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

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Conflict of interests

The authors declare no conflicts of interests. SS has received honoraria for speaking at meetings and serving on Advisory Boards for Novartis, Novo Nordisk, Janssen, MSD, Lilly and BI.

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Novelty statement

- This updated meta-analysis only suggests a modest benefit of aspirin in the prevention of major adverse cardiovascular events (MACE) in people with diabetes.
- Limited subgroup analyses suggest differences in the effect of aspirin by baseline CVD risk, medication compliance, and sex on MACE.
- 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 We sought to evaluate the benefits and harms of aspirin for the primary prevention of CVD and all-cause mortality events in people with diabetes by conducting a systematic review and meta-analysis.

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

Results Ten randomised trials were included. Comparing aspirin with placebo (or no treatment), there was a significant reduction in risk of major adverse cardiovascular events (MACE) 0.90 (0.81-0.99). Limited subgroup analyses suggested differences in the effect of aspirin by baseline CVD risk, medication compliance, and sex on MACE (*P* for interaction for all > 0.05).There was no significant reduction in the risk of myocardial infarction (MI), coronary heart disease, stroke, cardiovascular mortality, or all-cause mortality. Aspirin significantly reduced the risk of MI for a treatment duration of five years or less. 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 New emerging 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.

Systematic review registration: PROSPERO 2015: CRD42015026321

Keywords aspirin, diabetes, primary prevention, cardiovascular disease, meta-analysis

Introduction

Individuals with diabetes have a two-to-four fold increased risk of developing vascular events.(1) Cardiovascular disease (CVD) is the leading cause of mortality in people with diabetes, accounting for more than 70% of deaths in these people.(2) This has led to increasing interest over recent decades to develop 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 randomised controlled trials (RCTs) have reported on the role of aspirin for the primary prevention of CVD in people with diabetes, but, majority of these studies were often poorly powered with regard to the number of people with diabetes, reported results from subgroups, and have 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 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) In contrast, guidelines by the American Diabetes Association (ADA), the American Heart Association (AHA), and the American College of Cardiology Foundation (ACCF) advocate for 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 for CVD and risk for bleeding.(8) These recommendations were based on pooled analysis of nine trials which suggested a modest reduction (albeit precludes 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 ASCEND (A Study of Cardiovascular Events iN Diabetes) randomised trial which has recruited over 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 of 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 on 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 this 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 1**).(13) Two independent authors, in duplication, sought randomised 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 2**. 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. 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 randomised controlled, open or blinded trials (1) that assessed the effects of aspirin therapy compared to a placebo or no treatment; (2) which enrolled adults (≥ 18 years old) with diabetes mellitus (either exclusively or as a subgroup) without previous history or clinical evidence of CVD; and (3) and had a follow-up duration of at least 12 months. Studies were excluded if they were non-randomised 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 (SKK and SS) extracted data and a consensus was reached in case of any inconsistency with involvement of a third (KK). 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 randomised; allocation concealment; blinding; intervention and dosage; medication compliance; duration of treatment or follow-up; treatment comparisons; outcomes of major adverse cardiovascular events (MACE) [defined as composite of nonfatal myocardial infarction (MI), nonfatal 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 involvement of a third reviewer. This tool, which is well known and widely accepted for assessing the validity of randomised 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% confidence intervals (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 nonfatal MI), a within-study summary estimate for the composite event (e.g. MI) was obtained using a fixed effect analysis. For 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 minimise the effect of between-study heterogeneity. Subsidiary analyses employed fixed effects models. Statistical heterogeneity across studies was quantified using the Cochrane χ^2 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 contextualise our results, we also calculated the number needed to treat (NNT) using the formula: NNT = 1 / absolute risk reduction (ARR). The ARR 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 3,586 potentially relevant citations. After screening based on titles and abstracts, 13 articles remained for

further evaluation. Following 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 3; Fig. 1**).

Study characteristics and quality

Table 1 summarises the key characteristics of the randomised trials included in the review. In aggregate, the included trials published between 1988 and 2014, comprised 16,690 participants with diabetes. The majority (n=six) of 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 also included a small proportion of people with pre-existing CVD.(20) The dosage of aspirin ranged from 75 mg 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 demonstrated a high risk of bias within one or two areas of study quality, as assessed using the Cochrane Collaboration tool (**Appendix 4**). 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

Fig. 2 and **Appendices 6-11** presents RRs for cardiovascular outcomes and all-cause mortality events for aspirin therapy compared with placebo or no treatment in trials contributing to pooled analyses. Seven trials comprising of 15,988 participants reported on MACE (1,543 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 5**). 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 of 11,618 participants and 879 events) 0.84 (95% CI: 0.64 to 1.11; *p*=0.225) or CHD (five trials comprising of 5,485 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 CHD analysis.

Eight trials comprising of 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 of 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 of 10,058 participants and 1,094 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 nonfatal MI, CHD death, fatal stroke, nonfatal stroke, ischaemic stroke, haemorrhagic stroke, CVD, revascularization, angina pectoris, TIA, and sudden coronary death (**Fig. 3**; **Appendix 11**).

Subgroup analysis

For MACE, there was no statistically significant evidence of effect modification by several clinically relevant characteristics. However, compared to 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 ≥ 90% compliant showed a significant reduction in risk of MACE with aspirin therapy compared to 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 to participants with treatment duration more than five years, participants with treatment duration of five years or less had a significantly reduced risk of MI with aspirin 0.70 (95% CI: 0.53 to 0.93; *p*=0.012) (**Appendix 12**). 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 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 aspirin dosage of 100 mg per day or less compared to more than 100 mg per day. Similarly, compared to participants with treatment duration of five years or less, participants with treatment duration of more than five years had a significantly reduced risk of stroke with aspirin (**Appendix 13**). 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 14-15**). No evidence of effect modification by sex was found for both outcomes.

Adverse effects

Fig. 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 major adverse cardiovascular events in people with diabetes associated with aspirin therapy was 0.92% which translates into a NNT of 109 to prevent one major adverse cardiovascular event.

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 16**). In addition, we found no definitive evidence of selective reporting when studies were grouped by size in meta-regression analyses (**Fig. 4; Appendices 12-15**).

Discussion

Key findings

We have systematically summarised through a meta-analytical approach, available randomised 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 as well as 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 five years or less, with no benefit for treatment duration of more than five 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 and colleagues in pooled analysis of six trials showed an 8% reduction in MACE which was not statistically significant.(10) 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 characterised by no or low heterogeneity between contributing studies; except for evidence of moderate heterogeneity in the MI analysis, which was mainly due 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 and colleagues who pooled five trials.(9) Our findings also demonstrated

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 demonstrated a significant but modest benefit of aspirin in the primary prevention of MACE in our meta-analysis which was coherent with that observed in other high risk populations,(6, 21) but in contrast to the non-significant reduction demonstrated 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 and colleagues,(9) this could be due to low power to detect an effect. We pooled the results of seven trials of MACE resulting in a higher number of events compared to previous reviews, therefore the possibility of enhanced power to show a significant risk reduction in MACE. However, the results were not statistically significant on excluding the ETDRS trial.(20) Given that this study, which was the largest trial in our study in terms of event rate, the non-significant results on exclusion could indicate loss of power. Indeed, De Berardis and colleagues,(9) demonstrated 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 that of previous reviews together, there is a possibility that aspirin may have a beneficial but modest effect in the primary prevention of cardiovascular disease 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. Whiles 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 major adverse cardiovascular events 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 about 1,000 people

that need to be treated to prevent one major adverse cardiovascular event 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 have 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 due 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 ADA recommend the use of low-dose aspirin (75-162 mg/day) for the primary prevention of CVD in adults with type 1 and 2 diabetes who are at increased CVD risk (10 year risk more than 10%), whilst not recommended for people at low CVD risk (10 year risk less than 5%).(33) However, given the current data, the use of aspirin for the primary prevention of cardiovascular events in people with diabetes at increased CVD risk cannot be justified. Our 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 our study and that of previous reviews have mostly been mixed, due to aggregation of insufficiently powered studies and reporting of results from subgroup analyses. Carefully designed RCTs 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 on-going trials, A Study of Cardiovascular Events in Diabetes (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 more than 15,000 people with diabetes and may help address the existing inconsistencies.

Strengths and limitations

The current study has several advantages compared to previous reviews. It is a comprehensive, updated assessment and the largest meta-analysis on the topic to date. The generalisability of our findings were 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. There are also several limitations of this review and meta-analysis which deserve consideration. Though 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 (eg, 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

New emerging data suggests a modest potential benefit of aspirin in the primary prevention of major adverse cardiovascular events in people with diabetes. There were suggestions of differences in the effect of aspirin by baseline CVD risk, compliance, and sex on major adverse cardiovascular events. The current data 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. Additional evidence is required.

Contributors

All authors contributed to the study design and data interpretation. SKK and SS implemented literature search and extracted data. SKK analysed and interpreted the data and drafted the manuscript. SKK, SS, and KK critically revised the manuscript for important intellectual content. KK supervised the study.

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16. Peto R, Gray R, Collins R, Wheatley K, Hennekens C, Jamrozik K, et al. Randomised trial of prophylactic daily aspirin in British male doctors. British medical journal. 1988;296(6618):313-6.

