Should More Patients Continue Aspirin Therapy Perioperatively?

Clinical Impact of Aspirin Withdrawal Syndrome

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Background: For patients with established cardiovascular disease, taking aspirin is considered a critical therapy. The cessation of aspirin can cause a platelet rebound phenomenon and prothrombotic state leading to major adverse cardiovascular events. Despite the risks of aspirin withdrawal, which are exacerbated during the perioperative period, standard practice has been to stop aspirin before elective surgery for fear of excessive bleeding. Mounting evidence suggests that this practice should be abandoned.

Methods: We performed a PubMed and Medline literature search using the keywords aspirin, withdrawal, and perioperative. We manually reviewed relevant citations for inclusion.

Results/Conclusions: Clinicians should employ a patient-specific strategy for perioperative aspirin management that weighs the risks of stopping aspirin with those associated with its continuation. Most patients, especially those taking aspirin for secondary cardiovascular prevention, should have their aspirin continued throughout the perioperative period. When aspirin is held preoperatively, the aspirin withdrawal syndrome may significantly increase the risk of a major thromboembolic complication. For many operative procedures, the risk of perioperative bleeding while continuing aspirin is minimal, as compared with the concomitant thromboembolic risks associated with aspirin withdrawal. Those cases where aspirin should be stopped include patients undergoing intracranial, middle ear, posterior eye, intramedullary spine, and possibly transurethral prostatectomy surgery.


In the United States, cardiovascular disease, which includes coronary artery disease (CAD), cerebrovascular disease (CVD), and peripheral vascular disease (PVD), adversely affects over one third of adults1 and is by far the leading cause of morbidity and mortality.2 It is a contributing factor in nearly 60% of all deaths2 and is directly responsible for 900,000 deaths per year.3 Moreover, the lifetime risk of cardiovascular disease after the age of 40 is 66% for men and 50% for women.2 Together, CAD and stroke account for nearly 85% of deaths in diabetic patients older than 65 years.4

The perioperative setting can be an especially risky period for patients with established cardiovascular disease or cardiovascular risk factors. Patients undergoing noncardiac surgery are at significant risk for perioperative major adverse cardiovascular events. It is likely that the incidence of cardiovascular complications after noncardiac surgery is underestimated.5 Myocardial infarction is the most common perioperative complication in patients with risk factors for CAD and has an associated mortality rate of 15% to 25%.6 Furthermore, even a mildly elevated troponin postoperatively has been shown to be an independent predictor of increased perioperative morbidity and mortality.7

More than 50 million adults in the United States take aspirin regularly for the purposes of primary and secondary prevention of cardiovascular disease.8 A likely important contributor to perioperative morbidity and mortality includes the cessation of aspirin use preoperatively.7

We review the basis for aspirin use in atherosclerotic disease, aspirin pharmacology, and the aspirin withdrawal phenomenon or syndrome. We also examine the literature describing the cardiovascular risks of discontinuing versus maintaining aspirin therapy, and the documented bleeding risks associated with perioperative aspirin use.

ASPIRIN IN SECONDARY AND PRIMARY PREVENTION OF CARDIOVASCULAR DISEASE

Aspirin, by virtue of its ability to inhibit platelet aggregation and prevent thrombosis, plays a critical role in the treatment and in the secondary (preventing recurrence of disease) and primary (preventing first occurrence of disease) prevention of acute myocardial infarction and stroke.5,9 A multitude of randomized clinical trials and meta-analyses have provided strong support for aspirin therapy especially for secondary prevention, where the risk-versus-benefit ratio is clear.10–20 The benefits of aspirin in secondary prevention of cardiovascular disease are well established. According to guidelines from the American Heart Association (AHA)/American College of Cardiology (ACC) and the American College of Chest Physicians (ACCP), aspirin therapy should be started and continued indefinitely unless absolutely contraindicated in virtually all patients with established coronary artery or other atherosclerotic disease.21,22

It is widely understood that patients with preexisting cardiovascular disease should take aspirin indefinitely without interruption.23 The long-term benefit of aspirin in preventing subsequent adverse cardiovascular events has been closely studied by the Antithrombotic Trialists’ Collaboration. This group has published a large meta-analysis that drew on the results of nearly 200 randomized trials of antiplatelet therapy in high-risk patients with a history of cardiovascular disease. The analysis demonstrated an approximately 25% reduction of death from any vascular cause, myocardial infarction, and stroke with antiplatelet therapy versus placebo in patients with acute or preexisting cardiovascular events.17

The risk-versus-benefit ratio of aspirin therapy for primary prevention, however, is much less clear than for secondary prevention. This is because the absolute risk reduction achieved from aspirin

