Treatment Of Stroke Risk Factors

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STROKE

- 795,000 Strokes Occur each year
- 625,000 were ischemic strokes
- By 2025, the annual number is expected to be over 1 million
- 4.4 million Stroke Survivors exist today
STROKE

- Mortality
  - Third leading cause of death
  - Direct costs were 68.9 billion in 2009
  - Leading cause of disability
    - 26% need assistance daily
    - 30% need assistance walking
    - 26% require long term care placement
STROKE

- Race/Sex/Geography
  - Black risk of death is 1.49X Whites
  - Males greater risk than men
  - Hispanics higher risk for lacunar infarcts
  - Southeastern US has higher risk
- Age
  - Stroke occurs in all ages
  - Stroke increases with age
  - Age >64 is where 75% of occurrence
STROKE RISK FACTORS

- Non-modifiable Risk Factors
  + Age
  + Race
  + Sex
  + Ethnicity
  + History of Migraine
  + Sickle Cell Disease
  + Fibromuscular Dysplasia
  + Heredity
STROKE RISK FACTORS

- **Modifiable Risk Factors**
  - Hypertension*
  - Diabetes Mellitus
  - Cardiac Diseases
    - Atrial Fibrillation
    - Valvular Disease
    - R→L Shunting (PFO, Atrial and Ventricular Enlargement)
  - Hypercholesterolemia
  - Transient Ischemic Attacks
  - Carotid Stenosis
  - Hyperhomocystinemia
  - Lifestyles
    - Alcohol
    - Tobacco
    - Illicit Drug Use
    - Obesity
    - Physical Inactivity
STROKE RISK FACTORS

- Laboratory Monitoring Risk
  - Glucose and Electrolytes
  - CBC with Platelets
  - Prothrombin Time/ Partial Thromboplastin Time
  - Cholesterol/LDL/HDL
  - ANA/RF/Homocysteine/ESR
  - Protein C/ Protein S/ Antithrombin III/ Leiden
  - Anticardiolipin Antibody
  - Lupus Inhibitor/ Antiphospholipid Antibodies
PRIMARY PREVENTION

- Content
  + Management of vascular risk factors
  + Antithrombotic therapy
  + Carotid surgery and angioplasty
VASCULAR RISK FACTORS

- Conditions and lifestyle characteristics identified as a risk factors for stroke

  - High blood pressure
  - Atrial fibrillation
  - Diabetes mellitus
  - Carotid artery disease
  - Myocardial infarction
  - High Cholesterol
  - Hyper-homocysteinemia
  - Smoking
  - Heavy alcohol use
  - Physical inactivity
  - Obesity
Background
- High blood pressure (>120/80mmHg) is the most important and prevalent modifiable risk factor for stroke
- Significant reduction of stroke incidence with a decrease in BP\(^1\)
- No class of antihypertensive is clearly superior
  - LIFE: lorsatan is superior to atenolol\(^2\)
  - ALLHAT: chlorthalidone is more effective than amlodipine and lisinopril\(^3\)

DIABETES MELLITUS

Background

- Independent risk factor for ischemic stroke
- Improving glucose control may not reduce stroke
- BP in patients with diabetes should be <130/80mmHg
- Statin treatment reduces the risk of major vascular events, including stroke
- Elevated blood glucose in the early phase of stroke is associated with death and poor recovery

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\[ \text{HIGH CHOLESTEROL} \]

- **Background**
  - Statin treatment reduces the incidence of stroke from 3.4% to 2.7%\(^1\)
  - No significant effect for prevention of fatal stroke\(^1\)
  - Heart Protection Study found an excess of myopathy of one per 10,000 patients per annum\(^2\)
  - No data support statin treatment in patients with LDL-cholesterol <150 mg/dl (3.9 mmol/l)

Background

- Independent risk factor for ischemic stroke in men and women
- 2-3 fold increased risk compared to non-smokers\(^1\)
- Spousal cigarette smoking may be associated with an increased stroke risk\(^2\)
- 50% risk reduction by 2 years after stopping smoking\(^3\)

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ALCOHOL CONSUMPTION

- Background
  - Increased risk for both ischemic (RR 1.69) and hemorrhagic stroke (RR 2.18) with heavy alcohol consumption (>60g/day)\(^1\)
  - BP elevation might be a reasonable explanation\(^3\)
  - Light alcohol consumption (<12g/day) associated with reduced ischemic (RR 0.80) and hemorrhagic stroke\(^1\)
  - Red wine consumption carries the lowest risk\(^2\)

Background

- Regular exercise (at least 3x30min/week) is associated with a decreased risk of stroke.
- Physically active individuals have a lower risk of stroke or death than those with low activity (RR 0.73)\(^1\).
- This is mediated, in part, through beneficial effects on body weight, blood pressure, serum cholesterol, and glucose tolerance\(^2\).

