

The Society of Thoracic Surgeons Practice Guideline Series[?]

Aspirin and Other Anti-Platelet Agents during Operative Coronary Revascularization

A Report from The Society of Thoracic Surgeons Workforce on Evidence-Based Medicine

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Statement of the Problem

Anti-platelet agents have many applications in patients with cardiovascular disease, especially coronary artery occlusive disease. For example, multiple well-done studies indicate that aspirin prolongs event-free survival after myocardial infarction.¹⁻⁴ Similarly, aspirin decreases the risk of stroke in patients with carotid occlusive disease.⁵⁻¹⁰ For these and other reasons non-steroidal anti-inflammatory drugs (NSAIDs) are arguably the most widely used class of non-prescription drugs in North America and Europe. One consequence of the widespread use of NSAIDs is that a majority of patients (at least 60 to 70%) who need operative coronary artery revascularization (CABG) have taken aspirin within 24 hours of operation.¹¹

Aspirin, and many other NSAIDs, limit platelet function by interfering with secondary platelet aggregation. Aspirin is known to limit prostaglandin production by platelets.¹² The critical enzyme system for prostaglandin production is prostaglandin endoperoxide H synthase also called cyclo-oxygenase (COX). Aspirin acetylates COX irreversibly to limit prostaglandin production and platelet aggregation. For many years the effect of aspirin on COX was thought to be the sole effect of this agent. More recent work suggests that aspirin, and probably other NSAIDs, alters other cellular mechanisms (Table 1). One important clinical consequence of the various cellular effects of aspirin is to limit graft occlusion after operative coronary artery revascularization.¹³⁻¹⁸

Several randomized clinical trials suggest that aspirin administered before operative coronary revascularization using cardiopulmonary bypass (CABG) causes increased postoperative bleeding and blood transfusion (Table 2). Infection and other risks of blood transfusion raise concerns about agents like aspirin that increase postoperative blood loss.

Transfusion-associated risks may include disease transmission, major morbidity (especially stroke), and increased mortality.

This leads to the so-called ‘aspirin paradox’. On the one hand aspirin is beneficial (improving post-MI survival and improving graft patency), but on the other aspirin has detrimental effects in patients who require on-pump CABG. Our goal in developing these guidelines is to provide specific recommendations for managing anti-platelet medications, especially aspirin, in patients who require operative intervention. In developing these guidelines, we reviewed the available evidence and arrived at consensus recommendations that may prove useful to thoracic surgeons and cardiologists confronted with the ‘aspirin paradox’.

A great deal of information exists regarding the effects of aspirin in patients having operative coronary revascularization using cardiopulmonary bypass (on-pump CABG, or CABG) while much less information is available concerning the effects of aspirin in patients having off-pump CABG (OPCAB). Hence almost all of the guidelines described below apply to patients having on-pump CABG. When information was available concerning patients having OPCAB, an attempt was made to include this information in the guidelines, but the vast majority of information presented applies to patients having on-pump CABG.

Methods Used in Developing Guidelines

Tables 3 and 4 describe the methods used to quantify the types of evidence available to answer relevant questions (Table 3) and the classification system used to summarize recommendations about certain clinically important questions (Table 4). This classification system is the same as that used by the Joint Taskforce for Guidelines of the American College of

Cardiology and the American Heart Association

(http://circ.ahajournals.org/manual/manual_IIstep6.shtml).

It is apparent that any medical or surgical intervention has both systematic and random effects, some of which are beneficial and some of which are unintended negative consequences. The practice of medicine often necessitates a probabilistic balancing of these conflicting effects, recognizing that there will always be a residual level of uncertainty. Jenicek summarizes this probabilistic approach as follows: “...*the science of medicine becomes a structured and organized way of using probability, uncertainty, and facts in preventive medicine and clinical care to best benefit the patient and the community.*”¹⁹

Evidence-based guidelines are an attempt to reconcile often conflicting lines of evidence, giving greater weight to evidence derived from more methodologically rigorous studies and those for which the overall weight of evidence is most convincing. They must be viewed as guidelines and recommendations, not absolutes. With this in mind the authors searched several sources for available evidence about specific questions relating to the use of aspirin before, during and after cardiac operations.

Relevant Mechanisms of Action of Aspirin

Aspirin is used in patients with cardiovascular disease for its antithrombotic effects induced by inhibition of platelet function. Aspirin also has anti-inflammatory, anti-pyretic, and analgesic effects.

Anti-Platelet Effect

The anti-platelet effect of aspirin is mediated by the irreversible inhibition of the key enzyme in platelet arachidonate metabolism prostaglandin (PG) H-synthase-1 also referred to as

cyclooxygenase (COX-1).²⁰⁻²³ This enzyme is responsible for the formation of PGH₂, the precursor of thromboxane A₂ (TxA₂), which activates platelets. Aspirin selectively acetylates the hydroxyl group of serine residue 529 within the polypeptide chain of platelet PGH synthase. As a result, the platelet aggregation response to collagen, adenosine diphosphate (ADP), thrombin and TxA₂ is attenuated.