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in primary prevention is substantially lower than in secondary prevention, while the complication rate is similar.\textsuperscript{20} The Antithrombotic Trialists’ Collaboration has also recently published a meta-analysis of 6 randomized primary prevention trials. They concluded that aspirin reduced the incidence of vascular events (12\% proportional reduction or 0.07\% per year absolute reduction, $P = 0.0001$), mainly nonfatal myocardial infarction, by a small but statistically significant amount.\textsuperscript{20} The largest reduction was for nonfatal myocardial infarction; 23\% proportional reduction, $P < 0.0001$. The proportional reductions in the aggregate of all serious vascular events were similar for both men and women. There was no reduction in vascular-related mortality attributed to aspirin use. In addition, they found that aspirin significantly increased the rate of major gastrointestinal bleeding and also increased the risk of hemorrhagic stroke. The authors therefore concluded that aspirin therapy is of uncertain value for primary cardiovascular prevention and that strong consideration must be given to balancing the reduction in thrombotic events with the risk of major bleeding.\textsuperscript{20} Although several large randomized trials and meta-analyses have demonstrated a benefit with aspirin therapy in the primary prevention of cardiovascular disease, the net benefit of aspirin in primary prevention is most pronounced in high-risk patients, and unlike in secondary prevention, this benefit appears to be limited to the reduction of nonfatal cardiovascular events only.\textsuperscript{22} There remains controversy about whether there are gender-specific differences with respect to the benefit of aspirin in primary prevention.\textsuperscript{25} The 2009 United States Preventive Services Task Force (USPSTF) Statement incorporated results from 5 major randomized controlled trials plus results from the Women’s Health Study, as well as from a gender-based meta-analysis of aspirin trials.\textsuperscript{24} On the basis of these data, the USPSTF recommends aspirin for primary prevention for women aged 55 to 79 years when the benefit of reduction in ischemic stroke outweighs the risk of bleeding, and aspirin therapy for men aged 45 to 79 years when the benefit from a reduction in myocardial infarction outweighs the risk of increased bleeding.\textsuperscript{1}

A 2010 position statement by the American Diabetes Association (ADA)/AHA/American College of Cardiology Foundation (ACCF) on the primary prevention of CAD in diabetics recommends aspirin for those who are at increased cardiac risk (10-year risk of a cardiac event of $> 10\%$).\textsuperscript{4} The ADA/AHA/ACCF defines diabetic patients at increased risk as men older than 50 years and women older than 60 years who have at least one of the following additional issues: tobacco use, hypertension, significant cardiovascular disease family history, hypercholesterolemia, and albuminuria.\textsuperscript{4} It is not recommended for diabetic men younger than 50 years or women younger than 60 years who do not have significant risk factors. The statement was equivocal regarding aspirin use in those at intermediate risk (10-year risk of a cardiac event of $5\%$ to $10\%$); this group includes younger patients with risk factors and older patients without significant risk factors.\textsuperscript{4}

In general, aspirin in primary prevention does not seem to affect cardiovascular mortality (except possibly in high-risk diabetic patients) and its benefit in preventing adverse cardiovascular events is proportional to the degree of underlying risk.\textsuperscript{25}

PHARMACOLOGY OF ASPIRIN

Aspirin, the most widely used platelet function inhibitor,\textsuperscript{26} mediates its effects through the arachidonic acid (AA)-thromboxane A2 (TXA2) pathway.\textsuperscript{26} AA is a normal dietary unsaturated fatty acid and the key substrate for prostaglandin synthesis. The conversion of AA to prostaglandin occurs throughout the body and is catalyzed by the enzyme cyclooxygenase (COX). There are 2 isoforms of COX, termed COX-1 and COX-2. COX-1 is constitutively expressed in most cells.\textsuperscript{3} In platelets, the isoform COX-1 regulates the production of prostaglandin H2, which in turn generates TXA2 via thromboxane synthase. TXA2 is responsible for activating new platelets, stimulating platelet aggregation, and vasoconstriction—consequently causing thrombosis and hemostasis. Under normal conditions, thrombosis is kept in check by the intact endothelial cell lining that is resistant to interactions with platelets and coagulation factors. When endothelial damage occurs, however, the hemostatic process (including platelet aggregation and activation) is initiated to stop bleeding. If this process becomes exaggerated, excess thrombosis can lead to unwanted vascular occlusion\textsuperscript{27} and adverse cardiovascular events.\textsuperscript{2}

Aspirin irreversibly inactivates COX through acetylation of the amino acid serine,\textsuperscript{8} with a 170-fold affinity for COX-1 over COX-2. By inactivating COX-1, aspirin renders the platelet incapable of synthesizing prostaglandin H2. Consequently, aspirin is extremely effective at blocking the production of thromboxane in platelets, rendering the platelets incapable of functioning normally, and thus preventing thrombosis and the damaging cardiovascular events that may result. At higher doses, aspirin also inhibits COX-2 dependent prostacyclin (PGI2) synthesis in the endothelial cell, which further inhibits platelet aggregation and induces vasodilation, but the degree to which aspirin’s COX-2 pathway inhibition impacts thrombogenesis remains controversial.\textsuperscript{26} Beyond its impact on platelet activation and aggregation, aspirin also impairs secondary hemostasis and thrombus stability by acetylating fibrinogen and enhancing fibrinolysis.\textsuperscript{28,29} Aspirin may further diminish the risk of cardiovascular disease through its ability to decrease inflammation\textsuperscript{30} by blocking C-reactive protein,\textsuperscript{18} although this benefit probably only occurs at higher doses than those used clinically.

