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**INVITED REVIEW**

# Role of aspirin for prevention and treatment of perioperative cardiovascular events

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**Summary.** Among adults undergoing non-cardiac surgery who are at risk of a myocardial infarction, a long-standing question has been whether these patients should receive aspirin throughout the perioperative period. A large ($n$ = 10 010 patients) international trial (POISE-2) demonstrated that perioperative aspirin did not prevent myocardial infarction, and the result was consistent both for patients who had been taking aspirin before the trial (continuation stratum, 4382 patients) and for patients who had not been taking aspirin before the trial (initiation stratum, 5628 patients). Aspirin did, however, increase the risk of major bleeding. Therefore, the best evidence does not support the use of aspirin for the prevention of myocardial infarction in patients undergoing non-cardiac surgery. In patients who have an indication for long-term aspirin usage and have their aspirin held during the perioperative period, it is important to ensure aspirin is restarted after the high-risk period for bleeding has passed (i.e., 8–10 days after surgery).

**Keywords**: aspirin; cardiology; cardiovascular diseases; myocardial infarction; perioperative care.

The number of patients undergoing non-cardiac surgery is growing worldwide with an estimated 200 million major non-cardiac surgeries performed annually [1, 2]. Despite advances in surgical and anesthetic techniques, non-cardiac surgery is associated with significant postoperative morbidity and mortality. The 30-day mortality in patients following in-hospital non-cardiac surgery is > 1% [3], representing at least 2 million deaths worldwide every year with nearly 50 percentage of deaths attributed to a cardiovascular cause [4, 5]. These statistics establish perioperative cardiovascular events as a major public health issue.

Patients undergoing non-cardiac surgery are also at risk of postoperative major vascular complications (i.e., vascular death, non-fatal myocardial infarction [MI], non-fatal cardiac arrest, and non-fatal stroke), and MI is the most common major complication [6]. An estimated 6–10 million patients will suffer a MI during the perioperative period [5]. In the POISE-1 trial of 8 351 patients undergoing non-cardiac surgery, 5.7% of patients suffered an MI in the first 30 postoperative days, 0.5% suffered a stroke and 0.5% suffered a non-fatal cardiac arrest [6]. Of the patients with a perioperative MI, 11.6% died within 30 days, whereas only 2.2% of patients who did not suffer a perioperative MI died ($P < 0.001$). There are also a substantial number of patients who suffer a prognostically important ischemic cardiac event that do not meet the universal definition of MI [7]. In the VISION study, a prospective cohort study of a representative sample of 15 065 patients undergoing non-cardiac surgery, troponin levels were measured for the first three postoperative days [8]. The results showed that 8.3% of patients had a troponin elevation after surgery that was judged due to an ischemic etiology, and the majority (84.2%) of these patients did not experience any ischemic symptom. This phenomenon led to the establishment of the concept of myocardial injury after non-cardiac surgery [MINS] [8]. Patients who suffered MINS had significantly increased 30-day mortality, adjusted hazard ratio (HR) 3.87; 95% confidence interval (CI), 2.96–5.08; $P < 0.001$, and the risk remained increased regardless of whether patients fulfilled the universal definition of MI [8]. Analyses indicated that MINS was responsible for 34% of the perioperative deaths, making it the leading cause of death after non-cardiac surgery [8].

## Physiopathology of perioperative myocardial infarction

There remains uncertainty regarding the pathophysiology of perioperative MI. As in the non-operative setting,

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perioperative myocardial ischemia and subsequent infarction likely occur through several mechanisms.

Myocardial oxygen supply–demand mismatch (also referred to as type II MI) is a commonly proposed pathophysiology of perioperative MI [7, 9]. Several factors in the perioperative setting can lead to increase myocardial oxygen demand including sympathetic hyperactivity with a resultant increase in heart rate and arterial blood pressure [10, 11]. Several studies have demonstrated an association between tachycardia and perioperative myocardial ischemia [11–13]. Hypothermia, which leads to shivering, can also increase the myocardial oxygen demand in the perioperative period [14]. In a coronary artery with a high-grade stenosis or occlusion, the supply response is limited and can result in supply–demand mismatch MI when myocardial oxygen demand increases.

