

Canadian Stroke Best Practice Recommendations, seventh edition: acetylsalicylic acid for prevention of vascular events

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In 2016, 270 204 people in Canada (excluding Quebec) were admitted to hospital for heart conditions, stroke and vascular cognitive impairment, including 107 391 women and 162 813 men, of whom 91 524 died.¹ This equates to 1 out of every 3 deaths in Canada and outpaces other diseases; 13% more people die of heart conditions, stroke or vascular cognitive impairment than die from all cancers combined.¹

The benefits of acetylsalicylic acid (ASA) for secondary prevention of atherosclerotic cardiovascular disease are well established. In contrast, although low-dose ASA therapy for primary prevention of atherosclerotic cardiovascular disease was once commonly recommended, this practice is now being reconsidered in light of recent evidence. Three large randomized controlled trials on primary prevention found no net benefit of ASA for prevention of cardiovascular events or mortality in healthy older adults (defined in the ASPREE [Aspirin in Reducing Events in the Elderly] trial as > 65 yr) or persons with diabetes or other risk factors.²⁻⁴ Moreover, 2 recent systematic reviews incorporating the evidence from these trials provided somewhat conflicting results.^{5,6} Both found that the risk of major bleeding events was significantly increased in participants receiving ASA. However, 1 systematic review found that the use of ASA did not reduce the risk of all-cause mortality or ischemic stroke,⁶ while the other reported that ASA did reduce the risk of a composite of cardiovascular mortality, nonfatal myocardial infarction, nonfatal stroke and ischemic stroke.⁵

With greater awareness of the risks and benefits of ASA, overall lower rates of cardiovascular events in contemporary populations compared with those in older studies, and conflicting

KEY POINTS

- Acetylsalicylic acid is still strongly indicated for secondary prevention in patients who have had manifest cardiovascular, cerebrovascular or peripheral artery disease.
- Acetylsalicylic acid (ASA) is no longer recommended for primary prevention in individuals without a history of symptomatic cardiovascular disease, stroke or peripheral artery disease; the harms of daily ASA use could potentially outweigh the benefits.
- These revised recommendations present an opportunity for increased focus on primary prevention through healthy lifestyle choices, lifestyle modification and management of vascular risk factors.
- The decision to start, stop or continue ASA therapy is individualized, and the decision-making process should be shared between health professionals and patients, weighing risks, benefits, values and preferences.
- Important questions remain, including benefits of ASA for younger high-risk patients, individuals with subclinical vascular disease and asymptomatic atherosclerosis, and outcomes in patients who cease taking ASA after long-term use for primary prevention.

recommendations in guidelines and systematic reviews, clinicians are increasingly uncertain about the role of ASA for primary prevention.² The actual number of people in Canada who are taking ASA prophylactically (either as prescribed by a health professional or of their own volition) is not known, although it is likely substantial. A US study reported results from a public poll that found 29 million people were taking ASA in that country, with 23% doing so without a physician's recommendation.⁷

This set of recommendations is intended to provide guidance for the use of ASA for primary prevention of vascular events. Additionally, the guideline comments on secondary stroke prevention to highlight the differences between these 2 distinct clinical areas. The recommendation regarding the use of ASA for the primary prevention of vascular events is a new addition to the Canadian Stroke Best Practice Recommendations portfolio from the Heart and Stroke Foundation of Canada. The recommendation on secondary stroke prevention is drawn from an existing set of recommendations on secondary prevention that was updated simultaneously.

These recommendations provide an evidence-based response to a need for guidance by health care professionals and the public, and to ensure alignment and consistency across other Canadian organizations such as the Canadian Cardiovascular Society and Thrombosis Canada, which have also issued previous recommendations and clinical guidance regarding ASA use in primary prevention.^{8,9} The goals of developing, disseminating and implementing these recommendations among health care providers and the public are to optimize evidence-based care across Canada, reduce practice variations and narrow the gap between current knowledge and clinical practice.

