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Michael Pignone, Mark J. Alberts, John A. Colwell, Mary Cushman, Silvio E. Inzucchi, Debabrata Mukherjee, Robert S. Rosenson, Craig D. Williams, Peter W. Wilson and M. Sue Kirkman

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ADA/AHA/ACCF Scientific Statement

# Aspirin for Primary Prevention of Cardiovascular Events in People With Diabetes

## A Position Statement of the American Diabetes Association, a Scientific Statement of the American Heart Association, and an Expert Consensus Document of the American College of Cardiology Foundation

Michael Pignone, MD, MPH, FACP, Writing Group Chair; Mark J. Alberts, MD; John A. Colwell, MD, PhD, MACP; Mary Cushman, MD, MSc; Silvio E. Inzucchi, MD; Debabrata Mukherjee, MD, MS, FACC; Robert S. Rosenson, MD, FACC, FAHA, FACP; Craig D. Williams, PharmD, FNLA; Peter W. Wilson, MD; M. Sue Kirkman, MD

The burden of cardiovascular disease (CVD) among patients with diabetes is substantial. Individuals with diabetes are at 2- to 4-fold increased risk of cardiovascular events compared with age- and sex-matched individuals without diabetes. In diabetic patients over the age of 65 years, 68% of deaths are from coronary heart disease (CHD) and 16% are from stroke.[1] A number of mechanisms for the increased cardiovascular risk with diabetes have been proposed, including increased tendency toward intracoronary thrombus formation,[2] increased platelet reactivity,[3] and worsened endothelial dysfunction.[4]

The increased risk for cardiovascular events and mortality in patients with diabetes has led to considerable interest in identifying effective means for cardiovascular risk reduction. Aspirin has been shown to be effective in reducing cardiovascular morbidity and mortality in high-risk patients with myocardial infarction (MI) or stroke (secondary prevention).[5] The Food and Drug Administration has not approved aspirin for use in primary prevention, and its net benefit among patients with no previous cardiovascular events is more controversial, for both patients with and without a history of diabetes.[5] The U.S. Preventive Services Task Force recently updated its recommendation about aspirin use for primary prevention. The Task Force recommended encouraging aspirin use in men age 45–79 years and women age 55–79 years and not encouraging aspirin use in younger adults. They did not differentiate their recommendations based on the presence or absence of diabetes.[6,7]

In 2007, the American Diabetes Association (ADA) and the American Heart Association (AHA) jointly recommended that

From the Department of Medicine, University of North Carolina, Chapel Hill (M.P.); the Department of Neurology, Northwestern University, Chicago, Ill (M.J.A.); the Division of Endocrinology, Diabetes, and Medical Genetics (Emeritus), Medical University of South Carolina, Charleston (J.A.C.); the Department of Medicine, University of Vermont, Burlington (M.C.); the Section of Endocrinology, Department of Medicine, Yale University School of Medicine, New Haven, Conn (S.E.I.); the Division of Cardiovascular Medicine, Department of Medicine, Texas Tech University, Paul Foster School of Medicine, El Paso (D.M.); Mount Sinai Heart, Mount Sinai School of Medicine, New York, NY (R.S.R.); the College of Pharmacy, Oregon State University and Oregon Health and Science University, Portland (C.D.W.); the Division of Cardiology, Department of Medicine, Emory University, Atlanta, Ga (P.W.W.); and the American Diabetes Association, Alexandria, Va (M.S.K.).

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Correspondence to M. Sue Kirkman, MD, American Diabetes Association, 1701 N Beauregard St, Alexandria, VA 22311. E-mail skirkman@diabetes.org

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aspirin therapy (75–162 mg/d) be used as a primary prevention strategy in those with diabetes at increased cardiovascular risk, including those who are over 40 years of age or who have additional risk factors (family history of CVD, hypertension, smoking, dyslipidemia, or albuminuria).[8] These recommendations were derived from several older trials that included relatively small numbers of patients with diabetes. Results of 2 recent randomized controlled trials of aspirin performed specifically in patients with diabetes raised questions about the efficacy of aspirin for primary prevention in diabetes.[9,10]

Because of the scope of the problem of CVD in patients with diabetes and the conflicting evidence about the efficacy of aspirin for primary prevention in people with diabetes, the ADA, AHA, and the American College of Cardiology Foundation (ACCF) convened a group of experts to review and synthesize the available evidence and use this information to create updated recommendations. The group considered and organized this report around the following questions:

1. What is the evidence regarding aspirin to prevent initial cardiovascular events in people with diabetes?
2. How can we reconcile the results of the different primary prevention trials?
3. What are the risks of aspirin, and are these similar or different for people with diabetes compared to those without?
4. What do we know about the recommended dosage or dosage range?
5. How can we integrate potential benefits and risks of aspirin to determine which patients with diabetes should receive aspirin for the primary prevention of cardiovascular events?
6. What are the needs for future research?

