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Acetylsalicylic Acid for Primary Prevention of Cardiovascular Events: Clinical Effectiveness and Guidelines

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Research Questions

1. What is the clinical effectiveness for the use of acetylsalicylic acid in primary prevention of cardiovascular disease?
2. What are the evidence-based guidelines for the use of acetylsalicylic acid in primary prevention of cardiovascular disease?

Key Findings

Twenty-two systematic reviews and meta-analyses, eight randomized controlled trials and eleven non-randomized studies were identified regarding the clinical effectiveness of acetylsalicylic acid in primary prevention of cardiovascular disease. Three evidence-based guidelines were identified regarding the use of acetylsalicylic acid in primary prevention of cardiovascular disease.

Methods

A limited literature search was conducted by an information specialist on key resources including MEDLINE All and Embase via Ovid, the Cochrane Library, the University of York Centre for Reviews and Dissemination (CRD) databases, the websites of Canadian and major international health technology agencies, as well as a focused Internet search. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were aspirin and adult patients who need primary prevention of cardiovascular disease. Search filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, or network meta-analyses, randomized controlled trials, controlled clinical trials, observational studies, and guidelines. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2014 and July 29, 2019. Internet links were provided, where available.

Selection Criteria

One reviewer screened citations and selected studies based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Adult patients who need primary prevention of cardiovascular disease
Intervention	Acetylsalicylic Acid (i.e., Aspirin)
Comparators	No treatment, placebo
Outcomes	Q1: Clinical effectiveness (e.g., bleeding risk, mortality, cardiovascular events, stroke, myocardial infarction) Q2: Guidelines
Study Designs	Health technology assessments, systematic reviews, meta analyses, randomized controlled trials, non-randomized studies, evidence-based guidelines

Results

Rapid Response reports are organized so that the higher quality evidence is presented first. Therefore, health technology assessment reports, systematic reviews, and meta-analyses are presented first. These are followed by randomized controlled trials, non-randomized studies, and evidence-based guidelines.

Twenty-two systematic reviews and meta-analyses,[1-22] eight randomized controlled trials[23-30] (including follow-up reports to two randomized controlled trials[28,29] and one randomized controlled trial post hoc subanalysis[30]), and eleven non-randomized studies[31-41] (including follow-up to one non-randomized study[41]) were identified regarding the clinical effectiveness of acetylsalicylic acid in primary prevention of cardiovascular disease. Three evidence-based guidelines[42-44] were identified regarding the use of acetylsalicylic acid in primary prevention of cardiovascular disease. No relevant health technology assessments were identified.

Additional references of potential interest are provided in the appendix.

Overall Summary of Findings

Twenty-two systematic reviews and meta-analyses,[1-22] eight randomized controlled trials[23-30] (including follow-up to two randomized controlled trials[28,29] and one randomized controlled trial post hoc subanalysis[30]), and eleven non-randomized studies[31-41] (including follow-up to one non-randomized study[41]) were identified regarding the clinical effectiveness for the use of acetylsalicylic acid in primary prevention of cardiovascular disease. Detailed study characteristics are provided in Table 2.

Table 2: Summary of Included Studies on the use of Acetylsalicylic Acid for the Primary Prevention of Cardiovascular Disease

First Author, Year	Study Characteristics	Population	Intervention vs. Comparator	Outcomes Assessed	Conclusions
Systematic Reviews and Meta Analyses					
Abdelaziz 2019[1]	• SR • 15 RCTs included • n = 165,502	• NR	• Acetylsalicylic acid vs. control	• All cause death • CV death • MI • Stroke • TIA • MACE • Major bleeding • Intracranial bleeding • Fatal bleeding • Major GI bleeding	• *"Aspirin for primary prevention reduces nonfatal ischemic events but significantly increases nonfatal bleeding events."*[1]
Barbarawi 2019[2]	• MA • 17 RCTs • n = 164,862	• NR	• Acetylsalicylic acid vs. placebo	• All-cause mortality • MACE	• *"Aspirin use in primary prevention has resulted in a lower incidence of MACE and MI without significantly*

