The rise and fall of aspirin in the primary prevention of cardiovascular disease

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Aspirin is one of the most frequently used drugs worldwide and is generally considered effective for the secondary prevention of cardiovascular disease. By contrast, the role of aspirin in primary prevention of cardiovascular disease is controversial. Early trials evaluating aspirin for primary prevention, done before the turn of the millennium, suggested reductions in myocardial infarction and stroke (although not mortality), and an increased risk of bleeding. In an effort to balance the risks and benefits of aspirin, international guidelines on primary prevention of cardiovascular disease have typically recommended aspirin only when a substantial 10-year risk of cardiovascular events exists. However, in 2018, three large randomised clinical trials of aspirin for the primary prevention of cardiovascular disease showed little or no benefit and have even suggested net harm. In this narrative Review, we reappraise the role of aspirin in primary prevention of cardiovascular disease, contextualising data from historical and contemporary trials.

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Introduction

Extracted from willow bark, salicylates were first used as an analgesic by the ancient Sumerians and Egyptians.[1] Later civilisations found salicylates to be effective in the treatment of pain, inflammation, and fever; however, their use was limited by gastric side-effects. Under the instruction of Arthur Eichengrun, the German chemist Felix Hoffmann discovered that incorporation of an acetyl group to salicylic acid reduces its propensity for gastric irritation, resulting in the first production of acetylsalicylic acid, known more commonly as aspirin, in 1897 (figure).[16]

Almost a century later, in 1974, a randomised controlled trial showed a non-significant reduction in deaths among patients with a recent myocardial infarction who were assigned to 330 mg/day aspirin.[17] This outcome launched a series of trials that resulted in widespread acceptance of aspirin for the secondary prevention of major adverse cardiovascular events.[18–24] Enthusiasm for aspirin led to further randomised controlled trials investigating whether the drug might be effective for the primary prevention of cardiovascular disease.[3–8] Several primary prevention aspirin trials, mostly done before 2000, suggested reduction in myocardial infarction and stroke, although not mortality,[8] and at a cost of increased bleeding events.[4–7] These findings influenced guidelines, which recommended prescribing aspirin for primary cardiovascular disease prevention in high-risk individuals.[25–28] Aspirin is now one of the most widely used medications. In the USA alone, 35·8 million adults are estimated to take aspirin for the primary prevention of cardiovascular disease, often without consulting their physicians.[29]

Despite aspirin's popularity, its use for the primary prevention of cardiovascular disease is controversial. The US Food and Drug Administration (FDA) has never approved the labelling of aspirin for this purpose. The European Medicines Agency have not addressed this question. Furthermore, clinical trial data from 2018 have placed the use of aspirin for the primary prevention of cardiovascular disease back under scrutiny due to neutral results[13,14] or evidence suggestive of harm.[15] In this Review, we summarise aspirin's mechanism of action, review historical and contemporary trials evaluating the drug,[30–32] and reflect on future directions for aspirin in the prevention of cardiovascular disease.

Mechanism of action

Acetylsalicylic acid binds to, and irreversibly inhibits, cyclooxygenase (COX), which exists as two isoforms in humans: COX-1 and COX-2.[33] COX-1 is involved in platelet aggregation through production of thromboxanes. COX-2 is involved in the upregulation of prostaglandins that have vasodilator and anti-aggregatory actions.[34] Both isoenzymes are associated with protection of the gastric mucosa.[35] In experimental settings, low-dose aspirin (75 mg or 81 mg) inhibits COX-1 and disrupts the production of thromboxane (Tx)A2, thereby reducing platelet aggregation and formation of a thrombus.[36] Higher aspirin doses inhibit COX-2[37] leading to reduced production of prostacyclin (PGI2) and prostaglandin E (PGE), which is responsible for aspirin's analgesic and antipyretic effects but can cause vasoconstriction, renal dysfunction, hyponatraemia, and proaggregatory effects.[36] For patients with cardiovascular disease, doses of aspirin as low as 75 mg/day might suffice to block both COX systems for 24 h or longer.

Trials of aspirin for primary prevention before 2000

Non-selected populations

The first primary prevention trials investigating the utility of aspirin in preventing cardiovascular disease enrolled physicians, as was common at the time (table 1).

Search strategy and selection criteria

PubMed was used to identify relevant references using the search terms "aspirin" and "primary prevention". We also searched all of the references in recent systematic reviews and meta-analyses on this topic.[30–32] Only articles published in English between January, 1970, and January, 2019, were included in this narrative Review.

