Pros and Cons of Aspirin for the Primary Prevention of Cardiovascular Events: A Secondary Study of Trial Sequential Analysis

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Abstract

Background and aims

Aspirin leads to substantial benefits for the secondary prevention of cardiovascular disease (CVD). We aimed to cast more light on aspirin's role for the primary prevention of CVD.

Methods

Databases were searched for clinical trials comparing aspirin vs. no aspirin use in this meta-analysis. Efficacy and safety profiles were rigorously investigated. Trial sequential analysis (TSA) was used to determine the robustness of the results.

Results

Fourteen studies with 163 840 participants were eligible (mean follow-up 6.2 y). Aspirin intake was found to be associated with 9%, 13%, and 12% reductions in the risk of cardiovascular events (CV events) (relative risk [RR]: 0.91, 95% confidence intervals [CI]: 0.87–0.96), myocardial infarction (RR: 0.87, 95% CI: 0.77–0.97) and ischaemic stroke (RR: 0.88, 95% CI: 0.80–0.96), respectively; aspirin intake was also associated with 40%, 30%, and 57% increases in the risk of major bleeding (RR: 1.40, 95% CI: 1.29–1.53), intracranial bleeding (RR: 1.30, 95% CI: 1.11–1.52) and major gastrointestinal bleeding (RR: 1.57, 95% CI: 1.38–1.78), respectively. Further, populations with low doses of aspirin intake (≤ 100 mg), populations < 65 y old or populations with body mass index (BMI) ≧ 25 experienced more advantages; high-risk (10-y cardiovascular risk ≧ 10%) and full diabetic individuals reported hardly clinical benefits.

Conclusions

Aspirin intake was associated with a reduced risk of CV events and an increased incidence of bleeding profiles in primary prevention. It is necessary to identify individual's CVD risk using clear examinations or assessments before aspirin intake, and truly realize individualized prescription.

Introduction

Currently, many patients are at high risk because their health is influenced by occlusive vascular disease; indeed, a long-term antiplatelet regimen (e.g., aspirin therapy) reduces the yearly risk of worse vascular events (such as nonfatal myocardial infarction, nonfatal stroke and vessel-related death) by almost one-quarter[1]. Distinct benefits are observed with respect to the incidence of non-fatal cardiovascular events (CV events), with a small but definitive absolute risk reduction of approximately 10–20 CV events per 1000 per year. Despite the benefits of aspirin, the absolute risk of major gastrointestinal or other major extracranial bleeding is also increased by an order of magnitude, so in secondary prevention, the benefits exceed the risks[2].

For primary prevention in patients without prior cardiovascular disease (CVD), both the risk without aspirin and absolute benefits of aspirin are smaller than those in secondary prevention. Although rates of death from coronary heart disease (CHD) and stroke in America have significantly decreased, CVD and cerebrovascular disease remain a large health and economic burden[3]. New guidelines suggest that regardless of bleeding risk, the wide use of aspirin is recommended for patients with a moderate risk of CHD, and a low dosage of aspirin (75–100 mg daily) may be reasonably recommended to 40- to 70-year-old adults at high risk of CVD without increasing major bleeding (IIb grade). New guidelines also recommended that age should be considered as a key determinant of the CVD risk, as a daily dose aspirin (alone or in combination with other drugs) has been recommended for all people above a specific age. Low doses of aspirin should not be recommended as primary prevention for 70-year-olds or for individuals with a high risk of bleeding[3–11]. However, a moderate risk of CVD is hard to define, and whether the high CVD risk populations as well as the diabetic populations can get real benefits from aspirin or not.

Deferring the start of long-term aspirin use for primary prevention is a noted alternative that has the main advantage of avoiding an increased risk of slight or major bleeding events but has the disadvantage that the initial manifestation may be a disabling or fatal event. In previous primary prevention trials[12–25], control populations with non-fatal CVD (non-fatal CHD or non-fatal occlusive stroke) would probably be prescribed long-term aspirin use to avoid recurrence, hence helping to compare the efficacy of immediate versus deferred aspirin use.

A previous meta-analysis[26] noted that aspirin reduced all-cause mortality, myocardial infarction (MI), and ischaemic stroke while increasing the risk of major bleeding; another pooled study[27] showed that aspirin reduced nonfatal MI but did not significantly influence all-cause mortality. Above mentioned studies had heterogeneous results on all-cause mortality because they had involved different number of trials conducted in different time. Another key controversial point was on individuals' CVD risk classification that whether the higher risk individuals or the lower risk individuals could derive real prevention benefits from aspirin discussed by various guidelines or researchers. Actually, there are some meta-analysis discussing this topic emerging yearly, not so many addressed their "cost-effectiveness", which is to say if the conclusions are statistically sufficent and robust, no repetitive meta-analyses or further evidence are needed to some extent so that saving the cost on public health.

Given the large number of individuals affected by current studies and guidelines, and less helpful of the impact from no-innovative work on global health policy making, we conducted a comprehensive meta-analysis with the aim to resolve clinical controversial points under intention-to-treat principles and to evaluate the sufficiency of current synthesized evidence using trial sequential method.

Methods

The current study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (**Appendix Table S1**). The protocol is available in PROSPERO (**CRD42019127570**).

Data Source And Study Selection

A rigorous search was performed in the PubMed, EMBASE, Cochrane Library, Web of Science and ClinicalTrials.gov databases from inception to February 1, 2020, to retrieve randomized controlled trials (RCTs) relating to aspirin use in patients without prior CVD. The search had no language restrictions. The main key words used were “aspirin”, “cardiovascular disease”, “cardiovascular events”, “coronary heart disease”, and “randomized controlled trials”. Reference lists of the eligible studies and identified meta-analyses were also reviewed (**Appendix File S1**).

The inclusion criteria were as follows: (1) enrolled adult participants (≥ 18 y) without preexisting CV events (CV events here include peripheral arterial disease, CHD, prior myocardial infarction (MI), ischaemic stroke, prior percutaneous coronary intervention, prior coronary artery bypass grafting); (2) compared aspirin use to no aspirin use (placebo included); (3) had a follow-up no less than 1 year to confirm the high quality of primary studies; (4) provided reliable and available outcome data (at least one primary efficacy outcome of interest was reported); and (5) was an RCT.

Studies with the most comprehensive outcomes were included to avoid duplications; studies that assessed patients with diabetes but without atherosclerosis were also considered. JPAD[19] and JPAD2[22] trials were both included for they had different characteristics and proportion of the incorporated individuals as well as the differed follow-up. We excluded pure basic studies, reviews, and animal experiments.

Data Extraction And Outcome Definition

Two authors (Binghao Zhao, Yiping Wei) independently performed the study screening and extracted the baseline characteristics of each eligible trial. The baseline characteristics included demographic characteristics of included populations, clinical information about the intervention/control arms, and essential outcome data as well as the study design. The adjusted hazard ratio (HR), odds ratio (OR) and relative risk (RR) of analysed outcomes were adjusted for fully adjusted models. If some studies used intention-to-treat principles, we extracted the intention-to-treat data. Any discrepancies between the reviewers were resolved by a third author. If there were any missing data, the original authors were contacted.

