Aspirin for Primary Cardiovascular Risk Prevention and Beyond in Diabetes Mellitus

ABSTRACT: Daily administration of low-dose aspirin has proved to be beneficial in preventing recurrent cardiovascular events. However, the role of aspirin for primary prevention in patients with no overt cardiovascular disease is more controversial. In fact, in lower risk patients, the modest benefit in reducing serious vascular events can be offset by the increased risk of bleeding, including intracranial and gastrointestinal hemorrhage. Diabetes mellitus has been associated with a substantially increased risk of both first and recurrent atherothrombotic events, which makes aspirin therapy of potential value in these subjects. Moving from general aspects of aspirin pharmacology and specific issues in diabetes mellitus, this article reviews the literature on the topic of aspirin for primary prevention in general, and in subjects with diabetes mellitus in particular, to culminate with arguments pro and con and a practical risk-based algorithm for aspirin initiation in daily practice.

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STATE OF THE ART

Primary prevention aims to avert the onset of cardiovascular disease (CVD) by targeting its natural causes and risk factors. At a different level, secondary prevention includes strategies and therapies that address preclinical or clinical evidence of CVD progression. Both primary and secondary prevention of atherothrombosis—a key mechanism of nonfatal myocardial infarction (MI), ischemic stroke, and death—involve the use of pharmacologic agents that counteract the process of clot formation. Acetylsalicylic acid, also known simply as aspirin, has been manufactured and marketed since 1899, but it took ≈60years to appreciate its antithrombotic potential as an antiplatelet agent. The value of aspirin for primary CVD prevention is controversial because of concerns that increased bleeding may offset the overall modest benefits of the drug in adults with no overt manifestation of atherothrombosis.[1] In contrast, secondary prevention is a setting where the benefits of aspirin have been repeatedly and convincingly demonstrated to outweigh the risk of bleeding.[2] This benefit notwithstanding, the incremental merit and possible detrimental effect of aspirin, combined with agents targeting different pathways of platelet activation (ie, $P2Y_{12}$ inhibitors), have recently prompted a research line that investigates the net benefit of aspirin-free strategies after an acute coronary syndrome or percutaneous coronary intervention.

The individual likelihood of life-long cardiovascular events may be a significant modifier of the net benefit of aspirin in both the primary and secondary prevention settings. Diabetes mellitus (DM) has been associated with an increased risk of both first and recurrent atherothrombotic events. The total number of people with DM is projected to rise from 171 million in 2000 to 366 million in 2030, which poses substantial and urgent questions on how to impact the anticipated additional burden of new onset or recurrent CVD.[3] In this article, we revisit the topic of aspirin for CVD

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prevention in patients with DM. Because the benefit of aspirin for secondary prevention in DM (for which we refer elsewhere[2]) is currently undisputed, we will focus on the larger area of controversy (ie, primary CVD prevention). In particular, moving from general aspects of aspirin pharmacology and specific issues in DM, this article reviews aspirin for primary prevention in general, and in subjects with DM in particular, integrating considerations of noncardiovascular benefits and harms to end up with a practical risk-based algorithm for aspirin initiation in daily practice.

ASPIRIN PHARMACOLOGY AND IMPLICATIONS FOR ASPIRIN USE IN PATIENTS WITH DIABETES MELLITUS

Pharmacokinetics

After ingestion, immediate-release aspirin is completely and rapidly absorbed by passive diffusion across the membranes of the stomach and upper small intestine. The absorption rate depends on dosage form, presence or absence of food, and gastric pH. At variance with the uncoated form, enteric-coated aspirin is erratically absorbed by the gastrointestinal mucosa, resulting in lower bioavailability.[4] Plasma levels peak within 30 to 40 minutes of (uncoated formulation) or 3 to 4 hours after (enteric-coated formulation) oral intake. The half-life of aspirin is only 15 to 20 minutes, but the antiplatelet effect lasts longer because of the irreversible mechanism of action, which blocks the exposed platelet for its entire lifespan (ie, 7–10 days) and therefore can only be reversed through generation of new platelets. These estimates indicate that aspirin has a rapid onset of effect but a narrow window of opportunity to inhibit circulating platelets.

Mechanism of Action

Aspirin acts by irreversibly blocking cyclooxygenase (COX) activity of the prostaglandin H synthases 1 and 2 (COX-1 and COX-2, respectively), resulting in the inhibition of thromboxane A_2 (TXA_2) and prostacyclin (PGI_2) generation (Figure 1). In chronic administration, typical low-dose regimens ranging between 75 and 100 mg clearly exceed the minimum dose required for platelet inhibition, also addressing interindividual variability. Along the TXA_2 pathway, aspirin inhibits platelet activation and aggregation, 2 essential steps in the pathophysiology of thrombosis and MI. Inhibition of platelet activation at vascular injury sites has other indirect non-TXA_2-mediated consequences, such as reduced release of inflammatory cytokines, oxygen radicals, and growth factors.[4] In contrast to TXA_2, PGI_2 is implicated in several antiatherogenic effects and vascular thromboresistance.[5] Because low-dose aspirin has no measurable effects on COX-2- and PGI_2-mediated vascular functions, it does not increase blood pressure, impair renal function, or interfere with the antihypertensive effects of diuretics and angiotensin-converting enzyme inhibitors. However, permanent COX-1 inactivation may increase the risk of upper gastrointestinal bleeding through 2 distinct mechanisms: inhibition of TXA_2-mediated platelet aggregation and dose-dependent impairment of PGI_2-mediated cytoprotection in the gastrointestinal mucosa. The latter increases the risk of bleeding and perforation by promoting new mucosal lesions and worsening existing ones 4- to 10-fold when aspirin is used at analgesic doses.[4] Antisecretory therapy (ie, use of proton pump inhibitors) reduces the risk of upper gastrointestinal bleeding.[6,7]

Drug Interactions

Concomitant use of reversible COX-1 inhibitors (ie, nonsteroidal anti-inflammatory drugs [NSAIDs] such as ibuprofen and naproxen) exert a competitive effect on the irreversible acetylation of platelets by aspirin.[8,9] This pharmacodynamic interaction does not occur with NSAIDs that have some degree of COX-2 selectivity (ie, the "-coxibs").[8] In a large registry of patients with prior MI, the use of NSAIDs in combination with aspirin was associated with increased risk of both bleeding and thrombotic events, even after short-term treatment.[10] Therefore, although less data are available on the clinical consequences of this drug interaction for primary prevention, the association should be tentatively avoided, particularly with ibuprofen and naproxen, and a strategy preventing gastrointestinal complications should be put in place.

