Bleeding as a Predictor of Mortality Risk

Sunil V. Rao, MD

Durham VA Medical Center, Duke Clinical Research Institute, Durham, NC

The increased rate of bleeding during and after cardiac procedures is a concern. The best strategy is prevention of bleeding complications with anticoagulant therapy that provides an adequate anti-thrombotic effect while reducing bleeding. The independent relationship between bleeding and blood transfusion and mortality among patients with coronary artery disease is reviewed. Findings suggest that in the modern era of percutaneous coronary intervention, prevention of bleeding should be a goal of therapy, which can be achieved while preserving the low rate of ischemic complications.
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Outcomes after percutaneous coronary intervention (PCI) have markedly improved over the past decade. This is due to the simultaneous evolution of periprocedural pharmacology and interventional devices. The latter has allowed for shorter procedure times and durable results, whereas the former has allowed for safer procedures and a reduction in major adverse cardiac events (MACE). With this combination of drugs (unfractionated and low-molecular-weight heparin, glycoprotein (GP) IIb/IIIa inhibitors, clopidogrel) and devices (low-profile balloons, stents, drug-eluting stents), the combined rate

of unsuccessful PCI, periprocedural myocardial infarction, and death is less than 1%.[1] The improvement in these traditional "efficacy" measures has been counterbalanced by an expected increase in the rate of bleeding.[2,3] Recent data suggest that in the current era of PCI, achieving efficacy at the expense of safety (ie, bleeding) actually leads to increases in mortality.[4-6] Treatment of bleeding complications with blood transfusion also appears to put patients at risk.[7] The best strategy, therefore, is prevention of bleeding complications with anticoagulant therapy that provides an adequate anti-thrombotic effect while reducing bleeding. This section reviews the data supporting an independent relationship between bleeding and blood transfusion and mortality among patients with coronary artery disease.

Contribution of Bleeding Complications to Mortality Risk

It is now accepted that thrombin plays a central role in the generation of thrombus and activation of platelets.[8] Inhibition of thrombin, therefore, is paramount during PCI where there is injury to the coronary vessel wall and nidus for thrombus formation. During the early days of coronary angioplasty, high-dose unfractionated heparin was the extent of procedural anticoagulation.[9] Although never supported by randomized trials, several observational studies found an inverse relationship between the activated clotting time (ACT) and the probability of ischemic complications.[10,11] Despite this, the rate of acute ischemic complications from balloon angioplasty was 5% to 9%.[2] The development of low profile angioplasty balloons and coronary stents shortened procedure times and the introduction of GP IIb/IIIa inhibitors and thienopyridines further reduced ischemic complications.[2,3,12,13] Although this occurred at the expense of an increase in both minor and major bleeding complications,[2,14,15] GP IIb/IIIa inhibitors were widely adopted into clinical practice. However, as the outcomes from PCI improved, the use of GP IIb/IIIa inhibitors (which required 12 to 18 hours of infusion postprocedure) and the associated bleeding began to undergo scrutiny. A series of studies examined the association between bleeding and mortality in patients undergoing PCI and those with acute coronary syndromes. Their findings suggest that in the modern era of PCI, prevention of bleeding should be a goal of therapy, which can be achieved while preserving the low rate of ischemic complications.

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One of the first studies to examine the relationship between bleeding and adverse clinical outcomes was a multicenter observational study that retrospectively analyzed 10,974 PCI procedures and 3 centers.[6] The rate of any bleeding complication was 19.1%, with most patients experiencing minor bleeding (mostly groin hematomas). The rate of major bleeding (defined as either intracranial hemorrhage or bleeding resulting in a hemoglobin decrease of at least 5 g/dL) was 5.4%, and the rate of transfusion was 5.4%. Compared with patients who did not experience a bleeding event, there was a stepwise increase in the incidence of death and MACE as bleeding severity increased (death: no bleeding 0.6%, minor bleeding 1.8%, major bleeding 7.5%, $P < .001$; MACE: no bleeding 0.6%, minor bleeding 2.2%, major bleeding 6.6%, $P < .001$). After adjustment for differences in patient characteristics, major bleeding was associated with an odds ratio of 3.5 for in-hospital mortality. Similarly, in the Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events (REPLACE-2) trial comparing bivalirudin with unfractionated heparin plus GP IIb/IIIa inhibitors in patients undergoing PCI, the occurrence of bleeding was associated with an adjusted odds ratio of 3.53 for 1-year mortality.[16] This relationship was stronger than the relationship between in-hospital MI and 1-year mortality.