The primary efficacy outcomes were CV events, all-cause mortality and cardiovascular mortality due to their universal definitions and balance of efficacy and safety, which reduce heterogeneity among eligible studies. The secondary efficacy outcomes were all MI, total stroke, ischaemic stroke, cancer incidence and cancer mortality. The safety profile outcomes were major bleeding, intracranial bleeding and major gastrointestinal bleeding, as defined by each eligible trial. Intracranial bleeding was treated as a potential outcome of aspirin use in addition to CV events. All these definitions follow per included study’s definition[10].

Some studies even noted that aspirin increased the probability of cancer mortality, therefore, cancer outcomes were also appointed as exploratory outcome for robust evidence. The 10-y major adverse cardiovascular event rate (10-y MACE%) was extracted and calculated by multiplying the annualized event rate for cardiovascular mortality, nonfatal MI, and nonfatal stroke. A 10-y MACE% ≥ 10% was regarded as high risk; the others were regarded as low risk (**Appendix File S1**).

Study Quality Assessment

Methodological quality assessment was performed by three co-authors (Binghao Zhao, Li Wang, Wenxiong Zhang). We used the Cochrane Risk and Bias Tool[28] recommended by the Cochrane handbook to evaluate the quality of each eligible study. There were several terms regarding the methodological quality of RCTs, and each study could be categorized as low, high or unclear quality; low-quality studies and those with unclear quality had a high risk of bias. Details are provided in the **Appendix File S1**.

Statistical analysis

For descriptive purposes and statistical convenience, weighted frequencies were calculated for categorical variables using the provided sample size of each trial. Multivariable RRs and 95% confidence intervals (95% CIs) as well as prediction intervals (represented by credible intervals, CrIs)[29] for primary/secondary efficacy outcomes of interest and primary safety outcomes were estimated using the DerSimonian-Laird (D-L) random effects model considering the existence of within- and between-study variability. For further statistical purposes, HRs and ORs were considered RRs in this study. Fully adjusted effect sizes (ESs) were logarithmically transformed to stabilize the variance; hence, the data distribution could be normalized.

Between-study heterogeneity and variability were quantified by Cochran’s Q test and I^2, whereby an $I^2 > 50\%$ or a P-value for the Q test < 0.10 was considered to represent significant heterogeneity[30]. To provide more clinical implications, we conducted comprehensive subgroup analyses mainly focusing on several significant variables, including region, individuals’ main age, mean body mass index (BMI), aspirin dose taken and 10-y MACE%. For 10-y MACE%, the computed value of 10-y MACE% < 10% was defined as low risk, but the other populations were high risk. To provide more useful clinical data as well as to investigate the influence of individual studies on final results, we carried out sensitivity analyses by omitting one study each turn.

Publication bias was assessed by funnel plots and Egger's test[31], with $P < 0.05$ indicating significant bias. All analyses were performed using *R* project software (version 3.5.3, https://www.r-project.org/, USA) and other public packages (forest, ggplot2, survival, survminer etc.); a two-sided $P < 0.05$ was considered statistically significant except where otherwise specified. More details are provided in the **Appendix File S1**.

Trial Sequential Analysis

Previous studies have confirmed that the risk of type 1 error from interim analyses can be reasonably reduced through monitoring boundaries and modifying the *P*-value. Similar in meta-analyses, random errors caused by sparse data and repetitive testing also enhance the risk of type 1 error. Such a method setting analogous trial sequential monitoring boundaries to meta-analyses is called trial sequential analysis (TSA), is used to determine whether evidence is reliable or conclusive[32, 33]. Actually, random errors can be rectified and reduced using TSA software (version 0.9 beta (http://www.ctu.dk/tsa)) because it combines the estimation of the required information size (RIS) with an adjusted threshold for statistical significance. We assumed that if the Z-curve crossed the TSA boundary or entered the futility area, a sufficient effect was obtained, and further studies were not required; otherwise, the amount of evidence was considered insufficient. TSA was performed for a 10% relative risk reduction, conservatively, according to the TSA manual; there was also a 5% ($\alpha = 0.05$; two-sided) risk of a type 1 error and 80% statistical power. Other parameters were set empirically following default settings.

Results

Study selection and characteristics

Among 1 441 searched articles, we identified 26 studies for full-text review, of which 14 studies were eligible for qualitative and quantitative analyses (**Appendix Figure S1**). The 14 included studies[12–25] encompassed a total of 163 840 patients and used intention-to-treat principles. The detailed study characteristics are summarized in Table 1.

Table 1
Characteristics of included studies and participants.

Publication	Study population	Number of population	Mean age y/ Male (%)	Aspirin use (mg/day)	Control group	Diabetes No. (%)	Current smokers NO. (%)	Hypertension NO. (%)	Mean SBP (mean ± SD) mmHg	Total Cholesterol (mean ± SD) mmol/L	BM
Peto 1988; UK, (BDS)[12]	Male physicians	5139 (3429/1710)	61/ 5139 (100)	300 or 500	No aspirin	101 (2)	661 (13)	508 (10)	136 ± 17	NA	24 ± 2
Steering 1989; America, (PHS)[13]	Male physicians	22071 (11037/11034)	53/ 22071 (100)	325	Placebo	533 (2)	2438 (11)	5297 (24)	126 ± 12	5.5 ± 1.2	24 ± 3
Meade 1998; UK, (TPT)[14]	Males in the top 20–25% risk of CV events	2540 (1268/1272)[c]	57/ 2540 (100)	75	Placebo	51 (2)	83 (3)	278 (11)	139 ± 18	6.4 ± 1.0	27 ± 3
Hansson 1998; multi-nations, (HOT)[15]	Hypertensive populations	18790 (9399/9391)	61/ 9959 (53)	75	Placebo	1503 (8)	2988 (16)	18790 (100)	170 ± 14	6.0 ± 1.1	28 ± 4
De Gaetano 2001; Italy, (PPP)[16]	Populations with ≥ 1 CV risk factor	4495 (2226/2269)	64/ 1912 (42)	100	No aspirin	742 (17)	667 (15)	3065 (68)	145 ± 16	6.1 ± 1.2	27 ± 4
Ridker 2005; America, (WHS)[17]	Healthy females	39876 (19934/19942)	54/ 0 (0)	100	Placebo	1037 (3)	5224 (13)	10328 (26)	NA	5.2 ± 1.0	26 ± 5
Belch 2008; UK, (POPADAD)[18]	Diabetic populations (ABPI ≤ 0.99)	1276 (638/638)	60/ 563 (44)	100	Placebo	1276 (100)	NA	NA	145 ± 21	5.5	29
Ogawa et al, 2008; Japan, (JPAD)[19]	Diabetic populations	2539 (1262/1277)	65/ 1387 (55)	81 or 100	No aspirin	2539 (100)	537 (21)	1473 (58)	135 ± 15	5.2 ± 0.9	24 ± 4
Fowkes 2010; UK, (AAA)[20]	Populations with ≤ 0.95 ABPI	3350 (1675/1675)	62/ 954 (28)	100	Placebo	88 (3)	1085 (32)	NA	148 ± 22	6.2 ± 1.1	NA
Ikeda 2014; Japan. (JPPP)[21]	Hypertensive, hyperlipidemic or diabetic populations	14464 (7220/7244)	71/ 6123 (42)	100	No aspirin	4903 (34)	1893 (13)	12278 (85)	137 ± 16	5.3 ± 0.8	24 ± 3
Saito et al, 2017; Japan, (JPAD2)[22]	Diabetic populations	2160 (992/1168)	65/ 1195 (55)	81 or 100	No aspirin	2160 (100)	459 (21)	2142 (58)	135 ± 15	5.2 ± 0.9	24 ± 4
Bowman 2018; UK, (ASCEND)[23]	Diabetic populations	15480 (7740/7740)	63/ 9684 (63)	100	Placebo	15480 (100)	1279 (8)	9533 (62)	136 ± 15	4.2 ± 0.9	30 ± 6
Gaziano 2018; multi-nations, (ARRIVE)[24]	Males with ≥ 2 and females with ≥ 3 CV risk factors, with 10–20% 10-y MACE risk	12546 (6270/6276)	64/ 8838 (70)	100	Placebo	0 (0)	3594 (29)	7866 (63)	144 (90–199)[e]	NA	28 ± 4
McNeil 2018; multi-nations, (ASPREE)[25]	≥ 65 y populations	19114 (9525/9589)	74/ 8331 (44)	100	Placebo	2057 (11)	735 (4)	14283 (74)	140 ± 17	5.3 ± 1.0	28 ± 4