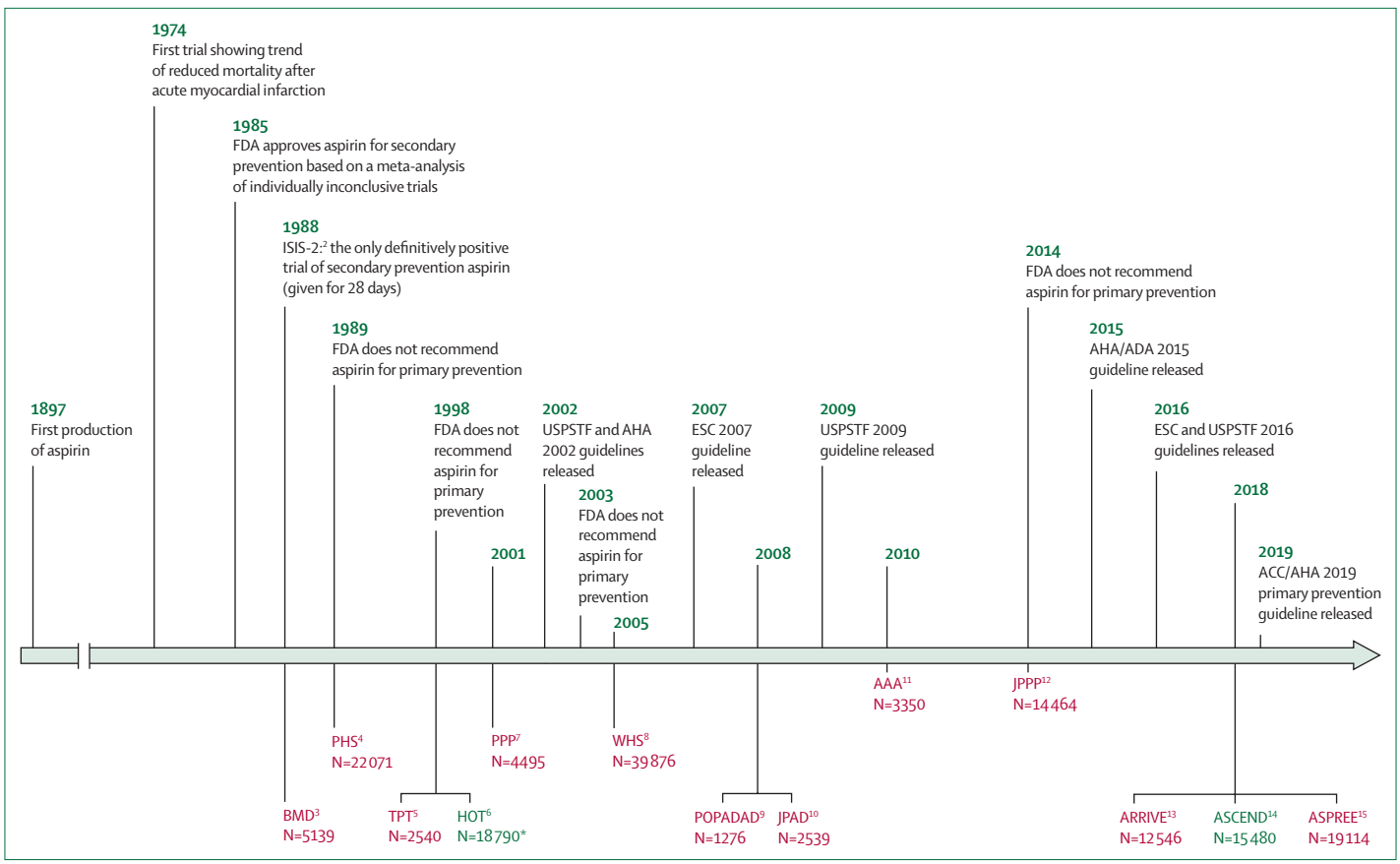

Figure: **History of aspirin for use in the primary prevention of cardiovascular disease**
Includes major completed trials, US FDA reviews, and international practice guidelines. Green indicates trials with significant reduction in the primary endpoint. Red indicates trials without significant reduction in the primary endpoint. AAA=aspirin for asymptomatic atherosclerosis. ADA=American Diabetes Association. AHA=American Heart Association. ARRIVE=aspirin to reduce risk of initial vascular events. ASCEND=a study of cardiovascular events in diabetes. ASPREE=aspirin in reducing events in the elderly. BMD=British male doctors. ESC=European Society of Cardiology. FDA=Food and Drug Administration. HOT=hypertension optimal treatment. ISIS-2=second international study of infarct survival. JPAD=Japanese primary prevention of atherosclerosis with aspirin for diabetes. JPPP=Japanese primary prevention project. PHS=physicians' healthy study. POPADAD=prevention of progression of arterial disease and diabetes. PPP=primary prevention project. TPT=thrombosis prevention trial (excluding warfarin arm). USPSTF=US Preventive Services Task Force. WHS=women's health study. *Ambiguity exists around the primary composite outcome in HOT[6] and the benefit for aspirin was susceptible to changes in the outcome tested.

In the British male doctors (BMD) trial,[3] 5139 men younger than 80 years, 10–15% of whom had a history of non-myocardial infarction cardiovascular disease, were randomly assigned to receive 300–500 mg/day aspirin or no aspirin (unblinded). After a 6-year follow-up, no difference was seen in the incidence of stroke, myocardial infarction, or other cardiovascular disease; or in mortality associated with these events. Importantly, the rates of non-fatal and fatal myocardial infarction were similar, with sudden death notably included in the fatal myocardial infarction endpoint.[3]

In the US physicians' health study (PHS),[4] 22071 healthy male physicians aged 40–84 years were randomly assigned to 325 mg aspirin every other day, or placebo (double-blinded). The trial was stopped for futility because cardiovascular mortality (the primary endpoint) was lower than expected in both groups and because of an observed reduction in non-fatal and fatal myocardial infarction, a key secondary endpoint. In the final report, the investigators found a 44% reduction in the incidence of non-fatal and fatal myocardial infarction in individuals assigned to aspirin (255 *vs* 440 per 100000 per year; p<0·0001). However, no reduction in angina, stroke, cardiovascular death, or all-cause mortality was seen. The ratio of fatal to non-fatal myocardial infarction was substantially different between the British and US trials (approximately 1·0 [British] *vs* approximately 0·1 [US]). The aspirin group in PHS had higher rates of bleeding (relative risk [RR] 1·32, 95% CI 1·25–1·40; p<0·0001].[4] The early termination of the US trial (PHS)for a reduction in a secondary endpoint, differences in population risk, and differences in the definition or ascertainment of myocardial infarction might account for the divergent results found in these early British and US aspirin primary prevention trials.

Selected populations with cardiovascular comorbidities

Subsequent studies shifted the focus to lower doses of aspirin and groups at higher risk for cardiovascular disease, such as patients with hypertension and diabetes.

