risk of stroke when compared to low active individuals (RR=0.80, p&lt;0.001).</td>
</tr>
</tbody>
</table>

![Relative Risk of Stroke Incidence and Mortality for Highly Active Individuals Across Different Study Types](image)

**Note:** All risk reductions significant (p<.05).

**Importance:** This meta-analysis demonstrated the benefits activity and that both high and moderate levels of activity decrease the risk of ischaemic and haemorrhagic strokes.

**Relevant SREBR Conclusion:** There is limited (Level 2) evidence that increasing physical activity is associated in a graded manner with reduction in risk of stroke (both ischaemic and haemorrhagic). Even moderate levels of physical activity are associated with a significant stroke risk reduction (20%).
Key Study: Behavioural Intervention


<table>
<thead>
<tr>
<th>Author, Year Country Pedro Score</th>
<th>Methods</th>
<th>Outcomes</th>
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<tbody>
<tr>
<td>Risk Factor Intervention Study (RIS) Fagerberg et al. 1998 (Sweden) 7 (RCT)</td>
<td>High-risk male patients, aged 50 – 72 with treated hypertension, were randomized to receive a multifactoral, behavioural intervention (n=253) or usual care (n=255). The behavioural intervention consisted of a program designed to change eating habits and a smoking cessation program. Patients were followed for a mean of 6.6 years.</td>
<td>Overall risk for cardiovascular events (both fatal and nonfatal) was 29% lower in the intervention group (p=0.41). Risk of stroke was lower in the intervention group (RR=0.53). Relative to the usual care group, the intervention group demonstrated lowered serum cholesterol (p&lt;0.0001) and higher adjusted smoking quit rates (p=0.12) after 3 years of follow-up.</td>
</tr>
</tbody>
</table>


Treated hypertensive men with at least one additional risk factor (defined as elevated cholesterol, diabetes mellitus or smoking) were randomly allocated to receive usual care (n=255) or a risk factor group intervention to encourage dietary change and smoking cessation (n=253). Mean follow-up time was 6.6 years. Outcomes included fatal and nonfatal cardiovascular events. Relative to usual care, the risk of fatal and nonfatal cardiovascular events was 29% lower in the behavioural intervention group.

*RR=Relative Risk; ** Relative Risk for cumulative stroke events.
Importance: Fagerberg et al. (1998) demonstrated that behavioural interventions can reduce overall risk for both fatal and nonfatal cardiovascular events. Results showed that, relative to the usual care group, the intervention group had lowered serum cholesterol ($p<0.0001$) and higher adjusted smoking quit rates ($p=0.12$) after 3 years of follow-up.

Relevant SREBR Conclusion: Behavioural intervention can be an effective means to reduce stroke risk.
G6. Homocysteine and Stroke
G6. Homocysteine and Stroke

G6.1 Case Study: Homocysteine

Case Study

A 45 year old male presented with a right subcortical stroke. The neurologist feels that it was probably due to a high homocysteine levels in his blood.

Q1. What is homocysteine and what are considered normal serum levels?

Answer
1. Homocysteine is a sulphur-containing amino acid.
2. Normal serum plasma homocysteine level is 5-15 umol/L.

Discussion
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. Mid to moderate elevations are from 16 to 100 µmol/L. Levels greater than 100µmol/L are considered to be severe hyperhomocysteinemia.

Q2. Is hyperhomocystinemia associated with secondary cardiovascular events?

Answer
1. Yes

Discussion
Bos et al. (2005) demonstrated that an elevated risk for secondary cardiovascular events including stroke and TIA was associated with high plasma homocysteine levels (≥13.7 µmol/L vs ≤ 10.7 µmol/L) among stroke patients 45 years or younger (HR=1.6; 95% IC 1 to 2.5).

Q3. What is the relationship between folic acid, vitamin B6, and Vitamin B12 levels and plasma homocysteine levels?

Answer
1. Folic acid, vitamin B6 and vitamin B12 levels are inversely related to plasma homocysteine levels.

**Discussion**

While it is true that levels of folic acid, vitamin B6 and Vitamin B12 are inversely related to plasma homocysteine levels, treatment with folic acid and/or B6 and B12 has not been shown to reduce the risk of stroke (Toole et al. 2004).

For patients with ischemic stroke or TIA and hyperhomocysteinemia, daily standard multivitamin preparations with adequate B6 (1.7 mg/d), B12 (2.4 µg/d), and folate (400 µg/d) are reasonable measures to reduce homocysteine levels, given their safety and low cost. However, there is no evidence that reducing homocysteine levels will lead to a reduction in stroke recurrence.

**Reference**


Key Study: Homocysteine and Stroke


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<tr>
<th>Author, Year Country, Pedro Score</th>
<th>Methods</th>
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<tbody>
<tr>
<td>VISP Trial Toole et al. 2004 USA/Canada/Scotland 8 (RCT)</td>
<td>N=3680 subjects with non-disabling cerebral infarction. All patients received best medical &amp; surgical care and, in addition, were randomly assigned to receive either daily high-dose supplementation of folic acid (2.5 mg), vitamin B₆ (25 mg) and vitamin B₁₂ (0.4 mg) or daily low-dose supplementation of the same vitamins (200μg, 6μg and 20μg respectively. Outcomes included recurrent cerebral infarction (primary), coronary heart disease (secondary) and death (secondary). Follow-up=2 years.</td>
<td>There was no treatment effect on any endpoint. RR for any of the outcomes (unadjusted) was 1.0. Chances of an outcome event within the 2-year follow-up period were 18% in high dose and 18.6% in the low dose group. There was, however, an association between baseline homocysteine levels and outcomes such that a 3μmol/L lower level was associated with a 10% risk reduction for stroke (p=0.05) in the low-dosage group and a non-significant trend to lowered risk (2%) in the high-dosage group.</td>
</tr>
</tbody>
</table>

**Importance:** A meta-analysis (Bouchy et al. 1995) suggested that high levels of homocysteine area associated with increased risk of atherosclerotic vascular disease and that a prolonged reduction of plasma homocysteine of 5 umol/L would reduce risk by approximately 33%. While an association was demonstrated between baseline homocysteine levels and stroke risk, treatment with folic acid, vitamin B₆ and vitamin B₁₂ supplementation did not result in the expected risk reductions. Study limitations that may have affected the results include a small sample population with only mildly elevated homocysteine levels, very modest reductions in homocysteine levels and a limited follow-up period. A recent post hoc analysis of VISP data identified a subgroup of participants most likely to benefit from VISP supplementation (Spence et al. 2005).

**Relevant SREBR Conclusion:** Treatment with folic acid and/or vitamins B₆ & B₁₂ does not reduce stroke risk.
G7. Antiplatelet Agents
G7. Antiplatelet Agents

**Canadian Stroke Guidelines (2008): Recommendation 2.5 – Antiplatelet therapy**

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 [Evidence Level A] (ASA, AU, CSQCS, ESO, NZ, RCP, VA/DoD).

i. ASA, combined ASA (25 mg) and extended-release dipyridamole (200 mg), or clopidogrel may be used depending on the clinical circumstances [Evidence Level A].

ii. For adult patients on ASA, the usual maintenance dosage is 80 to 325 mg per day [Evidence Level A] (CSQCS, VA/DoD), and in children with stroke the usual maintenance dosage of ASA is 3 to 5 mg/kg per day for the prevention of recurrent stroke [Evidence Level C] (AHA-P).

iii. Long-term combinations of ASA and clopidogrel are not recommended for secondary stroke prevention [Evidence Level B] (CHARISMA, MATCH).

