CANADIAN STROKE BEST PRACTICE RECOMMENDATIONS

Recommendations
for the use of acetylsalicylic acid (ASA)
for prevention of vascular events

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CANADIAN STROKE BEST PRACTICE RECOMMENDATIONS
Seventh Edition

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INTRODUCTION AND OVERVIEW

The Canadian Stroke Best Practice Recommendations (CSBPR) are intended to provide up-to-date evidence-based guidelines for the prevention and management of conditions championed by the Heart and Stroke Foundation (including stroke, transient ischemic attack and vascular cognitive impairment, and considerations of related issues for people with these and heart conditions) and to promote optimal recovery and reintegration for people who have experienced or been affected by any of these conditions (patients, families and informal caregivers). Recommendations on the use of *a*cetylsalicylic acid *(ASA) for prevention of vascular events* are a new addition to the group of recommendations included in the CSBPR portfolio. **These recommendations are unique in that they do not focus just on stroke; rather, they are applicable to the prevention of a range of conditions including cardiovascular disease, cerebrovascular disease, vascular cognitive impairment, and peripheral arterial disease** (PAD). This module was developed in response to compelling emerging evidence on the use of ASA for primary prevention, and an updated evaluation of the balance of risks and benefits of using ASA prophylactically for cardiovascular risk reduction. These recommendations have been developed in response to a need for guidance by healthcare professionals and the public following the publication of several recent research papers on this topic. Public information addressing this topic will also be updated based on the findings of this rigorous guideline development process.

Several organizations have been engaged with the development of these recommendations. This engagement promotes a single consistent message to health professionals and the public on this topic. The goal of developing, disseminating and implementing these recommendations is to optimize evidence-based care across Canada, reduce practice variations, and narrow the gap between current knowledge and clinical practice.

The theme of the Seventh Edition of the CSBPR is ***Building connections to optimize individual outcomes***. The collaboration between several organizations in the development of these recommendations on the use of ASA for prevention of vascular events is an excellent example of building these connections. This collaboration strengthens the credibility and uptake of these recommendations by providing a consistent message across all represented disease groups. Members of the writing group for these recommendations, who are specialists in heart conditions, stroke and vascular cognitive impairment, report receiving many calls by their community-based colleagues to advise on the use of ASA in primary prevention.

The Seventh Edition of the CSBPR includes a broader wholistic focus that takes into consideration the heart-brain connection and issues of multimorbidity and increasing complexity of people who experience stroke, heart conditions and vascular cognitive impairment. This collaboration and these recommendations on ASA provide a further demonstration of the heart-brain connection, a priority theme in which Heart & Stroke has launched a multipronged approach to build awareness and integration in research, systems planning and change, and care delivery. In addition, within the Seventh edition, a more purposeful review of sex and gender representation in the seminal clinical trials upon which the recommendations are based has been undertaken to determine the extent to which available evidence has included both male and female subjects in sufficient proportions to be able to detect outcomes and generalize to a broader population. These findings are presented in the discussion sections of the module and integrated into the actual recommendations where appropriate to do so.

Profile of Heart Conditions, Stroke and Vascular Cognitive Impairment in Canada

- Stroke is known to be a highly preventable disease, with all risk factors combined accounting for 88.8% of the global stroke burden (Feigin, 2017).
- The INTERHEART study (Yusuf, Lancet 2004) reported that smoking, raised ApoB/ApoA1 ratio, history of hypertension, diabetes, abdominal obesity, psychosocial factors, daily consumption of fruits and vegetables, regular alcohol consumption, and regular physical activity, were all significantly related to acute myocardial infarction ($p<0{\cdot}0001$ for all risk factors and $p=0{\cdot}03$ for alcohol). Collectively, these nine risk factors accounted for 90% of the PAR for myocardial infarction in men and 94% in women
- According to a poll commissioned by Heart & Stroke, less than half of Canadians were very aware of their specific risk factors. The most recognized risk is poor diet at 41%, followed by smoking at 28% and lack of exercise at 27%. Only 10% of Canadians recognize high blood pressure as a risk, even though it is one of the most significant risk factors for these conditions.
- In 2016, there were 270,204 hospitalizations for heart conditions, stroke and vascular cognitive impairment (excluding Quebec), including 107,391 females and 162,813 males.
- One person dies in Canada every five minutes from heart conditions, stroke or vascular cognitive impairment. This outpaces other disease: 13% more people die of heart conditions, stroke or vascular cognitive impairment related conditions than die from all cancers combined.
- 91,524 people in Canada died of heart conditions, stroke or vascular cognitive impairment in 2016. This equates to one out of every three deaths (Heart &Stroke analysis of CIHI data, 2018, https://www.heartandstroke.ca/articles/the-disconnected-story).
- 40% of people admitted to hospital with a heart condition, stroke or vascular cognitive impairment will be readmitted at least once more for another heart condition, stroke or vascular cognitive impairment.
- Every year, approximately 62,000 people with stroke and transient ischemic attack are treated in Canadian hospitals in emergency departments and or acute inpatient care. Moreover, it is estimated that for each symptomatic stroke, there are approximately nine covert strokes that result in subtle changes in cognitive function and processes.
- In 2016, 199,612 admissions to hospital for coronary artery and vascular disease (Heart & Stroke analysis of CIHI data, 2018, https://www.heartandstroke.ca/articles/the-disconnected-story)
- Stroke is the third leading cause of death in Canada and the second leading cause of death globally (CANSIM Table 2014, GBD 2017) and a leading cause of adult disability, with over 400,000 people in Canada living with the effects of stroke. (Krueger 2015)
- Cardiovascular disease alone is the most costly disease in Canada, totaling $21.2 billion in direct (medical) and indirect (lost earnings) costs. Stroke costs the Canadian economy $3.6 billion a year in physician services, hospital costs, lost wages and decreased productivity. In addition, the combined direct and indirect costs of dementia total $33 billion a year. If nothing changes, this number will climb to $293 billion a year by 2040. (Krueger 2012).
- The human cost of stroke on families and communities is immeasurable.

Guideline Development Methodology

The *CSBPR* present high-quality, evidence-based stroke care guidelines in a standardized framework to support healthcare professionals across all disciplines. Implementation of these recommendations is expected to reduce practice variations and close the gaps between evidence and practice.

The recommendations are targeted to health professionals throughout the health system who care for those affected by stroke. Health system policy makers, planners, funders, senior managers, and administrators who are responsible for the coordination and delivery of stroke services within a province or region will also find this document relevant and applicable to their work.

The methodology for updating the recommendations includes 13 distinct steps to ensure a thorough and rigorous process. These include the following (details available online):

1. Establish an expert interdisciplinary writing group for the module. (Appendix 1)
2. Develop a community consultation and review panel consisting of people with stroke, their families, and caregivers. (Listed in Acknowledgements)
3. Systematic search, appraisal and update of research literature and external reference guideline recommendations up to November 2019 and preparation of evidence summary tables.
4. Writing group review and revision of existing recommendations, and development of new recommendations as required, final internal review of full module.
5. Submission of proposed module update to the Canadian Stroke Best Practice and Quality Advisory Committee for internal review of proposed module update. Feedback to writing group, completion of edits.
6. External review by an independent panel of experts, and final edits based on feedback. (List of external reviewers included in Appendix 1).
7. Final approvals, endorsement and translation of module.
8. Update of educational materials and knowledge translation and implementation resources.
9. Knowledge translation launch including publication, public release & dissemination of final module and supporting resources through all channels.
10. Ongoing monitoring of research evidence, review and update at least every three years.

The detailed methodology and explanations for each of these steps in the development and dissemination of the *CSBPR* is available in the *Canadian Stroke Best Practice Recommendations Overview and Methodology* manual available on the Canadian stroke best practices website at https://www.strokebestpractices.ca/recommendations/overview-methods-and-knowledge-exchange

Conflicts of Interest: All potential participants in the recommendation development and review process are required to sign confidentiality agreements and to declare all actual and potential conflicts of interest in writing. Any conflicts of interest that are declared are reviewed by the Chairs of the Best Practices Advisory Committee and appropriate Heart & Stroke staff members for their potential impact. Potential members of any writing group who have conflicts that are considered to be significant are not selected for advisory or writing group. Participants who have conflicts for one particular topic area are identified at the beginning of discussions for that topic, and if it is the chair, then another non-conflicted participant assumes the chair role for that discussion to ensure balanced discussions. Declarations of Conflict of interest for writing group members can be found in Appendix 2.