The most common aspirin dosing regimen in the United States for purposes of platelet inhibition is either 81 mg or 325 mg once daily.\textsuperscript{4} However, as delineated in the Antithrombotic Trialists’ Collaboration, this dose is likely too high and that a lower dose range of 75 to 150 mg daily has an equally effective antiplatelet effect but with less associated bleeding risk than higher doses.\textsuperscript{19} As the inactivation of a given molecule of COX is irreversible, a single dose of 30 mg completely suppresses TXA2 production for 1 week.\textsuperscript{9,28} There is generally no additional effect on platelet activity at doses of aspirin more than 300 mg.\textsuperscript{9} Although the optimal dosing for particular indications remains uncertain, a body of evidence points to a better side-effect profile with lower aspirin doses.\textsuperscript{32–34} Coupled with the theoretical antithrombotic benefits of choosing a dose to inhibit COX-1 thromboxane production without inhibiting COX-2 prostacyclin synthesis, experts advocate for choosing the lowest effective dose based on the available evidence.\textsuperscript{9,35}

THE SCIENCE OF ASPIRIN WITHDRAWAL AND THE “ASPIRIN WITHDRAWAL SYNDROME”

As clinicians develop a patient-specific strategy for aspirin management in the perioperative period, it must be kept in mind that alternating between platelet inhibition and restoration of platelet function is not a simple “on-off” phenomenon. The basic science behind the aspirin–platelet interaction is vital to understanding the complex relationships between platelet inhibition, hemostasis, and inflammation related to perioperative stressors.

Platelets are anucleate cells produced daily from bone marrow megakaryocytes and have a lifespan of 8 to 10 days.\textsuperscript{36} Their role in hemostasis begins by detecting disrupted vascular endothelium and adhering to the newly exposed extracellular matrix. The adherent platelets aggregate and release platelet-activation mediators such as ADP and TXA2. TXA2 production is largely catalyzed by COX-1. Once activated, platelets generate thrombin and catalyze the coagulation cascade, ultimately resulting in a fibrin-platelet plug: the thrombus. Yet the platelet’s cell signaling ability via
After aspirin withdrawal. Beving et al.\(^5^4\) measured 12-L-hydroxy-rebound to levels beyond that of study controls and peaked at 7 to 14 days after aspirin withdrawal. Half of the subjects demonstrated normal platelet function at 72 hours and 80% normalized at 96 hours from aspirin withdrawal. However, it has been demonstrated that this catecholamine-induced platelet reactivity is only partly counteracted by aspirin therapy.\(^4^6\) Thus, platelets are fundamental to the processes of immunity and inflammation as well as hemostasis.

Upon withdrawal of aspirin therapy, the restoration of platelet function is variable and dependant on the prior aspirin dosing, the time interval from stopping therapy, and the patient’s inherent enzymatic response to aspirin therapy. As stated previously, after a single dose of aspirin, new platelet production begins to recover by approximately 10% per day and thus may take up to 10 days after discontinuing aspirin for full restoration of a platelet supply with normal COX activity.\(^4^9\) However, subjects may manifest normal hemostasis with as few as 20% of platelets maintaining normal COX activity.\(^5^0\) In one study of healthy subjects placed on a 2-week aspirin regimen that was subsequently withdrawn, half of the subjects demonstrated normal platelet function at 72 hours and 80% normalized at 96 hours from their last aspirin dose.\(^5^1\) Another study assessing platelet aggregation in cardiac surgery patients demonstrated that platelet inhibition vanished after 3 days from aspirin withdrawal.\(^5^2\) These small studies alone call into question the conventional practice of stopping aspirin therapy 7 days before surgery. However, the more rapid return of platelet aggregation is only part of the problem.

A growing body of evidence supports a platelet rebound phenomenon in the setting of acute aspirin withdrawal. This rebound period is characterized by increased thromboxane production, decreased fibrinolysis, and a resultant clinical prothrombotic state.\(^5^3\)–\(^5^5\) These studies evaluated return of platelet function in a variety of ways. Vial et al.\(^5^6\) measured urine metabolites of TXA\(_2\) and PGI\(_2\) before, during, and after cessation of a 1-week aspirin regimen. They found that these metabolites (and hence platelet TXA\(_2\) and PGI\(_2\)) rebound to levels beyond that of study controls and peaked at 7 to 14 days after aspirin withdrawal. Beving et al.\(^5^4\) measured 12-L-hydroxy-5,8,10-heptadecatrienoic acid (12-HHT: a platelet metabolite produced concomitantly in equal amounts to TXA\(_2\)) to approximate platelet TXA\(_2\) production in 32 patients who stopped aspirin therapy 2 weeks before coronary bypass surgery. Twenty-five percent of this cohort had 12-HHT levels beyond the normal range after 2 weeks of withdrawal.\(^5^4\) These investigators had previously documented this 12-HHT/TXA\(_2\) rebound in a cohort of healthy subjects after withdrawal of a 1-week aspirin regimen.\(^5^6\) In both studies, they observed that the platelet function rebound was dose dependent, with a more rapid rebound associated with withdrawal of lower aspirin doses. Furthermore, the aspirin withdrawal syndrome may not be limited to rebound of primary hemostasis as experimental evidence suggests an increase in fibrin strength after aspirin withdrawal compared to controls.\(^5^5\) These authors had previously demonstrated that patients with more rigid fibrin networks were more prone to cardiovascular events.\(^5^5\)

