Primary Prevention of CVD with Aspirin: Benefits vs Risks

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DISCLOSURES

Dr. Brunton discloses that he serves on the advisory board and speakers bureau for AstraZeneca, Bayer, and Novo Nordisk; on the speakers bureau for Lilly; and on the advisory board for Abbott Diabetes, Acadia, Sanofi, and Xeris.

Dr. Weisman discloses that he is Head of Clinical and Regulatory Support at Innovative Science Solutions, a consultancy to the pharmaceutical industry, and has received consultancy fees from Bayer related to the topic of this manuscript.

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ABSTRACT

Low-dose aspirin (acetylsalicylic acid [ASA]; 75 to 100 mg/d) is widely used in the prevention of cardiovascular (CV) events based on the results of large-scale studies supporting a benefit. However, questions remain regarding the benefit-risk relationship in certain settings since long-term use of ASA is not devoid of risk. Incontrovertible evidence supports the benefits of ASA treatment, which exceed the risks, in patients who have had a previous CV event (myocardial infarction, stroke, unstable angina, or transient ischemic attack). Nonetheless, the question remains for those patients who have not had a previous event (primary prevention), where the risk of CV events is lower and, consequently, the absolute benefit is also lower than in patients who have a history of a CV event or its equivalent (secondary prevention). Recent evidence from large-scale clinical trials shows that administration of low-dose ASA is associated with a reduced risk of CV events with a corresponding small absolute increase in the risk of major bleeding (eg, gastrointestinal bleeding and hemorrhagic stroke). Although the benefit and the risk of low-dose ASA in primary prevention are numerically similar, the clinical consequences of an increased risk of bleeding and a decreased risk of a CV event may not be equivalent. If these data are applied to patients with higher levels of CV outcome risk, more patients may potentially benefit from aspirin use in primary prevention.

BACKGROUND

Aspirin (acetylsalicylic acid [ASA]) is a well-studied and widely used drug, with a well-established safety profile. ASA has been marketed for over 120 years as an analgesic and for more than 25 years for cardiovascular (CV) prophylaxis and has a well-established risk profile that is independent of underlying CV risk. ASA is recommended and approved for use in multiple CV disease (CVD) prevention settings, including the secondary prevention of myocardial infarction (MI), fatal and nonfatal stroke following a stroke or transient ischemic attack (TIA), and for reducing the risk of death and reinfarction during an acute evolving MI.[1] In these settings the benefits of treatment have been deemed to exceed the risks, and such use is widely supported by treatment guidelines. In the primary prevention setting, ASA appears to be equally effective in reducing the risk of CV events based on the same underlying mechanism of action of preventing platelet aggregation. Though the relative risk reductions are similar across the CV risk strata, the benefit-risk relationship is less well established based on the lower rate of occurrence of CV events in the primary prevention setting, while the risks of complications (largely bleeding risks) remain largely the same.[2-4] As new data have become available, a reassessment of the overall benefit vs risk in primary prevention is now possible.

GASTROINTESTINAL BLEEDING WITH LOW-DOSE ASA

Due to the same antiplatelet mechanism of action supporting ASA's use in the prevention of CVD, one of the well-documented risks associated with long-term ASA use is

the increased risk of bleeding (minor and major), with the most common risk that of gastrointestinal (GI) bleeding.[5,6] A meta-analysis of clinical studies evaluating low-dose ASA in primary prevention of CV events reported a relative risk (RR) of major bleeding of 1.43 (95% confidence interval [CI]: 1.3-1.6), with major GI bleeding having an RR of 1.56 (95% CI: 1.4-1.8).[7] Of importance, the available data suggest a dose-dependent relationship for ASA, such that low-dose ASA regimens of 75 to 100 mg/d have been shown to be associated with a lower risk and incidence of GI bleeding compared to higher-dose ones.[8] While GI bleeding is dose-dependent, the antiplatelet effects that underlie ASA's utility in vascular disease in this dose range are not. Studies have shown similar efficacy with low-dose ASA compared with higher doses. Thus, low-dose ASA has emerged as the optimal regimen for the prevention of CVD.[8] Routine use of low doses of ASA along with potential preventive strategies including the use of proton pump inhibitors (PPIs) may further reduce the risk of GI bleeding with ASA. While long-term controlled studies haven't been conducted evaluating the benefit of combination PPI and ASA use, data suggest that eliminating *Helicobacter pylori* infection before ASA use could reduce the incidence of upper GI complications by approximately 25%.[9] Furthermore, a meta-analysis conducted by Mo et al (2015) evaluating the preventive effects of PPIs in ASA-associated upper GI injuries noted that PPIs decreased the risk of ASA-associated upper GI ulcers (odds ratio [OR] 0.16; 95% CI: 0.12-0.23) and bleeding (OR 0.27; 95% CI: 0.16-0.43) compared with control.[10,11]