Recently, an inducible form of PGH-synthase has been identified and termed PGH-synthase-2 or COX-2.²¹ Because aspirin more selectively inhibits COX-1 activity (found predominantly in platelets) than COX-2 activity (expressed in tissues following an inflammatory stimuli),²⁴ its ability to prevent platelet aggregation is seen at lower doses than the anti-inflammatory effect, which requires higher doses.^{22,23}

Other Non-platelet Effects of Aspirin

Multiple other actions of aspirin alter hemostasis.^{22,23} These mechanisms include inhibition of fibrinogen, limitation of platelet-white cell interactions, limitation of nuclear transcription of inflammatory mediator proteins, and inhibition of oxidative stress (Table 1). The impact of these aspirin-mediated effects on perioperative bleeding is often uncertain but in most cases results in limitation of normal hemostatic responses.

Beneficial Effects of Aspirin in the Perioperative Setting

Does Preoperative Aspirin Improve Outcomes After CABG?

Effect on graft patency

Multiple CABG studies show that aspirin reduces the frequency of saphenous vein graft occlusion compared to placebo, whether given 1 day before operation, on the day of operation or the on the day after operation.^{13,25} No similar benefit is conferred when only internal thoracic

artery grafting is used for CABG.^{14,15,18,26} Effective doses of aspirin that improve saphenous vein graft patency range from 100 to 975 mg per day.^{23,27-29} The majority of available Level A studies evaluating the effect of aspirin on graft patency suggest that 325 mg/day is the optimal dose for improving graft patency but both lower and higher doses may have equal efficacy.^{14,16,23,27-29} Dipyridimole therapy added to aspirin does not confer a significant additional benefit on graft patency compared to aspirin alone.^{15,17} Aspirin provides protection from cardiovascular events in patients with known atherosclerotic heart disease, especially CABG patients.^{30,31} For this reason, aspirin therapy should be continued beyond one year unless side-effects limit therapy. ***In summary, available evidence suggests that aspirin (325 mg/day) should be given for at least one year after operation in order to improve the patency of saphenous vein grafts (Class I recommendation).***

Effect on event reduction in patients with known CAD

Aspirin decreases short-term mortality after myocardial infarction and in patients with unstable coronary syndromes.^{1-4,32-34} Furthermore, aspirin also decreases long-term all-cause mortality in patients with known or suspected coronary disease.^{30,31,35,36} There are multiple Level A and B studies (including meta-analyses, randomized trials and observational studies) to suggest that aspirin is an extremely cost-effective and efficacious drug for the secondary prevention of myocardial events among patients with stable and unstable coronary artery disease.^{3,37} Direct and indirect comparisons of high-risk patients suggest no statistical differences in efficacy and hemorrhagic strokes across aspirin dosages.³⁸ These comparisons, however, suggest decreased risk of gastrointestinal symptoms with lower doses of aspirin. ***In fact, available evidence suggests that aspirin improves all-cause mortality and, unless contraindicated, should be given to patients with known CAD (Class I recommendation).***

In patients with known coronary disease who are having CABG, to deny aspirin for a prolonged period of time would be ill-advised. There are limited data available regarding the discontinuation of aspirin for short periods of time in either the elective or urgent/emergent pre-CABG situation (see recommendations below).

Harmful Effects of Aspirin in the Perioperative Setting

Does Preoperative Aspirin Cause Increased Postoperative Blood Loss?

Much has been written about the effects of preoperative aspirin on postoperative bleeding and blood transfusion. Table 2 summarizes the available evidence reviewing the effect of preoperative aspirin on postoperative bleeding. Of the 21 studies identified, there were 6 randomized controlled trials (RCT's) that were viewed as Level A evidence. All RCT's, except one, found that preoperative aspirin results in either increased blood loss as measured by drainage from mediastinal tubes, increased transfusion rates, or increased frequency of re-exploration. Multiple other articles with level B or C quality evidence have less clear cut association of preoperative aspirin with increased blood loss after cardiac procedures (Table 2). Because of the consistent finding of aspirin-associated increased blood loss in the highest quality studies, the panel feels that patients who receive aspirin before operation are at increased risk for above normal postoperative bleeding and blood transfusion after operation. There is a longitudinal trend to the risk of aspirin-induced postoperative bleeding with studies done earlier than 1994 being more likely to show aspirin-related postoperative bleeding and later studies less likely to show aspirin-related postoperative bleeding. It is likely that improvements in blood conservation, cardiopulmonary bypass techniques and other technical advances may lessen the

risk of bleeding in aspirin treated patients in the current era, but no certain explanation of this longitudinal trend is available.

