Aspirin in the perioperative period: a review of the recent literature

Mathew B. Kiberd and Richard I. Hall

Purpose of review
The indications for aspirin (ASA) for both primary and secondary prevention of thrombotic events continue to evolve. We review some of these indications and the recent literature regarding the perioperative administration of ASA.

Recent findings
ASA for primary prevention of cardiac ischemia, stroke, cancer, and death remains controversial. When used for primary prevention, ASA may be safely discontinued perioperatively. Patients with coronary or carotid artery stents should continue to receive ASA perioperatively. For patients with ischemic heart disease currently receiving ASA for secondary prevention of cardiac ischemia and stroke undergoing general surgery, orthopedic surgery, ophthalmological surgery, cardiovascular surgery, major vascular surgery, or a urological procedure, continuation of ASA is probably well tolerated, but further study is required. There is no indication to initiate ASA perioperatively in patients with stable ischemic heart disease as the risks outweigh the benefits. Until further data become available, decisions regarding the perioperative continuation of ASA should be made on a case-by-case risk–benefit analysis.

Summary
The continuation or discontinuation of ASA perioperatively remains a complicated issue. Further, well designed trials are needed for additional clarification.

Keywords
antiplatelet agents, aspirin, perioperative medicine

INTRODUCTION
Aspirin (ASA) inhibits platelet function by binding to a serine residue in the platelet cyclooxygenase (COX) receptor thus preventing the formation of thromboxane A2 and subsequent platelet aggregation [1]. The major adverse side-effect is increased bleeding risk [1]. Following ASA discontinuation, return of platelet function sufficient to produce thrombotic effects occurs within 2–4 days [2]. For perioperative physicians, consideration must be given to balancing the risk of major cardiovascular complications when ASA is discontinued against the increased risk of bleeding if ASA is continued [1]. Herein, we review the current uses of ASA and its perioperative management.

ASPIRIN FOR PRIMARY PREVENTION
ASA is commonly used for primary prevention of a wide range of conditions including prevention of stroke and coronary artery disease [3*,4–8], as well as malignancy [9*]. Regardless of the indication, when prescribed for primary prevention, ASA may be safely discontinued perioperatively.

ASPIRIN FOR SECONDARY PREVENTION
ASA administration is a cornerstone of secondary prevention of cardiovascular disease [3*,10]. In this section, the primary indications for its use are reviewed.

Ischemic heart disease
ASA therapy for patients following a previous nonfatal myocardial infarction (MI), coronary
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KEY POINTS

- Patients on ASA for primary prevention can safely discontinue ASA preoperatively.
- For patients with cardiac risk factors, ASA should not be initiated preoperatively even in high-risk groups.
- Patients on ASA for secondary prevention should continue or discontinue ASA on the basis of patient and surgical factors on a case-by-case basis.

revascularization, or stroke results in a significant reduction in subsequent mortality [10,11]. As a result, ASA is recommended as lifelong therapy in these patients. In this population, it has been estimated that perioperative withdrawal of ASA increases the odds of a major adverse cardiovascular event (MACE) by a factor of 3 [12]. When combined with the prothrombotic environment produced by surgery, abrupt cessation of ASA may lead to a rebound hypercoagulable state, which likely accounts for some of this excess risk [13]. In a meta-analysis of over 49,000 patients, continued perioperative ASA led to a 1.5 times increase in bleeding events but none requiring medical intervention [14]. As a result, current guidelines support continuation of ASA in the perioperative period for patients who are on it for secondary prevention of ischemic heart disease [15*] and in patients who have had previous coronary artery stenting [16*].

Cerebral vascular disease

Compared with placebo, ASA reduces the risk of recurrent stroke [10]. Furthermore, there is evidence that dual antiplatelet therapy may be superior to ASA alone at reducing this risk. In a meta-analysis of 24 studies, Malloy et al. [17] found that the combination of ASA and dipyridamole was associated with an approximately 20% reduction in stroke risk compared with ASA monotherapy [Rate ratio (RR) 0.78, 95% confidence interval (CI) 0.64–0.93]. Current guidelines recommend either monotherapy with ASA or dual therapy with ASA and dipyridamole. [18] For patients undergoing carotid revascularization, ASA should be continued perioperatively [19*].