ASA USE IN PRIMARY VS SECONDARY PREVENTION OF CVD

Extensive evidence from multiple clinical trials has demonstrated that daily, low-dose ASA reduces the risk of recurrent vascular events in patients who previously experienced an event or who are at high risk of CV events (secondary prevention).[12,13] While numerous clinical trials have demonstrated similar relative risk reductions in patients at low to moderate levels of risk but who have not had a previous event (primary prevention), these patients are at a lower risk of an event and thus would be expected to receive a lower absolute benefit while having a comparable risk of bleeding.[7]

The risk of CV events is impacted by a number of factors. ASA therapy (75-162 mg/d) may be considered as a primary prevention strategy in those with diabetes who are at increased CV risk, after a comprehensive discussion with the patient on the benefits vs the comparable increased risk of bleeding. Based on the large number of CV events in patients who have not had a previous event, preventive strategies that are safe and effective are desperately needed. As such, the obvious question is how to determine which patients would be candidates for ASA therapy such that the benefit-risk relationship can be optimized.

In 2013, the American College of Cardiology (ACC)/American Heart Association (AHA) developed the Arteriosclerotic Cardiovascular Disease (ASCVD) Risk Estimator to help calculate CVD risk and guide physicians in treating patients with increased risk. The ASCVD calculator is a peer-reviewed calculator that was designed to assess the 10-year primary risk of an initial CV event based on a Pooled Cohort Equation (ie, the Framingham Heart Study [FHS], the Atherosclerosis Risk in Communities [ARIC] study, the Coronary Artery Risk Development in Young Adults [CARDIA], and the Cardiovascular Health Study [CHS]), in patients without preexisting CVD. In practice, clinicians use the ASCVD Risk Estimator to help them assess risk and better treat patients who may benefit from ASA but have not had a prior CV event, with adults categorized into low (<5%), borderline (5 to <7.5%), intermediate (≥7.5 to <20%), or high (≥20%) 10-year risk categories.[14]

Additionally, the US Preventive Services Task Force (USPSTF) is in the process of updating its recommendations on ASA use for primary prevention of CVD.[15] When completed, its review of the evidence will provide additional guidance as to benefits and risks from low-dose ASA therapy in primary prevention.

RECENT TRIALS IN PRIMARY PREVENTION

A number of trials of low-dose ASA in primary prevention of CVD involving large numbers of subjects (N=47,140) have been recently completed and, when looked at with the larger overall database, provide additional safety and efficacy insight.

Meta-analysis of ASA in primary prevention of CVD

A meta-analysis conducted by Zheng et al (2019) reviewed the most up-to-date ASA studies conducted in primary prevention, including the 3 most recently completed studies (ie, Aspirin to Reduce Risk of Initial Vascular Events [ARRIVE],[16] A Study of Cardiovascular Events in Diabetes [ASCEND], and Aspirin in Reducing Events in the Elderly [ASPREE]).[7] The meta-analysis included randomized controlled trials conducted with low-dose ASA through 2018, enrolling at least 1000 participants with no known CVD and with a follow-up of at least 12 months. Included studies compared ASA use with no ASA (placebo or no treatment). The primary outcome assessed was a composite of CV mortality, nonfatal MI, and nonfatal stroke. The primary bleeding outcome was any major bleeding.[7]