First Author, Year	Study Characteristics	Population	Intervention vs. Comparator	Outcomes Assessed	Conclusions
				• MI • CV mortality • Cerebrovascular events • Bleeding events	*effecting cerebrovascular events. However, aspirin was associated with a higher bleeding risk."*[2]
Christiansen 2019[3]	• SR and MA • 20 randomized trials total • 10 trials in healthy patients/ patients with CV risk factors included in meta-analysis (n =144,930) • 4 trials in diabetic patients included in second meta-analysis (n =20,326)	• Healthy patients, patients with CV risk factors, patients with diabetes	• Acetylsalicylic acid vs. NR	• CV death • Nonfatal MI • Major bleeding • Intracranial hemorrhage	• *"This meta-analysis suggests that aspirin should not be used on a routine basis in the primary prevention of cardiovascular events, especially in individuals with diabetes."*[3]
Huang 2019[4]	• SR and MA • 13 RCTs • n = 134,446	• NR	• Acetylsalicylic acid ≤ 100 mg vs. control	• Intracranial hemorrhage • Intracerebral hemorrhage • Subdural or extradural hemorrhage • Subarachnoid hemorrhage	• *"Among people without symptomatic cardiovascular disease, use of low-dose aspirin was associated with an overall increased risk of intracranial hemorrhage, and heightened risk of intracerebral hemorrhage for those of Asian race/ethnicity or people with a low body mass index."*[4]
Judge 2019[5]	• MA • 11 trials • n =157, 054	• Populations without a history of clinical or subclinical CVD	• Acetylsalicylic acid vs. NR	• Nonfatal stroke • Hemorrhagic stroke • Nonfatal MI • All-cause mortality • CV mortality • Major GI bleeding	• *"Our meta-analysis reports no benefit of aspirin for primary stroke prevention."*[5]
Khan 2019[6]	• SR and MA • 10 RCTs • n =33,679	• Patients with diabetes	• Acetylsalicylic acid vs. NR	• MACE • CV mortality • MI • Stroke	• *"The use of aspirin for primary prevention of cardiovascular disease in patients with diabetes*

First Author, Year	Study Characteristics	Population	Intervention vs. Comparator	Outcomes Assessed	Conclusions
				• Total bleeding	*mellitus increases the risk of total bleeding without reducing the risk of major adverse cardiovascular outcomes."*[6]
Lin 2019[7]	• MA • n =29,814	• Patients with diabetes	• Low dose acetylsalicylic acid vs. NR	• MACE (including nonfatal MI, ischemia stroke, and CV death) • Major hemorrhage (major intracranial hemorrhage and major GI bleeding)	• *"We suggested the use of low-dose aspirin as the primary prevention strategy for CVD in diabetes, particularly in an older population. The absolute benefits were largely counterbalanced by the bleeding hazard."*[7]
Mahmoud 2019[8]	• MA • 11 trials • n = 157,248	• Patients without atherosclerotic disease	• Acetylsalicylic acid vs. placebo or control	• All-cause mortality • Major bleeding	• *"Among adults without established cardiovascular disease, aspirin was not associated with a reduction in the incidence of all-cause mortality; however, it was associated with an increased incidence of major bleeding."*[8]
Seidu 2019[9]	• MA • 12 RCTs • n = 34,227	• Patients with diabetes	• Acetylsalicylic acid vs. placebo or no treatment	• MACE • All-cause mortality • Major bleeding	• *"Aspirin has potential benefits in cardiovascular primary prevention in diabetes."*[9]
Shah 2019[10]	• MA • 14 RCTs • n = 164,751	• NR	• Acetylsalicylic acid vs. placebo	• MI • Major bleeding • Hemorrhagic stroke • All-cause stroke • CV death • All-cause mortality	• *"In the context of contemporary primary prevention guidelines, the effect of aspirin on myocardial infarction risk was significantly attenuated, whereas its major bleeding and hemorrhagic stroke complications were retained. Therefore, in contemporary practice routine use of aspirin for the primary prevention of cardiovascular events may have a net harmful effect."*[10]
Zheng 2019[11]	• SR and MA • 13 RCTs • n = 164,225	• NR	• Acetylsalicylic acid vs. placebo or no treatment	• Composite of CV mortality, nonfatal MI, nonfatal Stroke	• *"The use of aspirin in individuals without cardiovascular disease was associated with a lower risk*