G7.1 Case Study: Antiplatelet Agents

**Case Study**

A 68 year old man with a right MCA is admitted into the rehabilitation unit. He has had a carotid ultrasound that shows a cholesterol plaque occluding 40% of the lumen of the right internal carotid vessel.

**Q1. Assuming that he has had an atherotrombotic stroke, what treatment would you recommend to avoid a stroke recurrence?**

**Answer**

1. Antiplatelet agents.

**Discussion**

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 to a different location. As such, platelets and the mechanisms of adhesion, activation, and aggregation play an important role in thrombus development and progression of atherothrombosis (Serebruany et al. 2004, Goldszmidt and Caplan 2003, Easton 2001).
Q2. What is the major adverse side-effect of antiplatelet therapy?

Answer
1. Increased risk of bleeding.

Discussion
Antiplatelet agents increase the risk of bleeding (OR=1.2) (Antithrombotic Trialists’ Collaboration 2002).

Q3. Knowing there may be an increased risk of bleeding, would this influence your decision to use antiplatelet treatment and why?

Answer
1. No. Risk-benefit ratio is low with advantages for stroke prevention.

Discussion
In high risk individuals with a history of previous stroke or TIA, antiplatelet therapy is associated with a decrease in risk of ischemic stroke (OR=.75). This means that 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).

Q4. Describe the different types of antiplatelet therapy?

Answer
- ASA
- Thienopyridines – Clopidogrel and Ticlopidine
- Dipyridamole

Q5. If antiplatelet therapy is the treatment of choice, which drug would be the initial choice?

Answer
1. Monotherapy with low-dose ASA (81 mg/day) would be the initial choice.
Discussion
Aspirin is the least expensive, most widely studied, and most commonly used antiplatelet agent (Goldsmitz and Caplan 2003). Treatment with aspirin reduces the risk of a vascular event in high risk patients (including recurrent stroke) by 23% (Antithrombotic Trialists’ Collaboration 2002).

In a meta-analysis, Algra and Van Gijn (1999) evaluated the benefit of ASA monotherapy in patients with prior stroke or TIA and found that aspirin reduced the odds of stroke, myocardial infarction or vascular death by 16% and the relative risk reduction when compared to placebo was 13%.

Q6. The patient’s family believe the patient should get at least 325 mg of Aspirin per day. How do you respond?
Answer
1. ASA 81 mg/day is just as effective as 325 mg/day with less potential side effects.

Discussion
Low doses of ASA may be effective in interfering with platelet aggregation (blocking thromboxane A2 formation) while not substantially inhibiting the production of prostacyclin (an antiaggregation prostaglandin produced in the endothelial cells which can be inhibited with higher doses of ASA) (Easton 2001).

Doses of 75-150 mg/day of ASA appear to have the greatest effect, reducing the risk of stroke by 32% (Antithrombotic Trialists’ Collaboration 2002). 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 325 mg (Diener and Ringleb 2002, Antithrombotic Trialists’ Collaboration 2002). However, Serebuny et al. (2004) reported in a metanalysis that low dose ASA (<100mg/day) is associated with a lower risk (3.6%) for hemorrhagic events (including both major and minor events), while doses in excess of 100 mg/day were associated with a relatively high risk (9.1%). Higher doses of aspirin have also been shown to be associated with a greater risk of gastrointestinal hemorrhage (Hansson et al. 1998, Antithrombotic Trialists’ Collaboration 2002).

Q7. When should antiplatelet treatment be initiated and when should it be terminated?
Answer
Antiplatelet treatment should be initiated in the acute phase and is usually continued for the rest of the patient’s life.

Discussion
Antiplatelet therapy in acute stroke patients results in 9 fewer recurrent strokes for every 1000 patients treated. With prolonged therapy (mean 29 months) this number increases to 36 per 1000 treated (Antithrombotic Trialists’ Collaboration 2002).

**Case Study (continued)**

You tell the nurse that the patient is going to begin taking 81mg of aspirin/day but the nurse tells you that the patient is allergic to ASA.

**Q8. Which other treatment options are available?**

**Answer**
1. Clopidogrel.

**Discussion**
Clopidogrel, a thienopyridine, is an accepted alternative for patients in whom ASA therapy is contraindicated. Thienopyridines inhibit platelet activation and aggregation (Easton 2001, MacWalter and Shirley 2002, Goldszmidt and Caplan 2003).

**Q9. The nurse questions you about the difference between ASA and Clopidogrel in terms of effectiveness.**

**Answer**
1. ASA and Clopidogrel have comparable effectiveness.

**Discussion**
Among patients with previous TIA’s or stroke, Clopidogrel therapy has been found to reduce the risk of vascular events and further stroke events slightly more than aspirin therapy (OR= 0.9 and OR=0.86, respectively). This is equivalent to an absolute reduction in stroke events of 16 per 1000 patients (Hankey et al. 2004).

Clopidogrel is also indicated in patients who have an ischemic stroke while taking aspirin. There is no evidence that increasing the dose of aspirin provides additional benefit (Saco et al. 2006).

**Q10. The nurse asks you why Clopidogrel is not used more often as the first line treatment.**
Answer
1. Clopidogrel has more side-effects for the same efficacy.

Discussion
Although thienopyridines and ASA do not have a significant difference in terms of the risk of intracranial or extracranial haemorrhage, treatment with thienopyridines is associated with a reduced risk for gastrointestinal haemorrhage (OR=0.71), indigestion/nausea/vomiting (OR=0.84), an increased risk for diarrhea (OR=1.34 to 2.27), and skin rashes (OR=1.32 to 2.23) (Hankey et al 2004). Thienopyridines are more expensive and not available in a generic preparation. Treatment with ticlopidine requires frequent and ongoing blood testing and is no longer used.

Q11. Clopidogrel and Ticlopidine are both thienopyridines. Describe the differences between these two medications.

Answer
1. Ticlopidine has unacceptable side-effect profile, being associated with neutropenia and thrombotic thrombocytopenia purpura.

Discussion
Ticlopidine: Ticlopidine is associated with a higher rate of adverse effects than ASA (62.3% versus 53.2%). It is also associated with neutropenia more often than ASA (OR=2.7; Hankey et al. 2004) and has been linked to thrombotic thrombocytopenic purpura (Macwalter and Shirley 2002, Diener and Ringleb 2002). Furthermore, blood tests are required at 2 week intervals for the first 3 months of therapy and screening must be continued indefinitely (Easton 2001, Macwalter and Shirley 2002, Diener and Ringleb 2002). Given the above, ticlopidine is not considered an effective or acceptable alternative to aspirin in the secondary prevention of stroke (Sacco 2003).

Clopidogrel: The benefits of clopidogrel are similar to those of ticlopidine, while its side effects are similar to those seen with ASA therapy (Easton 2001, Macwalter and Shirley 2002, Diener and Ringleb 2002). Clopidogrel was compared with ASA in the CAPRIE study (1996). The primary end point, a composite outcome of ischemic stroke, MI, or vascular death, occurred in 8.7% fewer patients treated with clopidogrel compared with aspirin (P=0.043). However, in a subgroup analysis of those patients with prior stroke, the risk reduction with clopidogrel was slightly smaller and nonsignificant. Clopidogrel is an appropriate substitute for those patients who are intolerant of ASA or who have a stroke while on ASA (ASA-failures).