## 1. What is the Evidence Regarding Aspirin to Prevent Initial Cardiovascular Events in People With Diabetes?

Several randomized trials have examined the effect of aspirin for primary prevention of cardiovascular events and have included patients with diabetes (Table). In this section, we examine those findings with respect to the ability of aspirin to prevent cardiovascular events, which typically include ischemic or CHD events (MI, sometimes unstable angina), stroke, and vascular death (usually sudden cardiac death or death from stroke).

Six trials—British Medical Doctors (BMD),[11] Physicians' Health Study (PHS),[12] Thrombosis Prevention Trial (TPT),[13] Hypertension Optimal Treatment (HOT),[14] Primary Prevention Project (PPP),[15,16] and Women's Health Study (WHS)[17]—were population-based and did not focus specifically on patients with diabetes. The percentage of patients with diabetes in these studies ranged from 1–2% in TPT, BMD, and PHS to 22% in PPP. Two recent trials, the Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes (JPAD)[9] and the Prevention of Progression of Arterial Disease and Diabetes (POPADAD),[10] and 1 older trial, the Early Treatment of Diabetic Retinopathy Study (ETDRS),[18] enrolled only patients with diabetes. The available trials (except ETDRS) included mainly or exclusively patients with type 2 diabetes. ETDRS enrolled patients with both type 1 and type 2 diabetes (31% type 1, 31% type 2, and 38% unclassified).

Three trials (BMD, PHS, and TPT) did not include any women, and 1 (WHS) focused solely on women. The proportion of women in the remaining 5 trials varied from 44 to 56%. The dose of aspirin varied from 100 mg every other day to 650 mg daily. The 9 trials ranged from 3.7 to 10.1 years in mean duration, with most extending to 4–6 years. Each of the trials excluded potential participants at increased risk of gastrointestinal bleeding based on a history of peptic ulcer disease. Therefore, the findings of this meta-analysis, which are based on these trials, cannot be readily extended to patients with a history of gastrointestinal bleeding.

Only 2 of the 9 trials reported on use of statins or other lipid-lowering therapy. In JPAD, statin use was 26%, while in PPP lipid-lowering therapy use was 13%. Three trials (BMD, PHS, and ETDRS) were conducted prior to the availability of statins, and TPT and HOT were conducted well before the widespread use of statins for primary prevention. Rates of usage in the more recent POPADAD or WHS trials were not reported.

The PHS trial enrolled 533 men with diabetes and found a 41% relative risk (RR) reduction (RR 0.59, 95% CI 0.33–1.06) in fatal and nonfatal MI over 5 years for those assigned to 325 mg aspirin every other day compared with those assigned to placebo.[12] The HOT trial examined the effect of 75 mg of aspirin daily versus placebo in 18,000 patients ages 50–80 years, of whom 1,501 had diabetes. Among those with diabetes, the RR reduction for CHD events was 23% (RR 0.77, 95% CI 0.44–1.36).[14] The PPP trial enrolled 1031 patients with diabetes and found a nonsignificant reduction in the combined MI end point (fatal plus nonfatal MI) with 100 mg of aspirin daily compared with placebo (RR 0.50, 95% CI 0.17–1.46).[15]

The BMD and TPT studies enrolled relatively few patients with diabetes and did not identify important reductions in CVD risk for those with diabetes, but in each case confidence intervals were quite wide.[11,13] The WHS trial, the only trial that focused exclusively on women and used the lowest dose of aspirin (100 mg every other day), did not find a reduction in risk for CHD with aspirin overall or for the subset with diabetes ($N$=1027; RR 1.34, 95% CI 0.85–2.12). They did, however, identify a reduction in stroke with aspirin for women with diabetes (RR 0.45, 95% CI 0.25–0.82).[17]

Three trials focused on the effect of aspirin exclusively among patients with diabetes. The ETDRS trial examined the effect of 650 mg of aspirin daily versus placebo among 3,711 patients with type 1 or type 2 diabetes between ages 18 and 70 years who had some degree of retinopathy. Approximately one-half of participants reported some history of CVD, although it should be noted that the definition of CVD included the use of antihypertensive medication. Fewer than 10% had had a previous MI or stroke, and 9% had claudication. Intervention patients experienced a decreased risk of nonfatal or fatal MI (RR 0.85, 95% CI 0.73–1.00). In contrast, stroke occurred more frequently with aspirin, although the difference was not statistically significant (RR 1.18, 99% CI 0.88–1.58). Men appeared to derive more benefit from aspirin than women for prevention of MI (RR for men 0.74, 99% CI 0.54–1.00; RR for women 0.91, 99% CI 0.65–1.28), but this difference was not statistically significant and could represent a chance finding.[18]