It is possible to estimate the amount of increased bleeding associated with preoperative aspirin usage. In the randomized trials of CABG patients, preoperative aspirin results in between 200 and 400 cc of increased chest tube drainage and between 0.5 and 1 unit of increased packed red blood cell transfusion compared to controls.³⁹⁻⁴² At least one study suggests that smaller doses of preoperative aspirin (81 mg) have a beneficial effect on graft patency with less risk of postoperative bleeding.⁴³ Likewise, there is evidence from the cardiology literature that lower doses of aspirin are associated with a greater reduction in the vascular events than are higher doses (19% reduction with daily dose of 500-1500 mg compared to 32% reduction in patients taking 75-150 mg daily).⁴⁴ This suggests that lower doses of preoperative aspirin provide equal or better protection for prevention of vascular events while minimizing postoperative bleeding. The explanation for this may be related to the ability of lower doses of aspirin to inhibit platelet thromboxane production without significant impact on vascular prostacyclin synthesis, but other mechanisms are possible.^{23,44}

A single non-randomized study evaluated the risk of bleeding in patients having off-pump coronary artery bypass (OPCAB).⁴⁵ In 340 patients having OPCAB, there was no difference in blood loss between aspirin users and non-users. Coronary revascularization without the use of cardiopulmonary bypass may limit aspirin-related postoperative bleeding.

To summarize, there is mostly Level A evidence (somewhat distorted by conflicting Level B evidence) that aspirin causes increased bleeding after CABG. The amount of aspirin-

induced increased bleeding is small, is possibly dose related, and may be minimized with good perioperative blood conservation^{46,47} or by using off-pump procedures⁴⁵.

Should Aspirin Be Stopped Before Operation?

Aspirin is one of the essential treatments for patients with unstable angina or for patients who have had a recent myocardial infarction. Because of this treatment imperative, urgent/emergent patients require aspirin as part of their treatment regimen to reduce undesirable short- and long-term cardiovascular outcomes from coronary events some of which may require CABG. Patients on aspirin who present with an acute coronary syndrome have less severe clinical presentation, fewer hospital complications, and lower in-hospital death rates than patients not previously taking ASA.⁴⁸ Similarly a single observational study suggests that taking aspirin before CABG reduces the operative risk compared to non-aspirin users.⁴⁹ This suggests that patients who suffer peri-operative ischemic events may benefit from preoperative aspirin therapy. The panel feels that peri-operative ischemia is more likely in urgent/emergent CABG patients and that these same patients derive the most benefit from preoperative aspirin. ***Hence, for urgent/emergent CABG patients the small risk of bleeding is outweighed by the benefits of aspirin. This leads to a Class IIa recommendation to continue aspirin until the time of CABG in urgent/emergent patients.*** This recommendation applies to patients having CABG who are not in one of the aspirin-sensitive high-risk subgroups listed below (Table 5). A corollary of this recommendation is that unstable/emergent patients who are not on aspirin before operation should receive a dose of aspirin unless they fall into one of the aspirin-responsive high-risk categories listed in Table 5.

Aspirin inhibits platelet cyclooxygenase activity irreversibly. Whole body platelet function returns toward normal as new platelets are formed and released from the bone marrow.

Bleeding time and platelet thromboxane B2 levels return to normal once approximately half the platelet pool is regenerated, 3-5 days after stopping the drug.⁵⁰ Because of this, delay of elective operation and discontinuation of aspirin for a few days will allow the platelet effects of aspirin to dissipate. There is only anecdotal information available about the discontinuation of aspirin before elective CABG.⁵¹⁻⁵³ The substrate in the coronary circulation in elective patients is not expected to be as threatening as in the urgent/emergent situation where active platelet aggregation is likely to be an important physiologic process. The results of cessation of aspirin therapy for short periods (i.e. a few days) are uncertain but logic would dictate that no major harmful clinical effects on long-term outcome occur in elective patients. For the totally elective CABG patient, without recent myocardial infarction or without an acute coronary syndrome (estimated to be no more than 20% of the CABG population based on the STS database⁵⁴) it is reasonable (expert opinion – Level C evidence) to stop aspirin 3-5 days before elective operation. ***Based on expert opinion, on randomized trials and on multiple, somewhat divergent observational studies of aspirin-induced postoperative bleeding (Table 2), there is a Class IIa recommendation to stop aspirin for 3-5 days before elective CABG operations in order to reduce transfusion-related complications. There is a Class I recommendation to start aspirin in the early postoperative period after operation to improve bypass graft patency and all-cause mortality related to coronary artery disease in totally elective CABG patients.*** The panel recognizes that there is almost no evidence to document the effect on long-term cardiovascular end-points of discontinuing aspirin for a few days in this setting but feels that the risk is small and is outweighed by the benefit from reduced blood transfusion in non-aspirin users.