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Figure 1: PRISMA flow diagram

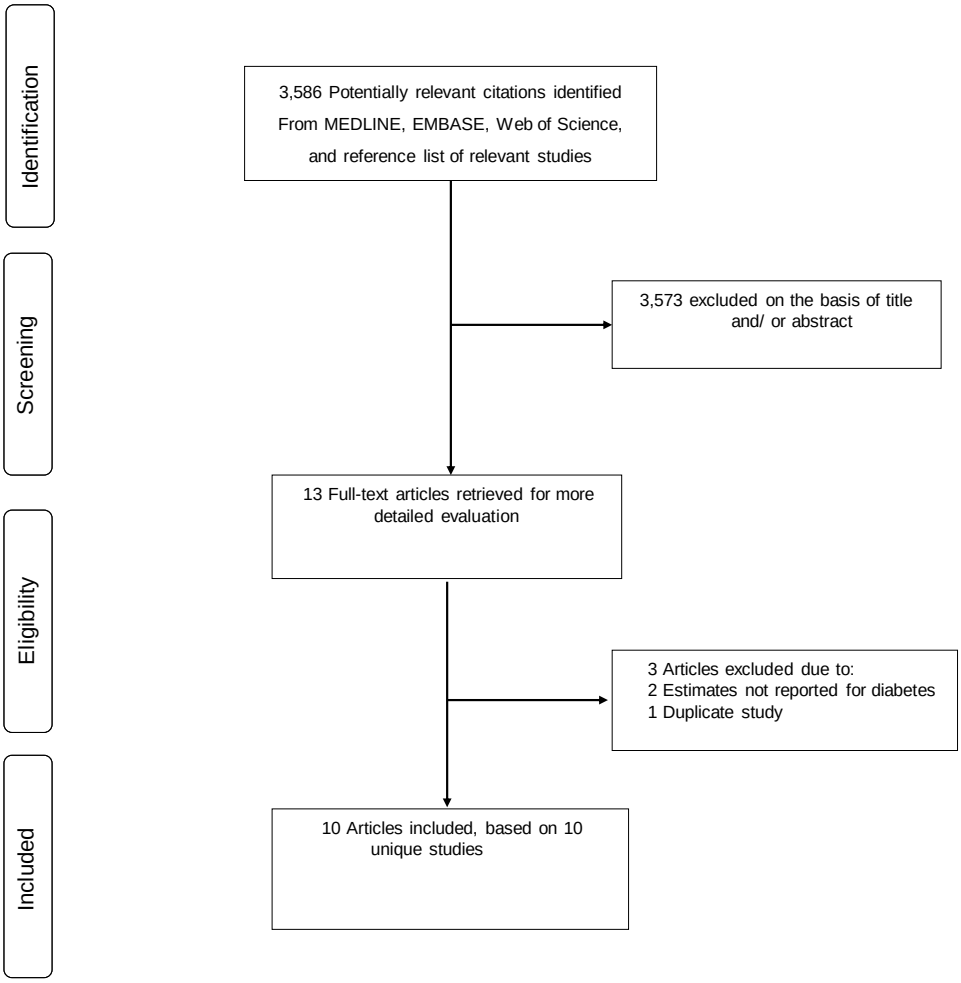
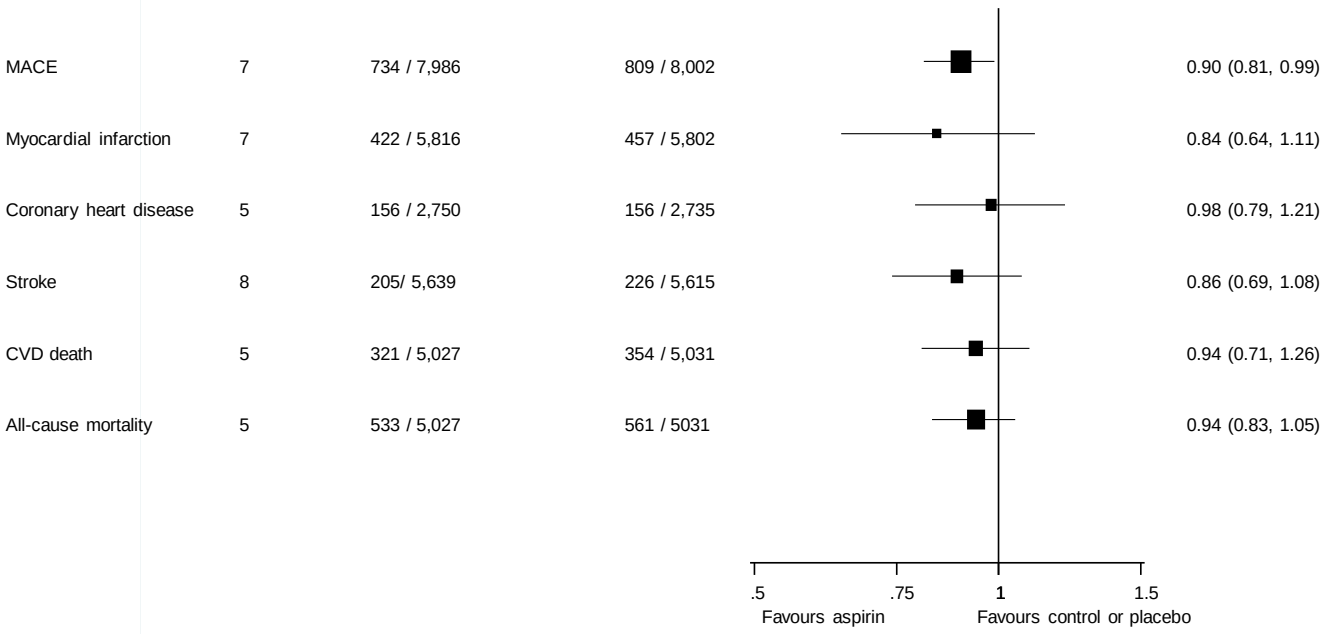
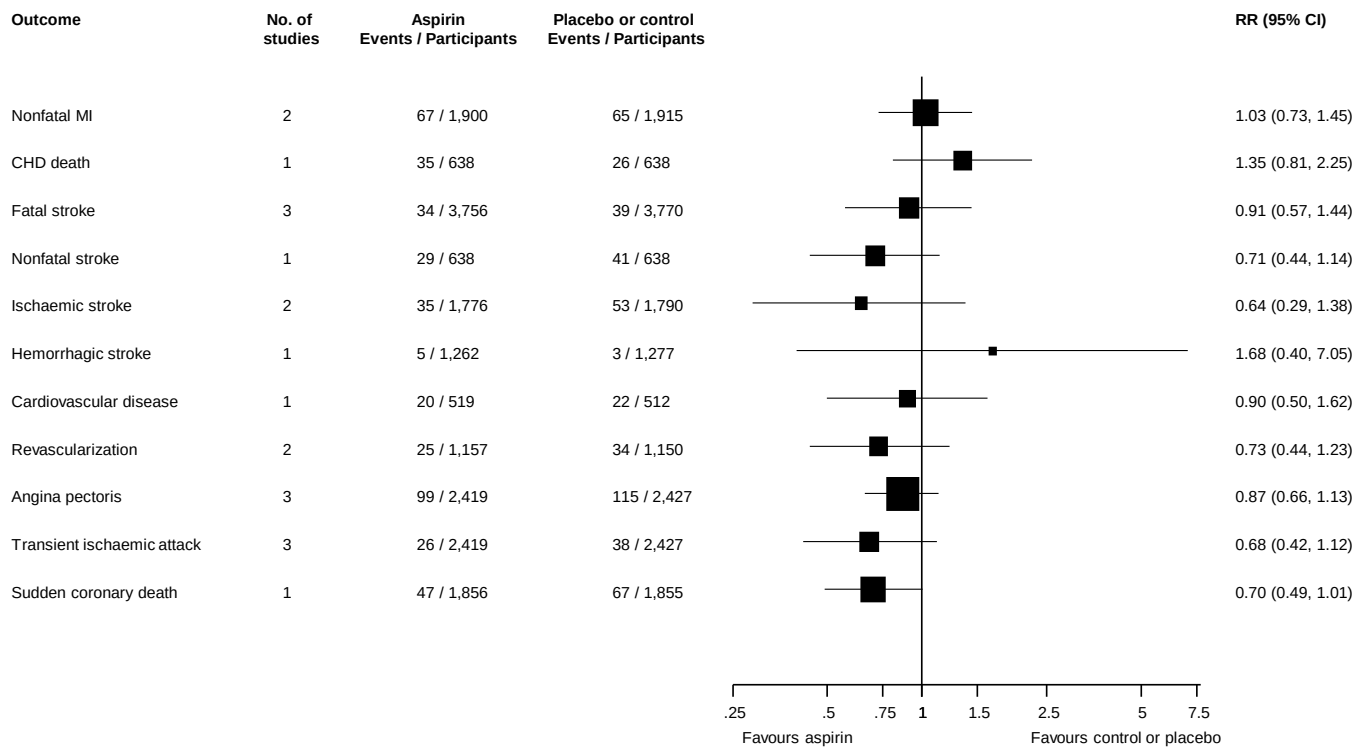


Figure 2: Effect of aspirin on the primary prevention of major adverse cardiovascular events, myocardial infarction, coronary heart disease, stroke, cardiovascular disease death, and all-cause mortality in people with diabetes



