

INTRODUCTION

Problem: reduce risk factors to prevent average 9 strokes in each family physician's practice
Objectives: 1. **Primary Prevention:** A. reduce risk factors to prevent the average prevalence of nine new strokes in each family physician's practice; B. detect patent foramen ovale (25% of population) by echocardiogram, assessing stroke risk and refer cardiology assessment for device to close foramen and stop shunt; 2. **Secondary Prevention of further strokes**
Design: Literature Review

RESULTS: Primary Prevention

- **PRIMARY PREVENTION: Context**
- Stroke is third leading cause of death in Canada
- Annually 62,000 strokes and TIAs in Canadian emergency departments or acute inpatient care
- 400,000 Canadians live with effects of a stroke (=average 9 in practices of 44,589 family physicians)
- For each symptomatic stroke, estimated 9 covert strokes resulting in subtle changes in cognitive function and processes

89% of population-attributable risk factors are modifiable: Stroke odds in INTERSTROKE study Risk factor	Increase in risk
Hypertension	2.5
heavy alcohol use	2
Smoking	> 1.5 times
Other risks: dyslipidemia, diabetes, BMI >23, diets low fruits/vegetables, high sodium, low physical activity levels	

PRIMARY PREVENTION: Should aspirin be prescribed?	
Aspirin: Low dose aspirin not recommended for primary prevention of a first vascular event for these individuals:	Evidence Level
with vascular risk factors who have not had a vascular event	A
healthy older individuals without vascular risk factors	B
uncertain net benefit with asymptomatic atherosclerosis	B

Evidence Level A = Evidence from a meta-analysis of randomized controlled trials or consistent findings from two or more randomized controlled trials. Desirable effects clearly outweigh undesirable effects or vice versa

The evidence for and against ASPIRIN is from three (2018) RCTs in individuals with no previous cardiovascular disease; median follow-up 4.7 to 7.1 years

RCT	Hazard ratio and 95% CI cardiovascular events	Hazard ratio and 95% CI major bleeding
ARRIVE (2018) men ≥ 55 years with 2 to 4 cardiovascular risk factors and women ≥ 60 years with 3 or more risk factors, excluded diabetics	0.96 (0.81 to 1.13)	any GI bleed 2.11 (1.36 to 3.28)
ASPREE (2018) men and women ≥65 or ≥70 years (11% diabetics)	0.95 (0.83 to 1.08)	1.38 (1.18 to 1.62)
ASCEND men and women ≥40 years with type 1 or 2 diabetes	0.88 (0.79 to 0.97; p=0.01)	1.29 (1.09 to 1.52)

- N.B.: Two organizations have cautious recommendations for use:
- 2019 ACC/AHA guidelines on primary prevention of cardiovascular disease suggest low-dose ASA (75-100 mg/day) might be considered among selected adults 40-70 years at higher risk of cardiovascular disease; avoid in >70 years
 - U.S. Preventive Services Task Force suggests 50 to 59 years of age initiate low-dose ASA if 10-year cardiovascular risk is >10% and risk of bleeding not increased. Insufficient evidence for < 50 or > 69 years

PRIMARY PREVENTION: Detecting Patent Foramen Ovale

- Patent foramen ovale (PFO) occurs in 25% of the population
- Cardiologists have published multiple systematic reviews on PFO. There is no concerted national detection strategy
- Thus family physicians need to be the first to identify PFOs, auscultate for interatrial shunt murmur, order echocardiogram with counting of bubbles passing across the inter-atrial shunt, refer to cardiology for potential placement of device to close foramen
- Risk of PFO for patient if siblings have shunt = RR 6.98 (95%CI 5.75 to 8.48)
- If 1st degree relatives = RR 5.64 (95%CI 4.76 to 6.68)

OUTCOMES OF SHUNT PLACEMENT

Systematic review and network analysis (Mir BMJ 2018): 10 RCTs (n=4416, average age ranged 44.2-63.6, so advice is for patients <60)

Risk	Risk with PFO closure + antiplatelet therapy per 1000 patient-years	Risk with only antiplatelet therapy per 1000 patient-years
ischemic stroke	13/1000	100/1000
TIAs	28/1000	34/1000
adverse events	36 /1000	
adverse events:	17/1000 (mostly in 1 st month after device placement)	5/1000
atrial fibrillation		

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METHODS

SEARCH: Medline and Embase to 5 February 2021: search terms stroke, TIA, prevention, therapy, systematic review, meta-analysis