Consistent with this hypothesis, two small retrospective autopsy studies (< 70 patients in total) reported that two-thirds of the patients who suffered a fatal perioperative MI had significant left main or 3-vessel coronary artery disease [15, 16]. Most patients did not exhibit plaque fissuring and about one-third had an intracoronary thrombus. Because the timing of the autopsies relative to the MIs may have allowed resolution of intracoronary thrombus, these data require cautious interpretation. Nevertheless, they suggest that some fatal perioperative MIs are secondary to supply–demand mismatch.

Atherosclerotic plaque rupture with superimposed coronary thrombosis is another proposed mechanism of postoperative MI. Stress and tissue injury lead to catecholamine release in the perioperative period, which has been linked to the alteration of fibrinolysis and the subsequent development of plaque fissuring and acute coronary thrombosis [17–19]. Postoperative hemostatic activation has also been shown to be associated with myocardial cell damage in patients who suffered perioperative myocardial ischemia [20]. One study provides supportive evidence of coronary artery thrombosis in patients with perioperative MI who underwent coronary angiography. The clinical and angiographic data of a prospective cohort of 120 patients with postoperative acute coronary syndrome [PACS] were compared to a random cohort of patients with spontaneous non-operative acute coronary syndrome [21]. The incidence of coronary lesion suggesting thrombosis (i.e., Ambrose's type II lesion) was similar in patients with PACS and spontaneous non-operative acute coronary syndrome (ACS) (45% vs. 56.7%, respectively); however, patients who were referred for cardiac catheterization for angina had a substantially lower incidence of Ambrose type II lesions (i.e., 16.4%, $P < 0.001$). These data suggest the patients with PACS were more similar to patients with non-operative ACS than the patients with angina regarding the angiographic findings suggestive of thrombosis. PACS compared to non-operative ACS was associated with a higher incidence of acute heart failure (35% vs. 12.5%, respectively; $P < 0.001$) and higher mortality (15% vs. 4.2%; $P = 0.02$). A longer delay between the event and angiography in patients with PACS compared to non-operative ACS might have resulted in an underestimate of the incidence of Ambrose II lesions in the patients with PACS ($5.5 \pm 8$ days vs. $1.3 \pm 1.4$ days, respectively; $P < 0.001$).

Given these data, it is likely that both mechanisms of perioperative MI (i.e., supply–demand mismatch and coronary thrombus) account for a portion of the perioperative MIs. Interventions that impact thrombosis (e.g., aspirin) may be beneficial to prevent the perioperative thrombotic MI events.

## Observational and experimental evidence regarding the effects of initiating and withdrawing aspirin in the non-operative setting

A meta-analysis of randomized-controlled trials undertaken by the Antithrombotic Trialists' Collaboration (ATC) showed that initiating aspirin in patients with or at high risk of atherosclerotic disease in the non-operative setting reduced non-fatal MI by one-third, non-fatal stroke by one-quarter, and mortality by one-sixth [22]. The ATC meta-analysis that included 195 trials involving 135 640 patients and 17 207 major vascular events also demonstrated that low-dose aspirin (i.e., 75–150 mg daily) was as effective as higher doses with less gastrointestinal side effects and less bleeding. This systematic review supports the benefit of aspirin on the prevention of vascular events in at-risk patients. Recent evidence also suggests that the withdrawal of aspirin might be associated with an increased risk of thrombotic events. A meta-analysis of three prospective cohort studies that included 34 344 patients showed that aspirin discontinuation was associated with an increased risk for thrombotic events (RR 1.82; 95% CI, 1.52–2.18; $I^2 = 0\%$) [23].

## Laboratory and physiology evidence that suggests aspirin may prevent vascular death and non-fatal myocardial infarctions in patients undergoing non-cardiac surgery

Platelet aggregability has been shown to increase in the early postoperative period following non-cardiac surgery. The hypercoagulable state seen in postoperative patients relates to several mechanisms including increased platelet reactivity to collagen, increased levels of von Willebrand factor, and a decrease in antithrombin levels [24]. Catecholamine release postoperatively can further promote platelet activation and aggregation [25] and is associated with alterations in fibrinolysis. Persistent platelet reactivity can often be seen more than 7 days after surgery [24]. Aspirin has been shown to reverse the abnormal platelet reactivity in vascular surgery patients [26].