Assigning Evidence Levels: The writing group was provided with comprehensive evidence tables that include summaries of all high-quality evidence identified through the literature searches. The writing group discusses and debates the value of the evidence and through consensus develops a final set of proposed recommendations. Through their discussions, additional research may be identified and added to the evidence tables if consensus on the value of the research is achieved. All recommendations are assigned a level of evidence ranging from A to C, according to the criteria defined in Table 1. When developing and including "C-Level" recommendations, consensus is obtained among the writing group and validated through the internal and external review process. This level of evidence is used cautiously, and only when there is a lack of stronger evidence for topics considered important system drivers for stroke care (e.g., transport using ambulance services or some screening practices). An additional category for Clinical Considerations has been added for the Sixth Edition. Included in this section are expert opinion statements in response to reasonable requests from a range of healthcare professionals who seek guidance and direction from the experts on specific clinical issues faced on a regular basis in the absence of any evidence on that topic.

Table 1: Summary of Criteria for Levels of Evidence Reported in the *Canadian Stroke Best Practice Recommendations* (Seventh Edition):

Level of Evidence	Criteria*
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.
B	Evidence from a single randomized controlled trial or consistent findings from two or more well-designed non-randomized and/or non-controlled trials, and large observational studies. Meta-analysis of non-randomized and/or observational studies. Desirable effects outweigh or are closely balanced with undesirable effects or vice versa.
C	Writing group consensus on topics supported by limited research evidence. Desirable effects outweigh or are closely balanced with undesirable effects or vice versa, as determined by writing group consensus.
Clinical Consideration	Reasonable practical advice provided by consensus of the writing group on specific clinical issues that are common and/or controversial and lack research evidence to guide practice.

* (adapted from Guyatt et al. 2008) [12]

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Community Consultation and Review Panel (CCRP) members

Heart & Stroke is grateful to the CCRP members who reviewed all sections of this module in parallel to the expert writing group, shared their personal experiences and insights on what did or would have made their journey optimal. The members of the *ASA for prevention of vascular events* CCRP included: Cheryl Beattie, Jennifer Bogart, Dan Dobbin, Glen Hilton, Judy Hilton, Allan Morrison and Anjie Valgardson. (Methodology for the CCRP will be available soon - *Lindsay et al, 2020 submitted for publication*).

Statements of Endorsement

These guidelines are endorsed by the Canadian Stroke Consortium, Canadian Cardiovascular Society, Thrombosis Canada, the Canadian Society of Hospital Pharmacists, the Canadian Pharmacists Association and the Nurse Practitioners' Association of Ontario.

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Declaration of Conflicts of Interest

All participants complete a conflict of interest declaration prior to participation and disclosures are provided in Appendix 2.

Citing this Module

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Comments

We invite comments, suggestions, and inquiries on the development and application of the *CSBPR.* Please forward comments to the Heart and Stroke Foundation's Stroke Team at strokebestpractices@heartandstroke.ca

CANADIAN STROKE BEST PRACTICE RECOMMENDATIONS
Seventh Edition

Acetylsalicylic Acid (ASA) for Prevention of Vascular Events

Definitions for this module:

Primary prevention

Primary prevention can be a population-based approach to prevent disease among communities or an individually based clinical approach to disease prevention, directed toward preventing the initial occurrence of a disorder in otherwise healthy individuals. Primary prevention can be implemented in the primary care setting, and the physician, nurse, physician assistant, pharmacist or patient may initiate a discussion of heart conditions, stroke and vascular cognitive impairment risk reduction. It can also be implemented at a population level using legislative, regulatory and public awareness interventions.

Primary prevention and health promotion recommendations related to heart conditions, stroke, TIA, vascular cognitive impairment and peripheral vascular disease emphasize the importance of screening and monitoring and treating those patients at high risk of a first clinical event. Primary prevention areas of focus include lifestyle (healthy diet, physical activity, being smoke-free, stress reduction and limiting alcohol, recreational drugs and cannabis use), and screening and management of risk factors such as hypertension screening, dyslipidemia screening, diabetes management, and management of atrial fibrillation.

Implementation of primary prevention strategies ideally would involve a Shared Decision-Making conversation between the patient and the provider to ensure the patient's goals are incorporated to therapy decisions.

Primary prevention also includes the development of strategies to improve population health such as policies that support the population by making healthy choices the easier choices (examples including smoke-free legislation, revised Canada's Food Guide), and policies that support active and public transportation. These strategies are often led by health-oriented organizations and agencies such as Heart & Stroke, Canadian Cardiovascular Society, Thrombosis Canada, Hypertension Canada, Diabetes Canada, Alzheimer Society of Canada, Health Canada, and national and provincial public health agencies and services.

Secondary prevention

Secondary prevention is an individually based clinical approach aimed at reducing the risk of a recurrent vascular event in individuals who have already experienced angina, myocardial infarction, heart failure, heart rhythm abnormalities, structural heart disease, stroke, transient ischemic attack, vascular cognitive impairment or peripheral vascular disease.

Secondary prevention recommendations are directed to those risk factors shown to reduce recurrent and prolong survival after vascular conditions, including attention to lifestyle (prudent diet, reduced sodium intake, increased level of activity, maintaining ideal body weight, smoking cessation, and controlling alcohol intake), and management of medical conditions such as hypertension, dyslipidemia, and heart rhythm management (e.g. atrial fibrillation). Secondary prevention recommendations can be addressed in a variety of settings—community-based care settings (primary care and subspecialty care), vascular prevention

clinics (generalized or specific to conditions such as stroke, heart failure, post myocardial infarction)emergency care, including emergency medical services, acute care, and rehabilitation. They pertain to patients initially seen in primary care, those who are treated in an emergency department and then released and those who are hospitalized and receive treatment in hospital because of angina, myocardial infarction, heart failure, heart rhythm abnormalities, structural heart disease, stroke, transient ischemic attack, vascular cognitive impairment or peripheral vascular disease.

Recommendations for secondary prevention of vascular conditions should be implemented throughout the recovery phase, including during inpatient and outpatient rehabilitation, reintegration into the community and ongoing follow-up by primary care practitioners. Secondary prevention should be addressed at all appropriate healthcare encounters on an ongoing basis following angina, myocardial infarction, heart failure, heart rhythm abnormalities, structural heart disease, stroke, transient ischemic attack, vascular cognitive impairment or peripheral vascular disease.

Cardiovascular Disease

Disease pertaining to the heart and blood vessels.

Cerebrovascular Disease

Disease pertaining to the blood vessel of the brain.

Peripheral Artery Disease

A circulation disorder that is caused by narrowed or blocked blood vessels in arteries located outside of the heart and brain.

Vascular Disease

Vascular disease refers to cerebrovascular and peripheral vascular diseases that stiffen, narrow or block the intra- and extracranial arteries or peripheral arteries and veins. Broadly speaking, vascular disease encompasses sclerosis, stenosis and occlusion of arteries or veins. Types of vascular disease include peripheral artery disease, carotid artery disease, venous disease, embolism and thrombosis, and aortic aneurysm and dissection. These abnormal vascular changes may result from endothelial dysfunction, inflammation, atherosclerosis, fibrosis or pathological differentiation including arterial plaque formation and venous thrombosis.

Recommendations for the Use of Acetylsalicylic Acid (ASA) in the Prevention of Vascular Events*

Recommendations

Secondary prevention**

Acetylsalicylic acid (ASA) is strongly recommended for **secondary prevention** in individuals with symptomatic cardiovascular, cerebrovascular or peripheral arterial disease [Evidence Level A].[15-17]

Primary prevention

The use of ASA is not recommended for **primary prevention** of a first vascular event [Evidence Level A].[2-4,6]

- This recommendation pertains to individuals with vascular risk factors who have **not** had a vascular event [Evidence Level A][2,4,6] and for healthy older individuals without vascular risk factors [Evidence Level B].[3]
- The net benefit of ASA in individuals with asymptomatic atherosclerosis is uncertain [Evidence Level B].[18,19]

Shared decision-making

Health professionals (such as physicians [primary care or subspecialty], nurses and nurse practitioners, pharmacists, physician assistants) should engage patients and caregivers in discussions regarding the use of ASA for primary prevention of vascular disease. An individual's risk, benefit, values and preferences should be considered in order to make an informed decision to initiate, continue or discontinue ASA for primary prevention of vascular disease [Evidence Level B].[25,26]

**Please refer to Appendix 2 for Evidence table comparing the key components of the three randomized trials and systematic reviews.*

*** For additional information regarding the use* of *acetylsalicylic acid* (ASA) *and other antiplatelet agents in secondary prevention, please see the Canadian Stroke Best Practice Recommendations Secondary Prevention of Stroke Module;[33] Canadian Cardiovascular Society guideline on antiplatelet and anticoagulant use[9]; and Thrombosis Canada clinical guides.[8]*

Rationale

This set of recommendations is intended to provide guidance for the use of acetylsalicylic acid (ASA) for primary prevention of a first vascular event. The use of ASA for the secondary prevention of vascular disease has been in practice since the 1950's, and research on the use of ASA in primary prevention since the late 1970's and early 1980's. This information was widely available to the public and ASA is available without prescription, therefore many people may have initiated daily ASA without discussions with healthcare professionals, such as in cases where there is a family history of some form of vascular disease.

