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Perioperative aspirin therapy in non-cardiac surgery: A systematic review and meta-analysis of randomized controlled trials☆

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ABSTRACT

Background: Aspirin is a key element in prevention of cardiovascular and thromboembolic events. During non-cardiac surgery however, its balance of bleeding risks and benefits remains unclear.
Methods: A systematic review and meta-analysis of randomized controlled trials was performed. Online databases were screened for clinical trials randomizing aspirin to no aspirin therapy in non-cardiac surgery. Clinical outcomes of all-cause mortality and cardiovascular mortality, arterial ischemic events, venous thromboembolic events and bleeding events were separately evaluated.
Results: Seven RCTs comprising 28,302 patients were included. All-cause mortality (3.7% vs. 3.8%; odds ratio (OR) 0.97, CI 0.86–1.10) and cardiovascular mortality (2.0% vs. 2.1%, OR 0.92; CI 0.78–1.09) were not different in aspirin vs. no aspirin groups. Arterial ischemic events showed no differences, including myocardial infarction (2.5% (aspirin) vs. 2.5% (no aspirin)), cerebrovascular events (0.6% (aspirin) vs. 0.6% (no aspirin)) and peripheral arterial events (0.2% (aspirin) vs. 0.3% (no aspirin)). Aspirin significantly reduced the risk for venous thromboembolic events (VTE; 1.5% (aspirin) vs. 2.0% (no aspirin); OR 0.74, CI 0.59–0.94, $p = 0.02$). Perioperative major bleeding was significantly more frequent in aspirin groups (4.4% vs. 3.7%; OR 1.18, CI 1.05 to 1.33, $p = 0.007$).
Conclusion: Aspirin remained neutral with respect to overall survival, cardiovascular mortality and arterial ischemic events. It reduced venous thromboembolic events at the expense of perioperative major bleedings. Thus, this analysis supports recommendations against perioperative aspirin continuation/initiation in cardiovascular disease patients at intermediate risk, as well as recommendations of aspirin for VTE prophylaxis in orthopedic patients only.

1. Introduction

An estimated 4% of the world population has a surgical procedure performed every year [1,2] — with a rising tendency [3]. Surgical procedures carry an inherent risk for complications, which depend on the type and quality of procedure and anesthesia, but also on patient comorbidities and safety precautions. Overall complication rate estimates range from 3 to 11% [4,5] to up to 40% [6], and among the leading causes – apart from technique-related complications – are cardiovascular adverse events and bleeding events [5].

Aspirin therapy for chronic platelet inhibition represents a cornerstone in the prevention of cardiovascular disease (CVD) related events. Irreversible cyclooxygenase-I inhibition reduces platelet activation by thromboxane A_2 [7,8] and thus aggregation in arterial and venous

Abbreviations: ACC, American College of Cardiology; ACCP, American College of Chest Physicians; AHA, American Heart Association; ASA, acetyl salicylic acid; BARC, Bleeding Academic Research Consortium; CABG, coronary artery bypass graft; CI, confidence interval; CVD, cardiovascular disease; DM, diabetes mellitus; ESC, European Society of Cardiology; HLP, hyperlipoproteinemia; HTN, hypertension; LOE, level of evidence; M–H, Mantel–Haenszel; MI, myocardial infarction; n/a, not available; NSAR, non-steroid anti-rheumatic drug; OR, odds ratio; PAOD, peripheral artery occlusive disease; PCI, percutaneous coronary intervention; PRISMA, Preferred Reporting Items for Systematic reviews and Meta-Analyses; RCT, randomized controlled trial; TIA, transient ischemic attack; VTE, venous thromboembolism.

☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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vessels. It more effectively reduces arterial ischemic events [9–14] in secondary prevention of CVD than it increases bleeding risk [10,11,15], making it a guideline-recommended standard for CVD patients [12, 13]. In the setting of non-cardiac surgery however – where bleeding represents a serious risk factor – aspirin's perioperative CVD prevention and prophylaxis of thromboembolism [16–19] must be weighed against its bleeding risks.

This delicate risk/benefit balance in the perioperative setting is not clear. We here aimed to comprehensively analyze and differentiate aspirin effects in non-cardiac surgical patients in a review and meta-analysis of randomized controlled trials (RCTs).

2. Materials and methods

This meta-analysis was performed according to established methods recommended by the Cochrane Collaboration and in compliance with the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) statement for reporting systematic reviews and meta-analyses in health care interventions [20,21]. All screening, study selection, data extraction and analysis processes were performed by independent investigators, who were not personally involved in any of the included trials or had any other conflict of interest on the topic.

2.1. Study design and endpoint selection

This analysis was designed to investigate cardiovascular and thromboembolic benefits and bleeding risks of perioperative aspirin therapy during non-cardiac surgery. All prospective randomized controlled clinical trials of aspirin vs. no aspirin therapy in non-cardiac surgery were included, which featured assessment of the primary outcome of all-cause mortality and were published in English language and in full text. Secondary outcomes were cardiovascular mortality, myocardial infarction, cerebrovascular events (as a combination of ischemic stroke and transient ischemic attack (TIA)), thromboembolic events (including venous thrombotic events and pulmonary embolism), peripheral arterial events and major bleeding.