	BMD[3]	PHS[4]	TPT[5]	HOT[6]	PPP[7]	WHS[8]
Publication year	1988	1989	1998	1998	2001	2005
Enrolment period	1978–79	1981–87	1984–89	1992–94	1994–98	1992–95
Sample size (N)	5139	22 071	5085	18 790	4495	39 876
Population	Male physicians without history of myocardial infarction, stroke, or peptic ulcer disease	Male physicians aged 40–84 years without history of stroke, myocardial infarction, cancer, or renal disease	Men age 45–69 years at high risk for cardiovascular disease	Men and women aged 50–80 years with hypertension	Men and women aged ≥50 years with one or more cardiovascular risk factors	Healthy women aged ≥45 years
Control group	No aspirin	Placebo	Placebo	Placebo	No aspirin	Placebo
Follow-up period (years)	Median 5·5	Median 5	Median 6·8	Mean 3·8	Mean 3·6	Mean 10·1
Participant age (%, mean, or median)	<60 years, 47%; 60–69 years, 39%; 70–79 years, 14%	40–49 years, 41%; 50–59 years, 34%; 60–69 years, 19%; 70–84 years, 7%	57 years	62 years	64 years	55 years
Smokers (%)	31%	11%	41%	16%	15%	13%
Hypertension	Mean SBP 136 mm Hg	Hypertension, 39%	Mean SBP 139 mm Hg	Mean BP 170/105 mm Hg	Mean BP 145/85 mm Hg hypertension, 68%	Hypertension, 26%
Hyperlipidaemia	..	Cholesterol ≥6·7 mmol/L, 4%	Mean cholesterol 6·4 mmol/L	Mean cholesterol 6·1 mmol/L	Mean cholesterol 6·1 mmol/L; hyperlipidaemia, 39%	30%
Statin use (%)	..	..	..	..	16%	..
Diabetes (%)	2%	2%	..	8%	17%	3%
Bodyweight	..	BMI ≥26 kg/m^2, 25%	Mean BMI 27·4 kg/m^2	Mean BMI 28·4 kg/m^2	Mean BMI 27·6 kg/m^2; obese, 23%	Mean BMI 26 kg/m^2
Women (%)	0%	0%	0%	47%	58%	100%
Men (%)	100%	100%	100%	53%	42%	0%
Aspirin dosage (mg)	300 mg or 500 mg	325 mg (alternate days)	75 mg	75 mg	100 mg	100 mg (alternate days)
Primary endpoint (aspirin *vs* control)	Definite myocardial infarction or stroke resulting in death (63·2 *vs* 62·3 per 10 000 person-years; p=NS)	Cardiovascular mortality (81 *vs* 83; RR 0·96, 95% CI 0·6–1·54)	IHD (154 *vs* 190 events; p=0·04) excluding warfarin arm (83 *vs* 107 events, p=NS)	Major cardiovascular events not including silent myocardial infarction (315 *vs* 368; RR 0·85, 95% CI 0·73–0·99; p=0·03)	Major cardiovascular events (45 *vs* 64; RR 0·71, 95% CI 0·48–1·04)	Major cardiovascular events (477 *vs* 522; RR 0·91, 95% CI 0·80–1·03; p=0·13)
Secondary endpoints (aspirin *vs* control)	Non-fatal stroke (32·4 *vs* 28·5 per 10 000 person-years; p=NS) and non-fatal myocardial infarction (42·5 *vs* 43·3 per 10 000 person-years; p=NS)	Myocardial infarction (139 *vs* 239; RR 0·56, 95% CI 0·45–0·70; p<0·0001); stroke (119 *vs* 98; RR 1·22, 95% CI 0·93–1·60; p=0·15)	Stroke (47 *vs* 48, 2·9 *vs* 3·0 per 1000 person-years, p=NS)	Myocardial infarction (82 *vs* 127; RR 0·64, 95% CI 0·49–0·85; p=0·002); stroke (146 *vs* 148; RR 0·98, 95% CI 0·78–1·24; p=0·88); cardiovascular mortality (133 *vs* 140; RR 0·95, 95% CI 0·75–1·20; p=0·65)	Total cardiovascular events (141 *vs* 187; RR 0·77, 95% CI 0·62–0·95); cardiovascular death (17 *vs* 31; RR 0·56, 95% CI 0·31–0·99); all-cause mortality (62 *vs* 68; RR 0·81, 95% CI 0·58–1–13)	Fatal myocardial infarction (14 *vs* 12; RR 1·16, 95% CI 0·54–2·51; p=0·70); fatal stroke (23 *vs* 22; RR 1·04, 95% CI 0·58–1·86; p=0·90); cardiovascular death (120 *vs* 126; RR 0·95, 95% CI 0·74–1·22; p=0·68)
Safety endpoint (aspirin *vs* control)	Extracranial bleeding (10·6 *vs* 7·4 per 10 000 person-years; p=NS)	Bleeding requiring transfusion (48 *vs* 28; RR 1·71, 95% CI 1·09–2·69; p=0·02)	Major bleeding event (8 *vs* 4; p=NS); intermediate bleeding event (48 *vs* 33; p=NS)	Fatal bleeds (7 *vs* 8); non-fatal major bleeds (129 *vs* 70; RR 1·8; p<0·001)	Severe bleeding (24 *vs* 6; p<0·0008)	Gastrointestinal bleeding requiring transfusion (127 *vs* 91; RR 1·40, 95% CI 1·07–1·83; p=0·02)
All-cause mortality (aspirin *vs* control)	143·4 *vs* 159·5 per 10 000 person-years; p=NS	205 *vs* 216; RR 0·95, 95% CI 0·79–1·15; p=0·60	216 *vs* 205; 13·0 *vs* 12·2 per 1000 person-years, p=NS	284 *vs* 305; RR 0·93, 95% CI 0·79–1·09; p=0·36	62 *vs* 78; RR 0·81, 95% CI 0·58–1·13	609 *vs* 642; RR 0·95, 95% CI 0·85–1·06; p=0·32
Myocardial infarction (aspirin *vs* control)	Non-fatal, 42·5 *vs* 43·3 per 10 000 person-years; p=NS	Non-fatal, 129 *vs* 213; RR 0·59, 95% CI 0·47–0·74; p<0·0001	Non-fatal, 94 *vs* 137; 5·8 *vs* 8·5 per 1000 person-years, p=0·004	Fatal or non-fatal, 82 *vs* 127; RR 0·64, 95% CI 0·49–0·85; p=0·002; fatal or non-fatal including silent, 157 *vs* 184; RR 0·85, 95% CI 0·69–1·05; p=0·13	Non-fatal, 15 *vs* 22; RR 0·69, 95% CI 0·36–1·33	Non-fatal, 184 *vs* 181; RR 1·01, 95% CI 0·83–1·24; p=0·90
Non-fatal stroke (aspirin *vs* control)	Non-fatal, 32·4 *vs* 28·5 per 10 000 person-years; p=NS	Non-fatal, 110 *vs* 92; RR 1·20, 95% CI 0·91–1·59; p=0·20	Fatal or non-fatal events, 47 *vs* 48; incidence 2·9 *vs* 3·0 per 1000 person-years; p=NS	Fatal or non-fatal, 146 *vs* 148; RR 0·98, 95% CI 0·78–1·24; p=0·88	Non-fatal, 15 *vs* 18; RR 0·84, 95% CI 0·42–1·67	Non-fatal, 198 *vs* 244; RR 0·81, 95% CI 0·67–0·97; p=0·02

Baseline charateristics refer to both aspirin and control groups. BMD=British male doctors. PHS=physicians' health study. TPT=thrombosis prevention trial. HOT=hypertension optimal treatment. PPP=primary prevention project. WHS=women's health study. SBP=systolic blood pressure. BP=blood pressure. BMI=body-mass index. NS=not significant. IHD=ischaemic heart disease. RR=relative risk.

Table 1: **Historical randomised controlled trials for aspirin in primary cardiovascular disease prevention, with enrolment before 2000**

In the primary prevention project (PPP),[7] 4495 men and women with one or more cardiovascular risk factors were randomly assigned to receive 100 mg/day aspirin or no aspirin, without masking. The trial was terminated at the second interim analysis, again despite no difference in the prespecified primary outcome, after a median follow-up of 4 years showed a 44% reduction in cardiovascular death (RR 0·56, 95% CI 0·31–0·99) and 23% reduction in total cardiovascular events (0·77, 0·62–0·95) with aspirin. No significant treatment effect was observed for all-cause mortality, and an increased rate of severe bleeding in the aspirin group (1·1% *vs* 0·3%; p=0·0008) was apparent. Similarly, the thrombosis prevention trial (TPT) found that men at high risk for myocardial infarction who received aspirin had a 32% reduction in non-fatal myocardial infarction (p=0·004) over a 6·8-year median follow-up. This effect was largely driven by the combination of aspirin with warfarin in this factorial trial.[5] Aspirin alone did not significantly reduce the primary endpoint of fatal or non-fatal myocardial infarction compared with placebo.

In the hypertension optimal treatment (HOT) study,[6] researchers found a 15% risk reduction in the primary endpoint of major cardiovascular events (RR 0·85, 95% CI 0·73–0·99; p=0·03) and a 36% reduction in patients hospitalised with myocardial infarction (0·64, 0·49–0·85; p=0·002) at 3·8-year mean follow-up. However, there were more silent myocardial infarction events on aspirin (n=73) than placebo (n=57), which would have rendered the trial outcome neutral had they been included in the primary endpoint.