Congestive heart failure

ASA use as secondary prevention in patients with nonischemic congestive heart failure (CHF) is controversial [20*]. In a retrospective study of 1500 patients, low-dose ASA was associated with a hazard ratio of 0.58 for reduction in CHF hospitalizations [20*]. A mechanistic explanation for these findings has not been fully elucidated, although it has been suggested that ASA affects the renin angiotensin system, which may account for its impact on fluid regulation [21]. There are no randomized trials addressing the specific question of ASA’s benefit in the perioperative period in patients with CHF. Given current data, it would seem reasonable to continue ASA in the perioperative period in patients with CHF unless the risk of bleeding is significant.

SPECIAL SURGICAL POPULATIONS

Unique considerations for the perioperative use of ASA in each of the surgical subspecialties are reviewed here.

General surgery

The Perioperative Ischemia Evaluation 2 (POISE-2) study randomized 10,010 patients with risk factors for vascular complications and scheduled for noncardiac surgery to ASA or placebo for 30 days perioperatively [22**]. The groups were stratified on the basis of whether participants were currently receiving ASA (continuation strata) or not (initiation strata). Overall, there was no difference in the rate of death or nonfatal MI between groups (7.0% vs. 7.1%, hazard ratio (HR) 0.99, 95% CI 0.86–1.15, P = 0.92); however, major bleeding events were increased in the ASA group (4.6% vs. 3.8%, HR 1.23, 95% CI 1.01–1.49, P = 0.04). POISE-2 results have been criticized for several reasons: patients who met the AHA criteria for primary or secondary indications for ASA made up only 36% of the ASA group, and there is insufficient information provided as to what the indication for ASA was in the remaining patients; in the continuation strata, it is unknown what proportion of patients were taking ASA for a primary or secondary indication raising the possibility that the effect of ASA was masked by a high proportion of low-risk patients receiving treatment; in the immediate postoperative period, approximately 65% of patients received an antithrombotic or anticoagulant agent that is a significant confounder for the primary outcome; about 9.5% of patients in the ASA group were prescribed a nonsteroidal anti-inflammatory agent that may have blocked the effect of ASA (see below) [23**]; ASA was stopped for 3–7 days prior to surgery in the continuation strata – a period which, it might be argued, would put them at increased risk for thrombotic complications [22**]. Although in the population as a whole there was no increased risk of kidney injury, in the continuation strata, there was a significant increase in the risk of kidney injury requiring dialysis in the ASA-treated group (HR 2.41,
95% CI 1.05–5.51, P = 0.04) [24**]. The conclusion from POISE-2 was that ASA should not be initiated perioperatively, even in high-risk groups [22**,25]. The findings from POISE-2 are consistent with the results of the Pulmonary Embolism Prevention trial, in which 13,356 patients undergoing hip surgery were randomized to receive either 160 mg ASA or placebo, and there was no difference in outcomes between groups [26]. On the basis of current evidence, the American Heart Association/American College of Cardiology (AHA/ACC) guidelines do not support initiation of ASA in the perioperative period [15**]. The AHA/ACC suggest and we support that for patients undergoing major general surgery and already receiving ASA for secondary prevention of ischemic complications, continuation of ASA may be reasonable in patients at high risk of cerebrovascular or coronary ischemic complications. However, the decision to continue ASA should be based on a risk–benefit analysis made between cardiologist, surgeon, and anesthesiologist.