The meta-analysis evaluated a total of 13 trials that randomized 164,225 participants. Participants were on average

TABLE 1. **Overview of studies**

	ARRIVE[17]	ASCEND[18]	ASPREE[19-21]	Meta-analysis[7]
N	12,546	15,480	19,114	164,225
Age, years	Men >55, women >60	>40	>70, or >65 if Hispanic or Black	>40
ASA dose, mg	100	100	100	75-500
Years of follow-up (median)	6.0	7.5	4.7	≥1
Country (year)	7 countries (2018)	United Kingdom (2018)	Australia and United States (2018)	-
Endpoints				
Efficacy analysis	Composite of time to first occurrence of CV death, MI, unstable angina, stroke, or TIA	First serious vascular event (ie, MI, stroke or TIA, or death from any vascular cause, excluding any confirmed intracranial hemorrhage)	Composite of all-cause mortality, incident dementia, and persistent physical disability	Composite of CV mortality, nonfatal MI, and nonfatal stroke
Safety analysis	GI bleeding by severity	Major bleeding	Major bleeding	Major bleeding
Special population	Older participants (average age 74)	Participants with diabetes	Participants with moderate to high estimated CV risk	Participants without known preexisting CVD

62 years of age (range, 53-74), 77,501 (47%) were men, and the median baseline risk of the primary CV outcome was 10.2% (range, 2.6%-30.9%) **(TABLE 1)**. Results of the meta-analysis show that ASA use was associated with significant reductions in the composite CV outcome compared with no ASA, with a total of 2911 (3.4%) events in the ASA arm and 3341 (4.2%) events in the no-ASA arm (HR 0.89; 95% credible interval variable [CrI]: 0.84-0.94), with an absolute risk reduction (ARR) of 0.41% (95% CrI: 0.23%-0.59%), which translated into number needed to treat (NNT) of 241 **(TABLE 2)**.

Major bleeding (defined by the individual studies) was reported in a total of 2029 (1.4%) patient events, with 1195 (1.6%) participants experiencing events in the ASA arm compared with 834 (1.1%) participants in the no-ASA arm (HR 1.43; 95% CrI: 1.30-1.56), with an absolute risk increase (ARI) of 0.47% (95% CrI: 0.34%-0.62%), translating into a number needed to harm (NNH) of 210.

The current data demonstrate that the absolute risk reduction for CV events and absolute risk increase for major bleeding associated with ASA use were of similar magnitude; the reduction in the risk of an MI or stroke is similar to the risk of a major bleeding event.

Overview of ARRIVE, ASCEND, and ASPREE safety findings

The 3 recently completed studies evaluating ASA in primary prevention, ARRIVE, ASCEND, and ASPREE, were all conducted in different settings and confirmed a consistent safety profile, as noted in earlier primary prevention studies, with no additional safety signals identified. These studies provided additional insight regarding the safety of low-dose ASA to better inform benefit-risk determination and are summarized below.

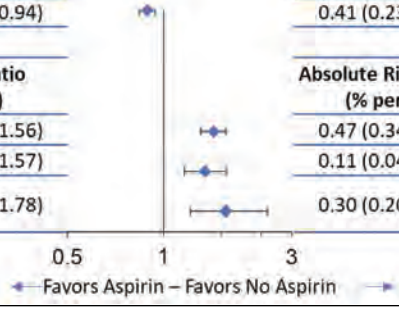
ARRIVE

ARRIVE[16] was a randomized, double-blind, placebo-controlled, multicenter study. The study enrolled 12,546 patients, who were followed for 6 years **(TABLE 1)**. The study included men older than 55 and women older than 60, who had a 10-year CV risk deemed to be moderate, ranging from 10% to 20%. The study excluded those patients at high risk of GI bleeding or other bleeding, or diabetes. Patients were assigned to receive 100 mg/d of ASA or placebo.[17]

GI bleeding events (mostly mild) occurred in 61 (0.97%) patients in the ASA group vs 29 (0.46%) in the placebo group (HR 2.11; 95% CI: 1.36-3.28; *P*=0.0007), with an ARI of 0.51%