Effect of sex

For the women's health study (WHS),[8] 39 876 women were randomly assigned to receive 100 mg aspirin on alternate days, or placebo. The primary endpoint of the trial was not met. Although the incidence of fatal and non-fatal stroke was reduced by 17% (RR 0·83, 95% CI 0·69–0·99; p=0·04), no change occurred in the rates of myocardial infarction or cardiovascular death over a mean follow-up of 10·1 years. Although subgroup analyses from the early trials and early meta-analyses suggested different effects of aspirin on men and women,[38,39] the 2009 Anti-Thrombotic Trials Collaboration meta-analysis of six primary prevention trials found no sex-stratified differences when correcting for multiple testing.[40]

Trials of aspirin for primary prevention, 2000–17

Major advances in cardiovascular risk reduction have been implemented in the past 20 years, including marked reductions in tobacco smoking,[41,42] widespread evidence-based prescribing of statin therapy,[43] and improved control of population blood pressure.[44] Thus, the turn of the millennium brought about a reappraisal of aspirin's safety and efficacy for the primary prevention of cardiovascular disease (table 2). Furthermore, the publication of a universal definition of myocardial infarction and advances

	POPADAD[9]	JPAD[10]	AAA[11]	JPPP[12]	ARRIVE[13]	ASCEND[14]	ASPREE[15]
Publication year	2008	2008	2010	2014	2018	2018	2018
Enrolment period	1997–2001	2002–05	1998–2008	2005–07	2007–16	2005–11	2010–14
Sample size (N)	1276	2539	3350	14 464	12 546	15 480	19 114
Population	Men and women aged ≥40 years with diabetes and ABI ≤0·99	Men and women aged 30–85 years with diabetes	Men and women aged 50–75 years with ABI ≤0·95	Men and women aged 60–85 years with hypertension, hyperlipidaemia, or diabetes	Men aged ≥55 years with 2–4 cardiovascular risk factors; women aged ≥60 years with ≥3 cardiovascular risk factors	Men and women aged ≥40 years with diabetes	Men and women aged ≥70 years
Control group	Placebo	No aspirin	Placebo	No aspirin	Placebo	Placebo	Placebo
Follow-up period (years)	Median 6·7	Median 4·4	Mean 8·2	Median 5	Median 5	Median 7·4	Median 4·7
Participant age (years)	Mean 60	Mean 65	Mean 62	Mean 71	Mean 64	Mean 63	Median 74
Smokers (%)	31%	21%	33%	13%	29%	8%	4%
Hypertension	Mean BP 145/79 mm Hg	Mean BP 135/77 mm Hg; hypertension, 58%	Mean BP 148/84 mm Hg	Mean BP 137/78 mm Hg; hypertension, 85%	Median SBP 145 mm Hg; hypertension, 63%	Mean SBP 136 mm Hg	Mean BP 139/77 mm Hg; hypertension, 75%
Hyperlipidaemia	Mean cholesterol 5·5 mmol/L	Mean cholesterol 5·2 mmol/L; hyperlipidaemia, 53%	Mean cholesterol 6·2 mmol/L	Mean cholesterol 5·2 mmol/L; hyperlipidaemia, 72%	Hyperlipidaemia, 58%	Mean cholesterol 4·2 mmol/L	Mean cholesterol 5·2 mmol/L; hyperlipidaemia, 66%
Statin use (%)	..	26%	4% at start, increased to 25%	..	43%	75%	34%
Diabetes (%)	100%	100%	3%	34%	0%	100%	11%
Bodyweight	Mean BMI 29·3 kg/m²	Mean BMI 24 kg/m²	..	Mean BMI 24·2 kg/m²; BMI >25 kg/m², 36%	Mean BMI 28·4; BMI >25 kg/m², 79%	Mean BMI 30·7; BMI >25 kg/m², 85%	BMI >30 kg/m², 30%

(Table 2 continues on next page)

	POPADAD[9]	JPAD[10]	AAA[11]	JPPP[12]	ARRIVE[13]	ASCEND[14]	ASPREE[15]
(Continued from previous page)							
Women (%)	56%	46%	72%	58%	30%	37%	56%
Men (%)	44%	54%	28%	42%	70%	63%	44%
Aspirin dosage (mg)	100 mg	81 mg or 100 mg	100 mg	100 mg	100 mg	100 mg	100 mg
Primary endpoint (aspirin *vs* control)	Major cardiovascular events (116 *vs* 117; RR 0·98, 95% CI 0·76–1·26; p=0·86); cardiovascular death (43 *vs* 35; RR 1·23, 95% CI 0·79–1·93; p=0·36)	Major cardiovascular events (68 *vs* 86; HR 0·80, 95% CI 0·58–1·10; p=0·16)	Major cardiovascular events (13·7 *vs* 13·3 per 1000 person-years; HR 1·03, 95% CI 0·84-1·27)	Major cardiovascular events (193 *vs* 207; HR 0·94, 95% CI 0·77–1·15; p=0·54)	Major cardiovascular events (269 *vs* 281; HR 0·96, 95% CI 0·81–1·13; p=0·60)	Major cardiovascular events (658 *vs* 743; rate ratio 0·88, 95% CI 0·79–0·97; p=0·01)	Death, dementia, or persistent physical disability (21·5 *vs* 21·2 per 1000 person-years; HR 1·01, 95% CI 0·92–1·11; p=0·79)
Secondary endpoints (aspirin *vs* control)	All-cause mortality; non-fatal myocardial infarction; other vascular events (not included)	Cardiovascular mortality (1 *vs* 10; HR 0·10, 95% CI 0·01–0·79; p=0·0037); coronary heart disease events (28 *vs* 35; HR 0·81, 95% CI 0·49-1·33; p=0·40)	Composite of primary endpoint or angina, claudication, or TIA (22·8 *vs* 22·9 per 1000 person-years; HR 1·00, 95% CI, 0·85–1·17) and all-cause mortality	Composite of primary endpoint or atherosclerosis (280 *vs* 319; HR 0·89, 95% CI 0·75–1·04; p=0·14); cardiovascular death (58 *vs* 57; HR 1·03, 95% CI 0·71–1·48; p=0·89)	Composite and individual outcomes of the time to cardiovascular death, myocardial infarction, or stroke; time to UA; time to TIA; and time to death (p=NS for all endpoints)	Any major vascular event (833 *vs* 936; rate ratio 0·88, 95% CI 0·80–0·97); gastrointestinal cancer (157 *vs* 158; rate ratio 0·99; p=NS)	Major cardiovascular events (10·7 *vs* 11·3 per 1000 person-years; HR 0·95, 95% CI 0·83–1·08)
Safety endpoint (aspirin *vs* control)	Gastrointestinal bleeding (28 *vs* 31; RR 0·90, 95% CI 0·53–1·52; p=0·69)	Haemorrhagic stroke or severe gastrointestinal bleeding (10 *vs* 7 p=NS)	Major haemorrhage requiring hospitalisation (34 *vs* 20; HR 1·71, 95% CI 0·99–2·97)	Extracranial bleed requiring transfusion or hospitalisation (62 *vs* 34; HR 1·85, 95% CI 1·22–2·81; p=0·004)	Gastrointestinal bleeding events (61 *vs* 29, HR 2·11, 95% CI 1·36–3·28; p=0·0007)	Major bleeding event (314 *vs* 245; rate ratio 1·29, 95% CI, 1·09–1·52; p=0·003)	Major haemorrhage (8·6 *vs* 6·2 per 1000 person-years; HR 1·38, 95% CI 1·18–1·62; p<0·001)
All-cause mortality (aspirin *vs* control)	94 *vs* 101; RR 0·93, 95% CI 0·71–1·24; p=0·63	34 *vs* 38; HR 0·90, 95% CI 0·57–1·14; p=0·67	176 *vs* 186; HR 0·95, 95% CI 0·77–1·16	297 *vs* 303; HR 0·99, 95% CI; 0·85–1·17; p=0·93	160 *vs* 161; HR 0·99, 95% CI 0·80–1·24; p=0·95	748 *vs* 792; rate ratio 0·94, 95% CI 0·85–1·04	12·7 *vs* 11·1 per 1000 person-years; HR 1·14, 95% CI 1·01–1·29
Myocardial infarction (aspirin *vs* control)	Non-fatal, 55 *vs* 56; RR 0·98, 95% CI 0·68–1·43; p=0·93	Non-fatal, 12 *vs* 9; HR 1·34, 95% CI 0·57–3·19; p=0·50	Non-fatal, 62 *vs* 68 p=NS	Non-fatal, 20 *vs* 38; HR 0·53, 95% CI 0·31–0·91; p=0·02	Non-fatal, 88 *vs* 98; HR 0·90, 95% CI 0·67–1·20; p=0·46	Non-fatal, 191 *vs* 195; rate ratio 0·98, 95% CI 0·80–1·19	Fatal or non-fatal, 171 *vs* 184; HR 0·93, 95% CI 0·76–1·15
Stroke (aspirin *vs* control)	Non-fatal, 29 *vs* 41; RR 0·71, 95% CI 0·44–1·14; p=0·15	Non-fatal, 22 *vs* 24, HR 0·93, 95% CI 0·52–1·66; p=0·80	Non-fatal, 37 *vs* 38 p=NS	Non-fatal, 117 *vs* 114; HR 1·04, 95% CI 0·80–1·34; p=0·78	Fatal or non-fatal, 75 *vs* 67; HR 1·12, 95% CI 0·8–1·55; p=0·51	Non-fatal, 202 *vs* 229; rate ratio 0·88, 95% CI 0·73–1·06	Fatal or non-fatal, 148 *vs* 167; HR 0·89, 95% CI 0·71–1·11