Q12. The resident asks about using combination therapy of different antiplatelet therapies.
**Answers**
1. The addition of aspirin to clopidogrel had little added benefit and the small demonstrated benefit when compared to Clopidogrel alone was outweighed by a higher rate of bleeding events associated with combined therapy (i.e. MATCH trial).
2. The addition of dipyridamole to ASA has a small benefit over ASA alone with a higher rate of side effects (largely headaches).
3. There does not appear to be a significant benefit to combination over single antiplatelet therapy.

**Discussion**
Because antiplatelet drugs work through different mechanisms, in theory the effects of different drugs may be cumulative. The only way to prove this is with comparative studies of different treatment strategies.

**Clopidogrel Plus ASA versus Clopidogrel Alone. The MATCH study:** compared treatment with clopidogrel plus ASA to clopidogrel monotherapy in high risk patients with recent ischaemic stroke or TIA. 7,559 patients with previous ischemic stroke and at least one additional vascular 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.

A small non-significant trend favouring the combination of clopidogrel and ASA vs clopidogrel alone (relative risk reduction=6.4%; p=0.244) was noted. In the combined group there were significantly more incidents of life-threatening bleeding as well as more incidents of major bleeding and minor bleeding (Diener et al. 2004).

**Clopidogrel Plus ASA verses ASA Alone. The CHARISMA study** compared the effectiveness of clopidogrel plus ASA to ASA alone in patients with either cardiovascular disease or multiple risk factors. There was no significant benefit associated with combination therapy when compared to ASA monotherapy. Combined therapy was associated with increased episodes of moderate to severe bleeding.

**Summary: Clopidogrel Plus ASA Combination Therapy.** Although both studies suggest that the combination of clopidogrel and ASA is ineffective, this could be due to the study limitations. Nevertheless, there is little convincing evidence that the addition of clopidogrel to aspirin improves outcome in high-risk individuals with previous TIA or stroke (Norris and Barnett 2006).

**Dipyridamole Plus ASA. The ESPS study** compared high doses of ASA plus dipyridamole to placebo in patients with a previous stroke or TIA. Both fatal and nonfatal strokes were reported to be reduced by 38.1% when compared to placebo. The ESPS-II compared ASA plus Dipyridamole to ASA monotherapy or dipyradole monotherapy in patients with a previous stroke or TIA. 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. The risk of stroke or death was reduced by 18% with ASA alone, 16% with dipyridamole alone and 24% with the combination.

**The ESPRIT study:** compared ASA plus dipyridamole versus ASA monotherapy in patients with previous stroke or TIA. A reduction in ischemic events was noted but was not quite significant. More patients withdrew from the combination therapy group than the ASA group, mostly due to headache-related side effects.

<table>
<thead>
<tr>
<th>Recommendations for Antiplatelet Drug Use (Heart and Stroke Foundation 2003) (modified)</th>
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<tbody>
<tr>
<td>• Use antiplatelet agents in secondary prevention of stroke when the origin is not cardioembolic.</td>
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<tr>
<td>• Current choices include ASA, Plavix and Aggrenox (strong evidence).</td>
</tr>
<tr>
<td>• Ticlid (ticlopidine) is no longer recommended for stroke prevention due to its side effect profile</td>
</tr>
<tr>
<td>• Dose of 81-325 mg ASA/day should be initiated within 48 hours after the first stroke.</td>
</tr>
<tr>
<td>• Aggrenox and Plavix are indicated in Canada only if there is an ASA failure, i.e. TIA/stroke on ASA.</td>
</tr>
<tr>
<td>• ASA use results in an 18% risk reduction of stroke vs. placebo.</td>
</tr>
<tr>
<td>• High doses of ASA are not required to achieve therapeutic effect, i.e. 81-325 mg daily is effective.</td>
</tr>
<tr>
<td>• Plavix is at least as effective as ASA and may be slightly more effective.</td>
</tr>
<tr>
<td>• Combo ASA and dipyridamole results in up to a 37% risk reduction of stroke vs. placebo and is up to 23% more effective than either alone.</td>
</tr>
<tr>
<td>• Combination of Plavix/ASA is no better than ASA alone.</td>
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<tr>
<th>AHA/ASA Recommendations for Antithrombotic Therapy for Noncardioembolic Stroke or TIA (Sacco et al. 2006).</th>
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<tr>
<td>For patients with noncardioembolic ischemic stroke or TIA, antiplatelet agents rather than oral anticoagulation are recommended to reduce the risk of recurrent stroke and other cardiovascular events.</td>
</tr>
<tr>
<td>• Aspirin (50 mg – 325 mg/day), the combination of aspirin and extended-release dipyridamole, and clopidogrel are all acceptable options for initial therapy.</td>
</tr>
<tr>
<td>• Clopidogrel may be considered over aspirin alone on the basis of direct-comparison trials. Insufficient data are available to make evidence-based recommendations with regard to choices between antiplatelet options other than aspirin. Selection of an antiplatelet agent should be individualized based on patient risk factor profiles, tolerance and other clinical characteristics.</td>
</tr>
<tr>
<td>• Addition of aspirin to clopidogrel increases the risk of haemorrhage and is not routinely recommended for ischemic stroke or TIA patients.</td>
</tr>
<tr>
<td>• For patients allergic to aspirin, clopidogrel is reasonable.</td>
</tr>
</tbody>
</table>
| • For patients who have an ischemic cerebrovascular event while taking aspirin, there is no evidence that increasing the dose of aspirin provides additional benefit. Although
alternative antiplatelet agents are often considered for noncardioembolic patients, no single agent or combination has been well studied in patients who have had an event while receiving aspirin.

References


Hankey G, Sudlow CLM, Dunbabin DW. Thienopyridines or aspirin to prevent stroke and other serious vascular events in patients at high risk of vascular disease? A systematic review of the evidence from randomized trials. Stroke 2004; 31:1779-84.


Key Study: Antiplatelet Agents


<table>
<thead>
<tr>
<th>Author, Year Country, Pedro Score</th>
<th>Methods</th>
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<tbody>
<tr>
<td>CAPRIE Steering Committee Gent et al. 1996 Canada/ International 8 (RCT)</td>
<td>Patients with a history of recent cardiovascular events were randomized to receive 75 mg clopidogrel + aspirin placebo (n=9553) or 325 mg aspirin + clopidogrel placebo (n=9546) for 1-3 years.</td>
<td>Patients treated with clopidogrel had a 5.32% annual risk of ischaemic stroke, MI or vascular death compared with 5.83% with aspirin. The difference in rates was statistically significant and reflects a relative risk reduction of 8.7% in favour of clopidogrel. There were no differences in terms of safety.</td>
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</table>

**Importance:** The CAPRIE trial demonstrated that Clopidogrel was a suitable substitute for ASA, although not significantly better.

