3. Secondary Prevention of Stroke

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3.1 Why Secondary Prevention?

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

The risk of stroke recurrence is as high as 25% within the first 2 years. Up to 40% of survivors of a stroke of TIA will have a stroke within 5 years. A second stroke can potentially reverse the benefits of stroke rehabilitation.

3.1.1 Treatment of Risk Factors

The key to secondary prevention of stroke is to treat risk factors for an additional stroke. These include:

- High blood pressure (HBP)
- Atrial fibrillation (AF)
- Congestive heart failure/cardio-myopathy
- Smoking
- Dyslipidemia
- Diabetes
- Carotid stenosis
- Obstructive Sleep Apnea

3.2 Hypertension

Hypertension is the most powerful risk factor after age. High blood pressure has high prevalence and is easily modifiable. Stroke mortality and incidence have declined over past 5 decades is partially attributable to better hypertension management. Risk of stroke rises proportionally with increasing systolic and diastolic blood pressure.

3.2.1 Treatment of Hypertension

There is strong evidence that a reduction in blood pressure is associated with decreased risk of stroke. Treatment of systolic hypertension in the elderly decreases the risk of stroke by 36%. The benefit is associated with reductions of approximately 10/5mmHg of blood pressure. Generally the lower the BP the better!

Target:

- Stroke or TIA patients, target blood pressure consistently <140/90 mmHg
- Diabetics, blood pressure target recommended for primary or secondary prevention of stroke is consistently < 130/80 mmHg
• Non-diabetic chronic kidney disease, blood pressure lowering treatment is recommended for the prevention of first or recurrent stroke to attain a BP consistently <140/90 mmHg

### 3.2.2 Antihypertensive Therapy and Functional Outcomes

The treatment of hypertension comes with a relative risk reduction of 42-48%. There is moderate evidence that antihypertensive therapy post stroke is associated with reduction in risk of functional disability and dependence. There is strong evidence that ACE-inhibitors (other than Captopril) are associated with a reduced risk of stroke (HOPE/PROGRESS). There is strong evidence that the addition of a Ca-antagonist (Diltiazem) to an antihypertensive regimen decreases the risk of stroke (Hansson et al. 2000). Most patients with hypertension will require 2 or 3 drugs to achieve blood pressure control. Preferred combinations include ACE inhibitor/diuretic, ARB/diuretic, ACE inhibitor/CCB and ARB/CCB. The treatment regimen will be dictated by patient’s considerations and tolerance.

**HIGHLIGHTED STUDY**

**PROGRESS Collaborative Group.** Randomized trial of perindopril-based blood pressure-lowering regimen among 6,105 individuals with previous stroke or transient ischaemic attack. Lancet 2001; 358(9287):1033-41.

**Methods:** 6105 patients (HBP and non-HBP) with history of ischemic stroke or TIA randomized to receive either perindopril 4 mg/day + indapamide or perindopril alone vs. placebo.

**Results:** Combined perindopril + indapamide is better than perindopril alone. Relative risk reduction was 28% with combination treatment.

**HIGHLIGHTED STUDY**


**Methods:** 3577 diabetic patients (age 55+ and history of cardiovascular disease) randomized to 10 mg Ramipril/day vs. placebo.

**Results:** Ramipril lowered risk of MI by 22%, stroke by 33%, cardiovascular death by 37% and total mortality by 24%.

**HIGHLIGHTED STUDY**


**Methods:** 9193 patients aged 55-80 with essential HBP and LVH randomized to Losartan or Atenolol.

**Results:** BP < 140/80 achieved in 48% of Losartan group, fewer side-effects than Atenolol and significantly reduced risk of cardiovascular (MI/stroke) morbidity and death more than Atenolol.

**HIGHLIGHTED STUDY**

Methods: 1352 individuals with hypertension and history of TIA, ischemic stroke or cerebral hemorrhage were randomly assigned to receive either nitrendipine (10 mg od, n=671) or eprosartan (600 mg od, n=681).

Results: Blood pressure reduction was similar in both groups. Mean target blood pressures were achieved in both groups by 3 months and remained stable throughout the study.

3.3 Diabetes

Diabetics have increased susceptibility to atherosclerosis, hypertension, obesity and hyperlipidemia. The relative risk of ischemic and hemorrhagic stroke for diabetics is 1.5-3.0. The risk of recurrent stroke is also significantly higher among patients with diabetes. Diabetic stroke patients have higher risk of death and disability in the first 28 days after stroke "FINNSTROKE study". Diabetic stroke patients are less likely to be discharged home from acute care, and less able to ambulate independently at the time of discharge. Tight glycemic control reduces microvascular complications (nephropathy, neuropathy, retinopathy) but has not yet been shown to reduce stroke.