These data are corroborated by 2 other studies that examined patients with acute coronary syndromes, many of whom underwent cardiac catheterization with subsequent PCI. Moscucci and colleagues reported on predictors and outcome of major bleeding from 24,045 patients enrolled in the Global Registry of Acute Coronary Events (GRACE).[5] "Major bleeding" in this study was defined as life-threatening bleeding requiring transfusion of 2 units or more of packed red cells, or leading to an absolute hematocrit decrease of 10% or greater, or subdural hematoma. The overall incidence of major bleeding was 3.9%. Among patients with unstable angina and non–ST-segment elevation MI, they found that advanced age, female gender, renal insufficiency, anticoagulant medications, and procedures were associated with major bleeding, and that major bleeding was associated with an adjusted odds ratio of 1.64 for in-hospital death. Rao and colleagues[4] examined longer-term outcomes in the ACS population by analyzing 24,112 patients enrolled in 3 international

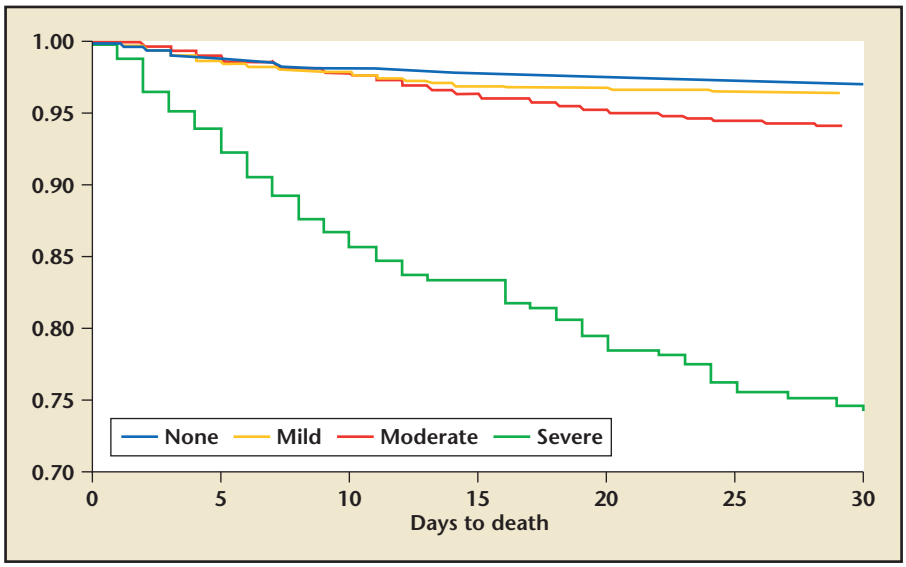

Figure 1. *Association between bleeding severity and 30-day mortality among patients with acute coronary syndromes. Reprinted from Rao SV et al[4] with permission from Excerpta Medica, Inc.*

clinical trials (Figure 1). Bleeding was defined as severe (either intracranial hemorrhage or bleeding resulting in hypotension), moderate (bleeding resulting in blood transfusion), or mild (clinical bleeding that does not qualify as moderate or severe). After using a statistical technique known as "time-dependent modeling" that minimizes bias by including only those outcomes that occurred after the bleeding event and adjusting for differences in patient baseline characteristics, they found a stepwise increase in the hazard of 30-day death (mild bleeding, 1.6 [1.3-1.9]; moderate bleeding, 2.7 [2.3-3.4]; severe bleeding, 10.6 [8.3-13.6]) that persisted at 6 months. The results were similar among patients undergoing coronary artery bypass grafting and those who experienced periprocedural bleeding.