2.2. Data sources, search strategy and study selection

Medline, PubMed, Web of Science, Cochrane Central Register of Controlled Trials (CENTRAL), Google Scholar, and Embase databases, along with the websites www.medscape.com/cardiology, www.clinicaltrials.gov, www.clinicaltrialresults.org and www.cardiosource.org, were systematically searched (GW, MB, YL, and MiK) up until July 2017 for relevant published trial reports. Search keywords included combinations of: aspirin, acetyl salicylic acid, ASA, randomized controlled trial, surgery, operation, bleeding. A bibliography search within landmark articles, meta-analyses and guidelines of medical societies on the subject was additionally performed and relevant trials were added. All articles were primarily screened at the title/abstract level and then retrieved as full text reports. Studies positively evaluated during eligibility assessment were finally selected for inclusion (GW, MB, YL, MiK).

2.3. Data collection and quality assessment

Data from included trials were abstracted into prespecified forms (MB, YL, GW, VS) and analyzed according to the intention-to-treat principle, where possible. Internal validity was ensured by cross-checking between investigators; divergences were resolved by consensus after discussion in the group (MB, YL, GW, EPN, VS). Bias assessment was performed by two unblinded investigators (MB, YL) according to the Cochrane Collaboration guidelines [21] and was again cross-checked for errors.

2.4. Secondary outcome definitions

Secondary outcome definitions showed heterogeneity across studies (Supplementary Table 3). Endpoints were analyzed as reported. For bleeding outcome, an event definition of *major bleeding* was used where available (corresponding to BARC >2 (Bleeding Academic Research Consortium, [22])), or was assumed (e.g. life-threatening, requiring transfusion, requiring reoperation etc.).

2.5. Data synthesis and statistical analyses

Odds ratios (ORs) and 95% confidence intervals (CIs) were used as summary statistics. Heterogeneity was assessed by the Cochran's Q test [23]. Statistical heterogeneity was summarized by the I^2 statistic, which quantifies the percentage of variation in study results that is due to heterogeneity rather than to chance [24]. I^2 values >20% were judged to indicate substantial heterogeneity, which prompted use of the DerSimonian and Laird random-effects model [25], instead of the less conservative fixed-effects model. Sensitivity analyses were performed to account for trial heterogeneity and further ascertain validity of the pooled analyses. The statistical level of significance of the Cochran–Mantel–Haenszel statistics estimate for the summary treatment effect was assumed at a 2-tailed p-value of <0.05. Review Manager version 5.3 (The Nordic Cochrane Centre, Copenhagen, Denmark), Microsoft Excel and SPSS version 23 (SPSS, Chicago, Illinois) were used for statistical computations.

3. Results

3.1. Study selection, trial protocols and patient populations

The process of article screening and selection is described in a PRISMA flow chart (Supplementary Fig. 1). Primary searches revealed a total of 9475 sources/reports, based on title and abstract, any duplicates and non-clinical studies were removed, and 72 studies were then subsequently evaluated and condensed to seven relevant prospective randomized controlled trials [26–32]. These were published between 1993 and 2014 and enrolled a total of 28,302 patients.

Study characteristics and randomization details are reported in Table 1: the largest included trials were the Pulmonary Embolism Prevention (PEP) trial [32] with 17,444 and the PeriOperative ISchemic Evaluation 2 trial (POISE-2) [27] with 10,010 patients; the smallest trials were APAP and Nielsen et al. with just over 50 patients [26,30]. Postoperative follow-up was one month in the majority of trials.

A wide range of procedures mainly corresponding to intermediate-cardiovascular-risk surgery [1] were performed (Table 1) in the trials: abdominal surgery (cholecystectomy, gastrectomy, hernia repair, bowel and colorectal surgery, oncologic surgery), orthopedic surgery (knee and hip surgery), urologic/prostate surgery, carotid endarterectomy, and retroperitoneal surgery (nephrectomy).

Patient characteristics of the included studies are shown in Supplementary Table 1. 10,858 patients in APAP, Lindblad et al., Nielsen et al., Oscarsson et al., STRATAGEM and POISE-2 [26–31] were assumed to suffer from CVD at average intermediate cardiovascular risk, as they were either on long-term aspirin therapy for prevention of CVD (Table 1) or were directly characterized as such in the published report. PEP patients were considered to be at low cardiovascular risk, as they were mostly lacking pre-randomization aspirin therapy [32]. Aspirin dosage varied from 75 mg to 300 mg daily. Six trials prescribed it for CVD prevention [26–31], PEP used it for prevention of venous thromboembolism [32]. Six studies randomized aspirin to placebo [27–32], APAP to discontinuation of aspirin [26].

Risk of bias of all included studies is depicted in Supplementary Table 2: trial quality in general was high, four trials used a multicenter design.

Details on secondary endpoint definitions and reporting of all included studies are listed in Supplementary Table 3.

3.2. All-cause mortality and cardiovascular mortality

The primary outcome of all-cause mortality was reported in all trials and all 28,302 patients [26–32]. The pooled meta-analysis showed similar rates of all-cause mortality (3.7% (aspirin) vs. 3.8% (no aspirin); OR 0.97 with CI 0.86–1.10; $I^2 = 0\%$; $p = 0.61$; Fig. 1A). Sensitivity analyses were performed to account for patient population differences (exclusion of the low-risk CVD population in PEP, Supplementary Fig. 2A) and heterogeneity in trial sizes (exclusion of heavy weight trials PEP and POISE-2, Supplementary Fig. 2B), however no significant differences in survival were found in either analysis.

All seven trials with 28,302 patients reported cardiovascular mortality [26–32] (Fig. 1B). The pooled analysis showed no difference for cardiovascular mortality (2.0% (aspirin) vs. 2.1% (no aspirin); OR 0.92 with CI 0.78–1.09; $I^2 = 0\%$, $p = 0.33$). When excluding the PEP trial for its low-CVD-risk population, results remained similar (sensitivity analysis, Supplementary Fig. 3A).