Aspirin in Primary Prevention: What Changed? A Critical Appraisal of Current Evidence

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Aspirin has been the mainstay of both secondary and primary prevention of cardiovascular disease for half a century. In 2018, 3 trials showed a modest reduction in cardiovascular outcomes that appeared counterbalanced by the risk of clinically significant bleeding. The latest ACC/AHA primary prevention guidelines downgraded their recommendation for aspirin use in primary prevention to that of physician preference. Despite the consistent and robust evidence previously supporting the use of aspirin in cardiovascular disease prevention, little discussion has been given to mechanisms or analytic explanations for this revision of recommendations. In this review, we explore 3 possible mechanisms that may have contributed to the alteration of our perception of aspirin's role in primary prevention. These include changes in the population potentially using aspirin in primary prevention, changes in cardiovascular disease and its presentation, and changes in aspirin itself. Here we present a translational look at knowledge gaps that should be addressed to better guide contemporary aspirin use in primary prevention. In conclusion, based on these considerations, the current recommendations might be improved by recalibration of the cardiovascular risk threshold above which aspirin should be recommended for primary prevention, including the incorporation of newer risk assessment modalities such as calcium scoring. A second enhancement would be developing a bleeding risk calculator to support clinicians' assessment of risk vs benefit. The use of enteric-coated aspirin vs non-coated aspirin should also be reassessed. **(Am J Cardiol 2021;141:38−48)**

Randomized controlled trials (RCTs) studying aspirin since the 1960s provided evidence for secondary prevention of myocardial infarction (MI) and stroke. Questions about aspirin for primary prevention of cardiovascular disease (CVD) in lower-risk individuals, dosing, and adverse events followed.[1] Dozens of RCTs, with numerous meta-analyses, on aspirin in primary prevention followed (Figure 1). Accordingly, American recommendations included aspirin for primary prevention in high-risk individuals.[2,3] Consequently, aspirin became a frequently used primary prevention medication.[2] Nevertheless, concerns about benefits and knowledge gaps in specific subgroups, such as the elderly and diabetics, emerged. So, 3-RCTs[4−6] attempted to clarify aspirin's primary prevention role in contemporary populations. Afterward, American guidelines revised aspirin recommendations in primary prevention to "physician's preference" and did not support use after age 70,[7] generating considerable media attention (Supplement Box 1). However, methodological and biological mechanisms that may explain this change are complex.[8] In this review, we explore possible mediators that may have changed in the past half-century to explain differences in study results, which provided the rationale to revise primary prevention guidelines away from recommending aspirin. We address themes that likely contributed; changes in the: Population for preventative care, disease and/or its presentation, and in aspirin preparation.

Basis for older primary prevention guidelines

Ten RCTs, from 1980 to 2010, assessed aspirin in primary prevention[9−17] (Table 1). Most used "regular" aspirin in populations with lower blood pressure and cholesterol control, less statin use, and higher smoking prevalence versus recent years. Only one early trial[10] showed beneficial aspirin effects for fatal-MI; other trials showed a benefit for nonfatal MI.[10,12,13] Thus, the 2002 American recommendations focused on "high-risk" individuals (5-year CVD risk ≥3%).[2] After a 2009 patient-level meta-analysis (660,000 person-years and 3554 major vascular events),[18] American recommendations included men (45 to 79 years old) and women (55 to 79 years old) with CVD risk that outweighed the bleeding risk.[19]

Basis for recent primary prevention guidelines

After 2010, 4-additional trials[16,17,20,21] continued to show reduced major vascular events, driven mainly by nonfatal MI, with a somewhat higher aspirin-associated bleeding risk. Nonetheless, the 2016 American guidelines continued to recommend aspirin for adults with increased CVD risk (adding colorectal-cancer prevention).[3]

Due to conflicting aspirin benefit signals in newer versus earlier studies, 3-RCTs followed[4−6] (Table 2). The Study of

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See page 46 for disclosure information.

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0002-9149/
https://doi.org/10.1016/j.amjcard.2020.11.014

