2012 Update to The Society of Thoracic Surgeons Guideline on Use of Antiplatelet Drugs in Patients Having Cardiac and Noncardiac Operations*

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Introduction and Rationale for Revision

The Society of Thoracic Surgeons (STS) Workforce on Evidence Based Surgery provides recommendations for practicing thoracic surgeons based on available medical evidence. Part of the responsibility of the Evidence Based Workforce is to continually monitor published literature and to periodically update recommendations when new information becomes available. In 2005, STS Workforce efforts included publication of recommendations regarding the use of antiplatelet agents during cardiac operations [1]. Since then, new antiplatelet agents appeared on the market and significant new information appeared in the literature, such that revision of the 2005 guidelines is justified. This document represents synthesis of new information regarding the use of antiplatelet agents in the perioperative period. Additional features of this publication include broader discussion of point-of-care testing to monitor platelet function and wider exploration of treatment options of patients exposed to antiplatelet drugs who need urgent operation.

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*The Society of Thoracic Surgeons Clinical Practice Guidelines are intended to assist physicians and other health care providers in clinical decision making by describing a range of generally acceptable approaches for the diagnosis, management, or prevention of specific diseases or conditions. These guidelines should not be considered inclusive of all proper methods of care or exclusive of other methods of care reasonably directed at obtaining the same results. Moreover, these guidelines are subject to change over time, without notice. The ultimate judgment regarding the care of a particular patient must be made by the physician in light of the individual circumstances presented by the patient.

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A. Search Methods

The search methods used to survey the published literature changed in the current guideline version compared with the previously published guideline [1]. In the interest of transparency, literature searches were conducted using standardized Medical Subject Heading (MeSH) terms from the National Library of Medicine PUBMED database list of search terms. The following terms comprised the standard baseline search terms for all topics and were connected with the logical "OR" connector: extracorporeal circulation (MeSH number E04.292 includes extracorporeal membrane oxygenation, left heart bypass, hemofiltration, hemoperfusion and cardiopulmonary bypass); cardiovascular surgical procedures (MeSH number E04.100 includes off-pump coronary artery bypass graft surgery [CABG], CABG, myocardial revascularization, all valve operations, and all other operations on the heart); vascular diseases (MeSH number C14.907 includes dissections, aneurysms of all types including left ventricular aneurysms, and all vascular diseases); and pharmacologic actions (MeSH number D27.505 includes molecular mechanisms, physiologic effects, and therapeutic use of drugs).

Use of these broad search terms allowed specific topics to be added to the search with the logical "AND" connector. This search methodology provided a broad list of generated references specific for the search topic. Individual members of the writing group read the retrieved references for their assigned topics and formulated recommendations based on assessment of the relevant literature. Only English language articles contributed to the final recommendations. For almost all topics reviewed,

Appendices for this article are available in the Auxiliary Annals section of the STS website http://www.sts.org/annals-thoracic-surgery/auxiliary-annals.

Abbreviations and Acronyms

ACC	= American College of Cardiology
ACS	= acute coronary syndrome
ADP	= adenosine diphosphate
AHA	= American Heart Association
CABG	= coronary artery bypass graft surgery
COX	= cyclooxygenase
CYP	= cytochrome P450
GP	= glycoprotein
ICU	= intensive care unit
MeSH	= Medical Subject Heading
MI	= myocardial infarction
PCI	= percutaneous coronary intervention
PDE	= phosphodiesterase
STS	= The Society of Thoracic Surgeons

only evidence relating to adult patients were entered into the final recommendations, primarily because of limited availability of high-quality evidence relating to pediatric patients having cardiac procedures.

B. Duties of the Writing Group

Members of the writing group, assigned to a specific topic made recommendations about use of antiplatelet agents in the perioperative period based on review of important articles obtained using the search technique described above. The quality of information for a given recommendation allowed assessment of the level of evidence as recommended by the American Heart Association (AHA)/American College of Cardiology Foundation (ACCF) Task Force on Practice Guidelines (available at: http://www.americanheart.org/downloadable/heart/12604770597301209methodology_manual_for_acc_aha_writing_committees.pdf). Writers assigned to the various antiplatelet drug topics wrote and developed new or amended recommendations, but each final recommendation that appears in this revision was approved by at least a two-thirds majority favorable vote from all members of the writing group. Table 1 and Appendix 1 (see Appendix in Auxiliary Annals section of the STS website http://www.sts.org/auxiliaryannals/Ferraris-2012-94-5-1761-Appendices1-2.pdf) contain summaries of recommendations and the results of the voting for each recommendation, and explain any major individual dissensions. Appendix 2 (see Appendix in Auxiliary Annals section of the STS website http://www.sts.org/auxiliaryannals/Ferraris-2012-94-5-1761-Appendices1-2.pdf) documents the authors' potential conflicts of interest and industry disclosures.

C. Types of Antiplatelet Drugs and Their Mechanisms of Action

1) Nonsteroidal Antiinflammatory Agents

Aspirin (acetylsalicylic acid) and other nonsteroidal antiinflammatory agents inhibit platelets by blocking the formation of thromboxane A2, a potent platelet activator (Table 2). The extent of platelet inhibition for each nonsteroidal antiinflammatory agent depends on the ratio of cyclooxygenase (COX)-1 to COX-2 activity, half-life, and reversibility. Although several nonsteroidal antiinflammatory agents possess antiplatelet activity, discussion is frequently limited to aspirin as it is frequently prescribed for the prevention of cardiovascular events and irreversibly inhibits platelet function for the life of the platelet.

The natural precursors to aspirin—including willow bark—have been exploited for centuries to alleviate pain [2]. It was not until the 1950s that Dr Lawrence Craven hypothesized that a small daily dose of aspirin could prevent coronary thrombosis, and this finding went largely unnoticed for some time [3]. Now, several therapeutic mechanisms for aspirin exist, including a rapid and direct antiplatelet effect. Aspirin irreversibly inhibits COX-1 in platelets by acetylating a serine residue, thereby preventing arachidonic acid binding to the active site of the enzyme [4]. In platelets, low doses of aspirin are effective because platelets do not have a nucleus and, consequently, have minimal capability to synthesize new COX-1 enzyme. Combined with this fact, the irreversible effect of aspirin implies that production and release of new platelets from the bone marrow is required to restore platelet function. There is no direct antidote available to reverse the antiplatelet effects of aspirin on circulating platelets. Platelet transfusion can indirectly reverse the effects of aspirin by increasing the total circulating pool of platelets while agents like recombinant factor VIIa can overcome the aspirin effect by stimulating other platelet receptors (eg, thrombin receptors) that are more potent platelet-activating agents.

There is strong clinical evidence to support the value of aspirin for reducing death, myocardial infarction, and stroke in patients at risk for thrombotic events; however, this benefit is accompanied by a higher risk of bleeding [5]. In general, smaller doses of aspirin (75 mg to 100 mg daily) are considered equally effective as higher doses (300 mg to 325 mg daily) and demonstrate the lowest level of bleeding risk [6]. In patients undergoing cardiac operations, the risk to benefit ratio for preoperative aspirin is dependent on the urgency of operation, cardiovascular risk of the patient, concomitant antithrombotic medications, and risk for bleeding [1].

There is documented variability in response to aspirin, and all antiplatelet drugs for that matter, as some patients have excessive platelet inhibition and may be at increased risk for bleeding whereas another volunteer has reduced inhibition and may demonstrate higher thrombotic risk [7]. Much less studied is the incidence of increased or accentuated response to antiplatelet agents. Consideration of simple population variation suggests that response to drugs is distributed normally with equal numbers of patients having accentuated response or lack of response to orally administered drugs. A simple example of this variation is shown in Figure 1. In the study depicted in Figure 1, aspirin administration to 7 normal volunteers resulted in 1 volunteer having a bleeding time in excess of 14 minutes whereas another volunteer had