In recent years the risk-benefit profiles of using ASA for primary prevention in an individual without vascular disease has come under scrutiny. Three recent randomized trials have consistently found that the risk of bleeding is higher and potentially outweighs the benefits achieved for vascular risk reduction in otherwise healthy populations. The decision to start, stop or continue ASA in individuals should be made through an informed discussion between the individual and their healthcare team, weighing individual risk, benefit and preferences. Some decision-making research is emerging that indicates some people may choose a risk of bleeding over a risk of a heart attack or stroke in choosing whether or not to take ASA. No specific sex and gender differences in outcomes have been reported in the current evidence.

System Implications

- Public access to reliable evidence-based information on the risks and benefits of using ASA for primary prevention of vascular disease, and the role of ASA for other health indications (such as pain management).
- Evidence-based education and information on vascular prevention available for healthcare professionals including primary care practitioners, pharmacists, and specialists across the continuum of care.
- Further education to health professionals to now routinely include assessment of current ASA use among their patients during their encounters.
- Collaboration and alignment of information and messaging on the use of ASA across professional groups including physicians, pharmacists, nurses and allied health disciplines.
- Mechanisms to be developed for systematic data collection to understand use of ASA in the public and changes in practice based on research evidence.

Performance Measures

1. Proportion of people taking *a*cetylsalicylic acid for primary vascular prevention.
2. Proportion of people taking *a*cetylsalicylic acid for primary vascular prevention who experience a bleeding complication (gastrointestinal, intracerebral).
3. Proportion of people taking *a*cetylsalicylic acid for primary vascular prevention who experience a vascular event (stroke, heart condition).
4. *Population indicator: public perceptions on use of ASA for primary prevention (based on polling Q TBD) – include valid measure of patient reported risk factors*
5. *Polling question: Have you heard about new research indicating that ASA is not being recommended for primary prevention of vascular diseases now? – would you stop, did you stop?*

Measurement Notes:

- Lack of centralized database to obtain data for these indicators; however, they remain important and healthcare professionals are urged to collect this data at least at a local level to help drive knowledge gaps and improvement opportunities.
- Public polling methods should be considered to obtain data for indicators 1, 4, 5.

Implementation Resources and Knowledge Transfer Tools

Health Care Provider Information

- Canadian Stroke Best Practice Recommendations: https://www.strokebestpractices.ca/
- Canadian Stroke Consortium
  - Main site: https://strokeconsortium.ca/
  - Education site: https://strokeconsortium.ca/patient-resources
- Canadian Cardiovascular Society:
  - Main site: http://www.ccs.ca/en/
  - Guidelines: https://www.ccs.ca/en/guidelines-library
  - The Use of Antiplatelet Therapy in the Outpatient Setting: Canadian Cardiovascular Society Guidelines: https://www.onlinecjc.ca/article/S0828-282X(10)00049-8/fulltext
- Thrombosis Canada:
  - Main site: https://thrombosiscanada.ca/
  - Clinical guide: https://thrombosiscanada.ca/clinicalguides/
- Canadian Society of Hospital Pharmacists
  - Main site: https://cshp.ca
- Canadian Pharmacists Association:
  - Main site: https://www.pharmacists.ca
  - Education site: https://www.pharmacists.ca/education-practice-resources/
- Shared Decision-Making
  - https://cdn.prod-carehubs.net/n1/56fab03a15e99046/uploads/2014/11/ASA_DA_avg.pdf
  - https://www.ncbi.nlm.nih.gov/pubmed/29358246

Information for People who have Experienced a Stroke, their Families and Caregivers

- ASA for Prevention infographic: Are you taking ASA to prevent heart disease or stroke?: https://strokebestpractices.ca/-/media/1-stroke-best-practices/asa-for-prevention/csbp-infographic-asa-for-prevention-en.ashx
- Community of Survivors: www.heartandstroke.ca/connect
- Care Supporter's Community: www.heartandstroke.ca/connect
- Are you at Risk for Heart Disease or Stroke: https://www.strokebestpractices.ca/resources/patient-resources
- Post Stroke Checklist: https://www.strokebestpractices.ca/resources/patient-resources
- Services and Resources Directory: https://www.heartandstroke.ca/services-and-resources
- Your Stroke Journey: https://www.strokebestpractices.ca/-/media/1-stroke-best-practices/resources/patient-resources/en-your-stroke-journey-v21.ashx
- Living Well with Heart Disease: https://www.heartandstroke.ca/-/media/pdf-files/canada/2017-lwwhd/livingwellwheartdisease-en.ashx?rev=80e4f94be9c0494d9c5308ad0ab9d527

- Living with Stroke Program: https://www.heartandstroke.ca/stroke/recovery-and-support/living-with-stroke
- Managing Your Blood Pressure: https://www.strokebestpractices.ca/resources/patient-resources
- How to Manage your Cholesterol: https://www.strokebestpractices.ca/resources/patient-resources

Summary of the Evidence

Acetylsalicylic Acid (ASA) for Secondary Prevention

The benefit of long-term acetylsalicylic acid (ASA) or aspirin use for secondary prevention is well established. Daily, low-dose ASA reduces the risk of vascular events including myocardial infarction (MI), stroke, and vascular death in patients who have experienced a previous vascular event or who are at high risk of vascular disease. A meta-analysis conducted by The Antithrombotic Trialists' Collaboration (2002) included the results of 287 RCTs (n=135,000) examining any antiplatelet therapy for the prevention of vascular events in high-risk patients. In 9 of these trials, long-term aspirin monotherapy was examined in patients who had experienced a previous stroke or TIA. In these trials, fewer patients receiving ASA therapy experienced a vascular event (8.2% vs. 9.1%) representing an 11% odds reduction. In 65 trials examining ASA monotherapy, the mean percentage odds reduction of any vascular event, across doses ranging from <75 mg to 1,500 mg, was 23%. Treatment with ASA reduced the number of serious vascular events by 36 per 1,000 per year over two years in patients with a previous myocardial infarction and by 36 per 1,000 per year in patients with a previous history of stroke or transient ischemic attack, compared with placebo. In patients with peripheral arterial disease, treatment with ASA reduced the odds of serious vascular events by 23%, compared with placebo. Similar risk reductions were seen for patients with stable or unstable angina.

ASA also helps to reduce the risk of recurrent vascular events following an acute stroke. Rothwell et al. (2016) included the results of 12 trials comparing ASA vs. placebo, of which 11 trials included comparisons of ASA monotherapy versus placebo, stratified by time periods (< 6 weeks, 6–12 weeks, and >12 weeks). ASA doses ranged from 50 to 1,200 mg per day. ASA monotherapy significantly reduced the risks of any ischemic stroke, disabling or fatal ischemic stroke, any stroke and any fatal stroke up to 12 weeks post event, with large risk reductions ranging from 40% to 70%. The greatest reduction in early stroke recurrence associated with ASA monotherapy was among patients presenting with mild or moderately disabling stroke. There was no reduction in risk of recurrent ischemic stroke with ASA use after 12 weeks (OR= 0·97, 95% CI 0·84–1·12, p=0·67). In an updated Cochrane review, Sandercock et al. (2014) included the results of the CAST (1997) and IST (1997), the two largest trials testing ASA, which contributed 98% of the data. ASA therapy, initiated within 48 hours of stroke onset, was associated with a significant reduction in the odds of being dead or dependent at final follow-up (OR= 0.95, 95% CI 0.91 to 0.99) and in the odds of death at a final follow-up (OR=0.92, 95% CI 0.87 to 0.98). ASA therapy was associated with a significant reduction in the odds of recurrent stroke during treatment (OR=0.77, 95% CI 0.69-0.87) and marginally increased odds of intracranial hemorrhage (OR=1.22, 95% CI 1.00- 1.50). For every 1,000 people treated with ASA, 13 fewer people would avoid death or dependency, 9 fewer would avoid death and 7 fewer would avoid a recurrent stroke. The results of an older meta-regression analysis including the results of 11 RCTs published up to 1996 (Johnson et al. 1999), suggested that the effectiveness of ASA is uniform across a wide range of doses (50-1,500 mg per day), although doses in the range of 75-100

mg are more typical of what is used in clinical practice currently. ASA was associated with a 15% reduction in recurrent stroke.