First Author, Year	Study Characteristics	Population	Intervention vs. Comparator	Outcomes Assessed	Conclusions
				• Major bleeding	*of cardiovascular events and an increased risk of major bleeding."*[11]
Upadhaya 2019[12]	• NR	• NR	• NR	• NR	• NR
Garcia 2016[13]	• SR • 39 observational studies • n= NR	• NR	• Low dose Acetylsalicylic acid (75 to 325 mg/day) vs. NR	• Bleeding events	• *"The risks of major bleeding with low-dose aspirin in real-world settings are of a similar magnitude to those reported in randomized trials."*[13]
Karmali 2016[14]	• Overview of SRs • 15 SRs • n= NR	• High risk patients	• Acetylsalicylic acid vs. placebo	• Fatal ASCVD • Nonfatal ASCVD	• *"This overview demonstrates high-quality evidence to support aspirin, BP-lowering therapy and statins for primary ASCVD prevention…"*[14]
Kokoska 2016[15]	• MA • 6 studies • n = 10,117	• Patients with diabetes	• Acetylsalicylic acid 100 mg every other day to 650 mg daily vs. NR	• All-cause mortality • Atherosclerotic events • Bleeding • GI bleeding • Hemorrhagic stroke	• *"It remains unclear whether aspirin may reduce the occurrence of a first atherosclerotic event or mortality in patients with diabetes."*[15]
Lei 2016[16]	• MA • 14 RCTs • n = NR	• Healthy patients, patients with CVD	• Acetylsalicylic acid vs. no treatment	• Ischemic stroke • Hemorrhagic stroke • Severe GI bleeding	• *"This meta-analysis of randomized trials indicated that both the apparently healthy adults and patients with cardiovascular diseases will derive little protective benefit from aspirin considering the increased risk of severe bleeding events."*[16]
Major 2016[17]	• SR and MA • 3 trials • n = 4468	• Patients with non-end stage chronic kidney disease and no history of cardiovascular disease	• Acetylsalicylic acid vs. control	• MACE • All-cause mortality • Bleeding events	• *"There is no clear benefit of aspirin for the primary prevention of cardiovascular events in CKD and no statistically significant reduction in mortality. Aspirin is likely to increase the risk of major bleeding events."*[17]
Whitlock 2016[18]	• SR • n = NR	• NR	• Acetylsalicylic acid ≤ 100 mg daily or every other day vs. NR	• Major bleeds • GI bleeds • Hemorrhagic stroke	• *"Consideration of the safety of primary prevention with aspirin requires an individualized assessment of aspirin's effects on bleeding*