The POPADAD trial studied whether aspirin and/or antioxidant therapy was more effective than placebo in reducing the incidence of cardiovascular events in patients with diabetes and asymptomatic peripheral arterial disease. This

**Table. Comparison of Primary Prevention Trials of Aspirin That Enrolled Patients With Diabetes (N=11 787)**

| Study/Year[Ref] | Aspirin Dose (Study Design) | Follow-Up, y | Number Enrolled With Diabetes | % Female | Age, y (Minimum/Mean) | CHD End Point |
|---|---|---|---|---|---|---|
| PHS DM/1989[12] | 325 mg every other day (2×2 factorial design with 50 mg beta carotene) | 5.0 | 533 | 0 | >40/NA | Fatal+nonfatal MI |
| ETDRS/1992[18] | 650 mg daily | 5.0 | 3711 | 44 | >18/NA | Fatal+nonfatal MI |
| PPP DM/2003[16]§ | 100 mg daily (2×2 design with 30 mg vitamin E) | 3.7 | 1031 | 52 | >50/64 | Fatal+nonfatal MI |
| WHS DM/2005[17] | 100 mg every other day (2×2 factorial design with 600 IU vitamin E every other day) | 10.1 | 1027 | 100 | >45/55 | Fatal+nonfatal MI‖ |
| JPAD/2008[10] | 81–100 mg daily (open label treatment assignment, blinded end-point assessment) | 4.4 | 2539 | 46 | >30/65 | Fatal+nonfatal MI |
| POPADAD/2008[9] | 100 mg daily (2×2 factorial design including antioxidants) | 6.7 | 1276 | 56 | >40/60 | CHD death+nonfatal MI |
| TPT DM/1998 (data from ATT)[5] | 75 mg daily | 6.7 | 68 | 0 | >45/58 | MCE |
| BMD/1988 (data from ATT)[5] | 500 mg daily | 5.6 | 101 | 0 | >50/NA | MCE |
| HOT DM/ 1998 (data from ATT)[5] | 75 mg daily (co–randomized to 1 of 3 diastolic BP goals) | 3.8 | 1501 | 47 | >50/62 | MCE |

ATT indicates Antithrombotic Trialists' (ATT) Collaboration; BMD, British Medical Doctors; BP, blood pressure; CHD, coronary heart disease; DM, diabetes mellitus; ETDRS, Early Treatment of Diabetic Retinopathy Study; HOT, Hypertension Optimal Treatment; IU, international unit; JPAD, Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes; MCE, major coronary event (CHD death+nonfatal MI+sudden death); MI, myocardial infarction; NA, not available; PHS, Physicians' Health Study; POPADAD, Prevention of Progression of Arterial Disease and Diabetes; PPP, Primary Prevention Project; PT, Thrombosis Prevention Trial; RR; relative risk; WHS, Women's Health Study.

*10-year extrapolated CHD event rate calculated by (10 ÷ study duration) × event rate.

†Calculated based on event counts.

‡Values slightly different from original PHS report based on updated ICD-9 coding information obtained by the ATT trialists.

§Data used from 2003 PPP diabetic substudy[16]; number with diabetes is discrepant from original PPP publication[15] due to continued enrollment and follow-up of diabetic patients beyond the original study period.

‖Event rates slightly different than original 2005 report due to 11 extra MI/CHD deaths (6 in aspirin group and 5 in placebo) reported to the ATT study group vs. original publication.

randomized, multicenter, double-blind, placebo-controlled trial involved 1276 adults over age 40 years with either type 1 or type 2 diabetes. All subjects had an ankle brachial pressure index less than 0.99 but no symptomatic CVD. They were randomized in a 2×2 factorial design to aspirin 100 mg daily, an antioxidant supplement daily, both, or neither. Two composite primary end points were 1) death from CHD or stroke, nonfatal MI or stroke, or amputation above the ankle for critical limb ischemia; and 2) death from CHD or stroke. Study medication discontinuation rates were high: 14% at 1 year and 50% at 5 years. Overall, 116 of 638 (18.2%) primary events occurred in patients assigned to aspirin therapy versus 117 of 638 (18.3%) in those on placebo (HR 0.98, 95% CI 0.76–1.26). There were 43 CHD or stroke deaths in the aspirin group and 35 in the placebo group (6.7% vs. 5.5%; HR 1.23, 95% CI 0.79–1.93). The rates of a wide variety of secondary end points and adverse events also did not differ between groups. Outcomes were also similar with or without the antioxidants; there was no interaction between the 2 active therapies.[10]