ASA for Primary Prevention

While low-dose ASA therapy for primary prevention of cardiovascular disease was once commonly recommended, it is now being reconsidered in light of recent evidence. Currently 2019 ACC/AHA guidelines on the primary prevention of cardiovascular disease suggest that low-dose ASA (75-100 mg/day) *might be considered* among selected adults, aged 40-70 years at higher risk of cardiovascular disease and should be avoided in persons >70 years (Arnett et al. 2019). This language was modified from the 2014 recommendation, which stated that "*the use of aspirin for cardiovascular (including but not specific to stroke) prophylaxis is reasonable for people whose risk is sufficiently high (10-year risk >10%) for the benefits to outweigh the risks associated with treatment."* (Meschia et al. 2014). The U.S. Preventive Services Task Force made age specific recommendations, suggesting that persons aged 50 to 59 years initiate low-dose ASA if their 10-year cardiovascular risk is >10% and the risk of bleeding is not increased. For persons aged 60-69 years, the recommendation was for the decision to be a personal one, given a similar 10-year risk, while the authors suggested the evidence is insufficient to make recommendations for person younger than 50 years or older than 69 years (Bibbins-Domingo et al. 2016). The 2016 European Guidelines on cardiovascular disease prevention (Piepoli et al. 2016) explicitly state that antiplatelet therapy is not recommended in individuals without cardiovascular disease due to the increased risk of major bleeding, as did older guidelines issued by the Canadian Cardiovascular Society (Bell et al. 2011).This is the first time that recommendations for ASA monotherapy in the context of primary prevention have been issued by the Canadian Stroke Best Practice Recommendations writing group.

Acetylsalicylic acid increases the risk of major bleeding. In a meta-analysis that examined intracranial bleeding outcomes exclusively, Huang et al. (2019) included the results of 13 RCTs (n=134,446) including persons without preexisting symptomatic cardiovascular diseases and compared low-dose ASA (≤100 mg/day, for ≥6 months) vs. placebo, or no treatment and. The use of ASA was associated with a significantly increased risk of any intracranial bleeding (RR=1.37, 95% CI, 1.13-1.66; n=8 trials; 2 additional intracranial hemorrhages in 1,000 people). In a sensitivity analysis, excluding the results from ASPREE (2018), which included elderly people only (≥70 years), the risk became nonsignificant. ASA was not associated with a significantly increased risk of intracerebral hemorrhage or subarachnoid hemorrhage. In subgroup analysis, Asians and persons with a BMI <25 taking ASA were at significantly higher risk for intracerebral hemorrhage. Another systematic review including the results of 15 trails (Abdelaziz et al. 2019) also reported an increased risk of major bleeding (1.47% vs. 1.02%; RR= 1.50; 95% CI: 1.33 to 1.69), intracranial bleeding including hemorrhagic stroke (0.42% vs. 0.32%; RR= 1.32; 95% CI: 1.12 to 1.55), and major GI bleeding (0.80% vs. 0.54%; RR= 1.52; 95% CI: 1.34 to 1.73).

In terms of efficacy to prevent ischemic strokes or TIA, three systematic reviews and meta-analyses have been published recently (Abdelaziz et al. 2019, Mahmoud et al. 2019, Zheng & Roddick 2019). The number of included trials ranged from 11 to 15. All reviews included the results of the ARRIVE, ASCEND and ASPREE trials, with much overlap among the remaining included trials. In two of the reviews the risk of ischemic stroke was reduced significantly with aspirin therapy. Abdelaziz et al. (2019) reported the relative risk of TIA and ischemic stroke were 0.79 (95% CI: 0.71 to 0.89) and 0.87 (95% CI: 0.79 to 0.95, respectively), with associated NNTs of 370, and 500. Zheng & Roddick (2019T) also found the use of aspirin was associated with a significant reduction in ischemic stroke (HR=0.81 [95% CrI, 0.76-0.87]; absolute risk reduction 0.16% [95% CI 0.06 to 0.30]; NNT=540). In contrast, in the third review (Mahmoud et al. 2019), the risk of ischemic stroke was not reduced significantly with

aspirin (1.7% vs. 1.8%; RR=0.94, 95% CI 0.86-1.04). The inclusion criteria in these reviews were restricted to participants who had no previous cardiovascular disease (Zheng & Roddick 2019) or preexisting cardiovascular diseases (Abdelaziz et al. 2019) and those without a prior history of atherosclerosis (Mahmoud et al. 2019).

Three trials have been published recently that assessed the potential benefit of 100 mg of ASA versus placebo in persons without pre-existing cardiovascular disease, which was defined slightly differently in each trial. All trials included large sample sizes (>12,000 to >19,000 participants). ARRIVE (2018) included men ≥ 55 years with 2 to 4 cardiovascular risk factors and women ≥ 60 years with 3 or more risk factors and excluded those with diabetes. ASPREE (2018) included men and women aged ≥65 or ≥70 years (11% with diabetes), depending on race and ASCEND included men and women ≥40 years with type 1 or 2 diabetes. Mean age of participants was 64 years in the ARRIVE (2018) and ASCEND (2018) trials, while median age in the ASPREE (2018) trial was 74 years. Current ASA +/- anticoagulants use was an exclusion criterion in all trials; however, 36% of participants in the ASCEND trial had used ASA prior to screening, while 11% used ASA previously in the ASPREE trial. Median duration of follow-up ranged from 4.7 to 7.1 years. Two trials were negative (ARRIVE, ASPREE), whereby the risks of cardiovascular events were not significantly lower in the ASA-treated group. In the ARRIVE and ASPREE trials, the hazard ratios associated with ASA use for the primary outcome were 0.96 (95% CI 0·81–1·13) and 0.95 (95% CI 0.83–1.08), respectively. In the ASCEND trial, the risk of the primary outcome (first serious vascular event [MI, stroke, TIA or cardiovascular death]) was significantly lower in the ASA group (8.5% vs, 9.6%, RR=0.88, 95% CI, 0.79 to 0.97; p=0.01). In all trials, the risk of major bleeding events was increased significantly with ASA therapy (ASPREE, HR=1.38; 95% CI 1.18-1.62; ARRIVE [any gastrointestinal bleeding], HR=2.11, 95% CI 1·36–3·28 and ASCEND, RR=1.29, 95% CI 1.09-1.52).

Marquis-Gravel et al. (2019) highlighted several areas of uncertainty that remain regarding ASA therapy, following the completion of the three latest RCTs. Factors such as body weight and sex were identified as potential effect modifiers. In a meta-analysis of pooled individual patient data from 10 RCTs (Rothwell et al. 2019), the risk of cardiovascular events associated with the use of 75–100 mg ASA decreased with increasing weight, while low-dose ASA had the greatest preventative effect among those participants weighing 50–69 kg. In the same study, ASA doses of 350 and 500 mg were associated with decreased risk of cardiovascular events in persons weighing ≥70 kg. The role of sex as a potential effect modifier is less clear. Although sex was not identified as one in in the ARRIVE, ASCEND or ASPREE trials, results from an older meta-analysis, which included the results of 6 RCTs (Berger et al. 2006) suggested that ASA reduced the risk of myocardial infarction only in men, and the risk of all stroke and ischemic strokes only in women.

ASA has also been evaluated with respect to its efficacy for reducing the risk of cardiovascular events including TIA, stroke, myocardial infarction, unstable angina or death among persons with asymptomatic atherosclerosis. While it has been suggested that low-dose ASA leads to a change in the composition of plaque within blood vessels, transforming it from a soft foamy material to a harder material that is less likely to rupture, and reduces inflammation, the use of 325 mg of daily ASA for two years in persons with carotid stenosis (≥50%) was not associated with reductions in vascular events compared with placebo (Cote et al. 1995). Nor was the risk of the composite of initial fatal or nonfatal coronary event or stroke or revascularization reduced among persons with an ankle brachial index ≤ 0.95, randomized to receive 100 mg ASA daily for an average of 8.2 years in the Aspirin for Asymptomatic Atherosclerosis trial (Fowkes et al. 2010). The results of trials examining the use of ASA therapy for the primary prevention of cardiovascular events for persons with peripheral artery disease have also been negative (Belch et al. 2008, Catalano et al. 2007).

