STATE-OF-THE-ART PAPER

Bleeding, Blood Transfusion, and Increased Mortality After Percutaneous Coronary Intervention

Implications for Contemporary Practice

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Advances in percutaneous coronary intervention (PCI) during the past decade have led to more widespread use of these procedures in older and sicker patients. Refinement of periprocedural antithrombotic therapy has played a particularly important role in reducing ischemic complications to very low levels in routine practice. Although the use of more powerful antiplatelet agents has been associated with increased risk of bleeding (especially among the elderly and patients with serious comorbidities), such complications have traditionally been viewed as benign in nature. Recent studies, however, have identified major bleeding after PCI as an important predictor of increased mortality. Whether this relationship between bleeding and risk of death is cause-and-effect, or merely an association based on shared risk factors, remains unclear. In this review, we examine the basis for a possible causal link between post-PCI bleeding and subsequent mortality. Possible mechanisms underpinning such a link are discussed, including a potential adverse role for blood transfusion in this setting. A framework for further clinical evaluation of this issue is presented.   (J Am Coll Cardiol 2009;53:2019–27)
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Recent studies have linked major bleeding after percutaneous coronary intervention (PCI) with increased mortality (1–8). The nature of this relationship, however, and its implications for clinical practice remain unclear. It is possible that bleeding may simply be a surrogate for high-risk patients, because those patients at increased risk for bleeding complications (such as the elderly) are also at increased risk of death after PCI (9). It is also possible that bleeding may be an important, but until now overlooked, cause of excess mortality. Support for this hypothesis is provided by accumulating mechanistic data that implicates direct and indirect effects of bleeding on subsequent adverse events (10,11). Growing suspicion also has focused on potentially harmful effects of red blood cell (RBC) transfusion (1,5,6,12,13).

The unraveling this complex relationship among bleeding, blood transfusion, and excess mortality is not merely of academic interest. In current practice, the risk for major bleeding is dependent not only on patient characteristics (6) but also to a large extent on choice of vascular access strategy (radial vs. femoral) (14), and to a lesser extent on the choice of an antithrombotic regimen (4,15). Physician preference in these matters may be heavily influenced by the perception

of bleeding as a nuisance complication, rather than a life-threatening one. Furthermore, the inclusion of bleeding as a part of the primary end point in some recent PCI trials is a significant development, drawing equivalence between this complication and other major adverse events (such as periprocedural myocardial infarction) in the evaluation of novel therapeutics (3,15). The validity of this approach that combines efficacy and safety end points is debated (16). In this review, we examine the evidence supporting a causal link between major bleeding and excess mortality in patients undergoing PCI, consider the implications of these data for contemporary clinical practice, and propose a framework for further evaluation of this controversial issue.

Impact of Major Bleeding and Blood Transfusion on Mortality After PCI

Studies that have examined the impact of major bleeding on mortality among patients undergoing PCI are summarized in Table 1. Data from more than 90,000 patients are now available, derived from a combination of unselected "real-world" cohorts (1,5–8) and randomized trial populations (2–4). Although bleeding definitions and patient characteristics varied, a consistent finding of increased mortality among patients who experience major bleeding has emerged.

The first study to address this question revealed markedly increased mortality among unselected patients with major bleeding (7.5% in-hospital mortality vs. 0.6% for patients with

no bleeding; p < 0.001) (1). After adjustment for differences in patient characteristics, major bleeding was associated with an odds ratio of 3.5 for in-hospital mortality (p < 0.0001) (1). Data from the REPLACE-2 (Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events) trial (comparing bivalirudin with unfractionated heparin plus glycoprotein IIb/IIIa inhibitors in patients undergoing PCI) extended these findings by associating major bleeding with an adjusted odds ratio of 3.53 for 1-year mortality (2). Of note, this hazard was greater than that observed between in-hospital myocardial infarction (MI) and 1-year mortality.

Similar findings have been published by other investigators (3–5,7). In these analyses, both access site and remote (e.g., intracranial) bleeding events were grouped together in the definition of major bleeding. This has led to some ambiguity regarding the importance of access-related bleeding. Hemorrhage at sites such as the intracranial space or the gastrointestinal tract are well recognized as potentially fatal events. Femoral bleeding complications have, in contrast, traditionally been viewed as benign and, as a result, there has been little impetus to consider more widespread use of the radial approach as part of a strategy to reduce overall rates of fatal bleeding complications.