Abbreviations: SBP: systolic blood pressure; BMI: body mass index; MACE: major adverse cardiovascular events; CV risk: cardiovascular risk; ABPI: ankle-brac myocardial infraction; NA: not available.

Two studies[13, 17] were conducted in America, 6 studies were conducted in Europe (5[12, 14, 18, 20, 23] in the UK and 1[16] in Italy), 3 studies[19, 21, 22] were performed in Japan, and 3 studies[15, 24, 25] were performed in multiple nations. The comparator treatment was a placebo group in 9 studies[13–15, 17, 18, 20, 23–25] and was a no aspirin group in 5 studies. Of note, in addition to aspirin and placebo, 6 studies used a factorial design, in which 1[14] study used warfarin, 2[16, 17] used vitamin E, 1[23] prescribed n-3 fatty acid, 1[18] used antioxidants, and 1[12] supplied anti-hypertension drugs. Three studies[12–14] exclusively enrolled male individuals (29 750 males), and 1 study[17] specially enrolled female individuals (39 876 females). Across the included studies, 78 696 (48%) patients were males. Four studies[18, 19, 22, 23] exclusively enrolled diabetic patients (including type I and type II diabetes). The mean BMI of eligible participants was 28.5, and the mean

10-y MACE% was 7.24. The median duration was 8.1 y (4[16] to 13[14, 22]), and the mean follow-up was 6.2 y. The studies were published between 1988[12] and 2018[23–25]. All studies were written in English, and there was no attempt to ask the primary authors for raw data.

Methodological quality assessment

Of the 14 included studies, 9 studies used double-blind methods and 5 studies[12, 16, 19, 21, 22] used open-label settings. Three studies[13, 14, 16] had selective reporting or other bias. Of the included studies, 7[15, 17, 18, 20, 23-25] were of low risk and 7[12-14, 16, 19, 21, 22] were of high risk (**Appendix Figure S2** and **Appendix Table S2**).

The Primary Efficacy Outcomes

For the primary efficacy outcomes, twelve studies[12, 13, 15–17, 19–25] involving 160 024 individuals reported CV event outcomes, and we found that the use of aspirin was associated with a 9% reduction in CV events (RR: 0.91, 95% CI: 0.87–0.96; P < 0.001; prediction interval: 0.91, 95% CrI: 0.86–0.96) compared to no aspirin use, and there was no significant heterogeneity (I^2 = 0; P = 0.64). Thirteen studies[12–21, 23–25] including 161 680 individuals examined all-cause mortality outcomes; aspirin use did not lead to a significant reduction in all-cause mortality (RR: 0.97, 95% CI: 0.93–1.02; P = 0.22; prediction interval: 0.97, 95% CrI: 0.92–1.02), and there was no heterogeneity (I^2 = 0; P = 0.60). Fourteen studies[12–25] (163 840 participants) examined cardiovascular mortality; aspirin use was not significantly associated with cardiovascular mortality reduction (RR: 0.95, 95% CI: 0.87–1.03; P = 0.23; Prediction interval: 0.95, 95% CrI: 0.86–1.04), and there was no significant heterogeneity (I^2 = 0; P = 0.57) (Fig. 1).

The Secondary Efficacy Outcomes

Regarding the secondary efficacy outcomes, fourteen studies[12–25] with 163 840 individuals revealed that aspirin intake was associated with a 13% reduction in all MIs (RR: 0.87, 95% CI: 0.77–0.97; P = 0.02; prediction interval: 0.87, 95% CrI: 0.60–1.26), and there was significant heterogeneity (I^2 = 58%; P < 0.01). Eleven studies[12–14, 16, 17, 19–23, 25] (131 228 individuals) revealed that aspirin intake was associated with a 12% risk reduction in ischaemic stroke (RR: 0.88, 95% CI: 0.80–0.96; P < 0.01; prediction interval: 0.88, 95% CrI: 0.79–0.98), and there was no significant heterogeneity (I^2 = 0; P = 0.62). Fourteen studies[12–25] (163 840 individuals) revealed that aspirin use was not significantly associated with total stroke (RR: 0.94, 95% CI: 0.88–1.02; P = 0.13; Prediction interval: 0.94, 95% CrI: 0.87–1.02), and there was no significant heterogeneity (I^2 = 0; P = 0.59).

Furthermore, we explored the cancer outcomes. Ten studies[12, 15–21, 23, 25] including 124 523 participants and 12 studies[12–21, 23, 25] including 149 134 participants reported cancer incidence and cancer mortality, respectively. There was no significant difference in cancer incidence (RR: 1.00, 95% CI: 0.95–1.06; P = 0.87; prediction interval: 1.00, 95% CrI: 0.88–1.15) or cancer mortality (RR: 1.03, 95% CI: 0.94–1.12; P = 0.87; prediction interval: 1.03, 95% CrI: 0.86–1.22) between the aspirin use and no aspirin use groups, and there was no significant heterogeneity (I^2 = 36%, P = 0.12; I^2 = 21%, P = 0.24, respectively). Aspirin showed the potential to increase the risk of cancer mortality (**Appendix Figure S3**).