Since cerebrovascular disease is known to play a pivotal role in the development and progression of mild cognitive impairment, it has been suggested that ASA might prevent cognitive impairment or slow worsening of cognitive function. Unfortunately, the evidence base does not support such a role. After an average of 6 years, ASA treatment did not reduce the odds of the development or cognitive impairment, nor was it associated with better global cognitive test scores among 36,196 participants who were cognitively intact at baseline (Veronese et al. 2017). In the REGARDS study, (Kelley et al. 2015) the odds of cognitive impairment were not significantly higher among non-aspirin users who were cognitively normal at baseline, after a mean duration of follow-up of 5.9 years (OR = 0.99, 95% CI = 0.89–1.09). Negative results were also reported in subgroups analyses from the Aspirin for Asymptomatic Atherosclerosis Trial (Price et al. 2008) and a cohort study within the Women's Health Study (Kang et al. 2007).

The Role of Shared Decision Making

Long-term use of ASA for primary prevention of vascular disease is not recommended for the primary prevention of a first vascular event in the current Canadian Stroke Best Practices Recommendations. Nevertheless, there is a recognition that the decision to initiate ASA therapy should be highly individualized and should be made following an assessment of the benefit/risk ratio and a clinician-patient discussion regarding potential benefits/harms, and alternatives. This process of shared decision making (SDM) is based both on clinical evidence and the patient's informed preferences and values (Charles et al. 1997; Munro et al. 2016), recognizing that many patients want to actively participate in decisions about their own medical care.

To facilitate SMD, interventions can target the clinician, the patient, or both. Examples of activities that target clinicians include educational meetings, educational material, and educational outreach visits, while examples of activities that target patients include decision aids, pamphlets/leaflets, videos and education sessions. Unfortunately, there are no studies that have evaluated SMD for ASA use in the primary prevention of cardiovascular disease although a few case studies have been presented and a decision support algorithm and mobile application for use by physicians, described (Mora et al. 2016). Montori et al (2003) examined the personal characteristics and preferences that affected the decision to take ASA to reduce cardiovascular risk among a group of 206 patients with diabetes attending an outpatient clinic. Of the participants surveyed, 67% (n=146) were using ASA. Those using ASA were at higher risk of cardiovascular disease, knew more about the benefits of ASA, but less about the risks, and placed a higher value on preventing cardiovascular events than on avoiding the side effects.

In the broader context, the evidence for SDM interventions is weak. A Cochrane review included the results of 87 studies (Légaré et al. 2018), of which 44 targeted patients, 15 evaluated interventions targeting healthcare professionals and 28 studies targeted both patients and healthcare professionals. The authors concluded that it was uncertain whether activities to enable SDM are effective compared with usual care because the certainty of the evidence was low or very low. In this review, a wide variety of medical conditions were represented including cancer, dementia, fibromyalgia, and mental health issues. However, another Cochrane review, (Stacey et al. 2017) that included the results of 86 randomized controlled trials (RCTs), specifically examined the effectiveness of patient decision aids (PDA). Patients who were exposed to decision aids were more knowledgeable, better informed and clearer about their values leading to having a more active role in decision making and had more accurate risk perceptions.

There is a substantial literature examining the use of SDM in the context of cardiovascular risk factor reduction, the results of which have been equivocal. A systematic review of 6 studies (5 RCTs) that included adults in primary care being treated for hypertension, compared the effects of shared decision-making interventions versus any comparator, targeting either the patient or physician reported that interventions did not increase measures of SMD, patient participation or blood pressure (Johnson et al. 2018). Following a 6-hour, multicomponent program of SDM training for 36 general practitioners (GP), patients in their practices with treated but uncontrolled hypertension reported no significant changes in perceived participation (SDM-Q-9), systolic blood pressure, diastolic blood pressure, knowledge, medication adherence or cardiovascular risk score compared with GPs who treated their patients as usual, at 6, 12 and 18 months (Tinsel et al. 2013). Persons with diabetes established on metformin but with persistent hyperglycemia who were recommended to consider medication intensification had significantly larger knowledge gains from baseline (35.0% vs. 9.9%, $p < 0.0001$) and greater improvements in Decision Self Efficacy Scale scores (3.7 vs.−3.9, $p < 0.0001$) and Decisional Conflict Scale scores (−22.2 vs. −7.5, $p < 0.0001$) following exposure to an online PDA (Bailey et al. 2016). Among a group of primary care patients, 20% of whom had a previous cardiovascular event, there were significantly higher levels of satisfaction and participation and lower decisional regret reported when treated by physicians who had attended two interactive continuing medical education sessions that focused on cardiovascular risk reduction (Krones et al. 2008).

ASA for Prevention Evidence Table and References

CANADIAN STROKE BEST PRACTICE RECOMMENDATIONS

Appendix 1

1.1 Writing Group members for the CSBPR Module: *A*cetylsalicylic Acid *(ASA) for Prevention of Vascular Events*

NAME	PROFESSIONAL ROLE	LOCATION	CONFLICT OF INTEREST DECLARATIONS
Wein, Theodore ***Chair and First Author***	Co-Chair, Assistant Professor of Neurology and Neurosurgery, McGill University Stroke Prevention Clinic, Montreal General Hospital	QC	**Potential Conflict:** Consultant: Bayer, Servier, Allergan, Ipsen **Potential Conflict**: Accredited CME: Servier, Allergan **Potential Conflict:** Travel: Servier **Potential Conflict**: Research Grant: Servier, Allergan **Potential Conflict:** Principal Investigator: Allergan, Servier, Bayer, Boehringer Ingelheim
Smith Eric E ***CoChair CSBPQ Advisory Cmte*** ***Senior Author***	Associate Professor, Dept of Clinical Neurosciences, Radiology and Community Health Sciences Member, Hotchkiss Brain Institute, University of Calgary	AB	**Potential Conflict:** Consultant for treatment of anticoagulant-associated hemorrhage (Portola Pharmaceuticals) and drug therapy for cerebral amyloid angiopathy (Alnylam Pharmaceuticals) **Potential Conflict:** Royalties for writing section on vascular dementia diagnosis : UpToDate
Gladstone, David *Co-Chair Secondary Prevention of Stroke WG*	Associate Professor of Medicine (Neurology), University of Toronto; Director, Regional Stroke Prevention Clinic, Sunnybrook Health Sciences Centre, Toronto	ON	**Potential Conflict:** Ad-hoc advisory boards: Bayer, BI, BMS/Pfizer (all pre- 2016, none since) **Potential Conflict:** Speaker fees for CME lectures: Bayer, BI, BMS/Pfizer (all pre- 2016, none since) **Potential Conflict:** Canadian National Co-PI for ARACIA (NIH-funded trial); Co-PI of a 2015 Ontario Centres of Excellence grant (provincial peer-reviewed grant); PI of a grant from the CIHR-funded CSPIN network **Potential Conflict:** Site Investigator for NAVIGATE ESUS, ESCAPE NA1, TEMPO-2, NASPAF-ICH (all site fees paid to my institution); PI of SCREEN-AF (uncompensated; CIHR-funded trial); Independent Medical Safety Monitor for ARCADIA (NIH-sponsored trial) (uncompensated) **Potential Conflict:** Co-Leader of the NAVIGATE ESUS atrial myopathy/atrial fibrillation working group (uncompensated)