However, the authors of an analysis of 17,901 patients who underwent PCI between 1995 and 2006 found that major femoral bleeding complications (including major hematoma, external bleeding, and retroperitoneal bleeding) also were associated with decreased long-term survival, driven by a marked increase in 30-day mortality (6). This association persisted after correction for multiple predictors of PCI-related mortality, with a 30-day adjusted hazard ratio of 9.96 (95% confidence interval: 6.94 to 14.3, p < 0.001) (6). Similar findings have been

published by Yatskar et al. (8), suggesting that major femoral bleeding should not be dismissed as a trivial complication of PCI.

Emerging evidence suggests that transfusion may be associated with risks over and above usual concerns regarding microbial transmission and acute antigen-antibody reactions (17). A number of studies have examined the impact of RBC transfusion on long-term outcomes after PCI. The findings are summarized in Table 2. Among high-risk patients with anemia (12) or severe bleeding (5), blood transfusion was required in >20% and was associated with increased in-hospital mortality (adjusted odds ratio: 2.02, p < 0.001) (12) and increased 1-year mortality (relative risk: 2.03, p = 0.028) (5). Among unselected patients blood transfusion was required in approximately 5% and was independently associated with increased mortality (1,6). A case-control study of 146 transfused patients versus 292 nontransfused patients with major bleeding found an independent association between blood transfusion and increased 1-year mortality (relative risk: 2.42, p = 0.0045) (5).

Collectively, these studies demonstrate a robust association among major bleeding, blood transfusion, and increased mortality in patients undergoing PCI and are in keeping with reports of decreased survival among patients with acute coronary syndromes who experience major bleeding (10) or require blood transfusion (18,19). It is important to emphasize, however, that none of these studies can establish a causal connection between bleeding events (or blood transfusion) and increased risk of death after PCI. Although the relationship between bleeding and mortality is described in several studies as an independent one, many of the correlates of bleeding (such as advanced age and renal failure) are themselves associated with mortality. No amount of statistical adjustment can provide certainty of a cause-and-effect relationship when there is this degree of correlation (16). As a result, resolving the question of association versus causality has been a tremendous challenge, but emerging mechanistic data have begun to enlighten the debate.

Table 1	Studies of the Impact of Major Bleeding on Mortality After PCI						
Author/Study (Ref. #)	Patients (n)	Patient Population	STEMI Included?	Definition	Frequency of Blood Transfusion (%)	Impact of Bleeding on Mortality [95% Confidence Interval]	p Value
Kinnaird et al. (1)	10,974	Unselected	Yes	TIMI	5.4	30-day adjusted OR: 3.5 [1.9–6.7]	<0.0001
REPLACE-2 (2)	6,001	Elective and 'urgent' PCI	No	Protocol†	3.2	1-year adjusted OR: 2.66 [1.44–4.92]	0.002
Ndrepepa et al. (3)	5,348	Elective, ACS	No	TIMI	4.0	1-year adjusted HR: 2.96 [1.96–4.48]	<0.0001
ACUITY (4)	13,819	ACS only	No	Protocol†	4.7	30-day OR: 7.55 [4.68–12.18]	<0.0001
Kim et al. (5)	6,799	Unselected	Yes	Protocol†	8.0	1-year RR: 2.03 (transfused patients)	0.0028
Doyle et al. (6)	17,901	Unselected	Yes	Protocol†	4.8	30-day adjusted HR: 9.96 [6.94–14.3]	<0.0001
GRACE registry (7)*	24,045	ACS	Yes	Protocol†	3.9	In-hospital adjusted OR: 1.64 [1.18–2.28]	<0.0001
Yatskar et al. (8)	6,656	Unselected	Yes	Protocol†	1.8	In-hospital adjusted OR: 3.59 [1.66–7.77]	0.001
						1-year adjusted HR: 1.65 [1.01–2.70]	0.048

*31% of patients in the GRACE (Global Registry of Acute Coronary Events) registry (7) underwent PCI. †Protocol definitions of major bleeding varied between these studies (8). Note: Doyle et al. (6) studied femoral bleeding complications only; Yatskar et al. (8) studied hematoma requiring blood transfusion only.