The safety profile outcomes

Safety profiles outcomes included major bleeding, intracranial bleeding and major gastrointestinal bleeding. Twelve studies[12-17, 19-23, 25] including 150 397 patients examined major bleeding events; aspirin use was found to significantly increase the risk of major bleeding by 40% (RR: 1.40, 95% CI: 1.29-1.53; P < 0.01; prediction interval: 1.40, 95% CrI: 1.27-1.54), and there was no significant heterogeneity (I^2 = 0%; P = 0.54). Thirteen studies[12-17, 19-25] (162 934 participants) examined intracranial bleeding; aspirin use was associated with a 30% increase in intracranial bleeding (RR: 1.30, 95% CI: 1.11-1.52; P < 0.01; prediction interval: 1.30, 95% CrI: 1.09-1.55), and there was no heterogeneity (I^2 = 0%; P = 0.84). Eleven trials[13-17, 19, 20, 22-25] (143 340 participants) examined major gastrointestinal bleeding; aspirin intake was associated with a 57% increase in major gastrointestinal bleeding (RR: 1.57, 95% CI: 1.38-1.78; P < 0.01; prediction interval: 1.57, 95% CrI: 1.36-1.82), and there was no heterogeneity (I^2 = 0%; P = 0.57). The finding that aspirin use significantly increased the risk of bleeding events led us to identify the proper indicators for balancing the benefits and harm of clinical routines (**Figure 2**).

Subgroup analysis for further clinical implications

Subgroups involving region, mean age, mean BMI, aspirin dosage in the intervention arm and 10-y MACE% were constructed, and subgroup analyses were performed (**Table 2**). We observed that populations with a dosage of ≤ 100 mg/d experienced more benefits with respect to CV events, MI, total stroke and ischaemic stroke than those with a dosage > 100 mg/d. Individuals with a BMI ≧ 25 seemed experience more aspirin-induced benefits with respect to cardiovascular and cerebrovascular outcomes (CV events, RR: 0.91, 95% CI: 0.86-0.98; total stroke, RR: 0.90, 95% CI: 0.82-0.99; ischaemic stroke, RR: 0.85, 95% CI: 0.76-0.95) than individuals with a BMI < 25 with similar bleeding events. Aspirin-induced cardiovascular benefits were consistently found in participants with a mean age < 65 y; however, they were not as robust in the patients with a mean age ≥65 y, with only one statistically significant outcome for CV events (RR: 0.90, 95% CI: 0.81-1.00). Participants with a low 10-y MACE% risk had the potential to obtain more cardiovascular advantages from aspirin use than those with a high 10-y MACE% risk. There was no significant difference in cardiovascular outcomes and bleeding events between patients from different regions. Across the subgroup analyses, aspirin still had no statistically significant effects on cancer incidence or mortality. All of the above results are presented in **Table 2**.

Table 2
Summarized results of total and subgroup analyses.

Items/Outcomes†	Total	By region				By mean age (y)		By mean BMI		By aspirin dose (mg)		By 10 MACE
		North America	Europe	Asia	Multiple nations	< 65	≧ 65	< 25	≧ 25	≤ 100	> 100	Low risk
CV events	0.91 (0.87-0.96)	0.88 (0.80-0.97)	0.94 (0.86-1.03)	0.97 (0.85-1.10)	0.90 (0.82-0.98)	0.92 (0.87-0.97)	0.90 (0.81-1.00)	0.91 (0.84-0.99)	0.91 (0.86-0.98)	0.92 (0.87-0.97)	0.91 (0.75-1.10)	0.89 (0.84-0.96)
All-cause mortality	0.97 (0.93-1.02)	0.95 (0.87-1.05	0.94 (0.88-1.01	0.98 (0.84-1.13)	1.03 (0.91-1.17)	0.95 (0.90-1.00)	1.06 (0.95-1.18)	0.94 (0.87-1.03	0.99 (0.92-1.06)	0.98 (0.93-1.03	0.93 (0.81-1.06)	1.00 (0.92-1.08)
Cardiovascular mortality	0.95 (0.87-1.03)	0.96 (0.79-1.17)	0.97 (0.85-1.11)	0.76 (0.31-1.90)	0.90 (0.77-1.07)	0.96 (0.88-1.06)	0.82 (0.53-1.29)	0.97 (0.84-1.12	0.92 (0.83-1.03	0.94 (0.85-1.03)	0.99 (0.80-1.23	0.91 (0.79-1.04)
All MI	0.87 (0.77-0.97)	0.78 (0.45-1.34	0.95 (0.86-1.05)	0.89 (0.69-1.16)	0.81 (0.66-1.01	0.87 (0.76-1.00)	0.90 (0.75-1.08)	0.78 (0.61-0.99)	0.93 (0.86-1.02)	0.91 (0.83-0.99)	0.78 (0.44-1.38)	0.81 (0.66-1.00)
Total stroke	0.94 (0.88-1.02)	0.99 (0.69-1.43)	0.89 (0.78-1.01	0.99 (0.82-1.18)	1.00 (0.87-1.14)	0.94 (0.86-1.02)	0.97 (0.84-1.13)	1.04 (0.92-1.17)	0.90 (0.82-0.99)	0.92 (0.85-1.00)	1.16 (0.94-1.44	0.97 (0.86-1.11)
Ischaemic stroke	0.88 (0.80-0.96)	0.91 (0.64-1.29)	0.89 (0.76-1.03)	0.88 (0.71-1.10)	0.89 (0.72-1.11)	0.88 (0.78-1.00)	0.88 (0.74-1.04)	0.98 (0.82-1.16)	0.85 (0.76-0.95)	0.85 (0.78-0.94)	1.14 (0.86-1.52)	0.87 (0.76-0.98)
Cancer incidence	1.00 (0.95-1.06)	1.01 (0.94-1.08)	0.98 (0.91-1.06)	1.06 (0.79-1.42)	1.01 (0.94-1.09)	0.99 (0.94-1.04)	1.05 (0.92-1.21)	1.02 (0.88-1.19)	1.01 (0.97-1.06)	1.02 (0.96-1.07)	0.91 (0.77-1.08)	1.05 (0.98-1.13)
Cancer mortality	1.03 (0.94-1.12)	1.00 (0.84-1.18)	0.94 (0.84-1.05)	1.07 (0.88-1.30)	1.18 (0.94-1.48)	0.97 (0.89-1.05)	1.19 (1.04-1.36)	1.03 (0.90-1.18)	1.04 (0.91-1.19)	1.03 (0.95-1.12)	0.97 (0.68-1.40)	1.11 (0.96-1.27)
Major bleeding	1.40 (1.29-1.53)	1.44 (1.15-1.82)	1.46 (1.10-1.95	1.35 (1.10-1.67)	1.49 (1.18-1.88)	1.39 (1.21-1.59)	1.42 (1.25-1.62)	1.47 (1.26-1.71)	1.36 (1.21-1.53)	1.39 (1.28-1.52)	1.40 (0.92-2.12)	1.42 (1.27-1.60)
Intracranial bleeding	1.30 (1.11-1.52)	1.40 (0.96-2.05)	1.26 (0.91-1.74)	1.21 (0.82-1.77)	1.18 (0.77-1.80)	1.18 (0.96-1.47)	1.46 (1.15-1.84)	1.25 (0.95-1.65)	1.31 (1.08-1.60)	1.28 (1.08-1.51)	1.57 (0.89-2.77	1.40 (1.15-1.70)
Major gastrointestinal bleeding	1.57 (1.38-1.78)	1.47 (1.17-1.86)	1.61 (1.02-2.54)	1.87 (1.02-3.44)	1.72 (1.40-2.11)	1.58 (1.35-1.85)	1.58 (1.24-2.01)	1.92 (1.47-2.51)	1.49 (1.28-1.72)	1.55 (1.36-1.77)	1.75 (1.10-2.78)	1.57 (1.33-1.85)