Baseline charateristics refer to both aspirin and control groups. POPADAD=progression of arterial disease and diabetes. JPAD=Japanese primary prevention of atherosclerosis with aspirin for diabetes. AAA=aspirin for asymptomatic atherosclerosis. JPPP=Japanese primary prevention project. ARRIVE=aspirin to reduce risk of initial vascular events. ASCEND=a study of cardiovascular events in diabetes. ASPREE=aspirin in reducing events in the elderly. ABI=ankle–brachial index. BP=blood pressure. SBP=systolic blood pressure. BMI=body-mass index. RR=relative risk. HR=hazard ratio. UA=unstable angina. TIA=transient ischaemic attack. NS=notsignificant.

Table 2: **Contemporary randomised controlled trials for aspirin in primary cardiovascular disease prevention, enrolment primarily after 2000**

in the use of cardiac biomarkers, including more sensitive measures like troponin,[45,46] improved the consistency of determining endpoints such as myocardial infarction.

Patients with diabetes

Several contemporary trials have focused on patients with diabetes. For the prevention of progression of arterial disease and diabetes (POPADAD) trial,[9] 1276 patients aged 40 years and older with type 1 or type 2 diabetes, an ankle–brachial pressure index of 0·99 or less, but no symptomatic cardiovascular disease, were randomly assigned to receive 100 mg aspirin daily or placebo. Aspirin did not reduce the primary composite endpoint of cardiovascular death, non-fatal myocardial infarction, stroke, or amputation for critical limb ischemia (RR 0·98, 95% CI 0·76–1·26) or the rate of non-fatal myocardial infarction alone. Similarly, the Japanese primary prevention of atherosclerosis with aspirin for diabetes (JPAD) trial,[10] in which patients with type 2 diabetes aged 30–85 years were enrolled, showed that aspirin at a dose of 81 mg or 100 mg daily (unblinded) did not significantly reduce a composite outcome of atherosclerotic events at 4·4 years follow-up (hazard ratio [HR] 0·80, 95% CI 0·58–1·10; p=0·16).

Patients with other cardiovascular comorbidities

In the aspirin for asymptomatic atherosclerosis (AAA) trial,[11] 3350 men and women aged 50–75 years with low ankle–brachial index and no history of cardiovascular disease were enrolled and randomly assigned to receive 100 mg aspirin daily or placebo. The trial outcome was neutral for the primary endpoint, a composite of fatal or non-fatal coronary events, stroke, or revascularisation

(HR 1·03, 95% CI 0·84–1·27) and for all-cause mortality (0·95, 0·77–1·16) over a mean follow-up of 8·2 years. In the Japanese primary prevention project (JPPP),[12] 14 464 individuals aged 60–85 years with multiple cardiovascular risk factors were randomly assigned to receive no aspirin or 100 mg aspirin daily (unblinded). The study was stopped early for futility on its composite outcome of cardiovascular death, non-fatal stroke, and non-fatal myocardial infarction, although a reduction in non-fatal myocardial infarction was observed (HR 0·53, 95% CI 0·31–0·91; p=0·02). An increase in extracranial haemorrhage requiring transfusion or hospitalisation was also reported (1·85, 1·22–2·81; p=0·004).

Trials of aspirin for primary prevention in 2018

In the aspirin to reduce risk of initial vascular events (ARRIVE) trial,[13] 12 546 men (aged ≥55 years) and women (aged ≥60 years) with moderate cardiovascular disease risk (defined as a 10-year risk of coronary heart disease of 10–20%) were randomly assigned to receive either 100 mg aspirin daily or placebo. The outcome of the primary endpoint, a composite of cardiovascular death, myocardial infarction, unstable angina, stroke, or transient ischaemic attack, was neutral (HR 0·96, 95% CI 0·81–1·13; p=0·60) and no difference in non-fatal myocardial infarction was seen. Gastrointestinal bleeding was higher in participants assigned to aspirin (2·11, 1·36–3·28; p=0·0007), but the rates of haemorrhagic stroke were similar on aspirin and placebo (0·13% [8/6270] *vs* 0·18% [11/6276]). The study population included patients with high blood pressure (63%), cigarette use (29%), and high LDL (44%). Although the mean estimated risk of cardiovascular disease in the study population calculated based on risk scores was 17·3%, the event rates of cardiovascular disease were much lower than expected for all patients (<10% over 10 years). The fact that the event rates were lower than anticipated perhaps reflects the benefits of contemporary cardiovascular disease preventive therapies.

In the study of cardiovascular events in diabetes (ASCEND)[14] trial, 15 480 participants were randomly assigned to receive either aspirin (100 mg daily) or placebo. The study had a population with a higher median BMI and a greater proportion of men, but a lower proportion of smokers compared with previous studies of prophylactic aspirin in diabetes. Aspirin resulted in a 12% reduction in non-fatal vascular events (rate ratio 0·88, 95% CI 0·79–0·97; p=0·01), but also increased major bleeding (1·29, 1·09–1·52; p=0·003). The incidence of fatal bleeding (0·2 % *vs* 0·2%) and haemorrhagic stroke (0·3% *vs* 0·3%) did not differ between groups. No reduction in hard endpoints, such as vascular death, was seen. During the trial, because of lower than expected event rates, the steering committee added transient ischaemic events to the primary composite endpoint, extended the study duration, and expanded the sample size. The large sample size enabled the detection of the relatively small absolute risk reduction of 1·1% in the efficacy endpoint; however, this outcome must be weighed against the increased absolute risk of major bleeding (0·9%) and the absence of effect on cardiovascular or all-cause mortality.

