Antiplatelet Drugs: Mechanisms and Risks of Bleeding Following Cardiac Operations

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ABSTRACT

Preoperative antiplatelet drug use is common in patients undergoing coronary artery bypass grafting (CABG). The impact of these drugs on bleeding and blood transfusion varies. We hypothesize that review of available evidence regarding drug-related bleeding risk, underlying mechanisms of platelet dysfunction, and variations in patient response to antiplatelet drugs will aid surgeons as they assess preoperative risk and attempt to limit perioperative bleeding. The purpose of this review is to (1) examine the role that antiplatelet drugs play in excessive postoperative blood transfusion, (2) identify possible mechanisms to explain patient response to antiplatelet drugs, and (3) formulate a strategy to limit excessive blood product usage in these patients. We reviewed available published evidence regarding bleeding risk in patients taking preoperative antiplatelet drugs. In addition, we summarized our previous research into mechanisms of antiplatelet drug-related platelet dysfunction. Aspirin users have a slight but significant increase in blood product usage after CABG (0.5 U of nonautologous blood per treated patient). Platelet adenosine diphosphate (ADP) receptor inhibitors are more potent antiplatelet drugs than aspirin but have a half-life similar to aspirin, around 5 to 10 days. The American Heart Association/American College of Cardiology and the Society of Thoracic Surgeons guidelines recommend discontinuation, if possible, of ADP inhibitors 5 to 7 days before operation because of excessive bleeding risk, whereas aspirin should be continued during the entire perioperative period in most patients. Individual variability in response to aspirin and other antiplatelet drugs is common with both hyper- and hyporesponsiveness seen in 5 to 25% of patients. Use of preoperative antiplatelet drugs is a risk factor for increased perioperative bleeding and blood transfusion. Point-of-care tests can identify patients at high risk for perioperative bleeding and blood transfusion, although these tests have limitations. Available evidence suggests that multiple blood conservation techniques benefit high-risk patients taking antiplatelet drugs before operation. Guidelines for patients who take aspirin and/or thienopyridines before cardiac procedures include some or all of the following: (1) preoperative identification of high-risk patients using point-of-care testing; (2) withdrawal of aspirin or other antiplatelet drugs for a few days and delay of operation in patients at high risk for bleeding if clinical circumstances permit; (3) selective perioperative use of evidence-based blood conservation interventions (e.g., short-course erythropoietin, off-pump procedures, and use of intraoperative

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blood conservation techniques), especially in high-risk patients; and (4) platelet transfusions if clinical bleeding occurs.

KEYWORDS: Aspirin, aspirin resistance, platelet glycoprotein receptors, postoperative bleeding, clopidogrel, thienopyridines, cardiac surgery, cardiopulmonary bypass

DEFINITION OF THE PROBLEM

Homologous blood transfusion during and after cardiac operations is associated with increased postoperative morbidity, including disease transmission,¹⁻⁴ risk of wound infection and immune suppression,^{5,6} increased procedural costs,^{7,8} and possibly increased operative mortality.⁹⁻¹¹ Coronary artery bypass grafting (CABG) and other cardiac procedures are among the most commonly performed operations and account for ~10% of all red blood cell (RBC) units transfused.¹² Competing forces have conspired to keep the usage of blood products at a constant or slightly increased level. Specifically, the patient population undergoing cardiac procedures is older and higher risk and frequently requires longer operation and concomitant increased use of blood products. At the same time, efforts have been undertaken to reduce patient exposure to homologous blood by using aggressive blood conservation strategies.¹³⁻²² The result of these factors is a spectrum of blood product transfusion similar to that shown in Fig. 1. The distribution pattern in Fig. 1 describes blood transfusion in 4445 patients undergoing cardiac procedures and is a surprisingly consistent reflection of transfusion incidence for CABG in particular, and for cardiac procedures in general. There are at least three remarkable features shown in Fig. 1. First, over 50% of patients undergoing cardiac procedures receive no autologous blood transfusion. Second, patients who receive more than 10 donor units of blood products are in the 90th percentile of the patient transfusion profile. Third, 10 to 20% of patients account for ~80% of the total blood product transfusions required in this population. The interaction of this

spectrum of blood transfusion with antiplatelet drug therapy is the subject of this review.

Analysis of the factors that are associated with excessive blood product usage in cardiac surgical patients suggests that patient factors, transfusion practices (process-related variables), procedure-related factors, and perioperative drug usage contribute to the disproportionate amount of blood products used in certain patients.

RISK FACTORS FOR POSTOPERATIVE BLEEDING

More than 30 published reports address the subject of multivariate predictors of postoperative bleeding and blood transfusion after cardiac operations and more than 120 reports document anecdotal or observational reports of acquired, congenital, or process variables associated with increased bleeding. Table 1 is a summary of these publications with the variables separated by patient-related, procedure-related, and process-related factors. The studies are far too heterogeneous to lend themselves to meta-analyses, and the level of evidence in most cases is low. Within each of the three major categories (patient-related, procedure-related, or process-related) listed in Table 1, the variables are arranged in descending order of importance. Certain of the variables stand out as high-risk predictors including advanced age, preoperative anemia or small body size, the type and duration of operative intervention, and the presence of antiplatelet or antithrombotic drugs taken shortly before operation. Any of these common risk factors should alert the clinician to bleeding risk and should trigger blood conservation measures aimed at addressing the specific risks.

Many studies suggest that platelet abnormalities are a source of hemostatic dysfunction associated with cardiopulmonary bypass (CPB). It is surprising that a consistent abnormality has not been found in the majority of these studies.²³⁻²⁶ In fact, contradictory results are reported in some cases.^{27,28} Abnormalities such as in vitro platelet aggregation defects,^{27,29} deficiencies in α -granule release,³⁰ and defects in thrombin-related platelet activation³¹ are associated with increased bleeding after operation, but at least one well-done study did not identify any intrinsic platelet abnormality resulting from CPB.³² Even though an intrinsic platelet function defect associated with CPB is difficult to identify, it is likely

Figure 1 Frequency distribution of blood product transfusion in 4445 patients undergoing open heart procedures between 1992 and 1995.