Moreover, acute withdrawal of chronic aspirin treatment increases thromboxane A2 and decreases fibrinolysis,

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which may lead to thrombosis [26, 27]. Given these physiological changes, initiation of aspirin in aspirin naïve patients or continuation of aspirin in chronic users may prevent major perioperative vascular events through the inhibition of platelet activation and prevention of subsequent thrombus formation.

## Pre-POISE-2 experimental evidence evaluating the effects of aspirin in patients undergoing non-cardiac surgery

One of the largest randomized-controlled trials (RCT) that studied aspirin in the perioperative setting is the Pulmonary Embolism Prevention (PEP) trial [28]. The trial included 13 356 patients undergoing surgery for hip fracture who were randomized to aspirin 160 mg daily or placebo, started preoperatively and continued for 35 days after surgery. The main outcome of interest in PEP was venous thromboembolism (VTE), but secondary outcomes included the occurrence of vascular arterial events and vascular mortality. In patients with hip fracture, aspirin showed an increase in non-fatal MI or fatal ischemic heart disease (HR 1.33; 95% CI, 1.00–1.78; $P = 0.05$), but the incidence in both groups was low (1.6% in the aspirin group vs. 1.2% in the placebo group). In the PEP trial, aspirin compared to placebo was also associated with an increased risk of gastrointestinal bleeding ($P = 0.0005$), greater postoperative fall in hemoglobin ($P < 0.0001$), and an increase in the need for transfusion ($P = 0.04$). The later represented an absolute increase in 6 per 1000 patients who would require transfusion when taking aspirin compared to placebo. It is possible that the increase in MI might have been related to the increased risk of bleeding. However, PEP was not designed primarily to detect a difference in MI and there was no systematic monitoring for events (e.g., troponin screening). As the majority of patients who suffer a perioperative MI are asymptomatic, as seen in the VISION study, it is likely that a substantial proportion of events were missed [8].

A systematic review of five RCTs totaling 816 patients who underwent infrainguinal bypass surgery assessed the impact of antiplatelet therapy vs. placebo on the occurrence of graft occlusion and major cardiovascular events [29]. Antiplatelet therapy was associated with a significant reduction in graft occlusion (relative risk [RR], 0.78; 95% CI, 0.64–0.95). There was no significant impact on MI (RR, 0.64; 95% CI, 0.37–1.10) or vascular mortality (RR, 0.71; 95% CI, 0.47–1.09). The systematic review was, however, underpowered to assess MI and vascular mortality.

Further, there was also uncertainty regarding the impact of withholding aspirin in patients treated chronically. A meta-analysis of perioperative withdrawal of aspirin had found that 10.2% of acute cardiovascular events were preceded by aspirin interruption [30]. The time interval between discontinuation and acute coronary syndrome was 8.5 ± 3.6 days, 14.3 ± 11.3 days for acute cerebral events, and 25.8 ± 18.1 days for acute peripheral arterial syndromes. A small trial suggested, however, that there was no increase in major thrombotic events when aspirin was withheld prior to non-cardiac surgery [31].

## POISE-2 trial

The POISE-2 trial, published in 2014, randomized 10 010 patients scheduled to undergo non-cardiac surgery who were at risk for vascular complications to aspirin or placebo [32]. Patients were stratified depending on whether they were already taking aspirin (continuation stratum) or naïve to aspirin (initiation stratum). Patients in the continuation stratum had to have stopped aspirin at least 72 h before surgery to be eligible, but the median interruption prior to surgery was 7 days. Patients were administered aspirin 200 mg or placebo just before surgery and continued aspirin 100 mg or placebo for 30 days in the initiation stratum and for 7 days in the continuation stratum before resuming their regular aspirin regimens. Patients who were undergoing intracranial surgery, carotid endarterectomy, or retinal surgery were excluded, as were patients with a drug-eluting coronary stent < 1 year or bare-metal coronary stent < 6 weeks prior to randomization.