Table 1. Summary of Recommendations Related to Antiplatelet Drugs

Recommendation	Class of Recommendation (Level of Evidence)
Risk factor screening	
Risk factor screening for bleeding in patients requiring cardiovascular procedures is indicated as soon as possible before operation to intervene and modify risk factors, if possible. Special attention should be given to patients with combinations of the major risk factors listed below.	Class I (Level B)
One of the few modifiable preoperative risk factors is use of antiplatelet drugs, and special attention should be given to this risk factor.	
Monitoring platelet function	
Because of their high negative predictive value, preoperative point-of-care testing to assess bleeding risk may be useful in identifying patients with high residual platelet reactivity after usual doses of antiplatelet drugs, and who can undergo operation without elevated bleeding risk.	Class IIb (Level B)
Point-of-care testing to assess perioperative platelet function may be useful in limiting blood transfusion.	Class IIb (Level B)
Perioperative management of patients taking antiplatelet drugs	
Discontinuation of P2Y12 inhibitors for a few days before cardiovascular operations is recommended to reduce bleeding and blood transfusion, especially in high-risk patients.	Class I (Level B)
Stopping antiplatelet drugs before operation is associated with reduced bleeding, blood transfusion, and reoperation but not with increased postoperative death, myocardial infarction, or stroke. The interval between discontinuation of antiplatelet drugs and operation is uncertain and depends on multiple factors mostly related to patient drug responsiveness and thrombotic risk.	
Preoperative discontinuation of aspirin in certain high-risk patients such as those who refuse blood transfusion for religious reasons (Jehovah's Witness) is reasonable.	Class IIa (Level B)
Aspirin discontinuation before purely elective operations in patients without acute coronary syndromes is reasonable to decrease the risk of bleeding. Aspirin increases perioperative bleeding and blood transfusion, but to a lesser extent than other antiplatelet drugs. This effect may depend on the dose of preoperative aspirin, with doses less than 100 mg daily having less bleeding risk but having important efficacy in patients with acute coronary syndromes.	Class IIa (Level A)
Numerous studies show no increased risk of myocardial events with discontinuation of aspirin for a few days before operation in these patients.	
Management of antiplatelet drugs in patients with intrinsic (hereditary) or acquired platelet defects	
Patients with known preoperative intrinsic (hereditary) platelet defects or with thrombocytopenia and who require cardiac operations should not receive antiplatelet drugs before operation.	Class III (Level C)
Patients with acquired preoperative platelet defects associated with thrombocytopenia or bleeding should not receive antiplatelet therapy before cardiac operations.	Class III (Level C)
Management of antiplatelet drugs during noncardiac operations	
Continuing antiplatelet monotherapy (with either aspirin or clopidogrel) is reasonable in patients undergoing most noncardiac operations, regardless of procedure urgency. Patients with very high risk from even modest bleeding (eg, intracranial procedures) or expected major bleeding complications represent the only significant exceptions to this recommendation and should have antiplatelet therapy discontinued before operation if possible.	Class IIa (Level B)
In patients with coronary stents who require noncardiac operations, perioperative continuation of dual antiplatelet therapy can be reasonable unless the bleeding risk is prohibitive.	Class IIb (Level C)
Antiplatelet drugs after cardiac operations	
For stable nonbleeding patients, aspirin should be given within 6 to 24 hours of coronary artery bypass graft surgery (CABG) to optimize vein graft patency.	Class I (Level A)
In patients undergoing CABG after acute coronary syndromes, Guideline-indicated dual antiplatelet drugs should be restarted when bleeding risk is diminished to decrease intermediate-term adverse cardiovascular outcomes (MACE). That may have secondary benefit of increasing early vein graft patency.	Class I (Level A)
Once postoperative bleeding risk is decreased, testing of response to antiplatelet drugs, either with genetic testing or with point-of-care platelet function testing, early after cardiac procedures might be considered to optimize antiplatelet drug effect and minimize thrombotic risk to vein grafts.	Class IIb (Level B)
For patients with high platelet reactivity after usual doses of clopidogrel, it may be helpful to switch to another P2Y12 inhibitor (eg, prasugrel or ticagrelor).	Class IIb (Level C)
Treatment options for patients on antiplatelet drugs who require urgent operations	
For patients who require urgent operation while on dual antiplatelet therapy, delay of even a day or two before operation is reasonable to decrease bleeding risk and minimize thrombotic risk in patients with acute coronary syndromes.	Class IIa (Level B)
For patients on dual antiplatelet therapy, it is reasonable to make decisions about surgical delay based on tests of platelet inhibition rather than arbitrary use of a specified period of surgical delay.	Class IIa (Level B)

(Continued)

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Table 1. Continued

Recommendation	Class of Recommendation (Level of Evidence)
For patients with high thrombotic risks who require urgent operation while on dual antiplatelet therapy, bridging strategies using short-acting antiplatelet agents might be helpful in limiting bleeding while avoiding thrombotic risks.	Class IIb (Level B)
For patients taking dual antiplatelet drugs for acute coronary syndrome or with drug-eluting stents less than 1 year old, operation should likely proceed at intervals less than 5 days to minimize prothrombotic risks of antiplatelet withdrawal, or with use of a short-acting antiplatelet agent "bridge" to minimize these risks.	Class IIb (Level C)
Platelet transfusions may be helpful in patients receiving dual antiplatelet drugs who require urgent operation and have excessive perioperative bleeding. Platelet transfusion amounts may be excessive in this setting.	Class IIb (Level C)
For intractable operative bleeding in patients on dual antiplatelet drugs, recombinant factor VIIa may be helpful, but carries the risk of thrombosis. Risk-benefit analysis is essential in this situation.	Class IIb (Level C)
Multidisciplinary management of patients taking antiplatelet drugs	
Efforts at team coordination among multiple providers involved in the management of patients taking antiplatelet drugs who need cardiac procedures are reasonable and likely to result in reduced bleeding with safe operative outcomes.	Class IIa (Level B)

decreased bleeding time after oral administration [7]. It is also possible that some patients may have recovery of platelet function within 24 hours after ingestion of antiplatelet agents and before the next dose, although the clinical implications of these findings are not yet apparent [8, 9]. There are no confirmed explanations for this range of response for the efficacy (thrombotic protection) and safety (bleeding risk) of aspirin; however, compliance, bioavailability, drug interactions,

platelet turnover, and other mechanisms may play a role [10]. Variable response to drugs is a law of life that should not surprise clinicians, nor should it limit guideline-recommended drug therapy [7, 11, 12]. Although it is important to recognize that antiplatelet drugs may not inhibit platelets to the same extent in all people, the lack of a reliable and standardized platelet assay for monitoring platelet reactivity hampers personalized treatment at this time.

Table 2. Antiplatelet Drugs Encountered in Patients Having Cardiac Operations

Drug [Reference]	Antiplatelet Mechanism	Pharmacologic Properties	Route of Administration	Elimination Half-Life	Time to Platelet Recovery[a]
Aspirin	Platelet COX-1 inhibitor	Irreversible	Oral (daily dosing)		Production of new platelets
Thienopyridines Ticlopidine Clopidogrel Prasugrel	ADP P2Y12 receptor antagonists	Irreversible Prodrugs	Oral (daily dosing)		Production of new platelets
Ticagrelor	ADP P2Y12 receptor antagonist	Reversible Noncompetitive	Oral (twice daily)	7 hours [29]	80% recovery by 72 hours [31][b]
Abciximab	Fibrinogen receptor (GP IIb/IIIa) receptor antagonists	Monoclonal antibody	Intravenous		≥50% recovery by 48 hours in most patients [232]
Eptifibatide [233]		Reversible	Intravenous	2.5 hours	50% recovery by 4 hours
Tirofiban [234]		Reversible	Intravenous	2 hours	4–8 hours in most patients
Cilostazol	PDE inhibitor	Reversible	Oral (twice daily)	11–13 hours [235]	
Dipyridamole (extended release)	PDE inhibitor and other mechanisms		Oral	14 hours [236]	
Intravenous P2Y12 receptor antagonists in development					
Cangrelor [33]	ADP P2Y12 receptor antagonist	Reversible Competitive	Intravenous	3–6 minutes	1–2 hours
Elinogrel	ADP P2Y12 receptor antagonist	Reversible Competitive	Intravenous Oral (twice daily)	11–12 hours [37]	

[a] Time to platelet recovery after cessation of drug as measured by pharmacodynamic testing.   [b] Compared with approximately 70% to 75% platelet recovery achieved after cessation of clopidogrel as measured by light transmittance aggregometry (31).

ADP = adenosine diphosphate;   COX = cyclooxygenase;   GP = glycoprotein;   PDE = phosphodiesterase.
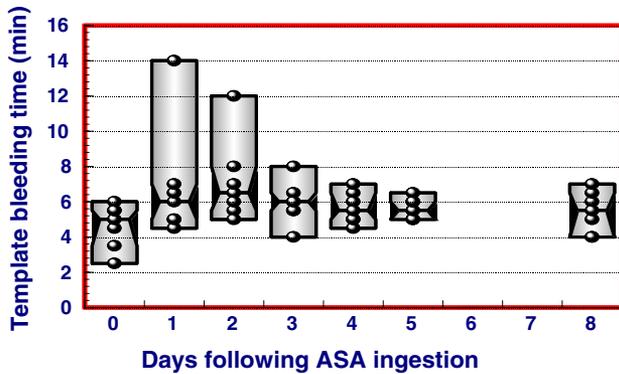
Fig 1. Template bleeding after ingestion of 360 mg aspirin (ASA) in 7 normal volunteers. (Reprinted with permission from Ferraris, et al, Int J Angiol 2011;20:1-18 [7].)