Background

- High body mass index (BMI ≥25) increases risk of stroke in men and women\(^1\)
- Abdominal adiposity is a risk factor for stroke in men but not women\(^2\)
- A randomized trial in women found no effect of dietary interventions to reduce the incidence of stroke\(^3\)
- Tocopherol and beta carotene supplementation do not reduce the risk of stroke. Vitamin E might increase mortality when used at high-dose (≥400 IU/d)

HORMONE REPLACEMENT THERAPY

- **Background**
  - Stroke rates rise rapidly in women after the menopause
  - Hormone replacement therapy in postmenopausal women is associated with an 44% increased risk of stroke

1: Gabriel S et al.: Cochrane Review (2005) CD002229
Blood pressure should be checked regularly. High blood pressure should be managed with lifestyle modification and individualized pharmacological therapy (Class I, Level A) aiming at normal levels of 120/80 mmHg (Class IV, GCP).
# RISK FACTOR MANAGEMENT

## Recommendations (2/4)

- Blood glucose should be checked regularly. Diabetes should be managed with lifestyle modification and individualized pharmacological therapy *(Class IV, Level C)*.

- In diabetic patients, high blood pressure should be managed intensively *(Class I, Level A)* aiming for levels below 130/80 mmHg *(Class IV, Level C)*. Where possible, treatment should include an angiotensin converting enzyme inhibitor or angiotensin receptor antagonist *(Class I, Level A)*.
RISK FACTOR MANAGEMENT

Recommendations (3/4)

- Blood cholesterol should be checked regularly. High blood cholesterol (e.g. LDL>150mg/dl [3,9mMol/l]) should be managed with lifestyle modification (Class IV, Level C) and a statin (Class I, Level A)
- Cigarette smoking should be discouraged (Class III, Level B)
- Heavy use of alcohol should be discouraged (Class III, Level B)
- Regular physical activity is recommended (Class III, Level B)
## RISK FACTOR MANAGEMENT

### Recommendations (4/4)

- A diet low in salt and saturated fat, high in fruit and vegetables and rich in fibre is recommended *(Class III, Level B)*
- Subjects with an elevated body mass index are recommended to take a weight-reducing diet *(Class III, Level B)*
- Antioxidant vitamin supplements are not recommended *(Class I, Level A)*
- Hormone replacement therapy is not recommended for the primary prevention of stroke *(Class I, Level A)*
ANTITHROMBOTIC THERAPY

- Background
  - In low risk persons low dose aspirin reduced coronary events, but not stroke\(^1\)
  - In women over 45 years aspirin reduces the risk of ischemic stroke (OR 0.76; 95%CI 0.63-0.93) \(^2\)
  - Aspirin reduces MI in patients with asymptomatic carotid artery disease\(^3\)

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ATRIAL FIBRILLATION (AF)

- Background
  - Average stroke rate of 5% per year
  - Aspirin reduces stroke (RR 0.78) in patients with non-valvular AF\(^1\)
  - Warfarin (INR 2.0-3.0) is more effective than aspirin at reducing stroke (RR 0.36; 95%CI 0.26-0.51)\(^1\)
  - Combination of aspirin and clopidogrel is less effective than warfarin and has a similar bleeding rate\(^2\)

Background

- Anticoagulation with an INR below 2.0 is not effective.
- Increased risk for bleeding complications with an INR > 3.5.
- Patients <65 years of age with “lone AF” (without other risk factors) are at low risk, whereas patients older than 65 years are at a higher risk for embolic stroke.
- Anticoagulation can be safe and effective in older individuals\(^1, 2\)

### Recommendations (1/4)

- Low-dose aspirin is recommended in women aged 45 years or more who are not at increased risk for intracerebral hemorrhage and who have good gastro-intestinal tolerance; however, its effect is very small (Class I, Level A)

- Low-dose aspirin may be considered in men for the primary prevention of myocardial infarction; however, it does not reduce the risk of ischemic stroke (Class I, Level A)
### ANTITHROMBOTIC THERAPY