Scope

The Canadian Stroke Best Practice Recommendations are intended to provide up-to-date, evidence-based guidelines for the prevention and management of conditions that are of concern to 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 (i.e., patients, families and informal caregivers).

This current set of recommendations is unique for the Canadian Stroke Best Practice Recommendations in that it is not focused just on stroke; rather, it is applicable to the primary prevention of a range of conditions including cardiovascular disease, cerebrovascular disease, vascular cognitive impairment and peripheral arterial disease. This guideline includes recommendations for the use of ASA for both primary and secondary prevention. The recommendation on secondary prevention in this guideline is limited exclusively to ASA monotherapy and does not address the broader selection of antiplatelet agents currently available for this purpose. Recommendations on secondary prevention related to these agents can be found in the Canadian Stroke Best Practice Recommendations guideline on secondary prevention of stroke, which was updated in parallel to this guideline on ASA, using the same rigorous methodology.¹⁰

These recommendations are intended for use by all health care professionals across the continuum of care; people with lived experience of stroke, heart conditions, vascular disease and vascular cognitive impairment; and for the general public. Health system policy-makers, planners, funders, senior managers and administrators who are responsible for the coordination and delivery of health services within a province or region may also find this document relevant and applicable to their work.

Recommendations

Three recommendations have been developed regarding the use of ASA for prevention of vascular events (Box 1). The first reinforces the continued important role of ASA for secondary prevention in people who have already had a first vascular event. The second directly responds to new evidence and recommends against the use of ASA in healthy individuals without a history of vascular events. The third emphasizes the importance of shared decision-making between clinician and patient to ensure patient values and preferences are considered. More discussion of the evidence supporting the recommendations is available in Appendix 1 (at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.191599/-/DC2) and the full guideline (www.strokebestpractices.ca/recommendations/ASA-for-prevention).

Secondary prevention

Acetylsalicylic acid is strongly recommended for secondary prevention in individuals with symptomatic cardiovascular, cerebrovascular or peripheral arterial disease (evidence level A).¹¹⁻¹³

The benefit of ASA for secondary prevention is well established. Daily, low-dose ASA reduces the risk of vascular events including myocardial infarction, stroke and vascular death in patients who have had a previous vascular event. The Antithrombotic Trialists' Collaboration (2002) has meta-analyzed data from many large trials showing consistent effects of ASA on preventing recurrent cardiovascular events.¹¹ For example, treatment with ASA instead

Box 1: Recommendations for the use of acetylsalicylic acid (ASA) in the prevention of vascular events*

Secondary prevention†

Acetylsalicylic acid is strongly recommended for secondary prevention in individuals with symptomatic cardiovascular, cerebrovascular or peripheral arterial disease (evidence level A).¹¹⁻¹³

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).^{14,15}

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 shared decision to start, continue or stop ASA for primary prevention of vascular disease (evidence level B).^{16,17}

*Please refer to Appendix 2 for evidence tables comparing elements of randomized trials and systematic reviews.

†For additional information regarding the use of ASA and other antiplatelet agents in secondary prevention, please see the Canadian Stroke Best Practice Recommendations Secondary Prevention of Stroke Module,¹⁰ Canadian Cardiovascular Society guideline on antiplatelet and anticoagulant use,⁹ and Thrombosis Canada clinical guides.⁸

of placebo reduced the number of serious vascular events by 36 (standard error [SE] 5) per 1000 per year in patients with a previous myocardial infarction and also by 36 (SE 6) per 1000 per year in patients with a previous history of stroke or transient ischemic attack. In patients with peripheral arterial disease, treatment with ASA instead of placebo reduced the odds of serious vascular events by 23% (SE 8%). Similar risk reductions were seen for patients with stable or unstable angina.¹¹ More information on the evidence supporting this recommendation is available at www.strokebestpractices.ca/recommendations/ASA-for-prevention.