NAME	PROFESSIONAL ROLE	LOCATION	CONFLICT OF INTEREST DECLARATIONS
Poppe, Alexandre *Co-Chair Secondary Prevention of Stroke WG*	Stroke Neurologist, Hopital Notre-Dame, Centre hospitalier de l'Universite de Montreal (CHUM), Clinical Assistant Professor, Department of Neurosciences, Universite de Montreal	QC	**Potential Conflict:** Site PI and Site co-investigator: NoNo, Bayer, Boehringer-Ingelheim **Potential Conflict:** Support for fellowship program: Servier
Bell, Alan *Thrombosis Canada representative*	Assistant Professor Department of Family and Community Medicine University of Toronto	ON	**Potential Conflict:** Advisory Board Member: Amgen, Bristol Myers Squibb, Janssen, Takeda, AstraZeneca Novartis, Pfizer, Bayer, Lilly, Boehringer Ingelheim, Canopy Sanofi, Bausch **Potential Conflict:** Paid speaker: Amgen, Bristol Myers Squibb, Janssen, Takeda, AstraZeneca, Novartis, Pfizer, Bayer, Lilly, Boehringer Ingelheim, Canopy Sanofi, Bausch **Potential Conflict:** Consultancy fees: Amgen, Bristol Myers Squibb, Janssen, Takeda, AstraZeneca Novartis, Pfizer, Bayer, Lilly, Boehringer Ingelheim, Canopy Sanofi, Bausch **Potential Conflict:** Consultancy, travel and speaking fees: Amgen, Bristol Myers Squibb, Janssen, Takeda, AstraZeneca Novartis, Pfizer, Bayer, Lilly, Boehringer Ingelheim, Canopy Sanofi, Bausch **Potential Conflict:** Shares of most pharmaceutical companies included in my investment portfolio eg. mutual funds **Potential Conflict:** Trial investigator: Astra Zeneca, Sanofi, Akcea, Eisai, Amgen, Lilly, Boehringer Ingelheim, Janssen **Potential Conflict:** Board of Directors Member, Guideline Author: Hypertension Canada, Thrombosis Canada, Canadian Cardiovascular Society, Heart and Stroke foundation
Casaubon Leanne K *Quality Chair CSBPQ Advisory Committee*	Associate Professor, University of Toronto Division of Neurology - Stroke Program; Director, TIA and Minor Stroke (TAMS) Unit	ON	**Potential Conflict:** Ad Board 2018: Bayer **Potential Conflict:** Independent neurological assessor, Surtavi Trial: Medtronic **Potential Conflict:** Speaker honorarium + 1-night accommodations 2017: Bayer **Potential Conflict:** Site PI - Frontier Trial; other trials as sub-investigator at our site: NoNo Inc
Coutts, Shelagh	Stroke Neurologist Professor, Departments of Clinical Neurosciences, Radiology, and Community Health Sciences. University of Calgary	AB	No Conflicts to Disclose

NAME	PROFESSIONAL ROLE	LOCATION	CONFLICT OF INTEREST DECLARATIONS
Cox, Jafna *CCS representative*	Cardiologist; Heart and Stroke Foundation of Nova Scotia Endowed Chair in Cardiovascular Outcomes Research; Professor of Medicine and of Community Health and Epidemiology, Dalhousie University * Appointed by Canadian Cardiovascular Society as their official rep	NS	**Potential Conflict:** Advisory/consulting work: Bayer, Servier, HLS Therapeutics **Potential Conflict:** Have given lectures on behalf of Bayer Potential Conflict: Educational grant for an investigator-initiated clinical trial : Bayer
Douketis, James *Thrombosis Canada representative*	Internist and Thrombosis Specialist; Divisions of General Internal Medicine, Hematology and Thromboembolism, McMaster University Department of Medicine; President of Thrombosis Canada (www.thrombosiscanada.ca)	AB	**Potential Conflict:** Personal fees - Monies received as personal fees are deposited in hospital based (St. Joseph's Healthcare Hamilton) and university-based (McMaster University) research accounts and/or charitable foundations: Janssen, Pfizer, Bayer, Bristol Myers Squibb, Sanofi, Servier Canada, Portola
Field, Thalia	Assistant Professor, Vancouver Stroke Program, Division of Neurology, Department of Medicine, University of British Columbia	BC	**Potential Conflict:** Advisory board member: Bayer Canada, Pfizer-BMS, Servier **Potential Conflict:** Speakers bureau: Bayer Canada, Pfizer-BMS **Potential Conflict:** Received honoraria for advisory board and speakers bureau activities: Bayer Canada, Pfizer-BMS, Servier **Potential Conflict:** Site PI for clinical trials with named sponsors in my role with the Vancouver Stroke Program: Bayer, NoNo Inc, Boehringer-Ingleheim, Heart and Stroke afoundation, CIHR, Alberta Innovates **Potential Conflict:** Advisory work (unpaid): Heart and Stroke Foundation
Gioia, Laura	Assistant Professor of Neurology, University of Montreal; Stroke Neurologist, CHUM-Centre Hospitalier de l'Université de Montréal	QC	**Potential Conflict:** Speaker Honoraria, Advisory Board: Bayer, BMS Pfizer, Servier
Habert, Jeff *Thrombosis Canada representative*	Family Physician, Lecturer, University of Toronto, Dept. of Family and Community Medicine; Investigating Coroner, City of Toronto	ON	**Potential Conflict:** Ad Board Member: Pfizer, Amgen, BMS, Bayer, Boehringer, Eli-Lilly, Purdue, Allergan, Astra-Zeneca, Lundbeck, Novo-Nordisk, Servier, Janssen, Aralez **Potential Conflict:** Speaker: Pfizer, Amgen, Bayer, BMS, Eli-Lilly, Purdue, Allergan, Lundbeck, Janssen, Aralez **Potential Conflict:** Scientific/Planning Committee: MDBriefcase, Liv, MedPlan. Brandaide. Academy, Bridge, Seacourses, Meducom, Antibody, CHRC, STA, CCRN, Four Health Comm, CPD Network

NAME	PROFESSIONAL ROLE	LOCATION	CONFLICT OF INTEREST DECLARATIONS
Lang, Eddy	Emergentologist, CAEP Stroke Sub Committee Lead, Interim Department Head, University of Calgary and Alberta Health Services	AB	No Conflicts to Disclose
Mehta, Shamir	Professor of Medicine McMaster University Director, Interventional Cardiology Hamilton Health Sciences Senior Scientist Population Health Research Institute Hamilton, Canada	ON	**Potential Conflict:** Research grants to PHRI, McMaster University, CIHR, AstraZeneca, Boston Scientific
Papoushek, Christine	Stroke survivor, PhD Pharmacist Pharmacotherapy Specialist, Primary Care; Toronto Western Family Health Team; Assistant Professor, Leslie Dan Faculty of Pharmacy, Department of Family and Community Medicine	ON	No Conflicts to Disclose
Semchuk, William	Pharmacist, member of the Canadian Cardiovascular Pharmacists Network executive committee (Regina) Assistant Clinical Professor – College of Medicine, University of Saskatchewan Assistant Clinical Professor – College of Pharmacy, University of Saskatchewan	SK	**Potential Conflict:** Advisory Board Member: BMS Pfizer **Potential Conflict:** Speaker Honorarium: BMS, Pfizer, AZ, Sanofi, Servier, Bayer, BI
Sharma, Mikul	Investigator – Stroke & Cognition Program, Population Health Research Institute Associate Professor – Division of Neurology, Department of Medicine	ON	**Potential Conflict:** Consultant: AZ Therapies, Daiichi Sankyo, Servier **Potential Conflict:** Speaker, Consultant: Boehringer Ingelheim, Bayer **Potential Conflict:** Funding of research/honorarium: Bristol Myers Squibb
Udell, Jacob *CCS representative*	Scientist, Women's College Research Institute Cardiologist, Women's College Hospital; Assistant Professor, Division of	ON	**Potential Conflict:** Consultant on clinical research development, no involvement in marketing: AstraZeneca, Boehringer Ingelheim, Janssen, Sanofi **Potential Conflict:** Grant to UHN for clinical

NAME	PROFESSIONAL ROLE	LOCATION	CONFLICT OF INTEREST DECLARATIONS
	Cardiology, Department of Medicine, Faculty of Medicine, University of Toronto; Affiliate Scientist, Li Ka Shing Knowledge Institute, St. Michael's Hospital; Adjunct Scientist, Cardiovascular & Diagnostic Imaging, Institute for Clinical Evaluative Sciences * Appointed as rep by Canadian Cardiovascular Society		trial (AstraZeneca); grant to UHN for clinical trial and honorarium for leadership of a multicenter RCT (Boehringer-Ingelheim); grant to WCH for clinical research study (Janssen); grant to WCH to be a site in a multicenter RCT and honorarium for steering committee membership in cohort study (Novartis); grant to WCH for site participation in a multicenter RCT and honorarium for national co-PI role in multicenter RCT (Sanofi) **Potential Conflict:** Grants to my institutions for clinical trial participation: Boehringer-Ingelheim; Novartis; Sanofi