The largest of the 2018 primary prevention aspirin trials examined the use of aspirin among older patients (aged ≥65 years). In the aspirin in reducing events in the elderly (ASPREE) trial,[15] 19 114 healthy patients aged 70 years or older (≥65 years of age for black and hispanic people) were randomly assigned to receive 100 mg aspirin or placebo daily. At a median follow-up of 4·7 years, no difference in cardiovascular events, including fatal and non-fatal myocardial infarction and stroke, was seen between the two groups (HR 0·95, 95% CI 0·83–1·08).[15] However, an increase in the risk of intracranial and extracranial haemorrhage (HR 1·38, 95% CI 1·18–1·62; p<0·001), and all-cause mortality (1·14, 1·01–1·29) was reported.[15,47] The trial also showed no reduction in the primary endpoint, a composite of dementia, death, or persistent physical disability,[48] which might be more important to many patients than the cardiovascular endpoints assessed, but less likely to have been influenced by aspirin therapy.

Certain limitations of the 2018 trials might have contributed to these null results. First, in all three of the 2018 aspirin trials, compliance with random assignment to aspirin was relatively poor, at 60–70%, resulting in substantial crossovers that might have affected the null results. Second, the populations studied in these trials had cardiovascular event rates that were lower than anticipated, which leaves unanswered the question of whether aspirin might have benefit in higher risk younger populations (people <70 years). Note that we specify younger here because the observed cardiovascular disease risk in ASPREE participants was more than 10% over 10 years, so these adults 70 years or older were technically high risk, but despite that, had no cardiovascular disease-related benefit from aspirin. Third, only a small proportion of patients were treated with proton-pump inhibitors, an intervention which might reduce aspirin-induced dyspepsia and upper gastrointestinal bleeding. Fourth, there was a scarcity of information regarding the use of non-steroidal anti-inflammatory drugs (NSAIDs) and alcohol, which might increase bleeding risk. Fifth, the median follow-up time ranged from 4·7 years to 7·4 years, which might be too short to appreciate primary prevention effects of aspirin on cardiovascular disease or on cancer outcomes (which are particularly important among people with increased colon cancer risk). Finally, the 2018 trials did not provide information on the effect of aspirin among high cardiovascular risk individuals when selected on the basis of modern risk stratification modalities such as the coronary calcium score.

Contemporary meta-analyses

A 2019 meta-analysis of 11 primary prevention aspirin trials with 157 248 participants found no reduction in

all-cause mortality overall, including for patients with diabetes or high cardiovascular risk.[30] However, a 0·6% increase in the absolute risk of major bleeding was observed, and intracranial haemorrhage increased by 0·1%.[30] The aggregate analysis of all trials found a reduction in myocardial infarction with aspirin use (RR 0·82, 95% CI 0·71–0·94; p=0·006); however, this reduction was not significant when only trials reported after 2000 were analysed (0·90, 0·79–1·02; p=0·10).

Another 2019 meta-analysis included data from 164 225 participants in 13 trials.[31] Aspirin reduced the composite outcome of cardiovascular mortality, non-fatal myocardial infarction, and non-fatal stroke (HR 0·89, 95% CI 0·84–0·95), with an absolute risk reduction of 0·38% (number needed to treat 265). No difference in all-cause or cardiovascular mortality was reported. An increased rate of major bleeding events (HR 1·43, 95% CI 1·30–1·56) was seen, with an absolute risk increase of 0·47% (number needed to harm 210). Again, this analysis showed less benefit in more recent trials, including no significant effect on myocardial infarction, although a modest reduction persisted in the composite cardiovascular outcome (0·90, 0·83–0·98).

Can the discordant findings between older and newer aspirin trials be harmonised?

Although some might reasonably argue that aspirin has never been conclusively shown to be efficacious in primary cardiovascular disease prevention, most would probably agree that any potential benefits of aspirin for this indication (specifically reductions in non-fatal cardiovascular disease) are much less evident in contemporary trials than before. How can this apparent change in effect of aspirin on reducing non-fatal myocardial infarction and stroke in primary prevention be explained? One of the leading hypotheses is that improved control of cardiovascular disease risk factors, including smoking, hypertension, and hyperlipidaemia, has rendered aspirin obsolete for primary prevention.[49] This theory is possible since aspirin is not known to directly inhibit atherogenesis or stabilise plaque, nor does it specifically target any primordial risk factor for cardiovascular disease. Rather, the presumed benefit of aspirin for primary prevention is to abort an impending or subclinical myocardial infarction from becoming manifest and clinically relevant by inhibiting platelet coagulation. Some evidence exists that most myocardial infarctions are small and subclinical, and that spontaneous lysis of a forming clot regularly aborts these events before clinical manifestations occur, even without aspirin.[50,51] However, if less of these subclinical myocardial infarctions are happening because of improved control of causal risk factors for atherosclerosis (eg, tobacco smoking, inflammation, hypertension, hyperlipidaemia, or dysglycaemia), then the role of aspirin will become less relevant for primary prevention.

Although contemporary trials sought to select study populations with high cardiovascular risk, such as patients with diabetes (eg, POPADAD,[9] JPAD,[10] and ASCEND[14]) or multiple cardiovascular risk factors (eg, ARRIVE[13]), the observed cardiovascular disease event rates in these trials (and thus the risk for the enrolled participants) were generally far lower than expected (consistent with temporal improvements in medical care). For example, the ARRIVE trial[13] had event rates of cardiovascular disease that were lower than expected (<10% over 10 years) and therefore the trial might not have captured aspirin's effect on a higher-risk younger population. Similarly, the ASCEND trial[24] had a small percentage of patients (17%) with high estimated cardiovascular risk, and again, event rates were lower than expected.

To understand whether contemporary care caused the difference in results between historical and modern trials (tables 1, 2), we compared the cardiovascular risk factors present in the study populations (table 3). The weighted average of mean systolic blood pressure (140 mm Hg *vs* 157 mm Hg), tobacco use rate (13·9% *vs* 15·6%), and mean total cholesterol (5·0 mmol/L [193 mg/dL] *vs* 6·1 mmol/L [235 mg/dL]) were all lower in trials reported after the year 2000, but these trials also reported more obesity (body-mass index

	Pre-2000 weighted average	Pre-2000 trials	Post-2000 weighted average	Post-2000 trials
Smokers	15·6%	BMD,[3] PHS,[4] TPT,[5] HOT,[6] PPP,[7] WHS[8]	13·9%	POPADAD,[9] JPAD,[10] AAA,[11] JPPP,[12] ARRIVE,[13] ASCEND,[14] ASPREE[15]
Hypertension	SBP 157 mm Hg	BMD, TPT, HOT, PPP	SBP 140 mm Hg	POPADAD, JPAD, AAA, JPPP, ARRIVE, ASCEND, ASPREE
Diabetes	4·4%	BMD, PHS, HOT, PPP, WHS	38·4%	POPADAD, JPAD, AAA, JPPP, ARRIVE, ASCEND, ASPREE
Bodyweight	BMI 26·9 kg/m²	TPT, HOT, PPP, WHS	BMI 27·7 kg/m²	POPADAD, JPAD, JPPP, ARRIVE, ASCEND
Cholesterol	6·1 mmol/L	TPT, HOT, PPP	5·0 mmol/L	POPADAD, JPAD, AAA, JPPP, ASCEND, ASPREE
Statin use	16%	PPP	47%	JPAD, AAA, ARRIVE, ASCEND, ASPREE

BMD=British male doctors. PHS=physicians' health study. TPT=thrombosis prevention trial. HOT=hypertension optimal treatment. PPP=primary prevention project. WHS=women's health study. POPADAD=progression of arterial disease and diabetes. JPAD=Japanese primary prevention of atherosclerosis with aspirin for diabetes. AAA=aspirin for asymptomatic atherosclerosis. JPPP=Japanese primary prevention project. ARRIVE=aspirin to reduce risk of initial vascular events. ASCEND=study of cardiovascular events in diabetes. ASPREE=aspirin in reducing events in the elderly. SBP=systolic blood pressure. BMI=body-mass index.