Aspirin Responsiveness

Recently, much debate has taken place over the prevalence of so-called aspirin resistance, particularly in high-risk patients, such as those with DM. However, *aspirin resistance* (defined as the failure of aspirin to fully inactivate the platelet COX-1) is a rare or nonexistent phenomenon.[11,12] The reason that the prevalence of aspirin resistance varies considerably in the literature is that it is often defined with assays that do not specifically assess COX-1 activity.[13,14] In fact, although a number of assays are able to detect aspirin-induced effects, the results obtained are not all specific to the degree of COX-1 inhibition and may be affected by other platelet-signaling pathways. Moreover, the prevalence of inadequate aspirin effects may be influenced by the patient population being tested: patients with DM, who are characterized by a hyperreactive platelet phenotype, may persist with high platelet reactivity despite receiving aspirin therapy.[2] These subjects may have complete COX-1 blockade and erroneously interpreted as having aspirin resistance because of the type of platelet function test used (ie, non-COX-1 specific). When tests that specifically assess

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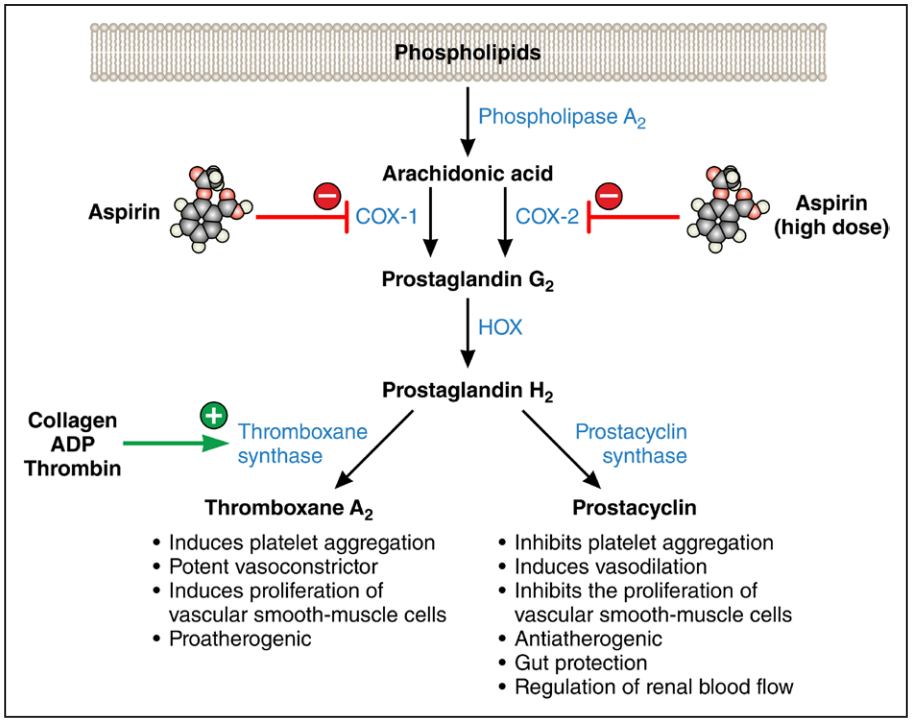

Figure 1. Aspirin mechanism of action.
Aspirin acts by irreversibly blocking the cyclooxygenase (COX) activity of the prostaglandin H synthases 1 and 2, also known as COX-1 and COX-2, respectively. This effect is achieved by acetylating a serine residue (serine 529 in COX-1 and serine 516 in COX-2), which prevents arachidonic acid from reaching the COX catalytic site of the enzyme. This causes the upstream block of prostanoid biosynthesis and, ultimately, inhibition of thromboxane A_2 (TXA_2) and prostacyclin (PGI_2) generation. Mature platelets express only COX-1 and produce TXA_2 in response to a variety of stimuli. Vascular endothelial cells, which express both COX-1 and COX-2, represent the main site of PGI_2 generation. Low-dose aspirin selectively inhibits COX-1 activity, whereas higher doses inhibit both COX-1 and COX-2. ADP indicates adenosine diphosphate; and HOX, hydroperoxidase.

COX-1 activity are used, aspirin resistance is observed infrequently and more commonly attributed to drug interactions (ie, with NSAIDs) or in some cases because of impaired absorption, potentially related to enteric-coating, also known as pseudoresistance.[11] In clinical practice, the foremost reason for the high prevalence of aspirin resistance with assays that specifically assess COX-1 activity is poor patient compliance.[15]

Diabetic Platelets and Implications for Aspirin Use

Platelets of patients with DM appear hyperreactive, with enhanced adhesion, activation, and aggregation compared with platelets of patients without DM. A full description of mechanisms explaining why these abnormalities occur goes beyond the scope of this article but can be found elsewhere.[2] Briefly, hyperglycemia exerts an osmotic effect, contributes to oxidative stress, induces the expression of P-selectin and other surface proteins responsible for adhesion, and activates protein kinase C, a mediator of platelet activation.[16–18] In parallel, insulin deficiency promotes an increase in intracellular calcium concentrations, prompting enhanced platelet degranulation and aggregation.[19,20] Insulin resistance has been associated with impaired response to antithrombotic stimuli, such as nitric oxide and PGI_2.[20] Metabolic conditions frequently associated with DM (ie, obesity, dyslipidemia, kidney disease, and enhanced systemic inflammation) are known contributors to platelet abnormalities because of augmented cytosolic calcium concentrations or endothelial dysfunction.[2] The latter, in particular, determines disequilibrium between nitric oxide and PGI_2, on the one hand, and tissue factor, on the other hand.[21] DM platelets also more frequently express glycoproteins IIb/IIIa and typically present with upregulated $P2Y_{12}$ signaling.[2] Finally, reduced platelet lifespan and increased turnover have been described, leading to increased platelet generation and release by the bone marrow.[22]

In view of the accelerated thrombopoiesis that characterizes DM, newly generated and hyperreactive platelets entering the circulation may have less time to be exposed to aspirin if aspirin is given once daily.[23] In this scenario, increasing the aspirin dose has been suggested to reduce platelet aggregation and overcome aspirin resistance or pseudoresistance in some studies[24–27] but not in others.[23,28] Indeed, increasing the dose may lower the production of prostaglandins and increase the risk

of adverse effects (ie, gastrointestinal and intracranial bleeding), with uncertain net benefit. The US Food and Drug Administration recently approved a new extended-release 162.5-mg aspirin formulation (Durlaza, New Haven Pharmaceuticals, Inc.) designed to provide a more stable antiplatelet effect during the 24 hours. Extended-release formulations provide a protracted period during which aspirin may inactivate platelets. However, the impact of this new therapy on CVD prophylaxis in patients with DM remains to be determined. Twice-daily administration of low aspirin doses is another option to lower the total daily number of uninhibited platelets. This approach provides an additional window of time for platelets exposure to aspirin during the 24 hours. In several pharmacodynamic studies conducted in patients with DM and coronary artery disease, twice-daily low-dose aspirin administration proved effective in determining greater platelet inhibition than once-daily administration,[23–25,28,29] but the clinical implications of a modified aspirin regimen tailored to patients with DM for primary CVD prevention also remain uncertain.