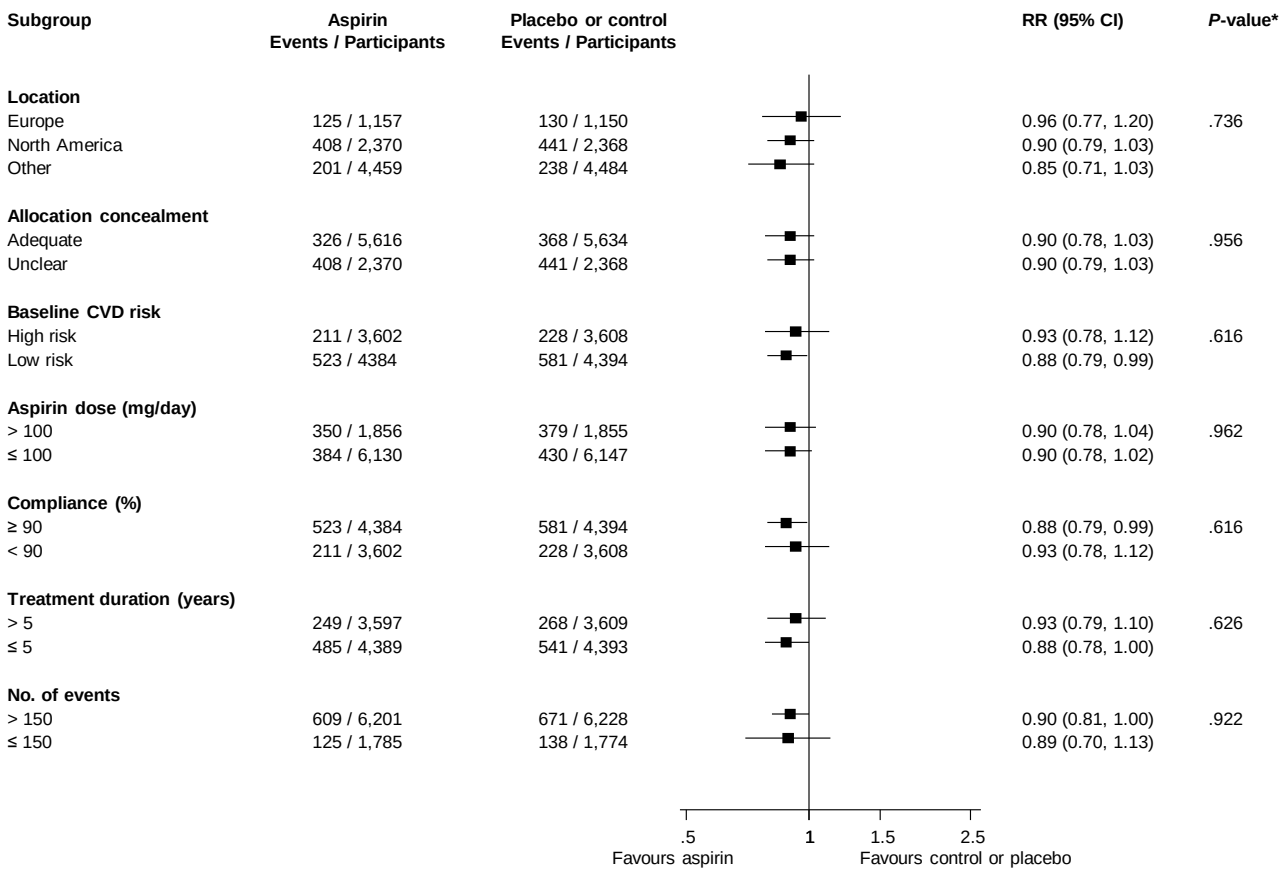
CI, confidence interval (bars); RR, relative risk

Figure 3: Effect of aspirin on the primary prevention of individual cardiovascular disease endpoints in people with diabetes



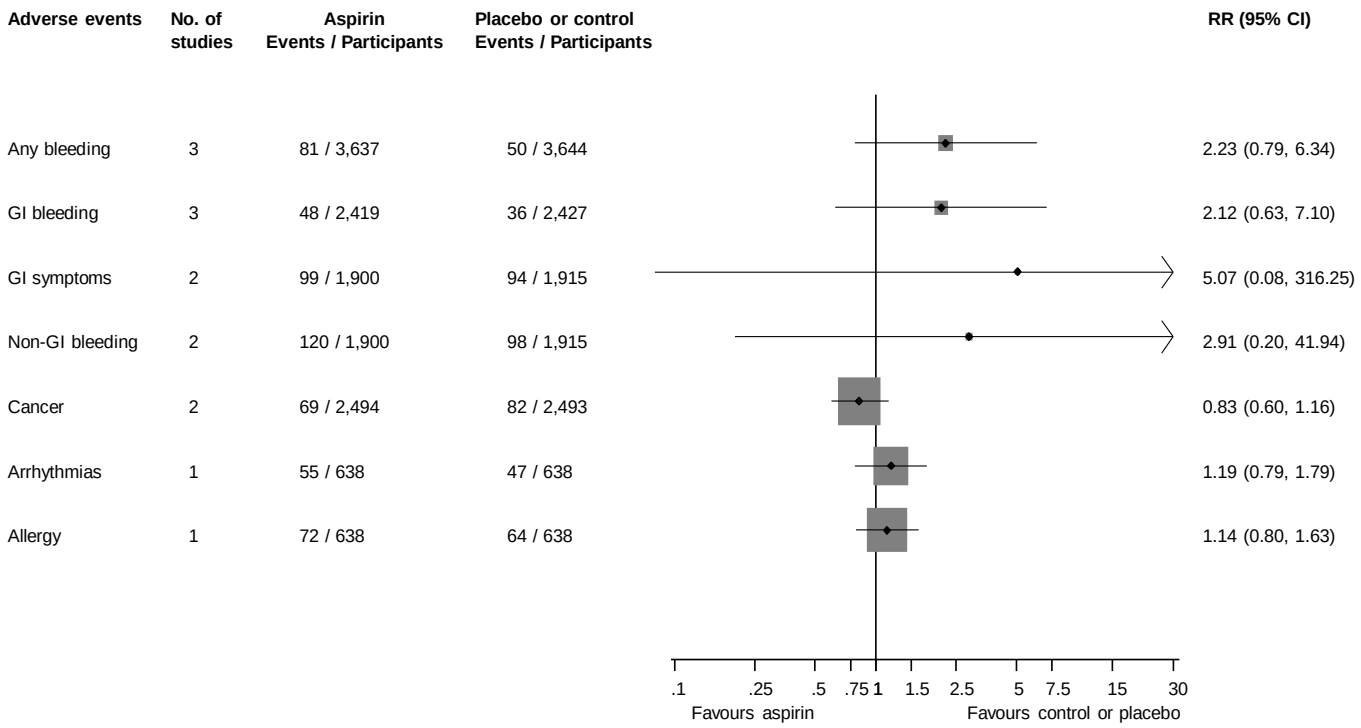
CHD, coronary heart disease; CI, confidence interval (bars); RR, relative risk

Figure 4: Effect of aspirin on the primary prevention of major adverse cardiovascular events in people with diabetes, grouped according to several study characteristics



CI, confidence interval (bars); *, *P*-value for meta-regression

Figure 5: Effect of aspirin on adverse events in people with diabetes



CI, confidence interval (bars); GI, gastro-intestinal; 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	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, 1988	BMD	Randomised, 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	RCT, double blinded	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	ETDRS	RCT, double blinded	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	3,711
MRC, 1998	TPT	Randomized, placebo controlled. Factorial with initial parallel group phase	Patients at high risk for IHD	UK	1989-1994	45-69	100.0	Adequate	Yes	Yes	75 mg daily	NR	6.7	98.9	68
Hansson, 1998	HOT	RCT, double blinded	Participants with hypertension	Multiple countries	1992-1994	50-80	NR	Adequate	Yes	Yes	75 mg daily	NR	3.8	97.4	1,501
Sacco, 2003	PPP	Randomised open trial with 2 x 2 factorial design	Participants > 50 years with one or more CV risk factors	Italy	NR	64.3*	48.2	Adequate	No	No	100 mg daily	71.8	3.6	99.3	1,031
Ridker, 2005	WHS	RCT, double blinded, 2 x 2 factorial	Healthy women	USA	1993	≥ 45	0.0	Unclear	Yes	Yes	100 mg on alternate days	NR	10.1	99.4	1,027
Belch, 2008	POPADAD	RCT, double blinded, 2 x 2 factorial	Patients >=40 years with type 1 and 2 diabetes, ABP <=0.99	Scotland	NR	≥ 40	44.1	Adequate	Yes	Yes	100 mg daily	50.0	6.7	99.5	1,276
Ogawa, 2008	JPAD	Randomised open label with blinded end point 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	2,539
Ikeda, 2014	JPPP	Randomised 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	4,903

*, average age; 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, randomised controlled trial; UK, United Kingdom; USA, United States of America; WHS, Women's Health Study

SUPPLEMENTARY MATERIAL

Appendix 1	PRISMA checklist
Appendix 2	MEDLINE literature search strategy
Appendix 3	Reference list of included studies
Appendix 4	Assessment of risk of bias
Appendix 5	Relative risks of major adverse cardiovascular events in participants with diabetes for aspirin intervention trials
Appendix 6	Relative risks of myocardial infarction in participants with diabetes for aspirin intervention trials
Appendix 7	Relative risks of coronary heart disease in participants with diabetes for aspirin intervention trials
Appendix 8	Relative risks of stroke in participants with diabetes for aspirin intervention trials
Appendix 9	Relative risks of cardiovascular disease mortality in participants with diabetes for aspirin intervention trials
Appendix 10	Relative risks of all-cause mortality in participants with diabetes for aspirin intervention trials
Appendix 11	Relative risks of other cardiovascular outcomes in participants with diabetes for aspirin intervention trials
Appendix 12	Effects of aspirin therapy on myocardial infarction in participants with diabetes, according to various characteristics
Appendix 13	Effects of aspirin therapy on stroke in participants with diabetes, according to various characteristics
Appendix 14	Effects of aspirin therapy on cardiovascular disease mortality in participants with diabetes, according to various characteristics
Appendix 15	Effects of aspirin therapy on all-cause mortality in participants with diabetes, according to various characteristics
Appendix 16	Assessment of small study effects by funnel plots and Egger's regression symmetry tests