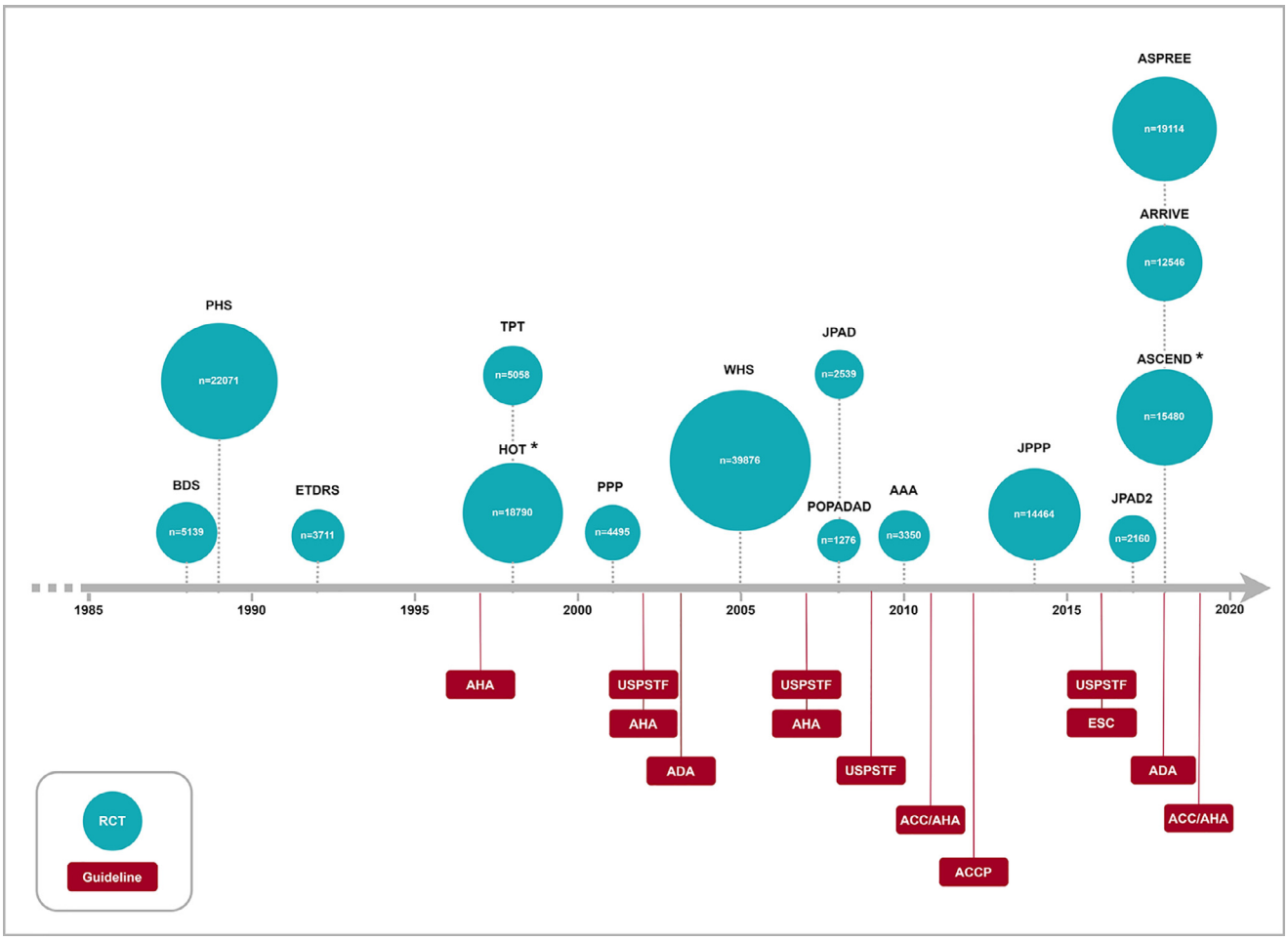

Figure 1. Time-line for major randomized controlled trials and international societal guidelines of aspirin use in primary prevention of cardiovascular disease
* Indicates a significant reduction in the primary endpoint.
Bubble size reflects the trial population size.
AAA = Aspirin for Asymptomatic Atherosclerosis Trial; ACC = American College of Cardiology; ACCP: American College of Chest Physicians; 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; BDS = British Doctors Study; ESC = European Society of Cardiology; HOT = Hypertension Optimal Treatment Trial; JPAD = Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes Trial; n = number of study participants; PHS = Physicians' Health Study; POPADAD = Prevention of Progression of Arterial Disease and Diabetes Trial; PPP = Primary Prevention Project; RCT = randomized controlled trial; TPT = Thrombosis Prevention Trial; USPSTF = United States Preventive Services Task Force; WHS = Women's Health Study.

Cardiovascular Events in Diabetes (ASCEND) showed aspirin reduced vascular events (hazard ratio [HR], 0.88; confidence interval [CI], 0.79 to 0.97) with 1.1% absolute risk reduction (ARR) versus 0.9% absolute risk of major bleeding.[4] The Aspirin to Reduce Risk of Initial Vascular Events (ARRIVE) trial planed for patients at moderate CVD risk had an actual 10-year event rate <10%, and the primary efficacy endpoint was neutral (HR 0.96; CI, 0.81 to 1.13).[5] The low event rate led investigators to add unstable angina and transient ischemic attack (TIA) to the outcome, but only the per-protocol analysis found a ~45% reduction in nonfatal MI (HR, 0.55; CI, 0.36 to 0.84). Both trials showed no effect on mortality with limited follow-up duration (5 to 7 years). At last, the Aspirin in Reducing Events in the Elderly (ASPREE) trial, with apparently-healthy older adults, showed no aspirin-related CVD benefit but higher all-cause mortality versus placebo (HR, 1.14; CI, 1.01 to 1.29).[6]

As expected, aspirin increased bleeding in all 3-trials. Several limitations likely contributed to these results. These trials were conducted on cohorts with lower blood pressure and cholesterol, more statin and enteric-coated (EC) aspirin use, and less smoking leading to lower-than-planned event rates. Moreover, they were based on more contemporary CVD and primary vascular outcome definitions. All trials had suboptimal (60% to 70%) compliance with the randomized assignment and substantial crossovers, limiting results. The trials also had less ideal reporting on risk factors related to bleeding, such as alcohol and nonsteroidal anti-inflammatory drugs (NSAIDs) use. At last, they had a relatively short follow-up time to assess CVD outcomes.