Table 1 Variables Associated with Increased Bleeding or Blood Transfusion during Cardiac Operations**Risk Factors****Preoperative risks**

Advanced age or age > 70 y
 Preoperative anemia
 Female gender
 Body size
 Antiplatelet therapy
 Insulin-dependent AODM
 Cardiogenic shock or poor left ventricular function
 Renal insufficiency
 Preoperative ICU stay more than 48 h
 Preoperative sepsis
 Hypoalbuminemia
 Use of polymerized starch for volume expansion
 Preoperative alcohol consumption
 Preoperative low-molecular-weight heparin
 Hereditary coagulopathy (Hermansky-Pudlak, Bernard-Soulier, Scott, Werlhof, Glanzmann's)
 Preoperative acquired coagulopathy (lupus anticoagulant, drug-related, polycythemia vera, myelodysplastic syndrome, ITP, β thalassemia)

Procedure-related risks

CPB time prolonged
 Reoperations
 Type of operation (other [aortic, complex, etc.] > valve/CABG > valve > CABG)
 Need for transfusion while on CPB
 Reduced heparin dose

Risks related to processes of care

Lack of multidisciplinary team managing blood conservation and transfusion
 No transfusion algorithm
 Limited use of point-of-care testing to manage bleeding and need for blood transfusion
 Use of IMA (either one or two)
 Low body temperature in ICU

AODM, adult-onset diabetes mellitus; ICU, intensive care unit; ITP, idiopathic thrombocytopenic purpura; CPB, cardiopulmonary bypass; CABG, coronary artery bypass grafting; IMA, internal mammary artery.

that multiple interactions of platelets with blood cell elements, with fibrinolysis products, with heparin, with synthetic surfaces, and with drugs administered before and during operation are responsible for the CPB-induced platelet-related hemostatic abnormality.

Excessive Postoperative Bleeding

For the purposes of this review, and based on results similar to those shown in Fig. 1, we consider patients who receive more than 10 donor units of nonautologous donor blood products as having been exposed to excessive blood transfusion after cardiac operation (i.e., patients who are above the 90th percentile for

postoperative blood transfusion). This means that ~10% of patients undergoing cardiac procedures will fall into a high-risk category, and this high-risk subset consumes greater than 70 to 80% of all the blood products transfused during cardiac procedures.

Multivariate Predictors of Excessive Blood Transfusion

From the large cohort of cardiac surgical patients represented in Fig. 1, it is possible to identify multivariate predictors of excessive blood transfusion. Logistic regression analysis was used to identify independent predictors of receiving 10 or more units of blood after operation, and these results are summarized in Table 2. The initial analysis was performed with preoperative variables only, and results are listed in Table 2. Regression models similar to this allow identification of high-risk patients who are most likely to benefit from aggressive blood conservation measures. Furthermore, using the risk model summarized in Table 2, it is possible to develop an institutional risk score based on the multivariate predictors of excessive transfusion for an individual practice. This risk score can be used as a quality improvement tool to improve transfusion practices and limit postoperative blood transfusion at a given institution.

The most important preoperative descriptors of excessive blood transfusion in this model are age and the RBC volume. This agrees with the findings of others shown in Table 1 for blood transfusion in general. The RBC volume is computed from the preoperative hematocrit multiplied by the blood volume. The blood volume is estimated from nomograms that account for age and body surface area and are a usual part of the preanesthetic screening routine. This composite variable accounts for two of the most important patient factors that reflect the preoperative patient reserves to withstand a hemorrhagic

Table 2 Multivariate Predictors of Excessive Blood Transfusion (Transfusion of 10 or More Donor Units) in 4445 Patients Undergoing Cardiac Procedures Using CPB

Variable	Improvement (χ^2)	p Value
Age/RBC volume	27.911	< 0.001
Preoperative platelet count	20.260	< 0.001
Type of operation	11.131	0.011
Preoperative CHF	10.691	0.001
Endocarditis	5.980	0.02
Reoperation	2.721	0.099
MI within 6 h	3.165	0.075
Preoperative IABP	2.330	0.127
IV NTG	3.921	0.048

CPB, cardiopulmonary bypass; RBC, red blood cell; CHF, congestive heart failure; MI, myocardial infarction; IABP, intra-aortic balloon pump; IV NTG, intravenous nitroglycerin.

Figure 2 The variation of age/red blood cell (RBC) volume with postoperative blood transfusion over the patient cohort of 4445 patients undergoing cardiac operations between 1992 and 1996.

insult: (1) small body size associated with a low blood volume, and (2) diminished RBC volume from preoperative blood loss or chronic anemia. The relationship of the two most important predictors of excessive blood transfusion (age and RBC volume) to postoperative blood transfusion over the entire patient cohort is shown in Fig. 2. For purposes of Fig. 2, age and RBC volume were combined into a single variable, age divided by RBC volume. As expected, transfusion of the greatest number of nonautologous donor units occurred in patients with low RBC volume and advanced age.

Another important variable that is associated with excessive postoperative blood transfusion is the type of cardiac procedure being performed. In general, the procedure associated with the least postoperative blood transfusion is first-time CABG. Cardiac reoperations are almost always associated with increased transfusion compared with first-time procedures. The procedures associated with the most postoperative blood transfusion are those that are not CABG or single valve operations. Procedures such as aortic aneurysm surgery, operations for aortic dissection, and multiple valve operations fall into this category. Figure 3 depicts the variation in postoperative blood transfusion with the type of operation performed. Again, Fig. 3 confirms the finding of few patients accounting for most of the postoperative blood transfusion and agrees with the consensus findings shown in Table 1 for blood transfusion in general (not only for *excessive* blood transfusion).

Does Aspirin Increase Postoperative Bleeding?

Drugs that interfere with platelet aggregation or adhesion alter postoperative hemostasis adversely and contribute to excessive blood transfusion. ASA use before cardiac procedures is common. There is abundant evi-

Figure 3 Variation of mean level of postoperative blood transfusion with type of cardiac procedure in 4445 patients undergoing various types of operations using cardiopulmonary bypass. CABG, coronary artery bypass grafting.

dence available about the effects of preoperative ASA on postoperative bleeding and blood transfusion. The Society of Thoracic Surgeons (STS) Evidence Based Workforce found 21 studies that reviewed the effect of preoperative ASA on postoperative bleeding.³³ Of the 21 studies identified, there were six randomized controlled trials (RCTs) that were viewed as level A evidence (Table 3). All RCTs except one found that preoperative ASA 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 evidence have less clear-cut association of preoperative ASA with increased blood loss after cardiac procedures. Because of the consistent finding of ASA-associated increased blood loss in the highest-quality studies, the STS Workforce suggests that patients who receive ASA before operation are at increased risk for above normal postoperative bleeding and blood transfusion after operation.

It is possible to estimate the amount of increased bleeding associated with preoperative ASA usage. In the randomized trials of CABG patients, preoperative ASA results in between 200 and 400 mL of increased chest tube drainage and between 0.5 and 1 U of increased packed RBC transfusion compared with controls.^{34–37} At least one study suggests that smaller doses of preoperative ASA (81 mg) have a beneficial effect on graft patency with less risk of postoperative bleeding.³⁸ Likewise, there is evidence that lower doses of ASA are associated with a greater reduction in nonoperative cardiovascular events than are higher doses (19% reduction with daily dose of 500 to 1500 mg compared with 32% reduction in patients taking 75 to 150 mg daily).³⁹ This suggests that lower doses of preoperative ASA provide equal or better protection for prevention of cardiovascular events while minimizing postoperative bleeding.

