Perioperative Aspirin Management After POISE-2: Some Answers, but Questions Remain

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Aspirin constitutes important uninterrupted lifelong therapy for many patients with cardiovascular (CV) disease or significant (CV) risk factors. However, whether aspirin should be continued or withheld in patients undergoing noncardiac surgery is a common clinical conundrum that balances the potential of aspirin for decreasing thrombotic risk with its possibility for increasing perioperative blood loss. In this focused review, we describe the role of aspirin in treating and preventing cardiovascular disease, summarize the most important literature on the perioperative use of aspirin (including the recently published PeriOperative ISchemic Evaluation [POISE]-2 trial), and offer current recommendations for managing aspirin during the perioperative period. POISE-2 suggests that aspirin administration during the perioperative period does not change the risk of a cardiovascular event and may result in increased bleeding. However, these findings are tempered by a number of methodological issues related to the study. On the basis of currently available literature, including POISE-2, aspirin should not be administered to patients undergoing surgery unless there is a definitive guideline-based primary or secondary prevention indication. Aside from closed-space procedures, intramedullary spine surgery, or possibly prostate surgery, moderate-risk patients taking lifelong aspirin for a guideline-based primary or secondary indication may warrant continuation of their aspirin throughout the perioperative period. (Anesth Analg 2015;120:570–5)

Surgery enhances thrombotic risk because the surgical milieu produces an inflammatory and hypercoagulable state, reduces fibrinolysis, and can lead to fluctuating hemodynamics that in turn may adversely affect underlying CV disease.[1] Although uncommon, perioperative myocardial infarction carries a mortality rate of up to 25%.[2] Conversely, intraoperative bleeding is associated with surgical complications, risks of blood transfusion, and myocardial ischemia. Until recently, there has been a paucity of literature prospectively examining the optimal strategy for the perioperative management of aspirin.

Aspirin is an antiplatelet drug prescribed to patients with established CV disease (secondary prevention) or with certain CV disease risk factors (primary prevention) to reduce major adverse thrombotic events such as myocardial infarction and stoke. Aspirin is also prescribed to patients with coronary stents to prevent restenosis and thrombosis and for bioprosthetic valves to reduce thromboemboli. The use of aspirin for secondary prevention of thrombotic events is based on high-quality evidence. In the 2002 Antithrombotic Trialists' Collaboration meta-analysis of 135 000 high-risk patients in 195 studies, antiplatelet drugs (principally aspirin) were associated with a 22% reduction in the death rate from any vascular cause.[3] On the basis of multiple sources,[4–6] the aforementioned meta-analysis, and the current American Heart Association (AHA) guidelines,[7] high-risk patients, including anyone with coronary artery disease, cerebrovascular disease, or peripheral occlusive-arterial disease, should be prescribed aspirin indefinitely unless the risk of bleeding outweighs the benefit. Patients with coronary stents require dual antiplatelet therapy, typically aspirin and a thiendopyridine, for a minimum of 6 weeks (bare-metal stent) to 12 months (drug-eluting stent). The evidence supporting the use of aspirin for primary prevention is less robust. Current indications for aspirin in primary prevention only include diabetic men >50 years age or women >60 years of age who have ≥1 of the following additional risk factors: tobacco use, hypertension, hypercholesterolemia, albuminuria, or a significant family history of CV disease.[8]

There are limited prospective data to guide the use of aspirin during the perioperative period. A 2010 trial by Oscarsson et al.[9] was specifically designed to address this question in high-risk patients. A total of 210 patients at high risk for a perioperative major adverse cardiac event were randomized to either 75 mg aspirin or placebo. Study medication was begun 7 days preoperatively and continued 3 days postoperatively, and subjects in the placebo group who had previously been taking aspirin had restarted it on postoperative day 3. The authors found that continuing aspirin during the perioperative period significantly reduced major adverse cardiac events and did not increase perioperative bleeding-related complications.[9] Another small (n = 291) prospective trial, entitled STRATAGEM, further investigated the impact of preoperative maintenance or interruption of aspirin on thrombotic and bleeding events after elective noncardiac surgery in patients taking aspirin for secondary prevention indications. The results