ACUITY = Acute Catheterization and Urgent Intervention Triage strategY; HR = hazard ratio; OR = odds ratio; PCI = percutaneous coronary intervention; REPLACE = Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events; RR = relative risk; STEMI = ST-segment elevation myocardial infarction; TIMI = Thrombolysis In Myocardial Infarction.

Table 2	Studies of the Impact of Blood Transfusion on Mortality After PCI					
Author (Ref. #)	Patients (n)	Patient Population	STEMI Included?	Frequency of Blood Transfusion (%)	Impact of Transfusion on Mortality [95% Confidence Interval]	p Value
Jani et al. (12)	4,623	Anemic patients with MI	Yes	22.3	In-hospital, adjusted OR: 2.02 [1.47–2.79]	<0.0001
Doyle et al. (6)	17,901	Unselected	Yes	6.8	30 days, 1–2 U adjusted HR: 8.9 [6.3–12.6]	<0.0001
					3+ U adjusted HR: 18.1 [13.7–24]	<0.0001
Kinnaird et al. (1)	10,974	Unselected	Yes	5.4	1 year, OR per unit transfused: 1.47 [1.36–1.55]	<0.0001
Kim et al. (5)*	567*	Severe bleeding	Yes	25.7	1 year, RR: 2.03	0.0028
Chase et al. (13)	38,872	Unselected	Yes	3.5	30-day adjusted OR: 4.01 [3.08–5.22]	<0.0001
					1-year adjusted OR: 3.58 [2.94–4.36]	<0.0001

*A subgroup (n = 567) of the overall cohort (n = 6,799) that had "severe" bleeding was studied in this analysis.

MI = myocardial infarction; other abbreviations as in Table 1.

Mechanisms Linking Bleeding With Excess Mortality

The biological impact of bleeding after PCI is likely to be multifaceted (Fig. 1). The location (intracranial) or torrential nature of the hemorrhage (gastrointestinal, retroperitoneal) may result in death, regardless of any previous cardiac procedure. However, other consequences of bleeding may have specific detrimental effects in patients who have recently undergone coronary intervention and may offer an explanation for the association
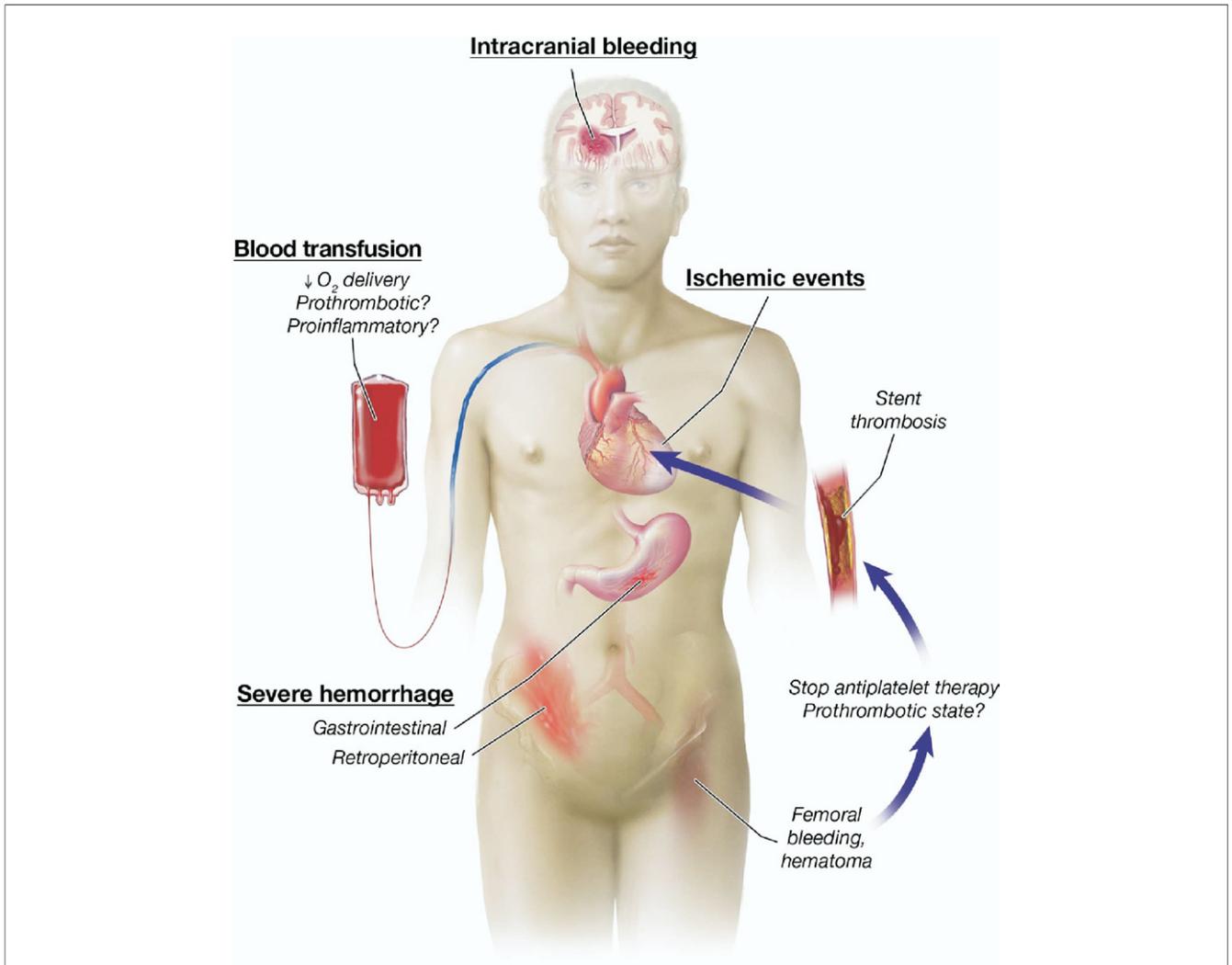

