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Review Article

Aspirin for primary prevention of cardiovascular and all-cause mortality events in diabetes: updated meta-analysis of randomized controlled trials

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What's new?

- This updated meta-analysis only suggests a modest benefit of aspirin in the prevention of major adverse cardiovascular event/s (MACE) in people with diabetes.
- Limited subgroup analyses suggest there are differences in the effect of aspirin on MACE according to baseline cardiovascular disease (CVD) risk, medication compliance and sex.
- The overall evidence does not clearly support guidelines that encourage the use of aspirin for the primary prevention of CVD in adults with diabetes who are at increased CVD risk.

Abstract

Aims To evaluate the benefits and harms of aspirin for the primary prevention of cardiovascular disease and all-cause mortality events in people with diabetes by conducting a systematic review and meta-analysis.

Methods Randomized controlled trials of aspirin compared with placebo (or no treatment) in people with diabetes with no history of cardiovascular disease were identified from MEDLINE, EMBASE, Web of Science, the Cochrane Library and a manual search of bibliographies to November 2015. Study-specific relative risks with 95% CIs were aggregated using random effects models.

Results A total of 10 randomized trials were included in the review. There was a significant reduction in risk of major adverse cardiovascular events: 0.90 (95% CI 0.81–0.99) in groups taking aspirin compared with placebo or no treatment. Limited subgroup analyses suggested that the effect of aspirin on major adverse cardiovascular events differed by baseline cardiovascular disease risk, medication compliance and sex (P for interaction for all > 0.05). There was no significant reduction in the risk of myocardial infarction, coronary heart disease, stroke, cardiovascular mortality or all-cause mortality. Aspirin significantly reduced the risk of myocardial infarction for a treatment duration of ≤ 5 years. There were differences in the effect of aspirin by dosage and treatment duration on overall stroke outcomes (P for interaction for all < 0.05). There was an increase in risk of major or gastrointestinal bleeding events, but estimates were imprecise and not significant.

Conclusions The emerging data do not clearly support guidelines that encourage the use of aspirin for the primary prevention of cardiovascular disease in adults with diabetes who are at increased cardiovascular disease risk.

Systematic Review Registration no.: PROSPERO 2015: CRD42015026321

Introduction

Individuals with diabetes have a two- to fourfold increased risk of developing vascular events [1]. Cardiovascular disease (CVD) is the leading cause of mortality in people with diabetes, accounting for $>70\%$ of deaths in these people [2]. This has led to increasing interest over recent decades in

developing interventions aimed at reducing cardiovascular risk in people with diabetes. In diabetes, there are several abnormalities in platelet function [3], leading to an accelerated state of atherosclerosis and inflammation which promotes vascular complications [4]. Given this, interventions that inhibit platelet activation and aggregation, such as aspirin therapy, have been proposed as key therapeutic strategies to reduce ischaemic risk in people with diabetes [4]. Low-dose aspirin has been used for many decades in the treatment and prevention of CVD. The effectiveness of aspirin in people with diabetes for the secondary prevention of CVD is well established [5]. A number of randomized controlled trials have reported on the role of aspirin in the primary prevention of CVD in people with diabetes, but, the majority of these studies were poorly powered with regard to the number of people with diabetes, reported results from subgroups, and reported conflicting results. Since the publication of the meta-analysis of individual-level data from six primary prevention trials by the Antithrombotic Treatment Trialists' Collaboration in 2009, which reported a non-significant reduction in serious vascular events in people with diabetes [6]; several other meta-analyses have been conducted on the topic and reported no significant benefit for aspirin in the primary prevention of cardiovascular disease in people with diabetes [7–10].

Consistent with the uncertain evidence, recent guidelines of the Fifth Joint Task Force of the European Society of Cardiology and Other Societies on CVD Prevention in Clinical Practice do not provide specific recommendations for the use of aspirin in people with diabetes [11]. By contrast, guidelines by the American Diabetes Association, the American Heart Association and the American College of Cardiology Foundation advocate the use of low-dose aspirin for the primary prevention of CVD in adults with diabetes, but which should be based on the individual risk of CVD and risk of bleeding [8]. These recommendations were based on pooled analysis of nine trials, which suggested a modest reduction (albeit precluding a precise estimate of the effect size) in risk of cardiovascular events with the use of aspirin. Given the uncertain role of aspirin in primary prevention of CVD in people with diabetes, the guideline authors cite ongoing studies which will add important new information in this area. The Study of Cardiovascular Events in Diabetes (ASCEND) randomized trial which has recruited >15 000 patients, may provide reliable evidence about the effects of low-dose aspirin for the prevention of cardiovascular events in people with diabetes, but the follow-up is not due to end until 2017 [12]. Given the high clinical interest in this topic and with the publication of newer trials since the last relevant meta-analysis on the topic, we aimed to address the persisting uncertainties about the benefits and harms of aspirin for the primary prevention of CVD and all-cause mortality events in people with diabetes by conducting an updated systematic meta-analysis. We also sought to compare the effectiveness of aspirin with placebo (or no treatment) for the primary prevention of CVD and all-cause mortality events in people with diabetes, under a range of relevant clinical characteristics such as baseline CVD risk, dosage of aspirin, compliance and treatment duration.