Are There High-risk Patients Who Are Made Worse by Giving Aspirin Before Operation?

Various drugs and disease states are reported to influence bleeding during and after CABG. In some cases preoperative aspirin may interact with these conditions. Table 5 is a partial list of some of these agents or diseases. There are no well-controlled studies to guide treatment in most of the high risk situations described in Table 5, but in each case an expert consensus based on available evidence was sought in order to provide recommendations.

Heparin

There is a substantial body of evidence to suggest that unfractionated heparin (UFH), when added to aspirin, is of benefit in patients with acute coronary syndromes (ACS) or with recent MI.^{55,56} There is no evidence to suggest that UFH, continued to within a few hours of CABG, increases postoperative blood loss, either in the presence or absence of preoperative aspirin (Table 5). *Unfractionated heparin should be continued up until a short time before the skin incision in CABG patients who have an appropriate indication for heparin (Class I).*

Low-Molecular-Weight Heparins

Some low molecular weight heparins (LMWH) improve outcomes, compared to UFH, after acute coronary syndromes.⁵⁷⁻⁶¹ Inevitably, some patients with ACS or recent MI will need CABG. In this setting, almost all patients will also have been given aspirin as part of the standard treatment of ACS. Some studies suggest a small benefit of LMWH compared to unfractionated heparin, but this remains to be validated.⁶² A preponderance of studies suggests that LMWH, when given within 12-24 hours of CABG, results in increased bleeding after operation (Table 5). Since LMWH has a 4-5 hour half-life, almost all of the dose is gone after 24 hours (5 half-lives). Jones and co-workers suggest that the bleeding risk may not go away for

at least 24 and possibly 48 hours.⁶³ *This leads to a Class IIa recommendation to stop LMWH 18-24 hours before operation and replace it with unfractionated heparin if anti-thrombin therapy is indicated.*

Warfarin

In patients with indications for long –term anticoagulation, warfarin is routinely stopped several days before major operative procedures to allow the INR to return to a normal or near-normal value. In patients at high risk of thromboembolism such as patients with atrial fibrillation and a mechanical valve or patients with two mechanical valves, UFH or LMWH therapy is started preoperatively within 24 to 48 hours of discontinuing warfarin. As discussed above, UFH should be continued up until a short time before CABG, while the last dose of LMWH should be given 18-24 hours before skin incision and replaced with UFH twelve hours before surgery (Table 5). In patients who will need long-term anticoagulation after CABG, warfarin is resumed on the first or second postoperative day and UFH or LMWH may be administered simultaneously, until a therapeutic INR has been achieved.

In these patients there is little data available to address the question of whether aspirin, when added to warfarin post CABG is effective for secondary prevention. Conflicting data have been obtained from randomized trials. Several randomized trials⁶⁴⁻⁶⁷ including a meta analysis⁶⁷ of over 20,000 patients with coronary artery disease show a greater cardiovascular risk reduction with moderate to high intensity warfarin alone or in combination with aspirin compared to aspirin alone. However, both the Coumadin Aspirin Reinfarction Study (CARS)^{44,68} and the Combination Hemotherapy and Mortality Prevention (CHAMP) study⁶⁹ found no benefit of low intensity warfarin therapy combined with aspirin compared to aspirin alone. However, in

patients with an absolute indication for warfarin therapy, none of these studies answers the question of whether aspirin plus warfarin is superior to warfarin alone post CABG.

In a double blind, randomized trial, Huynh, et al compared aspirin plus placebo and warfarin plus placebo to warfarin plus aspirin in 135 patients with prior CABG and acute coronary syndromes who were poor candidates for revascularization and found no significant difference in the primary endpoint of death, myocardial infarction or unstable angina at one year follow up.⁷⁰ In the Warfarin, Aspirin, Reinfarction Study (WARIS II), Hurlen, et al found that the combination of aspirin and warfarin resulted in a significant risk reduction compared to aspirin plus placebo but no reduction in risk compared to the warfarin alone in patients hospitalized for acute myocardial infarction.⁷¹ Taken together, the available data do not provide evidence that aspirin will add significantly to the secondary prevention provided by warfarin alone, but will likely increase the bleeding risk. ***Aspirin is not indicated in post CABG patients who are on long-term anticoagulant therapy with warfarin unless exceptional thrombotic risk is identified (Class III recommendation, level of evidence B).***

Direct thrombin inhibitors

Direct thrombin inhibitors are used to improve outcomes following ischemic coronary events and during percutaneous interventions.^{59,72} Because of the short acting nature of some of these agents (e.g. bivalirudin), they are unlikely to cause significant bleeding during CABG, although there is no published information on the preoperative administration of these agents before CABG. Some of the direct thrombin inhibitors are used as heparin substitutes during on-pump and off-pump CABG, especially in patients with heparin induced thrombocytopenia.⁷³⁻⁷⁵ ***If short acting direct thrombin inhibitors are indicated (e.g. bivalirudin), there is no need to stop them until immediately before operation (Class IIa recommendation).*** Other longer acting

direct thrombin inhibitors should be stopped and replaced with unfractionated heparin at an appropriate time before CABG consistent with the biologic half-life of the thrombin inhibitor.