In JPAD, investigators examined the efficacy of low-dose aspirin for primary prevention of cardiovascular events in a randomized, open-label trial conducted in 2539 Japanese patients with type 2 diabetes but no history of CVD. Patients were assigned to either aspirin (81–100 mg daily) or no aspirin and were followed for an average of 4.4 years. The primary end point was a composite of fatal or nonfatal ischemic heart disease, fatal or nonfatal stroke, and peripheral arterial disease. A total of 154 events occurred: 68 (5.4%) in the aspirin group and 86 (6.7%) in the nonaspirin group (HR 0.80, 95% CI 0.58–1.10). The combined secondary end point of coronary and cerebrovascular mortality occurred in 1 patient (stroke) in the aspirin group and 10 patients (5 fatal MIs and 5 fatal strokes) in the nonaspirin group (HR 0.10, 95% CI 0.01–0.79). Other secondary end points did not differ importantly between groups. Overall, mortality occurred in 34 patients in the aspirin group and 38 patients in the nonaspirin group (HR 0.90, 95% CI 0.57–1.14). According to prespecified subgroup analyses, however, in subjects over 65 years of age ($n$=1363), the incidence of the primary end point was lower with aspirin (HR 0.68, 95% CI 0.46–0.99).[9]

In summary, the currently available evidence on aspirin for CVD prevention includes 3 trials conducted specifically in patients with diabetes and 6 other trials in which patients with

**Table. Continued**

| CHD End Point Event Rate (Control vs. Aspirin) | 10-Year Extrapolated CHD Event Rates* | RR (95% CI)† | Stroke Events for Aspirin vs. Control: RR (95% CI) |
|---|---|---|---|
| 10.5% vs. 6.2%‡ (27/258 vs. 17/275) | 21% vs. 12.4% | 0.59 (0.33–1.06) | 16 vs. 10: 1.50 (0.69–3.25) |
| 15.3% vs. 13.0% (283/1855 vs. 241/1856) | 30.6% vs. 26.0% | 0.85 (0.73–1.00) | 92 vs. 78: 1.18 (0.88–1.58) |
| 2.0% vs. 1.0% (10/512 vs. 5/519) | 5.4% vs. 2.7% | 0.49 (0.17–1.43) | 10 vs. 11: 0.90 (0.38–2.09) |
| 5.9% vs. 7.9% (29/494 vs. 42/533) | 5.9% vs. 7.9% | 1.34 (0.85–2.12) | 15 vs. 31: 0.45 (0.25–0.82) |
| 1.1% vs. 1.0% (14/1277 vs. 12/1262) | 2.5% vs. 2.3% | 0.87 (0.40–1.87) | 22 vs. 34: 0.65 (0.39–1.11) |
| 12.9% vs. 13.9% (82/638 vs. 89/638) | 19.3% vs. 20.7% | 1.09 (0.82–1.44) | 37 vs. 50: 0.74 (0.49–1.12) |
| 15.4% vs. 13.8% (6/39 vs. 4/29) | 23.0% vs. 20.6% | 0.90 (0.28–2.89) | 1 vs. 2: 0.67 (0.06–7.06) |
| 18.8% vs. 18.8% (6/32 vs. 13/69) | 33.48% vs. 33.6% | 1.00 (0.42–2.40) | 3 vs. 1: 1.39 (0.15–12.86) |
| 3.6% vs. 2.8% (27/749 vs. 21/752) | 9.5% vs 7.3% | 0.77 (0.44–1.36) | 22 vs. 24: 0.91 (0.52–1.61) |

diabetes constitute subgroups within broader trials of aspirin prophylaxis. No single trial provides definitive results. As such, we sought, in question 2, to use meta-analysis to try to reconcile the available data.

## 2. How Can We Reconcile the Results of the Different Trials?

In order to synthesize and reconcile the results of the available trials, we examined existing meta-analyses of aspirin prevention trials (including those that focused on all patients and those that examined only patients with diabetes) and performed new meta-analyses with updated data.

The Antithrombotic Trialists' (ATT) Collaboration recently published an individual patient-level meta-analysis of the 6 large trials of aspirin for primary prevention in the general population.[5] These trials collectively enrolled over 95 000 participants, including almost 4000 with diabetes. Overall, the meta-analysis found that aspirin reduced the risk of vascular events by 12% (RR 0.88, 95% CI 0.82–0.94). The largest reduction was for nonfatal MI (RR 0.77, 95% CI 0.67–0.89). Aspirin had little effect on CHD death (RR 0.95, 95% CI 0.78–1.15) or total stroke (RR 0.95, 95% CI 0.85–1.06). The net effect on total stroke reflected a relative reduction in risk of ischemic stroke (−14%) and a relative increased risk of hemorrhagic stroke (+32%).