**Neurosurgery**

For neurosurgical patients, bleeding while receiving ASA into a noncompressible closed space can be catastrophic [27]. In patients undergoing elective craniotomy, and in the absence of guidelines specifically addressing this issue, we recommend cessation of ASA perioperatively as, even in patients at high risk for cardiovascular complications, on balance the complications of an intracranial bleed offset the cardiovascular risk. In the setting of intracranial hemorrhage (ICH), the administration of platelets has been used to attempt to reverse the antiplatelet effects of ASA. Owing to ASA's short half-life and lack of active metabolites, transfused platelets are unlikely to lose functional capacity [28**]. However, retrospective studies have shown that platelet transfusion does not appear to affect outcomes in the setting of ICH [28**]. The AHA and the American Stroke Association consider platelet transfusion an 'investigational' therapy [29]. The administration of desmopressin (0.3 mcg/kg) has been used under these circumstances, as it may also enhance platelet function [28**].

Discontinuation of ASA prior to lumbar fusion is controversial. Kang et al. [30] conducted a retrospective case study of 76 patients who had undergone spinal fusion and found that, as compared with those who were not receiving ASA, those who had stopped ASA for at least 7 days preoperatively had significantly higher blood drainage after surgery and postoperative transfusion requirements. Intraoperative blood loss between groups, however, was not different [30]. Patients who have lumbar decompression and fusion surgeries frequently take NSAIDs for pain relief. Park et al. [31] found that both ASA and NSAIDs independently increased total blood loss after lumbar fusion. Their concomitant use further increased the risk of serious bleeding perioperatively. For patients at low to moderate risk of cardiovascular complications, we recommend discontinuing ASA (and NSAIDs) prior to spine surgery. In the patient population undergoing cerebral endovascular repair, antiplatelet therapy with ASA and another antiplatelet agent is sometimes used, despite lack of high-quality evidence [32]. As a consequence of the increasing use of endovascular repair and stents for the management of cerebral aneurysms and vasospasm, more patients on dual antiplatelet therapy-initiated preprocedure may present for emergent neurosurgical procedures for device-related bleeding complications. Shimamura et al. [33**] reviewed 35 consecutive ruptured sacular aneurysms that underwent coiling. All these patients received loading doses of ASA and clopidogrel, and none had a higher bleeding or complication rate than the institutional rate experienced prior to dual antiplatelet therapy. Thrombotic events in patients who were receiving dual antiplatelet therapy were lower than institutional rates [33**].

Traumatized patients with closed head injury who have been on ASA before injury present a unique challenge. ASA has been implicated in increasing the risk of traumatic subdural hematoma [34]. However, in a study of 45 consecutive patients requiring craniotomy for subdural hematoma, it was found that ASA use was associated with a mortality benefit. The authors hypothesized that this may be related to a reduction in trauma-related microthrombotic complications [35].

**Ophthalmology**

Many patients with diabetes will require vitreoretinal surgery. Excessive intraoperative or perioperative bleeding can be sight threatening. However, there is emerging evidence that either ASA or clopidogrel continued through the perioperative period does not increase the risk of major bleeding. In a study of 85 patients with uninterrupted ASA and/or clopidogrel, there was a bleeding rate of 22% [36] However, none of the events had an effect on outcome. The only sight-threatening bleed occurred as the result of a technical error. Cataract surgery can also be safely performed with the continuation of ASA, dual antiplatelet therapy, or oral anticoagulation [37]. We urge caution with respect to these
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results, as the number of patients studied was small, and they were single center in design, thus limiting generalizability of the results. They should be considered hypothesis-generating until more data are available. In the interim, we suggest that the perioperative management of ASA in this population should be based on a risk–benefit analysis on a case-by-case basis.

Cardiac surgery
Perioperative ASA therapy has been associated with improved postoperative outcomes in patients having coronary artery bypass graft surgery (CABG) [38,39]. However, continuation of ASA prior to CABG has been associated with an increased risk of perioperative bleeding. Jacob et al. [40] analyzed bleeding and outcomes of 4143 CABG patients on chronic ASA, 2298 of whom discontinued ASA 6 or more days before surgery (early discontinuation) and 1845 of whom took ASA within 5 days of surgery (late use). They found no difference in in-hospital mortality, MI, or stroke between the groups. Those patients who took ASA within 5 days of surgery did have higher rates of both intraoperative and postoperative transfusion; nevertheless, reoperation rates were similar between the groups [40]. Weighing the balance of risk and benefit, the ACC/AHA and American College of Chest Physicians both advise no interruption in ASA therapy for patients who present for CABG surgery [5,41].