TABLE 2. **Primary prevention in meta-analysis—CV events and major bleeding[7,a]**

Event Type	Aspirin Events (% rate)	Placebo Events (% rate)	Hazard Ratio (95% CI)	Absolute Risk Reduction (% per year)	NNT
Composite CV outcome	2911 (3.7%)	3342 (4.2%)	0.89 (0.84 – 0.94)	0.41 (0.23 to 0.59)	241
			Hazard Ratio (95% CI)	**Absolute Risk Increase (% per year)**	**NNH**
Major Bleeding	1195 (1.6 %)	834 (1.1 %)	1.43 (1.30 – 1.56)	0.47 (0.34 to 0.62)	210
Intracranial bleeding	349 (0.4 %)	257 (0.3%)	1.34 (1.14 – 1.57)	0.11 (0.04 to 0.18)	927
Major gastrointestinal bleeding	593 (0.8 %)	380 (0.5%)	1.56 (1.38 – 1.78)	0.30 (0.20 to 1.78)	334



The composite CV outcome consisted of CV mortality, nonfatal MI, and nonfatal stroke. Hazard ratios and 95% credible interval variables (CrIs) were calculated using Bayesian meta-analysis of trial-level event counts. The absolute risk reductions and increases were calculated by multiplying the control event risk by the relative risk and 95% CIs derived by frequentist meta-analysis. NNT; NNH.

[a]Adapted from Zheng et al., 2019.

(TABLE 3). Of note, although significant, GI bleeding events were infrequent and mostly mild. Furthermore, there were no increases in fatal bleeding.

ASCEND

ASCEND[18] was a randomized, double-blind, placebo-controlled study that looked at 15,480 patients with diabetes who were older than 40 years of age **(TABLE 1)**. The study was conducted in subjects who had diabetes but no evident CVD. Patients were randomly assigned to receive 100 mg/d of ASA or placebo and followed for 7.5 years.

The primary safety outcome was the first occurrence of any major bleeding event, which was defined as a composite of any confirmed intracranial hemorrhage, sight-threatening bleeding event in the eye, GI bleeding, or any other serious bleeding (ie, a bleeding event that resulted in hospitalization or transfusion or that was fatal). Major bleeding events were experienced by 314 (4.1%) patients in the ASA group vs 245 (3.2%) patients in the placebo group (rate ratio 1.29; 95% CI: 1.09-1.52; *P*=0.003), with an ARI of 1.29% **(TABLE 2)**. Most of the differences noted were GI bleeding events. ASA increased the rate of major bleeding by 29% in relative terms and 0.9% in absolute terms.

ASPREE

ASPREE[19-21] was a randomized, double-blind, placebo-controlled, multicenter study **(TABLE 1)**. The study enrolled 19,114 patients older than 70 years of age, or older than 65 if black or Hispanic (5%), from Australia and the United States. Patients did not have CVD, dementia, or disability, and were assigned to receive 100 mg/d of ASA or placebo. Patients were followed for a median of 4.7 years.

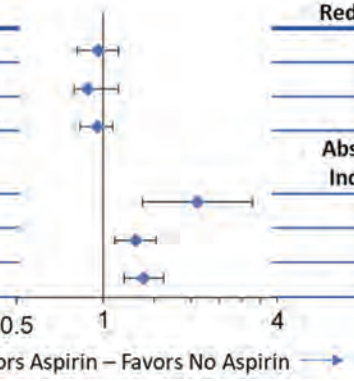
The primary endpoint was a composite of all-cause mortality, incident dementia, and persistent physical disability, with secondary endpoints including fatal and nonfatal CV events (ie, coronary heart disease death, nonfatal MI, fatal and nonfatal stroke, and any hospitalization for heart failure). Major hemorrhage was a secondary endpoint and defined as any hemorrhagic event (hemorrhagic stroke, symptomatic intracranial bleeding, or major GI bleeding or other extracranial bleeding).