Table 3 Does Preoperative Aspirin Cause Increase Postoperative Bleeding?³³

Study	Study Type	Number of Patients	Quality of Evidence	Increased Postoperative Bleeding?
Goldman (1991)	RCT	351	A	Yes (chest tube, transfusions, and reexploration rate)
Sethi (1990)	RCT	772 (471 ASA, 301 control)	A	Yes (chest tube, transfusions, and reexploration rate)
Goldman (1988)	RCT	555	A	Yes (chest tube and reexploration rate)
Kallis (1994)	RCT	100	A	Yes (chest tube, transfusion, and reexploration)
Ferraris (1988)	RCT	34 (16 ASA, 18 control, not blinded)	B	Yes (chest tube, transfusion, and reexploration)
Taggart (1990)	Observational, cohort study	202 (101 ASA, 101 control)	B	Yes (chest tube and transfusion)
Michelson (1978)	Observational, case control	25 (9 ASA, 16 control)	B	Yes (chest tube drainage only)
Torosian (1978)	Descriptive, longitudinal	100 consecutive (13 ASA, 6 Coumadin, 81 control)	B	Yes (chest tube drainage only)
Bashein (1991)	Observational, case control	270 (90 ASA, 180 control)	B	Yes (transfusion and ICU stay)
Reich (1994)	Observational, case control	197 (87 ASA, 110 control)	B	Yes (chest tube drainage only, not transfusion or reexploration)
Ferraris (2002)	Observational, case control	2606 (1641 ASA, 965 control)	B	Yes (chest tube drainage, transfusion, and reexploration—bleeding worse in high risk)
Karwande (1987)	RCT	36 (26 ASA, 10 control)	A	No
Srinivasan (2003)	Observational, case control (OPCAB only)	340 (170 ASA, 170 control)	B	No
Tuman (1996)	Descriptive, longitudinal	317 reoperations (102 ASA, 215 control)	B	No
Vuylsteke (1997)	Descriptive, longitudinal	240 consecutive (96 excluded because of abnormal coagulation screen)	B	No
Dacey (2000)	Observational, case control	1056 (368 ASA, 688 control)	B	No
Ray (2003)	Observational, case control	659 (151 ASA, 508 nonaspirin)	B	No (clopidogrel plus aspirin caused increased bleeding compared with control and to aspirin alone)
Schonberger (1993)	Observational, case control	50 (25 ASA, 25 control)	B	No (nonsignificant trend to increased bleeding with ASA)
Ferraris (1989)	Descriptive, longitudinal	159 (15 ASA, 144 control)	B	No (bleeding time and blood volume predicted transfusion)
Rawitscher (1991)	Descriptive, longitudinal	100 consecutive (with normal bleeding time only)	B	No
Bjessmo (2000)	Descriptive, longitudinal	200 (100 ASA, 100 control)	B	No

RCT, randomized controlled trial; ASA, aspirin; OPAB, off-pump bypass; ICU, intensive care unit.

Do Thienopyridines Cause Increased Bleeding?

Agents that block the platelet adenosine diphosphate (ADP) receptor provide important benefit to patients having coronary stent implantation, especially in patients with prior CABG.^{40–42} When clopidogrel is added to ASA for the treatment of ACS, there is significant incremental benefit^{43–45} but also increased bleeding risk.^{46,47} Additionally, ADP receptor blocking agents should be used in patients with coronary artery disease who require ASA but cannot take it because of sensitivity or gastrointestinal bleeding.⁴⁸ These factors and others result in many patients presenting for CABG taking clopidogrel, the most commonly used ADP receptor blocker. Multiple observational studies and post hoc analyses of randomized trials document the increased bleeding associated with the preoperative use of clopidogrel but no large randomized clinical trial has been performed.⁴⁹ Significant increased bleeding and blood transfusion occur in patients who receive thienopyridines within 5 days of operation either in the presence or absence of ASA.^{46,49} Because of the risk of excessive postoperative bleeding, ADP receptor blockers should be stopped 5 to 7 days before CABG. This is a recommendation of the American Heart Association/American College of Cardiology (AHA/ACC) and of the STS.^{33,48} Compared with ASA, there is an even stronger consensus that thienopyridines cause increased bleeding after cardiac operations.

Do Glycoprotein IIb/IIIa Inhibitors Cause Increased Postoperative Bleeding?

Clinically available short-acting and long-acting inhibitors of the platelet glycoprotein IIb/IIIa (GP IIb/IIIa) receptor for fibrinogen cause profound platelet dysfunction. There are three GP IIb/IIIa receptor antagonists currently available for clinical use in the United States—two short-acting (eptifibatide and tirofiban) and one long-acting (abciximab). The current AHA/ACC guidelines for unstable angina recommend these agents for patients having early catheterization and planned percutaneous intervention (class I recommendation) and for patients with ongoing ischemia or other high-risk features (class IIa recommendation).⁴⁸ Not surprisingly, some patients on GP IIb/IIIa receptor antagonists will require emergency surgical revascularization, and they are at increased risk for excessive postoperative bleeding, particularly with abciximab but less so with the shorter acting agents.^{50–54} Operation can be performed shortly after cessation of the short-acting agents,^{52,55} but within 12 to 24 hours for abciximab.⁵⁶ The STS guidelines suggest that these agents should be discontinued before CABG, because of the bleeding risk, although the evidence for this recommendation is not strong (class IIb recommendation).³³ The recommended time from stopping GP IIb/IIIa inhibitors until operation varies

depending on the agent used but ranges from 2 to 6 hours for the short-acting agents⁵⁵ to 12 to 24 hours for abciximab.⁵⁶ No level A or B evidence supports exact timing of discontinuation of these agents; hence, only rough estimates are available. Some authors suggest, based on observational data, that short-acting GP IIb/IIIa receptor antagonists can be continued up until operation,^{57,58} but given the conflicting conclusions in the literature, safe practices suggest that stopping short-acting agents before operation is preferred to minimize blood loss and blood transfusion, especially because no proven perioperative benefit occurs with coverage of short-acting or long-acting GP IIb/IIIa inhibitors during operation. Because of the increased blood loss associated with administration of long-acting GP IIb/IIIa agents (e.g., abciximab) within 12 to 24 hours of operation, they should be stopped before operation, if possible.^{53–55} Experience with short-acting agents is mixed, but most studies suggest stopping within 2 to 6 hours of operation.^{50–52,57,58} Overall, the evidence that short-acting GP IIb/IIIa receptor blockers cause increased bleeding after cardiac procedures is much less convincing and less robust than that for thienopyridines, or even for ASA. Consensus favors the notion that these drugs are associated with increased bleeding after operation because of their potent effects on the final common pathway of platelet aggregation.