ASPIRIN FOR PRIMARY CVD PREVENTION: THE EVIDENCE BASE

The Case for Efficacy

Between 1988 and 2014, 15 randomized clinical trials investigated the impact of aspirin for primary prevention of CVD events.[30–44] (Table 1) Of these studies, 3 were conducted in healthy men and women,[30,31,38] 6 in subjects with CVD risk factors,[32,34–36,42,44] 4 in subjects with documented subclinical atherosclerosis,[33,39,41,43] and 2 in subjects with prothrombotic hematologic conditions.[37,40] A landmark collaborative meta-analysis of individual participant data from 6 randomized trials conducted between 1988 and 2005 (including 95 000 individuals at low average risk with 3554 serious vascular events) and 16 randomized trials of secondary CVD prevention (including 17 000 individuals with 3306 vascular events) has been undertaken by the Antithrombotic Trialists' (ATT) collaboration in 2009 (Table 1).[45] Among trials available at that time, this meta-analysis excluded 1 trial mixing primary and secondary prevention patients with DM[32] and 4 trials including subjects with confounding clinical conditions (ie, carotid stenosis, peripheral artery disease, polycythemia vera, and antiphospholipid antibody syndrome).[33,37,39,40] In the pooled analysis of the 6 primary prevention studies included,[30,31,34–36,38] aspirin reduced the composite of serious vascular events (a composite of vascular death, MI, or stroke) by 12%, with no significant heterogeneity across prespecified subgroups. The relative risk reduction of aspirin was similar to that of secondary prevention studies (12% vs 19%, respectively; for heterogeneity, P=0.10), but the absolute risk reduction was markedly smaller (0.07% vs 1.49%), corresponding to 1429 and 67 patients needed to treat to prevent 1 serious vascular event in primary and secondary prevention studies, respectively. Most of the aspirin benefit in primary prevention was attributable to a 23% proportional reduction in nonfatal MI, whereas no effect was noted on ischemic stroke, vascular mortality, and all-cause mortality. Some evidence revealed a difference in the aspirin effect by sex. In fact, aspirin reduced cardiovascular events in men but not in women, and it reduced stroke in women but not in men. Nevertheless, the suggestion of a sex bias must be interpreted with caution because these results were essentially driven by 1 study,[38] were of borderline statistical significance, and were not observed in secondary prevention studies.

Since the publication of the ATT meta-analysis, 4 more randomized trials of aspirin for primary CVD prevention have been published, including POPA-DAD[41] (Prevention of Progression of Arterial Disease and Diabetes), JPAD[42] (Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes), AAA[43] (Aspirin for Asymptomatic Atherosclerosis), and the large JPPP[44] (Japanese Primary Prevention Project). Although still targeting asymptomatic patients, these studies included somewhat higher risk individuals than those included in previous trials represented in the ATT meta-analysis because of preexisting CVD risk factors, peripheral artery disease, or both. However, none of the 4 newer trials provided conclusive evidence to support the routine use of aspirin for primary prevention of CVD (Table 1).

Seven meta-analyses were then published to update the ATT collaboration (Table 2),[46–53] with only 2 of these studies including the most recent JPPP trial.[51,52] In general, these meta-analyses reported a 10% to 13% relative reduction in combined serious cardiovascular events, driven by a 19% to 22% reduction in nonfatal MI and a 13% to 14% reduction in ischemic stroke. The reduction in all-cause mortality was statistically significant in some meta-analyses,[47,50,52] but modest (5% to 6%).

The Case for Safety

In the ATT meta-analysis, aspirin numerically but nonsignificantly increased the risk of hemorrhagic stroke both in primary and secondary prevention trials (Table 2).[45] In addition, aspirin relatively increased major gastrointestinal and other extracranial bleeding risk by 54%, with no significant heterogeneity compared with secondary prevention trials (for heterogeneity, P=0.20). All subsequent meta-analyses incorporating the newer trials confirmed that aspirin increased the risk of bleeding by 33% to 43% for hemorrhagic stroke, 55% to 69% for major bleeding, and 29% to 64% for gastrointestinal bleeding (Table 2).[46–52] It is important to note that the risk of bleeding with aspirin is 5-fold higher in patients who are at higher risk

Table 1. Trials of Aspirin for Primary Cardiovascular Prevention

Study	Year	Patients	Aspirin Dose	DM*	Mean or Median Follow-Up	Study Population	Primary Outcome Measure	Significant Efficacy
BDT[30]	1988	5139	300–500 mg/d	2%	5.6 y	Healthy men	CV death	No
PHS[31]	1989	22 071	325 mg every other day	4%	5 y	Healthy men	CV death	No
ETDRS[32]	1992	3711	650 mg/d	100%	5 y	DM†	All-cause mortality	No
ACBS[33]	1995	372	325 mg/d	19%	2.4 y	Carotid stenosis	Death, MI, stroke, TIA, stroke, MI, UA	No
HOT[34]	1998	18 790	75 mg/d	8%	3.8 y	Hypertension	CV death, MI, stroke	Yes
TPT[35]	1998	5085	75 mg/d	NR	6.7 y	CV risk factors	Coronary death and MI	Yes
PPP[36]	2001	4495	100 mg/d	17%	3.7 y	CV risk factors	CV death, nonfatal MI, stroke	No
ECLAP[37]	2004	518	100 mg/d	5%	3 y	Polycythemia vera	CV death, nonfatal MI, stroke, PE, VT	Yes
WHS[38]	2005	39 876	100 mg every other day	3%	10.1 y	Healthy women	CV death, nonfatal MI, stroke	No
CLIPS[39]	2007	366	100 mg/d	78%	2 y	PAD	CV death, MI, stroke	Yes
APLASA[40]	2007	98	81 mg/d	8%	2.3 y	AA syndrome	Acute thrombosis	No
POPADAD[41]	2008	1276	100 mg/d	100%	6.7 y	Diabetes, PAD	CV death, nonfatal MI, stroke, CLI	No
JPAD[42]	2008	2539	81–100 mg/d	100%	4.4 y	DM	Ischemic heart disease, stroke, PAD	No
AAA[43]	2010	3350	100 mg/d	3%	8.2 yr	PAD	CV death, MI, stroke, revascularization	No
JPPP[44]	2014	14 464	100 mg/d	34%	5.0 yr	CV risk factors	CV death, nonfatal MI, stroke	No

AA indicates antiphospholipid antibody; AAA, Aspirin for Asymptomatic Atherosclerosis; APLASA, Antiphospholipid Antibody Acetyl-salicylic Acid; BDT, British Doctors Trial; CLI, critical limb ischemia; CLIPS, Critical Leg Ischemia Prevention Study; CV, cardiovascular; DM, diabetes mellitus; ECLAP, European Collaboration on Low-Dose Aspirin in Polycythemia Vera study; ETDRS, Early Treatment Diabetic Retinopathy Study; HOT, Hypertension Optimal Treatment; JPAD, Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes; JPPP, Japanese Primary Prevention Project; MI, myocardial infarction; NR, not reported; PAD, peripheral artery disease; PE, pulmonary embolism; PHS, Physicians Health Study; POPADAD, Prevention of Progression of Arterial Disease and Diabetes; PPP, Primary Prevention Project; TIA, transient ischemic attack; TPT, Thrombosis Prevention Trial; UA, unstable angina; VT, major venous thrombosis; and WHS, Women's Health Study.