Appendix 1 PRISMA checklist

Section/topic	Item No	Checklist item	Reported on page No
Title			
Title	1	Identify the report as a systematic review, meta-analysis, or both	1
Abstract			
Structured summary	2	Provide a structured summary including, as applicable, background, objectives, data sources, study eligibility criteria, participants, interventions, study appraisal and synthesis methods, results, limitations, conclusions and implications of key findings, systematic review registration number	2
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS)	4
Methods			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (such as web address), and, if available, provide registration information including registration number	4
Eligibility criteria	6	Specify study characteristics (such as PICOS, length of follow-up) and report characteristics (such as years considered, language, publication status) used as criteria for eligibility, giving rationale	4
Information sources	7	Describe all information sources (such as databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated	Appendix 2
Study selection	9	State the process for selecting studies (that is, screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis)	4-5
Data collection process	10	Describe method of data extraction from reports (such as piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators	5
Data items	11	List and define all variables for which data were sought (such as PICOS, funding sources) and any assumptions and simplifications made	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis	5
Summary measures	13	State the principal summary measures (such as risk ratio, difference in means).	5-6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (such as I^2 statistic) for each meta-analysis	5-6
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (such as publication bias, selective reporting within studies)	6
Additional analyses	16	Describe methods of additional analyses (such as sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified	6
Results			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram	6 and Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (such as study size, PICOS, follow-up period) and provide the citations	6-7, Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see item 12).	7, Table 1
Results of individual studies	20	For all outcomes considered (benefits or harms), present for each study (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot	7-10
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency	7-10, Figures 2-5; Appendices 5-11

Section/topic	Item No	Checklist item	Reported on page No
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see item 15)	10, Appendix 4
Additional analysis	23	Give results of additional analyses, if done (such as sensitivity or subgroup analyses, meta-regression) (see item 16)	Appendices 12-16
Discussion			
Summary of evidence	24	Summarise the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (such as health care providers, users, and policy makers)	10-11
Limitations	25	Discuss limitations at study and outcome level (such as risk of bias), and at review level (such as incomplete retrieval of identified research, reporting bias)	12-13
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research	13
Funding			
Funding	27	Describe sources of funding for the systematic review and other support (such as supply of data) and role of funders for the systematic review	None

Appendix 2 MEDLINE literature search strategy

Relevant controlled trials, published from inception to November 10, 2015 (date last searched), were identified through electronic searches not limited to the English language using MEDLINE, EMBASE, Web of Science, and Cochrane databases. Electronic searches were supplemented by scanning reference lists of articles identified for all relevant studies (including review articles), and by hand searching of relevant journals. The computer-based searches combined search 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*).

1 exp Aspirin/ or aspirin.mp. (57316)
2 salicylic acid.mp. or exp Salicylic Acid/ (12354)
3 salicylate.mp. or exp Salicylates/ (67574)
4 diabetes mellitus.mp. or exp Diabetes Mellitus/ (385192)
5 exp Diabetes Mellitus, Type 2/ or type 2 diabetes.mp. or exp Diabetes Mellitus, Type 1/ (175229)
6 primary prevention.mp. or exp Primary Prevention/ (129138)
7 1 or 2 or 3 (87752)
8 4 or 5 (400493)
9 7 and 8 (2474)
10 6 and 7 (1251)
11 9 or 10 (3511)
12 (controlled clinical trial or randomized controlled trial or meta analysis).pt. (553258)
13 (placebo* or random* or trial* or groups).ti,ab. (2468582)
14 drug therapy.fs. (1822690)
15 12 or 13 or 14 (3987797)
16 11 and 15 (2069)
17 limit 16 to humans (1900)

Each part was specifically translated for searching alternative databases.

Appendix 3 Reference list of included studies

1. Peto R, Gray R, Collins R, et al. Randomised trial of prophylactic daily aspirin in British male doctors. *Br Med J (Clin Res Ed)* 1988; **296**(6618): 313-6.

2. Final report on the aspirin component of the ongoing Physicians' Health Study. Steering Committee of the Physicians' Health Study Research Group. *N Engl J Med* 1989; **321**(3): 129-35.

3. Aspirin effects on mortality and morbidity in patients with diabetes mellitus. Early Treatment Diabetic Retinopathy Study report 14. ETDRS Investigators. *JAMA* 1992; **268**(10): 1292-300.

4. Thrombosis prevention trial: randomised trial of low-intensity oral anticoagulation with warfarin and low-dose aspirin in the primary prevention of ischaemic heart disease in men at increased risk. The Medical Research Council's General Practice Research Framework. *Lancet* 1998; **351**(9098): 233-41.

5. Hansson L, Zanchetti A, Carruthers SG, et al. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. HOT Study Group. *Lancet* 1998; **351**(9118): 1755-62.

6. Sacco M, Pellegrini F, Roncaglioni MC, et al. Primary prevention of cardiovascular events with low-dose aspirin and vitamin E in type 2 diabetic patients: results of the Primary Prevention Project (PPP) trial. *Diabetes Care* 2003; **26**(12): 3264-72.

7. Ridker PM, Cook NR, Lee IM, et al. A randomized trial of low-dose aspirin in the primary prevention of cardiovascular disease in women. *N Engl J Med* 2005; **352**(13): 1293-304.

8. Belch J, MacCuish A, Campbell I, et al. The prevention of progression of arterial disease and diabetes (POPADAD) trial: factorial randomised placebo controlled trial of aspirin and antioxidants in patients with diabetes and asymptomatic peripheral arterial disease. *BMJ* 2008; **337**: a1840.

9. Ogawa H, Nakayama M, Morimoto T, et al. Low-dose aspirin for primary prevention of atherosclerotic events in patients with type 2 diabetes: a randomized controlled trial. *JAMA* 2008; **300**(18): 2134-41.

10. Ikeda Y, Shimada K, Teramoto T, et al. Low-dose aspirin for primary prevention of cardiovascular events in Japanese patients 60 years or older with atherosclerotic risk factors: a randomized clinical trial. *JAMA* 2014; **312**(23): 2510-20.

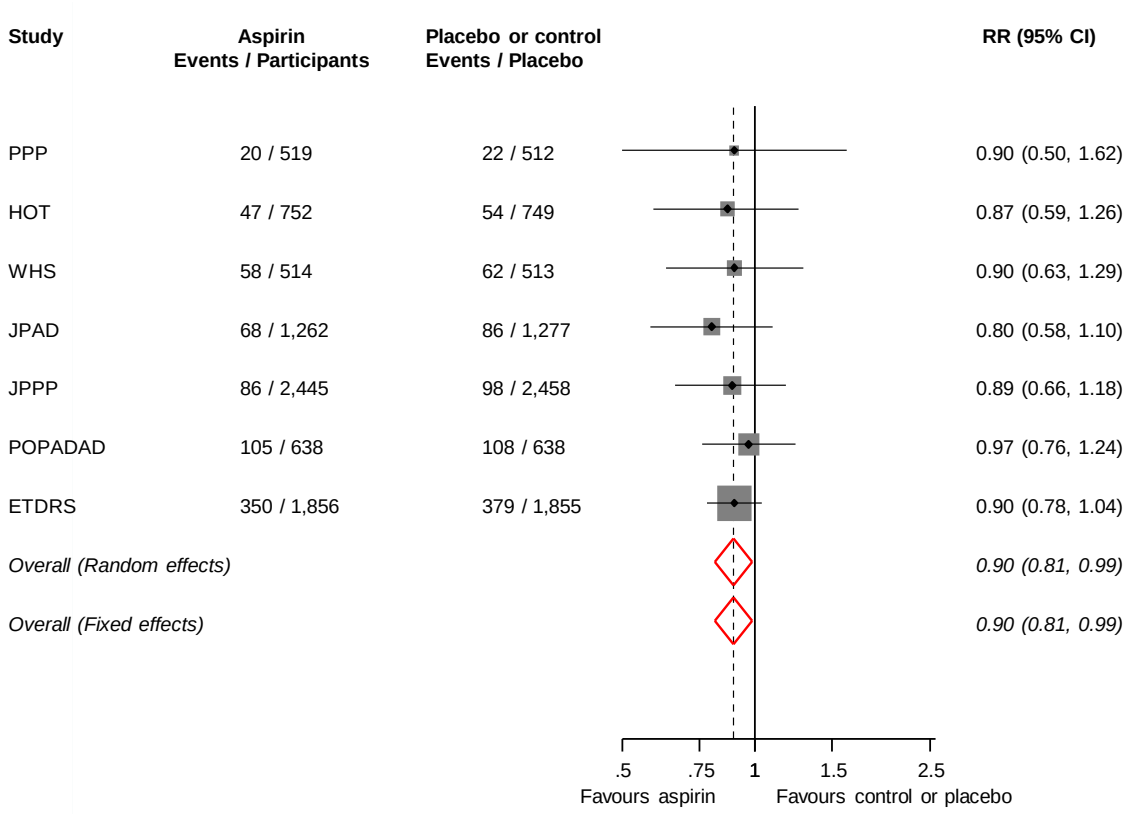
Appendix 4 Assessment of risk of bias

	Random sequence generation	*Allocation concealment*	*Blinding of participants & personnel*	*Blinding of outcome assessments*	*Incomplete outcome data*	*Selective reporting*	*Other bias*
BMD	?	-	-	+	?	-	?
PHS	+	?	+	+	+	-	?
ETDRS	+	?	+	+	+	+	?
TPT	+	+	+	+	+	-	+
HOT	+	+	+	+	+	-	+
PPP	+	+	-	-	+	+	?
WHS	+	?	+	+	+	-	+
POPADAD	+	+	+	+	+	+	+
JPAD	+	+	-	+	+	+	?
JPPP	+	+	-	+	+	-	?