Diabetes Diagnosis:
- Patients with ischemic stroke or TIA should be screened for diabetes with a fasting plasma glucose, glycated hemoglobin (A1C) or 75 g oral glucose tolerance test soon after admission to hospital (Evidence Level C)
- Patients with diabetes and either ischemic stroke or TIA, glycated hemoglobin (A1C) should be measured as part of a comprehensive stroke assessment (Evidence Level B).
- Fasting plasma glucose level of ≥126 mg/dL (>7mmol/L) is diagnostic for diabetes

3.3.1 Treatment of Diabetes

Heart and Stroke Foundation of Canada recommends tight glycemic control using diet, oral hypoglycemic agents and insulin.

TARGET:
Glycemic targets must be individualized; however, therapy in most stroke patients with type 1 or type 2 diabetes TIA should be treated to achieve:
- Glycated Hemoglobin A1C ≤7.0%, patients with type 1 or type 2 diabetes
- Fasting plasma glucose (preprandial) plasma glucose target of 4.0 to 7.0 mmol/L.
- Two-hour postprandial plasma glucose target is 5.0 to 10.0 mmol/L.
- If HbA1C targets cannot be achieved with a postprandial target of 5.0 to 10.0 mmol/L, further postprandial blood lowering, to 5.0 to 8.0 mmol/L, can be considered.

Aggressive treatment of blood pressure among patients with type 2 diabetes dramatically reduces the risk of stroke and stroke mortality. Most diabetic patients will require >1 antihypertensive agent. ACEIs and ARBs are more effective in reducing the progression of renal disease and are recommended as first choice medication for patients with DM.
Type 2 diabetes is associated with plasma lipid and lipid protein abnormalities that include low concentrations of HDL cholesterol, increases in small, dense, atherogenic LDL particles and elevated triglycerides

- Adults with diabetes and ischemic stroke are at high risk of further vascular events and should also be treated with a statin to achieve a LDL cholesterol ≤ 2.0 mmol/l

Unless contraindicated, low-dose acetylsalicylic acid (ASA) therapy (80 to 325 mg/day) is recommended in all patients with diabetes with evidence of stroke or cardiovascular disease.

### 3.4 Hyperlipidemia

Recent studies have shown an association between serum cholesterol and thrombotic stroke but it has not been established that it is an independent predictive risk factor for stroke. Elevated total serum cholesterol, triglycerides, and LDL appear to be associated with an increased risk of ischemic stroke.

#### 3.4.1 Canadian Stroke Guidelines

Patients who have had an ischemic stroke or TIA should have their serum lipid levels assessed and aggressively managed (Evidence Level A).

**Lipid Assessment**

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

#### 3.4.2 Treatment of Hyperlipidemia

**Why Treat?**

- Significant reduction in risk for total stroke associated with 1 mmol/L reduction of cholesterol.
- There is 20-25% reduction in cardiovascular disease mortality with every 1 mmol/L reduction in LDL.
- Total serum cholesterol was a significant independent predictor for motor recovery following stroke (Lai et al., 2012).

**Who To Treat?**

- Patients with ischemic stroke or TIA should be aggressively managed with lifestyle changes to lower lipid levels (Evidence Level B)
- Statin should be prescribed as *secondary prevention* to most patients who have had an ischemic stroke or TIA (Evidence Level B)
• Recent research suggests that a LDL-C/HDL-C ratio ≤2 may represent a viable cut off point for statin treatment in stroke patients to prevent stroke recurrence
• Statin therapy is not indicated for prevention of intracerebral hemorrhage

**Target:** LDL should be < 2.0 mmol/L (Evidence Level A) OR 50% reduction in LDL concentration (Evidence Level B); Apolipoprotein B level of <0.80 gm/L (Evidence Level B).

### 3.4.3 Statins

Statins are HMG-CoA reductase inhibitors. Statins are the first line of treatment for the management of dyslipidemia and hyperlipidemia. Statins regulate LDL receptor activity and reduces the entry of LDL cholesterol into circulation. Apart from lowering serum cholesterol, statins have anti-inflammatory effects, which may contribute to their success in reducing the risk of stroke
- Natural statins (lovastatin, pravastatin, simvastatin)
- Synthetic statins (atorvastatin, cerivastatin, fluvastatin).