There was some evidence of a difference in aspirin effect by sex. Aspirin reduced CHD events in men (RR 0.77, 95% CI 0.67–0.89) but not in women (RR 0.95, 95% CI 0.77–1.17). Conversely, aspirin had no effect on stroke in men (RR 1.01, 95% CI 0.74–1.39) but reduced stroke in women (RR 0.77, 95% CI 0.59–0.99). These potential differences in effect by sex were of borderline statistical significance, were affected strongly by the results of 1 trial (WHS), and cannot be considered definitive. Notably, sex differences in aspirin's effects have not been observed in studies of secondary prevention.[5] The ATT collaborators did not identify other clear sources of heterogeneity of effect, although there was some suggestion that current smokers derived less benefit from aspirin than nonsmokers.

In the 6 trials examined by the ATT, the effect of aspirin on major vascular events was similar for patients with and without diabetes: RR 0.88, 95% CI 0.67–1.15, and RR 0.87, 95% CI 0.79–0.96, respectively. The CI was wider for those with diabetes because of the smaller number of participants with diabetes and their smaller total numbers of CVD events.

We performed a new meta-analysis that added data from 3 trials performed specifically in patients with diabetes (JPAD, POPADAD, and ETDRS)[9,10,18] to the data from the subgroups of patients with diabetes from the 6 trials included in the ATT meta-analysis (Figure). Using a random-effects model, we found that aspirin was associated with a 9% decrease in risk of CHD events (nonfatal and fatal MI) that was not statistically significant (RR 0.91, 95% CI 0.79–1.05). We did not identify important heterogeneity ($\chi^2=8.71$, $P=0.367$, $I^2=8.2\%$), but a large portion of the summary estimate depended on the ETDRS trial. Excluding this trial, the estimate of effect for CHD events was smaller.

For stroke, our random-effects meta-analysis of the 9 trials found a reduction in the risk of stroke of 15% (RR 0.85, 95% CI 0.66–1.11) that was not statistically significant. There was some heterogeneity ($\chi^2=12.48$, $P=0.131$, $I^2=35.9\%$). The results of these diabetes-specific analyses are consistent with the findings of the ATT meta-analysis and suggest that aspirin likely produces a modest reduction in CVD risk, but