These studies collectively demonstrate a consistent, strong relationship between bleeding and short- and long-term mortality. A gradient of risk exists so that worse bleeding is associated with a higher risk for short- and long-term mortality. These studies also underscore the concept that in the modern era of PCI where there is a relatively low rate of ischemic complications, a pharmacologic strategy that reduces bleeding complications can potentially impact long-term outcomes.

The Negative Impact of Unfractionated Heparin and Glycoprotein IIb/IIIa Inhibitors

As mentioned previously, thrombin inhibition is the cornerstone of therapy for patients with ACS and PCI. This has been conventionally addressed with unfractionated heparin (UFH). Although early studies indicated that a greater degree of anticoagulation with UFH was associated with a lower incidence of ischemic complications, a larger study[17] found that doses of UFH large enough to increase the activated clotting time (ACT) to greater than 350 seconds was not only associated with increased bleeding, but also a higher incidence of death, MI, or revascularization after PCI. The reasons for this paradox (theoretically higher ACT being associated with a higher incidence of ischemic complications) are not clear, but are likely due to the fact that UFH is an indirect antithrombin. That is, as higher doses of UFH are used, it is likely that more and more thrombin is generated and ultimately the actions of thrombin (platelet activation, fibrinogen generation, etc.) overcome the therapeutic effects of UFH. In addition to higher rates of ischemic events, ACT values higher than 350 seconds were also associated with a higher rate of bleeding complications, suggesting that there is an optimal dose of UFH needed to achieve the balance between thrombosis and hemostasis.

As PCI evolved further, focus shifted from thrombin inhibition to platelet inhibition to further improve outcomes. The GP IIb/IIIa receptor on the platelet surface functions to bind fibrinogen and von Willebrand factor to form platelet aggregates, and is an ideal therapeutic target for anticoagulation. The introduction of GP IIb/IIIa inhibitors on the background of UFH improved ischemic outcomes but was associated with markedly higher rates of bleeding compared to UFH alone.[2] In the EPIC trial that compared UFH plus abciximab bolus, UFH plus abciximab bolus and infusion, and UFH alone, the rate of major bleeding was 14% in the group that received UFH plus abciximab bolus and infusion

The reasons that higher activated clotting times are associated with a higher incidence of ischemic complications are not clear, but are likely due to the fact that unfractionated heparin is an indirect antithrombin.

compared with 7% in the group that received UFH alone. Given that combination therapy with GP IIb/IIIa inhibitors and UFH targets both thrombin and the platelet, a higher bleeding rate would be expected. To address this issue, retrospective analyses found that lowering the UFH dose when GP IIb/IIIa inhibitors are used can reduce the incidence of bleeding.[17,18] Later studies comparing UFH with the combination of UFH and GP IIb/IIIa inhibitors used lower doses of UFH and found lower rates of major and minor bleeding.[12] It appears that the optimal ACT when using the combination of UFH and GP IIb/IIIa inhibitors during PCI is between 200 and 250 seconds.[19]

Although the previous ACT ranges are consistent with published guidelines on antithrombotic therapy during PCI,[19] it is much more difficult to achieve the optimal level of anticoagulation in clinical practice. In the Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events (ESSENCE) study of subcutaneous enoxaparin compared with UFH for patients with non–ST-segment elevation ACS, 25% of patients were supratherapeutic and 15% were subtherapeutic on UFH after 4 days of therapy despite close monitoring.[20] Suboptimal UFH dosing (whether sub- or supratherapeutic) is associated with either an increase in recurrent cardiovascular events or increased bleeding in the ACS population.[21] A recent analysis of 30,136 ACS patients at 387 hospitals found that 42% of patients received excessive dosing of either UFH or enoxaparin and 26.8% received excessive dosing of GP IIb/IIIa inhibitors.[22] Patients who received higher than recommended doses of UFH or enoxaparin and GP IIb/IIIa inhibitors had a markedly higher adjusted rate of in-hospital bleeding. These data suggest that despite knowledge of optimal heparin dosing, achieving appropriate levels of thrombin inhibition in practice can be challenging.