+	Low risk of bias
?	Unclear risk of bias
-	High risk of bias

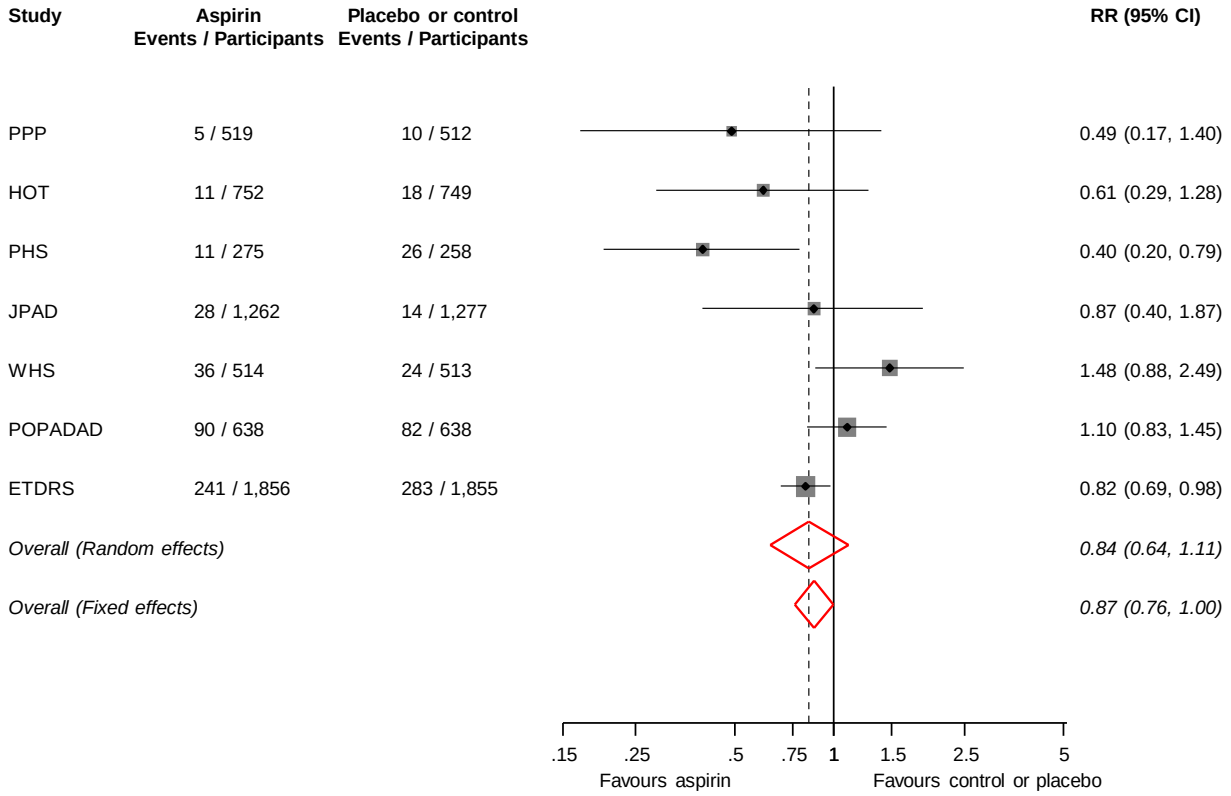
BMD, British male doctors; ETDRS, Early Treatment Diabetic Retinopathy Study; HOT, Hypertension Optimal Treatment; IHD, ischaemic heart disease; JPAD, Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes; JPPP, Japanese Primary Prevention Project; NR, not reported; PHS, Physicians' Health Study; POPADAD, Prevention Of Progression of Arterial Disease And Diabetes; PPP, Primary Prevention Project; WHS, Women's Health Study

Appendix 5 Relative risks of major adverse cardiovascular events in participants with diabetes for aspirin intervention trials



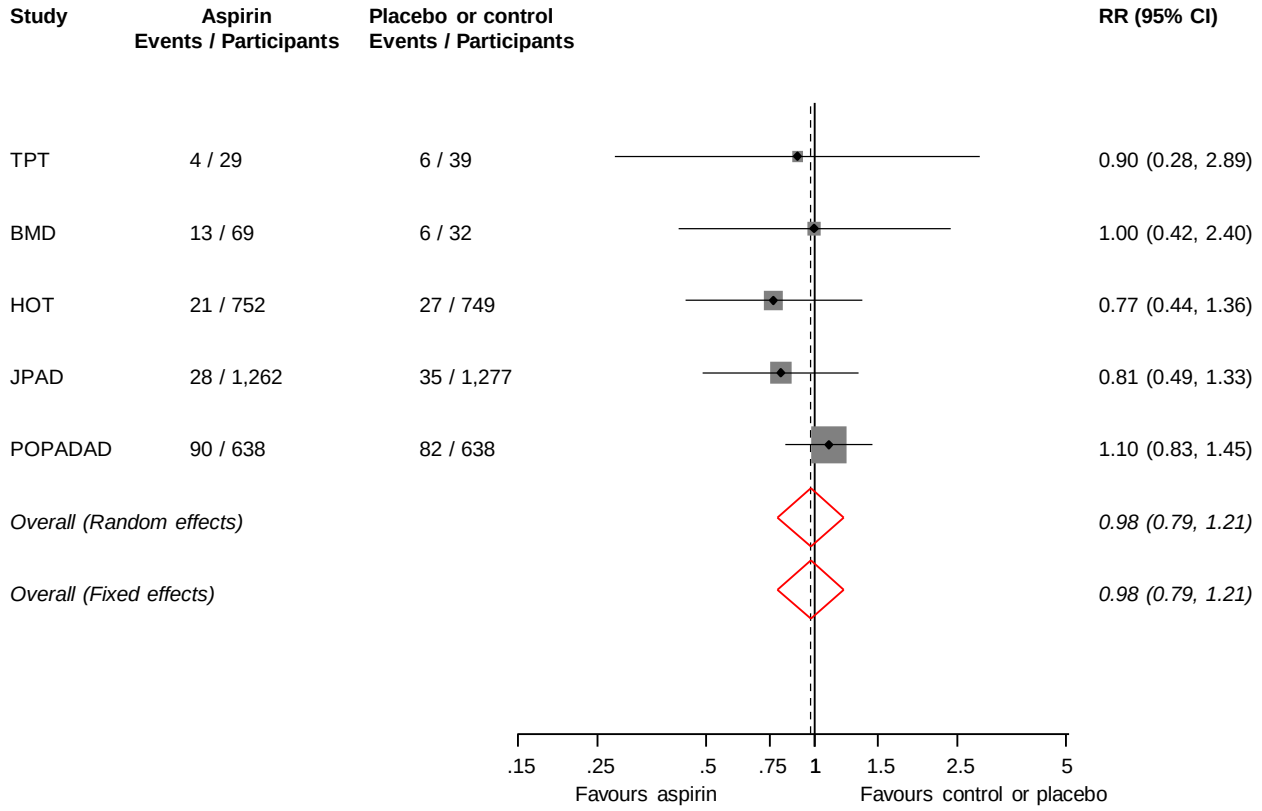
Study acronyms are provided in **Appendix 4**; CI, confidence interval (bars)

Appendix 6 Relative risks of myocardial infarction in participants with diabetes for aspirin intervention trials



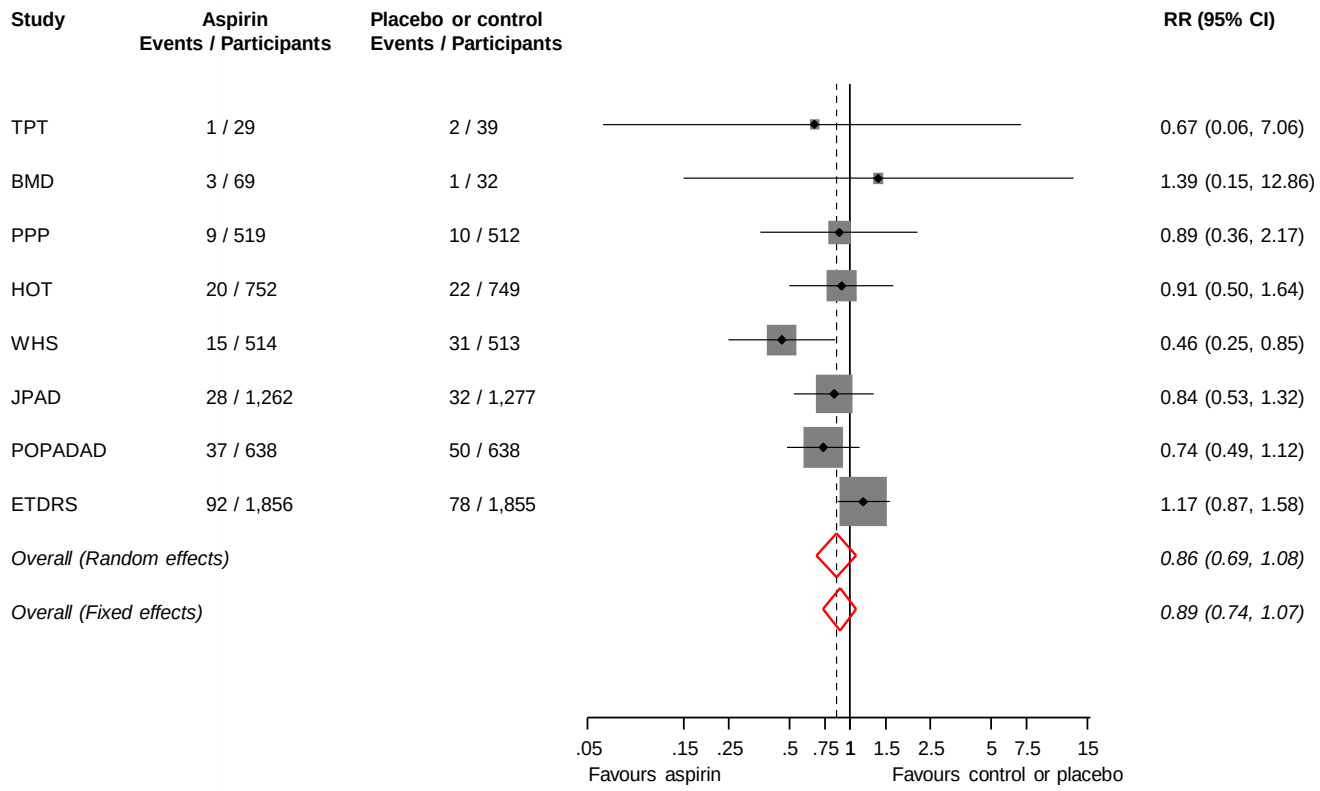
Study acronyms are provided in **Appendix 4**; CI, confidence interval (bars)