**Relevant SREBR Conclusion:** There is moderate (Level 1b) evidence that Clopidogrel is similar to aspirin with regard to safety, but as effective as ticlopidine in reducing the risk of recurrent stroke.
Key Study: Antiplatelet Agents


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<tr>
<td>MATCH Investigators Diener et al. 2004 International 8 (RCT)</td>
<td>7599 patients who had an ischaemic stroke or TIA within 3 months. Patients also had at least one of previous ischaemic stroke, previous myocardial infarction, angina pectoris, diabetes mellitus or symptomatic peripheral artery disease (PAD). Participants were randomly assigned to the ASA treatment group (clopidogrel 75 mg/day plus aspirin 75 mg/day; n=3797) or the placebo condition (75 mg/day clopidogrel plus matching placebo). Treatment continued for 18 months. Follow-up occurred at 1,3,6,12 and 18 months after randomization.</td>
<td>With regard to the primary outcome (composite of ischaemic stroke, myocardial infarction, vascular death or re-hospitalization for any acute ischaemic event), there was a small, nonsignificant trend favouring the combination of clopidogrel and ASA vs. clopidogrel alone (relative risk reduction = 6.4%; p=0.244). With regard to the secondary endpoint of ischaemic stroke, either fatal or non-fatal, there was a relative risk reduction of 7.1% in favour of combined therapy. However, this trend was not significant (p=0.353). In the combined therapy group, there were significantly more incidents of life-threatening bleeding (p&lt;0.0001) as well as more incidents of major bleeding (p&lt;0.0001) and minor bleeding (p&lt;0.0001). Gastrointestinal bleeding was the most common cause of both life-threatening and major bleeding events in the clopidogrel plus aspirin treatment group.</td>
</tr>
</tbody>
</table>

**Importance:** This study showed that the combination of Clopidogrel and ASA was no more effective than the two of them together and only served to increase the incidence of bleeding events.

**Relevant SREBR Conclusion:** The combination of clopidogrel and ASA is not more effective than either Clopidogrel or ASA alone and is associated with an increased incidence of bleeding events.
Key Study: Antiplatelet Agents


<table>
<thead>
<tr>
<th>Author, Year Country, Pedro Score</th>
<th>Methods</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESPS-2 Diener et al. 1996 Belgium 8 (RCT)</td>
<td>6602 patients with prior TIA or stroke were randomized to receive 50 mg ASA daily, dipyridamole, the 2 agents in combination or placebo. The primary end points were stroke death or the combined stroke/death.</td>
<td>After 24 months of follow-up, the risk of stroke or death was reduced by 18% with ASA alone; 16% with dipyridamole alone and 24% with combination therapy when compared to placebo. In the group receiving combination therapy, the risk for stroke was reduced by 36% vs. placebo. There was no statistically significant effect on the overall death rate.</td>
</tr>
</tbody>
</table>

**Secondary End Points for Various Drug Treatments**

- **Ischemic events**:
  - Placebo: 12%
  - ASA: 9%
  - DP: 7%
  - DP-ASA: 5%
  - p< .001

- **Other vascular events**: Placebo: 7%, ASA: 5%, DP: 4%, DP-ASA: 3%, p< .01

- **Myocardial Infarction**: Placebo: 2%, ASA: 2%, DP: 2%, DP-ASA: 2%, NS

ASA = aspirin; DP = dipyridamole; DP-ASA = combination of DP and ASA
Importance: This study showed an ASA-dipyridamole combination was more effective than ASA alone in preventing recurrent strokes.

Relevant SREBR Conclusion: ASA in combination with dipyridamole is more effective than ASA alone in reducing the risk for recurrent stroke.
G8. Atrial Fibrillation and Coumadin
G8. Atrial Fibrillation and Coumadin

**Canadian Stroke Guidelines (2008): Recommendation 2.6 – Antithrombotic Therapy in Atrial Fibrillation**

Patients with stroke and atrial fibrillation should be treated with warfarin at a target international normalized ratio of 2.5, range 2.0 to 3.0 (target international normalized ratio of 3.0 for mechanical cardiac valves, range 2.5 to 3.5) [Evidence Level A], if they are likely to be compliant with the required monitoring and are not at high risk for bleeding complications (ASA, AU, CSQCS, ESO, SIGN, VA/DoD).

G8.1 Atrial Fibrillation and Anticoagulation

**Case Study**

A 76 year old man is admitted to your rehabilitation unit with a left MCA stroke. In the emergency department atrial fibrillation was diagnosed and was thought to be the cause of the stroke.

**Q1. What is the relationship between atrial fibrillation and the development of stroke?**

**Answer**

1. AF is a powerful, independent risk factor for ischemic stroke.
2. Leads to embolic stroke, with emboli formed within the fibrillating left atrium.

**Discussion**

Atrial fibrillation (AF) has been identified as a powerful, independent risk factor for ischemic stroke (SPAF III writing committee 1998) increasing the risk of stroke by as much as 5-fold for individuals over the age of 70. 16% of all ischemic strokes within this age group are associated with non-valvular AF (Hart and Halperin 2001, Devuyst and Bogoşlavsly 2001). The formation of left atrial thrombi in AF patient is linked to stasis within the fibrillating atrium, although contributing factors have not been well defined (Hart and Halperin 2001, Khairy and Nattel 2002).

**Q2. What are some other cardiac disorders that could lead to an embolic stroke?**
Cardiac risk factors can be divided into atrial fibrillation, myocardial disease and cardiac valve factors.

Discussion

Cardiac Risk Factors for Ischaemic Stroke

<table>
<thead>
<tr>
<th>Definite Risk Factor</th>
<th>Possible Risk Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Atrial Fibrillation</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Myocardial Disease</strong></td>
<td>Patent foramen ovale</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>Atrial septic aneurysm</td>
</tr>
<tr>
<td>Cardiac failure</td>
<td>Spontaneous echo contrast</td>
</tr>
<tr>
<td>Left ventricular failure</td>
<td></td>
</tr>
<tr>
<td>Intracardiac thrombus</td>
<td></td>
</tr>
<tr>
<td><strong>Cardiac Valve Abnormalities</strong></td>
<td></td>
</tr>
<tr>
<td>Mitral stenosis</td>
<td>Valve strands</td>
</tr>
<tr>
<td>Mitral valvular calcifications</td>
<td></td>
</tr>
<tr>
<td>Prosthetic valves</td>
<td></td>
</tr>
<tr>
<td>Endocarditis</td>
<td></td>
</tr>
</tbody>
</table>

Q3. Once a patient with AF has had a stroke, what is the risk for recurrence of stroke?

**Answers**

1. Within the first 2 weeks following a stroke event, the risk of recurrence has been estimated to be 0.1%-1.3% per day. Conversely, the risk for AF patients with a history of prior stroke or TIA has been estimated to be 12% per annum (Devuyst and Bogousslavsky 2001).

2. The presence of AF in individuals following their first ischemic stroke has been shown to be associated with higher rates of stroke recurrence (6.9% vs 4.7%, p=0.04) (Marini et al. 2005).

Q4. Describe some contraindications for 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

**Q5. Which drug would you use for anticoagulant therapy in this patient?**

**Answer**
Warfarin (a vitamin K antagonist).

**Discussion**
The activity of warfarin is monitored by the measurement of INR. Because of the prolonged onset action of Warfarin, the results of dosage adjustments may not be seen until 3 to 5 days later. Warfarin is highly bound to plasma proteins and medications may increase its effect. Also other medications may decrease the effect of warfarin by inducing hepatic microsomal enzymes.