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demonstrated no difference in bleeding or thrombotic risks between groups.[10]

Because of the relatively small size of the aforementioned studies, a large trial was deemed necessary to definitively address this important issue, which led to the recently published POISE-2 trial.[11] The goal of POISE-2 (as described by its authors in a separate article published contemporaneously with the trial itself) was "to determine the impact of low-dose aspirin" on "at-risk" patients undergoing noncardiac surgery.[12] The study, a randomized controlled multicenter international double-blinded trial conducted from 2010 to 2013, enrolled 10 010 patients undergoing noncardiac surgery. Two randomized arms were included as follows: perioperative aspirin versus placebo and perioperative clonidine versus placebo. The subsequent discussion focuses on the aspirin component. The primary outcome of POISE-2 was a composite of death or nonfatal myocardial infarction within 30 days of surgery. Subjects were stratified into 2 groups based on whether they were prior users of aspirin (continuation stratum) or aspirin naive (initiation stratum) and then randomized to receive either aspirin or placebo perioperatively. Thus, there were 4 final study groups. Figure 1 describes each of the 4 groups. POISE-2 inclusion criteria were as follows: known CV disease, major vascular surgery, or those with ≥3 of 9 prespecified risk criteria. Patients who had undergone percutaneous coronary interventions with a bare-metal stent within 6 weeks of randomization or a drug-eluting stent within 1 year of randomization were excluded.

The primary outcome (composite of death or nonfatal myocardial infarction within 30 days) was statistically similar between groups (aspirin [7.0%] versus placebo [7.1%], $P = 0.92$) and had similar results in both the initiation and continuation strata. Major bleeding, mostly at the surgical site, occurred more often in the aspirin group compared with the placebo group (4.6% vs 3.8%, $P = 0.04$). However, there were no differences in "clinically important hypotension" or "life-threatening" bleeding between these 2 groups. On the basis of these results, the authors, along with the accompanying editorial, concluded that the risk of continuing perioperative aspirin may be greater than the risk of cessation.[11,13] Although the findings of POISE-2 are important and germane to all perioperative clinicians, certain components of the study methodology warrant scrutiny.

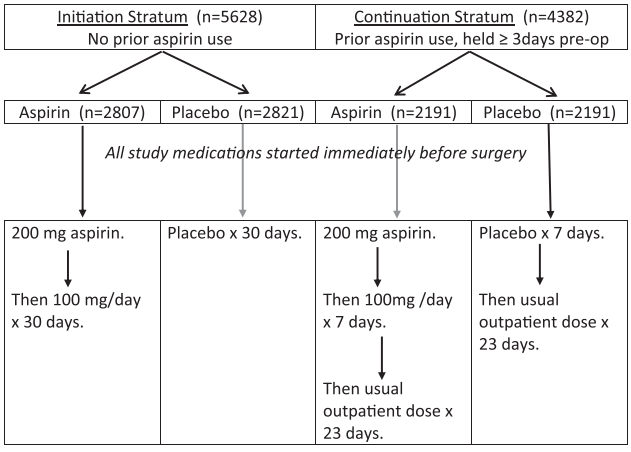

Figure 1. Explanation of PeriOperative ISchemic Evaluation-2 trial group stratification.