Insights from recent meta-analyses

Meta-analyses have since added ~50,000 subjects to pooled primary prevention data;[23–25] these new data should

Table 1
Randomized controlled trials of aspirin use in primary prevention before the year 2010

Trial (year of publication)	Period	Country	Trial design	Patient population[‡]	Aspirin dose (mg), formulation	Control	Number of participants	Mean age (Years)	Men	Mean BMI (Kg/m^2)	SH	DM	CS	10-year CV risk	Aspirin adherence	Mean follow-up (Years)
BDS[9] (1988)	1978-1984	UK	Randomized, open-label, blind	Male physicians	Ordinary, soluble or effervescent (500 mg) or enteric coated (300 mg)[*]	No aspirin	5139	61	100 %	24.4	10 %	2 %	13 %	15.4	75 %	6
PHS[10] (1989)	1982-1988	USA	Randomized, double-blind	Male physicians, age 40-84	325 EOD, mostly regular	Placebo	22071	53	100 %	24.9	20 %	2 %	11 %	6.7	85 %	5
ETDRS[11] (1992)	1980-1985	USA	Randomized, double-blind	Individual with age 18-70y, DM, and retinopathy	650 daily	Placebo	3711	NR [‡]	56 %	NR	85 %	100 %	44 %	40.8	70 %	5
HOT[12] (1998)	1992-1997	26 countries in Asia, Europe, and the Americas	Randomized, double-blind, factorial with HTN treatment targets	Individuals with SH, age 50-80	75 daily, NS	Placebo	18790	61	53 %	28.4	100 %	8 %	16 %	11.9	NR	3.8
TPT[13] (1998)	1984-1997	UK	Randomized, double-blind, factorial design with warfarin	Males, age 45-69, 20-25% CV risk score	75 daily, Controlled release capsule	Placebo	5058	57	100 %	27.4	16 %	2 %	41 %	15.3	NR	6.7
PPP[14] (2001)	1994-1998	Italy	Randomized, open-label, factorial design with Vitamin E	Individuals with ≥1 CV risk factor	100 daily, EC	No aspirin	4495	64	42 %	27.6	68 %	17 %	15 %	7.6	81 %	3.6
WHS[15] (2005)	1992-2004	USA	Randomized, double-blind, factorial design with Vitamin E	Female health professionals, age ≥ 45	100 EOD, regular	Placebo	39876	54	0 %	26.1	26 %	3 %	13 %	2.6	73 %	10.1
POPADAD[16] (2008)	1997-2006	UK	Randomized, double-blind, factorial design with antioxidant	Individuals with DM, ABPI ≤0.99, age ≥40	100 daily, regular	Placebo	1276	60	44 %	29.2	NR	100 %	NR	25.3	50 %	6.7[†]
JPAD[17] (2008)	2002-2008	Japan	Randomized, open-label	Individuals with DM aged 30-85	81 or 100 daily, regular	No aspirin	2539	65	55 %	24	58 %	100 %	21 %	79	90 %	4.37[†]

ABPI = Ankle Brachial Pressure Index; BDS = British Doctors Study; BMI = body mass index; CS = cigarette smoking; CV = cardiovascular; DM = diabetes mellitus; EOD = every other day; EC = enteric-coated; ETDRS = Early Treatment Diabetic Retinopathy Study; N = number; NS = not stated; NR = not reported; HOT = Hypertension Optimal Treatment Trial; JPAD = Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes Trial; PHS = Physicians' Health Study; PPP = Primary Prevention Project; POPADAD = Prevention of Progression of Arterial Disease and Diabetes Trial; SH = systemic hypertension; TPT = Thrombosis Prevention Trial; WHS = Women's Health Study; UK = United Kingdome; USA = United States of America.

* Patients had the option to select either effervescent aspirin, 500 mg/d, or an enteric-coated tablet, 300 mg/d;

† Median, not mean;

‡ Age in years.

Table 2
Randomized controlled trials of aspirin use in primary prevention after the year 2010

Trial (year of publication)	Period	Country	Trial design	Patient population†	Aspirin dose (mg), Formulation	Control	Number of participants	Mean age (Years)	Men	Mean BMI (Kg/m^2)	SH	DM	CS	10-year CV Risk	Aspirin adherence	Mean follow-up (Years)
AAA[20] (2010)	1998-2008	UK	Randomized, double-blind	Individuals with ABPI ≤0.95 age 50-75	100 daily, EC	Placebo	3350	62	28 %	No report	No report	3 %	32 %	9.9	88 %	8.2
JPPP[21] (2014)	2005-2012	Japan	Randomized, open-label	Individuals with SH, dyslipidemia, DM, age 60-85	100 daily, EC	No aspirin	14464	71	42 %	24.2	85 %	34 %	13 %	5.9	76 %	5
JPAD2[22] (2017)*	2002-2015	Japan	Randomized, open-label	Individuals with DM aged 30-85	81 or 100 daily, regular	No aspirin	2160	65	55 %	24	58 %	100 %	21 %	7.8	79 %	10.3
ASCEND[4] (2018)	2005-2017	UK	Randomized, double-blind; factorial design with n-3 fatty acid	Individuals with DM, age≥40	100 daily, EC	Placebo	15480	63	63 %	30.7	62 %	100 %	8 %	10.2	70 %	7.4
ARRIVE[5] (2018)	2007-2016	Europe and USA	Randomized, double-blind	Individuals with 10-year CV risk of 10%-20%	100 daily, EC	Placebo	12546	64	70 %	28.4	63 %	0 %	29 %	6.9	80 %	5
ASPREE[6] (2018)	2010-2014	Australia and USA	Randomized, double-blind	Individuals with age ≥70 Black or Hispanic individuals in the USA with age ≥65	100 daily, EC	Placebo	19114	74	44 %	28.1	74 %	11 %	4 %	8.2	62 %	4.7