Most common adverse effects associated with statins are GI upset, muscle aches, and hepatitis/hepatotoxicity (<1%). Rare complication is severe myopathy +/- rhabdomyolysis.

### 3.4.4 Treatment with Statins

The Cholesterol Treatment Trialists (2008) meta-analysis of 14 statin trials showed a dose-dependent relative reduction in cardiovascular disease with LDL lowering. There is strong evidence that statins are an effective treatment to lower cholesterol and reduce risk of stroke/TIA. There is strong evidence that intensive therapy may be more effective than less intense therapy in reducing the risk for ischemic stroke events. Statins have been shown to reduce the risk of stroke by 30% in patients with CAD despite serum cholesterol levels. Statins have been used for treating patients post MI and have been shown to reduce the risk of stroke by 24-34%. Statin therapy has been associated with increased risk for hemorrhagic stroke.

**HIGHLIGHTED STUDY**


**Methods:** Combined results of the CARE and LIPID trials of 13,173 patients
**Results:** Pravastatin associated with reduction in total strokes by 22% (95% CI: 7% to 35%, p=0.01) and a 25% reduction in nonfatal stroke (95% CI: 10% to 38%). Authors estimated would need to treat 588 patients per year to prevent one stroke. Post-hoc analysis of LIPID trial showed treatment benefits may extend to individuals with low LDL and HDL.

**HIGHLIGHTED STUDY**


**Methods:** 4732 patients with previous stroke/TIA 1-6 months prior to study and LDL 2.6-4.9 mmol and no known history of CAD. Randomized to Atorvastatin 80 mg/day or placebo and mean follow-up = 4.9 years.
Results: There were fewer strokes occurred in treatment group vs. placebo (p=0.05). There was a significant reduction of risk of stroke and TIA (OR=0.77; p<0.001). There was a significant reduction in LDL cholesterol levels and a 16% reduction in risk for fatal or nonfatal stroke when compared to placebo.

3.5 Lifestyle Modification

Lifestyle modification includes physical exercise, weight loss, low alcohol consumption and smoking cessation.

3.5.1 Physical Activity

Physical activity may have a positive effect on a number of important risk factors for stroke (obesity, arterial blood pressure, glucose metabolism, platelet aggregation). There is a dose-response relationship between physical activity and stroke risk. Recommendation is for patients to engage in moderate dynamic exercise such as brisk walking, jogging, cycling, swimming or dynamic exercises more than 4 to 5 days a week in addition to routine activities of daily living. Patients should be counselled to achieve ≥ 150 mins of moderate to vigorous activity per week, in episodes of ≥ 10 mins (Evidence Level B). Most stroke patients should be encouraged to start a regular exercise program. Supervision by a health-care professional (physiotherapist) at exercise initiation should be considered in individuals with stroke at risk of falls or injury, or in individuals with other comorbid disease (such as cardiac disease), which may place them at higher risk of medical complications.

3.5.2 Diet

Dietary modifications in secondary prevention tend to be underestimated. Diet influences a number of stroke risk factors including hypertension, hyperlipidemia, diabetes, and obesity. Dietary interventions center around fruits, vegetables, whole grains, and long-chain omega-3 polyunsaturated fatty acids (fish and fish oils).

Target weight: (Evidence Level B).
- Body mass index (BMI) of 18.5 to 24.9 kg/m2
- OR waist circumference of <88 centimeters for women
- Waist circumference <102 centimeters for men

HIGHLIGHTED STUDY


Methods: Patients randomized to control diet, diet rich in fruits and vegetables, or diet rich in fruits and vegetables and low in saturated fat/low in dairy products (DASH diet) x 8 weeks.
Results: For both systolic and diastolic blood pressures, there was a gradient across diet types with the greatest reduction involving the DASH diet.

Methods: 423 patients, age < 70 years, history of 1st myocardial infarction randomized to low-fat, low cholesterol Mediterranean-type diet or control group on “prudent Western-type” diet.

Results: Significant reduction in coronary events with Mediterranean diet, rich in nuts and omega-3 fatty acids.