For patients undergoing PCI, several studies have compared UFH with bivalirudin, a direct thrombin inhibitor, and found a lower rate of bleeding with equivalent rates of ischemic complications. In the Bivalirudin Angioplasty Trial, 4312 patients with unstable angina undergoing balloon angioplasty were randomized to receive bivalirudin or weight-adjusted UFH.[23] The rate of ischemic complications was lower in the group assigned to bivalirudin (7.9% vs 6.2%, $P = .039$) as was the rate of major bleeding (9.3% vs 3.5%, $P < .001$). Subsequent smaller trials comparing UFH with bivalirudin that included either planned or provisional use of GP IIb/IIIa inhibitors confirmed the lower rate of both ischemic and hemorrhagic complications in patients who received bivalirudin during coronary stenting.[24,25] In the REPLACE-2 Trial, 6010 patients undergoing either elective or urgent PCI were randomized to UFH plus planned GP IIb/IIIa inhibitor or bivalirudin with provisional GP IIb/IIIa inhibitor (for bailout purposes).[26] The trial was statistically powered to demonstrate the non-inferiority of bivalirudin with respect to the combined endpoint of death, MI, target vessel revascularization, or bleeding. The rate of the 30-day quadruple endpoint was statistically similar between the 2 arms (10.0% vs 9.2%, $P = .32$), thereby demonstrating the non-inferiority of bivalirudin. In terms of ischemic endpoints (death, MI, or target vessel revascularization), the rate was statistically similar between the 2 groups (6.2% vs 7.0%, $P = .44$). The rate of bleeding was significantly lower in the bivalirudin arm (4.1% vs 2.4%, $P = .008$). The use of a specific GP IIb/IIIa inhibitor, either abciximab or eptifibatide, was prespecified before randomization. A total of 1343 patients received abciximab plus UFH and 1658 patients received eptifibatide plus UFH. Both of these groups had similar rates of ischemic endpoints compared with bivalirudin but had a higher rate of bleeding compared with bivalirudin (Table 1).[27]

There are several conclusions that can be drawn from the previous data. First, judicious dosing of UFH during PCI is necessary to reduce the incidence of bleeding. Second, the dose of UFH should be reduced even further if GP IIb/IIIa inhibitors are being used. Third, judicious dosing is difficult to achieve in clinical practice and a large proportion of patients are dosed excessively with UFH and GP IIb/IIIa inhibitors. This excessive dosing is associated with a marked increase in the incidence of in-hospital bleeding. Finally, the use of bivalirudin during PCI appears to provide anticoagulation equal to UFH plus GP IIb/IIIa inhibitors while simultaneously reducing bleeding complications.

Association Between Blood Transfusion and Mortality

One reason the focus of PCI pharmacology has been on reducing ischemic complications at the expense of increasing bleeding is the ready availability of a therapy for bleeding—blood transfusion. Transfusion is one of the most common procedures performed, with over 12 million units of blood administered to 3.5 million patients annually.[28] The use of blood declined briefly during the early 1980s due to concerns over the transmission of bloodborne pathogens (eg, human immunodeficiency virus), but improved screening methods dramatically reduced the risk of viral infection.[29] Although the risk of viral transmission is now relatively low, it

Table 1
Rates of Ischemic Endpoints and Bleeding Complications With Unfractionated Heparin and Either Abciximab or Eptifibatide Compared With Bivalirudin and Provisional Abciximab or Eptifibatide in the REPLACE-2 Trial