AAA = Aspirin for Asymptomatic Atherosclerosis Trial; ABPI = Ankle Brachial Pressure Index; ASCEND = A Study of Cardiovascular Events in Diabetes; ARRIVE = Aspirin to Reduce Risk of Initial Vascular Events; ASPREE = Aspirin in Reducing Events in the Elderly; BMI = body mass index; CS = cigarettes smoking; CV = cardiovascular; DM = diabetes mellitus; EC = enteric coated; JPAD = Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes Trial; SH = Systemic Hypertension; UK = United Kingdome; USA = United States of America.

* JPAD 2 was a follow-up trial on JPAD after the trial ended in 2008; patients were followed until 2015;

† Age in years.

be considered in the totality of evidence. A meta-analysis[24] using the latest primary prevention trials found aspirin was still associated with a reduction in major adverse cardiovascular events (MACE) (HR, 0.89; credible interval [CrI] 0.84 to 0.95; ARR, 0.38%; CI, 0.20% to 0.55%); and number needed to treat (NNT) = 265. Aspirin was associated with increased risk of major bleeding (HR, 1.43; CrI, 1.30 to 1.56); absolute risk increase (ARI) (0.47%; CrI, 0.34% to 0.62%); and number needed to harm (NNH) = 210. Additionally, aspirin was associated with a reduction in MI (HR, 0.85; CrI, 0.73 to 0.99) and ischemic stroke (HR, 0.81; CrI; 0.76 to 0.87).[24]

Another meta-analysis[25] found all-cause mortality similar comparing aspirin and control groups (RR, 0.98; CI, 0.93 to 1.02). The results did not change in subgroup analysis or meta-regression by midenrollment year, age, % women, hypertension, or smoking. CVD mortality (RR, 0.92; CI, 0.83 to 1.01) and ischemic stroke (RR, 0.94; CI, 0.86 to 1.02) were similar in both groups. MI incidence was lower with aspirin (RR, 0.82; CI 0.71 to 0.94; NNT = 333). Nonetheless, the effect size was characterized by high-degree heterogeneity between included studies due to variation in MI definition. Secondary analysis, excluding older trials, showed a lack of aspirin benefit in more recent (RR, 0.90; CI, 0.79 to 1.02) versus older trials. Aspirin-related major bleeding was higher (RR,1.47; CI 1.31 to 1.65; NNH = 250), as well as intracranial hemorrhage (RR, 1.33; CI 1.13 to 1.58; NNH = 1000). Additionally, in a trial-sequential analysis assessing mortality (rare outcome), a cumulative Z-curve did not cross the traditional significance boundary but crossed the predetermined futility boundaries, supporting findings of the conventional meta-analysis (no aspirin benefit for all-cause mortality).[25]

In a third meta-analysis,[23] aspirin use had similar mortality rates for all-cause, cardiovascular, and noncardiovascular deaths, but aspirin was not only associated with lower nonfatal-MI risk (RR, 0.82; CI, 0.72 to 0.94; NNT = 357); also lower TIA risk (RR, 0.79; CI, 0.71 to 0.89; NNT = 370), and ischemic stroke (RR, 0.87; CI, 0.79 to 0.95; NNT = 500). MACE were lower with aspirin versus controls (RR, 0.903; CI, 0.85 to 0.96; NNT = 263). Aspirin was associated with a higher risk of major bleeding (RR, 1.5; CI, 1.33 to 1.69; NNH = 222), intracranial bleeding (RR, 1.32; CI, 1.12 to 1.55; NNH = 1000), and major gastrointestinal (GI) bleeding (RR, 1.52; CI, 1.34 to 1.73; NNH = 385), and similar fatal bleeding rates. Meta-regression analysis again showed favorable treatment effects for nonfatal MI in older versus recent studies. Women had favorable treatment effects on total stroke. Age, hypertension, diabetes, or statin use did not modify efficacy or safety outcomes. A prespecified sensitivity analysis confirmed aspirin remained associated with lower total-MI, nonfatal-MI, TIA, ischemic stroke, and MACE risks in 3 cohorts: (1) <100 mg/day aspirin; (2) estimated 10-year CVD risk >7.5%; and (3) outcomes reported after >5-years follow-up. All-cause death was lower with aspirin only at follow-up >5 years, and there was a trend toward lower cardiovascular death with aspirin only in cohorts with a high estimated 10-year CVD risk. Finally, cohorts receiving <100 mg/day aspirin showed a significant reduction in total stroke.[23]

Additionally, another meta-analysis[26] evaluated aspirin's safety and efficacy among patients with diabetes, and also performed a pooled analysis of individual patient data (IPD) from 3 trials.[10,14,15] Aspirin use was associated with 11% MACE reduction (RR, 0.89; CI, 0.83 to 0.95; NNT = 95), and no significant difference in all-cause mortality or other cardiovascular outcomes. Again, aspirin dose <100 mg/day significantly reduced stroke risk. However, estimates for major bleeding (RR, 1.30; CI, 0.92 to 1.82) and other adverse outcomes were imprecise and not statistically significant. IPD analysis showed no significant differences in primary safety outcomes, but there was evidence of a differential effect of aspirin on the risk of MACE by smoking status (RR, 0.70; CI 0.51 to 0.96; NNT = 33; nonsmokers vs smokers).[26]

Challenges interpreting absolute risk across different outcomes lie in the interpretation of the severity of each outcome. Moreover, despite current primary prevention strategies and difficulties in primary prevention trials, these meta-analyses confirm the consistency of newer versus previous studies with near similar NNTs and NNHs. Whereas subgroup analyses are limited, there are signals of important differences in aspirin's effects by dose, duration, smoking status, sex, and weight that demand future research.