The primary outcome of death or non-fatal MI occurred in 7% of patients, and there was no statistically significant difference between aspirin and placebo (HR in the aspirin group, 0.99; 95% CI, 0.86–1.15; $P = 0.92$). Non-fatal MI was defined according to the Third Universal Definition of MI [7]. There was no statistically significant difference in the secondary outcome of death, MI and stroke (HR 0.98; 95% CI, 0.85–1.13; $P = 0.80$) and composite of death, MI, revascularization, pulmonary embolism (PE), and deep vein thrombosis (DVT) (HR 0.99; 95% CI, 0.86–1.14; $P = 0.90$). The lack of demonstrated benefit for death or non-fatal MI was consistent between the two aspirin strata ($P = 0.96$ for interaction).

Aspirin significantly increased the risk of major bleeding compared to placebo (4.6% vs. 3.8%, respectively, HR 1.23; 95% CI, 1.01–1.49; $P = 0.04$). Surgical site (78.3%) and the gastrointestinal tract (9.3%) were the most common sites of postoperative bleeding. A *post hoc* analysis showed that the absolute increased risk of major bleeding or life-threatening bleeding with aspirin was statistically significant up to day 7 after surgery (see Fig. 1). The absolute increased risk of major and life-threatening bleeding associated with aspirin was 1.2% on the day of surgery and progressively decreased to 0.9% on day 4 and reach 0.3% at day 8 after surgery. In multivariable analysis, the composite of major or life-threatening bleeding was an independent predictor of the subsequent risk of MI (HR 1.82; 95% CI, 1.40–2.36; $P < 0.001$).

This finding raises the question: if aspirin increased bleeding and bleeding increased the risk of MI, why was

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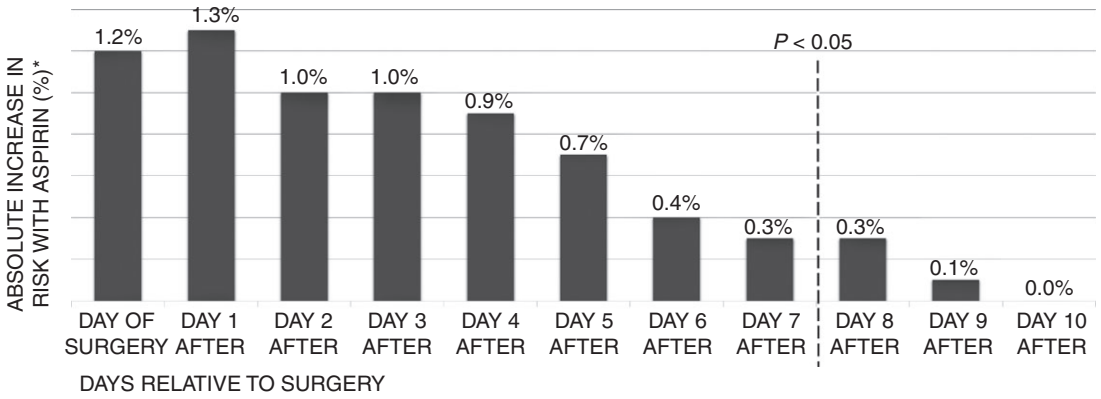


**Fig. 1.** Absolute increase in the risk of composite bleeding outcome with aspirin therapy starting on each of the first 10 postoperative days until 30 days after surgery in the POISE-2 trial. *Represents the cumulative incremental risk of bleeding attributable to aspirin if started on a certain day after surgery, over the remaining of the 30-day period.

there no increased risk of perioperative MI with aspirin therapy? One hypothesis is that aspirin was effective in preventing some MI's through thrombus inhibition, at the expense of increased bleeding-related MIs. The bleeding led to myocardial oxygen supply–demand mismatch, resulting in an overall neutral effect on cardiac events. The hypothesis of bleeding as a pathway to MI is supported by evidence from other trials. The findings in the PEP trial were consistent with POISE-2, and aspirin was associated with an increased risk of bleeding requiring a transfusion [28].

The risk of major and life-threatening bleeding among patients receiving aspirin was 6.3%, and the risk of MI was 6.2% [32]. To the extent that aspirin can prevent thrombotic MI and aspirin can cause MI through bleeding, the similar risk of MI and bleeding in the perioperative setting makes for an unfavorable situation regarding the overall impact of aspirin on MI in patients undergoing non-cardiac surgery.