PATIENT SENSITIVITY TO ANTIPLATELET DRUGS—DRUG “RESISTANCE” VERSUS “HYPERRESPONSIVENESS”

Most, but not all, studies show that preoperative ASA usage results in increased post-CPB bleeding (Table 3). These results notwithstanding, a consensus exists that preoperative ASA usage predisposes to increased blood loss after operation, but any ASA-associated increased bleeding risk is not apparent in most patients. One of the important goals of this review is to suggest possible reasons for differing patient sensitivities to ASA and other antiplatelet drugs. Patient-specific differences in ASA and other antiplatelet drug sensitivity may account for differences observed in postoperative bleeding after CPB in patients taking antiplatelet drugs before operation. An understanding of these patient-specific differences may help define a high-risk subset of ASA users, or antiplatelet drug users for that matter, who can benefit from more intensive blood conservation interventions.^{59,60}

ASA Hyperresponders

One important clinical manifestation of ASA ingestion is prolongation of the skin bleeding time. ASA therapy results in prolongation of the bleeding time but not always into the abnormal range. Fig. 4 shows the

Figure 4 Effect of oral aspirin (ASA) ingestion (365 mg) on template bleeding time in seven normal volunteers.

variation in template bleeding time in seven volunteers who took a single ASA tablet (365 mg). The mean bleeding time before ASA ingestion was 4.6 (95% confidence interval 2.5 to 6.0) and the mean bleeding time 24 hours after ASA was 6.9 (4.5 to 14). Only one of seven had prolongation of the bleeding time above 8 minutes (the upper limit of normal in our laboratory). This elevation of the bleeding time lasted for a few days until return to normal levels.

We observed a similar distribution of bleeding times in patients undergoing CABG. As part of a study of the effects of ASA on post-CABG bleeding, 40 patients were entered into a prospective randomized study.³⁷ Patients randomized to ASA therapy had template bleeding times measured before and 6 hours after ASA ingestion. Six of 40 patients were excluded from the study because their post-ASA bleeding time was prolonged beyond 10 minutes. In randomized patients with prolonged post-ASA bleeding times, operation was delayed and bleeding times were repeated daily. Over 2 to 3 days, bleeding times returned to normal in most cases, and patients with accentuated response to ASA were able to undergo an uneventful operation. There were no other hematologic abnormalities noted in any of the patients with the accentuated bleeding time response to ASA. Similar post-ASA bleeding time results were reported by Fiore and coworkers in 37 normal volunteers.⁶¹ In their study, 5 of 37 patients had excessively prolonged bleeding times after a single 325-mg oral dose of ASA. These observations suggest that there is a subgroup of ASA users who are hyperresponders. In hyperresponders, bleeding time prolongation well above normal values in response to ASA is the usual situation. At present, the skin bleeding time is the only way to identify ASA hyperresponders. Although it does not make sense to screen all patients having cardiac procedures with a skin bleeding time, it seems reasonable to perform this simple inexpensive test in high-risk patients defined by the important risk factors in Table 1 (e.g.,

advanced age, preoperative anemia, non-CABG operation, reoperative procedures, small body size with low RBC volume, and preoperative antiplatelet drug therapy) to identify ASA hyperresponders.

Is there a high-risk group of antiplatelet drug users who are at increased risk of postoperative *excessive* blood transfusion? The intuitive answer seems to be yes, but surprisingly little evidence exists to support this hypothesis. Some indirect evidence is available to answer this question. In 1989, we reported the results of a retrospective multivariate study evaluating the causes of excessive postoperative bleeding in 169 patients undergoing CABG.⁶² Preoperative ASA usage was not an independent risk factor for excessive bleeding but prolongation of the bleeding time was. This suggests that the subgroup of ASA users who have prolonged bleeding time are at increased risk for excessive blood loss and blood transfusion after operation. In another observational study of 2606 patients undergoing CABG, we found that preoperative ASA was an independent predictor of postoperative blood transfusion. Stratification of these results according to the propensity of patients to receive ASA before operation showed that ASA is an independent multivariate predictor of postoperative blood transfusion only in high-risk patients. Patients were divided into five equal quintiles based on their propensity scores (logistic probability of receiving ASA before surgery). Within each quintile, postoperative blood product transfusion in ASA users was compared with that in nonusers. The risk of receiving a postoperative blood transfusion was greatest for ASA users in the highest-risk quintile. This indicates that the patients least likely to receive ASA before operation (i.e., a high-risk group) were most likely to receive a blood transfusion after surgery if, for some reason, they did receive ASA before operation. Propensity score matching ensured that selected high-risk covariates known to be associated with increased postoperative bleeding (advanced age, female gender, small body size, renal insufficiency, redo procedure, and chronic lung disease) were similar for both ASA users and nonusers across all quintiles. Taken together, these results provide indirect evidence that high-risk subsets of ASA users (e.g., ASA hyperresponders or patients with multiple risk factors) are particularly prone to excessive blood transfusion after cardiac operations using CPB.

ASA Resistance

Recently, attention focused on "ASA resistance" that results in failure of ASA therapy to protect against cardiovascular events in certain individuals.⁶³⁻⁶⁶ As many as 20 to 30% of patients who take a low dose of ASA for cardioprotective effect (81 mg) may have subtherapeutic levels as measured by inhibition of the thromboxane cyclooxygenase (COX) pathway. More

importantly, these nontherapeutic patients have worse cardiovascular outcomes than those with effective doses of ASA.^{65,67,68} Interestingly, CABG is a potent stimulus for development of ASA resistance. Zimmerman and coworkers found that most patients are normal responders to ASA before CABG but after operation most patients become ASA insensitive.^{69,70} It seems logical that ASA resistance after CABG may predispose to graft occlusion and worse long-term outcomes, but this remains unproven.

Just as with any drug, there are differences in response to administration of antiplatelet drugs. Hyperresponders and resistant patients are just the ends of the spectrum of normal responses to antiplatelet drugs. The impact of operative intervention is likely to unmask these drug response variations. Understanding of these drug response variations is essential to unravel the effects of antiplatelet drugs on postoperative bleeding.