Major vascular and peripheral vascular surgery
Practice guidelines recommend ASA for patients with peripheral vascular disease [42]. In a meta-analysis of randomized clinical trials investigating the role of ASA in preventing complications in patients with peripheral vascular disease, Berger et al. [43] found a statistically significant reduction in nonfatal stroke but no difference in the primary end point of cardiovascular events (nonfatal MI, nonfatal stroke, and cardiovascular death). Dual antiplatelet therapy is generally not recommended in this population, and ASA continuation throughout the perioperative revascularization period is supported by guideline recommendations [5,44,45]. There is no contraindication to regional or neuraxial anesthesia in patients taking ASA therapy [46].

Transplant surgery
Perioperative ASA use prior to renal transplantation has been associated with an increased risk of blood transfusion [47] and is a risk factor for acute kidney injury [24,25,26,27]. In addition, postoperative blood transfusion is an independent risk factor for graft loss [48,49]. On the basis of these observations, for renal transplant patients, we recommend holding ASA prior to kidney transplant surgery such as those involving living related donors.

There has been limited research regarding the management of ASA in patients undergoing liver transplantation. Hepatic artery thrombosis (HAT) is one of the leading causes of graft failure, and in one retrospective study examining survival of segmental grafts in patients receiving ASA postoperatively, no incidence of HAT was observed [49]. One cohort study involving 469 patients examined the impact of early postoperative initiation of ASA 325 mg for the prevention of HAT [50]. They found reduced rates of early HAT in patients who received ASA without increased rates of major bleeding. These results indicate that there may be a role for ASA therapy after liver transplant, but further research is required before any recommendations can be made.

Orthopedics
In POISE-2, there was a large cohort of the patients (approximately 38% in both groups) undergoing orthopedic surgery. Those who were in the continuation group did not have a higher risk of major bleeding [22]. Guidelines suggest that patients undergoing total hip or other major joint arthroplasty may benefit from having ASA discontinued due to the bleeding risk [51]. Otherwise, continuing ASA when prescribed for secondary prevention of thromboembolic events is generally advisable.

Urology
Historically, there has been significant controversy about ASA use for patients undergoing urological procedures [52]. POISE-2 has provided data that continuing ASA is well tolerated in this population [22]. A recent systematic review undertaken by a multidisciplinary panel that included urologists, cardiologists, and hematologists reviewed the literature specific to urological surgery [52]. They concluded that, when prescribed as secondary prevention, ASA can be continued for all urological surgeries with appropriate attention to hemostasis. They make the caveat that if ASA is not clearly indicated; it should be stopped.

DRUG–DRUG INTERACTIONS
Several drugs are known to affect ASA’s antiplatelet and antithrombotic activity, including the ones commonly prescribed in the perioperative period. These drug–drug interactions are significant, as they
directly impact the effectiveness of ASA as an antithrombotic agent.

NSAIDs are commonly prescribed for pain management. Meek et al. [53] have shown that COX-1 inhibitors such as ibuprofen and naproxen given 2 h before ASA significantly inhibit ASA’s antithrombocyte activity [53]. Highly selective COX-2 agents such as etoricoxib and meloxicam did not alter ASA inhibition of thrombocyte function. However, these agents have been associated with increased cardiovascular complications in and of themselves [53,54]. Saxena et al. [55] were able to demonstrate that diclofenac and ketorolac, commonly prescribed perioperatively, do not alter platelet inhibition of ASA in vitro.

Metamizole is a nonopioid analgesic also used as part of a multimodal pain management strategy. In a small study involving 66 patients, coadministration of metamizole with ASA restored thromboxane levels to values consistent with non-ASA use [56]. It is believed that metamizole reversibly binds to the COX-1 enzyme preventing ASA from binding to its active site [56].