1.2 External Reviewers for the CSBPR Module: *A*cetylsalicylic Acid *(ASA) for Prevention of Vascular Events*

NAME	PROFESSIONAL ROLE	LOCATION	CONFLICT OF INTEREST DECLARATIONS
Lana Castellucci, MD FRCPC MSc	Associate Scientist, Clinical Epidemiology Program Ottawa Hospital Research Institute, Assistant Professor, Medicine University of Ottawa	ON	Honoraria – Bayer, BMS, Pfizer, BI, Sanofi, Servier, LeoPharma, Aspen
Connelly, Kim FRACP, PhD, MBBS	Chair, Canadian Cardiovascular Society Guidelines Committee; Cardiologist and scientist at and St Michael's Hospital and Sunnybrook Health Sciences Centre at the University of Toronto	ON	Advisory board member – Abbott, AstraZeneca, Boehringer Ingleheim, Eli Lilly, Janssen, Merck, Novo Nordisk, Sanofi, Servier Speakers' bureau member - Abbott, AstraZeneca, Boehringer Ingleheim, Eli Lilly, Janssen, Merck, Novo Nordisk, Sanofi Clinical trial participation – Boehringer Ingelheim, Eli Lilly, Sanofi, Abbott Vascular, AstraZeneca, Edwards lifesciences, Bristol-Myers Squibb, Servier
Cote, Robert, MD, FRCPC, FAHA	Professor, Department of Neurosurgery, McGill Univ	QC	Speaker/Honoraria Pfizer/Bayer
Eikelboom, John	Professor, Division of Hematology and Thromboembolism,	ON	Honoraria and grant support – Astra-Zeneca, Bayer, Boehringer-Ingelheim, Bristol-Myer-Squibb, Daiichi-Sankyo, Eli-Lilly, Glaxo-Smith-Kline, Pfizer,

NAME	PROFESSIONAL ROLE	LOCATION	CONFLICT OF INTEREST DECLARATIONS
	Department of Medicine, McMaster University		Janssen, Sanofit-Aventis
Farkouh, Michael E., MD, MSc, FRCPC, FACC, FAHA	Peter Munk Chair in Multinational Clinical Trials Director, Heart and Stroke Richard Lewar Centre of Excellent, University of Toronto Vice-Chair Research & Professor of Medicine, Department of Medicine, University of Toronto	ON	Research grant support – Amgen, Novo Nordisk
Harkness, Karen, RN,PhD, CCN(c) CHFN-K	Clinical Strategist – Corhealth Ontario Assistant Clinical Professor, McMaster University	ON	No conflicts to declare
Hegele, Robert, MD, FRCPC Cert. Endo. FACP FCAHS FAHA FCCS	Distinguished University Professor of Medicine and Biochemistry, Western University	ON	Scientific Advisory Board Member – Acasti, Amgen, HLS Therapeutics, Regeneron, Sanofi Speaker at CHE events – Amgen, Sanofi
Hill, Michael	Professor, Departments of Clinical Neurosciences & Hotchkiss Brain Institute, Cumming School of Medicine, University of Calgary & Foothills Medical Centre	AB	Advisory board member – Boehringer Ingelheim Grant support – Medtronic, Stryker, Bayer, Boehringer Ingelheim Investments – Calgary Scientific Inc Clinical trial participation – Stroke Clinical Trials Group in Calgary
Krahn, Andrew	Professor, Head of Division of Cardiology Department of Medicine UBC	BC	No conflicts to declare
Lewin, Gabriela, MD, CCFP	Family Medicine, Assistant Professor, Department of Faculty of Medicine, University of Ottawa	ON	No conflicts to declare
McCullough, Louise, MD, PhD	Professor and Chair, Department of Neurology, McGovern Medical School at UT Health	Texas	No conflicts to declare

NAME	PROFESSIONAL ROLE	LOCATION	CONFLICT OF INTEREST DECLARATIONS
Nerenberg, Kara, MD, MSc, FRCPC	Associate Professor, Depa University of Calgary	AB	No conflicts to declare
Oczkowski, Wes MD, FRCPC	Professor and Academic Head, Division of Neurology McMaster University and Hamilton Health Sciences	ON	Grant support – Northern Ontario Stroke Program (teaching session) Clinical trial participation – site investigator
Purvis, Heather RN, B.N., M.Sc	Patient Representative Cancer Care, Manitoba	MB	No conflicts to declare
Weinberg, Elissa MD, CFPC	Family Medicine, CFPC Specialist	ON	No conflicts to declare
Williams, Heather MD, FRCPC	Assistant Professor, Dalhousie University	NS	No conflicts to declare

Appendix 2

ASA for Prevention of Vascular Events Supplemental Tables

Table 1: Clinical Trials on the Use of ASA for Prevention of Vascular Events

	ARRIVE	ASPREE	ASCEND
Study/Type	**Gaziano et al. 2018** **RCT** ***ASA to Reduce Risk of Initial Vascular Events*** ***(ARRIVE)***	**McNeil et al. 2018** **RCT** ***ASA in Reducing Events in the Elderly (ASPREE) trial***	**ASCEND Study Collaborative Group 2018** **RCT** ***A Study of Cardiovascular Events in Diabetes***
Inclusion/Exclusion	*Inclusion Criteria:* Males ≥ 55 years and above with 2 to 4 risk factors. Male Risk Factors: Elevated cholesterol (Tchol>200 mg/dL or LDL>130 mg/dL), current smoking: defined as any cigarette smoking in the past 12 months, low HDL cholesterol (HDL<40 mg/dL), elevated blood pressure (SBP>140 mmHg), currently on any medication to treat high blood pressure, positive family history of early CHD (a first-degree relative suffered a heart attack before the age of 60 years) Women ≥ 60 years with 3 or more risk factors. Female Risk Factors: Elevated cholesterol (Tchol>240 mg/dL or LDL>160 mg/dL). Other risk factors as per men. *Exclusion criteria:* History of a documented vascular event, such as MI, stroke, coronary artery angioplasty or stenting, coronary artery bypass graft, relevant arrhythmias, or congestive heart	*Inclusion Criteria:* African American and Hispanic men and women, ≥ 65 years, any person from another ethnic minority group and Caucasian persons aged ≥ 70 years. *Exclusion Criteria:* A past history of cardiovascular or cerebrovascular event or established CVD, defined as myocardial infarction (MI), heart failure, angina pectoris, stroke, transient ischemic attack, >50% carotid stenosis or previous carotid endarterectomy or stenting, coronary artery angioplasty or stenting, coronary artery bypass grafting, abdominal aortic aneurysm, a clinical diagnosis of atrial fibrillation, dementia, physical disability, a serious intercurrent illness likely to cause death within the next 5 years, a current or recurrent condition with a high risk of major bleeding, ex: cerebral aneurysm, anemia, absolute contraindication or allergy to ASA, **current continuous use of ASA or other anti-platelet drug** or anticoagulant for secondary prevention. People with previous use of ASA for primary prevention may enter	*Inclusion Criteria:* Males or females **with type 1 or type 2 diabetes mellitus, aged ≥ 40 years w**ith no previous history of vascular disease. No clear contra-indication to ASA, no other predominant life-threatening medical problem. *Exclusion Criteria:* Definite history of myocardial infarction, stroke or arterial revascularisation procedure, **currently prescribed ASA**, warfarin or any other blood thinning medication.

	ARRIVE	ASPREE	ASCEND
	failure or vascular intervention, patients who are at higher than moderate risk on the basis of their diabetes status, other factors known to the investigator, or the currently used national risk score, chronic, high risk of gastrointestinal and other bleeding, frequent (> 5 days/month) **use of NSAIDs (including ASA)**, COX-2 inhibitors or metamizole, current use of an anticoagulant medication, sitting systolic blood pressure >170 mmHg	the trial, provided they agree to cease existing use of ASA and understand that they may be subsequently randomly allocated to low dose ASA or placebo, a systolic blood pressure ≥180 mmHg and / or a diastolic blood pressure ≥105 mmHg	
Sample Description	12,546 patients recruited primarily from primary care centres in 7 countries (Germany, Italy, Ireland, Poland, Spain, UK, and USA). Mean age was 63.9 years, 70.4% were men. Mean estimated ACC/AHA 10-year ASCVD risk score at baseline was 17.3%. Patients were considered to be at moderate risk of a first cardiovascular event.	19,114 persons ≥70 years (or ≥65 years of age among blacks and Hispanics in the United States) without cardiovascular disease, dementia, or disability, recruited from Australia and the US between 2010 and 2014. Median age was 74 years, 44% were men. 14% had used NSAIDS regularly. 11% had used ASA regularly. 42% of participants had 2 cardiovascular risk factors: 28% had 3 or 4.	15,480 participants >40 years, with diabetes with no known CVD. Mean age was 63 years, 63% were men, 36% had taken ASA previously. Median duration of diabetes was 7 years. 83% of participants had low or moderate vascular risk scores.
Method	Participants were randomized 1:1 to receive 100 mg ASA or placebo daily for the duration of the trial	Participants were randomly assigned (1:1) to receive 100 mg of enteric-coated ASA or placebo.	Participants were randomized 1:1 to receive 100 mg ASA or placebo daily for the duration of the trial
Outcomes	**Primary outcome:** Composite of time to first occurrence of confirmed MI, stroke, cardiovascular death, unstable angina, or TIA **Safety outcomes:** Hemorrhagic events	**Primary outcome:** CVD (fatal coronary heart disease, nonfatal MI, fatal or nonfatal stroke, or hospitalization for heart failure). **Safety outcomes:** Major bleeding events	**Primary outcome:** First serious vascular event (MI, stroke, TIA or cardiovascular death) **Secondary outcome:** Gastrointestinal tract cancers **Safety outcomes:** Hemorrhagic events
Key Findings and Recommendations	Median duration of follow-up was 5.1 years. 29.6% of patients terminated the study early. In the intention- to- treat analysis, the risk of the primary outcome and its component parts were not reduced significantly with ASA therapy Primary outcome: HR=0·96, 95% CI 0·81–1·13, p=0·6038	Median duration of follow-up was 4.7 years. In the final 12 months of the trial, 62% of the participants in the ASA group and 64% of those in the placebo group were still taking the assigned trial intervention. The number of CVD events did not differ significantly between groups (10.7 vs. 11.3/1,000-person years, HR=0.95, 95% CI	Mean duration of follow-up was 7.4 years. Estimated mean adherence was 70% in both groups. The risk of the primary outcome was significantly lower in the ASA group (8.5% vs, 9.6%, RR=0.88, 95% CI, 0.79 to 0.97; p=0.01).