ADP receptor blockers

Agents that block the platelet ADP receptor provide important benefit to patients having coronary stent implantation, especially in patients with prior CABG.⁷⁶⁻⁷⁸ When clopidogrel is added to aspirin for the treatment of ACS, there is significant incremental benefit but also increased bleeding risk.⁷⁹ ADP-receptor blocking agents should be used in patients with coronary artery disease who require aspirin but can not take the drug because of sensitivity or gastrointestinal bleeding.³⁴ These factors and others result in many patients presenting for CABG who have taken clopidogrel, the most commonly used ADP receptor blocker. Multiple observational studies document the increased bleeding associated with the preoperative use of clopidogrel but no large randomized clinical trial has been performed (Table 5). ***Because of the risk of excessive postoperative bleeding, ADP receptor blockers should be stopped 5-7 days before CABG (Class I recommendation – also recommendation of ACC/AHA).***

Glycoprotein IIb/IIIa inhibitors

Clinically available short-acting and long-acting inhibitors of the platelet glycoprotein IIb/IIIa (GP IIb/IIIa) receptor for fibrinogen cause profound platelet dysfunction. There are three GP IIb/IIIa receptor antagonists currently available for clinical use – two short-acting (eptifibatide and tirofiban) and one long-acting (abciximab). The current ACC/AHA guidelines for unstable angina indicate that GP IIb/IIIa inhibitors should be administered to patients having early catheterization and planned percutaneous intervention (Class I recommendation) and to patients with ongoing ischemia or other high risk features (Class IIa recommendation).³⁴ Patients on GP IIb/IIIa receptor antagonists who require emergency surgical revascularization

may be at increased risk for excessive postoperative bleeding, particularly with abciximab but less so with the shorter acting agents.⁸⁰⁻⁸³ Operation can be performed shortly after cessation of the short acting agents,⁸¹ but within 12-24 hours for abciximab.⁸⁴ Platelet transfusion has been shown to successfully reduce the incidence of post-CABG bleeding complications in patients taking GPIIb/IIIa receptor antagonists before operation.^{84,85} ***Because of the bleeding risk, these agents should be discontinued before CABG (Class IIb recommendation).*** The recommended time from stopping GP IIb/IIIa inhibitors until operation varies depending on the agent used but ranges from four to six hours for the short acting agents⁸⁶ to 12-24 hours for abciximab⁸⁷. No Level A or B evidence supports exact timing of discontinuation of these agents, hence, only rough estimates are available. Some authors suggest, based on observational data, that short-acting GP IIb/IIIa receptor antagonists can be continued up until operation,^{88,89} but given the conflicting conclusions in the literature, safe practices would suggest that stopping short acting agents before operation is preferred in order to minimize blood loss and blood transfusion.

Aspirin Resistance & Hyper-responders

Five to 10% of patients who take aspirin do not have a complete anti-platelet effect from the usual doses prescribed,⁹⁰ and the effect of a dose of aspirin may vary over time.⁹¹ These patients have more than a threefold increase in cardiovascular events when followed for a prolonged period of time.^{92,93} This incidence of aspirin resistance may be higher in patients undergoing CABG,⁹⁴ and may be related to a variety of gene polymorphisms.⁹⁵⁻⁹⁷ Higher doses of aspirin may ameliorate this aspirin resistance.^{98,99} Incidentally, there is likely to be variability in the therapeutic effect for ADP-receptor blockers also, similar to that seen with aspirin.¹⁰⁰ In patients with resistance to the usual doses of anti-platelet drugs, increased doses and the addition

of other anti-platelet drugs are the accepted method of obtaining a suitable anti-platelet response.¹⁰¹

There is evidence that certain patients have an accentuated response to the usual doses of preoperative aspirin.¹¹ Certain ‘hyper-responders’ to average doses of aspirin exhibit very prolonged skin bleeding times.^{42,102,103} This accentuated response to aspirin may result in increased perioperative blood loss worsened by preoperative aspirin therapy. The mechanisms of these effects of aspirin are undoubtedly multifactorial and include the anti-platelet, anti-inflammatory, anticoagulant and endothelial-protecting actions of aspirin (Table 1).

Thrombocytopenia - ITP, HIT/HITT, Myelodysplastic Syndrome, etc.