Table 3: **Cardiovascular risk burden and statin use in historical and contemporary trials**

	Definition
BMD[3]	Self-reported myocardial infarctions that were confirmed by cardiologist or neurologist review and classified as a "definite", "probable", or "doubtful" event, with "doubtful" events removed from the analysis
PHS[4]	WHO criteria (1971):[54] ECG with unequivocal changes; atypical or typical symptoms with equivocal ECG and elevated enzymes*; typical history and elevated enzymes* with ECG negative or not available; or fatal cases with evidence of myocardial infarction at necropsy
TPT[5]	WHO criteria (1976):[55] as in 1971, except with objective interpretation of ECG by Minnesota coding
HOT[6]	At least two of: central chest pain lasting for more than 15 min; transient elevation of enzymes* indicating myocardial damage; and typical ECG changes
PPP[7]	At least two of: chest pain of typical intensity and duration; transient increase of serum enzymes* concentration indicating myocardial damage; typical ECG changes
WHS[8]	Symptoms met WHO criteria[54,55] and if the event was associated with abnormal levels of cardiac enzymes* or diagnostic ECG
POPADAD[9]	Definition according to the WHO criteria[54,55]
JPAD[10]	Not reported
AAA[11]	American Heart Association Criteria:[56] evolving diagnostic ECG; diagnostic ECG and abnormal enzymes (CK, CK-MB, SGOT, LDH); prolonged cardiac pain and abnormal enzymes (CK, CK-MB, SGOT, LDH); or a combination thereof
JPPP[12]	European Society of Cardiology and American College of Cardiology Criteria:[57] evolving diagnostic ECG; or diagnostic biomarkers (CK, CK-MB, CK-MBm, or cTn)
ARRIVE[13]	At least two of: consistent clinical history; ECG consistent with ischaemia; and cardiac biomarker elevation
ASCEND[14]	Evidence of cardiac necrosis (cardiac biomarkers) and evidence of acute myocardial infarction (symptoms, new ECG changes, imaging, or angiography)
ASPREE[15]	European Society of Cardiology and American College of Cardiology Criteria;[58] ie, rise and fall of biomarkers (CK-MB or troponin) with at least one of the following: ischaemic symptoms; development of pathologic Q waves on ECG; ECG changes indicative of ischaemia (ST segment elevation or depression); or coronary artery intervention

ECG=electrocardiogram. CK=creatine kinase. CK-MB=creatine kinase myocardial band. SGOT=serum glutamic-oxaloacetic transaminase. LDH=lactate dehydrogenase. CK-MBm=creatine kinase myocardial band mass. cTn=cardiac troponin. *Cardiac enzymes available during this time were SGOT, CK, LDH.

Table 4: **Definitions of non-fatal myocardial infarction in primary prevention aspirin trials**

27·7 kg/m² *vs* 26·9 kg/m²) and higher rates of diabetes (38·4% *vs* 4·4%), even when trials on diabetic patients were excluded (14% *vs* 4·4%). Statin use was generally not reported in the early aspirin prevention trials and was presumably very low. The first FDA approval of a statin therapy was not until 1987, and landmark randomised trials reporting the use of statins in primary cardiovascular prevention did not report until the late 1990s and 2000s.[52,53] According to available data, however, statin use was markedly higher in the later aspirin primary prevention trials (47% *vs* 16%). Therefore, the greater use of statin therapy, along with improvements in blood pressure control and smoking cessation in more recent trials might have reduced the risk of plaque rupture events, thus limiting the opportunity for aspirin to prevent clinical cardiovascular events.

Revisions of the definition of myocardial infarction and the use of more sensitive cardiac biomarkers could also have reduced the reported benefit of aspirin in contemporary trials. Non-fatal myocardial infarction, in particular, is worth examining closely, as this is the endpoint that was most consistently improved in earlier aspirin trials (table 4). The early trials made use of WHO definitions of myocardial infarction from the 1970s,[54,55] which did not explicitly include a standardised cardiac biomarker, or threshold thereof, to categorise myocardial infarction, as not enough data existed at that time to support endorsement of a particular biomarker test. As such, objective cardiac biomarker elevations were not required for the diagnosis of myocardial infarction in many of the older trials.[59] In the absence of cardiac-specific biomarkers, these early definitions of myocardial infarction could be mimicked by pulmonary, gastrointestinal, or musculoskeletal disease, which would confound the clinical endpoint assessed in the trials. Furthermore, the absence of sensitive biomarkers meant that larger myocardial infarctions (such as those evident from an electrocardiograph) were more likely to be detected than smaller myocardial infarctions in these early trials.

Newer myocardial infarction definitions developed by the American Heart Association,[56] American College of Cardiology,[57,58] and European Society of Cardiology[57,58] subsequently began to incorporate novel biomarkers more specific to cardiac damage such as creatine kinase myocardial band (CK-MB) and cardiac troponin. The later aspirin trials adopted these contemporary definitions of myocardial infarction. These differing criteria, and ability of recent trials to detect smaller myocardial infarctions using sensitive biomarkers, might explain, in part, the discrepancy between historical and contemporary aspirin trials. Specifically, one hypothesis is that detecting the effect of aspirin on myocardial infarction prevention might depend on how large the infarction is. Aspirin might prevent an evolving myocardial infarction from progressing to the point where it can be diagnosed using older criteria, but have less effect in preventing small plaque rupture events detectable by sensitive cardiac biomarkers.[60]

The hypothesis that aspirin might modify the presentation of, but not prevent, myocardial infarction is

consistent with the increased proportion of so-called silent myocardial infarctions as a proportion of all myocardial infarctions among patients assigned to aspirin (48%) compared with placebo (31%) in the HOT trial.[6] This concept suggests that aspirin could be responsible for converting otherwise clinically manifest, or so-called loud myocardial infarctions to silent ones. Because the prognosis of myocardial infarctions appears similar whether or not they are silent,[61,62] this idea might help to explain the consistent absence of benefit for aspirin on cardiovascular disease death, or all-cause mortality. More contemporary trials using highly sensitive cardiac biomarkers might also be subject to more uncertainty or noise in the myocardial infarction endpoint (eg, some troponin elevations in more recent trials might reflect myocardial injury and not true type 1 myocardial infarction), which could also explain the diminishing benefit for aspirin that is evident in trials that make use of modern biomarkers. Despite the above arguments, any effective prophylactic of myocardial infarction should theoretically reduce downstream morbidity (eg, heart failure) and death. Although the absence of benefit for fatal cardiovascular disease in updated meta-analyses of primary prevention aspirin appears to confirm a diminishing effect of aspirin in contemporary trials reported since 2000, case-fatality from myocardial infarction has fallen in modern studies,[63,64] and the relatively short follow-up of recent trials (typically <5 years on average) means that extended follow-up of these studies will be important to report.