Treatment	Rate	*P* Value
Rate of Death, MI, or Total Valve Replacement (%)		
Heparin + abciximab	7.0	NS
Bivalirudin + prov. abciximab	8.5	
Heparin + eptifibatide	7.1	NS
Bivalirudin + prov. eptifibatide	7.0	
Rate of Major Bleeding (%)		
Heparin + abciximab	4.0	.025
Bivalirudin + prov. abciximab	2.5	
Heparin + eptifibatide	4.1	.002
Bivalirudin + prov. eptifibatide	2.2	

REPLACE, Randomized Evaluation in PCI Linking Angiomax to reduced Clinical Events; MI, myocardial infarction; prov, provisional. Adapted from Voeltz MD et al.[27]

is now becoming apparent that there are other risks associated with transfusion that may increase adverse cardiovascular outcomes.

Intuitively, raising the hemoglobin via transfusion should increase oxygen delivery, but studies show that measures of tissue oxygenation either decrease or do not change.[30-32] Alterations in erythrocyte nitric oxide biology in stored blood may be a partial explanation for this phenomenon. Nitric oxide (NO) is a gas that plays a central role in oxygen exchange.[33] Packed red cells are depleted of NO, and therefore may function as NO "sinks," promoting vasoconstriction, platelet aggregation, and ineffective oxygen delivery.[34] Packed red cells also have high oxygen affinity that further impairs oxygen delivery to hypoxic tissues[35] and can increase levels of inflammatory markers that are associated with exacerbation of myocardial ischemia.[36]

Two recent non-randomized studies have found an association between the liberal use of blood transfusion in patients with acute ischemic heart disease and increased mortality. Wu and colleagues[37] examined outcomes after transfusion among 78,974 Medicare beneficiaries with acute myocardial infarction. In logistic regression analysis, transfusion was associated with lower 30-day mortality among patients with an admission hematocrit concentration between 5% and 33%, but it was associated with a nonsignificant *increase* in mortality among patients with a baseline hematocrit greater than 33%. Rao and colleagues[7] examined the association between blood transfusion and mortality among 24,111 patients with non-ST segment elevation ACS and found that transfusion increased mortality when administered for a nadir hematocrit above 25% (Table 2). These data are further supported by an analysis of patients undergoing PCI in the REPLACE-2 Trial. Manoukian and colleagues[38] found that patients who received an in-hospital blood transfusion after PCI were at 4 to 5 times higher risk for 1-year mortality.

The largest randomized trial[39] comparing aggressive and conservative transfusion strategies included 838 critically ill patients with a hemoglobin concentration less than 9.0 g/dL within 72 hours of admission to the ICU. By an intention-to-treat analysis, there was no difference in 30-day all-cause mortality between the groups, but 30-day mortality was significantly higher with the liberal strategy of transfusion in patients who were younger than age 55 or had an Acute Physiology And Chronic Health Evaluation (APACHE) II score of less than 20. There also were significantly more MIs and cases of pulmonary edema with the liberal transfusion strategy.

In summary, blood transfusion does not lead to improvements in tissue oxygenation due to its lack of nitric oxide, high oxygen affinity, and potential effect on markers of inflammation. Both observational and randomized clinical data suggest that liberal use of transfusion is associated with increases in mortality among patients with coronary artery disease; therefore, the routine use of blood transfusion should be avoided. Because bleeding complications are a major driver of transfusion in the peri-PCI setting, the prevention of bleeding can play a fundamental role in the prevention of blood transfusion.