Primary prevention

The use of acetylsalicylic acid 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 acetylsalicylic acid in individuals with asymptomatic atherosclerosis is uncertain (evidence level B).^{14,15}*

Reduction in vascular events

We derived the evidence base used to formulate the recommendation regarding ASA use for primary prevention mainly from 3 recently published randomized controlled trials (RCTs). Each trial assessed the potential benefit of 100 mg of ASA versus placebo in people without pre-existing cardiovascular disease, which was defined slightly differently in each trial (Appendix 2, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.191599/-/DC2).

All trials included large sample sizes (> 12000 to > 19000 participants). The ARRIVE² (Aspirin to Reduce Risk of Initial Vascular Events) trial included men aged ≥ 55 years with 2 to 4 cardiovascular risk factors and women aged ≥ 60 years with 3 or more risk factors, and excluded people with diabetes. The ASPREE³ trial involved men and women from Australia and the United States who were aged ≥ 70 years (or ≥ 65 years among black and Hispanic people in the US). The ASCEND⁴ (A Study of Cardiovascular Events in Diabetes) trial included men and women aged ≥ 40 years with type 1 or 2 diabetes. The mean age of participants was 64 years in the ARRIVE² and ASCEND⁴ trials, and the median age in the ASPREE trial³ was 74 years. Current use of ASA or anticoagulants was an exclusion criterion in all trials; however, 36% of participants in the ASCEND trial⁴ had used ASA before screening, while 11% had used ASA previously in the ASPREE trial.³ Median duration of follow-up ranged from 4.7 to 7.1 years.

The results of 2 trials were negative (ARRIVE,² ASPREE³), whereby the risks of cardiovascular events were not significantly lower in the ASA-treated group. In the ARRIVE² and ASPREE³ trials, the hazard ratios associated with ASA use for the primary outcome were 0.96 (95% confidence interval [CI] 0.81–1.13) and 0.95 (95% CI 0.83–1.08), respectively. In the ASCEND trial,⁴ the risk of the primary outcome (first serious vascular event [myocardial infarction, stroke, transient ischemic attack or cardiovascular death]) was significantly lower in the ASA group (8.5% v. 9.6%; relative risk [RR] 0.88, 95% CI 0.79–0.97).

The results of these 3 trials were incorporated into 2 systematic reviews, the results of which conflicted.^{5,6} The use of ASA did

not reduce the risk of all-cause mortality or ischemic stroke⁶ but did reduce the risk of a composite outcome of cardiovascular mortality, nonfatal myocardial infarction, nonfatal stroke and ischemic stroke.⁵ Each of these reviews included the results of the same 11 RCTs, but the review by Zheng and Roddick⁵ included 2 additional trials (POPADAD [Prevention of Progression of Arterial Disease and Diabetes] 2008,¹⁸ and AAA [Aspirin for Asymptomatic Atherosclerosis] 2010¹⁴). The inclusion criteria were restricted to participants who had no previous cardiovascular disease in 1 review,⁵ and the other included people without a previous history of atherosclerosis.⁶

Risks

In the 3 aforementioned trials (ASPREE,³ ARRIVE² and ASCEND⁴), the risk of major bleeding events increased significantly with ASA therapy (ASPREE: hazard ratio [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).

In a systematic review and meta-analysis designed specifically to examine the risk of intracranial hemorrhage associated with the use of ASA, Huang and colleagues¹⁹ included the results of 13 RCTs ($n = 134\,446$) that comprised individuals without pre-existing symptomatic cardiovascular diseases (e.g., coronary artery disease, stroke or peripheral artery disease). The trials compared low-dose ASA (≤ 100 mg/d for ≥ 6 mo) versus placebo or no treatment, and examined intracranial bleeding outcomes exclusively. 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 1000 people). In a sensitivity analysis, excluding the results from the ASPREE trial,³ which included older people only (> 65 yr and ≥ 70 yr, depending on race), the risk became nonsignificant. Acetylsalicylic acid was not associated with a significantly increased risk of intracerebral hemorrhage or subarachnoid hemorrhage. In subgroup analysis, participants with Asian ethnicity and people with a body mass index < 25 taking ASA were at significantly higher risk for intracerebral hemorrhage. The risk of major bleeding was also increased in the results of 2 other recent meta-analyses.^{5,6}