On the basis of the aforementioned AHA guidelines, patients in POISE-2 who had a definitive primary or secondary prevention indication for lifelong aspirin made up <36.3% of all patients assigned to the aspirin group (history of vascular disease [32.7%] and transient ischemic attack [3.6%]). Regarding subjects included by the risk criteria, there is insufficient information to discern whether these additional subjects met AHA primary prevention criteria for aspirin therapy. It is also unclear whether the number of subjects who were already taking aspirin (continuation stratum) were taking it for a recommended primary or secondary indication. Based on the available study details, it appears that nearly two-thirds of subjects in the aspirin group may not have met primary or secondary prevention criteria for aspirin therapy but were included because of planned high-risk surgery of which only 4.9% was vascular. Thus, the high-risk eligible group may have been significantly diluted with lower-risk patients. Most study patients (whether already taking aspirin or not) appear to have been at low risk for thrombotic complications.[14] Furthermore, within 3 days postoperatively, a number of antiplatelet and anticoagulation drugs were administered to subjects: 65% received prophylactic anticoagulation, 4% to 4.5% of both groups received therapeutic anticoagulation, and 1.2% of both groups received a P2Y12 inhibitor. Any one of these regimens may have confounded the results.[14] Of particular significance may have been the concomitant administration of nonsteroidal anti-inflammatory drugs (NSAIDs). NSAIDs are relatively contraindicated in the setting of established CV disease because of the increased risk of thrombosis.[15–17] In POISE-2, 9.5% of patients in the aspirin strata had been prescribed NSAIDs.[11] Aspirin prescribed in the setting of NSAID administration may lead to the potential for aspirin resistance. Aspirin resistance has been defined according to clinical (a standard dose of the drug fails to prevent an atherothrombotic event) and pharmacological criteria (the failure of aspirin to inhibit platelet function).[18,19] The concurrent administration of certain NSAIDs has been postulated as a potential cause of aspirin resistance because of the inability of aspirin to access the receptor binding sites of the cyclooxygenase-1 enzyme because of substrate competition.[20–22]

Of 7 safety outcomes evaluated in POISE-2, major bleeding was the only one to reach significance, although there were not any differences in life-threatening bleeding or significant hypotension. However, in a post hoc analysis, a composite of major or life-threatening bleeding did demonstrate a significant increased risk for these events for up to 7 days postoperatively in the aspirin group. These findings contradict a previous large meta-analysis as well as a previous smaller prospective trial, suggesting that the bleeding-related risks for most nonclosed space procedures are not significant when patients continue low-dose aspirin perioperatively.[9,23] Also excluded were patients scheduled for carotid endarterectomy (CEA), a procedure associated with known significant coronary and cerebral thrombotic risks typically performed in a high-risk population. The American College of Chest Physicians (ACCP) recommends perioperative and lifelong low-dose aspirin therapy for patients undergoing CEA.[24] The multiple

methodological issues with the POISE-2 design attenuate the antithrombotic distinctions between the placebo and aspirin groups in patients at high risk for an adverse perioperative CV event. These include only one-third of recruited patients were at high risk, only two-thirds underwent high-risk procedures (of which only 4.9% included vascular surgeries), and the exclusion of patients undergoing CEA or those with a recent coronary stent. The small percentage of patients recruited who were undergoing vascular surgery leads one to speculate that the vascular surgeons, primary care physicians, or preoperative clinicians caring for this typically high-risk patient group were disinclined to enroll these patients into a trial that could lead to the temporary interruption of aspirin therapy. As a consequence, the ability to assess the impact of perioperative aspirin administration or cessation on high-risk patients alone or in patients