Conclusions

The evolution of PCI devices and pharmacology has led to a shift in the goal of therapy. In the past, the focus was on the reduction of ischemic complications, even if that meant an increase in bleeding. In the current era of PCI where ischemic complications are relatively low, bleeding complications remain an

Table 2
Adjusted Predicted Probabilities of 30-Day Death With and Without Transfusion by Nadir Hematocrit Value

	Nadir Hematocrit* (%)			
	20	25	30	35
Adjusted odds ratio (95% CI)†	1.59 (0.95-2.66)	1.13 (0.70-1.82)	168.64 (7.49-3797.69)	291.64 (10.28-8273.85)

*Nadir hematocrit value was incorporated into the multivariable logistic regression model as a continuous variable. The association between nadir hematocrit value and 30-day mortality was evaluated using restricted cubic splines. Because the association followed 2 lines, 1 below and 1 above a nadir hematocrit value of 25%, a linear spline transformation with a nadir hematocrit value of 25% as the knot point was used. Nadir hematocrit values in the table are sample values above and below 25%.
†Adjusted for US vs non-US site, age, race, weight in kilograms, diabetes mellitus, systolic and diastolic blood pressure, heart rate at baseline, time from symptom onset to hospitalization, prior stroke, prior myocardial infarction, sex, history of angina prior to qualifying episode, hypertension, hyperlipidemia, family history of coronary artery disease, history of congestive heart failure, peripheral vascular disease, prior percutaneous coronary intervention, prior coronary artery bypass graft surgery, Killip class, baseline hematocrit, maximum creatine kinase ratio at baseline, chronic renal insufficiency, ST-segment elevation or depression on initial electrocardiogram, β-blocker use at baseline, calcium channel blocker use at baseline, nitrate use at baseline, and current smoking.
CI, confidence interval. Reprinted with permission from Rao SV et al.[7]

issue. Several studies demonstrate a strong consistent association between bleeding and blood transfusion and short- and long-term mortality. One strategy that can reduce bleeding is to reduce the dose of UFH during PCI, especially when GP IIb/IIIa inhibitors are used, but the registry indicates that both UFH and GP IIb/IIIa inhibitors are often dosed excessively in clinical practice. Another strategy is to use the direct thrombin inhibitor bivalirudin as the anticoagulant during PCI. Randomized clinical trial data demonstrate that bivalirudin provides an adequate anticoagulant effect while reducing bleeding complications. ■

References

1. Smith SC, Jr, Feldman TE, Hirshfeld JW, Jr, et al. ACC/AHA/SCAI 2005 guideline update for percutaneous coronary intervention: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/SCAI Writing Committee to Update the 2001 Guidelines for Percutaneous Coronary Intervention). *J Am Coll Cardiol*. 2006;47:e1-e121.
2. The EPIC Investigators. Use of a monoclonal antibody directed against the platelet glycoprotein IIb/IIIa receptor in high-risk coronary angioplasty. *N Engl J Med*. 1994;330:956-961.
3. The EPILOG Investigators. Platelet glycoprotein IIb/IIIa receptor blockade and low-dose heparin during percutaneous coronary revascularization. *N Engl J Med*. 1997;336:1689-1696.
4. Rao SV, O'Grady K, Pieper KS, et al. Impact of bleeding severity on clinical outcomes among patients with acute coronary syndromes. *Am J Cardiol*. 2005;96:1200-1206.
5. Moscucci M, Fox KA, Cannon CP, et al. Predictors of major bleeding in acute coronary syndromes: the Global Registry of Acute Coronary Events (GRACE). *Eur Heart J*. 2003;24:1815-1823.
6. Kinnaird TD, Stabile E, Mintz GS, et al. Incidence, predictors, and prognostic implications of bleeding and blood transfusion following percutaneous coronary interventions. *Am J Cardiol*. 2003;92:930-935.
7. Rao SV, Jollis JG, Harrington RA, et al. Relationship of blood transfusion and clinical outcomes in patients with acute coronary syndromes. *JAMA*. 2004;292:1555-1562.
8. Yeghiazarians Y, Braunstein JB, Askari A, Stone PH. Unstable angina pectoris. *N Engl J Med*. 2000;342:101-114.
9. Ferguson JJ, Barasch E, Wilson JM, et al. The relation of clinical outcome to dissection and thrombus formation during coronary angioplasty. Heparin Registry Investigators. *J Invas Cardiol*. 1995;7:2-10.
10. Narins CR, Hillegass WB Jr, Nelson CL, et al. Relation between activated clotting time during angioplasty and abrupt closure. *Circulation*. 1996;93:667-671.
11. Ferguson JJ, Dougherty KG, Gaos CM, et al. Relation between procedural activated