2) Adenosine Diphosphate P2Y12 Receptor Antagonists
There are four approved antagonists of the adenosine diphosphate (ADP) P2Y12 receptor and at least two others in clinical development. The P2Y12 receptor antagonists reduce downstream platelet activation events, including platelet granule release and thromboxane A2 formation, and ultimately inhibit platelet aggregation mediated by binding of fibrinogen to activated glycoprotein (GP) IIb/IIIa receptors on platelets [13]. Several large-scale clinical trials have demonstrated the importance of P2Y12 receptor antagonism in addition to aspirin therapy for preventing atherothrombotic events after acute coronary syndrome (ACS) and cardiac procedures [14–17]. There are no antidotes available for any of the P2Y12 receptor antagonists.

a) THIENOPYRIDINES. The first ADP P2Y12 receptor inhibitors developed were the thienopyridines. In the United States, the second-generation clopidogrel became the preferred agent over the first-generation ticlopidine owing to a lower incidence of blood dyscrasias and bone marrow toxicity [18]. In 2009, a third-generation thienopyridine—prasugrel—was approved for use in the United States and Europe. The thienopyridines are prodrugs that require first-pass metabolism by the cytochrome P450 (CYP) enzyme system in the liver, and therefore are only administered orally. Ticlopidine and clopidogrel require two conversion steps by P450 CYP enzymes for active metabolite generation, whereas prasugrel is dependent on the CYP system for only one conversion step [19]. Variable absorption and first-pass metabolism, including variation in the *CYP2C19* gene, contribute to high variability in clopidogrel response that is not evident with prasugrel [20].

Prasugrel demonstrates more efficient generation of its active metabolite, and therefore more potent platelet inhibition; however, its improved efficacy is countered by an increase in bleeding, including fatal bleeding [17, 21, 22]. Based on this bleeding risk, prasugrel is contraindicated in patients with a history of transient ischemic attack or stroke and is not generally recommended for patients aged 75 years or older or those weighing less

than 60 kg [23]. All thienopyridines are irreversible inhibitors of the P2Y12 receptor and block ADP-mediated platelet response for the life of the platelet [24]. These properties may complicate treatment decisions for urgent surgery, including CABG, as patients remain at risk for increased bleeding. In fact, most previous guidelines recommend stopping clopidogrel 5 to 7 days before surgery if possible [1, 25–27].

b) TICAGRELOR. Based on limitations characteristic of all thienopyridines (irreversible antagonists, prodrugs), novel P2Y12 receptor antagonists are in development. Ticagrelor is an oral, reversible, and direct-acting antagonist of the P2Y12 receptor that demonstrated overall improved efficacy compared with clopidogrel in its phase III trial [16]. It was approved in July 2011 by the US Food and Drug Administration with a boxed warning to avoid administration with aspirin doses greater than 100 mg—a finding that was triggered by the lack of efficacy in the North American subgroup [28]. Ticagrelor is a noncompetitive antagonist of the P2Y12 receptor, implicating that it binds a separate site and is not replaced by the endogenous agonist ADP [30]. Compared with a 600-mg clopidogrel loading dose, the 180-mg ticagrelor loading dose demonstrates a faster onset and greater platelet inhibition [31]. Similarly, maintenance therapy with ticagrelor, which is dosed twice a day, has a faster offset than the standard clopidogrel 75-mg maintenance dose; however, platelet reactivity is not restored to levels higher than those obtained with maintenance clopidogrel until approximately 24 to 48 hours after terminating therapy, as more potent and consistent platelet inhibition is observed with ticagrelor [31]. Based on its novel structure, ticagrelor is associated with adverse effects including dyspnea, ventricular pauses, and increased serum uric acid and creatinine levels that were not previously identified with the thienopyridines [16].

c) SHORT-ACTING P2Y12 RECEPTOR ANTAGONISTS. Cangrelor, an ADP analog related to ticagrelor, is a direct, short-acting, reversible, and competitive P2Y12 receptor antagonist for intravenous administration [32]. Cangrelor achieves potent platelet inhibition within minutes of initiation, and almost complete platelet recovery occurs 1 to 2 hours after cessation of the infusion [33]. In its phase III trials, cangrelor did not meet the primary endpoint and was unable to demonstrate any additional benefit compared with clopidogrel in percutaneous coronary intervention (PCI) [34, 35]. The Maintenance of Platelet Inhibition With Cangrelor After Discontinuation of Thienopyridines in Patients Undergoing Surgery (BRIDGE) trial demonstrated pharmacodynamic efficacy for bridging patients before CABG with intravenous cangrelor. No difference in excessive CABG-related bleeding or ischemic events between cangrelor and placebo was reported [36].

Another novel P2Y12 receptor antagonist in development is elinogrel, a first in class sulfonylurea. Elinogrel is a direct-acting, reversible, and competitive antagonist that is being developed for both intravenous and oral

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administration [37]. The manufacturers of elinogrel expect to begin phase III testing in 2012 [38].

3) Glycoprotein IIb/IIIa Inhibitors

Unlike other antiplatelet agents that inhibit one activation pathway, the GP IIb/IIIa receptor antagonists block the final common pathway to platelet aggregation. Fibrinogen binds to activated GP IIb/IIIa receptors—also known as αIIbβ3 receptors—and is converted to fibrin in the final step of the coagulation cascade, allowing formation of the platelet-fibrin plug. Therefore, antagonists of the GP IIb/IIIa receptor are exceptionally potent antiplatelet agents. These medications exploit specific amino acid sequences on fibrinogen and other receptor ligands (such as von Willebrand factor, fibronectin, and vitronectin) to prevent platelet aggregation [39].

There are three GP IIb/IIIa receptor antagonists available—abciximab, eptifibatide, and tirofiban. These antiplatelet agents are characterized by an intravenous formulation, fast onset of action within minutes of administration, and exclusive use in the PCI setting. They are potent GP IIb/IIIa receptor antagonists and are effective for preventing death, myocardial infarction, and urgent revascularization in PCI patients, but at the expense of an increased risk of bleeding [40]. Although the GP IIb/IIIa receptor antagonists share similar contraindications and precautions related to bleeding risk, the three medications vary in mechanism and duration of action.

The long-acting abciximab is a monoclonal antibody that binds the β3 subunit of the GP IIb/IIIa platelet receptor. Unlike the other agents in the class, abciximab inhibits thrombin generation [41], blocks the vitronectin receptor αVβ3 that shares a subunit with the intended target, and demonstrates cross-reactivity with a leukocyte receptor [39]. Although the free antibody has a short plasma half-life, abciximab bound to platelets achieves potent platelet inhibition in most patients, with gradual platelet recovery occurring 24 to 48 hours after cessation of treatment [39].

Eptifibatide and tirofiban are reversible and short-acting GP IIb/IIIa receptor antagonists. Eptifibatide is a cyclic heptapeptide that includes the three amino acid sequence found in snake venom, with high specificity for the GP IIb/IIIa receptor (KGD); tirofiban is a nonpeptide mimetic of a similar amino acid sequence associated with fibrinogen (RGD) [39].

4) Other Agents With Antiplatelet Activity (eg, Phosphodiesterase Inhibitors, Dipyridamole)

d) PHOSPHODIESTERASE INHIBITORS. In platelets, adenylyl cyclase and guanylyl cyclase elevate cyclic monophosphate nucleotide levels (cyclic adenosine monophosphate and cyclic guanosine monophosphate), ultimately leading to platelet inhibition. The phosphodiesterase (PDE) inhibitors cilostazol and dipyridamole support this inhibitory effect by blocking the degradation of cyclic adenosine monophosphate and cyclic guanosine monophosphate [42].