Biological mechanisms explaining changes in aspirin-outcome relationship: what changed?

Changes in aspirin dose and formulation Buffered, or EC formulations did not improve aspirin safety, probably because GI bleeding and ulceration more likely result from systemic prostaglandin depletion by COX-1 inhibition.[27] EC-aspirin formulations may be less effective than regular aspirin. About 95% inhibition of thromboxane generation is required to inhibit platelet aggregation.[28] Also, some EC preparations may not be as acutely effective as regular aspirin.[29] In healthy volunteers, no aspirin resistance (platelet function testing) occurred with immediate-release aspirin versus substantial aspirin resistance with EC-aspirin.[30] Resistance may occur in up to 28% of treated individuals and could contribute to worse outcomes.[31] Most earlier studies used non-EC aspirin, including the only study showing favorable aspirin effects on fatal and nonfatal MI.[10]

One study concluded that low-dose EC-aspirin preparations are less likely to attain full aspirin benefit because they deliver a dose equivalent to 50 mg plain aspirin. Reduced aspirin bioavailability was associated with increased body weight: 10-kg (22-lb) increase in weight was associated with an approximate doubling of treatment failure.[32] Additionally, with higher body weight, twice-daily regimens can counteract the patient-to-patient variability of COX-1 recovery following once-daily aspirin.[33] This aspirin dose-weight signal was also present using individual patient data where 75 to 100 mg aspirin was only effective in preventing vascular events in patients weighing <70 kg.[34] Nonetheless, a post-hoc weight-based analysis of a recent RCT suggested bodyweight did not modify aspirin effects on CVD or major hemorrhage but did increase the risk of aspirin-associated bleeding in men.[35]

EC-aspirin potentially minimized beneficial primary prevention studies since 2010, but more research is needed to

address the "one-dose-fits-all" aspirin approach for primary prevention. Also, until now, there is no consensus on a universal definition or a reference assay for "aspirin resistance."

Changes in primary prevention population

Early prevention aspirin trials were conducted when smoking was more prevalent, blood pressure-lowering suboptimal, and aggressive lipid-lowering rare. This has changed in the newer studies. Statins use increased from 0% to 16% before 2001 to nearly 75% in a recent RCT.[4] Likewise, smoking rates in older studies ranged 11%[10] to 41%,[36] whereas the lowest smoking rates in recent trials were 4%[6] to 8%.[4] Americans smoking prevalence halved between 1987 and 2016.[37] These changes likely lowered CVD risk/event rates, thus limiting the ability to detect beneficial aspirin effects. However, overweight, obesity, and diabetes rates have increased with considerable effects on CVD and its presentation (Figure 2).[38]

Are contemporary study designs able to accommodate changes in the presentation and treatment of CVD occurring overtime?

For example, a recent RCT planned a 10% to 20% CVD risk, but the observed event rate was only ~8%.[5] Thus, participants should be considered to have low-to-moderate risk. These results are consistent with previous trials, where aspirin use conferred no vascular benefit with a significant increase in bleeding. Additionally, we estimate CVD risk using calculators developed with older data that mostly overestimate risk.[39]

In current practice, the focus on primary prevention helped decrease the total CVD burden versus older studies, with a shift in case-mix toward more nonfatal MI and unstable angina (vs ST-elevation MI). This has made it much more challenging to conduct large-scale primary prevention trials. Moreover, there has been a transition in the cause of death from CVD to non-CVD among survivors,[40] related in part to aging of the population, a shift in risk factor profile (less smoking, lower blood pressure, lower lipids), the increase in diabetes, metabolic syndrome, chronic kidney disease, dementia, and increased use of preventive medications (statins, B-blockers, angiotensin-converting enzyme inhibitors).[41]

Furthermore, outcome definitions changed over recent years incorporating advances in diagnostic techniques for CVD. Many developing CVD events might have been aborted very early in the process, at home, or with Emergency Medical Services (EMS), which would otherwise have previously counted as events. For instance, in 1 trial,[5] subjects were only seen annually and may have missed reporting minor events like an unstable angina episode aborted with an aspirin load or early EMS evaluation, and was not counted as an event. Another explanation for fewer events may be the prevention of MI or cardiac death as traditionally defined. Earlier trials used less sensitive markers capturing only large infarctions, whereas newer trials used more sensitive biomarkers detecting smaller myocardial injury and less type-1 MI; the type for which aspirin provides more benefit.

Thrombolytics, revascularization, and other treatments for acute coronary syndromes have also reduced the frequency of both MI and cardiac death. In practical trials, dropout rates were likely accelerated in the highest risk groups, such as those with angina in whom the appropriate prescription of aspirin resulted in the selective crossover of these highest-risk subjects out of the placebo group unless retained in an intention-to-treat analysis. Defining those minor events would be extremely difficult in large-scale practical studies requiring patients to seek care.

