Appendix 2 (as supplied by the authors): Summary table of major clinical trials and systematic reviews for the use of ASA in primary prevention of vascular events

Table 1: Aspirin Use for Primary Prevention of CVD Supplemental Table (3 newest RCTs)

Full detailed evidence tables on ASA for primary prevention of vascular events are available at www.strokebestpractices.ca

	ARRIVE	ASPREE	ASCEND
Study/Type	**Gaziano et al. 2018** **RCT** ***Aspirin to Reduce Risk of Initial Vascular Events (ARRIVE)***	**McNeil et al. 2018** **RCT** ***Aspirin 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	*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 aspirin, **current continuous use of aspirin or other anti-platelet drug** or anticoagulant for	*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 aspirin, no other predominant life-threatening medical problem. *Exclusion Criteria:* Definite history of myocardial infarction, stroke or arterial revascularization procedure, **currently prescribed aspirin**, warfarin or any other blood thinning medication.

Appendix to: Wein T, Lindsay MP, Gladstone DG, et al.; for the Heart and Stroke Foundation of Canada in collaboration with the Canadian Stroke Consortium. Canada Stroke Best Practice Recommendations, seventh edition: acetylsalicylic acid for prevention of vascular events. *CMAJ* 2020. doi: 10.1503/cmaj.191599.

	ARRIVE	ASPREE	ASCEND
	stenting, coronary artery bypass graft, relevant arrhythmias, or congestive heart 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 aspirin)**, COX-2 inhibitors or metamizole, current use of an anticoagulant medication, sitting systolic blood pressure >170 mmHg	secondary prevention. People with previous use of aspirin for primary prevention may enter the trial, provided they agree to cease existing use of aspirin and understand that they may be subsequently randomly allocated to low dose aspirin 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 aspirin 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 aspirin 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 aspirin or placebo daily for the duration of the trial	Participants were randomly assigned (1:1) to receive 100 mg of enteric-coated aspirin or placebo.	Participants were randomized 1:1 to receive 100 mg aspirin 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	Median duration of follow-up was 4.7 years. In the final 12 months of the trial, 62% of the participants in the aspirin group and 64% of those in the placebo group were still taking the assigned trial intervention.	Mean duration of follow-up was 7.4 years. Estimated mean adherence was 70% in both groups.

	ARRIVE	ASPREE	ASCEND
	were not reduced significantly with aspirin therapy Primary outcome: HR=0·96, 95% CI 0·81–1·13, p=0·6038 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 aspirin group (16.75% vs. 13.54%, p<0·0001). The authors suggested that the reason for the apparent lack of benefit of aspirin 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).	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 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 aspirin 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 aspirin therapy (0.3 vs. 03/1,000-person years; HR=1.01, 95% CI 0.47–2.17).	The risk of the primary outcome was significantly lower in the aspirin group (8.5% vs, 9.6%, RR=0.88, 95% CI, 0.79 to 0.97; p=0.01). The risk of any major bleeding was significantly increased in the aspirin 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: Selected Systematic Review & Meta Analyses

Full detailed evidence tables are available at www.strokebestpractices.ca

	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 aspirin (≤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 aspirin vs. placebo, or no treatment. Daily doses of aspirin 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 aspirin vs. placebo, or no treatment. Daily aspirin 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.

	Huang 2019	Mahmoud 2019	Zheng 2019
			Bleeding outcomes: Major bleeding events, intracranial bleeding, GI bleeding
Key Findings and Recommendations	Mean duration of follow-up ranged from 2.3 to 8.2 years. Aspirin 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). Aspirin 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) Aspirin 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 aspirin 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 aspirin (1.7% vs. 1.8%; RR=0.94, 95% CI 0.86-1.04, p=0.24) Aspirin 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 aspirin 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 aspirin 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.

