The Society of Thoracic Surgeons Practice Guideline Series: Aspirin and Other Antiplatelet Agents During Operative Coronary Revascularization (Executive Summary)*

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Statement of the Problem

Multiple well-done studies indicate that aspirin prolongs event-free survival after myocardial infarction (MI) [1, 2]. One consequence of the widespread use of aspirin 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 [3]. Aspirin, and many other NSAIDS, limit platelet function by interfering with secondary platelet aggregation. Among the many actions of NSAIDS, aspirin is known to limit prostaglandin production by platelets (Table 1). One important clinical consequence of the various cellular effects of aspirin is to limit vein graft occlusion after operative coronary artery revascularization [4]. Several randomized clinical trials suggest that aspirin administered before operative coronary revascularization using cardiopulmonary bypass causes increased postoperative bleeding and blood transfusion (Table 2). 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. A similar dilemma exists for many antiplatelet drugs and other beneficial agents that alter operative hemostasis. Our goal in developing these guidelines is to provide specific recommendations for managing antiplatelet medications, especially aspirin, in patients who require operative intervention. 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 (OPCABG). Hence almost all of the guidelines described below apply to patients having on-pump CABG. When information was available concerning patients having OPCABG, an attempt was made to include this information in the guidelines.

Methods Used in Developing Guidelines

The methods used to quantify the types of evidence available to answer relevant questions is the same as that used by the Joint Taskforce for Guidelines of the American College of Cardiology and the American Heart Association (available at: http://circ.ahajournals.org/manual/manual_IIstep6.shtml). 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.

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 with placebo, whether given 1 day before operation, on the day of operation, or the on the day after operation [4]. No similar benefit is conferred when only internal thoracic artery grafting is used for CABG [4]. Effective doses of aspirin that improve saphenous vein graft patency range from 100 to 975 mg/d [5]. Level A studies evaluating the effect of aspirin on graft

*For the full text of the STS Guideline on Aspirin and Other Anti-Platelet Agents During Operative Coronary Revascularization, as well as other titles in the STS Practice Guideline Series, visit http://www.sts.org/sections/aboutthesociety/practiceguidelines/ at the official STS website (www.sts.org).
Table 1. Hemostatic Mechanisms Altered by Aspirin

<table>
<thead>
<tr>
<th>Effect</th>
<th>Target Cell or Protein</th>
<th>Mechanism</th>
<th>Suspected Impact on Perioperative Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhibition of platelet aggregation</td>
<td>Platelet</td>
<td>Acetylation of cyclo-oxygenases</td>
<td>↓</td>
</tr>
<tr>
<td>Inhibition of fibrinogen</td>
<td>Fibrinogen</td>
<td>Acetylation of lysine residues on fibrinogen at high doses of aspirin increases fibrinolysis</td>
<td>↑</td>
</tr>
<tr>
<td>Inhibition of white cell-platelet interactions</td>
<td>White blood cells</td>
<td>Reduced platelet-leukocyte adhesion and expression of CD11a, CD11b, and CD18 ligand expression</td>
<td>↑</td>
</tr>
<tr>
<td>Inhibition of selectin expression</td>
<td>Platelets and white cells</td>
<td>Reduced expression of surface selectins on platelets and white cells [32, 33]</td>
<td>↑</td>
</tr>
<tr>
<td>Inhibition of nuclear transcription</td>
<td>Nucleus of inflammatory cells and endothelium</td>
<td>1. Inhibition (probably by acetylation) of NFkB nuclear transcription factor by aspirin suppresses cytokine mediators 2. Inhibition of DNA synthesis by high doses of aspirin limits inducible nitric oxide synthase transcription</td>
<td>Uncertain</td>
</tr>
<tr>
<td>Reduced oxidative stress</td>
<td>Low-density lipoprotein cholesterol in endothelium</td>
<td>Aspirin protects low-density lipoprotein cholesterol from oxidation by hydroxyl radicals</td>
<td>Uncertain</td>
</tr>
</tbody>
</table>

patency suggest that 325 mg/d is the optimal dose for improving graft patency but both lower and higher doses may have equal efficacy. Dipyridimole therapy added to aspirin does not confer a significant additional benefit on graft patency compared with aspirin alone [6]. Aspirin provides protection from cardiovascular events in patients with known atherosclerotic heart disease, especially CABG patients [7]. For this reason, aspirin therapy should be continued beyond 1 year unless side effects limit therapy. In summary, there is a class I recommendation to administer aspirin (325 mg/d) for at least 1 year (and probably indefinitely) after operation to improve the patency of saphenous vein grafts (level A evidence).