Patients with thrombocytopenia from whatever cause (defined as platelet count below 50,000) are at extremely high risk of excessive bleeding after CABG (Table 5). *Aspirin is harmful in these patients and should not be administered (Class III recommendation).*

Qualitative Platelet Defects

Additionally, patients who have average blood loss during CABG, but who start out with low red blood cell volumes either from small body size or from preoperative anemia (e.g. renal failure, repeated blood drawing during prolonged ICU stay, multiple recent percutaneous procedures, etc.) exhibit increased perioperative blood transfusion that could be worsened by preoperative aspirin.¹⁰³⁻¹⁰⁶ One of the earliest observations about anemia was that bleeding time was prolonged in anemic patients.^{107,108} Anemia-related bleeding abnormalities are likely to be worsened by aspirin.¹¹ Patients with other congenital or acquired qualitative platelet defects are at increased bleeding risk.¹⁰⁹⁻¹¹⁵ Congenital defects include vonWillebrand’s disease, Bernard-Soulier syndrome, Glanzmann’s thrombasthenia, storage-pool disease and others. Acquired qualitative defects are seen in liver disease, renal disease and drug induced qualitative platelet

defects. *Aspirin should be stopped in patients with a qualitative platelet defect, either related to anemia or to congenital or acquired platelet defects (Class IIa recommendation).*

How Should High-Risk Patients Be Managed If Aspirin Cannot Be Stopped Before CABG?

It is inevitable that some high-risk patients defined in Table 5 will have taken aspirin shortly before CABG. In some of these high-risk patients aspirin adds to the substantial risk of excessive blood transfusion but, for one reason or another, can not be discontinued before operation. There are multiple blood conservation interventions that should be used to reduce the risk in these aspirin-treated patients. Many authors emphasize the importance of a multifactorial approach to blood conservation.^{46,116-121} In the patient who falls into one of the aspirin-sensitive high risk groups listed in Table 5, evidence suggests that the optimal approach to blood conservation should employ a combination of several interventions including hemostatic drug therapy (aprotinin), peripheral blood sparing devices and permissive peri-operative anemia.⁴⁷ Perhaps the best documented of these interventions is the use of hemostatic drugs. At least eight randomized trials suggest that aprotinin limits blood loss and transfusion in patients given aspirin before CABG.¹²²⁻¹²⁹ Some residual concerns exist regarding the effect of aprotinin on graft patency. Although this is an area of controversy, emerging evidence suggests that aprotinin has limited effect on graft patency if adequate heparinization is used and other factors that influence graft patency are taken into consideration.¹³⁰⁻¹³⁵ ***Consensus suggests that there is level A and B evidence that aprotinin limits bleeding in aspirin-treated patients requiring CABG with a good safety profile. This leads to a Class IIa recommendation for the use of aprotinin in aspirin-treated CABG patients who fall into the high-risk categories listed in Table 5.***

These recommendations cannot be extrapolated to substitute the lysine analogue antifibrinolytics (tranexamic acid or epsilon aminocaproic acid) for aprotinin. The evidence is not nearly as compelling for non-aprotinin antifibrinolytics.^{136,137} The panel recognized that many surgeons use lysine analogues for their anti-fibrinolytic effect in aspirin-treated patients who require CABG, despite lack of available evidence of their benefit in this group. ***While lysine analogues are not the best option to reduce postoperative bleeding in high-risk aspirin-treated patients (Table 5) who require CABG, many surgeons use them for this indication without harmful side-effects. Consensus suggests that these drugs can be used to limit postoperative bleeding, recognizing that they are not the best option. (Class IIb recommendation).***

Perioperative blood sparing techniques, when combined with hemostatic drug therapy are likely to limit blood loss in the high-risk aspirin treated patient. These methods include salvage of blood from the heart-lung machine¹³⁸⁻¹⁴⁰, blood pooling at the onset of cardiopulmonary bypass¹⁴¹, and possibly the use of off-pump procedures¹⁴²⁻¹⁴⁵.

Other blood conservation methods that have proven efficacy in elective CABG procedures are not likely to be helpful in the setting of urgent/emergent high risk aspirin sensitive patients and are not indicated. These methods include predonation of autologous blood, erythropoietin treatment and preoperative platelet-pheresis (Class III).

Summary Recommendations

Aspirin is a mainstay of treatment for patients with coronary artery disease, especially those with unstable angina and myocardial infarction. In patients who require urgent/emergent

CABG and are not in one of the aspirin-sensitive high risk groups shown in Table 5, aspirin should be given before and after operation. For elective patients and for high-risk aspirin sensitive patients, aspirin should be stopped 3-5 days before CABG, if possible. In aspirin sensitive high risk patients who have not been able to discontinue aspirin before operation, multimodality blood conservation techniques, especially using aprotinin, should be employed.