In ASPREE there was a low rate of major hemorrhage, yet the rate was increased in the ASA group: 361 (3.8%) patients in the ASA group compared to 265 (3.2%) patients in the placebo group (HR 1.38; 95% CI: 1.18-1.62; *P*<0.001), with an ARI of 1.07% **(TABLE 2)**.

The ASPREE study focused on an older patient population (average age 74 years) than normally evaluated in CVD trials, with the hope of better understanding how this group of patients would benefit from low-dose ASA in a primary prevention setting. Of note, half of the excess bleeding events were GI bleeding cases, where such events could potentially have been prevented with concurrent PPIs; however, only a quarter of participants in the study actually were using PPIs.[22] Additionally, subgroup analysis demonstrated that the bleeding events were mostly driven by patients over 70 years of age, and that the 5-year absolute risk of serious bleeding was modest in younger individuals. Of note, the absolute risk of serious GI bleeding more than doubles in an 80-year-old person (5-year risk of around 0.60%) compared to a 70-year-old person (5-year risk of around 0.25%). Additionally, Mahady et al's (2018) review of the ASPREE trial noted that bleeding infrequently led to death or other long-term morbidity, with only 2 fatal bleeds in the placebo arm.[23]

TABLE 3. **Primary prevention in ARRIVE,[17] ASCEND,[18] and ASPREE[19-21] —CV events and major bleeding[a]**

Event Type	Aspirin	Placebo		
Composite CV outcome	Events (% rate)	Events (% rate)	Hazard Ratio (95% CI)	Absolute Risk Reduction (%)
ARRIVE	269 (4.3%)	281 (4.5%)	0.96 (0.81 – 1.13)	0.20
ASCEND	658 (8.5%)	743 (9.6%)	0.88 (0.79 – 0.97)	1.10
ASPREE	448 (4.7%)	474 (4.9%)	0.95 (0.83 – 1.08)	0.20
Major Bleeding			Hazard Ratio (95% CI)	Absolute Risk Increase (%)
ARRIVE	61 (0.97%)	29 (0.46%)	2.11 (1.36 – 3.28)	0.51
ASCEND	314 (4.1%)	245 (3.2%)	1.29 (1.09 – 1.52)	1.29
ASPREE	361 (3.8%)	265 (2.8%)	1.38 (1.18 – 1.62)	1.00



The composite CV outcome consisted of CV mortality, nonfatal MI, and nonfatal stroke.

[a]Adapted from: Gaziano et al. 2018[16]; The ASCEND Study Group, 2018[18]; McNeil et al., 2018.[19-21]

CONCLUSIONS

Mounting evidence, including data from 47,140 newly studied patients, shows that subjects who use low-dose ASA for the primary prevention of vascular disease reduce their relative risk of composite CV outcomes by 11%, with an absolute risk reduction of 0.41%. However, these subjects are 1.43 times more likely to experience GI bleeding than those receiving placebo. The effect is small in terms of absolute risk (0.47%; 95% CI: 0.34%-0.62%).[7]

In primary prevention it has been very difficult to clearly state the benefit and risk of extended use of low-dose ASA, where a decreased risk of CV events may be offset by an increased risk of major bleeding. The best way to enhance the overall benefit is to evaluate underlying CV risk more effectively, such that use of ASA in those at highest risk will yield the highest benefit. The routine use of risk calculators could help in this decision-making. Likewise, possible strategies for mitigating the risk of GI bleeding may help to reduce this bleeding risk. Initial research suggests that GI bleeding risk can potentially be mitigated by testing for *H. pylori* and treating it before starting ASA[9] and/or by treatment with PPIs,[10,24] with additional studies necessary to confirm benefit.

While questions remain as to how best to maximize the benefits and minimize the risks of low-dose ASA in primary prevention, the available evidence demonstrates that many vascular events could be prevented with broader appropriate use of ASA. This includes more comprehensive use in secondary prevention as well as in patients who are at higher-than-average risk of such events who have not had a previous event. Recent studies have provided additional data regarding the safety of ASA and demonstrated that, while significant, the absolute risk of a bleeding event is small, potentially leading to a favorable benefit-vs-risk discussion and determination for many more patients. ●

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