**Effect on Event Reduction in Patients with Known CAD.** Aspirin decreases short-term mortality in acute coronary [1], and decreases long-term all-cause mortality in patients with known or suspected coronary disease [8]. These comparisons, however, suggest decreased risk of gastrointestinal symptoms with lower doses of aspirin. Much level A and B 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 (RCTs) that were viewed as level A evidence. All RCTs, 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 reexploration. 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 cc and 400 cc of increased chest tube drainage and between 0.5 and 1 unit of increased packed red blood cell transfusion compared with controls. 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 [9]. 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 mg to 1,500 mg compared with 32% reduction in patients taking 75 mg to 150 mg daily) [10]. 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 or by using off-pump procedures. A single nonrandomized study evaluated the risk of bleeding in patients having OPCABG [11]. In 340 patients having OPCABG, there was no difference in blood loss between aspirin users and nonusers. Coronary revascularization without the use of cardiopulmonary bypass may limit aspirin-related postoperative bleeding.

**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. 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 (level A and B evidence). This recommendation applies to patients having CABG who are not in one of the aspirin-sensitive high-risk subgroups listed below (Table 3). 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 3.

Whole body platelet function after aspirin 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 to 5 days after stopping the drug [12]. There is only anecdotal information available about the discontinuation of aspirin before elective CABG [13–15]. 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. 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 to 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.

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 3 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 3, 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. 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 3). 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 recommendation).

LOW-MOLECULAR-WEIGHT HEPARINS. A preponderance of studies suggests that low-molecular weight heparin (LMWH), when given within 12 to 24 hours of CABG, results in increased bleeding after operation (Table 3). This leads to a class IIa recommendation to stop LMWH 18 to 24 hours before operation and replace it with unfractionated heparin if antithrombin 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 or a mechanical valve, UFH or LMWH therapy is started preoperatively within 24 to 48 hours of discontinuing warfarin (class IIa recommendation, level B evidence).

For these patients, there are few data available to address the question of whether aspirin, when added to warfarin post-CABG is effective for secondary prevention. Several randomized trials including a meta-analysis of more than 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 with aspirin alone [16]. However, two randomized trials found no benefit of low-intensity warfarin therapy combined with aspirin compared with aspirin alone [10, 17]. Taken together, the available data do not provide convincing evidence that aspirin will add significantly to the secondary prevention provided by warfarin alone, but will likely increase the bleeding risk [18]. Aspirin is not indicated for post-CABG patients who are on long-term anticoagulant therapy with warfarin unless exceptional thrombotic risk is identified (class III recommendation, level B evidence).

DIRECT THROMBIN INHIBITORS. Direct thrombin inhibitors are used to improve outcomes after ischemic coronary events and during percutaneous interventions. Because of the short acting nature of some of these agents (for example, 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. If short-acting direct thrombin inhibitors are indicated (for example, 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 (class IIa recommendation).

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. Multiple observational studies document the increased bleeding associated with the preoperative use of clopidogrel, but no large randomized clinical trial has been performed (Table 3). Because of the risk of excessive postoperative bleeding,
Table 3. Aspirin Interaction with High-Risk Drugs or Disease States