Intracranial bleeding

Blood transfusion
↓O₂ delivery
Prothrombotic?
Proinflammatory?

Ischemic events

Stent
thrombosis

Severe hemorrhage
Gastrointestinal
Retroperitoneal

Stop antiplatelet therapy
Prothrombotic state?

Femoral
bleeding,
hematoma

Figure 1	Possible Mechanisms Linking Post-Percutaneous Coronary Intervention Bleeding With Increased Mortality

Figure provided by the Mayo Clinic ©2008.

between femoral bleeding complications and mortality that is more difficult to comprehend.

Interactions between activated platelets and the clotting cascade produce a rapid hemostatic response at the site of vascular injury. Systemic amplification of this localized response is prevented by a number of mechanisms, including control of the activated procoagulants and platelets by antithrombotic pathways (20). These antithrombotic pathways are predominantly active within vascular endothelial cells (20), but little is known about the function of these pathways in patients with cardiovascular disease. Deficiency of such antithrombotic protective mechanisms (in tandem with systemic endothelial dysfunction) could lead to a hypercoagulable state induced by bleeding, which would pose obvious risks to the patient who had recently undergone PCI.

Furthermore, experimental data suggest that increased synthesis and release of erythropoietin in response to anemia caused by bleeding might sustain a systemic prothrombotic state beyond the acute phase, by causing platelet activation and inducing plasminogen activator inhibitor-1 (a procoagulant cytokine) (21,22). Treatment with erythropoietin has been associated with increased risk of thrombosis in critical care patients (23). Finally, aspirin, clopidogrel, or other antithrombotic medication may have to be discontinued after a major bleeding event, thus increasing the risk for stent thrombosis, a complication that frequently is fatal (24–26).