*Aspirin group.

†Mixed primary and secondary prevention patients.

of cardiovascular events within 10 years compared with those at lower risk.[54]

The Case for Net Clinical Benefit

Assessing the net benefit of aspirin use in primary CVD prevention is challenging because of the difficulty of weighing the consequences of ischemic and bleeding events. A systematic review of 27 trials and meta-analyses concluded that there is "a fine balance between benefits and risks from regular aspirin use in primary prevention of CVD."[55] Indeed, in people at moderate to high risk of CVD events, the reduction in MI is closely balanced by an increase in major bleeds, prompting aspirin use in individuals who value preventing an MI substantially more than avoiding gastrointestinal bleeding. Assuming total mortality as the ideal net benefit outcome, it should be noted that calculation of absolute effects per 100 000 patient-years of follow-up suggests aspirin to finally avert 33 to 46 deaths compared with controls.[55]

Overall, regardless of the relative benefits of aspirin, the absolute benefits appear an order of magnitude smaller in primary than in secondary prevention trials. This finding explains why the risk of extracranial major bleeding with aspirin given for primary prevention easily offsets the observed reduction in serious ischemic events. Conversely, in secondary prevention, the trade-

Table 2. Summary of Recent Meta-Analyses of Aspirin for Primary Cardiovascular Prevention

Study Characteristic	ATT[45]	Bartolucci[46]	Raju[47]	Berger[48]	Seshasai[49]	Xie[50]	Raju[51]	Guirguis-Blake[52,53]
Publication date	2009	2011	2011	2011	2012	2014	2015	2016
Type	Patient level	Study level	Study level	Study level	Study level	Study level	Study level	Study level
Pooled patients	95 000	100 038	100 076	102 621	102 621	107 686	114 734	118 445
Summary measure	RaR (95% CI)	OR (95% CI)	RR (95% CI)	RR (95% CI)	OR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)
Studies included	6	9	9	9	9	14	10	11
BDT[30]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
PHS[31]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
ETDRS[32]	No	No	No	No	No	Yes	No	Yes
ACBS[33]	No	No	No	No	No	Yes	No	No
HOT[34]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
TPT[35]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
PPP[36]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
ECLAP[37]	No	No	No	No	No	Yes	No	No
WHS[38]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
CLIPS[39]	No	No	No	No	No	Yes	No	No
APLASA[40]	No	No	No	No	No	Yes	No	No
POPADAD[41]	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
JPAD[42]	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
AAA[43]	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
JPPP[44]	No	No	No	No	No	No	Yes	Yes
Follow-up	330,000 PY	NR	3.8–10.1 yr	710,053 PY	≈700,000 PY	734,170 PY	NR	3.6–10.1 y
Serious vascular events	0.88 (0.82–0.94)*	0.87 (0.80–0.93)*	0.88 (0.83–0.94)*	0.90 (0.85–0.96)*	0.90 (0.85–0.96)*	0.90 (0.85–0.95)*	0.89 (0.82–0.97)*	NR
Any MI	NR	NR	0.83 (0.69–1.00)*	0.86 (0.74–1.00)*	NR	0.86 (0.75–0.98)*	0.78 (0.65–0.94)*	NR
Fatal MI	NR	NR	NR	NR	1.06 (0.83–1.37)	NR	NR	NR
Nonfatal MI	0.77 (0.69–0.86)*	0.81 (0.67–0.99)*	NR	NR	0.80 (0.67–0.96)*	NR	0.80 (0.64–0.99)*	0.78 (0.71–0.87)*
All-cause death	NR	0.95 (0.88–1.01)	0.94 (0.88–1.00)*	0.94 (0.89–1.00)	0.94 (0.88–1.00)	0.94 (0.89–0.99)*	0.94 (0.89–1.00)	0.94 (0.89–0.99)*
Cardiovascular	0.97 (0.87–1.09)	0.96 (0.80–1.14)	0.96 (0.84–1.09)	0.99 (0.85–1.14)	0.99 (0.85–1.15)	1.04 (0.86–1.25)	0.95 (0.84–1.07)	0.94 (0.86–1.03)
Any stroke	0.95 (0.85–1.06)	0.92 (0.83–1.02)	NR	0.94 (0.84–1.06)	0.94 (0.84–1.06)	0.95 (0.87–1.05)	0.94 (0.84–1.06)	0.95 (0.85–1.06)
Hemorrhagic	1.32 (1.00–1.75)*	NR	1.36 (1.01–1.82)*	1.35 (1.01–1.81)*	NR	1.34 (1.01–1.79)*	1.43 (1.10–1.86)*	1.33 (1.03–1.71)*
Ischemic	0.86 (0.74–1.00)*	NR	0.86 (0.75–0.98)*	0.87 (0.73–1.02)	NR	0.86 (0.75–0.98)*	NR	NR
Major bleeding	1.54 (1.30–1.82)*	NR	1.66 (1.41–1.95)*	1.62 (1.31–2.00)*	NR	1.55 (1.35–1.78)*	1.69 (1.43–1.98)*	NR
Gastrointestinal	NR	NR	1.37 (1.15–1.62)*	1.29 (1.24–1.47)*	NR	NR	1.64 (1.30–2.07)*	1.59 (1.32–1.91)*

Serious vascular events were defined as the composite of myocardial infarction, stroke, or death from a vascular cause. AAA indicates Aspirin for Asymptomatic Atherosclerosis; APLASA, Antiphospholipid Antibody Acetyl-salicylic Acid; BDT, British Doctors Trial; CLIPS, Critical Leg Ischemia Prevention Study; CHD, coronary heart disease; CI, confidence interval; ECLAP, European Collaboration on Low-Dose Aspirin in Polycythemia Vera study; ETDRS, Early Treatment Diabetic Retinopathy Study; HOT, Hypertension Optimal Treatment; JPAD, Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes; JPPP, Japanese Primary Prevention Project; MI, myocardial infarction; NR, not reported; PHS, Physicians Health Study; POPADAD, Prevention of Progression of Arterial Disease and Diabetes; PPP, Primary Prevention Project; PY, patients-year; RaR, rate ratio; RR, relative risk; OR, odds ratio; TPT, Thrombosis Prevention Trial; and WHS, Women's Health Study.

*Statistically significant.

off between ischemic protection and bleeding is more favorable (ie, aspirin reduces nonfatal vascular events more than it increases major extracranial bleeding), resulting in lower mortality and substantial net benefit.