Cilostazol potently inhibits PDE3A—a cardiovascular subtype of PDE3—in platelets as well as vascular smooth muscle cells, which causes vasodilation [42]. Hence, the medication is indicated and used for intermittent claudication. Cilostazol is primarily metabolized by CYP3A4/5 with some involvement by CYP2C19, and it is estimated that the elimination half-life for cilostazol is approximately 10 hours [43]. As an antiplatelet agent, cilostazol has been studied as triple antiplatelet therapy in combination with aspirin and clopidogrel, the standard dual antiplatelet therapy. In the CILON-T (Influence of Cilostazol-Based Triple Antiplatelet Therapy on Ischemic Complication After Drug-Eluting Stent Implantation) trial, triple antiplatelet therapy with cilostazol demonstrated reduced platelet reactivity in patients undergoing drug-eluting stent implantation, but this did not significantly affect clinical outcomes [44]. Cilostazol has primarily been studied in Koreans for additional platelet inhibition as this group has a high percentage of the population with CYP2C19 loss-of-function alleles, and therefore a high incidence of high residual platelet reactivity on clopidogrel [45].

Dipyridamole has several mechanisms of action. For one, it is an inhibitor of PDE3 and 5 and possesses vasodilatory and antiplatelet activity [46]. Dipyridamole also blocks adenosine uptake which limits adenylyl cyclase activation in platelets, cyclic adenosine monophosphate formation, and ultimately inhibits platelet aggregation. Evidence suggests that dipyridamole stimulates prostacyclin production and has antiinflammatory and antioxidant properties, among other effects [46]. Dipyridamole is metabolized to a glucuronide for excretion primarily in the bile with a small amount undergoing enterohepatic recirculation; its estimated terminal half-life is 19 hours [43]. Both cilostazol and dipyridamole require twice daily dosing. For its antiplatelet effect, dipyridamole is prescribed as the extended release product in combination with aspirin and is indicated for noncardioembolic stroke or transient ischemic attack [43]. Patients taking either cilostazol or dipyridamole are at increased risk for vasodilator-associated adverse effects including tachycardia, hypotension, and particularly headache [43].

D. Definition of Patients at High Risk for Perioperative Bleeding

Class I Recommendation

a. Risk factor screening for bleeding in patients requiring cardiovascular procedures is indicated as soon as possible before operation to intervene and modify risk factors, if possible. Special attention should be given to patients with combinations of the major risk factors listed below. One of the few modifiable preoperative risk factors is use of antiplatelet drugs, and special attention should be given to this risk factor. (Level of evidence B)

Previous literature reviews suggest that the following six risk factors herald increased bleeding and blood transfusion in association with cardiovascular procedures: (1) advanced age, (2) diminished red blood cell

Table 3. Recent Evidence Supporting Risk Factors for Increased Bleeding After Cardiovascular Procedures

Risk Factor	Intervention	Reference	Outcome
Advanced age			
Age >70 years	Cardiac operations with CPB	Vuylsteke, 2011; Vivacqua, 2011	Increased bleeding with advanced age
Low red blood cell volume or other blood abnormalities			
Preoperative anemia or small body size	CABG	Hannan, 2010; Boening, 2011; Bahrainwala, 2011	Increased bleeding, blood transfusion, and morbidity and mortality
Thrombocytopenia	STEMI Rx	Hakim 2011	Worse long-term outcome (death, MI, stroke)
Complex or urgent operations			
Prior operation for CAD	Resternotomy	Morales, 2010; Hannan, 2010	Bleeding and poor outcome
Non-CABG OR	TEVAR, DHCA, prolonged CPB	Chamogeorgakis, 2010	Serious postoperative bleeding
Aortic dissection	TEVAR versus open	Sachs, 2010; White 2011	Much less bleeding with TEVAR
Preoperative medications			
Aspirin	CABG	Jacob, 2011; Alghamdi, 2007; Ghafarinejad, 2007; Sun, 2008	Increased bleeding if aspirin given shortly before operation; depends on dose and length of time before operation
Clopidogrel plus aspirin	CEA, CABG	Rosenbaum, 2011; Nijjer, 2011, and many others	Increased neck hematoma with CEA patients treated with clopidogrel/ASA; increased reoperation in CABG patients with recent clopidogrel/ASA treatment
Patient comorbidities			
Advanced liver disease	Ultrafiltration, LVAD, cardiac catheterization	Andritsos 2011; Pillarisetti, 2011	Bleeding and increased transfusion
Renal failure	Off-pump procedures	Bruschi, 2010	Less bleeding than with on-pump procedures

ASA = acetylsalicylic acid;   CABG = coronary artery bypass graft surgery;   CAD = coronary artery disease;   CEA = carcinoembryonic antigen;   CPB = cardiopulmonary bypass;   DHCA = deep hypothermic cardiac arrest;   LVAD = left ventricular assist device;   MI = myocardial infarction;   non-CABG OR = cardiac procedures using cardiopulmonary bypass and involving more than CABG;   STEMI = ST-segment elevation myocardial infarction;   TEVAR = thoracic endovascular aortic repair.

volume (small body size or anemia), (3) complex operations (non-CABG, valve operations, thoracic aortic vascular procedures), (4) urgent operations, (5) preoperative medications (antiplatelet and anticoagulant drugs), and (6) chronic patient comorbidities (intrinsic platelet disorders, chronic illnesses like renal failure, chronic obstructive pulmonary disease, liver disease, and so forth) [1, 27, 47]. Table 3 outlines recent studies that support these already documented risk factors as precursors of bleeding and blood transfusion. For the most part, the evidence supporting these six factors as risks for bleeding is limited and not based on large randomized trials. However, large observational studies, other cohort studies, some anecdotal reports, and a few randomized trials used to uncover these risk factors leads to consensus on the part of the writing group that supports these six factors as major risks for bleeding and blood transfusion after cardiovascular procedures.

Early identification of bleeding risk is important. Of the six major risk factors listed above, several are targets for preoperative intervention. Preoperative interventions that may reduce bleeding risk include treating preoperative anemia, modifying operative approach to include less invasive techniques, treatment of chronic comorbidities, and discontinuation of antiplatelet drugs shortly before operation. Good evidence suggests that dual antiplatelet therapy with aspirin and clopidogrel should not be withheld when considering PCI in patients with ACS who might need CABG [48]. Once dual antiplatelet therapy is started in ACS patients, the risk of stopping antiplatelet drugs for a few days before operation is uncertain. Logic suggests that discontinuation of indicated antiplatelet therapy predisposes to thrombotic complications, especially in patients with drug-eluting stents. However, once started with a loading dose of dual antiplatelet therapy, discontinuation of indicated antiplatelet therapy for a few days before operation does not seem to alter long-term cardiovascular outcomes significantly, but is associated with reduced bleeding, blood transfusion, and early reoperation [49, 50]. In most studies that address the discontinuation of antiplatelet drugs before operation, perioperative bleeding is the primary focus. There is very little evidence in the literature to address the impact of discontinuation of indicated antiplatelet therapy for a few days before operation on thrombotic outcomes.

Modifying the operative procedure can limit bleeding and blood transfusion. An example is the use of thoracic endovascular grafts (thoracic endovascular aortic repair) rather than conventional open repair of thoracic aortic disease. Minimally invasive procedures such as thoracic endovascular aortic repair and off-pump CABG are associated with reduced bleeding and blood transfusion and appear to be reasonable alternatives for treatment of patients at high risk of bleeding [51–57].

E. Monitoring Platelet Function

Class IIb Recommendation

a. Because of their high negative predictive value, preoperative point-of-care testing to assess bleeding risk may be useful in identifying patients with high residual platelet reactivity after usual doses of antiplatelet drugs, and who can undergo operation without elevated bleeding risk. (Level of evidence B)
b. Point-of-care testing to assess perioperative platelet function may be useful in limiting blood transfusion. (Level of evidence B)

Traditionally, laboratory tests of platelet function evaluate patients with a history of bleeding and assess bleeding risk for planned procedures in patients with a history of bleeding. More recently, point-of-care platelet function tests guide the management of patients presenting with bleeding and coagulopathy. Recognition of the key role platelets play in atherothrombosis led to the increasing use of platelet function testing to monitor the efficacy of antiplatelet drugs used to treat cardiovascular conditions. There is a proliferation of point-of-care tests and instruments that allow bedside monitoring of antiplatelet therapy (58, 59). Table 4 summarizes currently available point-of-care tests of platelet function (59–72). The list

shown in Table 4 is constantly being updated and undoubtedly other point-of-care tests will emerge.