Abbreviations: BMI: body mass index; MACE: major adverse cardiovascular event rate; CV event: cardiovascular event; MI: myocardial infraction.

* A 10-y MACE% of at least 10% was regarded as high CV risk and less than 10% was low; † All the outcomes were shown in RR and 95% CI form.

Sensitivity analysis

In sensitivity analyses, many variables were classified into different subgroups. To better eliminate bias and heterogeneous interactions (TPT[14] trial was excluded for warfarin use), we used the inverse variance (IV) statistical method. Most of the results were consistent with the primary results and remained robust through sensitivity analyses. Interestingly, we observed increased aspirin-induced benefits for cardiac outcomes (CV events, RR: 0.90, 95% CI: 0.85-0.95; all MI, RR: 0.83, 95% CI: 0.72-0.96; ischaemic stroke, RR: 0.86, 95% CI: 0.76-0.97) among trials with diabetic and nondiabetic patients compared to the trials involving only diabetic patients. We also observed aspirin-induced benefits when excluding patients with asymptomatic peripheral artery disease (PAD). Furthermore, after excluding trials published before 2000, the cardiovascular benefits were still obvious. No effects on cancer were found across sensitivity analyses (**Table 3**). The omission process as well as the results of the heterogeneity analyses can be found in **Table 3** and **Appendix File S2-S12.**

These findings implied that aspirin use among diabetic individuals may not lead to the primary prevention of CVD because diabetes, which is known as a risk factor for CVD, might indirectly enhance the CV risk estimated by the MACE; similarly, the efficacy of aspirin use in studies including both diabetic and nondiabetic patients was excellent. Second, diagnosis technology is developing over time, which means that more patients with potential or asymptomatic CVD could be properly diagnosed and excluded before entering clinical trials or taking aspirin for “primary prevention”. Therefore, the preferable role of aspirin in the primary prevention of CVD would be highlighted, especially in recently published studies (after 2000). Finally, early screening for PAD was equally important to help identify individuals who may not benefit from aspirin.

Table 3
Summarized results of the sensitivity analysis.

Outcomes (RR, 95% CI)	Excluding before 2000 trials[a]	Excluding open-label trials[b]	Excluding high risk trials[c]	Excluding asymptomatic PAD trials[d]	Excluding 100% male individual trials[e]	Excluding 100% diabetic individuals trials[f]	Restricting on 100% diabetic individuals trials[g]	Excluding placebo use trials[h]	Excluding TPT study[i]
Primary efficacy outcomes									
CV events	0.91 (0.87-0.96)	0.90 (0.85-0.95)	0.91 (0.86-0.97)	0.91 (0.87-0.96)	0.92 (0.87-0.97)	0.90 (0.85-0.95)	0.95 (0.84-1.06)	0.92 (0.84-1.02)	NA
All-cause mortality	0.98 (0.93-1.04)	0.98 (0.93-1.03)	0.98 (0.92-1.04)	0.97 (0.93-1.02)	0.98 (0.93-1.03)	0.98 (0.93-1.04)	0.94 (0.86-1.03)	0.93 (0.83-1.03)	0.97 (0.93-1.02)
Cardiovascular mortality	0.93 (0.82-1.07)	0.95 (0.87-1.05)	0.95 (0.85-1.05)	0.93 (0.85-1.02)	0.94 (0.84-1.04)	0.94 (0.85-1.05)	0.97 (0.65-1.45)	0.85 (0.59-1.22)	0.95 (0.86-1.03)
Secondary efficacy outcomes									
All MI	0.95 (0.88-1.03)	0.86 (0.74-0.99)	0.93 (0.83-1.04)	0.84 (0.74-0.95)	0.92 (0.84-1.00)	0.83 (0.72-0.96)	0.97 (0.85-1.10)	0.94 (0.79-1.12)	0.88 (0.78-0.99)
Total stroke	0.92 (0.84-1.00)	0.94 (0.86-1.03)	0.92 (0.84-1.00)	0.95 (0.89-1.03)	0.92 (0.85-1.00)	0.96 (0.88-1.05)	0.90 (0.88-1.02)	0.98 (0.84-1.15)	0.95 (0.88-1.02)
Ischaemic stroke	0.86 (0.78-0.94)	0.88 (0.78-0.98)	0.85 (0.76-0.95)	0.88 (0.80-0.97)	0.86 (0.78-0.98)	0.86 (0.76-0.97)	0.92 (0.79-1.07)	0.89 (0.72-1.09)	0.88 (0.81-0.97)
Cancer incidence	1.01 (0.94-1.08)	0.99 (0.95-1.05)	0.99 (0.95-1.05)	1.02 (0.97-1.07)	1.00 (0.94-1.07)	1.02 (0.95-1.10)	0.94 (0.82-1.08)	1.06 (0.90-1.25)	NA
Cancer mortality	1.03 (0.93-1.15)	1.03 (0.92-1.15)	1.02 (0.89-1.16)	1.05 (0.96-1.14)	1.03 (0.94-1.12)	1.04 (0.93-1.16)	0.98 (0.86-1.12)	1,01 (0.86-1.19)	1.03 (0.94-1.12)
Safety outcomes									
Major bleeding	1.37 (1.12-1.50)	1.40 (1.28-1.54)	1.39 (1.26-1.53)	1.40 (1.28-1.52)	1.40 (1.28-1.54)	1.48 (1.33-1.64)	1.27 (1.11-1.47)	1.42 (1.11-1.80)	1.40 (1.29-1.52)
Intracranial bleeding	1.30 (1.10-1.54)	1.33 (1.11-1.59)	1.29 (1.07-1.56)	1.29 (1.10-1.52)	1.28 (1.08-1.51)	1.36 (1.14-1.63)	1.11 (0.80-1.54)	1.22 (0.89-1.68)	1.30 (1.11-1.52)
Gastrointestinal bleeding	1.49 (1.30-1.72)	1.52 (1.33-1.74)	1.51 (1.38-1.78)	1.58 (1.39-1.80)	1.55 (1.36-1.77)	1.63 (1.41-1.90)	1.43 (1.13-1.80)	2.23 (1.33-3.74)	1.56 (1.38-1.78)

Note: Sensitivity analysis was conducted by omitting one/several study/studies each turn to show more clinical useful data.