Aspirin for Cardiovascular Primary Prevention in Patients with Diabetes Mellitus

The 6 trials included in the ATT meta-analysis were population-based and did not focus specifically on patients with DM (with percentages of patients with DM ranging between 1% and 22%). In contrast, 1 older[32] and 2 newer[41,42] primary CVD prevention trials randomized only patients with DM. In ETDRS (Early Treatment Diabetic Retinopathy Study), which included 3711 patients with type I and II DM randomized to aspirin 650 mg/d or placebo, numeric but nonstatistically significant 9% and 17% reductions occurred in all-cause death and MI, respectively, consistent with studies that included mainly subjects without DM.[32] About half of patients included in ETDRS reported a history of CVD. Unfortunately, no separate analysis was performed for truly primary and secondary prevention patients, which—adding to the high dose of aspirin used—explains why ETDRS was not included into the ATT and most subsequent meta-analyses.[32] POPADAD was a 2x2 factorial trial of aspirin 100 mg/d and antioxidant therapy versus placebo, which randomized 1276 patients with type I or type II DM and an ankle brachial pressure index of 0.99 or less but no symptomatic CVD.[41] Compared with placebo, no difference was found in the composite of death from CVD or stroke, nonfatal MI, stroke, or amputation above the ankle for critical limb ischemia with aspirin, and no difference was found in the coprimary endpoint of deaths from CVD or stroke.[41] Finally, JPAD included only patients with type II DM with no history of atherosclerotic disease (N=2539), randomized to low-dose aspirin (81–100 mg/d), or no aspirin. Once again, aspirin was not found to reduce the risk of the primary outcome measure (ie, fatal or nonfatal ischemic heart disease, fatal or nonfatal stroke, and peripheral arterial disease).[42]

In the ATT meta-analysis, compared with subjects without DM, those with DM (≈4000) experienced similar nonsignificant relative reductions (12% vs 13%) and larger absolute reductions (0.24% vs 0.06% per year) for primary prevention of serious vascular events with aspirin versus controls.[45] The larger reduction was for nonfatal MI, with little effect on stroke and no impact on mortality. Since the publication of the ATT meta-analysis, other meta-analyses have addressed primary CVD prevention in DM (Table 3).[56–62] In general, these studies concluded for an 8% to 11% (mostly nonsignificant) relative reduction in serious vascular events and no effect on all-cause and cardiovascular mortality. The large confidence intervals do not exclude the potential benefit of aspirin in reducing MI and stroke,and the potential harm in increasing major bleeding. The most recent meta-analysis, which includes the 3 trials conducted specifically in patients with DM and 7 other trials in which DM patients represented a proportion of the study population, concluded that aspirin is associated with a 10% reduction in serious cardiovascular events, numeric but nonstatistically significant 16% and 14% reductions in MI and stroke, respectively, and a 2-fold nonsignificant increased risk of gastrointestinal bleeding.[62] Notably, none of the available meta-analyses had access to sufficient patient-level data in patients with DM to consider whether the effect of aspirin differs by sex, aspirin dose, or other factors.

Current Guidelines and Consensus Documents Recommendations

Numerous national and international guidelines are available on the use of aspirin for the primary prevention of CVD, with conflicting recommendations that reflect differences in selection of the evidence and timing of publication. The 2016 European Society of Cardiology (ESC) guidelines on CVD prevention do not recommend aspirin for primary prevention in patients with DM if they do not have overt CVD.[1] This recommendation is in line with the 2013 joint guidelines of the ESC and the European Association for the Study of Diabetes.[63] By contrast, the Working Group on Thrombosis of the ESC has issued a class IIa recommendation for aspirin use to prevent CVD events in patients at high risk of major cardiovascular events and no clear evidence of increased risk of bleeding.[64]

The 2016 guidelines from the American Diabetes Association (ADA) recommend a risk-based approach, with aspirin endorsed as a primary prevention strategy in DM patients with a 10-year risk of cardiovascular events >10% and on a case-by-case basis in patients with an intermediate 10-year risk of 5% to 10%.[65,66] This is similar to the recommendations included in a joint position statement by the ADA, the American Heart Association (AHA), and the American College of Cardiology (ACC) Foundation published in 2010,[67] and by an updated document from the ADA and AHA published in 2015.[68] The American College of Chest Physicians and the US Preventive Services Task Force (USPSTF) do not differentiate their recommendations for primary prevention based on the presence or absence of DM and advocate initiating low-dose aspirin based on age (ie, after 50 years).[54,69] In particular, the recent statement from the USPSTF recommends aspirin in adults 50 to 59 years of age who have a ≥10% 10-year cardiovascular risk, are not at increased risk for bleeding, have a life expectancy of ≥10 years, and are willing to take low-dose aspirin daily for at least 10 years (Table 4).[69]

Table 3. Summary of Recent Meta-Analyses of Aspirin for Primary Cardiovascular Prevention in Patients with Diabetes Mellitus

Study C haracteristic	De Berardis[56]	Calvin[57]	Zhang[58]	Pignone[59]	Stavrakis[60]	Butalia[61]	Kunotsor[62]
Publication date	2009	2009	2010	2010	2011	2011	2016
Type	Study level	Study level	Study level	Study level	Study level	Study level	Study level
Pooled patients	10,117	NR	11,618	NR	NR	11,618	16,690
Summary measure	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)
Studies included	6	8	7	9	5	7	10
BDT[30]	No	No	No	Yes	No	No	Yes
PHS[31]	Yes	Yes	Yes	Yes	No	Yes	Yes
ETDRS[32]	Yes	Yes	Yes	Yes	No	Yes	Yes
HOT[34]	No	Yes	Yes	Yes	Yes	Yes	Yes
TPT[35]	No	No	No	Yes	No	No	Yes
PPP[36]	Yes	Yes	Yes	Yes	Yes	Yes	Yes
WHS[38]	Yes	Yes	Yes	Yes	Yes	Yes	Yes
APLASA[40]	No	Yes	No	No	No	No	No
POPADAD[41]	Yes	Yes	Yes	Yes	Yes	Yes	Yes
JPAD[42]	Yes	Yes	Yes	Yes	Yes	Yes	Yes
JPPP[44]	No	No	No	No	No	No	Yes
Follow-up	3.6–10.1 y	2.3–10.1 y	3.7–10.1 y	NR	3.6–10.1 y	3.7–10.1 y	3.6–10.1 y
Serious vascular events	-	-	0.92 (0.83–1.02)	0.91 (0.79 to 1.05)	0.89 (0.70–1.13)	-	0.90 (0.81–0.99)*
Any MI	0.86 (0.61–1.21)	0.86 (0.67–1.11)	0.85 (0.65–1.11)	-	0.83 (0.40–1.72)	0.85 (0.66–1.10)	0.84 (0.64–1.11)
Fatal MI	-	-	-	-	-	-	-
Nonfatal MI	-	-	-	-	-	-	1.03 (0.73–1.45)
All-cause death	0.93 (0.82–1.05)	0.97 (0.87–1.08)	0.95 (0.85–1.06)	-	0.99 (0.82–1.20)	0.95 (0.85–1.06)	0.94 (0.83–1.05)
Cardiovascular	0.94 (0.72–1.20)	-	0.95 (0.71–1.27)	-	0.99 (0.62–1.60)	0.95 (0.71–1.27)	0.94 (0.71–1.26)
Any stroke	0.83 (0.60–1.14)	-	0.83 (0.63–1.10)	0.85 (0.66–1.11)	0.70 (0.44–1.11)	0.84 (0.63–1.11)	0.86 (0.69–1.08)
Hemorrhagic	-	-	-	-	-	-	-
Ischemic	-	0.62 (0.31–1.24)	-	-	-	-	0.64 (0.29–1.38)
Major bleeding	-	-	2.46 (0.70–8.61)	-	2.51 (1.11–5.70)*	-	-
Gastrointestinal	2.11 (0.64–6.95)	-	-	-	2.12 (0.63–7.08)	2.13 (0.63–7.20)	2.12 (0.63–7.10)