Areas of uncertainty

Owing to insufficient evidence of benefit of ASA for primary prevention of major adverse cardiovascular events, there is no rationale for using ASA for primary prevention in patients at any level of risk, including those at higher risk. However, Marquis-Gravel and colleagues²⁰ highlighted several areas of uncertainty that remain regarding the use of ASA for primary prevention after the completion of the ARRIVE, ASPREE and ASCEND trials. 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,²¹ the risk of cardiovascular events associated with the use of 75–100 mg ASA for primary prevention decreased with increasing weight, while low-dose ASA had the greatest preventive effect among those participants weighing 50–69 kg. In the same study, ASA doses of 350 mg and 500 mg for primary prevention were associated with decreased risk of cardiovascular events in people weighing ≥ 70 kg.

Acetylsalicylic acid has also been evaluated with respect to its efficacy for reducing the risk of cardiovascular events including transient ischemic attack, stroke, myocardial infarction, unstable angina or death among people with asymptomatic atherosclerosis. Although it has been suggested that low-dose ASA leads to a change in the composition of plaque within blood vessels, the use of 325 mg of daily ASA for 2 years in people with carotid stenosis ($\geq 50\%$) was not associated with reductions in vascular events compared with placebo.¹⁵

The role of sex as a potential effect modifier is less clear, as we identified no significant interactions between sex and the effectiveness of ASA in the ARRIVE, ASCEND or ASPREE trials. In an older meta-analysis, which included the results of 6 RCTs, Berger and colleagues²² suggested that ASA reduced the risk of myocardial infarction only in men, and the risk of all stroke and ischemic strokes only in women. The role of gender was not discussed in the results of any of these trials.

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 acetylsalicylic acid for primary prevention of vascular disease. An individual's risk, benefit, values and preferences should be considered in order to make an informed shared decision to start, continue or stop acetylsalicylic acid for primary prevention of vascular disease (evidence level B).^{16,17}

Although long-term use of ASA is not recommended for the primary prevention of a first vascular event in these recommendations, there is recognition that the decision to start, continue or stop ASA therapy should be highly individualized, following an assessment of the benefit–risk ratio and a clinician–patient discussion regarding potential benefits and harms, and alternatives. This process of shared decision-making is based on both clinical evidence and the patient's informed preferences and values.^{23,24}

For most patients, stopping ASA will be the best choice. However, some individuals may choose to remain on ASA for personal reasons, such as having a strong family history of vascular disease, or if they value prevention of vascular events more than avoiding the harm of major bleeding.

There is currently no evidence that directly addresses the role of shared decision-making in the context of ASA for primary prevention, although interventions to support shared decision-making have been evaluated for the treatment of hypertension,^{25,26} atrial fibrillation²⁷ and diabetes.²⁸

Methods

Guideline panel composition

An interdisciplinary expert writing group panel was convened by the Heart and Stroke Foundation of Canada to review the literature and address the utility of ASA use for primary prevention of vascular events. The panel included stroke neurologists, cardiologists, thrombosis specialists, family physicians, an emergency medicine physician, a physiatrist, pharmacists, nurses and an epidemiologist. Members

were selected after a call for nominations for participants for the Canadian Stroke Best Practice Recommendations primary and secondary prevention writing group panels. The writing group chair (T.W.) and members of the Canadian Stroke Best Practice Recommendations Advisory Committee selected the 18 members of the primary writing group panel, ensuring geographic, urban and rural, and interdisciplinary representation; gender balance; and years of experience.

As part of the Canadian Stroke Best Practice Recommendations methodology, a Community Consultation and Review Panel, composed of 8 patients and caregivers, took part in the review and development of these recommendations,²⁹ jointly with the writing group.