Abbreviations: MI: myocardial infraction; PAD: peripheral artery disease; NA: Not available; RR: Relative risk; CI: Confidence interval.

[a] Total 10 trials[16-25], N = 115300;

[b] Total 9 trials[13-15],17,18,20,23-25, N = 135042;

[c] Total 7 trials[15,17,18,20,23-25], N = 110432;

[d] Total 12 trials[12-17,19,21-25]; N = 159214;

[e] Total 11 trials[15-25], N = 134090;

[f] Total 10 trials[12-17,20,21,24,25], N = 142385;

[g] Total 4 trials[18,19,22,23], N = 21455;

[h] Total 5 trials[12,16,19,21,22], N = 28797;

[i] Total 13 trials[12,13,15-25], N = 161300.

Trial sequential analysis

In TSA, we observed the Z-curve cross the trial sequential analysis boundary (TSA boundary) for CV events, all MI, ischaemic stroke, major bleeding, intracranial bleeding and major gastrointestinal bleeding outcomes under conditions of 5% relative risk reduction, 5% for two-sided type 1 error risk, 80% statistical power and 5% control event incidence. The Z-curve did not cross the traditional boundary or the TSA boundary but crossed the futility boundary for cardiovascular mortality. The Z-curve crossed the traditional and futility boundaries but did not cross the TSA boundary for all-cause mortality. These findings showed that conclusions on the abovementioned outcomes were robust and were hardly modified with additional related trials. However, the Z-curve did not cross the TSA boundary or the futility boundary for total stroke, cancer incidence and cancer mortality, which suggested that additional studies should be conducted to evaluate those effects (**Figure 3** and **Appendix Figure S4**).

Egger's test revealed no significant publication bias for CV events (P = 0.882), all-cause mortality (P = 0.362), CV mortality (P = 0.390), major bleeding (P = 0.126), intracranial bleeding (P = 0.236), or major gastrointestinal bleeding (P = 0.152) (**Appendix Figure S5**).

Discussion

As one of the most widely used drugs worldwide, aspirin celebrated its 121st birthday in 2020 and the remarkable store is still going on[34]. In this study, aspirin was observed to be significantly associated with a 9%, 13%, and 12% reduction in the risk of CV events, all-MI and ischemic stroke, respectively; however, aspirin was associated with a 40%, 30%, and 57% increase in the risk of bleeding profiles, including major bleeding, intracranial bleeding and major gastrointestinal bleeding, respectively. No causal outcomes were found in all-cause mortality, cardiovascular mortality, total stroke, cancer incidence or cancer mortality. Low doses of aspirin (≤ 100 mg) might offer more clinical benefits than high doses of aspirin; individuals who are < 65 y old and have a BMI ≥ 25 demonstrated stronger effects of aspirin on the primary prevention of CVD; the data indicated that aspirin did not confer benefits in the high 10-y MACE% risk group. The results were not significantly modified after excluding asymptomatic PAD trials and trials with only diabetic individuals. Besides recommendations from contemporary guidelines, we hypothesized that aspirin might be prescribed depending on body size (BMI), that is, prescribing > 100 or ≤ 100 mg aspirin to individuals with a BMI ≧ 25 and prescribing ≤ 100 mg to individuals with a BMI < 25[35]. It is still crucial to perform complete screening and examinations on large populations to evaluate populations' CVD risk, hence quantifying their probability of obtaining real benefits from aspirin. Indeed, the one-dose-fits-all intake strategy is unlikely optimal, and a more tailored and wise dosing approach is called for to maximize substantial benefits and reduce potential risk.

The endorsed role of aspirin in the primary prevention of ischaemic events (all-MI, ischaemic stroke) has been supported by several studies[36]. The potential mechanism for preventing ischaemic events is based on the inhibition of thrombus propagation and plaque rupture[37]. This study also suggested a beneficial role of aspirin in all-MI and ischaemic stroke outcomes. Notably, only 2 eligible trials (HOT and PHS)[13, 15] exhibited significant risk reduction in all-MI; however, their conducting time was rather early, and no significant risk reduction was observed in cardiovascular mortality and all-cause mortality under the long follow-up period. Because the two trials were conducted early, researchers could not properly emphasize the biases from risk factors such as smoking status, blood glucose, blood cholesterol level or blood pressure. Another concern is that almost 50% of MIs are considered to be clinically silent; accordingly, it is not easy to ascertain the clinical benefit from long-term aspirin use through this endpoint[38]. It may be that all CV events are assessed to be proper endpoints to evaluate all these cases. Some studies have suggested that populations with substantially increased CVD risk may benefit from preventive aspirin use, and guidelines from the US Preventive Services Task Force also suggested prescribing low doses of aspirin in adults aged 50–59 years with a CVD risk of at least 10%[39], which was in contrast to our findings that low-risk individuals seemed to obtain more clinical benefits. We used the 10-y MACE% to reflect participants' CVD risk and hypothesized that the CVD risk of participants tended to be overestimated due to the lack of agreement on unified risk calculators in primary trials[40]. For example, the ARRIVE trial[24] mixed predicted and observed CVD risk, such that the enrolled moderate risk populations had a standard risk of 17.3% as estimated by American Heart Association (AHA)/American College of Cardiology (ACC) 10-y CV risk estimated criteria[40, 41] but had an observed CVD risk rate of 6.9%. Similarly, the ASPREE trial[25] enrolled patients who were older than 65 or 70 y old; the CVD risk of these older patients was hard to evaluate, and the reported 10-y MACE% of 7.8% differed from the 8.3% figure found herein, although both 10-y MACE% were less than 10%. The reason for this discrepancy was that MACE in the ASPREE trial was defined as a composite of fatal coronary heart disease, nonfatal MI and fatal or nonfatal ischaemic stroke, which differed from the unified definition. In this study, CV event risk was reduced by 11% in the low 10-y MACE% risk group.