The significance of these issues in everyday clinical practice is difficult to quantify, but recent data have confirmed an increased risk of acute ischemic events after major bleeding suggesting that the hypothetical concerns described previously may be justified (10). Definitively resolving the issue of causality will be a significant challenge. Although it is impossible to randomly allocate patients to bleeding, a randomized comparison of transradial versus transfemoral PCI with mortality as a primary end point may be a clinically relevant way to address the issue. Many small
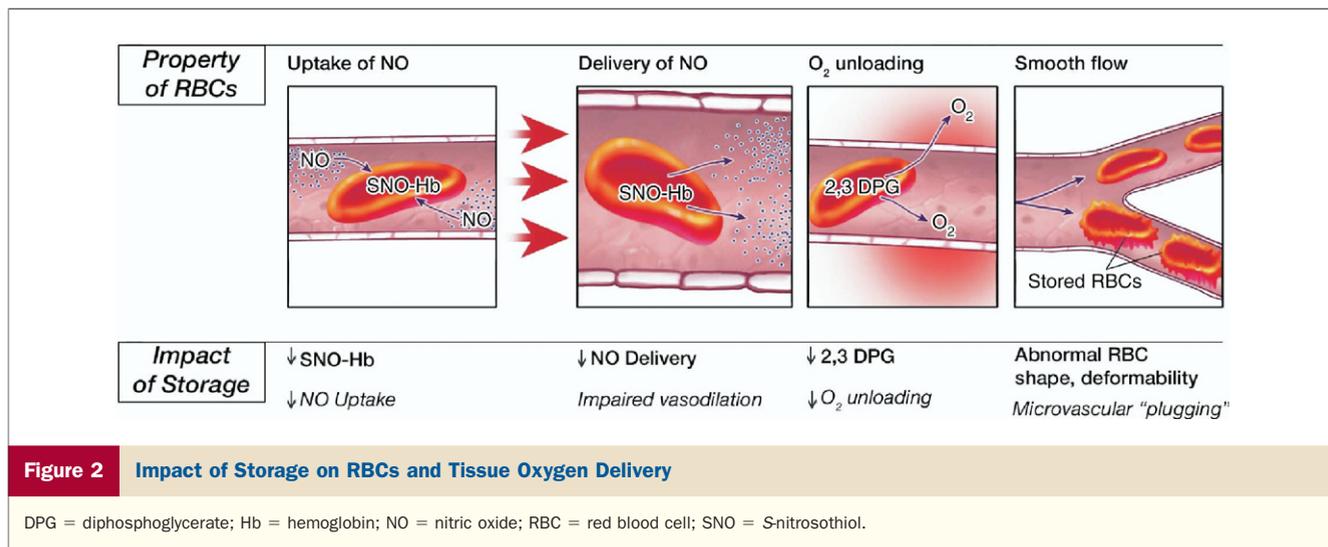
studies comparing these access strategies have already been published and presented (14), but there are multiple confounding factors that make interpretation difficult. It is possible that patients selected for a radial approach may be very different in terms of baseline demographics and risk profiles that are hard to adjust for. The publication of data from recent randomized PCI trials analyzing outcomes among subgroups of patients treated using a radial versus femoral approach are eagerly awaited and may provide the platform for a dedicated access strategy trial with mortality as a primary end point.

Mechanisms Linking Blood Transfusion With Excess Mortality

Impairment of oxygen delivery. Increasing hemoglobin level via transfusion increases oxygen delivery (27–29), but measures of tissue oxygenation either decrease or do not change (27,28,30,31). The reason for this paradox (greater oxygen delivery but no increase in tissue use) is unclear (18).

Stored RBCs are low in 2,3-diphosphoglyceric acid (2,3-DPG); therefore, the hemoglobin has high oxygen affinity (i.e., will tend not to release oxygen to the tissues). Traditionally, this finding been regarded as the pre-eminent mechanism underlying reduced tissue extraction of oxygen from the circulation after blood transfusion (32). However, 2,3-DPG levels partially recover within several hours after transfusion, and the results of experimental studies now indicate that the physiologic impact of 2,3-DPG depletion may have been overstated (33–35). Recent data suggest that other structural and biochemical changes that occur in RBCs during storage might have a greater impact on their function in vivo (Fig. 2).

Normally, erythrocytes have a flexible membrane and can reversibly alter their biconcave, discoid shape, thus allowing them to pass through capillaries smaller in diameter (2 to 6 μm) than RBCs (± 8 μm). This property of red cells also acts as an in vivo quality control marker, whereby older, less

Figure 2   **Impact of Storage on RBCs and Tissue Oxygen Delivery**

DPG = diphosphoglycerate; Hb = hemoglobin; NO = nitric oxide; RBC = red blood cell; SNO = S-nitrosothiol.

compliant cells are filtered in the spleen and cleared by phagocytosis from the circulation (36). During storage, there is a significant decrease in the deformability of RBCs. Other hemorheological alterations also have been documented, such as changes in RBC shape, decreased surface/volume ratio, increased mean hemoglobin concentration and osmotic fragility, increased aggregability, and intracellular viscosity (36–38). Together, these factors may predispose to "plugging" of transfused cells at the microvascular level, leading to tissue ischemia. It is reasonable to assume that vascular beds already compromised by microvascular dysfunction or obstruction (such as acutely infarcted myocardium) may be particularly vulnerable in this respect.