A group of 15 external reviewers, who were not involved in the guideline development process, was convened to conduct a final review of the guideline. The external review panel had a similar composition across disciplines as the writing group panel. They were selected from our original list of nominees who were not chosen for the writing group, and through review of the literature to identify knowledgeable professionals on this topic.

These recommendations were developed in collaboration with the Canadian Stroke Consortium, with several members of the consortium (T.W., D.J.G., A.P., L.K.C., S.B.C., T.F., L.G., M.S., G.G., D.D. and E.E.S.) participating in the guideline writing group. The Canadian Cardiovascular Society also had 2 official representatives (J.C., J.A.U.) participate as writing group members.

Guideline development

The process for developing and updating the Canadian Stroke Best Practice Recommendations follows a rigorous, standardized framework adapted from the Practice Guideline Evaluation and Adaptation Cycle,^{30,31} and addresses all criteria defined within the Appraisal of Guidelines for Research and Evaluation (AGREE) Trust model.³² The methodology has been applied in previously published Canadian Stroke Best Practice Recommendations updates and can be found on the Canadian Stroke Best Practices website at www.strokebestpractices.ca.

Experienced personnel conducted literature searches to identify peer-reviewed literature that examined the use of ASA monotherapy for the prevention of vascular events, and the role of shared decision-making for vascular risk reduction. We included systematic reviews, meta-analyses, randomized controlled trials and observational studies, as available. The literature for this module was current to November 2019. The search strategy is available in Appendix 2.

Following a standardized abstraction format, evidence tables were constructed by experienced personnel, including content from selected studies, and these were provided to the writing group for review. The writing group discussed and debated the strength, importance, clinical relevance and applicability of the evidence and, through consensus, developed a draft set of proposed recommendations. During this process, we identified additional literature and used it as we developed a final set of proposed recommendations. Definitions of terms used within the recommendations (e.g., primary prevention, secondary prevention) are available at www.strokebestpractices.ca/recommendations/ASA-for-prevention.

We assigned each recommendation a level indicating the strength of the evidence, ranging from A to C, according to the

criteria defined in Box 2. These criteria are adapted from work by Guyatt and colleagues.³³ When developing and including “C-level” recommendations, we obtained consensus among the writing group and validated it through the internal and external review process. We used this level of evidence cautiously, and only when there was a lack of stronger evidence for the topics of interest, and the writing group thought that some guidance was warranted for these areas.

During the work of developing the recommendations for the use of ASA for primary prevention, we became concerned about potential confusion regarding the use of ASA for secondary prevention among the public and health care providers. Most members could cite several instances in their clinical practices where patients with a history of stroke or coronary artery disease had stopped ASA on their own, based on exposure to media coverage of the new trials for ASA for primary prevention. Accordingly, we decided to expand the scope of this guideline to include a recommendation on secondary prevention. This recommendation was developed jointly with a separate guideline writing group working on secondary prevention of stroke, following the rigorous guideline development process for the Canadian Stroke Best Practice Recommendations. Several members of the primary prevention writing group participated in both groups. A full description of the methodology for the secondary prevention guideline can be found at strokebestpractices.ca.

Review

The draft set of recommendations underwent an internal review by the Canadian Stroke Best Practice Recommendations Advisory Committee, and was then sent to the external review group for review. The draft recommendations were also sent to the Canadian Stroke Consortium, Canadian Cardiovascular Society, Thrombosis Canada, the Canadian Society of Hospital Pharmacists and the Canadian Pharmacists Association for their review and consideration for endorsement. We gave all feedback careful consideration during the editing process and incorporated it into the final version of the recommendations as appropriate.

The 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.

More information on the guideline methods can be found in the full guideline, available at www.strokebestpractices.ca/recommendations/ASA-for-prevention. We will update these recommendations regularly, every 2 to 3 years, to integrate emerging evidence.