**Conclusions Regarding Diet**

- There is strong evidence that a low-fat diet rich in fruits, vegetables, legumes, whole grains and omega-3 fatty acids is effective in reducing BP and serum cholesterol in high risk coronary artery patients.
- There is strong evidence that consumption of a Mediterranean-type diet is associated with a reduction in coronary events.
- Counsel and educate individuals with stroke about following a Mediterranean-type diet, which is high in vegetables, fruits, whole grains, fish, nuts and olive oil (Evidence Level B).
- Counsel and educate individuals with stroke and high blood pressure to have a daily sodium intake from all sources to less than 2000 mg per day (Evidence Level A).

**3.5.3 Smoking**

- Approximately 18% of strokes may be attributed to active smoking.
- Stroke risk increases in a dose dependent manner with the number of cigarettes smoked daily.
- Smoking more than 20 cigarettes a day increases the risk of ischemic and hemorrhagic strokes by 2-4 folds.
- Smoking not only increases the risk of stroke, but also increased risk for death, dependency and disability.
- There is a reversal of smoking risk 2-5 years after smoking cessation.

**Treatment of Smoking**

- Interdisciplinary team members should address smoking cessation and a smoke-free environment at every healthcare encounter for active smokers.
- Interdisciplinary team members should counsel patients, family members and caregivers about the harmful effects of exposure to second-hand smoke (Evidence Level B) and offer assistance with the initiation of a smoking cessation attempt (Evidence Level A).
- People who are not ready to quit should be offered a motivational intervention to help enhance their readiness to quit (Evidence Level B).
- Expert opinion suggests that initiating nicotine withdrawal/replacement therapy should begin as soon as possible (Evidence Level C).
- Medications and behavioral therapies should be considered in combination (Evidence Level A)
- The three classes of pharmacological agents that should be considered as first-line therapy for smoking cessation are: (Evidence Level A).
  - Nicotine replacement therapy
  - Bupropion
  - Varenicline

**3.5.4 Alcohol Use**
• Light (1-2 drinks/day) alcohol consumption reduces the risk of ischemic stroke.
• Excessive alcohol intake increases the risk of ischemic stroke and intracranial hemorrhage.
• Women are encouraged to restrict intake of alcohol to 10 drinks per week (≤2 drinks per day) and men to no more than 15 drinks per week (≤3 drinks per day).
• Counsel and educate individuals with stroke to avoid heavy alcohol use (>5 drinks per day) (Evidence Level B).

3.5.5 Behavioural Change

• Moderate evidence that multi-factorial behavioural intervention can substantially reduce the risk of stroke even within a high-risk population
• Multi-factorial behavioural interventions focusing on smoking cessation and improved eating habits led to significantly reduced risk of cardiovascular events, incidence of stroke, smoking rates and lower serum cholesterol concentrations.

HIGHLIGHTED STUDY

Methods: Randomized 508 high-risk male patients, age 50-72 with treated hypertension to multifactorial, behavioural intervention (n=253) or usual care (n=255). 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.

Results: Overall risk of cardiovascular events was 29% lower in the intervention group (p=0.41). Risk of stroke was lower in the intervention group (RR=0.53). Intervention group demonstrated lower serum cholesterol (p<0.0001) and higher adjusted smoking quit rates (p=0.12) after 3 years of follow-up.

HIGHLIGHTED STUDY

Methods: Meta-analysis of 23 studies published between 1983 and 2002 examining the association between physical activity and stroke incidence or mortality. Cohort studies and 5 case control studies were included in the analysis.

Results: When both types of studies were examined together, 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<0.001).

HIGHLIGHTED STUDY

Results: Reported a four-fold increased risk of stroke associated with active smoking when active smokers were compared to non-smokers. However, when non-smokers who had been exposed to environmental smoke were removed from the comparison group, the risk increased to 6-fold.
3.6 Homocysteine

Homocysteine is a sulphur-containing amino acid. It has been linked to atherosclerotic vascular disease including stroke. Normal serum levels of homocysteine are 5-15 mmol/L, greater than 16 abnormal. Elevated levels of homocysteine may be attributable to deficiencies in folic acid, vitamin B6 and vitamin B12, as well as old age (over 70 years), renal insufficiency, drinking more than 4 cups of coffee per day, alcohol use, smoking and physical inactivity. Plasma homocysteine levels are inversely correlated with red cell level of folate, vitamin B12 and vitamin B6. Supplementation with folic acid, vitamins B6 and B12 is associated with significant reductions in plasma homocysteine levels (tHcy) up to one year from baseline.

HIGHLIGHTED STUDY

Methods: N=3680 subjects with nondisabling cerebral infarction. All patients received best medical and 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 (200ugm, 6ugm, and 20 ugm respectively).

Results: There was no treatment effect of 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.

