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Aspirin for primary prevention of cardiovascular disease in patients with diabetes: A meta-analysis ☆

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ABSTRACT

Aims: Aspirin use for primary prevention of cardiovascular disease (CVD) is controversial, especially in patients with diabetes. The objective of this meta-analysis was to evaluate aspirin's safety and efficacy for primary prevention of CVD [fatal or nonfatal myocardial infarction (MI), fatal or nonfatal stroke, angina, transient ischemic attack (TIA), peripheral artery disease (PAD) and revascularization] in patients with diabetes.

Methods: A literature search was conducted using the terms cardiovascular disease, aspirin, diabetes mellitus to identify trials of patients with diabetes who received aspirin for primary prevention of CVD. Study sample size, and ischemic and bleeding events were extracted and analyzed using RevMan 5.2.7.

Results: In total, 6 studies (n = 10,117) met criteria. Aspirin doses ranged from 100 mg every other day to 650 mg daily. Follow-up ranged from 3.6 to 10.1 years. In patients with diabetes, there was no difference between aspirin and placebo with respect to the risk of all cause mortality (OR 0.93, 95% CI 0.81–1.06), or individual atherosclerotic events compared to placebo. There were no differences in bleeding (OR 2.53, 95% CI 0.77–8.34), GI bleeding (OR 2.14, 95% CI 0.63–7.33) or hemorrhagic stroke rates (OR 0.90, 0.34–2.33) between groups.

Conclusions: It remains unclear whether aspirin may reduce the occurrence of a first atherosclerotic event or mortality in patients with diabetes. More research on this use of aspirin in patients with diabetes is required to supplement currently available research.

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1. Introduction

Cardiovascular disease (CVD) remains a large cause of morbidity and mortality in the United States [1]. Each year over 1.5 million Americans suffer from a CVD event (fatal or non-fatal myocardial infarction (MI) or stroke) and approximately 75% of these are a first event [1,2]. Patients with diabetes have a higher CVD event risk than patients without diabetes, and CVD is the leading cause of morbidity and mortality in patients with diabetes [3]. Historically, in addition to lifestyle modifications and control of diabetes mellitus, hypertension and hypercholesterolemia, aspirin has been widely recommended for the primary prevention of CVD in patients with diabetes. As recently as 2009, the American Diabetes Association (ADA) recommended prescribing aspirin 75–162 mg in patients with diabetes greater than 40 years old or with additional risk factors for CVD including family history of CVD, hypertension, smoking, dyslipidemia or albuminuria [4]. However, in recent years, the use of aspirin for CVD primary prevention in this population has become more controversial. With recent updates in the guidelines, the ADA now only recommends aspirin for primary prevention in patients with diabetes with a 10-year CVD risk score greater than or equal to 10% [5]. Similarly, in 2007, the American Association of Clinical Endocrinologists (AACE) recommended using low dose aspirin primary prophylaxis routinely in patients with diabetes unless a specific contraindication was present [6]. In 2011 the recommendation was revised, and now 75–162 mg of aspirin daily in patients with diabetes is only recommended if 10-year CVD risk score is greater than 10% [7].

Several meta-analyses of patients with diabetes have been performed to evaluate aspirin for prevention of CVD [8–13]. These analyses found no increase in bleeding with aspirin doses ranging from 100 mg every other day to 650 mg per day. Additionally, these analyses report no benefit of aspirin in preventing CVD endpoints including all-cause mortality, CVD mortality, MI, and/or stroke. However, these meta-analyses did not include other atherosclerotic endpoints (angina, transient ischemic attack (TIA), peripheral artery disease (PAD), revascularization) that may be clinically significant for patients. Therefore, the objective of this meta-analysis was to evaluate aspirin's safety and efficacy for primary prevention of CVD including additional atherosclerotic events in patients with diabetes.

2. Methods

2.1. Literature search

Two investigators (LK, HB) independently searched PubMed and Cochrane databases through February 2015 using the keywords cardiovascular disease, aspirin, diabetes mellitus to identify trials of patients with diabetes who received aspirin for primary prevention of CVD. Bibliographies of recent review articles, retrieved articles, and previous meta-analyses were also hand searched for other relevant studies.

2.2. Study selection and data extraction

LK and HB reviewed all titles and abstracts retrieved from the literature search to determine inclusion. Studies were evaluated for inclusion if the full text version was available, was published in English, and evaluated aspirin for the primary prevention of CVD in human patients with diabetes. Full text review was subsequently performed for inclusion of trials that reported event rates for all-cause mortality, CVD mortality, MI, stroke, TIA, PAD, angina, revascularization or bleeding. Additionally, the trials needed to report event rate data specifically for patients with diabetes if these patients were included as a subgroup.

The endpoints [all-cause mortality, CVD mortality, MI, stroke, TIA, PAD, angina, revascularization, any bleeding, gastrointestinal (GI) bleeding and intracranial hemorrhage (ICH)] were extracted from the included studies by the two investigators above independently. Information on study design, methodological quality, study participants, duration of follow up, interventions (i.e. aspirin dose) and country of study origin were also collected. Discrepancies between the two reviewers were resolved through discussion and consensus.

2.3. Quality assessment of methods

One investigator evaluated methodological quality of included studies using the Jadad scale for reporting randomized controlled trials (RCT) [14]. A second investigator independently verified accuracy of the assessment.

2.4. Study outcomes

The efficacy outcomes evaluated were mortality (all-cause, CVD and unknown cause) and atherosclerotic events (fatal or non-fatal MI, fatal or non-fatal stroke, angina, TIA, PAD, revascularization). The safety outcomes evaluated were any bleeding, GI bleeding and ICH. All outcomes evaluated were determined prior to literature review.

2.5. Statistical analysis

Odds ratios (OR) and 95% confidence intervals (95% CI) were calculated for each study outcome to compare aspirin versus placebo using the Mantel–Haenszel fixed effects model or the DerSimonian and Laird random effects model depending on heterogeneity. Heterogeneity amongst studies was examined using the I^2 statistic. We regarded I^2 of $\leqslant$25%, 25–50%, and $\geqslant$50% as low, moderate and high amounts of heterogeneity, respectively. A fixed effects model was used when low to moderate heterogeneity was present and a random effects model was used when high heterogeneity was present [15]. Data were analyzed using Review Manager (RevMan) 5.2.7. This meta-analysis was conducted and reported in line with the recommendations from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [16].

3. Results

A total of 516 potentially eligible articles were identified through literature and hand searches. Of these, 505 were excluded by reviewing their titles and abstracts. A total of

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