**Q6. The patient’s daughter asks you if treatment with warfarin is effective and also wants to know the optimal range of INR.**

**Answers**
1. Warfarin has been shown to reduce the risk of recurrent stroke in appropriate patients by almost two-thirds.
2. INR should range between 2.0 and 2.5 or 3.0.

**Discussion**
Anticoagulation therapy has been found to reduce the rate of stroke in patients with previous TIA by 56% (p=0.09) and by 63% (p<0.001) in patients with history of stroke (Hart et al. 2004). The most effective range of INR (International Normalized Ratio) has been identified as being between 2.0 and 2.5 (Albers et al. 2001, Khairy and Nattel 2002, Hart and Halperin 2001, Oden et al. 2006).

**Summary of Anticoagulation with Adjusted-dose Warfarin in Atrial Fibrillation**

<table>
<thead>
<tr>
<th>Study</th>
<th>INR Range</th>
<th>Reduced Stroke Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFASAK 1</td>
<td>2.8 – 4.2</td>
<td>+</td>
</tr>
<tr>
<td>BAATAF</td>
<td>1.5 – 2.7</td>
<td>+</td>
</tr>
<tr>
<td>SPAF 1</td>
<td>2.0 – 4.5</td>
<td>+</td>
</tr>
<tr>
<td>CAFA</td>
<td>2.0 – 3.0</td>
<td>+ (ns)</td>
</tr>
<tr>
<td>Dataset</td>
<td>Range</td>
<td>Effect</td>
</tr>
<tr>
<td>-------------------------------------</td>
<td>---------------</td>
<td>--------</td>
</tr>
<tr>
<td>VA-Stroke Prevention</td>
<td>1.5 – 2.7</td>
<td>+</td>
</tr>
<tr>
<td>EAFT</td>
<td>2.5 – 4.0</td>
<td>+</td>
</tr>
<tr>
<td>SPAFII</td>
<td>2.0 – 4.5</td>
<td>+</td>
</tr>
<tr>
<td>SPAFIII</td>
<td>2.0 – 3.0</td>
<td>+</td>
</tr>
<tr>
<td>Second Copenhagen Study AF</td>
<td>2.0 – 3.0</td>
<td>+</td>
</tr>
<tr>
<td>Japanese AF study</td>
<td>2.2 – 3.5 vs.</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>1.5 – 2.1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(both groups)</td>
<td></td>
</tr>
</tbody>
</table>

*ns = reduction in stroke risk was non-significant*

**Q7. The patient’s daughter asks you when treatment should be initiated.**

**Answer**

1. Warfarin should be initiated as soon as possible.
2. A delay in initiating warfarin is appropriate for patients with large infarcts or uncontrolled hypertension.

**Discussion**

Hart et al. (2002) suggest that ASA followed by early initiation of adjusted dose warfarin therapy is reasonable for AF patients following a primary stroke. The authors also suggested that anticoagulation could be undertaken as soon as the patient is both medically and neurologically stable.

The AHA/ASA Guidelines recommend initiation of oral anticoagulation within 2 weeks of an ischemic stroke or TIA; however, for patients with large infarcts or uncontrolled hypertension, further delays may be appropriate.

**Q8. The nurse asks you to explain to the patient any negative side effects associated with warfarin.**

**Answer**

1. Main side effect is an increased risk of bleeding.

**Discussion**

Anticoagulant therapy is associated with the increased risk of 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 INR (Devuyst and Bogoousslavsky 2001, MacWalter and Shirley 2002). Hart and Halperin (2001) reported that the rate of intracerebral haemorrhage while on an appropriately adjusted dose to be 0.5% per year.

**Q9. The resident asks why not use ASA alone as treatment for atrial fibrillation.**
Answer
1. ASA therapy (300-325 mg/day) is associated with a reduction in the risk of stroke with AF.
2. Meta-analyses clearly show Coumadin to be more effective than ASA.

Discussion
ASA therapy (300-325mg/day) is associated with a reduction in the risk of stroke in individuals with AF, as compared to no treatment. However, doses of 150-200 mg/day do not appear to be either safe or effective. Conversely, results of the EAFT trial as well as several meta analyses (Segal et al. 2000, Albers et al. 2001, Hart et al. 1999, Perret-Guillaume and Whal 2004) clearly suggest that anticoagulant therapy (dose adjusted warfarin) is more effective in preventing strokes among individuals with atrial fibrillation than antiplatelet therapy (ASA).

For patients unable to take oral anticoagulants, aspirin (325 mg/d) is recommended.

References


Perret-Guillaume C, Wahl DG. Low-dose warfarin in atrial fibrillation leads to more thromboembolic events without reducing major bleeding when compared to adjusted-dose. Thromb Haemost 2004; 91:394-02.

Key Study: Atrial Fibrillation and Coumadin


<table>
<thead>
<tr>
<th>Author, Year Country, Pedro Score</th>
<th>Methods</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albers et al. 2001 ns</td>
<td>Reviewed literature that examined the efficacy and safety of different anticoagulation therapies for the prevention of stroke in patients with non-rheumatic atrial fibrillation.</td>
<td>Found that adjusted dose warfarin therapy is substantially more effective than ASA in reducing risk of cardioembolic stroke in individuals with atrial fibrillation. The most effective INR was found to be 2.5, with a range from 2.0 and 3.0.</td>
</tr>
</tbody>
</table>

**Importance:** Albers et al. (2001) found that, for patients with atrial fibrillation who are at high risk of stroke, adjusted dose warfarin therapy is more effective than aspirin.

**Relevant SREBR Conclusion:** Atrial fibrillation increases the risk of cardioembolic stroke; stroke patients with AF are at high risk for recurrent stroke and should receive anticoagulation therapy.
Key Study: Atrial Fibrillation and Coumadin


<table>
<thead>
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<th>Author, Year Country, Pedro Score</th>
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<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hart et al. 1999 ns</td>
<td><strong>Meta-analysis</strong>&lt;br&gt;Identified 16 randomized trials that tested the efficacy and safety of antithrombotic agents used to prevent stroke in patients with atrial fibrillation.</td>
<td>Treatment with adjusted-dose warfarin was found to reduce stroke by 62% with absolute risk reductions of 2.7% per year for primary prevention and 8.4% per year for secondary prevention. In comparison, treatment with aspirin was found to reduce stroke by 22%. Overall, adjusted-dose warfarin was found to be more efficacious than aspirin.</td>
</tr>
</tbody>
</table>

**Importance:** Hart et al. (1999) demonstrated that while adjusted-dose warfarin and aspirin are both effective in reducing the risk of stroke in patients with atrial fibrillation, warfarin is substantially more efficacious than aspirin.