Methods

Data sources and search strategy

We conducted the present review using a predefined protocol, which has been registered in the PROSPERO prospective register of systematic reviews (CRD42015026321), and in accordance with PRISMA guidelines (Appendix S1) [13]. Two independent authors conducted a duplicate search for randomized controlled trials published before November 2015 (date last searched) using MEDLINE, EMBASE, Web of Science and the Cochrane electronic databases. The computer-based searches combined terms related to (1) the intervention, aspirin (e.g. 'aspirin', 'salicylic acid' and 'salicylates') and (2) diabetes (e.g. 'diabetes mellitus', 'Type 2 diabetes' and 'Type 1 diabetes') or primary prevention (e.g. 'primary prevention') in humans, without any language restriction. Details on the search strategy are provided in Appendix S2. Two independent reviewers screened the titles and abstracts of all initially identified studies according to the selection criteria. Full texts were retrieved from studies that satisfied all selection criteria. The reference lists of selected studies and relevant reviews identified on the topic were searched for additional publications.

Study selection and eligibility criteria

Intervention studies were sought that had reported on the use of aspirin for the primary prevention of CVD in diabetes mellitus and reported data on a variety of cardiovascular and all-cause mortality endpoints. Intervention studies were eligible if they were randomized controlled, open or blinded trials that: (1) assessed the effects of aspirin therapy compared with a placebo or no treatment; (2) enrolled adults (≥ 18 years old) with diabetes mellitus (either exclusively or as a subgroup) without a history or clinical evidence of CVD; and (3) had a follow-up duration of at least 12 months. Studies were excluded if they were non-randomized comparing aspirin with another antiplatelet agent, included people with known CVD, or were secondary publications of trials already included in the analysis.

Data extraction

Two independent authors (S.K.K. and S.S.) extracted data, and a consensus was reached in case of any inconsistency with the involvement of a third author (K.K.). A predesigned data extraction form was used to obtain relevant information. These included, where appropriate, study-level information on study design; baseline population including proportion of men; location; average age at baseline; numbers enrolled and randomized; allocation concealment; blinding; intervention and dosage; medication compliance; duration of treatment or follow-up; treatment comparisons; outcomes of major adverse cardiovascular event/s [MACE; defined as composite of non-fatal myocardial infarction (MI), non-fatal stroke and cardiovascular death], other cardiovascular outcomes, all-cause mortality, and adverse events; and risk estimates for each outcome of interest.

Assessing the risk of bias

Two reviewers independently rated the methodological quality of the studies using the Cochrane Collaboration's risk of bias tool [14] and a consensus was reached with the involvement of a third reviewer. This tool, which is well known and widely accepted for assessing the validity of randomized trials, evaluates seven possible sources of bias: random sequence generation; allocation concealment; blinding of participants and personnel; blinding of outcome assessment; incomplete outcome data; selective reporting; and other bias. For each individual domain, studies were classified into low, unclear and high risk of bias.

Statistical analysis

Summary measures were presented as relative risks (RRs) with 95% CIs. We assumed hazard ratios and odds ratios to approximate the same measure of RRs. We used reported RRs or calculated study-specific unadjusted RRs based on event rates. When studies published more than one RR estimate according to event subtypes (e.g. fatal and non-fatal MI), a within-study summary estimate for the composite event (e.g. MI) was obtained using a fixed effect analysis. For the three trials that did not report data on the subset of participants with diabetes [15–17], we extracted these data from previous reports [8]. The inverse variance weighted method was used to combine summary measures using random effects models to minimize the effect of between-study heterogeneity. Subsidiary analyses employed fixed effects models. Statistical heterogeneity across studies was quantified using the Cochrane chi-squared statistic and the I^2 statistic [18]. Study-level characteristics including geographical location, allocation concealment, baseline CVD risk, dose of aspirin, compliance, duration of treatment, number of outcomes and sex differences were prespecified as characteristics for assessment of heterogeneity, which was conducted using stratified analysis and random effects meta-regression. We assessed the potential for small study effects, such as publication bias, through formal tests, namely Begg's funnel plots and Egger's regression symmetry tests [19]. To contextualize our results, we also calculated the number-needed-to-treat using the formula: number-needed-to-treat = $1/\text{absolute risk reduction}$. The absolute risk reduction was derived by calculating the difference between the rate of events in the control group and the intervention group. STATA release 14 (StataCorp LP, College Station, TX, USA) software was used for all statistical analyses.