Main Points

- Compared with patients who did not experience a bleeding event, there was a stepwise increase in the incidence of death and major adverse cardiac events as bleeding severity increased.
- Studies collectively demonstrate a consistent, strong relationship between bleeding and short- and long-term mortality.
- It appears that the optimal activated clotting time when using the combination of unfractionated heparin and glycoprotein inhibitors during percutaneous coronary intervention is between 200 and 250 seconds.
- Two recent non-randomized studies have found an association between the liberal use of blood transfusion in patients with acute ischemic heart disease and increased mortality.
- Studies underscore the concept that in the modern era, where there is a relatively low rate of ischemic complications, a pharmacologic strategy that reduces bleeding complications can potentially impact long-term outcomes.

coagulation time and outcome after percutaneous transluminal coronary angioplasty. *J Am Coll Cardiol*. 1994;23:1061-1065.
12. The ESPRIT Investigators. Novel dosing regimen of eptifibatide in planned coronary stent implantation (ESPRIT): a randomised, placebo-controlled trial. *Lancet*. 2000;356:2037-2044.
13. Steinhubl SR, Berger PB, Mann JT, 3rd, et al. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. *JAMA*. 2002;288:2411-2420.
14. The RESTORE Investigators. Effects of platelet glycoprotein IIb/IIIa blockade with tirofiban on adverse cardiac events in patients with unstable angina or acute myocardial infarction undergoing coronary angioplasty: Randomized Efficacy Study of Tirofiban for Outcomes and REstenosis. *Circulation*. 1997;96:1445-1453.
15. Mehta SR, Yusuf S, Peters RJ, et al. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. *Lancet*. 2001;358:527-533.
16. Attubato MJ, Feit F, Bittl JA, et al. Major hemorrhage is an independent predictor of 1-year mortality following percutaneous coronary intervention: an analysis from REPLACE-2 (abstract). *Am J Cardiol*. 2004;94(suppl 1):39E.
17. Chew DP, Bhatt DL, Lincoff AM, et al. Defining the optimal activated clotting time during percutaneous coronary intervention: aggregate results from 6 randomized, controlled trials. *Circulation*. 2001;103:961-966.
18. Tolleson TR, O'Shea JC, Bittl JA, et al. Relationship between heparin anticoagulation and clinical outcomes in coronary stent intervention: observations from the ESPRIT trial. *J Am Coll Cardiol*. 2003;41:386-393.
19. Popma JJ, Berger P, Ohman EM, et al. Antithrombotic therapy during percutaneous coronary intervention: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest*. 2004;126(3 Suppl):576S-599S.
20. Cohen M, Demers C, Gurfinkel EP, et al. A comparison of low-molecular-weight heparin with unfractionated heparin for unstable coronary artery disease. Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events Study Group. *N Engl J Med*. 1997;337:447-452.
21. Anand SS, Yusuf S, Pogue J, et al., for Organization to Assess Strategies for Ischemic Syndromes Investigators. Relationship of activated partial thromboplastin time to coronary events and bleeding in patients with acute coronary syndromes who receive heparin. *Circulation*. 2003;107:2884-2888.
22. Alexander KP, Chen AY, Roe MT, et al., for CRUSADE Investigators. Excess dosing of antiplatelet and antithrombin agents in the treatment of non-ST-segment elevation acute coronary syndromes. *JAMA*. 2005;294:3108-3116. Erratum in: *JAMA*. 2006;295:628.