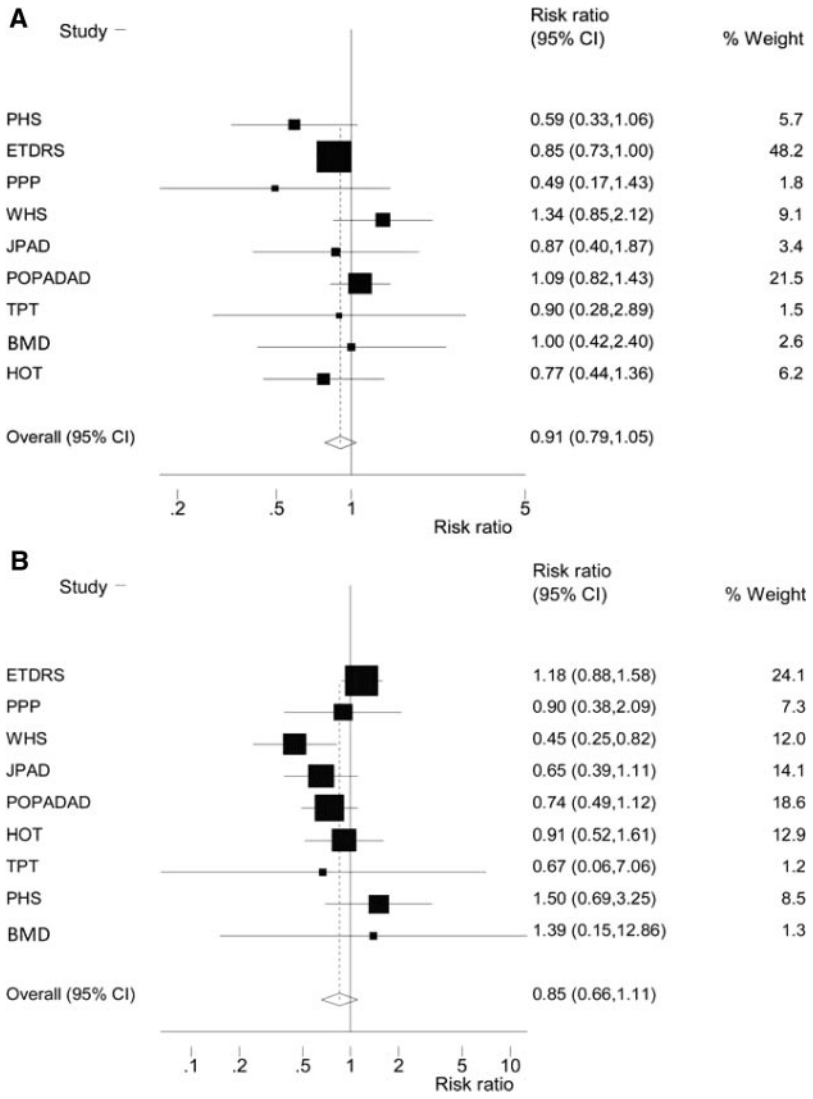


**Figure.** Meta-analysis of trials examining the effects of aspirin on risk of cardiovascular disease events in patients with diabetes. A, Effect of aspirin on coronary heart disease events. Tests for heterogeneity: $\chi^2=8.71$, $P=0.367$, $I^2=8.2\%$. B, Effect of aspirin on risk of stroke in patients with diabetes. Tests for heterogeneity: $\chi^2=12.48$, $P=0.131$, $I^2=35.9\%$. BMD indicates British Medical Doctors[11]; CI, confidence interval; ETDRS, Early Treatment of Diabetic Retinopathy Study[18]; HOT, Hypertension Optimal Treatment[14]; JPAD, Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes[9]; PHS, Physicians' Health Study[12]; POPADAD, Prevention of Progression of Arterial Disease and Diabetes[10]; PPP, Primary Prevention Project[15]; TPT, Thrombosis Prevention Trial[13]; WHS, Women's Health Study.[17]

limitations in the amount of available data preclude a precise estimate of effect. We also do not have access to sufficient patient-level data in patients with diabetes to consider whether the effect of aspirin on CHD events and stroke differs by sex, the dose of aspirin used, or other clinical factors.

Other recent meta-analyses have examined the effect of aspirin on CVD events in patients with diabetes. DeBerardis and colleagues[19] included 6 of the 9 trials included in our analysis (they did not include HOT, BMD, or TPT due to lack of data on patients with diabetes in the original publications) and found estimates of effect with aspirin similar to those of our analysis: for MI, RR 0.86 (95% CI 0.61–1.21) with moderate heterogeneity ($I^2=62.2\%$), mainly due to inclusion of WHS and PHS. For stroke, they included 5 trials (excluding PHS) and calculated a summary RR of 0.83 (95% CI 0.60–1.14) and also noted moderate heterogeneity ($I^2=52.5\%$), mainly due to inclusion of WHS. They also identified potentially important effect modification by sex: aspirin reduced MI for men (RR 0.57, 95% CI 0.34–0.94) but not for women (RR 1.08, 95% CI 0.71–1.65).

Zhang and colleagues[20] included 7 trials in their meta-analysis (they did not include BMD or TPT) and also found similar results (for MI, RR 0.85, 95% CI 0.65–1.11; for stroke, RR 0.83, 95% CI 0.63–1.10). They performed meta-regression and identified important differences in outcomes by sex. They found no evidence of publication bias based on funnel plots using Begg and Egger tests. Calvin and colleagues[21] included 7 trials from our meta-analysis of patients with diabetes (they did not include TPT or BMD) and for MI found RR 0.86 (95% CI 0.67–1.11) using the 7 trials. For ischemic stroke, they found RR 0.62 (95% CI 0.31–1.24) using only the results of WHS and JPAD for their analysis.

The trials pooled in all of the meta-analyses varied widely in the CHD event rates in the control group. If the RR reduction (the metric being pooled) is consistent across patients of differing underlying absolute risk, as suggested by secondary prevention trials and the individual patient-level meta-analysis,[5] then such analyses seem to be reasonable. Taken together, the other meta-analyses reinforce our main findings: aspirin appears to produce a modest-sized reduction in MI and stroke in patients with diabetes, but current evidence is not conclusive because there have been too few events in the available trials to precisely estimate its effects and because our findings rely on analyses of subgroups within larger

trials, which have more potential for bias. The currently available data also reinforce that the possible differences in outcomes for men and women require further study.

### 3. What are the Potential Harms of Aspirin, and are These Similar or Different for People With Diabetes Compared to Those Without?