While much of the literature on point-of-care platelet function tests focuses on assessing their utility in guiding antiplatelet treatment for patients with cardiovascular disorders, these devices have a role in cardiac surgery to assess perioperative bleeding risk and help guide the management of bleeding after cardiopulmonary bypass. Assessments of platelet function with devices such as HemoSTATUS, modified thromboelastography, Multiplate analyzer, VerifyNow, and PFA-100 proved useful in predicting increased bleeding risk [62, 73–76]. Although the positive predictive value of each of these tests is limited, patients found to have normal platelet function by these devices are unlikely to bleed secondary to platelet defects [62, 73]. These devices play a role in identifying those patients treated with antiplatelet agents who can undergo urgent/emergent operation without increased platelet-related bleeding risk.

Point-of-care platelet function testing can guide perioperative transfusion management and reduce blood component utilization [77, 78]. HemoSTATUS, modified thromboelastography, Multiplate analyzer, and PFA-100 are used as part of point-of-care–guided transfusion algorithms. The ICHOR PlateletWorks device contains an integrated platelet counter so that quantitative as well as qualitative platelet defects can be identified and treated with directed transfusion therapy. Although these point-of-care–guided algorithms can decrease utilization of transfused blood components and may reduce transfusion-related complications [27, 61, 64, 79, 80], their reproducibility, accuracy, and correlation among various tests are variable and suboptimal [81–86].

There are a number of other tests of platelet function that are not point-of-care tests. These tests are commonly found in traditional clinical or research laboratory set-

Table 4. Point-of-Care Tests of Platelet Function

Name of Test [Reference]	Principle
Bleeding time [237]	In vivo cessation of bleeding after standardized skin incision
Clot Signature Analyzer (Xylum) [64]	Platelet-mediated hemostasis time under flow conditions
ImpactCone and Platelet Analyzer (Matis Medical) [68]	Platelet adhesion and aggregation under flow conditions
Hemostasis Analysis System (Hemodyne) [65]	Platelet-mediated force transduction or clot retraction
HemoSTATUS (Medtronic) [63]	Shortening of activated clotting time by platelet activating factor
ICHOR PlateletWorks (Helena Laboratories) [66]	Adenosine diphosphate, collagen, and arachidonic acid stimulated platelet aggregation by whole blood single platelet counting
Modified Thromboelastography, Platelet Mapping (Haemoscope) [60, 62]	Increase in maximum clot strength by adenosine diphosphate and arachidonic acid stimulation
Multiplate Multiple Electrode Aggregometry (Verum Diagnostica GmbH) [69–71]	Impedance aggregometry
PFA-100 Platelet Function Analyzer (Dade-Behring) [61, 62]	Collagen-adenosine diphosphate and collagen-epinephrine stimulated aperture occlusion time
Sonoclot Coagulation and Platelet Function Analyzer (Sienco) [67]	Dynamic viscometer measuring time to peak viscosity as an index of platelet function
VerifyNow and Ultegra System Rapid Platelet Function Assay (Accumetrics) [72]	Turbidimetric-based optical detection system measuring platelet aggregation to fibrinogen-coated microparticles with adenosine diphosphate and iso-thrombin receptor activating peptide stimulation

tings and include optical aggregometry, platelet glass bead retention assay, and iron-induced platelet aggregation [59, 87–91]. Flow cytometry is used to assess platelet surface expression of activation markers including fibrinogen receptor (glycoprotein IIb/IIIa), thrombin PAR-1 receptor, ADP-specific platelet protein phosphorylation (VASP), and P-selectin [11, 86, 92–101]. Platelet activation can also be assessed indirectly by measuring the release of nitric oxide, thromboxane B2, soluble P-selectin, and other factors [88, 93, 102–106]. The clinical utility of these tests in assessing perioperative bleeding risk and transfusion rates is uncertain.

F. Management of Patients Taking Antiplatelet Drugs in Specific Clinical Situations

1) Antiplatelet Drugs and the Patient at High Risk of Bleeding

Class I Recommendation

a. Discontinuation of P2Y12 inhibitors for a few days before cardiovascular operations is recommended to reduce bleeding and blood transfusion, especially in high-risk patients. Stopping antiplatelet drugs before operation is associated with reduced bleeding, blood transfusion, and reoperation but not with increased postoperative death, myocardial infarction (MI), or stroke. The interval between discontinuation of antiplatelet drugs and operation is uncertain and depends on multiple factors mostly related to patient drug responsiveness and risk of thrombotic complications. (Level of evidence B)

Class IIa Recommendation

a. Preoperative discontinuation of aspirin in certain high-risk patients such as those who refuse blood transfusion for religious reasons (Jehovah's Witness) is reasonable. (Level of evidence B)
b. Aspirin discontinuation before purely elective operations in patients without ACS is reasonable to decrease the risk of bleeding. Aspirin increases perioperative bleeding and blood transfusion, but to a lesser extent than other antiplatelet drugs. This effect may depend on the dose of preoperative aspirin, with doses less than 100 mg daily having less bleeding risk but having important efficacy in patients with ACS. Multiple studies show no increased risk of myocardial events with discontinuation of aspirin for a few days before operation in these patients. (Level of evidence A)

Recent evidence confirms the bleeding risk associated with aspirin administration within 5 days of cardiac procedures [50, 107–109]. Interestingly, discontinuation of aspirin 6 or more days before operation showed no difference in postoperative death, MI, or stroke compared with outcomes in patients who received aspirin within 5 days of operation, provided that aspirin was restarted after operation [50]. However, in patients with ACS, no medicine has more efficacy in preventing death, MI, or stroke than aspirin. Aspirin causes a 50% reduction in the

triple endpoint in patients with ACS compared with placebo [110]. The number of patients who need to be treated to gain this benefit is between 10 and 20. The addition of clopidogrel to aspirin adds small, but significant, benefit to that of aspirin, in that approximately 50 patients need to be treated to prevent one death, MI, or stroke [111]. If an antiplatelet drug is given before CABG in patients with ACS, aspirin is the drug of choice. Discontinuation of aspirin before operation prevents some bleeding, but may have an as yet uncertain risk of adverse outcomes in patients with ACS [112].

Special attention applies to Jehovah's Witness patients who refuse blood transfusion for religious reasons. Cardiac surgical procedures are done in this population with safe and effective results [113–118]. The surgical technique used in these patients evolved over a 40-year period. Recent preoperative interventions in Jehovah's Witness patients include use of preoperative erythropoietin and discontinuation of antiplatelet drugs [113]. These measures coupled with careful intraoperative hemostasis employing guideline-recommended blood conservation interventions usually results in safe outcomes free from significant bleeding [113, 115].

Regarding clopidogrel, a large meta-analysis of mostly nonrandomized trials in more than 22,000 patients undergoing CABG suggests that there is no difference in the triple endpoint of death, MI, or stroke whether clopidogrel is continued until operation or not [49]. However, there is a significant increase in early reoperation (presumably for bleeding) among patients who receive clopidogrel shortly before CABG [49]. Importantly, discontinuation of clopidogrel for 5 to 7 days before operation did not confer increased risk of worse cardiac outcomes [49]. Numerous other recent studies found increased bleeding when clopidogrel was not discontinued before CABG, but the exact time when clopidogrel should be stopped before operation is less certain. Stopping clopidogrel within 3 days of operation did not result in increased bleeding for those patients compared with those patients who stopped clopidogrel 5 days or more before operation [119].

Newer P2Y12 receptor inhibitors of platelet function have different pharmacodynamics and differing bleeding risks [31, 120]. Both clopidogrel and prasugrel, two P2Y12 receptor blockers with different pharmacokinetics, have associated increased bleeding risks in patients who require urgent CABG while receiving these drugs [17]. The odds ratio for post-CABG bleeding risk in patients treated with prasugrel is 4.7 compared with clopidogrel. Ticagrelor is a potent short-acting P2Y12 receptor inhibitor with equivalent bleeding risk compared with clopidogrel, but importantly, the package insert warns against starting ticagrelor in patients with non–ST-segment elevation MI who might need CABG [28].

2) Antiplatelet Drugs in Patients With Known Intrinsic (Hereditary) or Acquired Platelet Disorders

Class III Recommendation

a. Patients with known preoperative intrinsic (hereditary) platelet defects and who require cardiac opera-

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tions should not receive antiplatelet drugs before operation. (Level of evidence C)

b. Patients with acquired preoperative platelet defects associated with thrombocytopenia or bleeding should not receive antiplatelet therapy before cardiac operations. (Level of evidence C)

There is surprisingly little information in the literature about the efficacy and safety of antiplatelet drugs for pediatric patients, the population most commonly identified with intrinsic platelet disorders [121]. There are isolated reports of cardiac operations in patients with Glanzmann's thrombasthenia [122, 123], Wiskott-Aldrich syndrome [124–126)], paroxysmal nocturnal hemoglobinuria [127, 128], Jacobsen syndrome [129], and DiGeorge syndrome [130], almost always associated with bleeding and transfusion with platelet concentrates. Patients with acquired or congenital von Willebrand's disease seem to have reduced incidence of bleeding related to cardiac operations compared with other congenital platelet defects, but comparative reports are nonexistent [131, 132]. This decreased bleeding in von Willebrand's disease patients may relate to treatment with specific hemostatic agents such as desmopressin [133]. Consensus suggests that antiplatelet therapy for these patients before cardiac procedures only worsens the known platelet defect and is, therefore, not indicated, but no comparative trials support this recommendation.