#### Recommendations (2/4)

- Antiplatelet agents other than aspirin are not recommended for primary stroke prevention **(Class IV, GCP)**

- Aspirin may be recommended for patients with non-valvular AF who are younger than 65 years and free of vascular risk factors **(Class I, Level A)**

- Unless contraindicated, either aspirin or an oral anticoagulant (international normalized ratio [INR] 2.0-3.0) is recommended for patients with non-valvular AF who are aged 65-75 years and free of vascular risk factors **(Class I, Level A)**
Antithrombotic Therapy

Recommendations (3/4)

- Unless contraindicated, an oral anticoagulant (INR 2.0–3.0) is recommended for patients with non-valvular AF who are aged >75, or who are younger but have risk factors such as high blood pressure, left ventricular dysfunction, or diabetes mellitus (Class I, Level A)
Patients with AF who are unable to receive oral anticoagulants should be offered aspirin (Class I, Level A).

Patients with AF who have mechanical prosthetic heart valves should receive long-term anticoagulation with a target INR based on the prosthesis type, but not less than INR 2–3 (Class II, Level B).

Low dose aspirin is recommended for patients with asymptomatic internal carotid artery (ICA) stenosis >50% to reduce their risk of vascular events (Class II, Level B).
ASYMPTOMATIC CAROTID ARTERY (ICA) STENOSIS

Background\(^1,2\)

- Carotid endarterectomy (CEA) is still a matter of controversy in asymptomatic individuals
  - RRR for stenosis >60\(^{\text{\%}}\)\(^{\text{NASCET}}\) is 38-53\(^{\%}\)
  - ARR is 5.9-12.6\(^{\%}\)
  - NNT to avoid one stroke/year is 63-166
- The combined surgical risk must not exceed 3\(^{\%}\)

ASYMPTOMATIC CAROTID ARTERY (ICA) STENOSIS

- Specific issues
  + No prospective trials tested the benefit of antiplatelet drugs in patients with asymptomatic carotid stenosis
  + The ipsilateral stroke risk increases with the degree of the stenosis
  + Patients with an occlusion of the contralateral ICA do not benefit from endarterectomy
  + Women have lower benefit from CEA than men
  + Aspirin reduces stroke risk during and after CEA

1: Chambers BR et al.: Cochrane Review (2005)
CAROTID SURGERY AND ANGIOPLASTY

Recommendations

- Carotid surgery is not recommended for asymptomatic individuals with significant carotid stenosis (NASCET 60-99%), except in those at high risk of stroke (Class I, Level C)
- Carotid angioplasty, with or without stenting, is not recommended for patients with asymptomatic carotid stenosis (Class IV, GCP)
- Patients should take aspirin before and after CEA (Class I, Level A)
SECONDARY PREVENTION

Content
- Management of vascular risk factors
- Antithrombotic therapy
- Surgery and angioplasty
Background

- Antihypertensive drugs reduce stroke recurrence risk after stroke or TIA (RR 0.76; 95%CI 0.63-0.92)\(^1\)
- Target BP level and reduction should be individualized
- The reduction in stroke occurs regardless of baseline BP and type of stroke\(^2\)

Background

- In people with type 2 diabetes with previous stroke pioglitazone reduces fatal or nonfatal stroke (HR 0.53; 95% CI 0.34-0.85; P=0.0085)\(^1\)

- In addition there is a trend to reduce the combined end point of death and major vascular events (HR 0.78; 95% CI 0.60-1.02; P=0.067)\(^1\)

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HIGH CHOLESTEROL

- Background
  - Atorvastatin (80mg) reduces stroke recurrence by 16%\(^1\)
  - Simvastatin (40mg) reduces risk of vascular events in patients with prior stroke, and of stroke in patients with other vascular disease (RR 0.76)\(^2\)
  - ARR for statin treatment is low (NNT 112-143 for 1 year)\(^1\)
  - Statin withdrawal at the acute stage of stroke may be harmful\(^3\)

VITAMINS

- **Background**
  - Beta carotene increased the risk (RR 1.10) of cardiovascular death\(^1\)
  - Antioxidant supplements may increase mortality\(^2\)
  - Folate, B12, B6 vitamins given to lower homocysteine levels may not reduce stroke recurrence and may increase vascular events\(^3\)

**HORMONE REPLACEMENT THERAPY**

- **Background**
  - Estrogen therapy is not effective in secondary prevention after TIA or stroke and may increase stroke severity

Sleep-disordered breathing (SDB) is both a risk factor and a consequence of stroke. More than 50% of stroke patients have SDB, mostly in the form of obstructive sleep apnoea (OSA). SDB is linked with poorer long-term outcome and increased long-term stroke mortality\(^1\). Continuous positive airway pressure is the treatment of choice for OSA.