	ARRIVE	ASPREE	ASCEND
	Fatal/nonfatal MI: HR=0·85, 95% CI 0·64–1·11, p=0·2325 Fatal/nonfatal stroke: HR=1.12, 95% CI 0·80–1·55, p=0·5072 Cardiovascular death: HR=0·97, 95% CI 0·62–1·52, p=0·9010 TIA: HR=0·93, 95% CI 0·61–1·42, p=0·7455 The risk of serious adverse events was similar between groups (20.19% vs. 20.89%). The overall incidence of treatment-related adverse events was significantly higher in the ASA group (16.75% vs. 13.54%, p<0·0001). The authors suggested that the reason for the apparent lack of benefit of ASA was due to the lower than expected event rate (1,500 expected, 500 actual), which was attributed to aggressive prevention measures, particularly, the treatment of hypertension).	0.83–1.08), nor did the number of ischemic strokes (3.5 vs. 3.9/1,000 person-years follow-up; HR=0.89, 95% CI 0.71–1.11). The risk of major bleeding events was significantly increased in the ASA group (8.6 vs. 6.2/1,000-person years; HR=1.38, 95% CI 1.18–1.62, p<0.001). The risk of fatal hemorrhagic stroke was not significantly increased with ASA therapy (0.3 vs. 03/1,000-person years; HR=1.01, 95% CI 0.47–2.17).	The risk of any major bleeding was significantly increased in the ASA group (4.1% vs. 3.2%, RR=1.29, 95% CI 1.09-1.52, p=0.003). There was no significant difference between groups in the risk of GI cancer (2% vs. 2%, RR=0.99, 95% CI 0.80–1.24).

Table 2: Systematic Review & Meta Analyses

	Huang 2019	Mahmoud 2019	Zheng 2019
Study/Country	**Huang et al. 2019** **Taiwan**	**Mahmoud et al. 2019** **USA**	**Zheng & Roddick 2019** **UK**
Included Trials	HOT 1998, Thrombosis Prevention Trial 1998, Primary Prevention Project 2001, ECLAP 2004, WHS 2005, APLASA 2007, POPADAD 2008, JPAD 2008, AAA 2010, JPPP 2014, ASCEND 2018, ASPREE 2018, ARRIVE 2018	British Male Doctors 1988, PHS 1989, HOT 1998, Thrombosis Prevention Trial 1998, Primary Prevention Project 2001, WHS 2005, JPAD 2008, JPPP 2014, ASCEND 2018, ASPREE 2018, ARRIVE 2018	British Male Doctors 1988, PHS 1989, HOT 1998, Thrombosis Prevention Trial 1998, Primary Prevention Project 2001, WHS 2005, POPADAD 2008, JPAD 2008, AAA 2010, JPPP 2014, ASCEND 2018, ASPREE 2018, ARRIVE 2018
Sample Description	13 RCTs (n= 134,446) that included persons without preexisting symptomatic cardiovascular diseases (eg, coronary heart disease, stroke, or peripheral artery disease). Mean age ranged from 42.9 to 74.0 years. Percentage of men ranged from 10% to 100%.	11 RCTs (n=157,248) that included persons without prior history of atherosclerosis (including peripheral arterial disease, coronary artery disease, prior MI, prior stroke or TIA, prior percutaneous coronary intervention, prior coronary artery bypass grafting), and which enrolled ≥500 patients. Mean age was 61.3 years, 48% were men.	13 RCTs (n=164,225), which enrolled at least 1,000 participants with no known cardiovascular disease and a follow-up of at least 12 months
Method	Trials compared low-dose ASA (≤100 mg/day, for ≥6 months) vs. placebo, or no treatment. Daily doses in active treatment arm were 75 mg (n=2), 81 mg (n=1), 100 mg (n=8), 100 mg every other day (n=1) and 81 or 100 mg (n=1)	Trials compared ASA vs. placebo, or no treatment. Daily doses of ASA were 75 mg (n=2), 100 mg (n=5), 325 mg every other day (n=1), 300 or 500 (n=1), 100 mg every other day (n=1) and 81 or 100 mg (n=1)	Trials compared ASA vs. placebo, or no treatment. Daily ASA dose was 75 mg (n=2), 100 mg (n=7), 325 mg every other day (n=1), 300 or 500 (n=1), 100 mg every other day (n=1) and 81 or 100 mg (n=1)
Outcomes	**Primary outcome:** Any intracranial hemorrhage **Secondary outcomes**: Intracerebral hemorrhage, subdural or extradural hemorrhage, and subarachnoid hemorrhage (SAH)	**Primary outcome:** All-cause mortality **Safety outcome:** Major bleeding	**Primary outcomes:** *Cardiovascular outcome* A composite of cardiovascular mortality, nonfatal MI, and nonfatal stroke **Secondary cardiovascular outcomes:** All-cause mortality, cardiovascular-related mortality, myocardial infarction, total stroke (ischemic, hemorrhagic, and unknown), and ischemic stroke. **Bleeding outcomes:**

	Huang 2019	Mahmoud 2019	Zheng 2019
			Major bleeding events, intracranial bleeding, GI bleeding
Key Findings and Recommendations	Mean duration of follow-up ranged from 2.3 to 8.2 years. ASA was associated with a significantly increased risk of any intracranial bleeding (RR=1.37, 95% CI, 1.13-1.66; n=8 trials; 2 additional intracranial hemorrhages in 1,000 people). In a sensitivity analysis, excluding the results from ASPREE, which included elderly people, the risk became non significant (RR=1.28, 95% CI, 0.99-1.65). ASA was not associated with a significantly increased risk of intracerebral hemorrhage (RR=1.23, 95% CI, 0.98- 1.54, n=10 trials) or SAH (RR= 1.13, 95% CI, 0.70-1.83, n=5 trials) ASA was associated with a significantly increased risk of subdural or extradural hemorrhage (RR=1.53, 95% CI, 1.08-2.18, n=4 trials, 1 additional event in 1,000 people).	Mean duration of follow-up was 6.6 years. The use of ASA was not associated with a lower incidence of all-cause mortality (4.6% vs. 4.7%; RR= 0.98, 95% CI 0.93–1.02; p = 0.30). The risk of ischemic stroke was not reduced significantly with ASA (1.7% vs. 1.8%; RR=0.94, 95% CI 0.86-1.04, p=0.24) ASA was associated with an increased incidence of major bleeding (1.8% vs. 1.2%; RR=1.47, 95% CI 1.31–1.65; P < 0.0001) and intracranial haemorrhage (0.4% vs. 0.3%; RR= 1.33, 95% CI 1.13–1.58; P = 0.001).	The use of ASA was associated with a significant reduction in the cardiovascular outcome (HR=0.89 [95% CrI, 0.84-0.95]; ARR, 0.38% [95% CI, 0.20%- 0.55%]; NNT= 265), and ischemic stroke (HR=0.81 [95% CrI, 0.76-0.87]; ARR, 0.16% [95% CI 0.06 to 0.30]; NNT=540). The use of ASA was associated with an increased rate of major bleeding (HR=1.43 [95% CrI, 1.30-1.56]; ARI, 0.47% [95% CI, 0.34%-0.62%]; NNH= 210), intracranial bleeding and GI bleeding. The risk of the cardiovascular outcome was reduced significantly in persons at high and low cardiovascular risk, and those with diabetes. Bleeding risk was also significantly increased in these groups.

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