First Author, Year	Study Characteristics	Population	Intervention vs. Comparator	Outcomes Assessed	Conclusions
					risks and expected benefits because absolute bleeding risk may vary considerably by patient."[18]
Brotons 2015[19]	• SR • n = NR	• NR	• Acetylsalicylic acid vs. NR	• NR	• *"Available data on aspirin in primary prevention suggest a modest benefit for patients at high risk of CVD…"*[19]
Xie 2014[20]	• MA • 14 RCTs • n = 107,686	• Patients with no pre-existing CVD with subgroup analyses by gender and diabetes status	• Low dose acetylsalicylic acid vs. NR	• MACE • MI • Ischemic stroke • All-cause mortality • Hemorrhagic stroke • Major bleeding	• *"The use of low-dose aspirin was beneficial for primary prevention of CVD and the decision regarding an aspirin regimen should be made on an individual patient basis. The effects of aspirin therapy varied by sex and diabetes status."*[20]
Systematic Reviews and Meta Analyses – Elderly Population					
Meinshausen 2017[21]	• SR and MA • 22 SRs and MAs, 11 RCTs, 2 observational studies • n= NR	• Older adults	• Acetylsalicylic acid vs. NR	• NR	• *"…the use of acetylsalicylic acid (ASA) for primary prevention of cardiovascular disease (CVD) in older people cannot be recommended due to an uncertainty in the risk-benefit ratio."*[21]
Guirguis-Blake 2016[22]	• SR • 11 RCTs • n= NR	• Adults 40 years or older	• Acetylsalicylic acid all doses and ≤ 100 mg vs. NR	• Nonfatal MI • Nonfatal stroke • All-cause mortality	• *"The beneficial effect of aspirin for the primary prevention of CVD is modest and occurs at doses of 100 mg or less per day. Older adults seem to achieve a greater relative MI benefit."*[22]
Randomized Controlled Trials					
Gaziano 2018[23]	• RCT • n= 12,546	• Men aged 55 years or older and women aged 60 years or older with a moderate cardiovascular risk	• Acetylsalicylic acid 100 mg daily vs. placebo	• Composite outcome of time to first occurrence of cardiovascular death, MI, unstable angina, stroke or TIA • Hemorrhagic events • Other adverse events	• *"The event rate was much lower than expected, which is probably reflective of contemporary risk management strategies, making the study more representative of a low-risk population. The role of aspirin in primary prevention among patients at moderate risk could therefore not be addressed."*[23]

First Author, Year	Study Characteristics	Population	Intervention vs. Comparator	Outcomes Assessed	Conclusions
Goicoechea 2018[24]	• RCT • n= 111	• Patients with chronic kidney disease without previous CV events	• Acetylsalicylic acid 100 mg daily vs. usual therapy	• Composite of CV death, acute coronary syndrome, cerebrovascular disease, heart failure, or nonfatal peripheral artery disease • Fatal coronary events • Nonfatal coronary events • Renal events • Bleeding	• *"Long-term treatment with low-dose aspirin did not reduce the composite primary endpoint; however, there were reductions in secondary events with fewer coronary events and renal outcomes."*[24]
ASCEND Study Collaborative Group 2018[25]	• RCT • n= 15,840	• Patients with diabetes and no evident CVD	• Acetylsalicylic acid 100 mg daily vs. placebo	• First serious vascular event (MI, stroke, TIA, death from any vascular cause) • First major bleeding event (intracranial hemorrhage, sight-threatening bleeding event, GI bleeding, serious bleeding)	• *"Aspirin use prevented serious vascular events in persons who had diabetes and no evident cardiovascular disease at trial entry, but it also caused major bleeding events. The absolute benefits were largely counterbalanced by the bleeding hazard."*[25]
Randomized Controlled Trials – Elderly Population					
McNeil 2018[26]	• RCT • n= 19,114	• Healthy elderly without CVD, dementia or disability	• Acetylsalicylic acid 100 mg vs. placebo	• Composite of death, dementia, or persistent physical disability • CVD • Major hemorrhage	• *"The use of low-dose aspirin as a primary prevention strategy in older adults resulted in a significantly higher risk of major hemorrhage and did not result in a significantly lower risk of cardiovascular disease than placebo."*[26]
Ikeda 2014[27]	• RCT • n=14,464	• Elderly patients with hypertension, dyslipidemia, or diabetes	• Acetylsalicylic acid 100 mg daily vs. no acetylsalicylic acid	• Composite of CV death, nonfatal stroke, nonfatal MI	• *"Once daily, low-dose aspirin did not significantly reduce the risk of the composite outcome of cardiovascular death, nonfatal stroke, and*