There is an elevated risk of thrombosis in neonates undergoing initial palliative cardiac operations [134]. These neonates are treated with empiric aspirin without much evidence of benefit [135]. In general, aspirin alone is not viewed as adequate in most settings associated with significant thromboembolic risk [121, 136]. Given the limited benefit of antiplatelet monotherapy in children requiring cardiac operations and the expected risk of bleeding in similar patients with congenital platelet defects, the preponderance of very limited evidence suggests that antiplatelet therapy is not indicated before cardiac procedures in patients with known congenital platelet defects.

On occasion, acquired platelet defects are identified in patients who require cardiac operations. Examples include idiopathic thrombocytopenic purpura, myelodysplastic syndrome, heparin-induced thrombocytopenia, thrombotic thrombocytopenic purpura, and platelet factor IV deficiency. These acquired defects are usually associated with thrombocytopenia, and may present with thrombotic events or with bleeding [137–140]. For most acquired platelet defects, antiplatelet drugs are not indicated, despite the prothrombotic nature of some of these disorders [141]. Possible exceptions include patients with essential thrombocythemia or some forms of polycythemia vera who can benefit from aspirin therapy for secondary prevention of thrombotic events [142, 143]. Anecdotal evidence suggests that patients with acquired platelet dysfunction are at increased risk for bleeding and blood transfusion after cardiac operations [144–146]. Evidence of benefit from antiplatelet drugs in patients with acquired platelet defects is almost nonexistent. Given the

uncertain benefit of antiplatelet drugs in patients with acquired platelet defects, and given the risk of perioperative bleeding associated with antiplatelet drugs in these patients, consensus suggests that these drugs should be stopped, or preferably not started, before cardiac operations or are not indicted for most patients with these platelet defects.

3) Antiplatelet Drugs and Noncardiac Operations

Class IIa Recommendation

a. Continuing antiplatelet monotherapy (with either aspirin or clopidogrel) is reasonable in patients undergoing most noncardiac operations, regardless of procedure urgency. Patients with very high risk from even modest bleeding (eg, intracranial procedures) or expected major bleeding complications represent the only significant exceptions to this recommendation and should have antiplatelet therapy discontinued before operation if possible. (Level of evidence B)

Class IIb Recommendation

a. Continuing dual antiplatelet therapy in patients with coronary stents who require noncardiac operations can be reasonable unless the risk of bleeding is prohibitive. (Level of evidence C)

Antiplatelet drugs are among the most commonly prescribed medications. It is to be expected that some patients taking antiplatelet medications will require elective or urgent noncardiac operations. The risk-benefit relationship associated with antiplatelet drugs during noncardiac operations depends on the type and urgency of operation, and on patient-specific risks. Most [147–150], but not all [151], evidence suggests that patients taking aspirin for secondary prevention have decreased thrombotic events if aspirin is continued during noncardiac operations. Clopidogrel monotherapy for secondary prophylaxis confers similar benefit [152]. Patients taking antiplatelet drugs after percutaneous coronary interventions are especially prone to perioperative coronary events if indicated dual antiplatelet therapy is discontinued for noncardiac operations [148, 153]. One study suggests that the rate of major adverse cardiac events is nearly doubled when dual antiplatelet therapy is stopped more than 5 days before noncardiac operations [154]. Antiplatelet drugs may be protective in some postoperative patients with prolonged intensive care unit (ICU) stay for various reasons, including prevention of organ dysfunction [155]. This benefit may be masked by bleeding risk, but at least no harm accrues to patients on antiplatelet drugs who required prolonged ICU stay [155].

Continuation of antiplatelet drugs during noncardiac operations has bleeding risk, especially with dual antiplatelet therapy [156–160]. For most noncardiac operations, aspirin increases the risk of perioperative bleeding, but not dramatically so [157]. In most clinical situations, antiplatelet monotherapy provides benefit that outweighs the bleeding risk and should be continued [150, 157]. Possible exceptions to this recommendation include

intracranial procedures, transurethral prostatectomy, intraocular procedures, and operations with extremely high bleeding risk. Intraoperative control of bleeding in patients taking antiplatelet drugs is more difficult than for patients not taking these medications. Despite this, most studies found that transfusion rates and reoperations are not increased in patients on antiplatelet drugs who undergo noncardiac operations [161–164]. Difficult bleeding problems occurred more commonly among patients on dual antiplatelet therapy who underwent moderate to high risk operations, including vascular reconstructions, complex visceral procedures, and transbronchial operations [158–160].

Patients receiving dual antiplatelet therapy (usually aspirin plus clopidogrel) because of percutaneous stent placement represent a special circumstance if noncardiac operations are required. Most patients who have stent thrombosis have premature discontinuation of indicated dual antiplatelet therapy [152, 165]. Expert recommendations advise that patients can have noncardiac operations 3 months after bare-metal stent PCI and 12 months after drug-eluting stent PCI, with continuation of aspirin therapy [153, 165, 166]. Real-world data indicate that noncardiac operations after drug-eluting stent placement is frequent, is associated with highly variable antiplatelet cessation, and seems to be associated with low cardiac morbidity [167]. Difficult decisions regarding antiplatelet management arise when a patient who is still receiving dual antiplatelet therapy has to undergo an operation that cannot be postponed. Discussions among the treating cardiologist, the surgeon, and the anesthesiologist about this situation are recommended to achieve a reasonable multidisciplinary consensus. The best option is to delay elective procedures until dual antiplatelet therapy is no longer necessary [148]. Delay of operation is not always possible. In certain high-risk situations (closed space procedures, high bleeding risk, and so forth), clopidogrel should be stopped for 5 days before operation. Most other procedures can proceed with continuation of dual antiplatelet therapy, but with modestly increased bleeding risk [168, 169].

4) Antiplatelet Drugs After Cardiac Operations

Class I Recommendation

a. For stable nonbleeding patients, aspirin should be given within 6 to 24 hours of CABG to optimize vein graft patency. (Level of evidence A)
b. For patients undergoing CABG after ACS, guideline-indicated dual antiplatelet drugs should be restarted when bleeding risk is diminished to decrease intermediate-term major adverse cardiovascular outcomes. That may have the secondary benefit of increasing early vein graft patency. (Level of evidence A)

Class IIb Recommendation

a. Once postoperative bleeding risk is decreased, testing of response to antiplatelet drugs, either with genetic testing or with point-of-care platelet function testing,

early after cardiac procedures might be considered to optimize antiplatelet drug effect and minimize thrombotic risk to vein grafts. (Level of evidence B)
b. For patients with high platelet reactivity after usual doses of clopidogrel, it may be helpful to switch to another P2Y12 inhibitor (eg, prasugrel or ticagrelor). (Level of evidence C)

Several studies, including meta-analyses and consensus guidelines, suggest benefit from early administration of aspirin shortly after CABG to optimize vein graft patency [1, 170–172]. Evidence is not available to support a similar benefit for arterial graft patency [171]. However, many patients undergoing CABG fall into the categories subsumed by large cardiology trials such as CURE, CAPRIE, CREDO, and CLARITY-TIMI 28. Based on these trials, ACCP guidelines recommend dual antiplatelet therapy with aspirin and clopidogrel for 9 to 12 months after PCI regardless of whether patients underwent CABG [173]. Subsequently, AHA/ACC guidelines give Class I recommendation to dual antiplatelet therapy for patients undergoing PCI with or without subsequent CABG [174, 175]. Significant numbers of ACS patients with indications for dual antiplatelet therapy after CABG do not receive this indicated therapy. One study suggests that only 27% of patients with indications for dual antiplatelet therapy received this treatment after CABG for recent MI [176]. Patients who do receive appropriate dual antiplatelet therapy have better survival and less recurrent MI than those who do not [176]. Patients who do get guideline indicated dual antiplatelet therapy may also have improved early vein graft patency [177].