Serious vascular events were defined as the composite of myocardial infarction, stroke, or death from a vascular cause (including sudden death, pulmonary embolism, and hemorrhage). APLASA indicates Antiphospholipid Antibody Acetyl-salicylic Acid; BDT, British Doctors Trial; CI, confidence interval; ETDRS, Early Treatment Diabetic Retinopathy Study; HOT, Hypertension Optimal Treatment; JPAD, Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes; JPPP, Japanese Primary Prevention Project; MI, myocardial infarction; NR, not reported; PHS, Physicians Health Study; POPADAD, Prevention of Progression of Arterial Disease and Diabetes; PPP, Primary Prevention Project; RR, relative risk; TPT, Thrombosis Prevention Trial; and WHS, Women's Health Study.

*Statistically significant.

CONSIDERATIONS ON ASPIRIN USE FOR PRIMARY CVD PREVENTION IN DIABETES MELLITUS

Arguments Contra

The use of aspirin in adults without DM may increase the risk of intracranial and extracranial bleeding, principally gastrointestinal. The lack of statistical significance for these endpoints in DM meta-analyses (when reported) is likely related to the low number of events, reflecting a power issue, but in these studies the risk is numerically increased 2-fold. It should also be noted that randomized trials of aspirin for primary prevention generally excluded patients at increased risk of gastrointestinal bleeding (including those with a history of prior peptic ulcer), and elderly were underrepresented; therefore, these results might also not represent the true hazard of routine aspirin use in daily practice.

Whether patients have sufficient risk to warrant aspirin intake depends on the use of other effective strategies for CVD risk reduction, including statins,

Table 4. Current Guidelines and Consensus Documents Recommendations on Low-Dose Aspirin Use for Primary Prevention in Patients with Diabetes Mellitus

Guideline	Recommendation(s)
2010 ADA/AHA/ACCF Position Statement[67]	Reasonable for adults with DM and no previous history of vascular disease who are at increased CVD risk (10-y risk of CVD events >10%) and who are not at increased risk for bleeding (based on a history of previous gastrointestinal bleeding or peptic ulcer disease or concurrent use of other medications that increase bleeding risk, such as NSAIDS or warfarin). Those adults with increased CVD risk include most men >50 years of age and women >60 years of age who have 1 or more of the following additional major risk factors: smoking, hypertension, dyslipidemia, family history of premature CVD, and albuminuria (ACCF/AHA Class IIa, LOE B) (ADA Grade C).
	Not recommended for CVD prevention for adults with DM at low CVD risk (men <50 years of age and women <60 years of age with no major additional CVD risk factors; 10-year CVD risk under 5%) as the potential adverse effects from bleeding offset the potential benefits (ACCF/AHA Class III, LOE C) (ADA Grade C).
	Might be considered for those with DM at intermediate CVD risk (younger patients with 1 or more risk factors, or older patients with no risk factors, or patients with 10-year CVD risk of 5% to 10%) until further research is available (ACCF/AHA Class IIb, LOE C) (ADA Grade E).
2012 ACCP[54]	Suggested for persons ≥50 years of age without symptomatic CVD (Grade 2B).
2013 ESC/EASD guidelines on diabetes, prediabetes, and cardiovascular diseases[63]	Not recommended in patients with DM at low CVD risk (Class III, LOE A).
	May be considered in high-risk patients with DM on an individual basis (Class IIb, LOE C).
2014 ESC Working Group on Thrombosis[64]	Consider in both sexes at a level of risk of major cardiovascular events (death, MI, and stroke) >2 per 100 subject-years, provided they have no clear evidence of increased risk of bleeding (gastrointestinal bleeding or peptic ulcer disease, no concurrent use of other medications that increase bleeding risk) (Class IIa, LOE B).
2015 AHA/ADA Scientific Statement[68]	Reasonable among those with a 10-year CVD risk of at least 10% and without an increased risk of bleeding (ACC/AHA Class IIa, LOE B) (ADA Grade C).
	Reasonable in adults with DM at intermediate risk (10-year CVD risk, 5% to 10%) (ACC/AHA Class IIb, LOE C) (ADA Grade E).
2016 ESC and other Societies on CVD Prevention in Clinical Practice guidelines[1]	Not recommended for people with DM who do not have CVD (Class III, LOE A).
2016 ADA guidelines[66]	Consider in those with type I or type II DM who are at increased CVD risk (10-year risk >10%). This includes most men or women with DM ≥50 years of age who have at least 1 additional major risk factor (family history of premature atherosclerotic CVD, hypertension, smoking, dyslipidemia, or albuminuria) and are not at increased risk of bleeding (Grade C).
	Not recommended for adults with DM at low atherosclerotic CVD risk (10-year atherosclerotic CVD risk <5%), such as in men or women with DM aged <50 yr with no major additional atherosclerotic CVD risk factors, as the potential adverse effects from bleeding likely offset the potential benefits. (Grade C)
	Clinical judgment required in patients with DM <50 years of age with multiple other risk factors (ie, 10-year risk 5% to 10%) (Grade E).
2016 USPSTF Recommendation statement[69]	Initiate in adults 50 to 59 years of age with a ≥10% 10-year CVD risk (Grade B).
	Individual judgment in adults 60 to 69 years of age with a ≥10% 10-year CVD risk (Grade C).
	No recommendation in adults <50 years of age (Grade I: insufficient evidence).
	No recommendation in adults ≥70 years of age (Grade I: insufficient evidence).

ACCP indicates American College of Chest Physicians; ADA, American Diabetes Association; CVD, cardiovascular disease; DM, diabetes mellitus; EASD, European Association for the Study of Diabetes; ESC, European Society of Cardiology; LOE, level of evidence; MI, myocardial infarction; NSAIDS, nonsteroidal anti-inflammatory drugs; TIA, transient ischemic attack; and USPSTF, US Preventive Services Task Force.

antihypertensive agents, and smoking cessation. It may be argued that widespread adoption of evidence-based drug prevention with these other agents may make the use of aspirin futile by lowering the overall CVD risk. Finally, there may be less rationale to support a role for aspirin in actually preventing the onset and progression of CVD rather than its thrombotic complications.