Results

Study identification and selection

Our initial search of relevant databases and manual scanning of reference lists identified 3586 potentially relevant citations. After screening based on titles and abstracts, 13 articles remained for further evaluation. After detailed assessments, three articles were excluded. The remaining 10 articles

based on 10 unique studies met our inclusion criteria and were included in the review (Appendix S3 and Fig. 1).

Study characteristics and quality

Table 1 summarizes the key characteristics of the randomized trials included in the review. On aggregate, the included trials published between 1988 and 2014 comprised 16 690 participants with diabetes. The majority (six) of the trials were double-blinded and four were open-label trials. Four of the trials were conducted in Europe (UK and Italy), three in North America (USA), two in Asia (Japan), and one recruited patients from 26 countries in Europe, North and South America and Asia. The baseline age of participants ranged from 18 to 90 years. There was considerable variability in study populations, which included healthy participants, participants with pre-existing conditions such as hypertension, as well as participants at high cardiovascular risk. Three trials were conducted specifically in people with diabetes and the seven others were based on data from subgroups of people with diabetes. Only one trial made a distinction between Type 1 and Type 2 diabetes in their results and that trial also included a small proportion of people with pre-existing CVD [20]. The dosage of aspirin ranged from 75 to 650 mg daily and the duration of therapy ranged from 3.6 to 10.1 years. Medication compliance was reported in five trials using a variety of subjective (self-reports) and objective (biochemical monitoring and pill counts) measures. Six trials had a high risk of bias within one or two areas of study quality, as assessed using the Cochrane Collaboration tool (Appendix S4). The majority of the trials had a high risk of bias for selective reporting. Only one trial was found to have a low risk of bias in all areas and seven trials had an unclear risk of bias in one or more areas of study quality.

Major cardiovascular outcomes and all-cause mortality

Figure 2 and Appendices S6–11 show the RRs for cardiovascular outcomes and all-cause mortality events for aspirin therapy compared with placebo or no treatment in trials included in the pooled analyses. Seven trials comprising 15 988 participants reported on MACE (1543 events). A significant reduction in risk of MACE was found with aspirin compared with placebo or no treatment 0.90 (95% CI 0.81 to 0.99; $P=0.031$). The pooled RR remained unchanged using a fixed effects model (Appendix S5). There was no evidence of heterogeneity between the contributing studies ($I^2=0\%$, 0 to 71%; $P=0.989$). When the Early Treatment Diabetic Retinopathy Study (ETDRS), the trial that involved a small proportion of patients with previous CVD, was excluded from the analysis, the pooled RR was 0.90 (95% CI 0.78 to 1.02; $P=0.106$).

Aspirin therapy was not associated with a significant reduction in risk of MI (seven trials comprising 11 618 participants and 879 events) 0.84 (95% CI 0.64 to 1.11; $P=0.225$) or coronary heart disease (five trials comprising 5485 participants and 312 events) 0.98 (95% CI 0.79 to 1.21; $P=0.747$). There was evidence of moderate heterogeneity ($I^2=57\%$, 1 to 82%; $P=0.029$) for the MI

analysis and no evidence of heterogeneity ($I^2=0\%$, 0 to 79%; $P=0.747$) for the coronary heart disease analysis.

Eight trials comprising 11 254 participants found no significant reduction in risk of stroke events with aspirin 0.86 (95% CI 0.69 to 1.08; $P=0.226$) and there was evidence of low heterogeneity between the contributing studies ($I^2=20\%$, 0 to 62%; $P=0.272$).

No significant reduction in risk of CVD mortality with aspirin compared with placebo or no treatment was found (five trials comprising 10 058 participants and 675 events) 0.94 (95% CI 0.71 to 1.26; $P=0.228$). There was evidence of low heterogeneity ($I^2=38\%$, 0 to 77%; $P=0.166$).