MECHANISMS OF ANTIPLATELET DRUG-INDUCED BLEEDING

Molecular Mechanisms of ASA-Related Postoperative Bleeding

Molecular mechanisms responsible for ASA-related postoperative blood transfusion may involve the well-known effects of ASA on the COX enzyme system. At least three COX isoforms have been characterized and two COX genes have been cloned. These isoforms have differing responses to ASA, with *COX-1* being the most sensitive (perhaps 50 to 100 times more than *COX-2*) to ASA.⁷¹ We hypothesized that ASA hyperresponders have COX gene polymorphisms or other heterogeneities that result in sensitivity to ASA because of imbalances of *COX-1* and *COX-2* expression either in platelets, monocytes, endothelium, or other sensitive cells.⁷² The exact functional significance of COX gene variations is uncertain, but active investigations are ongoing.

With the explosion of molecular genetics and pharmacogenomics, gene polymorphisms are being identified in most of the important platelet receptors. Gene polymorphisms are present in the platelet surface GP IIb/IIIa gene and reported population differences of this gene expression may account for increased thrombogenicity in certain patients.^{73,74} Additionally, a gene polymorphism exists for the platelet ADP receptor (P2Y₁₂), targeted by the antiplatelet thienopyridines (ticlopidine and clopidogrel).⁶³ Significance of this ADP receptor gene heterogeneity may explain clopidogrel resistance seen in some patients. Gene polymorphisms exist for the P-selectin gene,⁷⁵ for the platelet PAR-1 receptor gene,⁷⁶ and for the platelet GP Ia gene,⁷⁷ but the clinical significance of these genetic variations remains uncertain.^{78,79}

Pharmacogenomics of Antiplatelet Drugs

With the rapid expansion of tools to assess molecular genetic variation in response to drugs, new information about individual responses to drugs is available (pharmacogenomics). Gene microarray chips are available that contain the bulk of expressed human genes (c-DNA) on a single chip. It is possible to extract m-RNA from human peripheral blood leukocytes from an individual before and after antiplatelet drug therapy. Comparison of gene microarrays before and after a given drug gives an accurate picture of the individual genetic response to drug therapy. We used this approach to study the changes in gene microarrays in a few normal responders to ASA and in hyperresponders.⁸⁰ The results were astonishing. In normal responders, ASA caused significant gene differences in more than 100 genes (upregulation, downregulation, disappearance, or appearance of a gene). In hyperresponders, there were also more than 100 gene differences induced by ASA. ASA caused the same gene changes in both hyperresponders and normal responders in only 5 of more than 200 gene differences. Significant gene differences ($p < 0.05$) were entered into the DAVID Program (Database for Annotation, Visualization and Integrated Discovery) supplied by the National Institutes of Health for classification of genes into known metabolic pathways. This analysis showed that ASA alters gene expression in multiple metabolic pathways, especially pathways involving gene transcription and signal transduction (Table 4). Interestingly, ASA hyperresponders did not exhibit any changes in the complement or coagulation cascades in response to ASA, but normal responders did (Table 4). Most of the gene differences induced by ASA in both normal responders and hyperresponders involved genes that were as yet unclassified in any metabolic pathway. With this unexpected and astounding amount of ASA-related gene changes, there is too much information to process in a short period of time and too few patients to make meaningful conclusions. It will take months to years to confirm and unravel this information but suffice it to say that ASA does more than simply inhibit COX isoforms.

It is likely that genetic variations in key genes along the pro- and antithrombotic pathways, either at the transcriptional or messenger RNA levels, account for some of the antiplatelet drug hyperresponders or for antiplatelet drug resistance. Some limited information supports this notion. For example, ASA alters the gene transcription factor nuclear factor kappa B and limits the production of COX-2 gene transcripts.⁸¹ Additionally, ASA inhibits the COX-2 gene transcription promoter protein, DNA binding proteins (C/EBP-beta), and limits COX-2 production in response to inflammatory stimuli.⁸² Furthermore, screening of candidate gene polymorphisms suggests that a single substitution in the ADP receptor gene *P2Y1* is associated with ASA

Table 4 Aspirin-Induced Changes in Metabolic Pathways for Normal Responders and for Hyperresponders

Pathways	Number of Genes Changed	
	Normal Responders (n = 3)	Hyper-Responders (n = 2)
Complement and coagulation cascades	4	0
Basal transcription factors	4	0
Phosphatidylinositol signaling system	8	2
Fatty acid metabolism	5	4
Glycerolipid metabolism	5	2
Oxidative phosphorylation	5	12
Apoptosis	4	4
Cell cycle	4	3
Purine metabolism	4	1
Glycolysis/gluconeogenesis	3	4
Inositol phosphate metabolism	3	1
Integrin-mediated cell adhesion	3	4
MAPK signaling pathway	3	6
Pyruvate metabolism	2	4
Butanoate metabolism	2	6
Proteasome	1	6
Lysine degradation	1	5
ATP synthesis	2	5
Ribosome	0	3
Benzoate degradation via CoA ligation	0	3
Fatty acid biosynthesis (path 2)	0	3
Unclassified	> 100	> 100

MAPK, mitogen-activated protein kinase; ATP, adenosine triphosphate.

resistance.⁶⁴ With more careful investigation, it is apparent that more and more gene variations will turn up and that inevitably some of these polymorphisms will prove to be responsible for hyperresponse or resistance to antiplatelet drugs.

Bioavailability and Other Individual Variations in Response to Antiplatelet Drugs

There are other mechanisms that might explain differing responses to antiplatelet drugs. For example, ASA pharmacokinetics may explain some of the individual differences in response to this drug. Buchanan and Brister showed that a single dose of ASA did not uniformly inhibit patient platelet function tests.⁸³ Thirty to 40% of patients who ingest a single dose of ASA will not have complete inhibition of COX-related platelet functions. These authors suggest that bioavailability of orally ingested ASA is variable and may

account for interindividual differences in platelet response. Similarly, Beving and coworkers found that doses of 1500 mg or more are required to provide consistent and reproducible inhibition of platelet COX function in all patients.⁸⁴ Again, these interindividual variations were attributed to differences in ASA bioavailability.

Several authors proposed other causes of incomplete or accentuated responses to antiplatelet drugs besides gene polymorphisms.^{78,85} For example, isoprostane formation is a possible cause of individual variation in ASA response. These substances are formed from oxidative degradation of arachidonic acid and are capable of activating thromboxane receptors and causing a procoagulant effect despite effective ASA dosage.⁸⁶ Similarly, cysteinyl leukotrienes are potent vasoconstrictors that are generated during CABG or in patients with unstable angina.⁸⁵ Because leukotrienes may be preferentially generated in patients taking ASA, it is possible that these vasoactive agents have differential expression to account for hyper- or hyporeponsiveness to antiplatelet drugs.