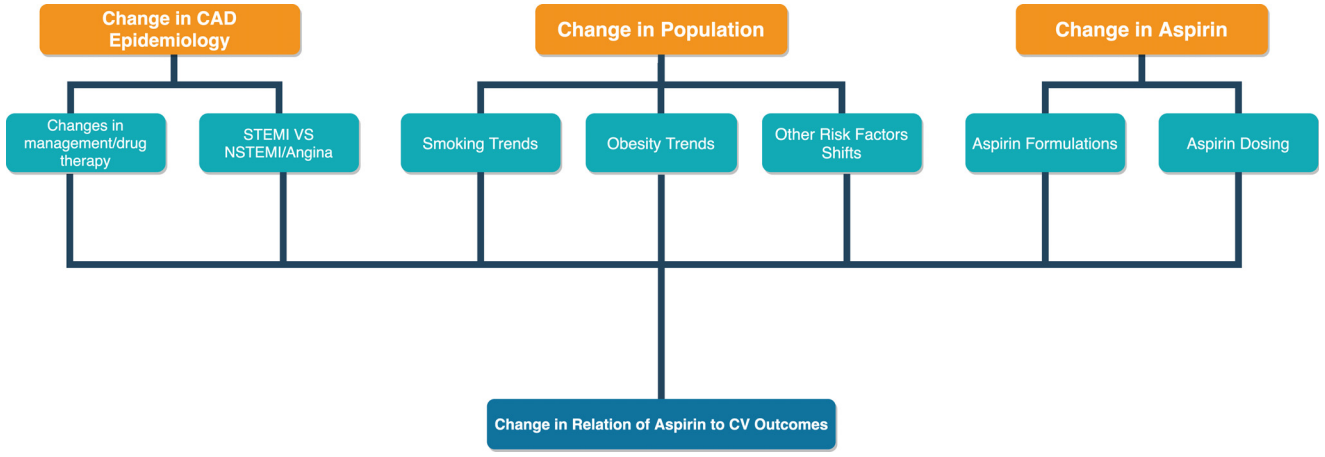

Figure 2. Proposed mechanisms of change in primary prevention outcomes related to aspirin over time.
The illustration describes the interplay between possible changes in aspirin's relationship with outcomes in primary cardiovascular disease prevention. This includes changes in atherosclerotic coronary artery disease epidemiology with newer and more sensitive diagnostic coronary artery disease techniques, more advanced transluminal treatments, and less incidence of STEMI compare with NSTEMI/unstable angina; changes in aspirin interaction with alterations in the primary prevention population such as lower smoking rates, stricter blood pressure control, and better cholesterol management, whereas on the other hand rates of obesity and type II diabetes mellitus are increasing. Finally, differences in aspirin dosing and formulations (plain VS enteric-coated) and its interaction with obesity could have modified cardiovascular outcomes in subjects using aspirin for primary prevention.

Aspirin and increased risk of bleeding

Aspirin inhibits tissue prostaglandins (COX-1, COX-2), disrupting gastroduodenal cryoprotection provided via COX-1, thereby promoting bleeding.[42] The 2016 USPSTF summary[40] found low-dose aspirin for primary prevention increased major GI bleeding risk by 58%. Age was the most important bleeding risk (increasing 1.5-2-fold in each subsequent decade >50-year) and, to a lesser extent, male sex. Other factors included previous GI-bleeding hospitalization, body mass index, diabetes, smoking, medications, *H. pylori* infection, previous ulcer, and alcohol; many are established CVD risk factors.[43,44] The RR for major bleeding in the meta-analyses ranged from 1.4 to 1.5.[23–25] Primary prevention trials have considerable heterogeneity in reporting and classifying bleeding outcomes (Supplement Table 1).

Other studies showed low-dose aspirin associated with 2- to 4-fold increased risk for upper GI bleeding (UGIB), that is not reduced using EC or buffered aspirin.[45,46] UGIB risk increases with aspirin dose-escalation, age, male sex, and use with other NSAIDs or anticoagulants.[47] One analysis showed a 0.12% absolute increase in UGIB risk with aspirin versus placebo.[48] *H. pylori* eradication or adding proton pump inhibitors (PPIs) to daily aspirin may reduce UGIB risk.[49–51] In a meta-analysis of ~1200 RCTs, gastroprotectant medications were effective in the treatment and prevention of peptic ulcer disease and its main complications in patients taking NSAIDs (including aspirin).[26] Nonetheless, in patients with low bleeding risk, long-term PPIs offer a small benefit.[52] It is noteworthy that, even with increased aspirin use, there was no increase in area UGIB hospitalizations in a population-based study.[48] National data for UGIB hospitalizations also observed a 14% decline between 1998 and 2006. Similarly, rates of hemorrhagic stroke are decreasing.[53]