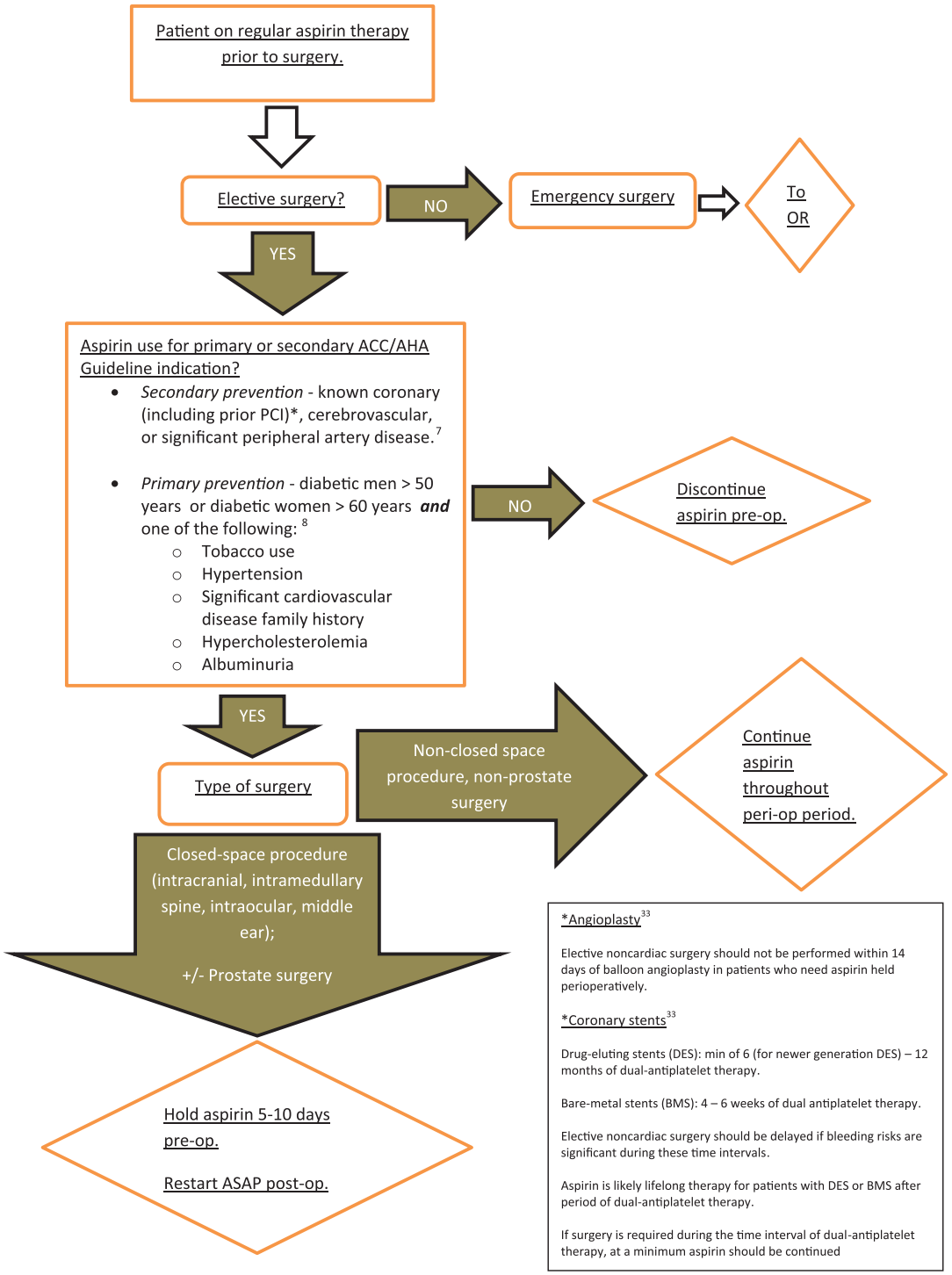

Figure 2. Algorithm for the management of patients presenting for surgery while receiving aspirin therapy. OR = operating room; ACC = American College of Cardiology; AHA = American Heart Association; PCI = percutaneous coronary intervention.

undergoing high-risk procedures is limited. POISE-2 does affirm that aspirin continued in the perioperative period may contribute to bleeding-related complications.