Aspirin therapy was not associated with a significant decrease in risk of all-cause mortality (five trials comprising 10 058 participants and 1094 events) 0.94 (95% CI 0.83 to 1.05; $P=0.280$) and there was no evidence of heterogeneity between contributing studies ($I^2=0\%$, 0 to 79%; $P=0.807$).

Other cardiovascular outcomes

Aspirin therapy compared with placebo or no treatment, was not associated with a significant reduction in risk of other cardiovascular outcomes such as non-fatal MI, death from coronary heart disease, fatal stroke, non-fatal stroke, ischaemic stroke, haemorrhagic stroke, CVD, revascularization, angina pectoris, transient ischaemic attack and sudden coronary death (Fig. 3 and Appendix S11).

Subgroup analysis

For MACE, there was no statistically significant evidence of effect modification by several clinically relevant characteristics; however, compared with people with high CVD risk, participants with low CVD risk had a significantly reduced risk of MACE with aspirin (P value for meta-regression = 0.616) and people who were $\geq 90\%$ compliant showed a significant reduction in risk of MACE with aspirin therapy compared with those who were $< 90\%$ compliant (P value for meta-regression = 0.616; Fig. 4). In addition, stratified analysis by sex showed that aspirin significantly reduced the risk of MACE in men 0.79 (95% CI 0.64 to 0.98; $P=0.033$) but not in women 0.95 (95% CI 0.77 to 1.16; $P=0.591$; P value for meta-regression = 0.437).

For MI, the moderate heterogeneity was partly explained by treatment duration (P value for meta-regression = 0.012). Compared with participants with a treatment duration of >5 years, participants with treatment duration of ≤ 5 years had a significantly lower risk of MI with aspirin 0.70 [95% CI 0.53 to 0.93; $P=0.012$ (Appendix S12)]. There was no evidence of effect modification by sex. In further exploration of heterogeneity, exclusion of the Women's Health Study (WHS) and the Physicians' Health Study (PHS) substantially reduced heterogeneity to ($I^2=23\%$, 95% CI 0 to 82%; $P=0.270$) and the pooled estimate of 0.87 (95% CI 0.71 to 1.06; $P=0.176$) was similar to the main finding.

For stroke, there was evidence of effect modification by aspirin dosage (P value for meta-regression = 0.019) and treatment duration (P value for meta-regression = 0.026). The risk of stroke

was significantly reduced for trials using an aspirin dosage of ≤ 100 mg per day compared with > 100 mg per day. Similarly, compared with participants with treatment duration of ≤ 5 years, participants with treatment duration of > 5 years had a significantly lower risk of stroke with aspirin (Appendix S13). There was no evidence of effect modification by sex.

There was no evidence of effect modification by any of the covariates explored for the outcomes of CVD death and all-cause mortality (Appendices S14–15). No evidence of effect modification by sex was found for either outcome.

Adverse effects

Figure 5 presents RRs of the effects of aspirin therapy compared with placebo or no treatment on any and gastrointestinal bleeding, non-gastrointestinal bleeding, gastrointestinal symptoms, cancer, arrhythmias and allergy. There was no significant increase in risk of any of these adverse events.

Absolute benefit and harm

For the primary analysis, the absolute risk reduction of MACE in people with diabetes associated with aspirin therapy was 0.92%, which translates into a number-needed-to-treat of 109 to prevent one MACE.

Publication bias

Under visual examination, funnel plots for those analyses that involved five or more studies were mostly symmetrical, and Egger's regression tests showed no statistical evidence of publication bias for all analyses (Appendix S16). In addition, we found no definitive evidence of selective reporting when studies were grouped by size in meta-regression analyses (Fig. 4 and Appendices S12–15).

Discussion

Key findings

We systematically summarized, using a meta-analytical approach, the available randomized controlled trials that have assessed the role of aspirin for the primary prevention of CVD and all-cause mortality events among people with diabetes. We found a modest and significant reduction (10%) in the risk of MACE with aspirin therapy compared with placebo or no treatment. The modest reduction, however, lost significance when the ETDRS trial was excluded. There was no significant reduction in the risk of individual cardiovascular endpoints or of all-cause mortality. Except for MI, there was no or low heterogeneity in analyses of relevant outcomes. In stratified analyses, there were suggestions of differences in the effect of aspirin by baseline CVD risk, medication compliance and sex on MACE; however, given that there was no statistically significant evidence of effect modification in