Interest also has focused on the transport of nitric oxide (NO) by RBCs. Nitric oxide produced by the vascular endothelium may be bound by erythrocytes in protected form as an *S*-nitrosothiol (SNO) on the highly conserved hemoglobin β-93 Cys residue (39,40). Upon release of oxygen, SNO-hemoglobin may dispense NO bioactivity to microvascular cells, physiologically coupling hemoglobin deoxygenation to vasodilation (39). This elegant mechanism facilitates increases in regional blood flow in zones of hypoxia and, intriguingly, may enable NO bioactivity to be imported from a healthy vascular bed to one that is compromised by endothelial dysfunction (as would pertain in the coronary circulation of patients undergoing PCI).

Recent data indicate that this biochemical function is significantly disrupted by storage of RBCs, with a rapid decrease in SNO-hemoglobin concentrations to 30% of initial levels observed within 1 day of storage (<20% within 1 week) (41). It is important to note that it takes 48 h from the time of donation to complete the required testing and preparation of a unit of RBCs for transfusion. Hypoxic vasodilation by banked RBCs correlated strongly with the amount of SNO-hemoglobin, underscoring the physiologic significance of the findings (41).

Prothrombotic effects. The transfusion of blood products has been associated with an acute platelet release of CD40 ligand (42). Transfusion also is associated with increased exposure to another procoagulant protein, plasminogen activator inhibitor (PAI)-1. There is a 3- to 6-fold increase in PAI-1 content of packed RBCs stored for greater than 35 days (43), and serum levels of PAI-1 increase after allogeneic blood transfusion (44). Adenosine diphosphate, a well-recognized mediator of platelet activation, might also participate in transfusion-related vascular thrombosis. Adenosine diphosphate is released from activated platelets and damaged endothelial cells and is also released by erythrocytes in stored blood (42). Finally, free NO acts not only as a potent vasodilator but also as an inhibitor of platelet activation (42). Deficiencies of NO transport and release by stored RBCs may therefore not only impact adversely on regional blood flow in zones of hypoxia but also on risk for thrombosis at sites of endothelial dysfunction.

Other adverse effects of blood transfusion. Transfusion-related immunomodulation (TRIM) is an immunosuppressive, or in some cases proinflammatory, effect of blood transfusion that may contribute to adverse outcomes among recipients of blood (42,45). The proposed mechanism for TRIM is induced alterations of endogenous cytokine levels in the recipient that participate in protective inflammatory responses to pathogens. Infusion of bioactive substances such as histamines, cytokines, lipids, microparticles (cell membrane fragments), and HLA class 1 antigens that accumulate in blood during storage may play a role (45). Such derangement of the immune system may predispose to infections and, driven by augmented humoral responses, acute lung injury.

The specific effects of this phenomenon on plaque biology, thrombosis, and microvascular function are as yet undefined, but given the inflammatory nature of atherosclerosis, the potential for such interplay is of obvious concern. Finally, severe hemolytic reactions and the consequences of large-volume transfusion (such as coagulopathy and electrolyte disturbance) also may increase mortality associated with blood transfusion (46), although these effects are not specific to the post-PCI population.

Duration of storage of transfused blood. Many of the aforementioned concerns ultimately appear to hinge upon the duration that blood is kept in storage before use. The Food and Drug Administration allows packed red cells to be stored for up to 42 days, allowing blood centers the flexibility to manage this scarce resource but also influencing the quality of blood that is transfused. Whether clinical outcomes are adversely affected by longer storage, however, is still uncertain.

In a recent study by Koch et al. (47), patients undergoing cardiac surgery who received older (>14 days) blood had greater in-hospital mortality than patients receiving newer blood (2.8% vs. 1.7%, p = 0.004). Patients who were given older blood were also at greater risk for a composite outcome of multiple serious adverse events (such as prolonged ventilatory support, renal failure, sepsis, or multiorgan failure). At 1 year, mortality remained significantly lower in patients given newer blood (7.4% vs. 11.0%, p < 0.001). The results of previous studies evaluating the effect of storage duration on outcomes have been contradictory (47), possibly relating to small sample size and methodological limitations. The sample size in the study by Koch et al. (47) was large and, notably, the analysis was restricted to patients given only newer blood or only older blood, enabling the effect of duration of storage on outcomes to be better characterized. Limitations of the study include potentially important differences in baseline characteristics between the 2 groups (including worse left ventricular systolic function and greater prevalence of peripheral vascular disease in the "old-blood" group). Furthermore, no attempt was made to correct for type of transfusion or use of additional blood products; transfusion of unmatched blood and use of fresh-frozen plasma or platelets may identify a

population at greater risk for bad outcomes that may not relate to the RBC transfusion. Nevertheless, the results of the study raise the possibility of clinically meaningful harm associated with transfusion of blood that has been stored for longer than 14 days.