Subgroup analysis of the 605 vascular surgery patients and patients at higher risk for perioperative MI (i.e., according to the Revised Cardiac Risk Index score [RCRI] of which 508 patients had an RCRI score of 3 and 64 patients had an RCRI score $\geq 4$) did not show a statistically significant benefit for aspirin ($P = 0.16$ and $P = 0.89$ for interaction, respectively). This suggests that even in a higher risk population, there is no evidence suggesting the benefit of aspirin for the prevention of perioperative major vascular complications.

For patients on chronic aspirin therapy, resuming the antiplatelet therapy should be considered between days 8 and 10 after surgery when the bleeding risk has diminished. The decision to resume aspirin earlier or not in patients at higher cardiovascular risk should take into account the patient's thrombotic risk vs. the bleeding risk associated with the surgical intervention, assuming an absolute increase of 1.0–1.3% in the risk of major and life-threatening bleeding.

Patients with recent coronary artery stent (i.e., bare metal stent (BMS) within 6 weeks and drug-eluding stent (DES) within 12 months) are at high thrombotic risk. The American College of Cardiology and American Heart Association (ACC/AHA) Guidelines recommend that elective non-cardiac surgery should be delayed 30 days after BMS implantation and 365 days after DES implantation [33]. These patients were excluded from the POISE-2 trial. In the POISE-2 trial, 427 participants had a history of a prior stent and a substudy will report the results of these patients.

### Treatment of myocardial injury after non-cardiac surgery

In patients who suffer a perioperative ischemic event, the risk of mortality and further ischemic events is significantly increased. The risk of bleeding also decreases as time from surgery passes, resulting in a greater burden of risk from a further subsequent ischemic event than bleeding each day after surgery.

Observational evidence from the POISE-1 trial suggests antithrombotic agents may benefit patients suffering MINS. Multivariable regression analysis among the patients who suffered MINS in POISE-1 demonstrated that acetyl-salicylic acid usage among patients who had suffered MINS was associated with a reduction in the risk of 30-day mortality (adjusted odds ratio, 0.54; 95% CI, 0.29–0.99) [34]. A propensity-matched study in vascular surgery patients further supports the benefit of cardiovascular medications (including aspirin) in patients with MINS [35]. In patients who suffered MINS, therapeutic intensification with $\geq 1$ of four cardiac medications (i.e., antiplatelet, statin, beta-blocker, angiotensin converting enzyme inhibitor) resulted in a HR of 0.63, (95% CI, 0.10–1.19; $P = 0.45$) for 1 year major cardiac outcomes (i.e., death, MI, coronary revascularization, or pulmonary edema requiring hospitalization). In contrast, patients not receiving intensified cardiovascular therapy after suffering

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a MINS were at increased 1-year risk of major cardiac outcomes (HR 1.77; 95% CI, 1.13–2.42; $P = 0.004$). Collectively, these data suggest aspirin is beneficial in patients who suffer MINS.

### Perioperative aspirin and postoperative renal outcomes

Previous evidence suggested that aspirin might reduce the risk of postoperative acute kidney injury through the inhibition of thromboxane A2 and a reduction of platelet aggregation and micro-embolization [36, 37]. Thromboxane A2 is a potent vasoconstrictor found in increased levels in the urine in patients with acute kidney injury [37]. Platelet aggregation and microthrombi can potentially increase the risk of acute kidney injury at time of decrease renal perfusion. Benefit in the prevention of postoperative acute kidney injury and need for dialysis with aspirin were suggested in a cohort study of cardiac surgery patients [36]. However, it is possible that bleeding and associated hypovolemia might precipitate prerenal acute injury. As shown in the POISE-2 trial, perioperative administration of aspirin increases the risk of major bleeding.