<table>
<thead>
<tr>
<th>Preoperative Drug or Disease State</th>
<th>Effect in CABG Patients</th>
<th>Interaction With Aspirin</th>
<th>Level of Evidence</th>
<th>Recommendation in Preoperative CABG Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heparin (UFH)</td>
<td>No discernible effect on postoperative bleeding if stopped shortly before skin incision.</td>
<td>Most urgent/emergent patients given heparin are also on aspirin. No known interaction with aspirin.</td>
<td>B</td>
<td>Continue heparin until 1–2 hours before CABG (class I).</td>
</tr>
<tr>
<td>Low-molecular-weight heparin (LMWH)</td>
<td>Increased bleeding, blood transfusion, and reexploration within 12–24 hours of dose.</td>
<td>Almost all patients studied were taking aspirin for unstable coronary syndromes or recent MI. No known interaction with aspirin.</td>
<td>B</td>
<td>Stop LMWH 18–24 hours before operation — replace with unfractionated heparin 12 hours before operation (class IIa).</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Routinely stopped several days before operation with conversion to unfractionated heparin until operation. No increased bleeding risk at operation. Warfarin restarted 1–2 days after operation. Addition of postoperative aspirin to warfarin does not provide clear benefit but increases bleeding risk.</td>
<td>Aspirin combined with warfarin almost always results in increased bleeding events but questionable benefit in secondary prevention.</td>
<td>B</td>
<td>Aspirin is not indicated in patients who require warfarin therapy after CABG unless exceptional thrombotic risk exists (class III).</td>
</tr>
<tr>
<td>Direct thrombin inhibitors (eg, hirudin, bivalirudin, etc)</td>
<td>No information available on the preoperative administration of these agents. Unlikely to be a problem in the case of short acting Agents (eg, bivalirudin). Longer-acting agents (hirudin and argatroban) are associated with increased bleeding.</td>
<td>Unknown.</td>
<td>C</td>
<td>Continue short-acting agents up until immediately before CABG if appropriate indication. Longer-acting agents should be replaced with unfractionated heparin before CABG (class IIb).</td>
</tr>
<tr>
<td>Platelet ADP receptor blockers (eg, ticlopidine and clopidogrel)</td>
<td>Significant increased bleeding and blood transfusion in the presence or absence of aspirin.</td>
<td>Aspirin worsens the platelet defect induced by ADP receptor blockers.</td>
<td>A</td>
<td>Stop ADP receptor blocker for 5–7 days before CABG (class I—also the recommendation of ACC/AHA [51]).</td>
</tr>
<tr>
<td>Platelet glycoprotein IIb/IIIa inhibitors (eg, abciximab, tirofiban, aggrastat)</td>
<td>Increased blood loss if administered within 12–24 hours of operation with long-acting agents. Experience with short-acting agents is mixed, but most studies suggest stopping with in 4–6 hours of operation.</td>
<td>Aspirin worsens the platelet defect induced by GPIIb/IIIa receptor blockers.</td>
<td>B</td>
<td>Discontinue GP IIb/IIIa inhibitors before operation. Timing varies with agent used (class IIb).</td>
</tr>
<tr>
<td>Aspirin resistance or hyperresponders (increased preoperative template bleeding time &gt;10 minutes)</td>
<td>Increased blood loss and transfusion in hyperresponders [3,29]. Uncertain effect in aspirin resistance.</td>
<td>Unpredictable.</td>
<td>B</td>
<td>Stop aspirin in hyperresponders (bleeding time ≥10 min) and continue or increase dose of aspirin in nonresponders (class IIb).</td>
</tr>
<tr>
<td>Thrombocytopenia (platelet count &lt;50,000)</td>
<td>Increased blood loss and transfusion—often excessive.</td>
<td>Aspirin adversely affects the few platelets that remain.</td>
<td>C</td>
<td>Aspirin is not indicated in patients with thrombocytopenia from whatever cause (class III).</td>
</tr>
<tr>
<td>Qualitative platelet defects (renal failure, low blood volume, von Willebrand’s, etc)</td>
<td>Anecdotal evidence of increased blood loss is the usual outcome.</td>
<td>Aspirin worsens these defects.</td>
<td>C</td>
<td>Aspirin is not indicated in patients with a qualitative platelet defect (class III).</td>
</tr>
</tbody>
</table>

ADP = adenosine phosphate; CABG = coronary artery bypass graft surgery; MI = myocardial infarction; UFH = unfractionated heparin.