The authors of the aforementioned studies sought to explore platelet rebound mechanisms in an effort to explain worrisome observations in their clinical practice. They initially appreciated an increased incidence of unstable angina and myocardial infarction in patients who stopped aspirin therapy 2 weeks before cardiac surgery.\(^5^4\)\(^,\)\(^5^5\) However, one need not rely on this anecdotal evidence to support a correlation between studies of thromboxane levels after aspirin cessation and clinical thrombotic events. A robust body of literature substantiates an increased risk of cardiovascular events during the acute aspirin withdrawal period.\(^5^8\)–\(^6^2\) The remarkably consistent findings in both bench and bedside research on the aspirin withdrawal syndrome have led many authors, experts, and society guidelines to caution clinicians against aspirin cessation in the perioperative period unless the risks of bleeding exceed the benefits of cardiovascular protection.

### THROMBOTIC RISKS OF ASPIRIN WITHDRAWAL IN THE PERIOPERATIVE PERIOD

As discussed earlier, aspirin has been shown to be significantly effective in preventing future cardiac or ischemic events in patients with known CAD, CVD, or PVD with a relative risk (RR) reduction of approximately 25%.\(^6^0\) However, it is still common practice for surgeons or other physicians to counsel their patients to stop their aspirin therapy 7 to 10 days before surgery out of concern that continuing aspirin in the perioperative period may increase the risk of bleeding.\(^5^8\) Evidence is accumulating that this perceived bleeding risk does not outweigh the risk of an ischemic event, yet there has been no significant change in clinical practice except in patients with known coronary artery stents.\(^5^9\)\(^,\)\(^6^4\)\(^–\)\(^6^7\)

The literature on perioperative outcomes for patients on aspirin for secondary prevention, excluding the presence of coronary artery stents, is reviewed below. This available literature suggests that stopping aspirin confers a significant threat to the patient because of increased rates of significant perioperative ischemic events in patients undergoing noncardiac surgery. The data on perioperative adverse cardiac events show that a patient history of a remote myocardial infarction is independently associated with a serious and severe perioperative cardiac event with an odds ratio of 2.2 (95% CI [confidence interval]: 1.4–3.5).\(^5^9\)\(^–\)\(^6^2\) Prospective studies have also shown that a perioperative myocardial infarction has an in-hospital mortality rate of approximately 17% to 21%.\(^5^9\)\(^,\)\(^7^0\) Considering these risks, the discontinuation of aspirin in a population with known CAD or atherosclerotic disease will only increase the chance of a catastrophic ischemic event in the perioperative period.

Copit et al.\(^7^0\) prospectively evaluated 1358 patients admitted with acute coronary syndrome. They found that recent withdrawing of oral antiplatelet therapy (97% of subjects were aspirin users) had a twofold increase in rates of death compared to prior users and nonusers of aspirin therapy. Scheduled surgery was the reason for oral antiplatelet therapy discontinuation in 64% of these cases. The average time interval between stopping therapy and cardiac event was 11.9 days, consistent with the expected time interval for platelet rebound. Multivariate analysis showed that oral antiplatelet cessation was found to be an independent predictor of both death and major ischemic events.

In 2005, Burger et al.\(^7^1\) performed a meta-analysis of retrospective studies on the cardiovascular risks associated with perioperative withdrawal of aspirin versus the bleeding risks when aspirin was continued. Aspirin withdrawal preceded 10.2% of acute cardiovascular events and 6.1% of lower limb ischemic events. The mean timing of...
event after discontinuation of aspirin was 8.5 days for coronary events and 25.8 days for a lower limb event. The authors acknowledged the limitations of these conclusions because of the lack of information about number of patients who did not suffer from an event after discontinuation of aspirin in the perioperative period and advocated for randomized controlled trials to address this issue. They encouraged reconsidering the routine withdrawal of aspirin in the perioperative period.