HIGHLIGHTED STUDIES

Results: There is limited evidence elevated homocysteine levels (>15umol/L) associated with increased risk of atherosclerotic vascular disease, including stroke, and that levels of folic acid and vitamins B6 and B12 are inversely related to plasma homocysteine levels. There is strong evidence that supplementation with folic acid and vitamins B6 and B12 is associated with significant reductions in plasma homocysteine levels. There is moderate evidence same treatment is associated with reduced risk of stroke in patients with vascular disease but not individuals with previous stroke.

Pharmacology of Secondary Prevention of Stroke

3.7 Anti-Platelet Drugs

Anti-platelet agents retard thrombus formation. These medications are used in ischemic strokes where the origin is not cardioembolic. Antiplatelet medication options include Aspirin, Ticlopidine, Clopidogrel, Dipyridamole Cilostazol, Lotrafiban and Abciximab.

3.7.1 Aspirin (ASA) in Stroke Prevention

ASA is a cyclo-oxygenase inhibitor. Small doses of Aspirin block the formation of thromboxane A2 (a platelet aggregating prostaglandin), which reduces the likelihood for thrombus formation. ASA also inhibits the production of prostacyclin, an anti-aggregating prostaglandin produced in endothelial cells.

- There is strong evidence ASA therapy effectively reduces the risk of recurrent stroke.
- Higher doses not required to achieve therapeutic effect.
- Doses of 75 – 150 mg/day are sufficient to produce the greatest effect with the least risk.
- Acutely, ASA therapy reduces the risk for recurrent ischemic stroke or death by 13%.
- Long-term use, Aspirin reduced the risk for serious vascular events in patients with history of previous TIA or minor stroke by 22%.
- Therapy should be initiated as soon as safe post stroke and maintained over the long-term.

ASA Dose Regimens, Associated Risk Reduction and Proportional Increase in Risk for Major Extracranial Bleed (Baigent et al. 2002)

<table>
<thead>
<tr>
<th>ASA Dose/Day</th>
<th>Risk Reduction</th>
<th>Risk of Major Extracranial Bleed (odds ratio of ASA compared to control; 95% CI)</th>
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<tbody>
<tr>
<td>&lt;75 mg</td>
<td>13%</td>
<td>1.7 (0.8 – 3.3)</td>
</tr>
<tr>
<td>75 – 100 mg</td>
<td>32%</td>
<td>1.5 (1.0 – 2.3)</td>
</tr>
<tr>
<td>160 – 325 mg</td>
<td>26%</td>
<td>1.4 (1.0 – 2.0)</td>
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<tr>
<td>500 – 1500 mg</td>
<td>19%</td>
<td>N/A</td>
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3.7.2 Clopidogrel (Plavix)

Clopidogrel is more expensive than ASA and is generally reserved for ASA failures or contraindications to ASA. Relative risk reduction is 8.7% when compared to ASA (Gent 1996). There is moderate evidence Clopidogrel is similar to ASA with regard to efficacy and safety. Combination of ASA (81 mg) and clopidogrel 75 mg demonstrated the efficacy in reducing the absolute risk of stroke in a Chinese population (CHANCE clinical trial). However, generalization of these findings remains unclear.
HIGHLIGHTED STUDY

Methods: 19,185 patients with atherosclerotic vascular disease randomized to 75 mg Clopidogrel or 325 mg ASA for 1-3 years.
Results: Clopidogrel had 5.32% annual risk of ischemic stroke, myocardial infarct or vascular death vs. 5.83% with ASA. Relative risk reduction of 8.7% in favour of Clopidogrel; no differences in terms of safety.

HIGHLIGHTED STUDY

Methods: 7599 patients with previous ischemic stroke and at least one additional risk factor randomized to clopidogrel 75 mg + ASA 75 mg daily vs. clopidogrel 75 mg daily only. Treatment was continued for 18 months.
Results: There was a small but nonsignificant benefit of combination therapy for combination of stroke, myocardial infarction, vascular death and rehospitalisation for an acute ischemic event. The combination treatment had significantly more bleeding event.

HIGHLIGHTED STUDY

Methods: 15,603 patients with either established cardiovascular disease or multiple risk factors were randomly assigned to receive either 75 mg/day clopidogrel placebo and 75 – 162 mg/day ASA (n=7801) vs. ASA.
Results: 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 event.

3.7.3 Dipyridamole + Aspirin (Aggrenox)

Aggrenox contains two anti-platelet drugs – 25 mg ASA and 200 mg Dipyridamole.