There are few studies on lower GI bleed (LGIB) and aspirin with even less data on the long-term risk/benefit profile of resuming aspirin after LGIB. One study showed that aspirin's continuation was associated with an increased risk of recurrent LGIB but a reduced risk of serious CVD events and death in high CVD risk patients.[54] In a recent population-based cohort (5.4-year median follow-up), new aspirin users for primary prevention had incidence rates of UGIB and LGIB per 1000 person-years of 0.97 and 1.68 among low-dose aspirin users and 0.67 and 0.76 among matched nonusers, respectively. Men had a higher incidence of UGIB than women (1.03 vs 0.90 per 1000 person-years), whereas for LGIB, incidence rates were slightly lower in men (1.60 vs 1.76 per 1000 person-years). Case-fatality rates were 5.7% for UGIB and 0.8% for LGIB.[55]

Finally, since aspirin-associated GI bleeding is usually nonfatal and most often managed with a nonsurgical approach, a search for new cancer diagnosis has the potential to unmask malignant GI pathology early in its course and affect longer mortality.[56] Hence, in real-world settings, should GI bleeding occur, the fatality rate could actually be reduced. This was observed in a meta-analysis of RCTs to ascertain fatal bleeding events, that showed a RR of 1.55 (CI, 1.33 to 1.83) for major GI bleeding with low-dose aspirin, whereas the risk of bleeding attributable to aspirin being fatal was 0.45(CI, 0.25 to 0.80) versus no aspirin. There was no significant increase in the risk of a fatal bleed. Low-dose aspirin was associated with 1 death and 1 disabling hemorrhagic stroke per year in every 10,000 people taking low-dose aspirin.[57]

Aspirin discontinuation risk

Unlike other NSAIDs, aspirin at low doses, irreversibly inhibits cyclooxygenase enzymes, COX-1 more than COX-2, resulting in a decreased production of thromboxane A2 (promotes platelet clotting and a vasoconstrictor) and continued production of prostaglandin I2 (platelet inhibitor and a vasodilator).[35,58] The resulting balance explains aspirin's potential to prevent thrombosis and reduce CVD events. Stopping daily aspirin has the potential to increase risk due to a "rebound" increase in platelet aggregability, possibly related to rebound elevations in platelet thromboxane synthesis.[59] Previous studies suggest a 3-fold increase in thrombotic events upon aspirin discontinuation, highest within 10 days of discontinuation.[60]

Current data on aspirin discontinuation remain limited, observational, and mainly address discontinuation in secondary prevention. Caution should be exercised when discontinuing aspirin for primary prevention in patients without a history of bleeding. This is especially true in subjects with moderate-to-high cardiovascular risk, who may harbor multiple coronary atherosclerotic plaques at different stages of instability. Vulnerable plaques may be more prone to rupture/erosion with thrombosis due to rebound platelet aggregability and loss of aspirin's plaque stabilizing effects (Figure 3).

Discussion

Accumulated evidence continues to support the cardioprotective effects of aspirin in reducing nonfatal MI and stroke. Furthermore, current evidence appears sufficient to recommend aspirin for primary prevention in carefully selected patients, after accounting for bleeding risks and their views on the balance of risk versus benefit. All 3 meta-analyses discussed earlier showed a reduced incidence of nonfatal-MI and CVD events. Despite the decline in the magnitude of this effect in newer versus older studies, it continues to be present and in the same direction. Moreover, recent trials have been underpowered to evaluate mortality due to dramatically lower death rates from MI in contemporary studies.[61] Additionally, the brief follow-up periods in recent trials are insufficient to evaluate aspirin's full effects and its impacts on life-time mortality and cancer incidence. This was suggested in the recent meta-analysis where all-cause death was lower with aspirin only when follow-up was >5 years.[23]

Because either an MI or stroke results in some permanent tissue loss, there is potential for much more serious long-term effects on quality of life than a nonfatal bleeding event; thus, the decision should be shared and individualized. Developing ischemia-related downstream complications can have long latency periods and require extended follow-up (>10 years) to fully evaluate clinical sequelae.