Many drugs, including clopidogrel, are metabolized via the mitochondrial cytochrome P450 enzyme systems in the liver. Clopidogrel is primarily metabolized by the CYP 3A4 subsystem. In one study, increased CYP 3A4 metabolic activity was inversely related to response to clopidogrel.⁸⁷ Drugs that are capable of limiting the activity of CYP 3A4 (e.g., rifampin) can increase effective drug levels of clopidogrel.⁸⁷ Differential drug metabolism may explain some of the variable responses seen with antiplatelet drugs. Whether it is variable drug absorption, altered drug metabolism, alternate prothrombotic pathways, or gene polymorphisms, there are multiple possible explanations for variable responses to antiplatelet drugs.

BLOOD CONSERVATION STRATEGY—THE MULTIMODALITY APPROACH

Many blood conservation interventions are employed in cardiac operations. These interventions include three broad categories: (1) preoperative interventions, (2) periprocedural interventions, and (3) process of care interventions. Table 5 is a list of the commonly used blood conservation interventions that are likely to be helpful in patients treated with antiplatelet drugs who need cardiac procedures.

Additionally, several studies suggest that a combination of blood conservation interventions is likely to provide the best reduction in blood transfusion.^{19,22,88–92} It seems likely that the sum of the combinations of blood conservation interventions is more beneficial than each of the individual components. Any viable strategy for limiting excessive blood transfusion after cardiac procedures should identify the institution-specific blood

Table 5 Best Practices to Prevent Perioperative Bleeding in Patients Treated with Antiplatelet Drugs (Adapted from STS Blood Conservation Guidelines⁴⁶)

Recommendation	Level of Evidence	Class
Preoperative interventions		
Preoperative autologous donation augmented with erythropoietin is indicated in selected patients when possible	B	IIa
Treat preoperative anemia, or high-risk patients, with erythropoietin if drug can be administer a few days before operation	B and C	IIa/IIb
Avoid preoperative antiplatelet and antithrombotic drugs when possible	B and C	IIb
Limit preoperative blood drawing and use alternatives to blood sampling (e.g., oximetry)	B and C	IIa
Perioperative interventions		
Off-pump coronary artery bypass is indicated to limit blood transfusion provided emergent conversion to on-pump is unlikely	A	IIa
Transfuse patients with Hgb ≤ 7 g/dL (or with ≤ 8 g/dL in high risk) on CPB	B and C	IIa
Transfuse fully warmed postoperative patients with Hct $\leq 22\%$	C	IIa
Lysine analogues are indicated to limit blood transfusion after operation but not to decrease the risk of return to the operating room	B	IIb/III
Transfuse non-red blood cell products based on clinical indications, not transfusion triggers	C	IIa
Open venous reservoir membrane oxygenator systems are preferred during CPB	C	IIb
Use centrifugal system for blood pump because of perfusion safety features	B	IIb
Routine use of cell saver is indicated for pump salvage and harvest of mediastinal blood	A	I
Retrograde autologous priming of the CPB circuit is indicated	B	IIb
Process of care interventions		
Transfusion algorithms with point-of-care testing are indicated for blood conservation	B	IIa
Implement multimodality institutional blood conservation program	B	IIa
Identify high-risk patient (elderly, non-CABG, redo, small body size, renal failure, female, anticipated prolonged operation) and optimize blood conservation strategy in this subgroup	B and C	IIa

STS, Society of Thoracic Surgeons; Hgb, hemoglobin; CPB, cardiopulmonary bypass; Hct, hematocrit; CABG, coronary artery bypass grafting.

conservation interventions that are helpful and employ these interventions in combination, especially for the high-risk subset of patients.

Multiple blood conservation interventions are used routinely in cardiac operations requiring CPB. Table 5 is a summary of some of these interventions with consensus recommendations based on available evidence. A few points are worth mentioning about the various interventions.

Triggers for Transfusion of Blood Products and Point-of-Care Testing

It is hard to pin down the benefits of blood transfusion, as conventional randomized trials to support the use of blood products to treat disease do not exist. Many traumatic injuries (especially war-related injuries) were almost universally fatal before the advent of blood transfusion. The simple practice of blood transfusion saved countless lives long before the complications of this therapy were recognized.

Enhanced oxygen-carrying capacity,⁹³ improved hemostasis associated with blood component therapy,^{94,95} and volume support of cardiac output are three

accepted benefits of blood transfusion. There is a lack of clear evidence regarding the benefit of blood transfusion. However, clinical reports^{96–98} of survival benefit support transfusion in certain clinical situations. A task force of the American Society of Anesthesiology developed a consensus statement based mostly on level B and C evidence that concluded that “red blood cell transfusions should not be dictated by a single hemoglobin ‘transfusion trigger’ but instead should be based on the patient’s risk of developing complications of inadequate oxygenation.”⁹⁹ They developed guidelines for transfusion of packed red cells in adults that were accepted by others without much argument and without much high-level evidence to support them.¹⁰⁰ Certain consensus indications for blood transfusion such as transfusion for hemoglobin levels below 7 g/dL make intuitive sense but have little support in the literature.

During cardiac operations, CPB provides oxygenation and systemic perfusion in a nonphysiological manner. Utilizing systemic heparinization, hemodilution, and nonpulsatile blood flow in addition to hypothermia creates several physiological consequences that affect systemic physiology and blood-formed elements.¹⁰¹ The physiological threshold at which oxygen

consumption starts to decrease because of insufficient oxygen delivery in humans has been defined as a hemoglobin of 4 g/dL, an oxygen extraction ratio of 0.44, a mixed venous oxygen of 34 mm Hg, and a mixed venous oxygen saturation of 56%.¹⁰² In the context of coronary artery disease, however, moderate hemodilution during clinical CPB is well tolerated in cardiac patients.¹⁰³ However, the coronary artery blood flow reserve and oxygen extraction may be exceeded by extreme hemodilution to 6 g/dL.¹⁰⁴ Weisel and associates found that patients at risk for perioperative ischemia showed a delay in myocardial metabolic recovery, with substantial hemodilution when postoperative hematocrit levels were reduced to 21 to 24%.¹⁰² Increases in cardiac output are the primary compensatory mechanism to overcome reduced oxygen-carrying capacity; however, microvascular disease may limit enhancements in tissue oxygenation. There are few data in cardiac surgery patients to address critical end-organ oxygen delivery and utilization in the diseased state, although there are studies that report that tissue oxygenation is maintained in healthy, normovolemic individuals with a hemoglobin of 7 g/dL and hematocrits of 15 to 20%.^{105,106} These observational studies provide general parameters that have historically guided practice. Practice guidelines suggest that patients with severe anemia on CPB (hemoglobin $\leq$ 7.0 g/dL or $\leq$ 8 g/dL in elderly patients) or acute blood loss ($\geq$ 30% of blood volume) should receive blood transfusions to support cardiac output and sustain oxygen-carrying capacity with the expectation that operative mortality will be improved. This is as close to a "transfusion trigger" as evidence supports. The situation is even more confusing when transfusion of non-red cell blood components is considered, with most guidelines recommending transfusion for clinical indications after CPB rather than for specific transfusion triggers.^{107,108} Because of these rather nebulous guidelines, there is an understandable variation in transfusion practices.