There was moderate evidence that dipyridamole in combination with ASA was more effective than either agent alone in reducing risk for recurrent stroke. The ProFESS study was designed to compare Aggrenox to clopidogrel + ASA however, since clopidogrel + ASA was associated with increased bleeding events, the study was modified to compare Aggrenox to clopidogrel monotherapy.

HIGHLIGHTED STUDY

Methods: 2500 patients with recent history of atherothrombotic cerebrovascular disorders randomized to 75 mg dipyridamole + 330 mg ASA vs. placebo for 2 years.
Results: 38.1% reduction (p<0.001) in strokes in the treatment group.
HIGHLIGHTED STUDY

Methods: 6602 patients with prior TIA or stroke randomized to 50 mg ASA daily, dipyridamole, the 2 agents in combination or placebo x2 years.

Results: Risk of stroke and death was reduced by 18% with ASA alone; 16% with dipyridamole alone and 24% with combination therapy when compared to placebo. Risk of stroke alone reduced by 36% when compared to placebo.

HIGHLIGHTED STUDY

Methods: 2739 patients with stroke or TIA randomized to treatment with ASA 30-325 mg/day (mean 75 mg) vs. same dosage of ASA + 200 mg ER dipyridamole BID. Mean follow-up was 3.5 years.

Results: Primary outcome (composite of vascular death, stroke, myocardial infarction or major bleeding complication) in 173 patients in combination therapy vs. 216 in ASA-alone group. Reduction for ischemic events was not quite significant. More patients withdrew from combination therapy group than ASA-alone group, most due to headaches.

HIGHLIGHTED STUDY

Methods: 20332 patients with stroke were randomized to treatment with 25mg of ASA + 200mg of extended-release dipyridamole twice daily or to receive 75mg of clopidogrel daily. The mean follow-up was 2.5 years.

Results: The primary outcome was first recurrence of stroke, which occurred in 916 patients (9.0%) treated with ASA+dipyridamole, and in 888 patients (8.8%) treated with clopidogrel. The risk of recurrent stroke and the secondary outcome (composite of stroke, death from vascular causes, and myocardial infarction) was similar in both groups (13.1%), suggesting no superiority of one treatment over the other. There were however more hemorrhagic events in patients taking the combination therapy (4.1%) compared to those taking clopidogrel monotherapy (3.6%).

3.8 Anticoagulation in Embolic Stroke

3.8.1 Causes of Embolic Stroke

Atrial Fibrillation (AF)
Atrial fibrillation is the most common cause of embolic stroke and is regarded as a powerful independent risk factor for stroke. AF is responsible for 50% of thromboembolic strokes and 16% of all ischemic strokes. The prevalence of AF increases with age; it effects 6% of the population over 65 years. The risk of recurrent stroke among patients with AF and a stroke/TIA is 12% per year. Screening for all stroke/TIA patients using a 12-lead ECG (to assess cardiac rhythm, identify atrial fibrillation or flutter,
rule out structural heart disease, previous myocardial infarction, left ventricular hypertrophy) is recommended. If the initial ECG is normal does not show atrial fibrillation but a cardioembolic mechanism is suspected, prolonged ECG monitoring is recommended (e.g. 24 or 48 h ECG monitoring) (Evidence Level B)

**Other Cardiac Risks:**
Other cardiac risks include Coronary artery disease, valvular heart disease, heart failure, mural thrombus and infective endocarditis.

**Why Anticoagulate?**
- Secondary risk of embolic stroke recurrence within first 2 weeks is 1% per day.
- Prompt anticoagulation within 48 hours reduces the risk of recurrent embolic stroke from 13% to 5% within the first 2 weeks of stroke onset.
- Must rule out cerebral hemorrhage on CT scan.