Furthermore, in 2005, Maulaz et al. performed a retrospective case-control study including 309 patients admitted to the hospital over 2 years with a diagnosis of an ischemic stroke or transient ischemic attack (TIA), and who had received long-term aspirin before the index event. These patients were compared to 309 age- and sex-matched controls with a history of CVA or TIA on long-term aspirin, and no acute event in previous 6 months. Thirteen patients compared with 4 controls had discontinued aspirin in previous 4 weeks (4.2% vs 1.3%, P = .03), odds ratio 3.34 (95% CI: 1.07–10.39). Even after controlling for the presence of CAD, aspirin cessation still remained a significant risk factor for a cerebral vascular event in the 4 weeks after aspirin cessation. Here again, the most common reason for aspirin discontinuation was surgery. The mean interval between aspirin discontinuation and CVA was 9.5 days.

A recent systematic review of 50,279 patients on aspirin therapy for primary and secondary prevention sought to evaluate the hazards of aspirin withdrawal. Three of the studies examined patients with known CAD; the risk of an adverse cardiac event with discontinuation of aspirin was 1.82 (95% CI: 1.52–2.18, P < 0.00001). Pooling of the available data showed an average of 10.66 days (95% CI: 10.25–11.07) between day of discontinuation and thrombotic event. The data indicated that aspirin nonadherence or withdrawal was associated with a threefold higher risk of major cardiac events. Again, the mean time between aspirin withdrawal and thrombotic events was 10 days, which is consistent with the timing of peak thromboxane levels in prior studies. The authors concluded that aspirin discontinuation has ominous prognostic implications and recommend continuation of aspirin throughout the perioperative period unless there is a high risk of major bleeding.

A 2009 review by O’Riordan et al. of 99 articles examined antplatelet agents and the risks associated with premature withdrawal in the perioperative period. They found that this withdrawal is associated with a 10% risk of all vascular events and concluded that aspirin should not be withdrawn in the perioperative period unless there is a major risk of bleeding.

In 2010, Sung et al. published the results of their randomized blinded placebo-controlled study designed to evaluate the risk of recurrent bleeding with continuation of low-dose aspirin in patients with active bleeding peptic ulcer (PU). Patients were eligible if they presented with active PU bleeding and continued to require aspirin for secondary prevention. Patients were excluded if there was unsuccessful endoscopic hemostasis, had sensitivity to PPIs, or had concomitant anticoagulation in addition to aspirin. Patients (n = 156) were randomized after esophagogastroduodenoscopy to aspirin 80 mg or placebo for 8 weeks. The 30-day incidence of recurrent bleeding was 10.3% in the aspirin group versus 5.4% in placebo group, but the all-cause mortality at 8 weeks was significantly lower in the aspirin group than in the placebo (1.3% vs 12.9%, 95% CI for the difference: 3.7%–19.5%). This difference persisted even when they excluded deaths due to gastrointestinal complications. The authors asserted that continuous aspirin therapy for secondary prevention, even in the setting of active bleeding PU disease, may reduce mortality rates because of the reduced risk of cardiovascular and cerebral vascular events.

To date, the only published randomized controlled clinical trial evaluating whether to continue aspirin in the perioperative period was published in 2010 by Oscarsson et al. They conducted a randomized, double blind, placebo-controlled trial of 220 high-risk CAD patients (excluding those with coronary stents) undergoing intermediate-to-high-risk noncardiac surgery. Patients were randomized to either daily low-dose aspirin or placebo 7 days before surgery until 3 days postprocedure: 1.8% of aspirin-treated patients versus 9.0% of placebo-treated patients had a major adverse cardiac event (P = 0.02) within 30 days postoperatively. Aspirin conferred a 7.2% absolute risk reduction, with a RR reduction of 80%, with a number needed to treat of 14 patients. In addition, there was a significantly lower incidence of perioperative CVA or TIA in the aspirin group.

In summary, the current literature strongly supports the continued use of aspirin in patients on it for secondary prevention when undergoing most surgeries. The evidence indicates that patients have a significantly increased risk of a major ischemic event when aspirin is discontinued. The perceived risks of bleeding do not justify the practice of counseling patients to hold their aspirin before surgery, except in cases where surgical bleeding may lead to major perioperative complication (ie, surgery in a closed space such as the cranium or eye, as discussed later). There is enough accumulating evidence to suggest that it does not meet the standard of care to stop aspirin perioperatively for patients on it for secondary prevention. A subsequent perioperative thromboembolic event in a patient told to stop their aspirin could be considered potentially preventable.

### SURGICAL BLEEDING AND PERIOPERATIVE BLEEDING COMPLICATIONS RELATED TO ASPIRIN CONTINUATION

The bulk of the evidence to date indicates that the temporary cessation of aspirin therapy should only be considered for procedures where the risk of bleeding exceeds the risk of a major adverse cardiovascular event. However, it is important to note that most of the information on the risks of continuing aspirin in the perioperative period is observational and retrospective. The perioperative management of aspirin should be based on an optimal risk–benefit assessment—weighing the increased risk of bleeding with aspirin continuation versus the thrombotic risk associated with aspirin cessation.

There are 2 major groups of operative procedures to consider when contemplating aspirin cessation. The first group consists of procedures where any additional or excessive blood loss would lead to worse outcomes related to morbidity or mortality. This group of procedures includes intracranial surgery, spinal canal procedures, poster chamber eye surgery, middle ear surgery, and possibly prostate surgery. The other group consists of those procedures in which an increase in surgical blood loss may have minimal consequences (no change in transfusion requirements or no increase in major morbidity or mortality).