Table 1. Hemostatic Mechanisms Altered by Aspirin

<u>Effect</u>	<u>Target cell or protein</u>	<u>Mechanism</u>	<u>Suspected impact on perioperative bleeding</u>
Inhibition of platelet aggregation	Platelet	Acetylation of cyclo-oxygenases. ²⁰⁻²³	↑
Inhibition of fibrinogen	Fibrinogen	Acetylation of lysine residues on fibrinogen at high doses of aspirin increases fibrinolysis. ¹⁴⁶⁻¹⁴⁹	↑
Inhibition of white cell-platelet interactions	White blood cells	Reduced platelet-leukocyte adhesion and expression of CD11a,CD11b & CD18 ligand expression. ¹⁵⁰	↑
Inhibition of selectin expression	Platelets and white cells	Reduced expression of surface selectins on platelets & white cells. ^{151,152}	↑
Inhibition of nuclear transcription	Nucleus of inflammatory cells & endothelium	1. Inhibition (probably by acetylation) of NFκB nuclear transcription factor by aspirin suppresses cytokine mediators. ¹⁵³⁻¹⁵⁶ 2. Inhibition of DNA synthesis by high doses of aspirin limits inducible nitric oxide synthase transcription. ^{155,157}	Uncertain
Reduced oxidative stress	LDL cholesterol in endothelium	Aspirin protects low-density lipoprotein cholesterol from oxidation by hydroxyl radicals. ^{158,159}	Uncertain

Table 2. Does preoperative aspirin cause increase postoperative bleeding?

Study	Study Type ¹⁹	Number of patients [?]	Quality of Evidence	Does aspirin increase postoperative bleeding?
Goldman, 1991 ¹⁶⁰	RCT	351	A	Yes (chest tube, transfusions and re-exploration rate)
Sethi, 1990 ³⁹	RCT	772 (471 ASA, 301 control)	A	Yes (chest tube, transfusions and re-exploration rate)
Goldman, 1988 ⁴⁰	RCT	555	A	Yes (chest tube and re-exploration rate)
Kallis, 1994 ⁴¹	RCT	100	A	Yes (chest tube, transfusion, and re-exploration)
Ferraris, 1988 ⁴²	RCT	34 (16 ASA, 18 control, not blinded)	B	Yes (chest tube, transfusion and re-exploration)
Taggart, 1990 ⁴³	Observational, cohort study	202 (101 ASA, 101 control)	B	Yes (chest tube, and transfusion)
Michelson, 1978 ¹⁶¹	Observational, case-control	25 (9 ASA, 16 controls)	B	Yes (chest tube drainage only)
Torosian, 1978 ¹⁶²	Descriptive, longitudinal	100 consecutive (13 ASA, 6 coumadin, 81 control)	B	Yes (chest tube drainage only)
Bashein, 1991 ¹⁶³	Observational, case-control	270 (90 ASA, 180 control)	B	Yes (transfusion and ICU stay)
Reich, 1994 ¹⁶⁴	Observational, case-control	197 (87 ASA, 110 control)	B	Yes (chest tube drainage only, not transfusion or re-exploration)
Ferraris 2002 ¹¹	Observational case-control	2606 (1641 ASA, 965 control)	B	Yes (chest tube drainage, transfusion, and re-exploration – bleeding worse in high-risk)
Karwande, 1987 ¹⁶⁵	RCT	36 (26 ASA, 10 control)	A	No
Srinivasan, 2003 ⁴⁵	Observational, case-control (OPCAB only)	340 (170 ASA, 170 control)	B	No
Tuman, 1996 ¹⁶⁶	Descriptive, longitudinal	317 reoperations (102 ASA, 215 control)	B	No
Vuylsteke, 1997 ¹⁶⁷	Descriptive, longitudinal	240 consecutive (96 excluded because of abnormal coagulation screen)	B	No
Dacey, 2000 ⁴⁹	Observational case-control	1056 (368 ASA, 688 controls)	B	No
Ray, 2003 ¹⁶⁸	Observational case-control	659 (151 ASA, 508 non-aspirin)	B	No (Clopidogrel plus aspirin caused increased bleeding compared to control and to aspirin alone)
Schonberger, 1993 ¹⁶⁹	Observational case-control	50 (25 ASA, 25 control)	B	No (non-significant trend to increased bleeding with ASA)
Ferraris, 1989 ¹⁰³	Descriptive, longitudinal	159 (15 ASA, 144 control)	B	No (bleeding time and blood volume predicted transfusion)
Rawitscher, 1991 ¹⁷⁰	Descriptive, longitudinal	100 consecutive (with normal bleeding time only)	B	No
Bjessmo, 2000 ¹⁷¹	Descriptive, longitudinal	200 (100 ASA, 100 control)	B	No

Abbreviations used: RCT = randomized, controlled trial; ASA = aspirin;

Table 3. Classification of the Quality of Evidence Available.