First Author, Year	Study Characteristics	Population	Intervention vs. Comparator	Outcomes Assessed	Conclusions
					nonfatal myocardial infarction among Japanese patients 60 years or older with atherosclerotic risk factors."[27]
Randomized Controlled Trials – Follow-up Studies					
Saito 2017[28]	• 10-year follow-up of RCT • n= 2539	• Patients with type 2 diabetes and without pre-existing CVD	• Acetylsalicylic acid 81 or 100 mg daily vs. no acetylsalicylic acid	• Cardiovascular events (sudden death, fatal or nonfatal coronary artery disease, fatal or nonfatal stroke, and peripheral vascular disease) • Hemorrhagic events (GI bleeding, hemorrhagic stroke, bleeding from other sites)	• *"Low-dose aspirin did not affect the risk for cardiovascular events but increased risk for gastrointestinal bleeding in patients with type 2 diabetes mellitus in a primary prevention setting."*[28]
Van Kruijsdijk 2015[29]	• Long-term follow up of RCT • n= 27, 939	• Women	• Acetylsalicylic acid 100 mg every other day vs. placebo	• CVD • Cancer • Major GI bleeding	• *"Concurrent evaluation of the absolute effects on cancer, CVD and major gastrointestinal bleedings showed that alternate-day use of low-dose aspirin is ineffective or harmful in the majority of women in primary prevention."*[29]
Randomized Controlled Trials – Post Hoc Sub analysis					
Goto 2019[30]	• Post hoc subanalysis of RCT • n= 14,194	• Patients >70 or <70 with hypertension, dyslipidemia, or diabetes	• Acetylsalicylic acid 100 mg daily vs. no acetylsalicylic acid plus standard of care	• Composite of CV death, nonfatal stroke and nonfatal MI • Composite of above plus TIA, angina pectoris, and arteriosclerotic disease requiring medical or surgical intervention	• *"Aspirin did not reduce the risk of the primary or secondary outcomes in old patients. Aspirin treatment may have reduced CVEs within a high CVE risk elderly population subgroup."*[30]

First Author, Year	Study Characteristics	Population	Intervention vs. Comparator	Outcomes Assessed	Conclusions
Non-Randomized Studies					
Garcia 2019[31]	• Cohort study with nested case-control • n= 199,049	• NR	• Acetylsalicylic acid 75 to 300 mg daily vs. no treatment	• Upper gastrointestinal bleeds • Lower gastrointestinal bleeds	• *"Low-dose aspirin is associated with an increased risk of nonfatal UGIB/LGIB but not fatal UGIB/LGIB."*[31]
Iacono 2019[32]	• Retrospective study • n= 746	• Patients with rheumatoid arthritis	• Acetylsalicylic acid vs. no treatment	• CV events	• *"Low dose ASA may have a role in the primary prophylaxis of CV events in RA patients."*[32]
Huang 2018[33]	• Observational study • n= 440,277	• Patients without a history of CVD • Patients with a history of CVD	• Acetylsalicylic acid daily or ≥ twice daily vs. NR	• Mortality	• *"…our data suggest that caution should be exercised in more frequent use, particularly among individuals without a history of cardiovascular disease."*[33]
Duran 2017[34]	• Case-crossover study • n= 99 • Cohort study • n= 1836	• Patients with rheumatoid arthritis aged 60 years or older	• Low dose acetylsalicylic acid vs. non user	• Fatal MI • Nonfatal MI	• *"We did not find a protective effect of ASA on MI in patients with RA when used as primary prophylaxis."*[34]
Lee 2017[35]	• Cohort study • n=31,115	• Uncomplicated hypertensive patients	• Acetylsalicylic acid vs. no treatment	• All-cause mortality • CV mortality	• *"Primary prevention with aspirin and/or statins is beneficial in reducing both all-cause and cardiovascular mortality in uncomplicated hypertensive participants. Nevertheless, as aspirin administration is associated with an increased risk of major bleeding, care must be taken to assess the risk/benefit of using aspirin in primary prevention."*[35]
Iudici 2016[36]	• Cohort study • n= 167	• Patients with systemic lupus erythematosus	• Low dose acetylsalicylic acid vs. no treatment	• CV events	• *"Low-dose ASA is a safe treatment and may be beneficial in the primary prophylaxis of CV events in SLE patients."*[36]
Lou 2016[37]	• Cross-sectional study • n= 202	• Patients with dyslipidemia	• Acetylsalicylic acid vs. no treatment	• Coronary heart disease • Bleeding events	• *"Aspirin is beneficial for reducing incident CHD, while modestly increases gastrointestinal bleeding risk."*[37]