Burger et al’s 2005 meta-analysis discussed previously examined the perioperative risk of aspirin withdrawal versus bleeding-related complications with its continuation for a variety of procedures. There were 41 studies (reporting on 49,590 patients; 14,981 on aspirin) that examined the risk of bleeding during aspirin continuation. Baseline frequency of bleeding complications varied between 0 (skin lesion excision, cataract surgery) and 75% (transrectal prostate biopsy). Procedures included dental extractions, solid organ biopsies, transbronchial biopsies, multilevel spine surgery, hip arthroplasty, carotid endarterectomy (CEA), tonsillectomy, transurethral prostatectomy (TURP), and transrectal prostate biopsies. Although aspirin was shown to increase the rate of bleeding complications by a factor of 1.5 (median; interquartile range: 1.0–2.5), its continuation did not qualitatively increase the severity of bleeding complications except during intracranial surgery and TURP. These authors also noted a study in which surgeons blinded to aspirin status detected...
no bleeding differences between CEA patients taking aspirin and those not taking it.80 Burger’s group concluded that low-dose aspirin should be continued throughout the perioperative period unless there is a significant associated risk of bleeding.71

In the randomized, double blind, placebo-controlled trial by Oscarsson et al.,84 they compared 109 patients undergoing elective noncardiac high-risk (esophageal, liver, and pancreatic surgery) and intermediate-risk (head and neck surgery, intrathoracic surgery, advanced bowel surgery, gastric surgery, prostate surgery [open or transurethral], cystectomy, nephrectomy, hip or knee arthroplasty, and intra-abdominal or pelvic cancer surgery) surgery while on low-dose aspirin (75 mg) with a matched group of 111 not taking aspirin. Two patients (2%) in the aspirin group but none in the placebo group (P = 0.24) had bleeding, which necessitated reoperation in the perioperative period. Both patients had urologic procedures (one transurethral resection of the prostate and the other open prostatectomy for benign prostatic hypertrophy). There were no significant differences in the amount of intraoperative aspirin (300 mL vs placebo 300 mL, P = 0.61) or postoperative bleeding between the 2 groups and the surgeon’s assessment of intraoperative bleeding did not show any significant differences between the groups. Lastly, there were no statistically significant differences in administered crystalloids, packed red blood cells, or plasma transfusions between the groups.75 However, this study used older definitions of medium- and high-risk surgery from 2002. Newer 2010 guidelines from the European Society of Cardiology and European Society of Anesthesiology have reclassified as low-, intermediate-, and high-risk procedures on the basis of the respective procedures’ risk of myocardial infarction and cardiac death within 30 days postoperatively.81 These newer guidelines vary in terms of the level of associated risk ascribed to a given surgical procedure as compared to those in the trial by Oscarsson et al.73,81 Hence, discussion about the safety of aspirin continuation versus cessation might differ on the basis of the level of cardiac risk associated with a given surgical procedure and the findings by Oscarsson et al should be viewed in the context of older surgical risk definitions.

Vascular

A recent retrospective review of patients undergoing CEA examined the bleeding-related complications of patients on various antiplatelet regimens. Of 260 consecutive patients, 171 were continued on their aspirin in the perioperative period. The authors reported no difference in the incidence of neck hematoma or other bleeding-related complication.85 In another recent prospective trial,86 bleeding-related complications were studied in patients presenting for lower-extremity vascular surgery (infrainguinal bypass, femoral endarterectomy, or lower limb amputation) while maintained on low-dose aspirin with and without clopidogrel. Compared to aspirin alone, dual therapy did not increase the risk of major bleeding (aspirin + clopidogel 7 [14%] vs aspirin alone 6 [10%]; RR: 1.4, 95% CI: 0.49–3.76; P = 0.56) or minor bleeding (aspirin + clopidogel 17 [34%] vs aspirin alone 12 [21%]; RR: 1.64, 95% CI: 0.87–3.1, P = 0.12). Although the authors did find an increase in the transfusion rate with dual therapy, their results indicate that aspirin alone did not impact bleeding-related issues.