<u>Level of Evidence</u>	<u>Description</u>
Level A	Data from well-designed placebo-controlled, blinded, randomized clinical trials or meta-analyses.
Level B	Data from less well done single randomized trials or from non-randomized, analytical observational studies.
Level C	Consensus 'expert' opinion or data from descriptive studies or informative case reports.

Table 4. Classification Scheme Used to Summarize Clinical Recommendations

<u>Class</u>	<u>Description</u>
Class I	Evidence or general agreement that given procedure or intervention is useful or effective.
Class II	Conflicting evidence exists about the usefulness of an intervention or procedure.
IIa	Weight of evidence favors intervention or procedure.
IIb	Usefulness of intervention or procedure is less well established.
Class III	Evidence exists that intervention/procedure is not useful and/or is possibly harmful.

Table 5. Aspirin Interaction with High Risk Drugs or Disease States.

<i>Preoperative Drug or Disease State</i>	<i>Effect in CABG Patients</i>	<i>Interaction with Aspirin</i>	<i>Level of Evidence</i>	<i>Recommendation in Preoperative CABG Patients</i>
Heparin (UFH)	No discernible effect on postoperative bleeding if stopped shortly before skin incision. ^{54,103,172,173}	Most urgent/emergent patients given heparin are also on aspirin. No known interaction with aspirin.	B	Continue heparin until 1-2 hours before CABG (<i>Class I</i>)
Low Molecular Weight Heparin (LMWH)	Increased bleeding, blood transfusion, and re-exploration within 12-24 hours of dose. ^{63,174-178} Effects gone within 24 hours.	Almost all patients studied were taking aspirin for unstable coronary syndromes or recent MI. No known interaction with aspirin.	B	Stop LMWH 18-24 hours before operation - replace with unfractionated heparin 12 hours before operation. (<i>Class IIa</i>)
Warfarin	Routinely stopped several days before operation with conversion to unfractionated heparin until operation. No increased bleeding risk at operation. ¹⁷⁹ Warfarin restarted 1-2 days after operation. Addition of postoperative aspirin to Warfarin does not provide clear benefit but increases bleeding risk. ^{68-71,180}	Aspirin combined with Warfarin almost always results in increased bleeding events but questionable benefit in secondary prevention.	B	Aspirin is not indicated in patients who require Warfarin therapy after CABG unless exceptional thrombotic risk exists (<i>Class III</i>)
Direct thrombin inhibitors (e.g. hirudin, bivalirudin, etc.)	No information available on the preoperative administration of these agents. Unlikely to be a problem in the case of short acting agents (e.g. bivalirudin). Longer acting agents (hirudin & argatroban) are associated with increased bleeding. ¹⁸¹	Unknown	C	Continue short acting agents up until immediately before CABG if appropriate indication. Longer acting agents should be replaced with unfractionated heparin before CABG (<i>Class IIb</i>).
Platelet ADP receptor blockers (e.g. ticlopidine & clopidogrel)	Significant increased bleeding and blood transfusion in the presence or absence of aspirin. ^{79,168,182-185}	Aspirin worsens the platelet defect induced by ADP receptor blockers	A	Stop ADP receptor blocker for 5-7 days before CABG (<i>Class I – also the recommendation of ACC/AHA³⁴</i>)
Platelet glycoprotein IIb/IIIa inhibitors (e.g. abciximab, tirofiban, aggrastat).	Increased blood loss if administered within 12-24 hours of operation with long acting agents. ^{82,83,86} Experience with short acting agents is mixed, but most studies suggest stopping with 4-6 hours of operation. ^{80,81,88,89}	Aspirin worsens the platelet defect induced by GPIIb/IIIa receptor blockers.	B	Discontinue GP IIb/IIIa inhibitors before operation. Timing varies with agent used. (<i>Class IIb</i>).

Aspirin resistance or hyper-responders (increased preoperative template bleeding time > 10 minutes)	Increased blood loss & transfusion in hyper-responders. ^{11,103} Uncertain effect in aspirin resistance. ⁹⁴	Unpredictable	B	Stop aspirin in hyper-responders (bleeding time = 10 min.) and continue or increase dose of aspirin in non-responders (<i>Class IIb</i>)
Thrombocytopenia (platelet count < 50,000)	Increased blood loss and transfusion – often excessive. ¹⁸⁶⁻¹⁹⁰	Aspirin adversely effects the few platelets that remain	C	Aspirin is not indicated in patients with thrombocytopenia from whatever cause (<i>Class III</i>)
Qualitative platelet defects (renal failure, low blood volume, vonWillebrand's, etc.)	Anecdotal evidence of increased blood loss is the usual outcome. ^{11, 103-106, 109-115}	Aspirin worsens these defects	C	Aspirin is not indicated in patients with a qualitative platelet defect. (<i>Class III</i>)

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