RESULTS: Secondary Prevention

SECONDARY PREVENTION: Canadian Stroke Best Practice Recommendations For Secondary Prevention of Stroke (2017)	
1. React promptly to a TIA	Risk of stroke is highest next 2 days; then in next 90 days 12%-20%; over five years 5 times greater
2. Treat risk factors: systematic review of 147 RCTs	
if Bp decrease 10 mm Hg systolic and 5 mm Hg diastolic	41% reduced stroke risk
Treating to new targets (TNT) trial: statins for LDL	15% reduced stroke risk
Rapid access to TIA/stroke clinics	reduces risks

Secondary Prevention of Stroke	
Risk factor and investigations	Evidence level
12 lead ECG to detect atrial fibrillation/flutter in suspected ischemic stroke or TIA	B
24 hour ECG monitoring to detect paroxysmal AF in suspected ischemic stroke or TIA	A
At least 2 weeks ECG monitoring if acute embolic ischemic stroke or TIA undetermined source and cardioembolic mechanism suspected	A
If ischemic stroke or symptomatic TIA and 50-99% carotid stenosis, MRI (better than CTA); urgent revascularization if 70-99% stenosis;	A

SECONDARY PREVENTION: How large are the effects in RCTs and systematic reviews?		
Systematic review	Number of RCTs and participants	Outcome; Relative Risk; GRADE evidence assessment
Abdelhamid 2020; Omega-3 fatty acids (Cochrane review)	86 RCTs (n=162,796); RCTs 12-88 months duration; mainly high income countries; dose ranged 0.5 to > 5 g/day	Stroke: RR 1.02 (0.94 to 1.12) moderate certainty evidence; All-cause mortality RR = 0.97 (0.93 to 1.01), high certainty evidence Stroke: RR ranged from 0.64 (0.48 to 0.88) to 0.90 (0.87 to 0.93)
Saule 2019; Mediterranean diet Jacob 2016; Fibrates (Cochrane Review)	6 meta-analyses of high adherence to Mediterranean diet 6 RCTs (n=16,135); 4 trials included only DM2; average duration treatment 4.8 years	Cardiovascular death, non-fatal MI, or non-fatal stroke: RR = 0.84 (0.74 to 0.96); moderate quality evidence; detection bias, attrition and reporting bias unclear
Schandelmaier 2017; Niacin (Cochrane Review)	23 RCTs (n=39,195); median % prior MI = 48%; average treatment duration 11 months	Strokes: RR = 0.95 (0.74 to 1.22), low quality evidence; Mortality: RR 1.05 (0.97 to 1.12), high quality evidence. Cardiovascular mortality: RR = 1.02 (0.93 to 1.12), moderate quality evidence
Karmali 2018; BP lowering strategies based on predicted cardiovascular risk assessment compared to systolic Bp (Blood Pressure Lowering Treatment Trialists Collaboration)	11 RCTs (n=47,872) median 4 years follow up	Number of cardiovascular events (measured by Area Under the Curve [AUC]); CVD risk + BP strategy avoids more cardiovascular events AUC = 0.71 (0.70 to 0.72) than Bp only strategy, AUC = 0.54 (0.53 to 0.55) and prevents 16% (14% to 18%) more CVD events
Naqvi 2020 single vs. multiple antiplatelet agents (Cochrane review)	15 RCTs (n=17,091) participants	Risk of stroke recurrence: multiple antiplatelet agents 5.78% vs. single platelet agent 7.84%; RR = 0.73 (0.66 to 0.82; P < 0.001), moderate-certainty evidence. Multiple platelet agents higher risk of intracranial hemorrhage 0.42% versus 0.21%, RR = 1.92 (1.05 to 3.50; P = 0.03), low-certainty evidence); higher risk extracranial hemorrhage 6.38% versus 2.81%, RR = 2.25 (1.88 to 2.70; P < 0.001), high-certainty evidence

CONCLUSIONS:

1. Family physicians have main role in reducing stroke risks and are key first contact to identify/treat interatrial shunts
2. Primary and secondary prevention. Reduce these risks: BP, heavy alcohol use, smoking, dyslipidemia, diabetes, BMI >23, diets low fruits/vegetables, high sodium, low physical activity levels.
3. 25% of population have PFO. Listen for murmurs, refer echocardiogram for bubble test for PFO.
4. Implement Canadian Stroke Best Practice Recommendations as above and on their excellent website for your specific patient.

Naqvi IA, Kamal AK, Rehman H. Multiple versus fewer antiplatelet agents for preventing early recurrence after ischaemic stroke or transient ischaemic attack. Cochrane Database of Systematic Reviews. 8:CD009716, 2020

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