Management of competing interests

All potential participants in the recommendation development and review process were required to sign confidentiality agreements and to declare all direct and indirect competing interests in writing. Any declared competing interests were reviewed by the Chairs of the Canadian Stroke Best Practice Recommendations Advisory Committee and appropriate staff members of the Heart and Stroke Foundation of Canada with respect to potential impact. Potential members of the writing group who had direct competing interests were not invited to participate.

We identified participants who had indirect competing interests for a topic area at the beginning of discussions for that topic. The writing group and external reviewers work in a wide range of health care settings. This interdisciplinary approach ensured that the perspectives of relevant health disciplines and care settings were considered in the development of the recommendations, and no one member was more influential than the others, thus mitigating the risk of potential or real competing interests from individual members.

Given there were no direct competing interests related to ASA, all members participated in the voting process. All 18 members voted in support of the recommendations on secondary prevention and shared decision-making, and 17 of 18 members voted in support of the recommendation on primary prevention. Therefore, any potential indirect competing interests were mitigated by the broad support across the members of the writing group panel.

Box 2: Description of levels of evidence reported in Canadian Stroke Best Practice Recommendations³³

Level of evidence	Criteria
A	Evidence from a meta-analysis of RCTs or consistent findings from 2 or more RCTs. Desirable effects clearly outweigh undesirable effects or vice versa. Phrases used in recommendations with this level of evidence include “strong recommendation”; actions “should be (or not be) done.”
B	Evidence from a single RCT or consistent findings from 2 or more well-designed nonrandomized or noncontrolled trials, and large observational studies. Meta-analysis of nonrandomized or observational studies. Desirable effects outweigh or are closely balanced with undesirable effects, or vice versa. Phrases used in recommendations with this level of evidence include “is recommended”; “should be considered”; and in some cases where there is strong agreement by the writing group, “actions should be (or not be) done on most or specific groups as applicable.”
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. Phrases used in recommendations with this level of evidence include “may be considered” or “is reasonable.”
Clinical consideration	Reasonable practical advice provided by consensus of the writing group on specific clinical issues that are common or controversial and lack research evidence to guide practice. No evidence levels are assigned to clinical considerations.

Note: RCT = randomized controlled trial.

Implementation

These recommendations are accompanied by supporting information found at www.strokebestpractices.ca/recommendations/ASA-for-prevention. This information includes a rationale for including this topic in the Canadian Stroke Best Practice Recommendations, which describes the problem and burden; system implications to ensure the structural elements and resources are available to achieve recommended levels of care, including professional education and public awareness efforts; performance measures to monitor implementation, care delivery and patient outcomes; implementation resources for clinicians and the public to support integration of the actions within the recommendations to daily practice; and a more detailed summary of the evidence on which the recommendations were based. Knowledge translation information for the recommendations can also be found on the website.

A wide range of professional and public education activities are planned that include messaging on mainstream and social media, public and health professional webinars, presentation at conferences, email campaigns and inclusion in newsletters for health professionals and the public, updated information on Heart and Stroke Foundation of Canada websites and on those of the professional groups that endorsed these recommendations, and an infographic explaining the recommendations to the public.

At the practice level, we advise that people taking ASA for primary prevention be informed of the newest evidence that suggests there is less benefit than previously believed and that newer guidelines recommend against it. Practitioners are strongly encouraged to promote medical, lifestyle and behavioural changes that are more effective than ASA in preventing cardiovascular events, including management of hypertension, diabetes and hypercholesterolemia; smoking cessation; increased physical activity; maintaining a healthy weight; and eating a healthy diet.^{34,35}

Other guidelines

This guideline includes the most recent clinical trials and systematic reviews on this topic. In contrast to some previous guidelines, we do not recommend ASA for primary prevention of a first vascular event for any subgroups, including patients at higher estimated 10-year risk. Recent trials fail to provide consistent evidence that ASA reduces the risk of first vascular events, with clear evidence of increased harm from major bleeding.