23. Bittl JA, Chaitman BR, Feit F, et al. Bivalirudin versus heparin during coronary angioplasty for unstable or postinfarction angina: final report reanalysis of the Bivalirudin Angioplasty Study. *Am Heart J*. 2001;142:952-959.
24. Lincoff AM, Kleiman NS, Kottke-Marchant K, et al. Bivalirudin with planned or provisional abciximab versus low-dose heparin and abciximab during percutaneous coronary revascularization: results of the Comparison of Abciximab Complications with Hirulog for Ischemic Events Trial (CACHET). *Am Heart J*. 2002; 143:847-853.
25. Lincoff AM, Bittl JA, Kleiman NS, et al. Comparison of bivalirudin versus heparin during percutaneous coronary intervention (the Randomized Evaluation of PCI Linking Angiomax to Reduced Clinical Events [REPLACE]-1 trial). *Am J Cardiol*. 2004;93:1092-1096.
26. Lincoff AM, Bittl JA, Harrington RA, et al. Bivalirudin and provisional glycoprotein IIb/IIIa blockade compared with heparin and planned glycoprotein IIb/IIIa blockade during percutaneous coronary intervention: REPLACE-2 randomized trial. *JAMA*. 2003;289:853-863.
27. Voeltz MD, Lincoff AM, Feit F, Manoukian SV. Bivalirudin significantly reduces bleeding while maintaining efficacy compared to either abciximab or eptifibatide in percutaneous coronary intervention: lessons from REPLACE-2. Abstract presented at: American Heart Association Scientific Sessions; November 13-16, 2005; Dallas, TX.
28. Goodnough LT, Soegiarso RW, Birkmeyer JD, Welch HG. Economic impact of inappropriate blood transfusions in coronary artery bypass graft surgery. *Am J Med*. 1993;94:509-514.
29. Goodnough LT, Brecher ME, Kanter MH, AuBuchon JP. Transfusion medicine. Second of two parts—blood conservation. *N Engl J Med*. 1999; 340:525-533.
30. Fortune JB, Feustel PJ, Saifi J, et al. Influence of hematocrit on cardiopulmonary function after acute hemorrhage. *J Trauma*. 1987;27: 243-249.
31. Casutt M, Seifert B, Pasch T, et al. Factors influencing the individual effects of blood transfusions on oxygen delivery and oxygen consumption. *Crit Care Med*. 1999;27:2194-2200.
32. Dietrich KA, Conrad SA, Hebert CA, et al. Cardiovascular and metabolic response to red blood cell transfusion in critically ill volume-resuscitated nonsurgical patients. *Crit Care Med*. 1990;18:940-944.
33. McMahon TJ, Moon RE, Luschinger BP, et al. Nitric oxide in the human respiratory cycle. *Nat Med*. 2002;8:711-717.
34. Stamler JS, Jia L, Eu JP, et al. Blood flow regulation by S-nitrosohemoglobin in the physiological oxygen gradient. *Science*. 1997;276:2034-2037.
35. Welch HG, Meehan KR, Goodnough LT. Prudent strategies for elective red blood cell transfusion. *Ann Intern Med*. 1992;116:393-402.
36. Fransen E, Maessen J, Dentener M, et al. Impact of blood transfusions on inflammatory mediator release in patients undergoing cardiac surgery. *Chest*. 1999;116:1233-1239.
37. Wu WC, Rathore SS, Wang Y, et al. Blood transfusion in elderly patients with acute myocardial infarction. *N Engl J Med*. 2001;345:1230-1236.
38. Manoukian SV, Voeltz MD, Attubato MJ, et al. Bivalirudin reduces the risk of transfusion-associated mortality in patients undergoing percutaneous coronary intervention. Abstract presented at: Cardiovascular Revascularization Therapies; March 28-31, 2005; Washington, DC.
39. Hebert PC, Wells G, Blajchman MA, et al. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. *N Engl J Med*. 1999;340:409-417. Erratum in: *N Engl J Med*. 1999;340:1056.