**Relevant SREBR Conclusion:** There is strong (Level 1a) evidence that the use of anticoagulation therapy, particularly with adjusted dose warfarin, substantially reduces the risk of primary and secondary stroke in individuals with atrial fibrillation.
Key Study:  Atrial Fibrillation and Coumadin


<table>
<thead>
<tr>
<th>Author, Year Country, Pedro Score</th>
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</tr>
</thead>
<tbody>
<tr>
<td>EAFT European Atrial Fibrillation Study Group 1993 Netherlands 7 (RCT)</td>
<td>1,007 non-rheumatic atrial fibrillation patients with a recent TIA or minor ischaemic stroke were grouped by eligibility to receive anticoagulation therapy. Anti-coagulation eligible patients (group 1) were randomized to receive adjusted dose anticoagulation (INR 2.5 – 4.0), aspirin (300 mg/day) or placebo. Those not eligible for anticoagulation therapy (group 2) were randomized to receive either ASA or placebo. Mean duration of follow-up was 2.3 years.</td>
<td>Among group 1 patients, risk of stroke was reduced from 12% per year to 4% per year when anticoagulation therapy was compared to placebo (HR = 0.34). Among all patients receiving ASA, the rate of events was 15% compared to 19% for those patients receiving placebo (HR=0.83). Anticoagulation therapy was significantly more effective in preventing stroke than ASA (HR=0.60). The rate of major bleeding events while on anticoagulation therapy was 2.8% and 0.9% while taking ASA.</td>
</tr>
</tbody>
</table>

**Importance:** This study showed that Coumadin was significantly more effective than ASA in reducing the risk of stroke in patients with non-rheumatic atrial fibrillation following a TIA or minor ischemic event.

**Relevant SREBR Conclusion:** There is strong (Level 1a) evidence that the use of anticoagulation therapy, particularly with adjusted dose warfarin, substantially reduces the risk of primary and secondary stroke in individuals with atrial fibrillation.
Key Study: Atrial Fibrillation and Coumadin


<table>
<thead>
<tr>
<th>Author, Year Country, Pedro Score</th>
<th>Methods</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>EAFT (European Atrial Fibrillation Study Group) 1995 Netherlands ns</td>
<td>Using a subset of 214 patients with non-rheumatic atrial fibrillation from the EAFT, the authors calculated INR-specific incidence rates of stroke.</td>
<td>The ideal intensity of anticoagulation was found to be between an INR of 2.0 and 3.9. INRs below 2.0 were not found to have any treatment effect, while INRs above 5.0 were found to increase the occurrence of bleeding complications.</td>
</tr>
</tbody>
</table>

Importance: This trial demonstrated that the ideal intensity of anticoagulation for patients with atrial fibrillation and a recent minor cerebral ischemia is between an INR of 2.0 and 3.9. Based on their findings, the authors recommended that INRs below 2.0 and above 5.0 should be avoided.

Relevant SREBR Conclusion: There is strong (Level 1a) evidence that treatment with ASA 300 – 325 mg/day is associated with reduced risk of stroke when compared to no treatment in individuals with atrial fibrillation. However, anticoagulant therapy (dose-adjusted warfarin) is more effective in preventing strokes among individuals with atrial fibrillation than antiplatelet therapy (ASA).
Key Study: Atrial Fibrillation and Coumadin


<table>
<thead>
<tr>
<th>Author, Year Country, Pedro Score</th>
<th>Methods</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Veterans Affairs Stroke Prevention in Nonrheumatic Atrial Fibrillation Investigators Ezekowitze et al. 1992 USA 8 (RCT)</td>
<td>571 men with chronic non-rheumatic atrial fibrillation were randomly allocated to a treatment condition receiving adjusted dose, low intensity warfarin (INR 1.5 – 2.7) or to a matching placebo condition. Mean follow-up was 1.7 years.</td>
<td>Among patients with no history of stroke, the reduction in risk for stroke associated with warfarin therapy was 0.79 (p=0.001). The annual event rate in patients over age 70 was 4.8%/annum in the placebo group and 0.9%/annum in the warfarin therapy group. Stroke was more common among patients with a history of previous cerebral infarction (9.3%/annum in the placebo group vs. 6.1%/annum in the warfarin group). Major haemorrhages occurred at the rate of 1.3% per annum with warfarin therapy.</td>
</tr>
</tbody>
</table>

The Relationship between Primary and Secondary End Points in Patients with no History of Cerebral Infraction for Warfarin vs. Placebo Treatment

![Graph showing the relationship between primary and secondary end points in patients without a history of cerebral infarction for warfarin vs. placebo treatment.](image-url)
**Importance:** Coumadin reduces the risk of stroke in chronic atrial fibrillation when compared to placebo.

**Relevant SREBR Conclusion:** There is strong (Level 1a) evidence that the use of anticoagulation therapy, particularly with adjusted dose warfarin, substantially reduces the risk of primary and secondary stroke in individuals with atrial fibrillation.
G9. Patent Foramen Ovale
G9. Patent Foramen Ovale

G9.1 Case Study: PFO

Case Study
You see a 45 year old woman in your outpatient clinic. She has had a TIA and her echocardiogram shows a patent foramen ovale (PFO).

Q1. What is a PFO?

Answer
1. Patent foramen ovale is a congenital defect in the interarterial septum.
2. Associated with a right-left shunt.

Discussion
Patent foramen ovale (PFO) is a persistence of an embryonic defect in the interatrial septum and is present in up to 27% of the general population. Atrial septal aneurysms, defined as >10-mm excursions of the interatrial septum, are less common and are present in approximately 2% of the population. The prevalence of PFOs and atrial septal aneurysms does not appear to vary by race/ethnicity (Rodriquez 2003).
Q2. Is PFO a stroke risk factor?

Answer
1. Studies have found an association between PFO and strokes of unknown etiology.

Discussion

Q3. How can PFO be treated?

Answer
1. Antiplatelet therapy unless there is some other indication for anticoagulation.

Discussion
For patients with an ischemic stroke or TIA and a PFO, antiplatelet therapy is reasonable to prevent a recurrent event. Warfarin is appropriate for high-risk patients who have other indications for oral anticoagulation, such as those with an underlying hypercoagulable state or evidence of venous thrombosis (Sacco et al. 2006).

Q4. The resident asks you if it is necessary to close the PFO.

Answer
1. Operation is not recommended unless it is a recurrent stroke despite optimal medical therapy.

Discussion
Insufficient data exists to make a recommendation about PFO closure in patients with a first stroke and a PFO. PFO closure may be considered for patients with recurrent stroke of unknown etiology despite optimal medical therapy. Can choose either an open surgical or a transcatheter closure.

Open Surgical: In a study involving 32 young patients with stroke of unknown etiology or TIA who underwent surgical closure of a PFO, there were no major complications or recurrent vascular events at the 19 month follow-up (Ruchat et al. 1997, Devuyst et al. 1996). In a 2-year
follow-up of a cohort of 91 patients with stroke of unknown etiology or TIA who underwent surgical closure, 7 TIAs but no major complications were reported (Dearani et al. 1999).

**Transcatheter:** A review of 10 non-randomized unblinded transcatheter closure studies for secondary prevention reported a 1-year rate of recurrent neurological events of 0% to 4.9% in patients undergoing transcatheter closure compared with 3.8% to 12.0% in medically treated patients (Khairy et al. 2003).

**References**


G10. Carotid Artery Stenosis
G10. Carotid Artery Stenosis

**Canadian Stroke Guideline (2008): Recommendation 2.7 – Carotid Intervention**

**2.7a Symptomatic carotid stenosis**

Patients with transient ischemic attack or nondisabling stroke and ipsilateral 70%–99% internal carotid artery stenosis (measured on a catheter angiogram or by 2 concordant noninvasive imaging modalities) should be offered carotid endarterectomy within 2 weeks of the incident transient ischemic attack or stroke unless contraindicated [Evidence Level A] (ASA, AU, CSQCS, ESO, NZ, SIGN 14).

i. Carotid endarterectomy is recommended for selected patients with moderate (50%–69%) symptomatic stenosis, and these patients should be evaluated by a physician with expertise in stroke management [Evidence Level A] (ASA, AU, CSQCS, NZ, SIGN 14).

ii. Carotid endarterectomy should be performed by a surgeon with a known perioperative morbidity and mortality of < 6% [Evidence Level A] (ASA, CSQCS, ESO, NZ).

iii. Carotid stenting may be considered for patients who are not operative candidates for technical, anatomic or medical reasons [Evidence Level C].

iv. Carotid endarterectomy is contraindicated for patients with mild (< 50%) stenosis [Evidence Level A] (ASA, CSQCS, SIGN 14).