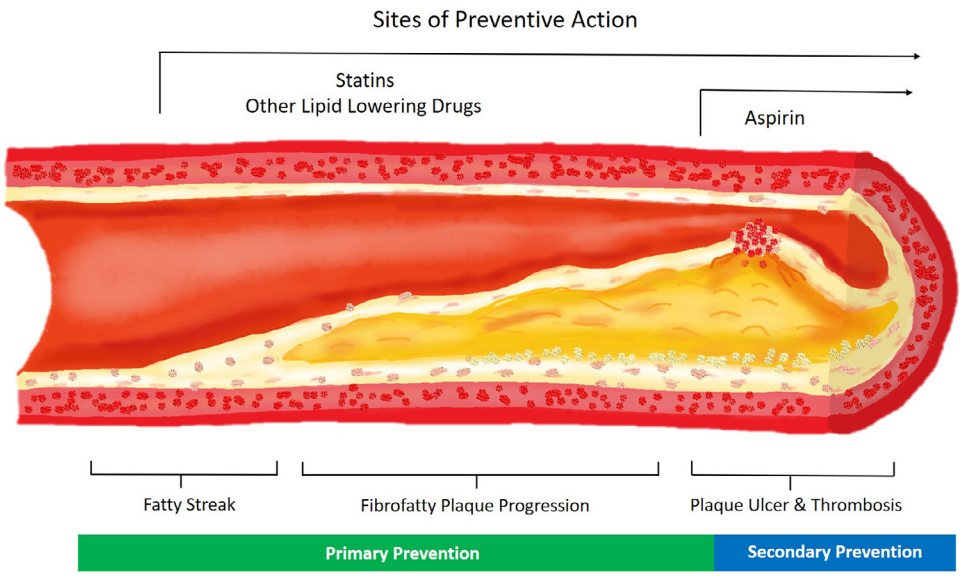

Figure 3. Targets for preventive therapeutics for atherosclerotic plaque progression.
Atherosclerotic plaque progression from the subclinical fatty streak and fibrofatty plaque to atherosclerotic plaque ulceration, acute thrombosis presenting as an acute myocardial infarction. Before the first coronary event, statins, other lipid-lowering agents, and possibly anti-inflammatory medications work in primary prevention to halt atherosclerotic plaque growth progression. At the other end of the disease spectrum, whereas it does not necessarily prevent plaque progression, aspirin stabilizes plaques, helps prevent plaque ulceration, and prevents or reduces the odds of acute thrombosis. Patients with at least moderate atherosclerotic cardiovascular disease risk, who are likely to harbor multiple atherosclerotic plaques at different stages of the disease, will likely benefit from tackling various targets in the disease spectrum to obviate a first acute coronary event.

After a MACE, most aspirin studies do not continue to follow-up. Whereas bleeding events may acutely draw more attention to patients, they are usually followed by recovery without permanent sequelae, and there has been no evidence of increased mortality from GI bleeding. The absolute risk of fatal or intracranial bleeding with aspirin is far lower than the absolute risk of a CVD event. With near similar NNT and NNH, evidence confirms that most patients would prefer to avoid a MI or stroke than an episode of bleeding.[62]

Interest should shift toward means of assessing the most favorable risk-benefit profile where aspirin can be used with greater precision following a well-informed decision. Decision-making tools should include evidence-based calculators to assess CVD and GI bleeding risks, along with the composite NNT/NNH estimated for each person. In terms of CVD risk calculations, limiting aspirin use to high-risk individuals may deny patients the opportunity to prevent a significant number of CVD events that may present with a large MI or sudden cardiac death.[63] The ACC/AHA recommends using the current pooled cohort equation to calculate current 10-year CVD risk for patients age 40 to 79. As discussed above, this calculator is not comprehensive, does not include new risk markers, and tends to overestimate risk. One potential risk marker to improve risk discrimination and reclassification is coronary artery calcium (CAC), which predicts a nearly 10-fold increase in CVD events in patients with elevated scores.[64] Using the CAC score could potentially help guide therapy to higher-risk patients with net benefit whereas avoiding aspirin use in lower-risk individuals in whom risk/benefit profiles are unfavorable. This will reduce the risk of withholding aspirin from lower-risk patients who represent a majority of the primary prevention population and in whom a very large proportion of cardiovascular events eventually occur.[65]

C-reactive-protein (CRP) and high-sensitivity (hs) CRP are other potential risk markers for atherosclerosis to be incorporated in risk calculators. However, most data on low aspirin in primary prevention populations showed no differential effect across hs-CRP levels.[66] Newer evidence is emerging on using genome-wide polygenic score (GPS) to identify individuals at increased risk for CAD. In one study, GPS was able to identify 8% of the population at >3-fold increased risk for CAD, a category difficult to identify using conventional risk scores.[67]

Nevertheless, GI bleeding risk estimation continues to be a challenge. The evidence is not based on well-validated tools with large heterogeneity between trials. One UGIB risk-calculator for persons taking low-dose aspirin mainly included age, sex, previous history of GI ulcers, and cotreatment with NSAIDs or antiplatelets or anticoagulants,[68] but this calculator was not externally validated. Another prognostic bleeding risk model from a cohort is under development.[69] Hence, a more robust, comprehensive, and validated bleeding-risk tool is clearly needed.

Moreover, pooling outcomes from primary prevention trials are not ideal. Most primary prevention studies are heterogeneous in terms of aspirin dose, duration, patients' characteristics, and CVD risk. The 3 most recent large studies were obliged to present their results as "negative." Besides, the ability of large-scale primary prevention studies to detect outcomes whereas conducted on a background of multiple other preventive interventions is challenging. Most trials were powered for clusters of outcomes combining fatal and nonfatal events with limited power for relatively infrequent individual outcomes in primary

prevention populations.[70] Up to 45% of MIs are "silent" but are associated with permanent tissue loss, increased mortality, and worse prognosis, especially among women.[71] Many of these MIs are neither captured nor reported as outcomes in primary prevention trials.

Conclusions

In light of declining aspirin utilization rates, recommendations to prevent first-MI or stroke should provide guidance to clinicians after weighing an individual's risk-benefit profile and their personal preferences. We have summarized the available evidence that supports aspirin use for primary prevention in persons who have moderate to high risk for CVD. The risk for GI bleeding should be taken into consideration, acknowledging transient nonfatal bleeding events should not carry the same long-term health implications as ischemic cardiovascular events. Likewise, it should be clarified to patients that the recommendations stemming from these recent primary prevention clinical trials should not affect or be confused with established aspirin benefits for secondary prevention. At last, a well-validated bleeding risk calculator is critically needed using data from the modern aspirin trials to provide clinicians a tool to better compare the benefits and risks of low-dose aspirin in primary prevention.

Disclosures

Osama Dasa and Carl J. Pepine have nothing to disclose, no industry relations. Thomas A Pearson has been at the Coordinating Board for the ARRIVE trial. A study funded by Bayer pharmaceuticals.

Declaration of Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2020.11.014.

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