these stratified analyses, the results should be interpreted with caution. For all other specific endpoints explored, there was no significant reduction in risk with aspirin therapy in men or women. Aspirin significantly reduced the risk of MI by 30% for a treatment duration of ≤ 5 years, with no benefit for treatment duration of > 5 years. In addition, the risk of stroke was significantly reduced for trials with lower intervention doses and longer average intervention periods. For the effects of aspirin therapy on adverse events, there was suggestion of increased risk of bleeding and gastrointestinal symptoms with aspirin therapy in people with diabetes, but the estimates were imprecise and not significant. Pooled analysis of two trials suggested a protective effect of aspirin therapy on cancer outcomes, but this was not significant.

Comparison with previous work

Some of our findings generally concur with that of previous reviews on the topic. We also provide several relevant findings that have not been previously reported. In contrast to previous reviews, we found a modest-sized reduction in MACE which was statistically significant and based on pooled analysis of seven trials in our primary analysis. De Berardis *et al.* [9] and Butalia *et al.* [7] in pooled analyses of five and six trials respectively, found no significant reduction in the risk of MACE with aspirin therapy compared with placebo or no treatment; however, their pooled estimate verged on statistical significance. Zhang *et al.* [10], in a pooled analysis of six trials, showed an 8% reduction in MACE which was not statistically significant. Furthermore, our analyses provided suggestions of differences in the effect of aspirin by baseline CVD risk, compliance and sex for MACE (albeit *P* values for meta-regression > 0.05). For the effects of aspirin therapy on specific cardiovascular endpoints and all-cause mortality, our non-significant estimates of effect are consistent with previous reviews on the topic [7–10]. Our analyses were characterized by no or low heterogeneity between contributing studies; except for evidence of moderate heterogeneity in the MI analysis, which was mainly attributable to the inclusion of the WHS and PHS and which was also demonstrated by De Berardis *et al.* [9] and Pignone *et al.* [8]. In contrast to our findings, De Berardis *et al.* [9] and Pignone *et al.* [8] also identified moderate heterogeneity in the stroke analyses. In subgroup analyses involving eight stroke trials, we found evidence of effect modification by aspirin dosage and treatment duration, consistent with that of De Berardis *et al.* [9] who pooled five trials. Our findings also showed effect modification by treatment duration for MI outcomes, but no important differences by sex, which was identified by De Berardis *et al.* [9] and Zhang *et al.* [10]. Consistent with Butalia *et al.* [7] and Zhang *et al.* [10], we found no evidence of publication bias in our analyses. We additionally grouped studies by size and found no evidence of selective reporting.

Possible explanations for findings

We showed a significant but modest benefit of aspirin in the primary prevention of MACE in the present meta-analysis which was coherent with that observed in other high-risk populations [6, 21],

but was in contrast to the non-significant reduction reported in several previous reviews. Our results may appear at first to be at odds with previous reports on the topic, but this is not quite the case. The effect estimates and confidence intervals reported in previous reviews are consistent with a potential benefit of aspirin, but were not significant or were on the verge of significance. As discussed by De Berardis *et al.* [9], this could be attributable to low power to detect an effect. We pooled the results of seven trials of MACE resulting in a higher number of events compared with previous reviews and the possibility therefore of enhanced power to show a significant risk reduction in MACE; however, the results were not statistically significant after excluding the ETDRS trial [20]. Given that this study was the largest trial included in the present review in terms of event rate, the non-significant results on exclusion could indicate loss of power. Indeed, De Berardis *et al.* [9] observed no material effect in their results when the ETDRS trial was excluded from their pooled analysis of only five trials of MACE. We were unable to show a significant reduction in the risk of other specific cardiovascular endpoints and all-cause mortality, which were consistent with findings from previous reviews. Taking our overall findings and those of previous reviews together, there is a possibility that aspirin may have a beneficial but modest effect in the primary prevention of CVD in people with diabetes, but the current evidence is not conclusive. Previous studies have interpreted the data to indicate low efficacy of aspirin in people with diabetes [9,10]. Several plausible mechanisms have been postulated for a lower efficacy of aspirin in people with diabetes. Aspirin resistance has been suggested to be a contributing factor for the low efficacy of or poor response to aspirin therapy. People with diabetes have altered platelet function, have abnormalities in endothelial and vascular smooth muscle cell functions, and have increased production of prothrombotic clotting factors and proinflammatory markers [22–24] which all contribute to the capacity to diminish the effects of aspirin on platelet function [25]. The prothrombotic and proinflammatory states have been suggested to result in failure of aspirin to modify platelet response and with little effect on thrombus formation [23]. Hyperglycaemia, which is associated with diabetes, may interfere with the acetylation process which contributes to increased aspirin resistance [26]. Other factors specific to diabetes, such as hyperlipidaemia, hypertension and hyperinsulinaemia, have also been suggested to be involved in aspirin resistance [24,27].