Guidelines driven by the AHA/American Diabetes Association (ADA) recommend aspirin use in diabetic populations with intermediate risk (5%-10% 10-y MACE%) for primary prevention[36]. JPAD[19] and ASCEND[23] trials specifically incorporated diabetic populations, but the cardiovascular benefits seemed to be higher in the ASCEND trial. The total proportion of statin use was 75% in the ASCEND trial vs. 25% in the JPAD trial, which might have resulted in higher benefits seen in the ASCEND trial. Additionally, this study indicated fewer CVD benefits among populations with diabetes, which was supported by recent European Society of Cardiology guidelines recommending against aspirin use in diabetic populations who have no history of CVD[9]. Routine aspirin use was not enough for primary prevention among individuals with a high risk of CVD; at that time, blood pressure and blood glucose were controlled, cholesterol levels were reduced with statins, and physical activity and healthy eating were reduced. are also necessary. Aspirin use increased the risk of bleeding profiles but was not associated with cardiovascular mortality considering that deaths caused by bleeding were rare. Since the strategy to reduce harm of long-term aspirin use is not understood from current evidence, prescribing proton pump inhibitors (PPIs) might limit the risk of major gastrointestinal bleeding and enhance the benefit-risk ratio towards intended populations[20]. Aspirin appears to be not associated with all-cause mortality; however, several trials revealed that aspirin reduced the risk of colorectal cancer (RR: 0.73, 95% CI: 0.69–0.78), squamous-cell oesophageal cancer (RR: 0.67, 95% CI: 0.57–0.79), gastric cancer (RR: 0.64, 95% CI: 0.51–0.82) and pancreatic cancer (RR: 0.78, 95% CI: 0.68–0.89)[42]. At this time, the reduction in cancer mortality appeared after 5 y of follow-up, and this result was not duplicated in the ASCEND trial[23]. Current findings suggest a neutral role of aspirin in cancer outcomes; therefore, no suggestions could be made regarding benefit-risk balance from current evidence.

Added Value And Limitations

Mahmoud et al[43] conducted a TSA meta-analysis, the authors mainly focused on CVD-related outcomes including all-cause mortality, all MI, bleeding events. Comparing to Mahmoud et al[43], current study is more comprehensive because we also investigated cancer outcomes. Study from Mahmoud et al[43] included 11 RCTs, in our prospective, it was not enough, trials like POPADAD[18], AAA[20] were not reasonably included. Also, several 10y-MACE% values presented in that study were not in consistent with current study, for example ASCEND[23], ARRIVE[24] and ASPREE[25]. 10y-MACE% for BDS[12] and TPT[14] was also absent in Mahmoud et al[43] study. Lin et al[44] investigated the role of low-dose of aspirin on CVD primary prevention, they demonstrated low-dose aspirin had no role in all MI, but did reduce stroke incidence, which was in contrast to findings from current paper (that aspirin might significantly reduce all MI incidence instead of total stroke, ischemic stroke could be reasonably reduced). Current study had included more comprehensive RCTs than Lin et al[44], subgroup analyses aiming to low-dose of aspirin (< 100 mg/d) were also conducted. This study clearly pinpointed low CVD risk individuals might get more clinical benefits than the high risk from aspirin. Only one TSA for MACE outcome in Lin et al[44] was far enough to draw robust conclusions. Major controversial issues from current study and Gelbenegger et al[45] were the outcomes on diabetic populations, this study supported there were no substantial benefits of aspirin on diabetic populations primary prevention. POPADAD[18], JPAD[19], JPAD2[22] and ASCEND[23] were special trials conducted on full diabetic populations (100% diabetic individuals), to our great knowledge, it was more proper to investigate the intended results on the four trials, data stem from calculation on other small diabetic-proportion trials[17, 21] would add extra reporting bias. Zheng et al[27] also performed a similar research, however, no TSA results were revealed and merits from network meta-analysis methods seemed not so obvious. Overall, current study with particular subgroup and sensitivity analyses clearly addressed the less priority of aspirin on high 10y-MACE% risk and diabetic populations, such populations may need more aggressive therapy or combined pharmaceutical intervention. We believe these results add new evidence to the discussion on aspirin primary prevention in CVD and may arouse new disputes.

Limitations were also detected. First, definitions of reported outcomes were different, reflecting advances in CVD diagnosis and treatment. To best overcome this heterogeneity, we defined unified primary and secondary efficacy outcomes and safety profiles and then properly extracted the required data in eligible studies. Second, aspirin use in the included studies was not consistent with the major dose of 75 mg to 100 mg. Importantly, more clinical benefits with bleeding risk were found in trials restricted to ≤ 100 mg/d intake. Third, several trials (BDS (1998), PHS (1989), TPT (1998), HOT (1998)) were published rather early, and thus, some examinations and screening methods may not have been as accurate as expected. This contributed to an overestimated 10-y MACE%. A more precise study based on individual-patient data is encouraged.

Conclusion

Aspirin intake was associated with reduced risk of CV events, all MI, and ischaemic stroke, and was associated with increased incidences of major bleeding, intracranial bleeding, and major gastrointestinal bleeding in the primary prevention of CVD. The use was not associated with an increased risk of all-cause mortality, cardiovascular mortality, total stroke, cancer incidence or cancer mortality. No substantial benefits with respect to CVD were observed in the diabetic and high 10-y MACE% risk group populations. A one-dose-fits-all strategy is not optimal, and BMI may be a potential indicator to guide aspirin prescription. It is also necessary to identify individuals who may benefit from aspirin by more accurate cardiovascular-relating examinations. Overall, the benefits and harm of aspirin for primary prevention should be re-evaluated. Based on these findings, we believe it is not yet the time to quit the aspirin era.

Abbreviations

CVD
cardiovascular disease; TSA:Trial sequential analysis; CV:events cardiovascular events; RR:relative risk; CI:confidence intervals; BMI:body mass index; CHD:coronary heart disease; MI:myocardial infarction; PRISMA:Preferred Reporting Items for Systematic Reviews and Meta-Analysis; RCTs:randomized controlled trials; HR:hazard ratio; OR:odds ratio; MACE:major adverse cardiovascular event; CrIs:credible intervals; D-L:DerSimonian-Laird; Ess:effect sizes; IV:inverse variance; PAD:peripheral artery disease; AHA:American Heart Association; ACC:American College of Cardiology; ADA:American Diabetes Association.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analyzed during this study are included in this published article and its Additional information fles.

Competing interests

The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. The authors declare that they have no competing interests.

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Authors' contributions

All authors designed and conducted this review. Binghao Zhao wrote the paper. Qian Wu, Li Wang, Chen Liao, Yifei Dong, Jingsong Xu, Yiping Wei and Wenxiong Zhang helped the study design. Binghao Zhao, Yiping Wei and Wenxiong Zhang revised the statistical methodology. Binghao Zhao and Wenxiong Zhang had primary responsibility for the final content. All authors read and approved the final manuscript. Notably, Binghao Zhao and Wenxiong Zhang equally share the corresponding authorship.