Arguments Pro

Low-dose aspirin has been consistently found to reduce the risk of serious ischemic events and nonfatal MI in patients without DM with any overt CVD, although this benefit is generally small. In DM, evidence of the efficacy and safety of aspirin is lacking or, at best, inconclusive, with the exception of one meta-analysis suggesting a 10% reduction in serious vascular events.[62] Indeed, almost all the available meta-analyses indicate that existing trials of aspirin in DM are still limited by small patient numbers and low event rates. On this background, one may speculate that aspirin probably exerts a modest reduction in the risk of CVD, but the limited amount of data specific to DM patients precludes a firm estimate of the effect size. As far as the risk of bleeding is concerned, with the exception of intracranial bleeding, a nonfatal major bleed is likely preferable to a nonfatal MI or stroke.

It is important to note that aspirin has been associated with beneficial noncardiovascular effects, including prevention of venous thromboembolism, chemoprevention of colorectal (and other) cancer, and neuroprotection with reduced risk of dementia.[64,70] In a recent meta-analysis of primary prevention trials from the USPSTF, the benefits of aspirin on cancer mortality and incidence were not clearly established.[71] However, evidence from pooled CVD primary and secondary prevention trials suggests that aspirin reduces the incidence of colorectal cancer and mortality ≈10 years after initiation.[71] The follow-up of primary CVD prevention trials of aspirin is too short to display meaningful effects on the incidence and related mortality of cancer. How low-dose aspirin is eventually implicated in chemoprevention, with its effects limited to COX-1 inactivation, is difficult to reconcile but may suggest a platelet-mediated process in the initiation, for example, of colorectal carcinogenesis.[70] In contrast, the effect of low-dose aspirin on neuroprotection and prevention of cognitive decline could be explained by inhibition of the proinflammatory effects of platelets due to complex formation with circulating leukocytes and secretion of soluble factors, 2 mechanisms at play even in the absence of COX-2 activity.[70] These platelet-mediated processes may be particularly enhanced in patients with DM. If these noncardiovascular benefits of low-dose aspirin are firmly established by future studies, then the bar for aspirin use in primary prevention will need to be lowered.

Risk Stratification

In patients with no overt CVD, the estimated risk of future events (ie, as reflected by the risk estimator provided by the AHA and the ACC)[72] is low (Figure 2). However, the absolute decrease in events depends on the underlying cardiovascular risk. In fact, in patients at higher risk of cardiovascular events over a 10-year time horizon, even a similar relative risk reduction may translate in larger benefit when evaluated in absolute terms. Although the annual risk of CVD events can vary ≈10-fold in DM, the annual risk of gastrointestinal bleeding has been estimated to vary by ≤100-fold depending on factors such as age and history of prior peptic ulcer.[67] Therefore, risk stratification is essential for identifying higher risk subjects who may derive a benefit from

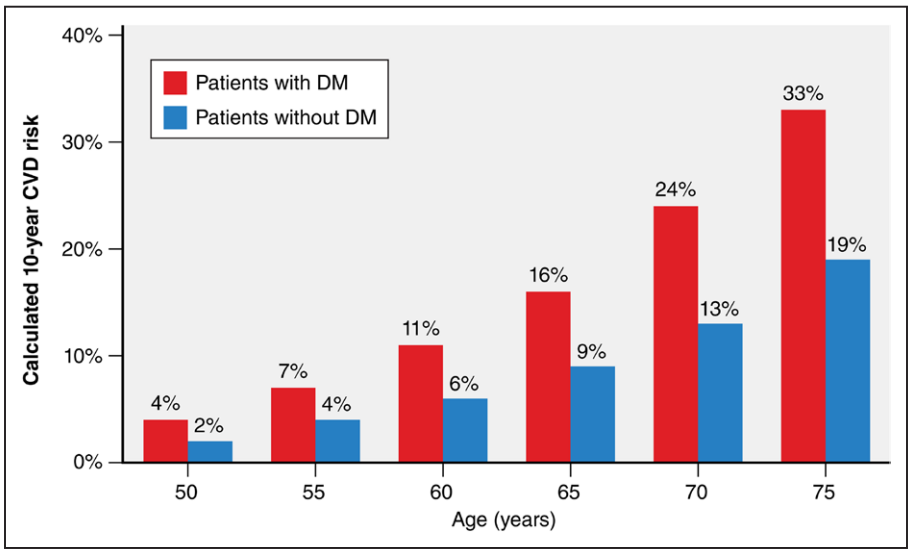

Figure 2. Risk of cardiovascular disease (CVD) events over a 10-year time horizon for patients with and without diabetes mellitus (DM) assuming optimal control of CVD risk factors others than hyperglycemia.
Optimal control is defined as total cholesterol 170 mg/dL, HDL-cholesterol 50 mg/dL, systolic blood pressure 110 mm Hg on treatment with antihypertensive drugs, and being a nonsmoker. Estimates were calculated for prototypical white patients with and without DM over a range of age categories with the calculator of the American College of Cardiology and the American Heart Association.[72]

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aspirin that offsets the increased risk of bleeding. To this aim, several risk stratification tools and statements have been introduced in the context of guidelines and task force reports.[1,54,72]

A ESC Working Group on Thrombosis position paper proposed a threshold risk level of ≥2 major cardiovascular events (death, MI, or stroke) per 100 patient-years above which aspirin is expected to produce more benefit than harm.[64] This threshold is higher and therefore more conservative than those proposed by the ADA and the USPSTF.[64,66] At variance with the HeartScore endorsed by the ESC,[1] the calculator for the estimate of 10-year risk of CVD from the ACC and AHA includes DM as a prognostic risk factor.[72] Based on the latter, the risk of 10-year CVD events in a patient with DM may vary significantly from 1% (ie, a 40-year-old female with no additional CVD risk factors) to >50% (ie, a 55-year-old male smoker with uncontrolled hypercholesterolemia and severe hypertension). The risk of CVD at 10 years is abated in case of optimal risk factor control, which is a mandatory step before considering aspirin initiation for primary CVD prevention. The 10-year risk of CVD events for white patients with DM or no DM on a background of optimal risk factors control (defined as total cholesterol 170 mg/dL, HDL-cholesterol 50 mg/dL, systolic blood pressure 110 mm Hg on treatment with antihypertensive drugs, and being a nonsmoker) is displayed in Figure 2. Based on these estimates and integrating recommendations from latest guidelines and consensus documents (**Table 4**), a practical algorithm for deciding when to initiate or consider aspirin for primary CVD across age categories is provided in Figure 3. Following this approach, recommendations for aspirin use are given for combinations of age and 10-year CVD risk. At variance with existing guidelines, we introduced a distinction between patients with and without family history of colorectal cancer. In the former, in fact, the threshold for initiating aspirin should be lower. Because the reduction in risk of colorectal cancer is apparent after at least 10 years of therapy, the initiation of aspirin may be less justified over 70 years if not otherwise justified by CVD risk considerations. Among patients with no family history of colorectal cancer, a general consensus exists across guidelines that those with between 50 and 59 years of age and 10-year CVD >10% should initiate aspirin (Table 4). This recommendation is less established for patients <50 years of age, those 50 to 59 years of age with <5% to 10% CVD risk, and patients >60 years. In all these categories, clinical judgment applies, which includes a balanced assessment of risk and benefits of aspirin therapy, and factors patients' preference and their willingness to comply with aspirin therapy. Ultimately, any decision on aspirin initiation should be based on the underlying risk of bleeding. Patients at high risk of bleeding should not be offered aspirin therapy for primary prevention, with the possible exception of patients >50 and <70 years of age with a family history of colorectal cancer and a 10-year CVD risk >10%.