**Contraindications to Anticoagulant Therapy**

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<thead>
<tr>
<th>Absolute Contraindications</th>
<th>Relative Contraindications</th>
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<tbody>
<tr>
<td>• Subarachnoid or cerebral hemorrhage</td>
<td>• Severe hypertension</td>
</tr>
<tr>
<td>• Malignant hypertension</td>
<td>• Major recent surgical operation</td>
</tr>
<tr>
<td>• Serious active bleeding</td>
<td>• Recent major trauma</td>
</tr>
<tr>
<td>• Recent brain, eye or spinal cord injury</td>
<td>• Active GI bleeding</td>
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<tr>
<td>• Lack of patient compliance, i.e. monitoring of INR</td>
<td>• Bacterial endocarditis</td>
</tr>
<tr>
<td></td>
<td>• Severe renal or hepatic failure</td>
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<td>• Hemorrhagic diasthesis</td>
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**3.8.2 Warfarin (Coumadin)**

Coumadin inhibits the synthesis of vitamin K-dependent clotting factors (Factors II, VII, IX, X) leading to the synthesis of inactive clotting proteins. Therapeutic anticoagulation requires inactivation of Factor II, which has a half-life of 60 hours, the longest acting of the clotting proteins. The activity of warfarin is monitored by the International Normalized Ratio (INR). Warfarin has a prolonged onset of action. Hence, the results of dosage adjustments may not be seen until 3 to 5 days later. The target level for anticoagulation is an INR of 2.0-3.0. In the elderly > 75 years of age, keep INR < 2.5 because of the risk of intracranial hemorrhage. Side effects of Coumadin include bleeding, skin necrosis, syndrome of painful blue toes, drug and food interactions. Contraindications to Anticoagulation include GI bleeding, active peptic ulcer, frequent falls, alcohol misuse and a history of intracranial bleedings.

**3.8.3 Atrial Fibrillation and Anticoagulation**

Anticoagulation results in a (43-80%) stroke risk reduction with NNT of 12 whereas ASA therapy results in a 21% risk reduction of stroke with NNT of 59. Anticoagulation is more effective than ASA for stroke prevention in atrial fibrillation.

It is recommended one start anticoagulation as soon as it is thought to be safe for the patient. There is moderate evidence that direct oral anticoagulants (DOAC) such as apixaban, dabigatran, rivaroxaban, or edoxaban, should be prescribed in preference over warfarin. There is moderate evidence that for patients with acute ischemic stroke and AF, routine use of bridging with heparin is not recommended.
Physicians should use antiplatelet agents until the patient is anticoagulated to ensure some anti-embolic coverage. For patients on apixaban, dabigatran, rivaroxaban, or edoxaban, adjusted renal dose and annual monitoring of renal function is recommended.

HIGHLIGHTED STUDY

Methods: Pooled data from (SPAF III 1996 & EAFT 1993 clinical trials) with previous history of stroke or TIA.

Results: Annualized stroke rate for patients treated with ASA was 7% and 11% for prior TIA and stroke respectively. Anticoagulation reduced rate of stroke by 56% (p=0.09) and 63% (p<0.001) for previous TIA and stroke respectively.

3.8.4 Dabigatran (Canadian Stroke Guidelines)

Dabigatran is a reversible direct thrombin inhibitor. There is strong evidence that dabigatran is preferred over warfarin for patients with atrial fibrillation who meet the inclusion criteria for the RE-LY trial. A dose of 150 mg twice daily is appropriate for most individuals. A dose of 110 mg twice daily is recommended for patients aged 80 or more years and for patients at risk of bleeding. The long-term safety and effectiveness of dabigatran is currently under investigation.

3.8.5 Rivaroxaban and Apixaban

There are Factor Xa inhibitors and do not require lab monitoring. There is moderate evidence rivaroxaban (20 mg p.o. o.d.) is equally effective to a dose-adjusted warfarin for the prevention of stroke in high risk individuals with atrial fibrillation. Apixaban may be superior to dose-adjusted warfarin for stroke prevention in patients with atrial fibrillation. Both Rivaroxaban and Apixaban are associated with less risk for major bleeding events when compared to warfarin.

3.9 Carotid Stenosis

7-10% of men and 5-7% of women over the age of 65 have more than 50% internal carotid artery stenosis. The rate of ipsilateral stroke in significant carotid artery stenosis is 1-2% annually. Carotid stenosis should be measured by CTA alone or two concordant noninvasive imaging modalities such as MRA and carotid ultrasound or digital subtraction angiography (DSA).

3.9.1 Symptomatic Carotid Stenosis

Patients with TIA or nondisabling stroke and ipsilateral 50% to 99% internal carotid artery stenosis should be evaluated and offered carotid endarterectomy (removing the atherosclerotic plaque) as soon as possible:
- within 48 h of symptom onset if stable
- within 14 days for patients who are not clinically stable within the first 48 hours
There is strong evidence that carotid endarterectomy should be performed by a surgeon with a known perioperative morbidity and mortality of less than 6%. If the patient is not a candidate for endarterectomy, carotid stenting may be considered.