Aspirin also has a role in the context of venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and pulmonary embolism (PE). Virtually all hospitalized patients have at least a single VTE risk factor, whereas surgical patients typically have multiple risk factors and a greater overall risk.[25] In POISE-2, DVT and PE were both tertiary outcomes. Neither the aspirin nor placebo groups demonstrated a difference in the occurrence of either DVT or PE; however, the trial was not powered adequately to assess either of these outcomes.[11] It is also unclear whether the reported VTE outcomes in POISE-2 were recurrent or de novo during the study period. A broader examination of the literature highlights the role of aspirin in primary and secondary VTE prevention. In primary VTE prevention in the perioperative period, there is mixed literature in terms of the defined end points (i.e., asymptomatic versus symptomatic DVT, PE, and death), and the trials are mostly limited to lower-limb orthopedic surgery. The early seminal trial in this area was the Pulmonary Embolism Prevention trial, in which 13 356 patients undergoing hip fracture repair and 4088 patients undergoing elective hip arthroplasty were given daily aspirin or placebo starting preoperatively until 35 days postoperatively. Regardless of heparin use, PE risk was decreased by 43%, and symptomatic DVT risk was decreased by 23% in the aspirin group.[26] A 2013 trial by Anderson et al.[27] in 778 patients undergoing elective hip arthroplasty demonstrated that 28 days of aspirin prophylaxis was noninferior compared with 10 days of dalteparin prophylaxis. The most recent conference of ACCP focused its recommendations on clinically relevant VTE-related outcomes, less on asymptomatic DVT, and more on bleeding concerns. None of these ACCP recommendations were graded 1A. The following 1B recommendations for VTE prophylaxis included the use of a single drug from a list that includes: aspirin, low-molecular-weight heparin, low-dose unfractionated heparin, fondaparinux, dabigatran, apixaban, and rivaroxaban.[28] For the secondary prevention of VTE (especially in a previous "unprovoked" or idiopathic DVT), aspirin does confer a significant benefit in reducing the risk of recurrent VTE by one-third and should likely be continued perioperatively.[29–31] In a recent editorial, the issue of aspirin use in recurrent VTE was parsed out between those at high risk versus moderate risk of recurrence. High-risk patients likely need long-term or lifetime warfarin or a similarly effective novel oral anticoagulant, whereas those considered moderate risk should be maintained on aspirin. Interestingly, these editorialists do not say with certainty whether aspirin should be lifelong.[32] Patients presenting for nonclosed surgery taking aspirin for one of the aforementioned VTE-related indications should likely be maintained on it throughout the perioperative period.

In July 2014, the American College of Cardiology/AHA released an updated set of guidelines on perioperative CV evaluation and management of patients having noncardiac surgery.[33] These guidelines include a number of recommendations regarding perioperative aspirin management. For patients who have not had previous coronary stenting, these guidelines recommend that "it may be reasonable to continue aspirin when the risk of potential increased cardiac events outweighs the risk of increased bleeding." The guideline authors note that only 23% of the study population in POISE-2 had known prior coronary artery disease; therefore, continuation of aspirin throughout the perioperative period may still be reasonable in high-risk patients. The guidelines also state that "initiation or continuation of aspirin is not beneficial in patients undergoing elective noncardiac noncarotid surgery who have not had previous stenting."[33] These recommendations seem to be focused primarily on cardiac disease and more specifically on the perioperative management of aspirin in the patient with a coronary stent. It is important to note that there is no discussion in these new guidelines regarding aspirin in the perioperative period for those with cerebrovascular disease, severe peripheral arterial disease, or those with a history of an acute coronary syndrome that is managed medically. Because the literature examining the use of perioperative aspirin in high-risk patients is still limited, aspirin should likely be continued in these patients as well. Figure 2 presents a guideline-based algorithm and recommendations on the management of a patient presenting for surgery while taking aspirin.

In summary, as affirmed by POISE-2, in patients without a definitive guideline-based indication for aspirin, the drug should likely be held preoperatively in those already receiving it, and it should not be initiated to prevent thrombotic events. However, it is still not possible to conclude whether temporary cessation of aspirin for surgery is warranted in high-risk patients. High-risk patients taking lifelong aspirin for a guideline-based primary or secondary indication likely warrant continuation of their aspirin throughout the perioperative period except when undergoing a closed-space procedure, intramedullary spine, or prostate surgery. A trial specifically designed to examine the bleeding and thrombotic risks associated with continuation versus cessation of aspirin in high-risk patients undergoing high-risk surgery is needed.

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