Urologic

Eng et al.87 retrospectively examined the use of antiplatelet agents during renal transplantation. Fifty-nine patients were on preoperative aspirin. Compared with a group of 213 patients who received no anti-platelet medications preoperatively, the aspirin group had no statistically significant increase in transfusion requirements, change in mean hemoglobin level, or difference in their hospital length of stay. However, there was a nonsignificant increase in the incidence of reoperation with preoperative aspirin use (5.1% vs 1.4% for no preoperative therapy, RR = 3.61, P = 0.12). Because of the limited number of patients, the 95% CI for the RR was very wide (0.84–15.21).87

Multiple prospective studies have demonstrated no significant increase in major bleeding or bleeding-related complications during transrectal prostate biopsy with patients who are maintained on aspirin therapy.88–91 The evidence surrounding aspirin and perioperative bleeding risks in patients undergoing conventional TURP is equivocal. Aspirin may cause significant bleeding complications in TURP procedures, partly because of the vascular bed and partly because of endogenous urokinase. Two studies in the 1990s demonstrated increased postoperative bleeding and the need for significantly more blood transfusion in TURP patients maintained on aspirin.92,93 During the same time period, however, contradictory evidence was published. Ala-Opas and coworkers94 recently performed a retrospective study of 220 patients undergoing 363 dermatologic procedures while on combination clopidogrel therapy (clopidogrel plus aspirin, warfarin, or both). Their control groups were patients on no antiplatelet agent or on aspirin monotherapy. In Mohs procedures, they found that patients taking any combination clopidogrel therapy were 28 times more likely to have severe bleeding (bleeding that significantly generates a threat to the wound or patient) related complication versus controls on no antiplatelet agent (P < 0.001). In patients on clopidogrel alone, severe complications were 8 times more likely than those on aspirin alone (P = 0.009). They also noted that none of the severe complications were life threatening, only wound threatening, and that the culprit agent was likely the clopidogrel.84

**Procedure Type, Bleeding, and Relation to Aspirin Continuation**

**Dermatologic**

In a 2011 review by Chu et al.,82 bleeding complications related to continuation of antiplatelet agents were assessed in dermatologic procedures that included biopsies, excisions, and Mohs procedures. Their review concluded that dermatologic procedures by nature are low bleeding risk cases and that single (aspirin, clopidogrel) or dual therapy did not increase the risk of major bleeding (aspirin + clopidogel 7 [14%] vs aspirin alone 6 [10%]; RR: 1.4, 95% CI: 0.49–3.76; P = 0.56) or minor bleeding (aspirin + clopidogel 17 [34%] vs aspirin alone 12 [21%]; RR: 1.64, 95% CI: 0.87–3.1, P = 0.12). Although the authors did find an increase in the transfusion rate with dual therapy, their results indicate that aspirin alone did not impact bleeding-related issues.

**General/Trauma**

In a small observational study of patients undergoing unplanned general surgery (appendectomy and cholecystectomy), perioperative aspirin use had no impact on bleeding-related complications.80 A 2010 retrospective review of 212 patients

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admitted to a level 1 trauma center (excluding those with an intracranial injury), 67 were taking aspirin, clopidogrel, warfarin, or a combination of the 3 before their admission. In this study, patients taking antplatelet or anticoagulant medication had longer hospitalizations (11.5 days vs 8.8 days, \( P = 0.04 \)) but with no difference in intensive care unit length of stay (4.7 days vs 3.9 days, \( P = 0.5 \)). Injury Severity Scores (21.4 vs 21.0, \( P = 0.76 \)), or mortality (13.4\% users vs 9.7\% nonusers, \( P = 0.41 \)). Although this study was not on patients undergoing an elective surgical procedure, it is germane to the trauma surgical population.

**Orthopedic**

Thaler et al\(^9\) examined platelet function in patients taking aspirin during hip arthroplasty with a platelet function analyzer (PFA-100). The authors then correlated qualitative platelet function to blood loss. Ninety-eight patients had continued taking aspirin in the perioperative period, and 64 (65\%) of these patients demonstrated impaired platelet function by platelet function analysis. There was, however, no significant correlation of aspirin continuation with mortality, major bleeding, transfusion requirements, or postoperative drainage. In a prospective case-control trial of patients with femoral neck fractures, those taking perioperative aspirin had no significantly greater intraoperative blood loss or drop in hematocrit; however, they were more likely to require a postoperative transfusion (37.5\% vs 17.3\%, \( P < 0.05 \)).\(^9\)

In patients undergoing proximal femur fracture surgery, Ankestein et al\(^10\) found that 39 patients taking low-dose (100 mg) aspirin perioperatively (out of 104 total patients included) were transfused an average of 0.5 units more than those not on aspirin. This was statistically significant (\( P = 0.007 \)). However, the groups did not differ in perioperative hemoglobin levels, complications, or wound drainage. The authors concluded that surgery for proximal femur fractures is safe for patients maintained on low-dose aspirin.\(^10\)

Nuttall et al\(^10\) evaluated predictors of blood transfusion after spine surgery including 19 (7.9\%) of 244 who were on aspirin perioperatively. Multiple regression analysis demonstrated that perioperative aspirin use was not associated with increased bleeding. In contrast to these findings, Kang et al\(^10\) retrospectively compared 38 patients who had their low-dose aspirin held 7 days preoperatively versus 38 patients who had no prior aspirin use whatsoever undergoing lumbar fusion with pedicle screw instrumentation. In this study, there was no difference in intraoperative blood loss but aspirin users did have greater postoperative blood loss in their drainage systems (864.4 mL vs 458.4 mL, \( P < 0.001 \)) and the mean postoperative blood transfusion was greater in the aspirin group (2.4 units vs 1.6 units, \( P = 0.03 \)). These authors acknowledge the major limitations of their study that include its retrospective nature, small sample size, and the prior aspirin users having significantly more preoperative comorbidities.\(^10\)