### Recommendations (1/3)

- Blood pressure should be checked regularly. Blood pressure lowering is recommended after the acute phase, including in patients with normal blood pressure *(Class I, Level A)*
- Blood glucose should be checked regularly. Diabetes should be managed with lifestyle modification and individualized pharmacological therapy *(Class IV, GCP)*
- In patients with type 2 diabetes who do not need insulin, treatment with pioglitazone is recommended after stroke *(Class III, Level B)*
## Recommendations (2/3)

- Statin therapy is recommended *(Class I, Level A)*
- Cigarette smoking should be stopped *(Class III, Level C)*
- Heavy use of alcohol should be discouraged *(Class IV, GCP)*
- Regular physical activity is recommended *(Class IV, GCP)*
- A diet low in salt and saturated fat, high in fruit and vegetables, and rich in fibre is recommended *(Class IV, GCP)*
### Recommendations (3/3)

- Subjects with an elevated body mass index are recommended to take a weight-reducing diet (**Class IV, Level C**)
- Antioxidant vitamins supplements are not recommended (**Class I, Level A**)
- Hormone replacement therapy is not recommended for the secondary prevention of stroke (**Class I, Level A**)
- Sleep-disordered breathing such as obstructive sleep apnoea is recommended to be treated with continuous positive airway pressure breathing (**Class III, Level GCP**)
ANTITHROMBOTIC THERAPY

- Background: Aspirin
  + 13% relative risk reduction for stroke after TIA or stroke\(^1\)
  + Most widely studied dosages of aspirin are 50-150mg
  + The incidence of GI-disturbances with aspirin is dose dependent
  + No difference in effectiveness amongst low (<160mg), medium (160 – 325mg) or high (500 - 1500mg) dose aspirin

ANTITHROMBOTIC THERAPY

- Background: Dipyridamole plus aspirin
  - Relative risk reduction of vascular death, stroke or myocardial infarction with the combination is significantly greater (RR 0.82; 95%CI 0.71-0.91) than with aspirin alone\(^1,2\)
  - ARR 1.0% per year (NNT 100)\(^2\)
  - Incidence of dipyridamole induced headache may be reduced by increasing the dose gradually\(^3\)

ANTITHROMBOTIC THERAPY

Dipyridamole plus aspirin versus aspirin: Meta-analysis

Reduced vascular endpoint (vascular death, stroke, myocardial infarction) with dipyridamole plus aspirin

Background: Clopidogrel:

- Clopidogrel is slightly but significantly more effective than medium-dose aspirin (RRR 8.7%, ARR 0.5%) in preventing vascular events in patients with previous stroke, MI or PAD.

ANTITHROMBOTIC THERAPY

- Background: Clopidogrel plus aspirin
  - Compared with clopidogrel the combination of aspirin and clopidogrel does not reduce the risk of ischemic stroke, myocardial infarction, vascular death, or re-hospitalization\(^1\)
  - Compared with aspirin alone the combination does not reduce the risk of myocardial infarction, stroke, or cardiovascular death\(^2\)
  - Risk of life-threatening or major bleeding is increased\(^1,2\)

# ANTITHROMBOTIC THERAPY

## Recommendations (1/4)

- Patients should receive antithrombotic therapy *(Class I, Level A)*
- Patients not requiring anticoagulation should receive antiplatelet therapy *(Class I, Level A)*. Where possible, combined aspirin and dipyridamole, or clopidogrel alone, should be given. Alternatively, aspirin alone, or triflusal alone, may be used *(Class I, Level A)*
<table>
<thead>
<tr>
<th>Recommendations (2/4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• The combination of aspirin and clopidogrel is not recommended in patients with recent ischemic stroke, except in patients with specific indications (e.g. unstable angina or non-Q-wave MI during the last 12 months, or recent stenting); treatment should be given for up to 9 months after the event (Class I, Level A)</td>
</tr>
<tr>
<td>• Patients who have a stroke on antiplatelet therapy should be re-evaluated for pathophysiology and risk factors (Class IV, GCP)</td>
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ANTICOAGULATION