Appendix 7 Relative risks of coronary heart disease in participants with diabetes for aspirin intervention trials



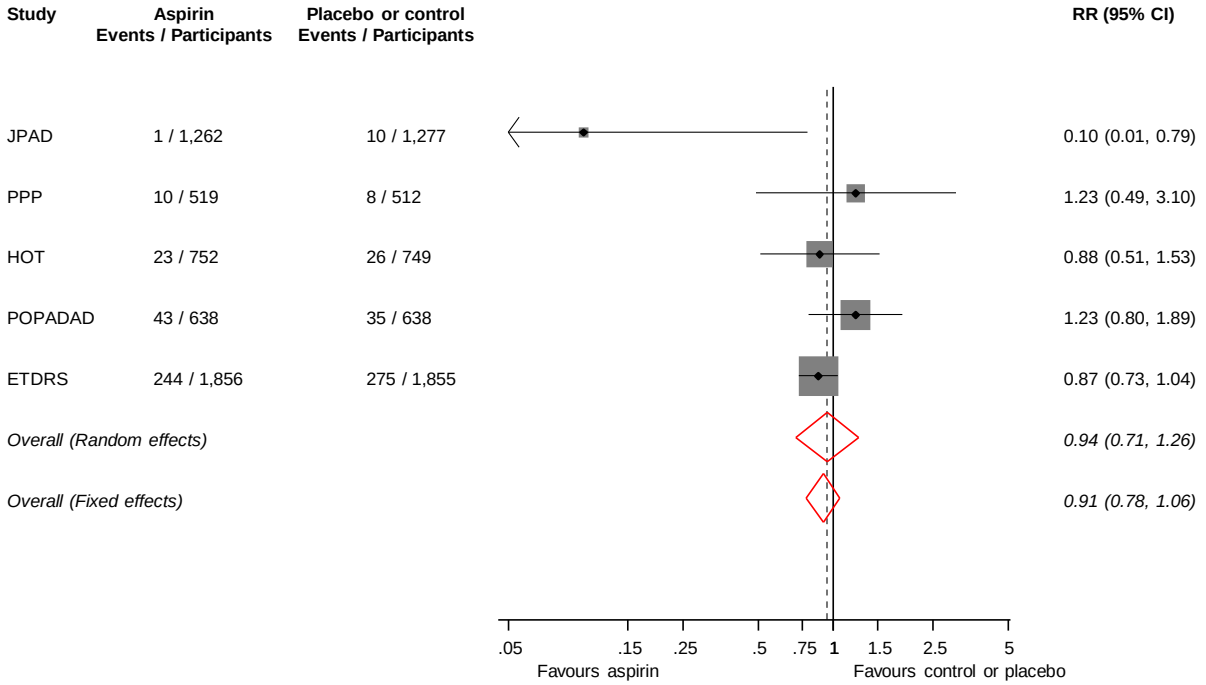
Study acronyms are provided in **Appendix 4**; CI, confidence interval (bars)

Appendix 8 Relative risks of stroke in participants with diabetes for aspirin intervention trials



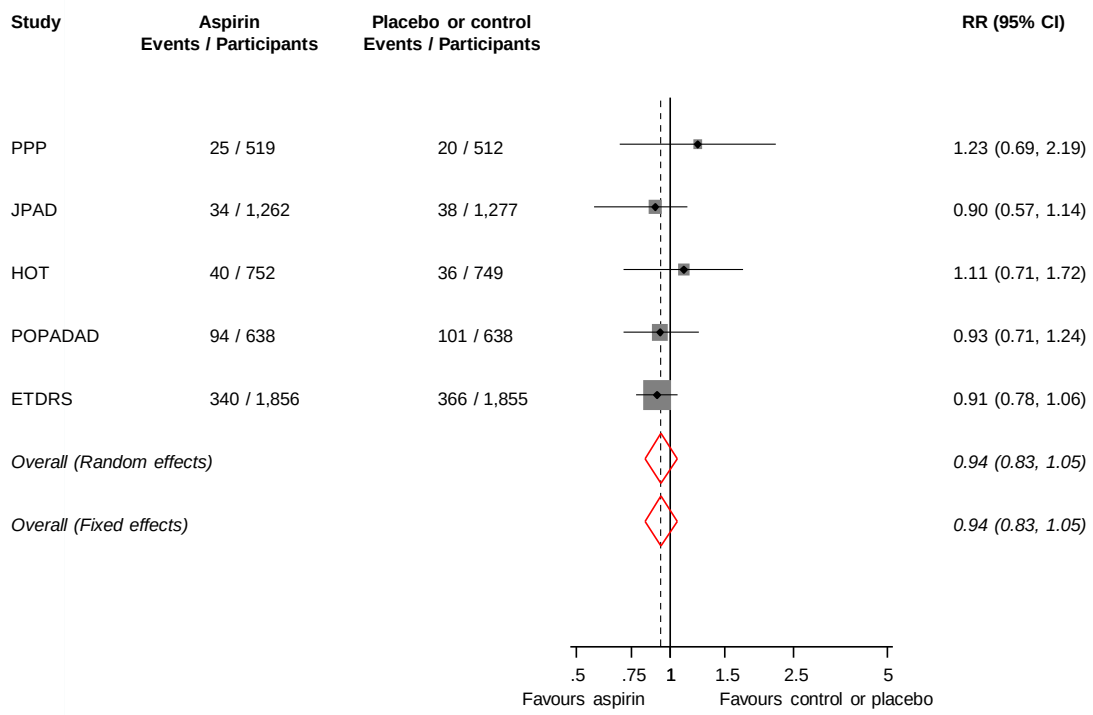
Study acronyms are provided in **Appendix 4**; CI, confidence interval (bars)

Appendix 9 Relative risks of cardiovascular disease mortality in participants with diabetes for aspirin intervention trials



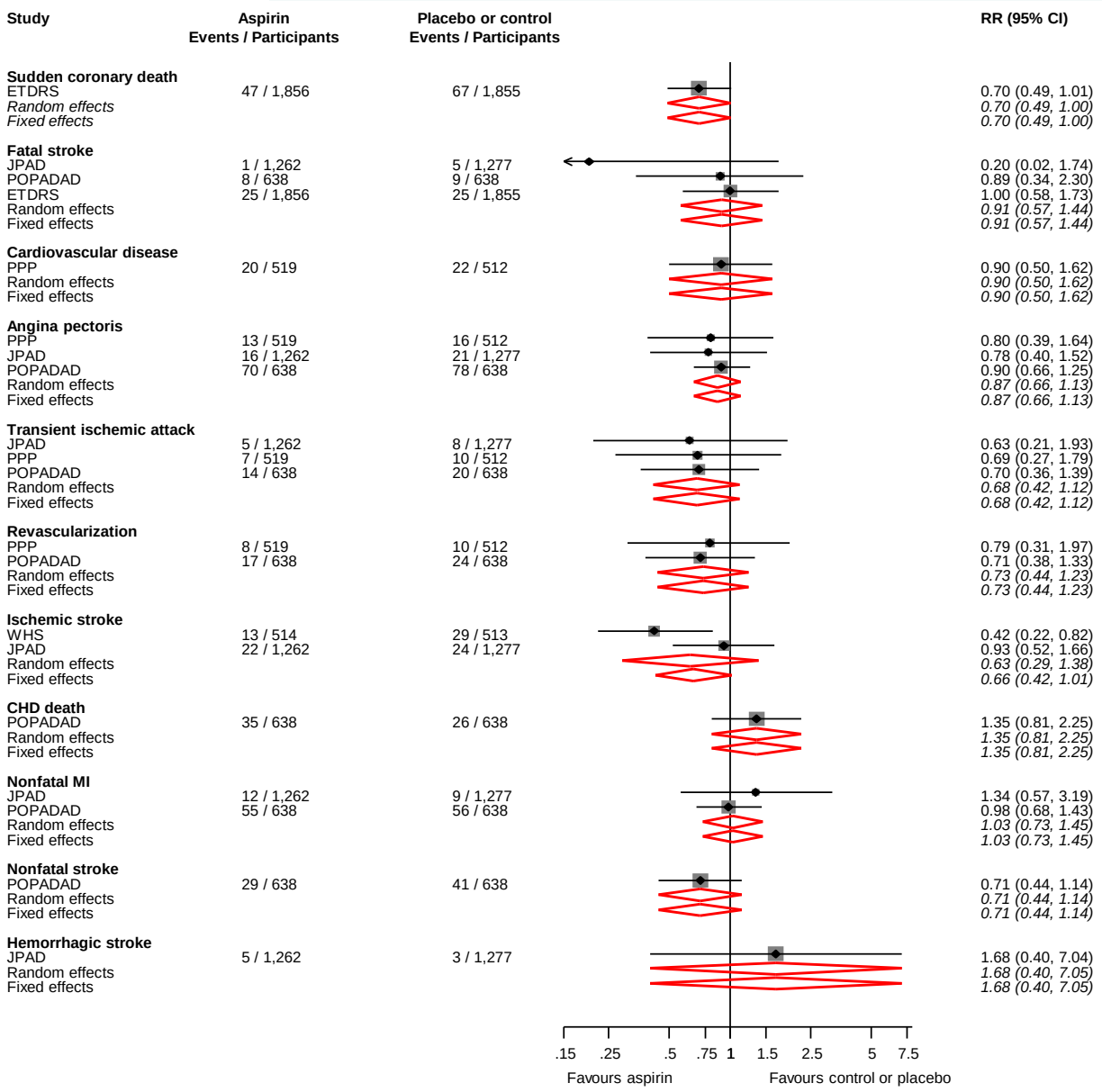
Study acronyms are provided in **Appendix 4**; CI, confidence interval (bars)