An earlier guideline issued by the Canadian Cardiovascular Society in 2011 stated that antiplatelet therapy was not recommended in individuals without cardiovascular disease because of the increased risk of major bleeding.⁹ The 2016 European guideline on prevention of cardiovascular disease³⁶ includes similar recommendations. In 2018, Thrombosis Canada suggested that ASA be used only in special circumstances for primary prevention of cardiovascular morbidity and mortality.⁸

The current 2019 American College of Cardiology/American Heart Association guideline on the primary prevention of cardiovascular disease suggests that low-dose ASA (75–100 mg/d) might be considered among selected adults aged 40–70 years at higher risk of cardiovascular disease, and should be avoided in persons aged > 70 years.³⁷ This language was modified from the 2014 recommendation, which stated that “the use of ASA 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.”³⁸

In 2016, the US Preventive Services Task Force made age-specific recommendations, suggesting that individuals aged 50 to 59 years start low-dose ASA if their 10-year cardiovascular risk is > 10% and the risk of bleeding is not increased. For those aged 60 to 69 years, the recommendation was for the decision to be a personal one, given a similar 10-year risk; the task force suggested the evidence was insufficient to make recommendations for people younger than 50 years or older than 69 years.³⁹ The Canadian Task Force on Preventive Health Care has not published recommendations on this topic. Box 3 includes details of the guidelines reviewed and discussed by the writing group.

Gaps in knowledge

The recent evidence and the accumulating guidance that routine use of ASA is not recommended for primary prevention of vascular disease will likely lead to a substantial shift in approaches to primary prevention of vascular disease and public perception and affect clinical practice. However, important questions remain that have not yet been addressed by research.

Most trials have focused on older people because they are generally at the highest risk of new cardiovascular events; whether ASA could provide net benefit in younger, very high-risk patients with lower likelihood of gastrointestinal bleeding is possible but unproven. With increasing sensitivity of imaging, it is possible to identify persons with subclinical disease (such as silent myocardial infarction or stroke, or asymptomatic atherosclerosis) but it is not clear whether these patients would derive more benefit from ASA. The available trials in such populations fail to show that ASA makes a clinically substantial difference in the risk of first-ever clinical events.^{14,15}

Finally, there is the challenging question of how to advise patients who have been taking ASA for primary prevention for many years without experiencing adverse events such as gastrointestinal bleeding. There is a paucity of research on outcomes after ceasing daily ASA use in this setting, with no controlled trials. Stopping ASA may not be advisable in all patients if there are rebound prothrombotic effects from doing so. Further, the shared decision-making literature does not address this specific topic and poses an opportunity to apply the principles of shared decision-making on this subject, which likely affects a substantial number of Canadians.

Box 3: Statements from other guidelines on the use of ASA for primary prevention of vascular events