Edmunds et al\(^10\) prospectively followed 107 patients who had 121 hand surgeries on single (aspirin or clopidogrel) or dual antplatelet therapy. There was only a single complication (hematoma) for a patient on clopidogrel. They concluded that antplatelet therapy should not be discontinued in patients having hand surgery.\(^10\)

**Cardiac**

Multiple studies support the safety of low-dose aspirin continuation in the context of cardiac surgery.\(^103–106\) Tuman et al compared perioperative use of aspirin versus placebo in patients undergoing reoperation coronary artery bypass graft (CABG). Of 317 total patients, 215 patients had taken aspirin within 7 days of their procedure versus none in their 102 matched controls. They found no significant differences in postoperative hematocrit, mediastinal drainage, the need for reoperation, or transfusion requirements.\(^103\) Srinivasan et al\(^10\) retrospectively examined 170 aspirin users presenting for first-time off-pump coronary artery bypass compared to 170 matched controls, using propensity matching. They found no differences in mean postoperative blood loss (845 mL vs 775 mL, \( P = 0.157 \)), the rate of reoperation for bleeding (3.5\% vs 3.5\%, \( P > 0.99 \)), blood product requirements, or in-hospital mortality.\(^10\)

In 2010, Preisman et al\(^10\) used a modified thromboelastogram to assess platelet dysfunction and bleeding correlation in patients undergoing CABG and treated with various antplatelet agents. Twenty-five of 59 patients were on aspirin alone. Aspirin-induced platelet dysfunction demonstrated by modified thromboelastogram did not reflect an increased bleeding tendency.

Sun et al\(^10\) published a review of the mixed evidence surrounding the risks and benefits of aspirin continuation up to the time of CABG surgery. They reported on 6 prospective studies that showed increased bleeding tendency with perioperative aspirin use, compared to 9 studies of varying methodologies (retrospective and prospective) indicating that perioperative aspirin did not increase transfusion needs. Although the authors do not make a definitive conclusion, they summarize their article by stating that overall, the bleeding risk posed to a patient by continuing on low-dose aspirin (<325 mg) for CABG surgery is likely to be less serious than the risk of a thromboembolic event.\(^10\)

In a 2005 Society of Thoracic Surgery Executive Summary,\(^108\) the authors acknowledge that evidence they judged as level A (RCTs) in perioperative aspirin use in CABG surgery indicates greater risks of postoperative bleeding (overall 200–400 mL of increased chest tube drainage vs controls), increased transfusion rates (0.5–1 unit of red cell transfusion vs controls), and greater rates of reoperation. Despite that increase, the group argued that bleeding risk is likely outweighed by atherothrombotic risks in urgent or emergent patients and that even in elective cases, aspirin causes a relatively small increased bleeding risk (which might be dose related) that can likely be superseded by appropriate intraoperative blood conservation techniques (ie, cell saver).\(^10\)

**CONCLUSIONS**

On the basis of the available evidence, the practice of empirically discontinuing aspirin preoperatively should be abandoned. The evidence strongly supports continued use of aspirin in patients on it for secondary prevention of CAD, CVD, or PVD when undergoing surgery. Routine discontinuation of aspirin 7 to 10 days preoperatively is not only unjustified but likely significantly compounds patient’s thromboembolic risk because of the described aspirin withdrawal syndrome that occurs contemporaneously during this time interval. For an at-risk patient, the hypercoagulable state engendered by the surgical procedure compounded by the aspirin withdrawal syndrome creates an ideal scenario for a major cardiac or vascular thromboembolic complication.

As nearly all of the current data are observational and retrospective, there remains an urgent need for prospective randomized trials to evaluate the optimal management strategy of perioperative aspirin therapy. The POISE-2 trial (currently in progress) will add to our understanding by prospectively evaluating the administration of low-dose aspirin to aspirin-naive patients undergoing noncardiac surgery.\(^10\) Future trials should address the precise time interval for safe perioperative aspirin cessation in patients where any perioperative bleeding is unacceptable, as well as a comparison of continuing versus stopping aspirin therapy in appropriate patients. A recent survey elucidating surgeon’s attitudes regarding perioperative aspirin arrived at similar conclusions and found that most surgeons felt that there is sufficient clinical equipoise to enroll their patients in such trials.\(^10\)

Aspirin is a lifelong therapy for patients with known CAD, CVD, PVD, or significant risk factors for cardiovascular disease.
Surgical procedures that involve particular anatomic locales (middle ear, posterior chamber of the eye, intracranial, intramedullary spine, and possibly TURP) confer the highest risk of complicating hemorrhage while on aspirin therapy. Aside from such procedures, the thromboembolic risks of aspirin cessation in the at-risk patient often outweigh the minor bleeding risks in the vast majority of operative procedures.

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REFERENCES


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