Stenting is done by experienced interventionalists with an expected risk of peri-procedural morbidity and mortality rate of less than 5%. Carotid endarterectomy is more appropriate than carotid stenting for patients over age 70 who are otherwise fit for surgery because stenting carries a higher peri-procedural risk of stroke and death (Evidence Level A).

### 3.9.2 Asymptomatic and remotely symptomatic carotid stenosis

Carotid endarterectomy may be considered for selected patients with 60% to 99% carotid stenosis who are asymptomatic or were remotely symptomatic (> six-months). Stroke patients with asymptomatic carotid stenosis should receive aggressive medical management of risk factors including antiplatelet therapy. There is strong evidence carotid endarterectomy should be performed by a surgeon with a less than 3% risk of perioperative morbidity and mortality. There is strong evidence carotid stenting may be considered in patients who are not operative candidates for technical, anatomic or medical reasons provided there is a less than 3% risk of peri-procedural morbidity and mortality.

### 3.9.3 Intracranial Stenosis

Intracranial stenting is not recommended for treating a recent symptomatic intracranial 70% to 99% stenosis. Medical management of risk factors and dual antiplatelet therapy with ASA 325 mg and Clopidogrel 75 mg, started within 30 days of stroke or TIA and treated for up to 90 days. (SAMMPRIS trial). Intracranial stenting may be reasonable for patients with intracranial stenosis who experience a recurrent stroke despite maximal medical therapy. However, patients should be carefully selected.

**HIGHLIGHTED STUDY**


**Methods:** 2 predetermined strata: 30-69% and 70-99% carotid stenosis randomized to medical or surgical treatment.

**Results:** 70-99% stenosis (n=659) absolute risk reduction of stroke at 2 years was significantly greater in the surgical group. 30-69% stenosis (n=2226) at 5 years divided into two groups: 1) 50-69% stenosis saw a significant reduction in stroke in the surgical group; 2) < 50% stenosis saw no benefit of surgery over medical treatment.

**Table. Results of Carotid Endarterectomy Trials**

<table>
<thead>
<tr>
<th>Clinical</th>
<th>Absolute Risk Reduction</th>
<th>Number Needed to Treat</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic ≥70% stenosis</td>
<td>13.1%</td>
<td>7.6</td>
</tr>
<tr>
<td>Symptomatic 50-69% stenosis</td>
<td>4.9%</td>
<td>20.4</td>
</tr>
<tr>
<td>Asymptomatic ≥ 60% stenosis</td>
<td>1.5%</td>
<td>67</td>
</tr>
<tr>
<td>Asymptomatic &lt; 60% stenosis</td>
<td>0</td>
<td>-</td>
</tr>
</tbody>
</table>
3.10 Sleep Apnea and Stroke

Obstructive sleep apnea (OSA) should be considered a risk factor for stroke and has also been shown to be present in many patients following a stroke (Evidence Level B).

3.10.1 Screening and assessment for sleep apnea

Patients who have experienced a stroke or TIA should be screened for the presence of sleep apnea symptoms using a validated sleep apnea screening tool. Patients with symptoms suggestive of sleep apnea on screening should be referred to a sleep specialist.

3.10.2 Management of OSA in patients with stroke

First line therapies for the treatment of sleep apnea include:

- Avoidance of hypnotic and sedative medications and alcohol (Evidence Level B);
- Positional therapy (Evidence Level B);
- Weight loss (Evidence Level B);
- Continuous positive airway pressure (C-PAP) (Evidence Level B);
- Dental appliances (Evidence level B) in consultation with dental specialists.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Effectiveness</th>
<th>Applicability</th>
</tr>
</thead>
<tbody>
<tr>
<td>tPA</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>ASA</td>
<td>Low</td>
<td>Wide</td>
</tr>
<tr>
<td>Warfarin</td>
<td>High</td>
<td>Moderate</td>
</tr>
<tr>
<td>Endarterectomy</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Treat Risk Factors</td>
<td>Moderate</td>
<td>Wide</td>
</tr>
<tr>
<td>Rehabilitation</td>
<td>High</td>
<td>Wide</td>
</tr>
</tbody>
</table>
References


VITATOPS Trial Study Group. The VITATOPS (Vitamins to Prevent Stroke) trial: Rationale and design of an international, large, simple, randomised trial of homocysteine-lowering multivitamin therapy in patients with recent transient ischaemic attack or stroke. *Cerebrovascular Diseases* 2002; 13(2):120-126.