Appendix 10 Relative risks of all-cause mortality in participants with diabetes for aspirin intervention trials



Study acronyms are provided in **Appendix 4**; CI, confidence interval (bars)

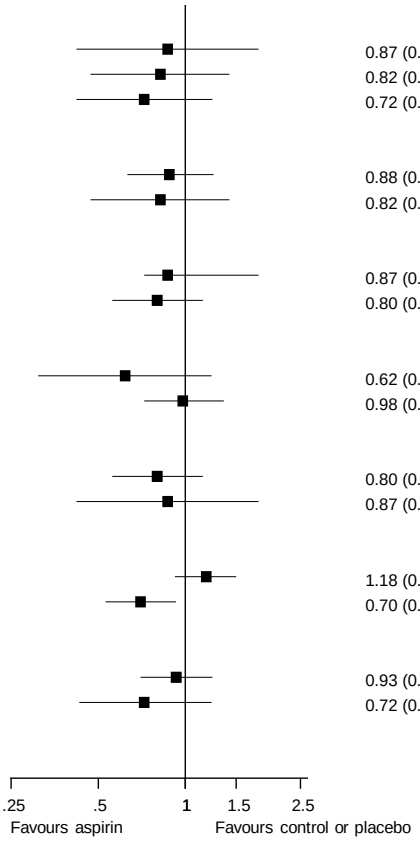
Appendix 11 Relative risks of other cardiovascular outcomes in participants with diabetes for aspirin intervention trials



Study acronyms are provided in **Appendix 4**; CI, confidence interval (bars)

Appendix 12 Effects of aspirin therapy on myocardial infarction in participants with diabetes, according to various characteristics

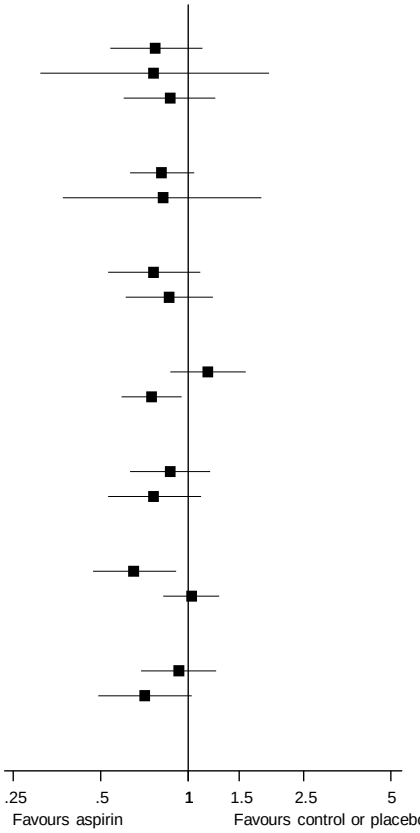
Subgroup	Aspirin Events / Participants	Placebo or control Events / Participants	RR (95% CI)	*P*-value*
Location				
Europe	95 / 1,157	92 / 1,150	0.87 (0.42, 1.79)	.932
North America	288 / 2,645	333 / 2,626	0.82 (0.47, 1.42)	
Other	39 / 2,014	32 / 2,026	0.72 (0.42, 1.24)	
Allocation concealment				
Adequate	134 / 3,171	124 / 3,176	0.88 (0.63, 1.25)	.971
Unclear	288 / 2,645	333/ 2,626	0.82 (0.47, 1.42)	
Baseline CVD risk				
High risk	95 / 1,157	92 / 1,150	0.87 (0.72, 1.79)	.721
Low risk	327 / 4,659	365 / 4,652	0.80 (0.56, 1.15)	
Aspirin dose (mg/day)				
> 100	252 / 2,131	309 / 2,113	0.62 (0.31, 1.23)	.232
≤ 100	170 / 3,685	148 / 3,689	0.98 (0.72, 1.36)	
Compliance (%)				
≥ 90	327 / 4,659	365 / 4,652	0.80 (0.56, 1.15)	.721
< 90	95 / 1,157	92 / 1,150	0.87 (0.42, 1.79)	
Treatment duration (years)				
> 5	126 / 1,152	106 / 1,151	1.18 (0.92, 1.50)	.012
≤ 5	296 / 4,664	351 / 4,651	0.70 (0.53, 0.93)	
No. of events				
> 150	331 / 2,494	365 / 2,493	0.93 (0.70, 1.24)	.454
≤ 150	91 / 3,322	92 / 3,309	0.72 (0.43, 1.23)	



The summary estimates presented were calculated using random effects models; CI, confidence interval (bars);*, *P*-value for meta-regression

Appendix 13 Effects of aspirin therapy on stroke in participants with diabetes, according to various characteristics

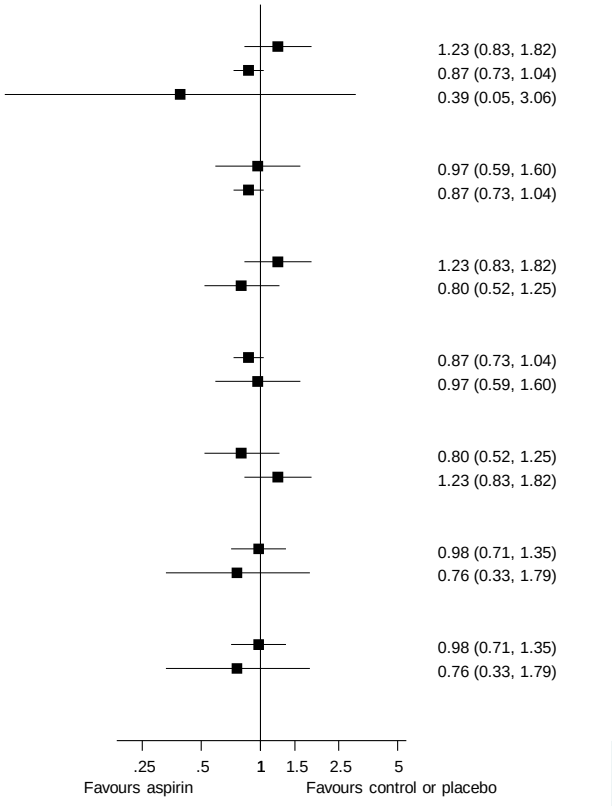
Subgroup	Aspirin Events / Participants	Placebo or control Events / Participants	RR (95% CI)	*P*-value*
Location				
Europe	50 / 1,255	63 / 1,221	0.77 (0.54, 1.12)	.974
North America	107 / 2,370	109 / 2,368	0.76 (0.31, 1.90)	
Other	48 / 2,014	54 / 2,026	0.87 (0.60, 1.24)	
Allocation concealment				
Adequate	95 / 3,200	116 / 3,215	0.81 (0.63, 1.05)	.708
Unclear	110 / 2,439	110 / 2,400	0.82 (0.37, 1.79)	
Baseline CVD risk				
High risk	47 / 1,186	62 / 1,189	0.76 (0.53, 1.10)	.599
Low risk	158 / 4,453	164 / 4,426	0.86 (0.61, 1.22)	
Aspirin dose (mg/day)				
> 100	95 / 1,925	79 / 1,887	1.17 (0.87, 1.58)	.019
≤ 100	110 / 3,714	147 / 3,728	0.75 (0.59, 0.95)	
Compliance (%)				
≥ 90	159 / 4,482	166 / 4,465	0.87 (0.63, 1.19)	.632
< 90	46 / 1,157	60 / 1,150	0.76 (0.53, 1.11)	
Duration (years)				
> 5	56 / 1,250	84 / 1,222	0.65 (0.47, 0.91)	.026
≤ 5	149 / 4,389	142 / 4,393	1.03 (0.82, 1.28)	
No. of events				
≥ 50	157 / 3,756	160 / 3,770	0.93 (0.69, 1.25)	.218
< 50	48 / 1,883	66 / 1,845	0.71 (0.49, 1.03)	