Guidelines for the management of bleeding during cardiac procedures are available but are relatively unsuccessful in limiting nonautologous blood transfusion.^{16,17,109} There is still marked variability in transfusion practices and blood conservation interventions. There are at least two reasons for this failure of guidelines. First, accurate and timely information about the platelet and coagulation status of patients in the operating room or in the intensive care unit is difficult to obtain. Second, patient, physician, and institutional variability in decisions about transfusion (i.e., transfusion trigger) are difficult to control and manage. These shortcomings caused several investigators to evaluate transfusion algorithms in a prospective manner using institution-derived transfusion guidelines in conjunction with accurate point-of-care testing to guide responses to bleeding and to direct blood transfusion. In most, but not all, studies, the combination of point-of-care testing

and transfusion algorithms used to direct valuable blood resources was both cost-effective and efficacious in limiting nonautologous blood product transfusions, in providing adequate hemostasis, and in producing satisfactory outcomes.⁴⁶

Multiple point-of-care tests were used in the analyses described above, and it is hard to recommend one over the other. Further, it is not clear whether the algorithms developed for guiding transfusion and the multidisciplinary approach are more important than the point-of-care testing used. At least one study strongly suggests that it is the multimodality approach that is important rather than the individual components of the process.⁹²

Recombinant Human Erythropoietin

Recombinant human erythropoietin (EPO) is a potent treatment to augment RBC volume. Abundant evidence exists, including three meta-analyses, to justify the preoperative administration of EPO to reduce the preoperative anemia in patients having autologous blood donation.⁴⁶ EPO is safe and effective for the improvement of preoperative anemia, with the main side effect being hypertension. Adequate iron supplementation is required in conjunction with EPO. A typical preoperative regimen of EPO might cost as much as \$250 and it remains to be seen if this is a cost-effective measure in patients undergoing autologous blood donation before cardiac procedures. A significant disadvantage of EPO is the requirement for delay of operation because the effect of the drug takes as long as 14 days for maximal benefit.

Evidence supporting the preoperative use of EPO in anemic patients (hemoglobin $\leq$ 13 g/dL) is less compelling, but still supportive, when autologous predonation is not undertaken. Most of the literature in support of using EPO to reduce preoperative anemia is anecdotal and relates successful case reports in a handful of patients, especially in Jehovah's Witnesses.^{110,111} Because preoperative anemia increases operative mortality and morbidity in cardiac procedures,¹¹ limited evidence but logical consensus suggests that EPO augments the red cell mass in anemic patients treated with iron before operation and may provide benefit.

Still fewer objective data points are available regarding the use of EPO to treat peri- and postoperative anemia. Because the onset of action of the drug is 4 to 6 days, it is necessary to administer EPO a few days in advance of operation, a luxury that is not always available. Logic supports the addition of EPO to patients expected to have a large blood loss during operation or who may be anemic preoperatively. Drugs like postoperative β -blockers suppress endogenous EPO production.¹¹² Cytokines stimulated by the inflammatory response associated with CPB limit production of EPO.¹¹³ Perioperative renal ischemia may limit the production of EPO. Likewise,

careful perioperative management might be expected to improve tissue oxygen delivery and suppress endogenous EPO production despite postoperative anemia. All of these factors support the addition of preoperative (a few days before operation) administration of EPO without much solid literature evidence base. Nonetheless, EPO represents one of the few options to increase preoperative anemia and to augment blood volume in patients with small body size. There is almost no evidence to support use of EPO in patients treated with preoperative antiplatelet drugs, but consensus favors EPO use whenever clinically possible.

Antifibrinolytic Drugs

Using drugs for blood conservation in cardiac operations turned full circle in the late 1980s with the observation that aprotinin, given to humans in a far higher dose than any reported previously, was able to reduce bleeding to the point where the majority of patients did not require transfusions. This was seen even in patients having repeat surgery through a previous sternotomy,¹¹⁴ a patient population regarded at that time as being at a very high risk for transfusion. The mechanism of action of aprotinin to improve hemostasis and prevent the need for transfusion is unknown. As a result of interest in fibrinolysis as an underlying mechanism of operative bleeding during CPB, it seemed reasonable to investigate the lysine analog antifibrinolytics, epsilon-aminocaproic acid (EACA) and tranexamic acid, as beneficial agents for postoperative bleeding despite having entirely different modes of action on the hemostatic and physiological fibrinolytic process. Reports in the late 1980s and early 1990s from observational and certain randomized studies showed convincing data that the postoperative chest tube losses were reduced significantly by lysine analogs. Since the early 1980s, multiple randomized and observational studies were added to the body of literature about antifibrinolytic agents, and it is possible to make evidence-based decisions about their use.

More than 20 studies compared high-dose aprotinin to controls in patients having CABG only. Meta-analysis of these studies showed a highly significant reduction in blood transfusion in aprotinin-treated patients. Similar results were found in studies of patients having redo CABG operations and in patients having valve or valve/CABG operations. Unfortunately, more recent evidence suggests that aprotinin risks adverse outcomes that overshadow the benefit of reduced bleeding and blood transfusion.^{115–117}

Evidence supporting the use of the lysine analogues for limiting blood transfusion after cardiac procedures is less compelling than that for aprotinin. However, multiple studies compared patients taking tranexamic acid or epsilon aminocaproic acid (only commercially available lysine analogs) to controls in

patients undergoing CABG-only operations. The meta-analysis of these studies suggests that lysine analogs are associated with reduced number of patients who require blood transfusion after CABG.¹¹⁸ The safety profile of the lysine analogs is less well studied than that of aprotinin, but at present, no excess adverse outcomes occur with use of these agents. Lysine analogs are the preferred antifibrinolytic agents in the United States, where aprotinin is no longer available.