Organization (year)	Recommendation*
American Diabetes Association (2019) ⁴⁰	<ul style="list-style-type: none"> Aspirin therapy (75–162 mg daily) may be considered as a primary prevention strategy in those with diabetes who are at increased risk of CVD, after a discussion with the patient on the benefits versus increased risk of bleeding (evidence level C).
ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease (2019) ³⁷	<ul style="list-style-type: none"> Low-dose aspirin (75–100 mg orally daily) might be considered for the primary prevention of ASCVD among select adults 40 to 70 years of age who are at higher ASCVD risk but not at increased bleeding risk (class IIb recommendation, evidence level A). Low-dose aspirin (75–100 mg orally daily) should not be administered on a routine basis for the primary prevention of ASCVD among adults > 70 years of age (class III recommendation, evidence level B-R). Low-dose aspirin (75–100 mg orally daily) should not be administered for the primary prevention of ASCVD among adults of any age who are at increased risk of bleeding (class III recommendation, evidence level C-LD).
Thrombosis Canada (2018) ⁸	<ul style="list-style-type: none"> Only in special circumstances in patients without manifest vascular disease in whom vascular risk is considered high and bleeding risk is considered low. Examples include: asymptomatic carotid or coronary atherosclerosis demonstrated on vascular imaging studies and patients at very high risk of vascular events due to multiple cardiovascular risk factors. (No evidence levels provided in Thrombosis Canada statements.)
USPSTF (2016) ³⁹	<ul style="list-style-type: none"> The USPSTF recommends initiating low-dose aspirin use for the primary prevention of CVD and CRC in adults aged 50 to 59 years who have a 10% or greater 10-year CVD risk, are not at increased risk for bleeding, have a life expectancy of at least 10 years, and are willing to take low-dose aspirin daily for at least 10 years (grade B recommendation). The decision to initiate low-dose aspirin use for the primary prevention of CVD and CRC in adults aged 60 to 69 years who have a 10% or greater 10-year CVD risk should be an individual one. Persons who are not at increased risk for bleeding, have a life expectancy of at least 10 years, and are willing to take low-dose aspirin daily for at least 10 years are more likely to benefit. Persons who place a higher value on the potential benefits than the potential harms may choose to initiate low-dose aspirin (grade C recommendation). The current evidence is insufficient to assess the balance of benefits and harms of initiating aspirin use for the primary prevention of CVD and CRC in adults younger than 50 years (I statement). The current evidence is insufficient to assess the balance of benefits and harms of initiating aspirin use for the primary prevention of CVD and CRC in adults aged 70 years or older (I statement).
The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (2016) ³⁶	<ul style="list-style-type: none"> Antiplatelet therapy is not recommended in individuals free from CVD, due to the increased risk of major bleeding (class III recommendation; evidence level B).
American College of Chest Physicians (2012) ⁴¹	<ul style="list-style-type: none"> For persons aged 50 years or older without symptomatic CVD, we suggest low-dose aspirin 75 to 100 mg daily over no aspirin therapy (grade 2B).
Canadian Cardiovascular Society (2011) ⁹	<ul style="list-style-type: none"> For men and women without evidence of manifest vascular disease, the use of ASA at any dose is not recommended for routine use to prevent ischemic vascular events (class III recommendation; evidence level A). For men and women without evidence of manifest vascular disease, the use of clopidogrel 75 mg daily plus ASA at any dose is not recommended to prevent ischemic vascular events (class III recommendation; evidence level B). In special circumstances in men and women without evidence of manifest vascular disease in whom vascular risk is considered high and bleeding risk is low, ASA 75–162 mg daily may be considered (class IIb recommendation; evidence level C).

Note: ACA/AHA = American College of Cardiology/American Heart Association, ASA = acetylsalicylic acid, ASCVD = atherosclerotic cardiovascular disease, CRC = colorectal cancer, CVD = cardiovascular disease, USPSTF = US Preventive Services Task Force.

*Definitions of the class or strength of recommendations and level of evidence can be found in the cited guidelines.

Conclusion

The use of ASA for prevention (primary and secondary) of vascular events has been a common practice in Canada and elsewhere for decades. Based on a reappraisal of the evidence in light of recent

publications of large neutral trials, we now recommend that ASA no longer be routinely used for primary prevention in most individuals. The general population should be advised that daily ASA is not recommended for primary prevention of vascular events because the bleeding risks potentially outweigh the benefits.

Acetylsalicylic acid is still strongly recommended for secondary prevention in patients who have had manifest cardiovascular, cerebrovascular or peripheral artery disease.

The decision to start, stop or continue ASA therapy is individualized and the decision-making process should be shared between health professionals and patients, after weighing the risks, benefits, values and preferences.

Finally, clinicians are strongly encouraged to promote medical, lifestyle and behavioural changes that are more effective than ASA in preventing cardiovascular events.

These recommendations are intended to change practice, increase awareness, and drive policy, systems change and quality improvement for prevention of vascular events, as well as further highlight the importance of ensuring supportive environments and effective strategies for primary prevention.

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