ADP receptor blockers should be stopped 5 to 7 days before CABG (class I recommendation, level B evidence; also recommendation of ACC/AHA).
IIb/IIIa) receptor for fibrinogen cause profound platelet dysfunction. 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. Operation can be performed shortly after cessation of the short-acting agents [19], but within 12 to 24 hours for abciximab [20]. Platelet transfusion has been shown to successfully reduce the incidence of post-CABG bleeding complications in patients taking GPIIb/IIIa receptor antagonists before operation [20]. 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 4 to 6 hours for the short-acting agents [21] to 12 to 24 hours for abciximab [22]. Some authors suggest, based on observational data, that short-acting GP IIb/IIIa receptor antagonists can be continued up until operation [23]. However, given the conflicting conclusions in the literature, safe practices suggest that stopping short-acting agents before operation is preferred in order to minimize blood loss and blood transfusion (level B and C evidence; class IIb recommendation).

**ASPIRIN RESISTANCE AND HYPERRESPONDERS.** Five percent to 10% of patients who take aspirin do not have a complete antiplatelet effect from the usual doses prescribed, and the effect of a dose of aspirin may vary over time. These patients have more than a threefold increase in cardiovascular events when followed up for a prolonged period of time. This incidence of aspirin resistance may be higher in patients undergoing CABG [24], and may be related to a variety of gene polymorphisms [25]. Higher doses of aspirin may ameliorate this aspirin resistance [26]. There is likely to be variability in the therapeutic effect for ADP-receptor blockers also, similar to that seen with aspirin [27]. In patients with resistance to the usual doses of antiplatelet drugs, increased doses and the addition of other antiplatelet drugs are the accepted method of obtaining a suitable antiplatelet response (class IIb recommendation, level B evidence).

There is evidence that certain patients have an accentuated response to the usual doses of preoperative aspirin. Certain “hyperresponders” to average doses of aspirin exhibit very prolonged skin bleeding times [28]. Anecdotal evidence suggests that certain patients are very sensitive to the antiplatelet actions of aspirin, and these patients should have aspirin discontinued several days before elective operation (class IIb recommendation, level B evidence).

**THROMBOCYTOPENIA—ITP, HIT/HITT, MYELODYSPLASTIC SYNDROME.** Patients with thrombocytopenia from whatever cause (defined as platelet count below 50,000) are at extremely high risk of excessive bleeding after CABG (Table 3). Aspirin is harmful in these patients and should not be administered (class III recommendation, level B evidence).

**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 (for example, renal failure, repeated blood drawing during prolonged intensive care unit stay, multiple recent percutaneous procedures, and so forth) exhibit increased perioperative blood transfusion that could be worsened by preoperative aspirin [29]. Aspirin should be stopped in patients with a qualitative platelet defects, 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 3 will have taken aspirin shortly before CABG. For the patient who falls into one of the aspirin-sensitive high risk groups listed in Table 3, evidence suggests that the optimal approach to blood conservation should employ a combination of several interventions including hemostatic drug therapy (for example, aprotinin), peripheral blood-sparing devices, and permissive perioperative anemia [30]. Perhaps the best documented of these interventions is the use of hemostatic drugs [31]. 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 (class IIa recommendation for the use of aprotinin in aspirin-treated CABG patients who fall into the high-risk categories listed in Table 3).

These recommendations cannot automatically be extrapolated to substitute the lysine analogue antifibrinolytics (tranexamic acid or epsilon aminocaproic acid) for aprotinin. The Panel recognized that many surgeons use lysine analogues for their antifibrinolytic effect in aspirin-treated patients who require CABG, despite lack of available evidence of their benefit in this group. Although not the best option to reduce postoperative bleeding in high-risk aspirin-treated patients (Table 3) who require CABG, many surgeons use them for this indication without harmful side effects. Consensus suggests that lysine analogues can be used to limit postoperative bleeding, recognizing that they are not the best option (class IIb recommendation, level B and C evidence).

Perioperative blood-sparing techniques such as salvage of blood from the heart-lung machine, blood pooling at the onset of cardiopulmonary bypass, and possibly the use of off-pump procedures are likely to limit blood loss in the high-risk aspirin treated patient (class IIa recommendation, level B evidence).

Some 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 recommendation, level B and C evidence).
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 3, aspirin should be given before and after operation. For elective patients and for high-risk aspirin-sensitive patients, aspirin should be stopped 3 to 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.

References