The major adverse effects of aspirin therapy include intracranial bleeding (hemorrhagic stroke) and extracranial bleeding, principally gastrointestinal. Based on data from primary and secondary prevention trials conducted in mixed populations of patients with and without diabetes, low-dose aspirin appears to be associated with an absolute risk of hemorrhagic stroke of ≈1 in 10 000 people annually.[22] Analyses that examined the primary prevention trials separately have reached similar results.[5,23] These hemorrhagic strokes are incorporated in the estimate of the effect of aspirin on all strokes considered above in question 2.

For extracranial (mainly gastrointestinal) bleeding, aspirin use is associated with a 54% increase in risk based on meta-analysis of the 6 primary prevention trials (RR 1.54, 95% CI 1.30–1.82). The absolute increase in risk was on the order of 3 in 10 000 per year in mainly middle-aged adults enrolled in the aspirin primary prevention trials. The ATT collaboration authors found that several risk factors for CVD also increased the risk for extracranial bleeding from aspirin, suggesting that those at higher CVD risk are also at higher risk for aspirin-related adverse effects. Those with diabetes taking aspirin experienced a 55% increased risk (RR 1.55, 95% CI 1.13–2.14) compared with those without diabetes.[5] Since the primary prevention trials used by the ATT collaboration and by this meta-analysis excluded patients with a history of peptic ulcer disease, the risk calculations for bleeding cannot be extended to that population.

Notably, the absolute excess risk of gastrointestinal bleeding with aspirin is likely higher among free-living older adults, with rates of 1–10 per 1000 annually reported in a large cohort study.[24] While evidence supports that use of proton-pump inhibitors (PPIs) can decrease the risk of recurrent aspirin-related gastrointestinal bleeding,[25] it is not clear whether routine use of a PPI is cost-effective or should be recommended for primary prevention of gastrointestinal bleeding.

### 4. What Do We Know About the Recommended Dosage or Dosage Range?

The optimal dosage of aspirin for prevention of cardiovascular events is not clearly established from the outcomes literature. The average daily dose used in the primary prevention trials involving participants with diabetes ranged from 50 to 650 mg daily (Table 1). Indirect evidence from the ATT collaboration suggests that the risk reductions achieved with low doses (75–162 mg/d) are as large as those obtained with higher doses (500–1500 mg/d) and larger than those in the few trials that have used doses below 75 mg/d.[26] The failure of higher doses to produce greater reductions in thrombotic events may in part be due to the fact that the inhibitory effects of aspirin on the platelet are permanent. Thus, even low doses will achieve a full effect after several days of dosing. Additionally, the effects of aspirin begin in the portal circulation and are thereby presystemic. This removes the variability of hepatic metabolism, which accounts for much of the pharmacodynamic variability with other agents such as clopidogrel.[27,28]

Although platelets from patients with diabetes have altered function, it is unclear what, if any, impact that finding has on the required dose of aspirin for cardioprotective outcomes in the diabetic patient.[29] Many alternate pathways exist for platelet activation and aggregation (adenosine diphosphate, thrombin, epinephrine, von Willebrand factor) that are independent of thromboxane $A_2$ and thus not sensitive to the effects of aspirin.[30] Therefore, while aspirin resistance appears higher in the diabetic patients when measured by a variety of ex vivo and in vitro methods (platelet aggregometry, measurement of thromboxane $B_2$), these observations alone are insufficient to empirically recommend higher doses of aspirin be used in the diabetic patient at this time.[31–33]

### 5. How Can We Integrate Potential Benefits and Harms of Aspirin to Determine Which Patients With Diabetes Should or Should not Receive Aspirin for the Primary Prevention of CV Events?

On the basis of the currently available evidence, aspirin appears to have a modest effect on cardiovascular events (RR reduction of ~10%), with the absolute decrease in events depending on the underlying CVD risk (those with higher baseline risk should have greater absolute benefit). The main adverse effects appear to be an increased risk of gastrointestinal bleeding. The excess risk may be as high as 1–5 per 1000 per year in real-world settings. In adults with CVD risk greater than 1% per year, the number of CVD events prevented will be similar to or greater than the number of bleeding events induced, although the events considered (MI, stroke, and gastrointestinal bleeding) do not have equal effects on long-term health.[34] We have developed recommendations based on these data.