**2.7b Asymptomatic carotid stenosis**

Carotid endarterectomy may be considered for selected patients with asymptomatic 60%–99% carotid stenosis.

i. Patients should be less than 75 years old with a surgical risk of < 3%, a life expectancy of > 5 years and be evaluated by a physician with expertise in stroke management [Evidence Level A] (AAN, AHA, AU, CSQCS).

**G10.1 Case Study: Carotid Endarterectomy (CEA)**

**Case Study**

A 62 year old woman was admitted to your rehabilitation unit with a left MCA ischemic stroke. 75% stenosis of the left internal carotid artery due to atherosclerotic plaque was found on carotid ultrasound.
Q1. What issues must be considered when deciding on therapeutic options?

Answers
1. Grade of occlusion (< 50%, 50-69%, >70%)
2. Cost-benefit of surgery (Risk of medical treatment, Benefit of surgery)
3. Surgical risk

Q2. In this case, what will be your recommendation and why?

Answers
1. Carotid endarterectomy
2. NASCET trial showed that >70% occlusion benefits from carotid endarterectomy.

Discussion
Carotid endarterectomy (CEA) has become the standard treatment for severe symptomatic carotid artery stenosis following ECST and the NASCET trial publications. In both studies, treatment was found to be effective and durable at the 8 year follow-up. The number needed to treat in order to prevent one stroke at 2 years is 8 (Goldsmidt and Caplan 2003).

In order to examine the benefit of carotid endarterectomy (CEA), 659 patients with symptomatic, high-grade (70 – 99%) carotid artery stenosis were randomized to receive either optimal medical treatment (n=331) or surgical intervention (n=328). Rates of stroke and death were reported at two years post CEA. 30-day rate of stroke and/or death was reported to be 5.8%. At two years, CEA was associated with an absolute reduction in risk for ipsilateral stroke of 17±3.5% (p<0.001). (NASCET 1991, Bettman et al. 1998, Hill et al. 2004).

Q3. The medical student asks you why you think carotid endarterectomy (CEA) should be used instead of carotid artery stenting (CAS).

Answer
1. CAS is a good as CAS over the short to medium term, but the risk of severe restenosis is higher.

Discussion
The CAVATAS I investigation (2001) compared CEA and CAS. The researchers found no difference between CEA and CAS in rates of disabling stroke and death or the rate of ipsilateral stroke at both 30-day and 3 year follow-ups. However, one year following treatment, severe restenosis was more frequent among patients who had received CAS treatment (p<0.001).
CAS may fulfil a role in treating carotid artery stenosis in specific subgroups of patients: (Connors et al. 2003, Cohen et al. 2003)
- Patients not eligible for CEA.
- Patients with contralateral occlusion.
- PostCEA restenosis.
- Radiation-induced stenosis.
- Surgically inaccessible lesions.

Case Study (continued)
The radiologist revises his report; the grade of stenosis was 60%, not 75%.

Q4. Does this change your treatment decision?

Answer
1. Results of NASCET were less impressive for the 50-69% stenosis group. One must carefully calculate the risk of the intervention but CEA is still an option.

Discussion
While CEA has been found to result in significant benefits in patients with moderate stenosis (50-69%), the results are less convincing than they are in patients with more severe stenosis (Barnett and Meldrum 2001, Rothwell et al. 2003a, Rothwell et al. 2003b). In this case, the number needed to treat to prevent one stroke at 2 years is 20 (Goldsmidt and Caplan 2003).

Thus, for patients with moderate stenosis, one must calculate the risk of the intervention. The American Heart Association (Biller et al. 1998) recommended that the combined risk of stroke/death resulting from the 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. Rothwell et al. (1999) proposed the following risk assessment model, which encompasses both medical and surgical risk.

Proposed Risk Assessment Model (Rothwell et al. 1999)

<table>
<thead>
<tr>
<th>Prognostic Variable</th>
<th>Risk Points</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Medical Model:</strong></td>
<td></td>
</tr>
<tr>
<td>Cerebral vs. ocular events</td>
<td>1</td>
</tr>
<tr>
<td>Plaque surface irregularity</td>
<td>1</td>
</tr>
<tr>
<td>Any events in past 2 months</td>
<td>1</td>
</tr>
<tr>
<td>Carotid Stenosis (pick one):</td>
<td></td>
</tr>
<tr>
<td>70-79%</td>
<td>0</td>
</tr>
<tr>
<td>80-89%</td>
<td>1</td>
</tr>
<tr>
<td>90-99%</td>
<td>2</td>
</tr>
</tbody>
</table>

**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 .

CEA is only of significant benefit in patients with a score ≥ 4. In patients with prognostic scores of less than 4, the procedure was of no significant benefit and may have been harmful to patients with prognostic scores of one or less.

Based on data from the Ontario Carotid Endarterectomy Register History, there are some risk factors that are significantly associated with higher rates of adverse outcomes (death or nonfatal stroke) within 30 days following CEA.
- History of stroke or TIA (OR=1.75)
- Atrial Fibrillation (OR=1.89)
- Contralateral carotid occlusion (OR=1.72)
- Congestive heart failure (OR=1.8)
- Diabetes (OR=1.8)

In this model, one point is added for each risk factor that is present and total scores reflect increasing levels of risk. A risk score of 4 in this model was found to be associated with a 15.8% increase in risk of death and/or stroke (Tu et al. 2003).

Q5. How long after the symptomatic event do you recommend performing the CEA?

Answer
1. The sooner the better.

Discussion
Both the NASCET and ECST trials demonstrated that the amount of time between the 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 et al 2004).

Early CEA within 2 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) (Rothwell et al. 2004, Fairhead et al. 2005).

In patients with moderate stenosis, absolute benefit was observed only for those patients randomized to CEA treatment within 2 weeks of the initial symptomatic event (Rothwell et al 2004).

G10.2 Case Study: Symptomatic Stenosis (<50%)
Case Study

A 62 year old woman was admitted to your rehabilitation unit with a left MCA ischemic stroke. A 40% stenosis due to atherosclerotic plaque was found on the carotid ultrasound.

Q6. What will be your recommendation in this case and why?

Answer
1. Medical treatment is the only option.
2. Not a surgical candidate.

Discussion
Medical treatment would be the recommended option. In symptomatic patients with less than 50% stenosis, there appears to be no benefit associated with surgical treatment (Barnett and Meldrum 2001, Rothwell et al. 2003a, Rothwell et al. 2003b).