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Figures

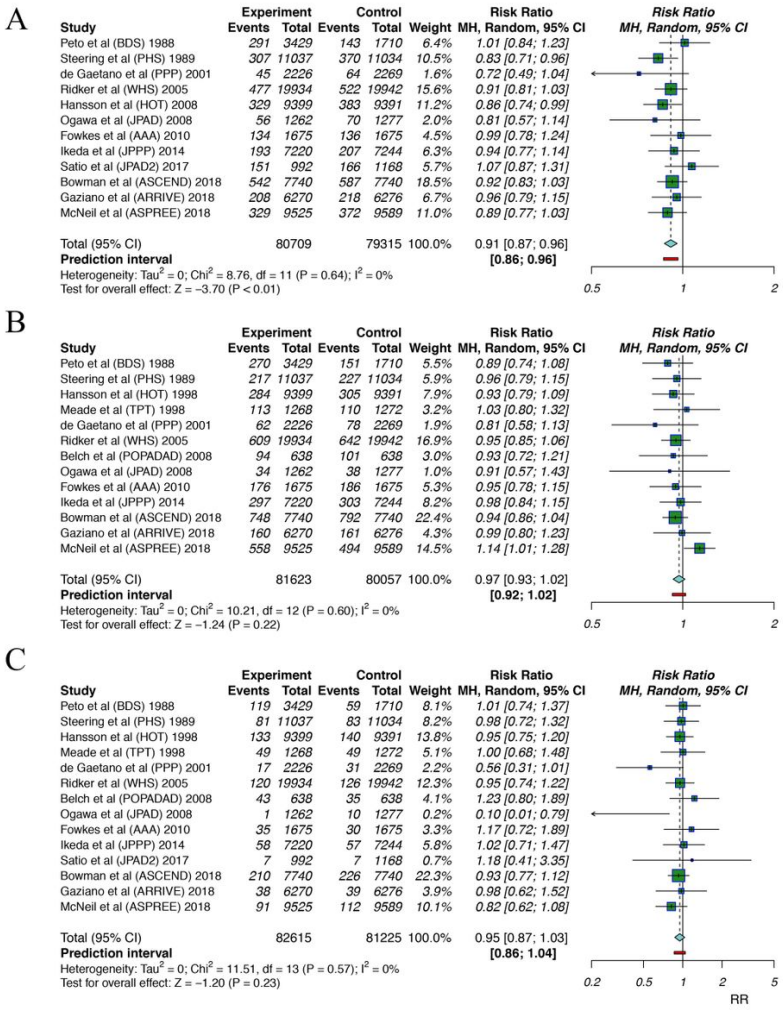

Figure 1

Summary forest plots for the primary efficacy outcomes. (A) Forest plot for CV events. (B) Forest plot for all-cause mortality. (C) Forest plot for cardiovascular mortality.

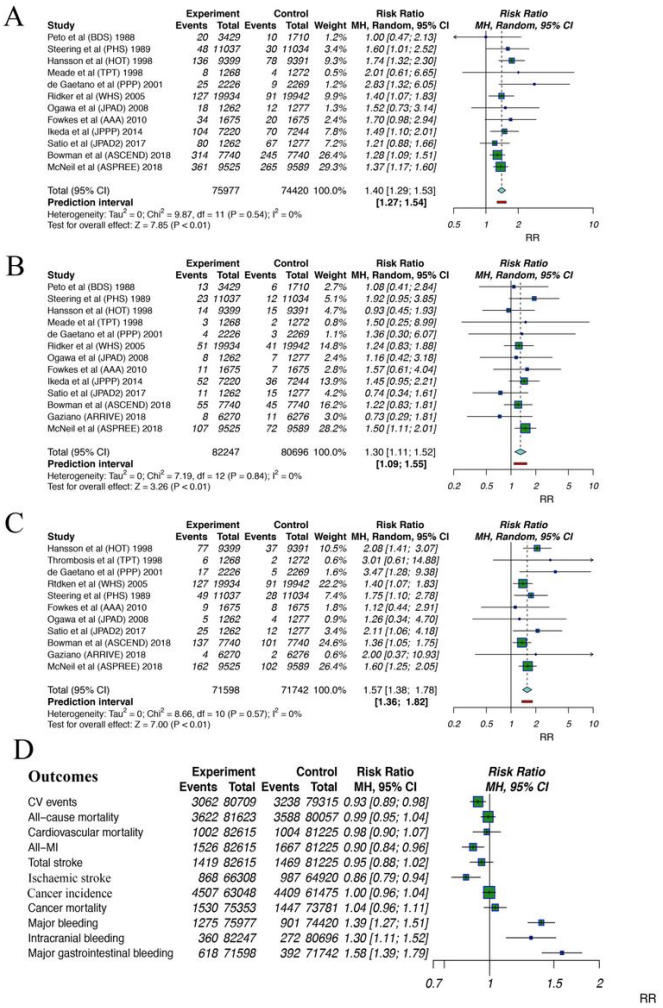

Figure 2

Summary forest plots for the outcomes of bleeding. (A) Forest plot for major bleeding. (B) Forest plot for intracranial bleeding. (C) Forest plot for major gastrointestinal bleeding. (D) Forest plot for summarized outcomes analysed in the current study. MI, myocardial infarction; 95% CI, 95% confidence interval.

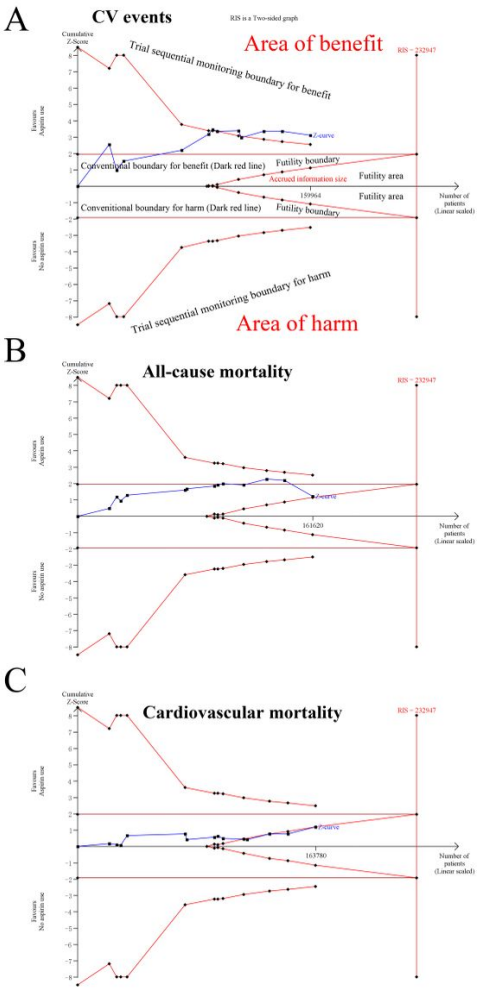

Figure 3

Trial sequential analysis of CV events, all-cause mortality, and cardiovascular mortality under 5% relative risk reduction, 5% for two-sided type 1 error risk, 80% statistical power and 5% control event incidence conditions. (A) For CV events. (B) For all-cause mortality. (C) For cardiovascular mortality.

Supplementary Files

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