We found differences in the effect of aspirin by treatment duration on MI and stroke. While aspirin reduced the risk of MI for shorter average intervention periods, the risk was reduced for stroke in longer average intervention periods. Given that these vascular outcomes have somewhat diverse aetiology [28], these findings may reflect a true differential effect. In addition, we observed a difference in the effect of aspirin by dosage on stroke; however, the differences seen in the effect of aspirin by treatment duration and dosage is potentially misleading, as stroke outcome was a combined endpoint of stroke subtypes (e.g. haemorrhagic and ischaemic stroke), which have different aetiologies. Given that aspirin is known to have a differential effect on these stroke subtypes (aspirin is used as first line antiplatelet drug for the secondary prevention of ischaemic stroke [29] and

contraindicated in patients who have had a haemorrhagic stroke) and the limited number of studies available for such subgroup analyses, these findings may have arisen from the effects of low statistical power or chance. We were unable to conduct separate analyses for the subtypes of stroke because of the limited amount of data; therefore, these results may require replication in further studies.

Implications of our findings

Our findings are relevant, provide further insight on aspirin therapy in primary cardiovascular prevention therapy in diabetes, and may have implications for clinical practice. Aspirin may have a beneficial effect on the prevention of MACE in people with diabetes (relative risk reduction of 10%) and may have specific effects by baseline CVD risk, compliance and gender. Our absolute risk reduction based on our primary analyses translates to ~1000 people that need to be treated to prevent one MACE in a year. The main adverse effects of aspirin therapy appear to be gastrointestinal bleeding, which have been based mainly on data from general and secondary prevention populations [21]. An absolute excess of gastrointestinal bleeding complications has been demonstrated in these populations with both low-dosage and long-term aspirin therapy [30]. A higher risk of bleeding events has been reported among people at low cardiovascular risk and the elderly [31]; however, we and others have not been able to demonstrate this in primary prevention populations with diabetes. Nonetheless, data from real-world settings in general populations suggest higher rates of bleeding in people with diabetes on aspirin therapy [32]. Given the overall evidence and the imprecise estimates reported, these results may mainly be attributable to inadequate power of these trials to detect these events. Before any guideline recommendations should be made, the benefits of aspirin on CVD in primary prevention populations with diabetes need to be balanced against the potential for harm. Given our absolute risk reduction estimates and the potential for an increased risk of major bleeding events, it is likely that the benefits might not exceed the harms. Recent guidelines by the American Diabetes Association recommend the use of low-dose aspirin (75–162 mg/day) for the primary prevention of CVD in adults with Type 1 and Type 2 diabetes who are at elevated CVD risk (10-year risk >10%), whilst they do not recommend this for people at low CVD risk (10-year risk < 5%) [33]. Given the present data, however, the use of aspirin for the primary prevention of cardiovascular events in people with diabetes at increased CVD risk cannot be justified. The present review also suggested a protective effect of aspirin therapy on cancer outcomes, but this was based on pooled results of two trials and the estimate was not significant. Given that Type 2 diabetes is known to be associated with an increased risk of colorectal carcinomas [34], these findings are of interest. The role of the potential prevention of cancer with aspirin therapy is of emerging interest especially in people with Type 2 diabetes and is a topic for further investigation.

Our updated study also highlights the existing scientific gaps in trial evidence, which stimulates the need for further research. There may be important differences in the effect of aspirin by treatment dosage and compliance, treatment duration and sex, but the findings from the present study and that of

previous reviews have mostly been mixed as a result of aggregation of insufficiently powered studies and reporting of results from subgroup analyses. Carefully designed randomized controlled trials with large-sample sizes involving individuals with diabetes are warranted to evaluate the role of aspirin in the primary prevention of cardiovascular events in people with diabetes. Quoting previous reviews on this extensively researched but unresolved topic [8,9], two ongoing trials, ASCEND (International Standard Randomized Controlled Trial Number ISRCTN60635500)[12] and the Aspirin and Simvastatin Combination for Cardiovascular Events Prevention Trial in Diabetes (ACCEPT-D; Current Controlled Trials ISRCTN48110081) [35], are expected to enrol >15 000 people with diabetes and may help address the existing inconsistencies.