As many as 50% of patients do not have adequate response to aspirin on the first postoperative day after cardiac procedures, and this percentage increases in the first week after operation, especially for off-pump procedures [178–180]. Interestingly, the addition of clopidogrel did not seem to alter this nonresponse to aspirin. The clinical consequences of this lack of response remain uncertain, but evidence suggests lack of response to aspirin correlates with early vein graft occlusion after CABG and with recurrent cardiac events [180–182]. Evidence supports the use of increased dosing of antiplatelet drugs to try to obtain a therapeutic effect [183]. In patients with high residual platelet reactivity after the usual doses of clopidogrel, newer antiplatelet agents are more effective at reducing platelet reactivity compared with increasing the dose of clopidogrel [184]. Whether giving increased doses of antiplatelet agents to nonresponders shortly after CABG will provide increased protection from vein graft occlusion or other thrombotic events is unknown.

A significant number of patients treated with P2Y12 platelet inhibitors exhibit drug resistance. Patients who lack a sufficient platelet inhibition response to P2Y12 inhibitors have worse outcome, both early and late, after presenting with coronary syndromes [185, 186]. The rate of drug resistance depends on multiple factors including assays used to measure platelet function, patient comorbidities, drug interactions, and genetic factors [186].

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Point-of-care monitoring of platelet reactivity after clopidogrel administration may help identify patients for whom individualized strategies are indicated to limit bleeding complications after coronary intervention [183].

Patients who lack a sufficient platelet inhibition response to P2Y12 inhibitors have worse outcomes, both early and late, after presenting with coronary syndrome [185, 186]. Diminished platelet response to clopidogrel is not uncommon and may be due to multiple factors including assays used to measure platelet function, patient comorbidities, drug interactions, and genetic factors [186]. Genetic polymorphisms involved in clopidogrel absorption, metabolism, and activity at the platelet surface may interfere with its antiplatelet actions. Further, proton pump inhibitors may interfere with the action of clopidogrel by functionally reducing the ability of CYP2C19 to convert clopidogrel to its active metabolite [187]. There are at least two loss-of-function polymorphisms of the CYP2C19 gene, and there is some controversy as to whether patients with these loss-of-function alleles will benefit from clopidogrel therapy for ACS [188, 189].

Certain patients with high platelet reactivity after usual maintenance doses of clopidogrel will benefit from increased daily dosing treatment regimens [183], especially patients who are heterozygous for the loss-of-function CYP2C19*2 allele [189]. Patients who are homozygous for this allele do not seem to respond to increased daily doses of clopidogrel, and other antiplatelet alternatives may be appropriate [189].

G. Treatment Options for Patients Taking Antiplatelet Drugs Who Require Urgent Operations

Class IIa Recommendation

a. For patients who require urgent operation while on dual antiplatelet therapy, delay of even a day or two before operation is reasonable to decrease bleeding risk and minimize thrombotic risk in patients with ACS. (Level of evidence B)
b. For patients on dual antiplatelet therapy, it is reasonable to make decisions about surgical delay based on tests of platelet inhibition rather than arbitrary use of a specified period of surgical delay. (Level of evidence B)

Class IIb Recommendation

a. For patients requiring urgent operation while on dual antiplatelet therapy, bridging strategies using short-acting antiplatelet agents might be helpful in limiting bleeding while avoiding thrombotic risks. (Level of evidence B)
b. For patients taking dual antiplatelet drugs for ACS or with drug-eluting stents less than 1 year old, operation should likely proceed at intervals less than 5 days to minimize prothrombotic risks of antiplatelet withdrawal, or with use of a short-acting antiplatelet agent "bridge" to minimize these risks. (Level of evidence C)

c. Platelet transfusions may be helpful for patients on dual antiplatelet drug therapy who require urgent operation and have excessive perioperative bleeding. Platelet transfusion amounts may be excessive in this setting.
d. For intractable operative bleeding in patients on dual antiplatelet drugs, recombinant factor VIIa may be helpful, but carries the risk of thrombosis. Risk-benefit analysis is essential in this situation. (Level of evidence C)

Five percent to 15% of patients with an ACS will require an urgent cardiac operation after recent ingestion of antiplatelet drugs [190]. This situation encompasses three important areas of decision: (1) timing of operation and the definition of "urgent," (2) examination of the extent of the platelet function defect, and (3) management of the platelet defect in the perioperative setting. Of these, information is available that guides appropriate timing of operation given patient preoperative risks, the extent of platelet defects, and anticipated bleeding/transfusion risks [174, 191]. Much less information guides validated coagulation factor and platelet transfusion protocols and other blood conservation measures that will be effective in this setting.

Numerous studies, including two meta-analyses, examined the outcomes of cardiac operations after administration of the two most commonly used antiplatelet agents, aspirin and clopidogrel [55, 192]. Consensus suggests that bleeding risk is increased when operation proceeds shortly after ingestion of dual antiplatelet drugs. This consensus resulted in a Class I recommendation from the AHA/ACC and the STS to delay operation, if possible, in patients with recent exposure to clopidogrel/aspirin dual therapy [27, 174]. Fewer studies describe the results of cardiac operations in patients taking newer and possibly reversible P2Y12 and GPIIb/IIIa inhibitors. The Platelet Inhibition and Patient Outcomes (PLATO) trial contains information about CABG after ticagrelor administration, and the TRITON-TIMI 38 trial examines CABG after prasugrel administration [17, 31, 120, 193]. Studies involving patients taking newer antiplatelet agents and who require urgent CABG suggest that bleeding risk is at least as great as, or greater than, that for patients taking the more common aspirin/clopidogrel dual antiplatelet therapy [16, 17].

1) Timing of Operation and Determination of Platelet Inhibition

There is compelling evidence that delaying cardiac operations for a period of time ranging from 1 to 7 days after administration of clopidogrel reduces bleeding and transfusion risks significantly in patients undergoing cardiac operations requiring cardiopulmonary bypass [119, 191, 194, 195]. By reducing bleeding risk in these patients, transfusion-related complications are decreased and operative morbidity and mortality may be improved. For this reason and others, most professional organizations recommend discontinuation of dual antiplatelet therapy before CABG, if possible [27, 196].

There is significant heterogeneity of platelet inhibition responses to the administration of antiplatelet agents like clopidogrel [43, 197, 198]. The causes of this heterogeneous response to antiplatelet therapy are multiple but are at least partly related to genetic variability in drug metabolism [199]. As a result, it appears that laboratory testing of levels of platelet functional inhibition are more reliable predictors of bleeding and transfusion risk than the more arbitrary use of a specified period of surgical delay [200]. Accordingly, use of point-of-care tests that assess platelet reactivity are likely to add value in the assessment of which patients requiring "urgent" operation while receiving dual antiplatelet therapy can undergo operation with reduced bleeding risk (see Section G).

While an absolute threshold for "safe" levels of platelet inhibition is not clearly defined, it seems likely that a level of platelet inhibition of less than 20% (normal) defines a group of patients at least risk, and platelet inhibition levels greater than 60% to 70% (fully inhibited) define a population at greatest risk for bleeding and transfusion after antiplatelet therapy [200, 201]. Return toward normal in patients with significant platelet inhibition occurs in reasonably predictable manner over a period of hours to days, depending on drug half-life, the biologic turnover and production of new platelets (approximately 10% per day), and the mechanism of action of these drugs (eg, reversible versus irreversible receptor binding) [194, 201, 202]. Two recent observational studies suggest that operation related to the timing of the last clopidogrel dose is associated with significant reductions in bleeding complications on a "per day of delay" basis [194, 202]. Allowing time for platelet inhibition to decrease from the highest to lowest tertiles, in one recent study, decreased bleeding and transfusion by approximately 30% and 20%, respectively [119]. A similar study demonstrated an 11-fold increase in transfusion rate between the first and third tertiles in platelet inhibition, as assessed by thromboelastography [200]. Hence, delay of operation within the variable definition of urgent surgery is an extremely important component of managing these patients.

As described elsewhere, the optimal laboratory testing to determine platelet inhibition is not established, but techniques such as thromboelastography, platelet aggregometry, and other platelet function point-of-care tests have varying levels of utility in measuring platelet inhibition [201, 203]. Although clopidogrel represents the most commonly encountered antiplatelet agent in the perioperative setting, analogous considerations apply to the use of other newer and more potent antiplatelet agents. It is likely that careful adherence to similar preoperative protocols will be critical with such agents. These agents have greater bleeding risk and, in the case of prasugrel, there is an associated fivefold increase in bleeding rates in patients who require urgent operations [17, 204].