Ongoing Studies and Future Directions

Four randomized trials are currently ongoing to test the benefit of aspirin for primary prevention of CVD (Table 5). Three of them are double-blind (ARRIVE [Aspirin to Reduce Risk of Initial Vascular Event], NCT00501059; ASPREE [Aspirin in Reducing Events in the Elderly], NCT01038583; ASCEND [A Study of Cardiovascular Events in Diabetes], NCT00135226) and one (ACCEPT-D [Aspirin and Simvastatin Combination for Cardiovascular Event Prevention Trial in Diabetes], ISRCTN48110081) is open label. Similar to JPPP, all of these trials targeted patients at some risk of CVD events: with multiple coro-

		Family history of CRC		No family history of CRC	
Age (years)	10-year CVD risk	HBR	no HBR	HBR	no HBR
<50	<5%	No ASA	No ASA	No ASA	No ASA
<50	5–10%	No ASA	Initiate ASA	No ASA	Clinical judgment
50–59	5–10%	No ASA	Initiate ASA	No ASA	Clinical judgment
50–59	10–20%	Clinical judgment	Initiate ASA	No ASA	Initiate ASA
60–69	10–20%	Clinical judgment	Initiate ASA	No ASA	Clinical judgment
≥70	≥20%	No ASA	Clinical judgment	No ASA	Clinical judgment

Figure 3. Risk stratification approach for aspirin use in primary prevention of cardiovascular disease for a patient with diabetes mellitus, on the background assumption of optimal management of other cardiovascular disease risk factors.

High bleeding risk (HBR) is defined as a history of bleeding without reversible causes and concurrent use of other medications that increase bleeding risk. Clinical judgment includes a balanced assessment of risk and benefits of aspirin therapy and factors patients' preference and willingness to comply with aspirin for the subsequent 10 years. CRC indicates colorectal cancer; and CVD, cardiovascular disease.

Table 5. Ongoing Randomized Clinical Trials of Aspirin for Primary Prevention

Study Name	ARRIVE	ASPREE	ASCEND	ACCEPT-D
Identifier	NCT00501059	NCT01038583	NCT00135226	ISRCTN48110081
Study design	Randomized, double-blind	Randomized, double-blind	Randomized, 2x2 factorial, double-blind	Randomized, open label
Patient population	Men ≥55 years of age with 2 to 4 risk factors; women ≥60 years of age with ≥3 risk factors	Men or women ≥65 years of age	Men or women ≥40 years of age with type I or II diabetes mellitus	Men or women with type I or II diabetes mellitus on statin therapy or candidates to statin therapy
Sample size	12,551	19,000	15,480	5170
Investigational arm	EC ASA 100 mg	EC ASA 100 mg	ASA 100 mg	ASA 100 mg
Control arm	Placebo	Placebo	Placebo	No ASA
Primary endpoint	CV death, MI, UA, stroke, or TIA	All-cause death, dementia or persistent physical disability	Nonfatal MI, nonfatal stroke or TIA, or vascular death (excluding confirmed cerebral hemorrhage)	CV death, nonfatal MI, nonfatal stroke, or inpatient or outpatient hospital admission for CV causes
Follow-up	6 y	5 y	7.5 y	5 y
Study start date	July 2007	January 2010	March 2005	October 2007
Estimated study completion date	November 2016	January 2018	September 2017	Event driven

ACCEPT-D indicates Aspirin and simvastatin combination for cardiovascular event prevention trial in diabetes; ARRIVE, Aspirin to Reduce Risk of Initial Vascular Event; ASCEND, A Study of Cardiovascular Events in Diabetes; ASPREE, Aspirin in Reducing Events in the Elderly; ASA, acetylsalicylic acid; CV, cardiovascular; EC, enteric-coated; TIA, transient ischemic attack; and UA, unstable angina.

nary risk factors in ARRIVE, elderly ≥65 years of age in ASPREE, with type I or II DM in ASCEND and ACCEPT-D. Indeed, the latter 2 trials are specifically designed to shed some light on the topic of primary prevention in DM (Table 5). The results of ASCEND (N=15,480) are expected in 2017. The study features a 2x2 factorial design to also test the benefit of primary prevention with omega-3 fatty acid supplementation. ACCEPT-D, which is event-driven, is testing the hypothesis that low-dose aspirin provides additional primary prevention benefits on top of statins.[73] Although these studies will shed light on the topic of primary CVD prevention with aspirin for patients with DM, many important questions will remain unsolved, including the impact of sex and statin therapy on the net benefit of aspirin. Individual patient meta-analyses of studies specifically conducted in DM or those where DM is traceable are warranted to clarify these issues once ASCEND and ACCEPT-D will be completed. Yet if these studies will collectively fail to prove a net benefit of aspirin for primary CVD prevention in DM, other strategies will need to be investigated (ie, anti-inflammatory, lipid-lowering agents, or newer generation glucose-lowering medications), a description of which is beyond the scope of this manuscript.

CONCLUSIONS

The benefit of aspirin for patients with CVD clearly exceeds the risk of bleeding, which makes the role of aspirin for secondary prevention undisputed. A modest benefit has also been demonstrated in primary prevention, but the trade-off of aspirin initiation versus the increased risk of intracranial and gastrointestinal bleeding is more uncertain in patients with no overt CVD. When chosen for primary CVD prevention, aspirin should be prescribed at the lowest effective daily dose (ie, 75–100 mg), preferring uncoated formulations with higher bioavailability (with concurrent use of proton pump inhibitors in those at high risk of gastrointestinal bleeding), avoiding concurrent administration of NSAIDs, and with considerations on twice daily dosing in patients with rapid platelet turnover. Contemporary guidelines and position statements recommend a risk-based approach for identifying subjects who may gain a net benefit from aspirin use in primary prevention. Patients with DM are at heightened risk of CVD, but for the meantime, the mere presence of DM does not appear sufficient for aspirin to confer a benefit clearly exceeding the risk of bleeding. Ongoing clinical trials are designed to meaningfully address whether DM is a modifier of the net benefit of aspirin in patients with no overt CVD.

DISCLOSURES

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FOOTNOTES

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