The effect of aspirin for primary prevention of CVD events in adults with diabetes is currently unclear. Trials to date have reached mixed results, but overall suggest that aspirin modestly reduces risk of cardiovascular events. More research is needed to better define the specific effects of aspirin in diabetes, including any sex-specific differences. For now, we recommend the following:

- Low-dose (75–162 mg/d) aspirin use for prevention is reasonable for adults with diabetes and no previous history of vascular disease who are at increased CVD risk (10 year risk of CVD events over 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 diabetes at increased CVD risk include most men over age 50 years and women over age 60 years 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, Level of Evidence: B) (ADA Level of Evidence: C)
- Aspirin should not be recommended for CVD prevention for adults with diabetes at low CVD risk (men under age 50

years and women under 60 years 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, Level of Evidence: C) (ADA Level of Evidence: C)

- Low-dose (75–162 mg/d) aspirin use for prevention might be considered for those with diabetes 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 5–10%) until further research is available. (ACCF/AHA Class IIb, Level of Evidence: C) (ADA Level of Evidence: E)

### *Cardiovascular Risk Assessment*

These recommendations depend on the accurate assessment of cardiovascular risk as part of the decision-making process about aspirin use. All patients with diabetes do not have high cardiovascular risk, despite the assumptions of some previous guidelines.[35] We have provided treatment guidance based on either a combination of age, sex, and other risk factors or on an estimate of absolute cardiovascular risk. An important consideration is that patients may acquire additional risk factors over time, which would necessitate a reassessment of their overall risk profile. The absolute risk-based recommendations require the use of a risk prediction tool. Tools that can be used in patients with diabetes are available from several sources, for example:

1. UKPDS Risk Engine: http://www.dtu.ox.ac.uk/riskengine/index.php
2. ARIC CHD Risk Calculator: http://www.aricnews.net/riskcalc/html/RC1.html
3. American Diabetes Association Risk Assessment Tool, Diabetes PHD: http://www.diabetes.org/phd

### *Concurrent Therapies*

Whether patients have sufficient CVD risk to warrant aspirin use under these assumptions will also depend on the use of other effective techniques for CVD risk reduction, including statins, blood pressure control, and smoking cessation.[36,37] Each of these therapies also lowers the risk of CVD events and should be considered when deciding about aspirin use. If these other effective treatments are adopted first, then fewer patients with diabetes will remain at sufficient risk to warrant aspirin use, in light of its potential adverse effects. For example, a patient at 20% 10-year risk based on elevated blood pressure and suboptimal lipid levels would have his risk reduced from 20 to 13% by taking a statin and from 13 to 10% based on effective blood pressure control, which makes the decision about whether to take aspirin more complex. Although the risk reduction with these additional therapies does not occur immediately, their effects can be assumed to occur with rapidity sufficient to incorporate them in the initial decision-making process.

## 6. What are the Needs for Future Research?

Two ongoing studies will provide additional information on the role of low-dose aspirin for the prevention of cardiovascular events specifically in patients with diabetes. Aspirin and Simvastatin Combination for Cardiovascular Events Prevention Trial in Diabetes (ACCEPT-D) is an open-label Italian primary prevention trial comparing aspirin 100 mg daily to no aspirin among adults over age 50 years with diabetes who are also taking simvastatin.[38] The planned enrollment is 5170, and the investigators will examine several prespecified subgroups to detect differences in effect of aspirin, including men versus women and older versus younger age, as well as baseline lipid levels and use of statins. A second trial, A Study of Cardiovascular Events in Diabetes (ASCEND), is being conducted in the U.K. and will also examine the effects of 100 mg aspirin daily versus placebo among men and women over age 40 years who have either type 1 or type 2 diabetes but no previous vascular events.[39] It uses a double-blind placebo-controlled and $2 \times 2$ factorial design that will also examine the effects of $\omega$-3 fatty acid supplements. The planned enrollment is 10 000, which was designed to provide adequate power to detect a 20% reduction in major vascular events including both MI and stroke.

Although these trials will provide important additional information, it is possible that they will not definitively determine whether aspirin is effective for prevention of CHD events in people with diabetes. This may be especially true for important subgroups such as patients on statins, women, and patients with type 1 diabetes. Although ASCEND is powered for a 20% RR reduction, an RR reduction of 10% among patients with an underlying incidence of 10% in the control group would require over 36 000 participants if 90% power is desired and 26 000 for 80% power. To achieve this event rate among moderate-risk patients with diabetes (annual event rates of 1–2%), a trial would need to be 5–10 years in duration. Thus, while the ongoing trials may not provide definitive answers, their combined enrollment of over 15 000 patients will add important new information on the role of aspirin for primary prevention in patients with diabetes.

In addition, development of reliable surrogate testing for platelet reactivity and response to antiplatelet therapies would be helpful in the management of patients for whom concerns have been raised about aspirin resistance, such as those with diabetes.[27,28] Such testing could also allow more precise determination of the dose-response relationship for aspirin in patients both with and without diabetes and better inform the design of large outcomes studies. However, while some encouraging epidemiologic and retrospective data exists for current methods of surrogate platelet testing for aspirin, these data lack sufficient rigor to inform clinical decision making, particularly in the setting of primary prevention.[32,33,40]

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