Importantly, in contrast to these increasingly potent "next generation" antiplatelet agents, evidence now suggests that no delay in surgery is necessary after the administration of aspirin, except for very low risk elective patients, or for Jehovah's Witness patients. The anti-thrombotic benefits of aspirin administration appear to outweigh its relatively limited associated risk of operative hemorrhage [191, 205–207]. The evidence suggests that aspirin should be continued up to the time of operation, possibly at a reduced dose of 81 mg. A meta-analysis of more than 50,000 patients with moderate-high risk coronary artery disease found a threefold increased risk of major adverse cardiac events within 10 days of aspirin discontinuation [149]. Importantly, it may be that differences in morbidity/mortality outcomes with or without continued aspirin treatment are related to the presence of ACS status and urgency of operation, whereas bleeding complications appear more directly correlated with levels of antiplatelet inhibition [55, 194, 201].

The bleeding risk associated with antiplatelet drugs must always be weighed against the thrombotic risk of major adverse cardiovascular events (death, stroke, MI) associated with "excessive" delays in operation. A meta-analysis of 34 studies including more than 22,000 patients attributed increased thrombotic risks to those presenting with ACS and needing urgent cardiac procedures [55]. The phenomenon of "rebound" high platelet reactivity that is associated with the sudden cessation of antiplatelet agents and "stress" responses to surgery may explain the thrombotic risk with cessation of these drugs [208–210]. Concerns about rebound high platelet reactivity with cessation of antiplatelet drugs must be balanced against increasing evidence that bleeding and blood transfusion associated with PCI is a highly significant adverse prognostic factor for short-term and long-term outcomes [211, 212]. Thus, it is extremely important for the surgeon and anesthesiologist to work closely with cardiology colleagues to manage and adjust antiplatelet regimens for the patient likely to need urgent surgical intervention to optimize surgical risk. "Bridging" strategies with short-acting antiplatelet agents may play an important role in resolving conflicts between antithrombotic and hemostatic priorities [26, 36, 193, 206].

2) Perioperative Blood Conservation Strategies

Once a decision has been made that surgery cannot be delayed because of myocardial ischemia or other risk factors, several strategies may help facilitate avoidance of excessive bleeding and transfusions in the setting of residual antiplatelet effects [191]. Limited data suggest that as many as half of all early cardiac reoperations for patients receiving antiplatelet therapy are ultimately related to surgical bleeding [195]. In certain patients, especially those taking dual antiplatelet medications, diffuse coagulopathic bleeding masks the surgical team's ability to identify and resolve surgical bleeding sites. A key surgical strategy that should be established is the correction of excessive coagulopathic bleeding and establishment of a dry surgical field before surgical closure so that surgical bleeding points are properly identified. Control of surgical bleeding/transfusion in patients taking antiplatelet agents improved over time, likely reflecting increased experience, improved surgical techniques, and revised strategies for addressing these challenges [55, 209].

Very little information exists to suggest the best means of reversing antiplatelet effects intraoperatively. Platelet transfusions are a mainstay of reversing the effects of antiplatelet agents, and can be effective at decreasing bleeding regardless of the mechanism of action of the antiplatelet agent. There are no studies that address the appropriate dose of platelets in this setting. Nevertheless, platelet transfusion data from studies of patients demonstrating residual drug-related platelet inhibition suggest a dose of 12 (and as many as 17) random donor units may be necessary to reverse antiplatelet agent effects [193, 201, 213]. Because a retrospective extrapolation of platelet dosing from the literature may reflect excessive transfusion, platelet administration should be guided by strict algorithmic protocols (as yet not well established in the literature), both to avoid excessive transfusion and to minimize undertransfusion [200, 201]. One such study reported decreased transfusions using such an algorithm, titrated to bleeding rates and assays of coagulation and platelet function [201]. Interestingly, there is very little information regarding the risks of excessive platelet transfusions inducing adverse thrombotic events. Inferences drawn from thrombotic events in the setting of withdrawal of antiplatelet agents suggest that such transfusions may be of some risk [208–210].

For most antiplatelet agents, there is typically little residual drug in the blood stream after 24 hours, as most is tightly and irreversibly bound to the platelet receptors and the half-life of the active metabolite is short. Guideline recommendations for blood conservation offer the best options in patients with dual antiplatelet drug effects who undergo urgent operations [191]. Intraoperative blood salvage, perfusion interventions that minimize decreases in red blood cell volume, topical hemostatic agents, use of antifibrinolytic agents, and algorithm-driven transfusion combined with point-of-care testing offer the best options to reduce bleeding in these high-risk patients [27]. Platelets should almost never be transfused prophylactically, and only once a coagulation defect is identified [206]. Limited evidence exists suggesting that the use of off-pump CABG strategies may limit blood transfusion and bleeding with coronary bypass surgery in platelet-inhibited patients [55–57]. Antifibrinolytics such as tranexamic acid and aprotinin can reduce bleeding and transfusion, potentially by improving platelet function [214, 215], although the clinical availability of aprotinin is currently limited. Off-label use of recombinant activated factor VIIa may be useful for intractable bleeding associated with antiplatelet defects [215, 216], but it is both extremely expensive and potentially prothrombotic [217–219]. Its clinical applicability is uncertain but may be useful in extreme situations.

3) Summary: Dual Antiplatelet Drugs And Cardiac Operation

Delay of operation may be appropriate for patients taking dual antiplatelet therapy and likely represents the most effective strategy for addressing bleeding/transfusion risks. Operation can reasonably be delayed for 5 to 7 days after administration of dual antiplatelet

agents for patients without ACS and with low thrombotic risk. For patients with ACS or with drug-eluting stents less than 1 year old, operation should likely proceed at intervals of less than 5 days to minimize prothrombotic risks of withholding antiplatelet therapy, or with use of a short-acting antiplatelet agent bridge to minimize these risks. Aspirin should likely be continued in both scenarios. Decisions about surgical delay are best guided by clinical factors determining the balance of risk of bleeding versus risk of thrombosis and by laboratory determinations of residual platelet functional inhibition. Validated, absolute levels of such inhibition have not yet been established, but may need to be as low as 20% to 40%. Beyond these measures, assurance of a dry surgical field with appropriate and adequate platelet transfusions is likely the most effective strategy for dealing with bleeding risks in this patient population. In extreme circumstances of excessive bleeding despite appropriate platelet transfusions, use of procoagulant agents such as activated factor VII may be of added benefit.

H. Multidisciplinary Approach to Use of Antiplatelet Drugs

Class IIa Recommendation

a. Efforts at team coordination among multiple providers involved in the management of patients taking antiplatelet drugs who need cardiac procedures are reasonable and likely to result in reduced bleeding with safe operative outcomes. (Level of evidence B)

Previous guideline recommendations related to blood management suggest that health care teams are an important part of delivery of key cardiovascular interventions [27]. In modern medicine, the doctor-patient relationship viewed as a one-on-one interaction is more apparent than real. Teams, not individual persons, care for patients in the ICU, in the operating room, and on the ward. Importantly, lack of team coordination is associated with perceptions of inappropriate or inadequate care [220]. Nowhere is the importance of health care teams more apparent than in the management of antiplatelet drugs around the time of cardiac operations. Sharing of responsibilities for management of antiplatelet drugs among all providers leads to a division of labor that brings other providers into the mix [221]. That is important because key patient events and interventions are often supervised by nonsurgeons (eg, cardiologists, anesthesiologists, ICU care providers, housestaff, nurses, pharmacists, and so forth).

Accumulating evidence suggests that non–surgeon-driven guidelines and protocols are usually more successful than those that rely only on surgeons [222, 223]. For example, literature reports suggest that multidisciplinary teams make better decisions than individual physicians about postoperative bleeding and blood transfusion, resulting in low transfusion rates and safe outcomes [114, 224–227]. Further, reports suggest that, in addition to technical skills of individual physicians, human factors such as teamwork and leadership affect

adherence to algorithms, and hence the outcome of interventions such as cardiopulmonary resuscitation [228]. High-performing teams are more resilient, displaying effective teamwork when interventions become more difficult [229]. Adaptation of coordination activities among providers is related to improved team performance in anesthesia [230]. Team building for management of antiplatelet drugs around the time of cardiac operative intervention is a reasonable approach that is likely to provide patient benefit [231]. Consensus suggests that coordinated team efforts among multiple providers, including cardiologists, anesthesiologists, intensivists, nurses, pharmacists, house staff, and surgeons is likely to provide optimal management of patients requiring antiplatelet drugs and needing cardiac operations.

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