The summary estimates presented were calculated using random effects models; CI, confidence interval (bars);*, *P*-value for meta-regression

Appendix 14 Effects of aspirin therapy on cardiovascular disease mortality in participants with diabetes, according to various characteristics

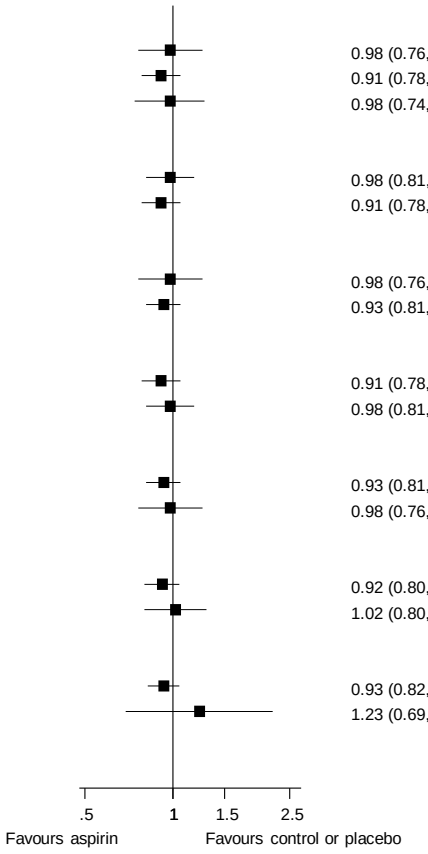
Subgroup	Aspirin Events / Participants	Placebo or control Events / Participants	RR (95% CI)	*P*-value*
Location				
Europe	53 / 1,157	43 / 1,150	1.23 (0.83, 1.82)	.533
North America	244 / 1,856	275 / 1,855	0.87 (0.73, 1.04)	
Other	24 / 2,014	36 / 2,026	0.39 (0.05, 3.06)	
Allocation concealment				
Adequate	77 / 3,171	79 / 3,176	0.97 (0.59, 1.60)	.793
Unclear	244 / 1,856	275 / 1,855	0.87 (0.73, 1.04)	
Baseline CVD risk				
High risk	53 / 1,157	43 / 1,150	1.23 (0.83, 1.82)	.172
Low risk	268 / 3,870	311 / 3,881	0.80 (0.52, 1.25)	
Aspirin dose (mg/day)				
> 100	244 / 1,856	275 / 1,855	0.87 (0.73, 1.04)	.793
≤ 100	77 / 3,171	79 / 3,176	0.97 (0.59, 1.60)	
Compliance (%)				
≥ 90	268 / 3,870	311 / 3,881	0.80 (0.52, 1.25)	.172
< 90	53 / 1,157	43 / 1,150	1.23 (0.83, 1.82)	
Treatment duration (years)				
≥ 5	287 / 2,494	310 / 2,493	0.98 (0.71, 1.35)	.639
< 5	34 / 2,533	44 / 2,538	0.76 (0.33, 1.79)	
No. of events				
≥ 50	287 / 2,494	310 / 2,493	0.98 (0.71, 1.35)	.639
< 50	34 / 2,533	44 / 2,538	0.76 (0.33, 1.79)	



The summary estimates presented were calculated using random effects models; CI, confidence interval (bars);*, *P*-value for meta-regression

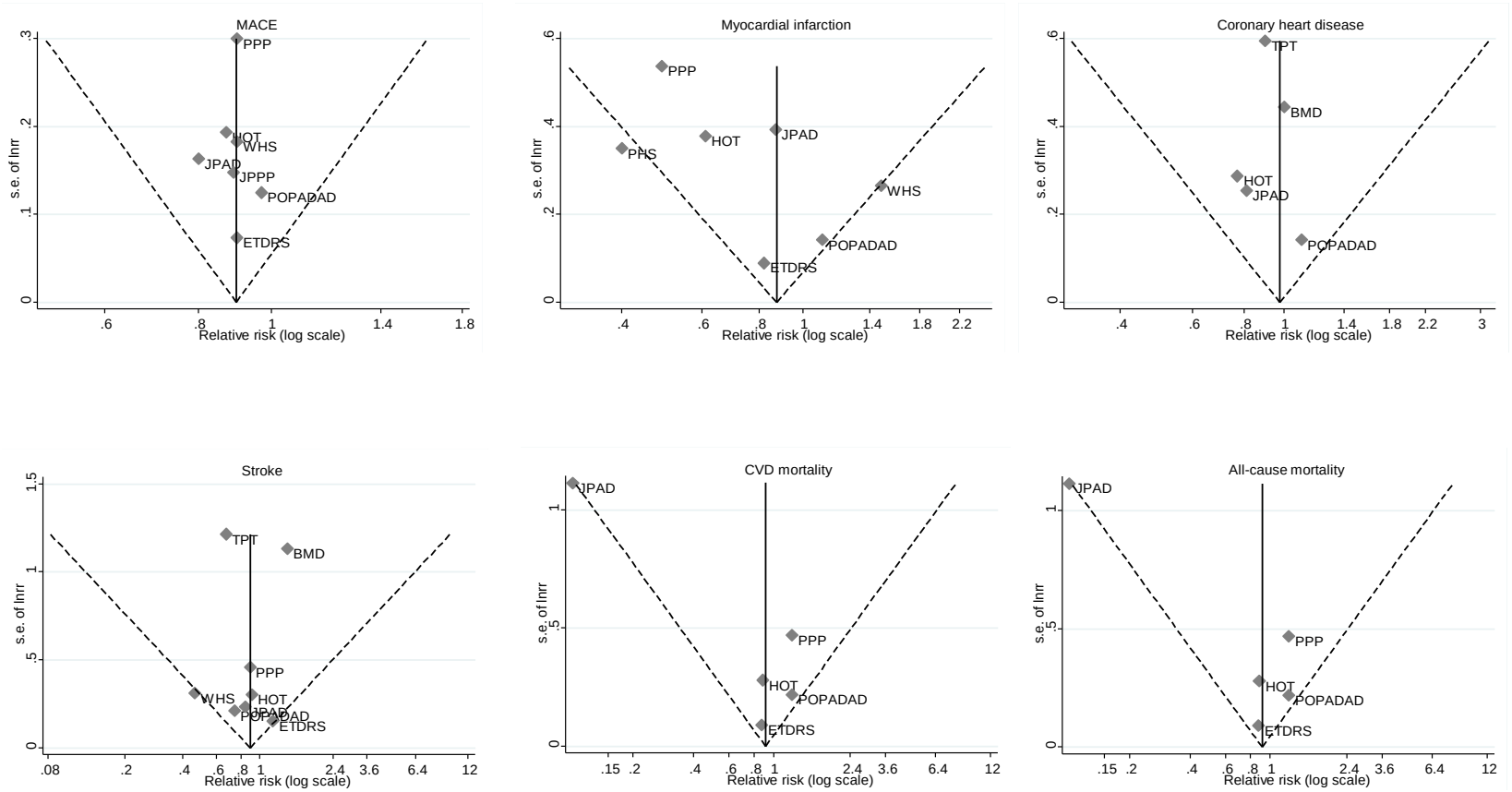
Appendix 15 Effects of aspirin therapy on all-cause mortality in participants with diabetes, according to various characteristics

Subgroup	Aspirin Events / Participants	Placebo or control Events / Participants	RR (95% CI)	*P*-value*
Location				
Europe	119 / 1,157	121 / 1,150	0.98 (0.76, 1.26)	.841
North America	340 / 1,856	366 / 1,855	0.91 (0.78, 1.06)	
Other	74 / 2,014	74 / 2,026	0.98 (0.74, 1.28)	
Allocation concealment				
Adequate	193 / 3,171	195 / 3,176	0.98 (0.81, 1.18)	.557
Unclear	340 / 1,856	366 / 1,855	0.91 (0.78, 1.06)	
Baseline CVD risk				
High risk	119 / 1,157	121 / 1,150	0.98 (0.76, 1.26)	.689
Low risk	414 / 3,870	440 / 3,881	0.93 (0.81, 1.06)	
Aspirin dose (mg/day)				
> 100	340 / 1,856	366 / 1,855	0.91 (0.78, 1.06)	.557
≤ 100	193 / 3,171	195 / 3,176	0.98 (0.81, 1.18)	
Compliance (%)				
≥ 90	414 / 3,870	440 / 3,881	0.93 (0.81, 1.06)	.689
< 90	119 / 1,157	121 / 1,150	0.98 (0.76, 1.26)	
Treatment duration (years)				
≥ 5	434 / 2,494	467 / 2,493	0.92 (0.80, 1.05)	.459
< 5	99 / 2,533	94 / 2,538	1.02 (0.80, 1.30)	
No. of events				
≥ 50	508 / 4,508	541 / 4,519	0.93 (0.82, 1.05)	.346
< 50	25 / 519	20 / 512	1.23 (0.69, 2.19)	



The summary estimates presented were calculated using random effects models; CI, confidence interval (bars);*, *P*-value for meta-regression

Appendix 16 Assessment of small study effects by funnel plots and Egger's regression symmetry tests



Study acronyms are provided in **Appendix 4**; CI, confidence interval (bars)**.** The dotted lines show 95% confidence intervals around the overall summary estimate calculated using a fixed effect model;; *P*-values for bias calculated using Egger's test were 0.599; 0.597; 0.311; 0.462; 0.796; and 0.796 for major adverse cardiovascular events; myocardial infarction; coronary heart disease; stroke; cardiovascular disease mortality; and all-cause mortality