Recommendations for Carotid Endarterectomy in Symptomatic Carotid Artery Stenosis (Barnett et al. 2002)

Patients with symptomatic stenosis ≥ 70% face greater risk when treated medically than surgically. CEA is most beneficial in the following patients:
- healthy elderly ≥ 75 years of age
- hemispheric TIA
- tandem extracranial and intracranial lesions
- without angiographic evidence of collateral pathways
- widespread leukoaraiosis (higher perioperative risk)
- occlusion of contralateral carotid artery (higher perioperative risk)
- intraluminal thrombus (higher perioperative risk)

Patients with symptomatic stenosis of 50% - 69%. Only some patients in this category benefit from intervention and benefits realized are much smaller. The following patients may be harmed:
- patients with transient monocular blindness only, especially those with few risk factors
- women with few risk factors

Patients with near occlusion of the symptomatic artery AND patients with lacunar strokes and stenosis >50%:
- medical treatment carries a lower risk of stroke than for patients without these conditions
- CEA is still indicated with no additional perioperative risk, “but the benefit is
G10.3 Case Study: Non-symptomatic Stenosis

**Case Study**

You see a 55 year old man in your outpatient clinic. He has an asymptomatic 55% stenosis in his right internal carotid artery.

**Q7. What is the risk of stroke for this patient?**

**Answer**

1. The one year risk of stroke in patient with ICA stenosis is 1-3%. The 10 and 15 year risk of stroke if >50% stenosed is 9.3% and 16.6% respectively.

**Discussion**

The short term risk for stroke associated with internal carotid artery stenosis is 1-3% per year, depending on the degree of stenosis (Norris et al 1991, European Carotid surgery trials Collaborative 1995).

Over the long term, the 10 and 15 year risk for stroke has been reported to be 5.7% and 8.7%, respectively, in individuals with less than 50% internal carotid artery stenosis, and 9.3% and 16.6% in individuals with 50% or greater stenosis (Nadareishvili et al. 2002).

However, at all degrees of stenosis, more than 40% of strokes in asymptomatic arteries have been found to be 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 (Barnett et al 2002).

**Guidelines for the Use of Carotid Endarterectomy (Canadian Neurological Society, Findlay et al. 1997)**

**CEA is clearly recommended for patients with ICA stenosis ≥ 70% if:**

- stenosis is symptomatic
- there is no worse distal, ipsilateral, carotid distribution arterial disease
- patient is in stable medical condition
- rates of major surgical complications (stroke & death) among patients of the treating surgeon are less than 6%
Surgery is not recommended for asymptomatic stenoses of less than 60%.
- CEA should not be considered for asymptomatic stenoses unless the combined rate of stroke and death among patients of the treating surgeon is less than 3%

Symptomatic stenoses of less than 70% and asymptomatic stenoses of less than 60% are uncertain indications.

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G10.4 Case Study: Recurrent Carotid Stenosis

**Case Study**

You see a 52 year old man in your outpatient clinic who was treated with CEA for his symptomatic 70% stenosis of his left internal carotid artery. In his new ultrasound you find a restenosis of 80% and he is complaining about recurrent numbness in his right side.
Q8. Which treatment do you recommend in this situation, carotid endarterectomy or carotid artery stenting?

Answer
1. For recurrent carotid stenosis post carotid endarterectomy, carotid artery stenting results in similar outcomes.

Discussion
In the treatment of early and late recurrent carotid stenosis post CEA, CAS has been found to result in similar anatomic and neurologic outcomes when compared to repeat CEA (Bowser et al. 2003).

References


Key Study: Carotid Artery Occlusion and Reperfusion Interventions


<table>
<thead>
<tr>
<th>Author, Year Country, Pedro Score</th>
<th>Methods</th>
<th>Outcomes</th>
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<tbody>
<tr>
<td>Alamowitch et al. 2005 ns</td>
<td>Using data from two large trials (NASCET and ACE), the efficacy of CE and medical therapy was compared in women and men with symptomatic ICA stenosis.</td>
<td>Female sex was found to be 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. Similar long-term benefits were found for men and women with &gt;70% stenosis in terms of absolute risk reduction; however, among patients with 50-69% stenosis, CEA was of benefit among men only.</td>
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</table>

**Importance:** Carotid endarterectomy was shown to be efficacious for both men and women if ≥70% stenosis but only men if stenosis was 59-69%.

**Relevant SREBR Conclusion:** There is strong evidence (Level 1a) that carotid endarterectomy is an effective and durable means by which to reduce the risk of stroke in individuals with symptomatic carotid artery stenosis of 70 – 99%.
Key Study: Carotid Artery Occlusion and Reperfusion Interventions


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<td>NASCET Trial Collaborators Barnett et al. 1998 Canada/USA 8 (RCT)</td>
<td>Patients with moderate carotid stenosis were stratified to degree of stenosis and randomized to receive medical treatment (n=1118) or surgical intervention (n=1108) and followed for an average of 5 years.</td>
<td>Among patients with 50-69% stenosis treated surgically, there was a significant reduction in the failure rate (fatal or nonfatal ipsilateral stroke). Among patients with less than 50% stenosis treated surgically, there was not a statistically significant reduction in the failure rate.</td>
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Importance: Patients with carotid artery stenosis of 50-69% benefit more from carotid endarterectomy surgery when compared to medical therapy; < 50% carotid artery stenosis do not benefit from the surgery when compared to medical therapy.

Relevant SREBR Conclusion: There is strong evidence (Level 1a) that carotid endarterectomy is an effective and durable means by which to reduce the risk of stroke in individuals with symptomatic carotid artery stenosis of 70 – 99%.
Key Study: Carotid Artery Occlusion and Reperfusion Interventions


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<td>NASCET Trial Collaborators Barnett et. al. 1991 Canada/USA 8 (RCT)</td>
<td>Patients in 2 predetermined strata based on severity of carotid stenosis – 30-69% &amp; 70-99% were randomized to receive medical treatment or surgical intervention (carotid endarterectomy). All patients received optimal medical care, including antiplatelet therapy. The results of 659 patients in the severe stenosis stratum (70 to 99%) were reported.</td>
<td>The absolute risk reduction of any ipsilateral stroke and for a major or fatal ipsilateral stroke at two years was significantly greater in the surgical patients (n=328) than in the medical patients (n=331).</td>
</tr>
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**Importance:** This RCT showed that there is a benefit of carotid endarterectomy in preventing ipsilateral strokes when there was ≥ 70% stenosis.

**Relevant SREBR Conclusion:** There is strong evidence (Level 1a) that carotid endarterectomy is an effective and durable means by which to reduce the risk of stroke in individuals with symptomatic carotid artery stenosis of 70 – 99%.
Key Study: Carotid Artery Occlusion and Reperfusion Interventions


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| Coward et al. 2005 ns | **Meta-analysis**
To evaluate the safety and efficacy of endovascular techniques, a literature search was conducted to identify randomized trials investigating carotid angioplasty and/or stenting as compared to surgery. Five trials involving 1269 patients were included. | No significant differences between the two treatments were found regarding the odds of treatment-related death or any type of stroke at either the 30-day or 1 year follow-ups. However, endovascular treatment was found to significantly reduce the risk of cranial nerve injury (OR, 0.13; CI, 0.06 to 0.25) |

**Importance:** Although no significant differences were found regarding the major risks of treatment, this study demonstrates that minor complication rates favor endovascular treatment over stenting.

**Relevant SREBR Conclusion:** There is strong evidence (Level 1a) that carotid endarterectomy is an effective and durable means by which to reduce the risk of stroke in individuals with symptomatic carotid artery stenosis of 70 – 99%.
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