First Author, Year	Study Characteristics	Population	Intervention vs. Comparator	Outcomes Assessed	Conclusions
Kim 2015[38]	• Cohort study • n= 261, 065	• Patients with diabetes	• Low dose acetylsalicylic acid vs. no treatment	• Ischemic stroke	• *"In this study of patients with diabetes, the use of low-dose aspirin showed an increased risk of hospitalization for ischemic stroke."*[38]
Sirois 2014[39]	• Case-control study • n= 28, 067	• Patients with type 2 diabetes	• Acetylsalicylic acid vs. no treatment	• MI • GI bleeding	• *"Our results suggest that individual assessment of bleeding risk and cardiovascular risk is mandatory among elderly people with diabetes before introducing aspirin therapy."*[39]
Non-Randomized Study – Elderly Population					
Ando 2019[40]	• RCT • n= 12,278	• Elderly patients with hypertension, dyslipidemia, and/or diabetes, but without cardiovascular disease. Patients subgrouped by blood pressure.	• Acetylsalicylic acid 100 mg daily vs. no treatment	• CV death • Nonfatal stroke • Nonfatal MI • Bleeding • Hemorrhagic stroke	• *"In aged Japanese hypertensive patients, these data demonstrated no overall benefit of low-dose aspirin therapy although treatment was associated with an elevated risk of hemorrhagic events."*[40]
Non-Randomized Study – Follow-up Study					
Sasso 2015[41]	• 8-year follow-up to cohort study • n= 564	• Patients with type 2 diabetes and nephropathy	• Acetylsalicylic acid 100 mg daily vs. no treatment	• MACE	• *"…low dose aspirin is ineffective in primary prevention for patients with nephropathy."*[41]

ASA = acetylsalicylic acid; ASCEND= a study of cardiovascular events in diabetes; ASCVD = atherosclerotic cardiovascular disease; BP = blood pressure; CHD = coronary heart disease; CKD = chronic kidney disease; CV = cardiovascular; CVD = cardiovascular disease; CVE = cardiovascular event; GI = gastrointestinal; LGIB = lower gastrointestinal bleed; MA = meta-analysis; MACE = major adverse cardiac events; mg = milligram; MI = myocardial infarction; NR = not reported; RA = rheumatoid arthritis; RCT = randomized controlled trial; SLE = systemic lupus erythematosus; SR = systematic review; TIA = transient ischemic attack; UGIB = upper gastrointestinal bleed

Three evidence-based guidelines[42-44] were identified regarding the use of acetylsalicylic acid in primary prevention of cardiovascular disease. Guidelines from Hypertension Canada[42] recommend that consideration should be given to the addition of acetylsalicylic acid (ASA) for the primary prevention of cardiovascular disease in patients 50 years of age or older who have hypertension. Guidelines from the Scottish Intercollegiate Guidelines Network[43] do not recommend the use of ASA for the primary prevention of cardiovascular disease. Lastly, the guidelines from Kaiser Permanente[44] recommend use of ASA vary based on age and atherosclerotic cardiovascular disease risk. If the patient is 50 to 59

years of age with a 10% or greater risk of atherosclerotic disease over 10 years, low dose ASA is recommended. If the patient is 60 to 69 years of age with a 10% or greater risk of atherosclerotic disease over 10 years, a shared decision making between the patient and the prescriber should be done after weighing the risks and benefits of treatment. Finally, if the patient is under 50 or over 70 years of age, the guideline does not make a recommendation as there is insufficient evidence.

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Health Technology Assessments

No literature identified.

Systematic Reviews and Meta-analyses

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Appendix — Further Information

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