Some herbal supplements and vitamins have also been implicated in drug–drug interactions with ASA. Both Ginkgo biloba and vitamin E may increase ASA’s anticoagulant effects [57,58]. New data suggest that N-3 polyunsaturated fatty acid supplementation is well tolerated in patients on ASA and does not alter its efficacy [59].

PREVENTION OF THROMBOEMBOLIC COMPLICATIONS

ASA has been used in the postoperative period to reduce the risk of deep venous thrombosis or pulmonary embolism [26,60]. In the Pulmonary Embolism Prevention study, 17 444 patients’ status after hip fracture surgery or elective arthroplasty were randomized to receive ASA (160 mg once a day) or placebo for up to 35 days postoperatively [26]. ASA reduced the risk of pulmonary embolism or deep venous thrombosis by 34% (95% CI 17–47%, \( P = 0.0003 \)). However, among hip fracture patients, the risk of nonfatal MI or fatal ischemic heart disease was also increased (hazard ratio 1.33, 95% CI 1.00–1.78) [24*]. This study has been criticized as the use of unfractionated or low molecular weight heparin was unrestricted between the groups. In addition, the majority of ASA’s clinical benefit was observed among hip fracture patients, not those undergoing elective arthroplasty.

COMPLIANCE

As many as 28% of patients prescribed ASA do not take it as prescribed, making the question of whether to continue it in the perioperative period moots [61*]. Point-of-care tests may allow clinicians to determine patient compliance prior to undergoing surgery [62]. Conversely, ASA has been well marketed and available over the counter. Many patients start ASA without seeking a physician’s opinion. Careful attention to identifying over-the-counter use of ASA should be part of routine perioperative assessment. In these patients, the drug may be safely discontinued 7 days preoperatively, as by definition it is being used for primary prevention, and there should be full return of platelet function at that time [2].

CONCLUSION

The question of whether or not to initiate or continue ASA in the perioperative period is a frequently encountered problem. The POISE-2 trial is one of the largest randomized trials to address the role of ASA in the perioperative period. In this trial, there was no benefit to the initiation of ASA in patients with risk factors for vascular complications. In patients already on an ASA regimen, temporary cessation prior to surgery did not result in an increased risk of death or MI. However, issues with the study methodology should temper conclusions from this study. In the absence of evidence of significant bleeding risk, for most surgeries, the current trend is to continue ASA use preoperatively in patients taking it for secondary prevention of cardiovascular disease. However, decisions about perioperative ASA should be made with all providers in consensus and on an individualized basis, weighing the risks of bleeding against the risk of thrombotic complications.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as: of special interest ** of outstanding interest

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21. basis of methodology. Sustained by CHF exacerbation. However, these results cannot be considered causal on the

20. stenosis. They recommend that ASA not be discontinued in the perioperative

19. use of antithrombotic therapy in patients with carotid artery

18. patients with coronary stents.

17. The effect of ASA on primary prevention of cardiovascular disease and cancer is

16. The ACC/AHA guideline provides guidance on the perioperative management of

15. The current consensus article on the perioperative management of patients with coronary stents.

14. This is the European Consensus article on the perioperative management of patients with coronary stents.


11. The ACC/AHA guideline provides guidance on the perioperative management of patients with cardiovascular disease. This includes recommendations on the perioperative management of ASA and other antiplatelet drugs.


8. This is the European Consensus article on the perioperative management of patients with coronary stents.


6. The authors review the use of antithrombotic therapy in patients with cardiac artery stenosis. They recommend that ASA not be discontinued in the perioperative period as the risk of MI is greater than the risk of life-threatening bleeding.


4. In this retrospective cohort study, ASA use was associated with fewer admissions for CHF exacerbation. However, these results cannot be considered causal on the basis of methodology.

This review discusses the literature for ASA in the perioperative period in patients having lower extremity bypass and endovascular revascularization. The authors conclude that there is level-one evidence to recommend the use of ASA in these populations.


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