Strengths and limitations

The present study has several advantages compared with previous reviews. It is a comprehensive, updated assessment and the largest meta-analysis on the topic to date. The generalizability of our findings was enhanced by the involvement of data from 10 trials, which included 16 690 people with diabetes, and therefore the ability to examine the efficacy of aspirin therapy on a wider range of cardiovascular endpoints, as well as adverse events including arrhythmias, cancer and allergy. We also conducted detailed analyses under a broader range of individual and study-level circumstances which included sample size, geographical location and baseline CVD risk. Formal tests were unable to detect publication bias for all analyses. There was evidence of no or low heterogeneity among contributing studies for the majority of the analyses. For the only analysis that involved moderate heterogeneity (MI outcome), we systematically explored possible sources of heterogeneity using stratified and meta-regression analyses.

The present review and meta-analysis also has several limitations which deserve consideration. Although the meta-analysis was very comprehensive, it was based on a limited number of published studies, which precluded the ability to perform clinically relevant subgroup analyses (e.g. baseline age, appropriate baseline CVD risk groups, appropriate treatment dosages, type of diabetes, duration of diabetes, etc.). Results for several cardiovascular outcomes were based on pooled estimates of only up to three studies. The new trial included in our updated review only contributed to the pooled estimate of MACE. As with aggregate reviews, the definitions of some of the clinical outcomes as well as secondary endpoints such as medication compliance were not consistent across all studies, which could potentially have led to biased estimates. There appeared to be selective reporting bias, as data on some cardiovascular endpoints and adverse events were not reported by some of the included studies. Pooled estimates for adverse events were based on the limited amount of data reported by eligible trials and were imprecise. Given the limitations, the findings should be interpreted with caution and intensify the need for detailed future intervention studies and individual patient data meta-analysis to help clarify any beneficial role of aspirin in primary prevention.

Conclusions

Recent data suggest a modest potential benefit of aspirin in the primary prevention of MACE in people with diabetes. There were suggestions of differences in the effect of aspirin by baseline CVD risk, compliance and sex on MACE. The present data do not clearly support guidelines that encourage the use of aspirin for the primary prevention of CVD in adults with diabetes who are at increased CVD risk. Additional evidence is required.

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Competing interests

The authors declare no conflicts of interests. S.S. has received honoraria for speaking at meetings and serving on Advisory Boards for Novartis, Novo Nordisk, Janssen, MSD, Lilly and BI. K.K. has received funds for research, honoraria for speaking at meetings and or served on Advisory Boards for Astra Zeneca, Lilly, Novartis, Pfizer, Servier, Sanofi Aventis, MSD and Novo Nordisk.

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Supporting information

Additional Supporting Information may be found in the online version of this article:

Appendix S1 PRISMA checklist.

Appendix S2 MEDLINE literature search strategy.

Appendix S3 Reference list of included studies.

Appendix S4 Assessment of risk of bias.

Appendix S5 Relative risks of major adverse cardiovascular events in participants with diabetes for aspirin intervention trials.

Appendix S6 Relative risks of myocardial infarction in participants with diabetes for aspirin intervention trials.

Appendix S7 Relative risks of coronary heart disease in participants with diabetes for aspirin intervention trials.

Appendix S8 Relative risks of stroke in participants with diabetes for aspirin intervention trials.

Appendix S9 Relative risks of cardiovascular disease mortality in participants with diabetes for aspirin intervention trials.

Appendix S10 Relative risks of all-cause mortality in participants with diabetes for aspirin intervention trials.

Appendix S11 Relative risks of other cardiovascular outcomes in participants with diabetes for aspirin intervention trials.

Appendix S12 Effects of aspirin therapy on myocardial infarction in participants with diabetes, according to various characteristics.

Appendix S13 Effects of aspirin therapy on stroke in participants with diabetes, according to various characteristics.

Appendix S14 Effects of aspirin therapy on cardiovascular disease mortality in participants with diabetes, according to various characteristics.

Appendix S15 Effects of aspirin therapy on all-cause mortality in participants with diabetes, according to various characteristics.

Appendix S16 Assessment of small study effects by funnel plots and Egger's regression symmetry tests.

FIGURE 1 PRISMA flow diagram.