CABG WITHOUT USE OF CPB (OFF-PUMP CABG)

Several randomized trials compared the results of off-pump bypass to on-pump bypass. In the majority of these studies, reduction in the use of allogeneic blood transfusions is associated with off-pump bypass.⁴⁶ Looking at the data more carefully, however, it is interesting to note that the number of patients who crossed over from off-pump to on-pump was not uniform among these reports. In one randomized trial that showed no difference in transfusion requirements or blood loss between on-pump and off-pump groups, crossovers from off-pump to on-pump were common, occurring in 22.5% of patients.¹¹⁹ Every unfavorable outcome, including bleeding requiring reoperation, was more common in the emergency off-pump to on-pump conversion subgroup, when compared with patients in whom either on-pump or off-pump bypass without emergency conversion was performed.¹²⁰ As a result of these observations, off-pump bypass is recommended in preference to on-pump bypass as a means of blood conservation, provided that emergent conversion to on-pump bypass is unlikely either based on surgeon experience or patient characteristics.

Interventions during the Conduct of Extracorporeal Circulation (CPB)

Progress in cardiac surgery could not proceed without improvements in extracorporeal circulation. Improvements occurred in both equipment and in technique over the 50 years since inception of CPB. There are almost no RCTs to validate methods used for CPB. Nonetheless, there is a recognizable consensus among surgeons that allows best practices recommendations for blood conservation to be made.

OXYGENATORS AND BLOOD PUMPS

The central apparatus of CPB is the oxygenator. Membrane oxygenators are the predominant oxygenators used for several reasons. Bubble oxygenators compare favorably to membrane oxygenators in most comparisons except for bypass runs exceeding 2 hours, an increasingly more common clinical situation as case complexity increases.^{121–128} Advantages found with membrane oxygenators included less cerebral emboli, better biocompatibility, and reduced blood utilization. Without

much class I evidence, membrane oxygenators have mostly replaced bubble oxygenators in modern clinical practice. In the event of loss of venous return during CPB, large amounts of air can be transported across the oxygenator membrane, but not into the patient, with membrane oxygenators, whereas bubble oxygenators risk immediate embolization of air into the arterial circuit. This constitutes an important potential safety benefit of membrane oxygenators and consensus favors membrane oxygenators for this reason.

A core component of the heart–lung machine is the blood pump. Current clinical use is about evenly divided between centrifugal and roller pumps. Fundamental differences exist between the two types with centrifugal pumps being nonocclusive and roller pumps being able to generate unlimited pressure because of occlusion at the roller head. The nonocclusive nature of the centrifugal pumps is one of the positive features of this pump system, especially for long-term support. Perfusion blood pumps do not impact blood transfusion in a significant way. Nine randomized trials compared blood loss in patients perfused with centrifugal pumps versus roller pumps. No significant differences in bleeding or blood transfusion were found in patients perfused with roller or centrifugal pumps. All commercially available blood pumps provide acceptable blood conservation during CPB with a slight advantage given to centrifugal pumps because of perfusion safety features.

CELL SAVERS

Intraoperative salvage of RBCs, using cell saver apparatus, is an important part of blood conservation in cardiac operations using CPB. Multiple reports document the safety of cell savers and at least 10 published reports, including some RCTs, support the routine use of cell savers to reduce bleeding and blood transfusion, although the reduction in transfusions may be modest.⁴⁶ With usual cell saver protocols, about half of the blood suctioned from the patient is ultimately reconstituted. With careful attention to intraoperative hemostasis in patients at low risk for operative bleeding, it may be that use of the cell saver is not a cost-effective measure, although most assessments of cost favor routine use of cell savers. Patients whose blood is exposed to topical clotting agents or who have active blood-borne infections are not suitable candidates for use of cell salvage.

RETROGRADE AUTOLOGOUS PRIMING OF THE CPB CIRCUIT

This method replaces the crystalloid prime volume of the CPB circuit with the patient's own blood immediately prior to beginning CPB. Typically, the arterial limb of the circuit is allowed to back bleed and displace crystalloid prime solution into a separate fluid bag. The displaced crystalloid is collected and excluded from the

circuit. This technique maintains colloid osmotic pressure and reduces extravascular lung water compared with standard priming techniques. In two of three randomized trials comparing retrograde autologous priming to usual practice, a significant reduction in the frequency of allogeneic blood transfusion resulted.⁴⁶ Two other studies showed a trend toward lower usage of allogeneic blood transfusions but did not reach statistical significance. The consensus is that retrograde autologous priming of the CPB circuit may be useful for blood conservation.

BLOOD CONSERVATION IN PATIENTS TREATED WITH ANTIPLATELET DRUGS

Surprisingly few studies have addressed the issue of blood conservation in patients undergoing cardiac procedures who are treated with antiplatelet drugs. The most carefully studied intervention in ASA-treated patients is use of aprotinin to limit blood transfusion. All of these studies indicate that aprotinin is very effective in limiting blood transfusion in ASA-treated patients undergoing cardiac procedures. Much less evidence favors lysine analogs, but these drugs are viewed as an acceptable substitute for aprotinin, especially as aprotinin is no longer readily available in the United States.

Several studies evaluated the use of desmopressin in ASA-treated patients undergoing cardiac procedures. Meta-analysis of these studies suggests that prophylactic administration of desmopressin does not reduce bleeding after cardiac procedures.^{33,46}

Almost no evidence, except occasional anecdote, is available to indicate the best blood conservation methods in patients treated with GP IIb/IIIa inhibitors who require urgent CABG. Platelet transfusions reduce the incidence of post-CABG bleeding complications in patients taking GP IIb/IIIa receptor antagonists before operation, but no other blood conservation interventions have been evaluated.^{56,129}

CONCLUSIONS AND SUMMARY

Several conclusions regarding limitation of post-CPB bleeding in patients treated with preoperative antiplatelet drugs can be made based on available information. An important first step in limiting postoperative blood transfusion is to recognize the causes. The negative impact of advanced age, small body habitus, preoperative anemia (combined in the age/RBC volume composite variable), and non-CABG or redo procedures must be recognized. The mechanisms of action and the variability of response to antiplatelet drugs should be understood and hyperresponders should be identified where possible. Unfavorable preoperative risk factors should be corrected where possible and operation should be

delayed while this is going on, consistent with clinical urgency. Interventions such as withholding antiplatelet drugs and use of EPO for treatment of preoperative of anemia are likely to prove useful in high-risk patients.

Multiple blood conservation interventions are likely to be more successful than one or two interventions alone. This multifaceted approach is likely to have the most benefit in high-risk patients. Other blood conservation interventions should be combined with antifibrinolytic therapy. Two important components of any blood conservation strategy are often overlooked and should be emphasized: (1) frequent audits of results of blood conservation interventions, and (2) cost-benefit analysis for each new intervention added. This continual reassessment is an important part of ensuring a high-quality approach to blood utilization in patients treated with antiplatelet drugs undergoing cardiac operations.

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