A POISE-2 substudy looked at the impact of aspirin on renal outcomes after non-cardiac surgery [38]. Similar to cardiac events, major perioperative bleeding was associated with a greater risk of subsequent acute kidney injury (aHR 2.20; 95% CI, 1.72–2.83). Aspirin did not alter the risk of the primary outcome of acute kidney injury (AKI). The primary definition of AKI was an increase in serum creatinine concentration from the preoperative concentration by either an increase of 0.3 mg $dL^{-1}$ or greater ($\geq$ 26.5 μmol $L^{-1}$) within 48 h of surgery or an increase of 50% or greater within 7 days of surgery. There was, however, an increased risk of acute dialysis within 30 days of surgery in the aspirin group compared with placebo that approximated statistical significance (15% vs. 9%, respectively, $P = 0.05$). For the subgroup of patients with preoperative chronic kidney disease, the risk of AKI resulting in dialysis was significantly increased with aspirin compared with placebo ($P = 0.04$ for interaction). These results should be interpreted cautiously given the small number of severe AKI events. Still, the results raise the possibility that the risk of severe AKI might be increased with aspirin through increased perioperative bleeding, more so in patients with chronic kidney disease. There is a biologically plausible link between perioperative AKI and major bleeding, but it remains uncertain if the increased risk is mediated by postoperative anemia, hypovolemia, or blood transfusion used to treat it [39, 40].

### Perioperative aspirin and postoperative venous thromboembolism

Anticoagulant is often used after non-cardiac surgery for VTE prophylaxis but aspirin offers an effective alternative [28]. The incidence of VTE at 30 days after non-cardiac surgery is 1–5% and includes DVT and pulmonary embolism (PE) [41]. Aspirin is less expensive than anticoagulants and one-third of patients already take aspirin preoperatively [6]. The Antiplatelet Trialists' Collaboration meta-analysis showed a statistically significant reduction in DVT associated with antiplatelet therapy, and the benefit was consistent across general surgery (37% reduction; $P < 0.00001$), trauma surgery (60% reduction; $P < 0.005$), and elective orthopedic surgery (51% reduction; $P = 0.04$) [41]. Reduction in PE associated with aspirin was also significant in the three surgical groups: general surgery (71% reduction; $P < 0.00001$), trauma surgery (60% reduction; $P < 0.005$), and elective orthopedic surgery (51% reduction; $P = 0.04$). Consistent with the findings in the Antiplatelet Trialists' Collaboration meta-analysis, the PEP trial demonstrated that aspirin compared to placebo reduced VTE by almost 30% in patients who underwent surgery for hip fracture (HR 0.71; 95% CI, 0.54–0.94) and also reduced fatal PE (HR 0.42; 95% CI, 0.24–0.73) [28]. A recent randomized-controlled trial compared low-dose aspirin (i.e., 80 mg) to prophylactic dalteparin in 786 patients who underwent hip arthroplasty [42]. Patients were randomized after 10 days of dalteparin to aspirin or continued dalteparin for 28 days. Aspirin was shown to be non-inferior to dalteparin for the prevention of VTE, and there was no statistically significant difference in bleeding between both regimens. This evidence suggests that aspirin offers an effective alternative to an anticoagulant for postoperative VTE prevention. Although aspirin has no impact on VTE in POISE-2, there were very few VTE events (1%) and two-thirds of patients received prophylactic anticoagulation therapy [32]. Taken in totality, the data demonstrate that aspirin does prevent VTE in the perioperative setting; however, there is uncertainty if aspirin is as effective as a prophylactic anticoagulant.

## Conclusion

The current evidence does not support the administration of aspirin before and after non-cardiac surgery for the primary prevention of MI. Aspirin administration is associated with an increased risk of perioperative bleeding that remains significant up to 8 days after surgery.

Despite the neutral effect of aspirin to prevent perioperative MI, there is evidence suggesting that aspirin is beneficial in patients who suffer a perioperative MI, and if this signal is true it likely reflects the shift in risk between a major vascular complication and bleeding after surgery compared with before surgery.

## Disclosure of Conflict of Interests

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Bristol-Myers Squibb, Covidien, Octapharma, Philips' Healthcare, Stryker, and Roche Diagnostics. He has also participated in an advisory boarding meeting for GlaxoSmithKline, an expert panel meeting for Astra Zeneca, and a consultancy meeting for Boehringer Ingelheim. The other authors state that they have no conflict of interest.

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