FIGURE 2 Effect of aspirin on the primary prevention of major adverse cardiovascular events (MACE), myocardial infarction, coronary heart disease, stroke, cardiovascular disease death, and all-cause mortality in people with diabetes. RR, relative risk

FIGURE 3 Effect of aspirin on the primary prevention of individual cardiovascular disease endpoints in people with diabetes. CHD, coronary heart disease; RR, relative risk.

FIGURE 4 Effect of aspirin on the primary prevention of major adverse cardiovascular events in people with diabetes, grouped according to several study characteristics. CVD, cardiovascular disease. **P* value for meta-regression.

FIGURE 5 Effect of aspirin on adverse events in people with diabetes. GI, gastrointestinal; RR, relative risk.

Table 1 Characteristics of clinical trials of aspirin therapy included in meta-analysis

Lead author, Publication Date	Name of study or source of participants	Study design	Patient population	Location	Baseline year of study	Age group, years	Males (%)	Allocation concealment	Blinding to subjects	Blinding to carers	Aspirin dose	Medication compliance (%)	Duration of therapy (years)	Completeness of follow-up	Trial participants with diabetes
Peto <i>et al.</i> , 1988 [16]	BMD	Randomized, open-label with no placebo	Healthy male doctors	UK	1978-1979	19-90	100.0	No	No	No	500 mg daily	NR	5.6	Unclear	101
PHS Steering Committee, 1989	PHS	Randomized controlled trial, double-blind	Healthy men	USA	1982	40-84	100.0	Unclear	Yes	Yes	325 mg every other day	NR	5.0	99.7	533
ETDRS Investigators, 1992 [20]	ETDRS	Randomized controlled trial, double-blind	Participants with type 1 and 2 diabetes	USA	1980-1985	18-70	56.5	Unclear	Yes	Yes	650 mg daily	91.8	5.0	94.7	3711
MRC, 1998 [17]	TPT	Randomized, placebo controlled. Factorial with initial parallel-	Patients at high risk of IHD	UK	1989-1994	45-69	100.0	Adequate	Yes	Yes	75 mg daily	NR	6.7	98.9	68
Hansson <i>et al.</i> , 1998 [15]	HOT	Randomized controlled trial, double-blind	Participants with hypertension	Multiple countries	1992-1994	50-80	NR	Adequate	Yes	Yes	75 mg daily	NR	3.8	97.4	1501
Sacco <i>et al.</i> , 2003	PPP	Randomized open trial with 2 × 2 factorial design	Participants > 50 years with one or more cardiovascular risk factors	Italy	NR	64.3*	48.2	Adequate	No	No	100 mg daily	71.8	3.6	99.3	1031

Lead author, Publication Date	Name of study or source of participants	Study design	Patient population	Location	Baseline year of study	Age group, years	Males (%)	Allocation concealment	Blinding to subjects	Blinding to carers	Aspirin dose	Medication compliance (%)	Duration of therapy (years)	Completeness of follow-up	Trial participants with diabetes
Ridker <i>et al.</i> , 2005	WHS	RCT, double blinded, 2 × 2 factorial	Healthy women	USA	1993	≥ 45	0.0	Unclear	Yes	Yes	100 mg on alternate days	NR	10.1	99.4	1027
Belch, 2008	POPADAD	Randomized controlled trial, double-blind, 2 × 2 factorial	Patients aged ≥40 years with Type 1 and 2 diabetes, ABP ≤0.99	UK	NR	≥ 40	44.1	Adequate	Yes	Yes	100 mg daily	50.0	6.7	99.5	1276
Ogawa, 2008	JPAD	Randomized open-label with blinded endpoint assessment	Patients with Type 2 diabetes	Japan	2002	65.0*	55.0	Adequate	No	No	81 or 100 mg daily	90.0	4.4	92.4	2539
Ikeda, 2014	JPPP	Randomized open-label, parallel group	Elderly with multiple atherosclerotic risk factors	Japan	2005–2007	60–85	NR	Adequate	No	No	100 mg daily	76.0	5.0	~98.7	4903

BMD, British male doctors; ETDRS, Early Treatment Diabetic Retinopathy Study; HOT, Hypertension Optimal Treatment; IHD, ischaemic heart disease; JPAD, Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes; JPPP, Japanese Primary Prevention Project; MRC, Medical Research Council; NR, not reported; PHS, Physicians' Health Study; POPADAD, Prevention of Progression of Arterial Disease and Diabetes; PPP, Primary Prevention Project; RCT, randomized controlled trial; WHS, Women's Health Study.

*Average age.

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