Background

- Oral antiocoagulation (target INR 2.0 – 3.0) reduces the risk of recurrent stroke in patients with AF\(^1\)
- Oral anticoagulation is well established for other causes of embolism such as mechanical prosthetic valve replacement, rheumatic valvular heart disease, ventricular aneurysm and cardiomyopathy
- There is no indication for oral anticoagulation in patients with non-cardiac cause of ischemic stroke\(^2\)

ANTICOAGULATION

Specific issues

- In patients with AF and stable coronary disease, aspirin should not be added to oral anticoagulation\(^1\).
- Some retrospective studies suggest that anticoagulation may be beneficial in aortic atheroma\(^2\), fusiform basilar artery aneurysms\(^3\), or arterial dissection\(^4\).
- It is unclear if patients with patent foramen ovale (PFO) benefit from oral anticoagulation\(^5\).

Recommendations (3/4)

- Anticoagulation should not be used after non-cardio-embolic ischemic stroke, except in some specific situations, such as aortic atheromas, fusiform aneurysms of the basilar artery, cervical artery dissection, or patent foramen ovale in the presence of proven deep vein thrombosis (DVT) or atrial septal aneurysm (Class IV, GCP)

- If oral anticoagulation is contraindicated, combined low dose aspirin and dipyridamole should be given (Class IV, GCP)
Recommendations (4/4)

- Oral anticoagulation (INR 2.0–3.0) is recommended after ischemic stroke associated with AF *(Class I, Level A)*. Oral anticoagulation is not recommended in patients with co-morbid conditions such as falls, poor compliance, uncontrolled epilepsy, or gastrointestinal bleeding *(Class III, Level C)*. Increasing age alone is not a contraindication to oral anticoagulation *(Class I, Level A)*.

- Patients with cardioembolic stroke unrelated to AF should receive anticoagulants (INR 2.0-3.0) if the risk of recurrence is high *(Class III, Level C)*.
Background\textsuperscript{1,2}

- CEA reduces the risk by 48\% of recurrent disabling stroke or death in patients with 70-99\%\textsuperscript{NASCET} ipsilateral carotid artery stenosis.
- If perioperative complications exceed 6\%, the benefit of CEA will diminish; if it approaches 10\%, the benefit will vanish entirely.
- There is also some risk reduction in male patients with 50 - 69\% stenosis of the ipsilateral carotid artery, provided that the complication rate is below 3\%.

Specific issues

+ CEA should be performed as soon as possible (ideally within 2 weeks) after the last cerebrovascular event\(^1,2\)
+ Elderly patients (>75 years) without organ failure or serious cardiac dysfunction benefit from CEA\(^1\)
+ Women with symptomatic stenosis >70% should undergo CEA. Women with moderate stenosis should be treated medically\(^2\)

Specific issues

- The benefit from CEA is lower with lacunar stroke
- Patients with leuko-araiosis should be made aware of the increased operative risk
- Occlusion of the contralateral ICA carries a higher perioperative risk
- Continuation of aspirin is required until surgery, but heparin may be used in very severe stenosis
- All grading of stenoses should be according to NASCET-criteria
TREATMENT OF STROKE RISK FACTORS

- **Hypertension**
  - Ideal 120/80 certainly < 140/90 and <130/80 Diabetics

- **Hypercholesterolemia**
  - LDL < 100
  - HMG CoA Inhibitors/Statins

- **Diabetes Mellitus**
  - Glucose < 126
  - HBA1C < 7.0

- **Atrial Fibrillation**
  - Warfarin Therapy INR 2.0-3.0

- **TIA**
  - Antiplatelets – ASA, Aggrenox, Plavix

- **Lifestyle Modifications**
  - Alcohol: < 2 drinks a day
  - Exercise: 30 minutes 3X a week
  - Tobacco/Drugs: Cease Tobacco and Illicit drugs
  - Obesity: Ideal 18-24 BMI; Waist <40 Men and <35 Women
  - Nutrition: 5 servings fruits and/or vegetables a day

- **Carotid Stenosis**
  - Evaluation of asymptomatic carotid stenosis between 60-99% for surgery

- **Hypercoagulable States**
  - Condition specific anticoagulation with warfarin
  - Minimizing Hormone Replacement Therapy/Oral Contraceptives only after risk assessment done

- **Hyperhomocysteinemia**
  - Folic Acid in combination with Vitamin B6 and B12 showed no decrease in stroke reduction