	Guideline	Recommendation
2002	USPSTF	Consider use of aspirin in adults at risk for coronary heart disease (5-year risk >3%)
2002	AHA	Consider use of aspirin in adults with >10% 10-year risk of cardiovascular disease
2007	ESC	Consider use of aspirin when the 10-year risk of cardiovascular mortality is increased (SCORE risk >10%) and blood pressure is controlled
2009	USPSTF	Recommend aspirin for men aged 45—79 years, and women aged 55—79 years when cardiovascular benefit outweighs the risk of bleed (grade A)
2015	AHA/ADA	Recommend aspirin for diabetes patients who have a 10-year cardiovascular disease risk of at least 10% but are not at increased risk of bleeding (class IIa); aspirin is reasonable for adults who have diabetes and a 10-year cardiovascular disease risk between 5% and 10% (class IIb)
2016	USPSTF	Recommend aspirin in patients aged 50–59 years with a 10% or greater 10-year cardiovascular disease risk and low risk of bleeding (grade B)
2016	ESC	Recommend against initiating aspirin in individuals without overt cardiovascular disease
2019	AHA/ACC	Recommend against aspirin in individuals older than 70 years and provide a weak recommendation (class IIb) that aspirin might be considered among adults aged 40–70 years

USPSTF=US Preventive Services Task Force. AHA=American Heart Association. ESC=European Society of Cardiology. SCORE=Systematic Coronary Risk Evaluation. ADA=American Diabetes Association. ACC=American College of Cardiology.

Table 5: **Summary of major international guidelines on aspirin in primary cardiovascular prevention**

Current guidelines

Guidelines on the prophylactic use of aspirin to prevent cardiovascular disease vary internationally but have become more conservative in the past 20 years (table 5). The 2016 European Society of Cardiology primary prevention guideline recommends against initiating aspirin in individuals without overt cardiovascular disease.[65] This recommendation was a downgrade from the 2007 guideline, which stated that aspirin could be considered when the 10-year risk of cardiovascular mortality was substantial (ie, a Systematic Coronary Risk Evaluation [SCORE] risk >10%) and blood pressure was controlled.[26] In contrast to current European recommendations, the 2016 US Preventative Services Task Force guideline recommends aspirin for patients aged 50–59 years with a 10% or greater 10-year cardiovascular disease risk and a low risk of bleeding (grade B recommendation), but recommends an individualised decision regarding aspirin use in patients aged 60–69 years.[25] The 2015 American Heart Association (AHA) and American Diabetes Association guidelines recommend low-dose aspirin for patients with diabetes who have a 10-year cardiovascular disease risk of at least 10% but are not at increased risk of bleeding (class IIa). These recommendations also state that low-dose aspirin is a reasonable choice for adults who have diabetes and a 10-year cardiovascular disease risk between 5% and 10% (class IIb).[66] An updated joint AHA and American College of Cardiology guideline released in March, 2019, downgraded the role of aspirin in primary prevention by advising against aspirin for adults older than 70 years and providing a weak class IIb recommendation that aspirin might be considered among high-risk adults aged between 40 years and 70 years.[67]

Conclusion and future directions

The 2018 trials support the argument for a major change in how we prescribe aspirin for the prophylaxis of cardiovascular disease. However, one caveat is that evidence, albeit inconsistent, continues to suggest that aspirin might reduce non-fatal myocardial infarction (eg, this finding was evident in the ASCEND trial[14] and in the on-treatment analyses of the ARRIVE trial[13]). The prognosis of well managed myocardial infarction has improved greatly over the past 20 years and case fatality has fallen dramatically.[63] Therefore, the three 2018 trials might have been underpowered to detect reductions in fatal myocardial infarction with aspirin and, because the sequalae of non-fatal myocardial infarction can take decades to manifest, extended follow-up is now required to determine whether reductions in non-fatal myocardial infarction translate into a reduction in disability (eg, heart failure) or death over the longer term.

Modern approaches might also help tailor treatment more precisely to an individual's risks and benefit. Coronary artery calcium scores combined with risk calculators might enable personalised risk stratification and identification of primary prevention adults who are at sufficiently high risk for cardiovascular disease to potentially benefit from aspirin.[68,69] Cardiovascular risk scores also need to be continually updated and validated

to capture temporal changes in demographics, smoking rates,[41,42] pharmacological management of cardiovascular risk,[43] and obesity.[70]

Methods to mitigate the risk of bleeding might affect the risk–benefit ratio of aspirin. In this regard, some interest exists in weight-based aspirin dosing,[71] although the 2018 aspirin trials have not shown effect modification by weight.[72] Enteric coating or different formulations of aspirin might reduce gastrointestinal toxicity,[73] although this benefit must be weighed against potential reductions in antiplatelet effects present with certain enteric-coated aspirin formulations.[74] The concomitant use of proton-pump inhibitors reduces gastrointestinal bleeding events.[75,76] Compared with chronic proton-pump inhibitor use, assessment and treatment of *Helicobacter pylori* offers a similar degree of protection from recurrent bleeding among aspirin users.[77] Lifestyle modifications, such as minimising NSAID or alcohol intake, might decrease gastrointestinal bleeding risk.[78] Additionally, the use of bleeding risk scores specific to aspirin can inform decisions surrounding aspirin prescribing.[79]

The inability of contemporary trials of aspirin for primary prevention to consistently show a benefit for non-fatal and fatal cardiovascular disease outcomes[30,31] should also lead to reassessment of its role in secondary prevention, particularly in the postacute setting (ie, >1 year after myocardial infarction, stroke, or revascularisation).[80] Intensive treatment of cardiovascular disease risk factors might also have diminished the benefit of aspirin for secondary prevention among people with stable cardiovascular disease, although for now, guidelines continue to recommend life-long aspirin for secondary prevention. Various clinical trials have suggested that primary prevention aspirin could reduce the risk of cancer,[81,82] although ASPREE[15] unexpectedly showed an increase in cancer deaths with aspirin. Longer follow-up in all the 2018 aspirin trials will be necessary to improve understanding of this issue.[83–86] Regardless, aspirin's cost-effectiveness for primary prevention was questionable even before the more recent neutral-outcome trials.[87,88] In an era with a growing number of cardiovascular disease therapies and increasing complexity of care, withdrawal of aspirin therapy in primary prevention should consequently be considered where appropriate.

In conclusion, aspirin does not reduce fatal cardiovascular events in patients who have not yet had a first event, but it does increase the risk of bleeding. However, case-fatality from cardiovascular disease has fallen dramatically in the past few decades, so the potential importance of non-fatal endpoints must be borne in mind because aspirin still appears to reduce non-fatal myocardial infarction, albeit less consistently and convincingly in contemporary trials. Thus, longer follow-up of pivotal 2018 trials will be important to see if aspirin might prevent heart failure and other morbid complications of myocardial infarction in the longer term. Similarly, although no reliable evidence exists to support such a supposition, further randomised trials done in younger participants at higher risk than those enrolled in contemporary trials might yet identify a niche for aspirin in the primary prevention of cardiovascular disease.

Contributors

JWM was responsible for the concept of the Review, with all authors contributing to its development. IR and CPM completed the literature search. IR, CPM, and JWM wrote the first draft of the manuscript. JWM, MV, DLB, DAW, JGFC, and RSB were responsible for critical appraisal and editing of the manuscript. All authors approved the final version.

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