No data are available currently regarding the impact of storage duration on outcomes for patients who require transfusion after PCI. There are, however, reasonable grounds for concern that administration of blood that has been stored for longer than 14 days also may be associated with worse outcomes for PCI patients, given the similarities in clinical characteristics with cardiac surgery patients. Indeed, SNO-hemoglobin levels (and their physiologic correlate RBC-dependent vasodilation) become depressed within days of collection (41), suggesting that even "fresh" blood may have developed adverse biological characteristics that may have clinical relevance.

Implications for clinical practice. The concerns outlined herein should not lead clinicians to withhold blood transfusion when it is clearly indicated (i.e., severe anemia causing symptoms or other evidence of ischemia, especially for patients who exhibit signs of oxygen-supply dependency) (48–50). Efforts to reduce the impact of bleeding complications on the PCI population should rather focus on: 1) the identification of measures to decrease the incidence of bleeding complications without increasing risk for ischemic events; and 2) the development of strategies for more targeted and safer use of blood transfusion.

Reducing bleeding complications. A prognostic risk score for major bleeding in patients undergoing PCI via the femoral approach has been published, allowing the identification of high-risk patients before the procedure (51). Seven variables were proposed based on an analysis of bleeding events from the REPLACE-2 trial: age >55 years, female sex, estimated glomerular filtration rate <60 ml/min/1.73 m^2, pre-existing anemia, use of low-molecular-weight heparin within 48 h before PCI, use of glycoprotein IIb/IIIa inhibitors, and the use of the intra-aortic balloon pump (51). Weighting for each was assigned by the use of different integer scores, with a total score of >10 associated with a major bleeding risk of >5%. Although this risk-scoring system remains to be validated in real-world cohorts, such a tool may help inform decisions regarding initial management strategy (for patients with borderline indications for PCI) and enable the interventionalist to tailor the strategic approach according to bleeding risk for those who do proceed with intervention.

The single most effective way for the operator to reduce major bleeding is to use radial rather than femoral access (14). A systematic review of randomized trials revealed an odds ratio of 0.20 (95% confidence interval: 0.09 to 0.42; p < 0.0001) for access-site complications after radial rather than femoral PCI (14). Furthermore, in a retrospective study of almost 39,000 procedures, transradial PCI was associated with one-half the number of bleeding complications, markedly reduced transfusion

requirements, and lower adjusted 30-day and 1-year mortality (p < 0.001) (13).

Selection bias could certainly account for the finding of decreased mortality, as it seems likely that the most complex cases requiring large devices and hemodynamic support would have been performed from the femoral route. However, it is possible that decreased bleeding complications (and transfusion requirements) also could have contributed, at least in part, to the finding of lower mortality among patients treated via the radial artery. It is important to emphasize that there are no published randomized data to indicate that use of the radial approach is associated with lower mortality when compared with a femoral approach. When femoral access is chosen, the routine use of fluoroscopy (52) (and perhaps ultrasound) to guide puncture may reduce the incidence of serious complications. Although vascular closure devices have so far failed to reduce bleeding complications (53), it is hoped that further evolution of this technology may ultimately achieve this goal.

The selection of periprocedural antithrombotic therapy also may influence bleeding risk, with debate focusing mainly on the choice between bivalirudin and the combination of heparin with a glycoprotein IIb/IIIa receptor blocker. Although bivalirudin reduces major bleeding in elective and urgent PCI (15), as well as non–ST-segment elevation acute coronary syndromes (4), some questions have remained regarding its efficacy in preventing ischemic complications (54). Although there was an excess of ischemic events among patients treated with bivalirudin, use of a pre-defined 25% margin for noninferiority combined with use of a quadruple end point that included major bleeding events resulted in no statistically significant difference between the 2 treatment groups (4,15).

Both the size of the noninferiority margin and use of major bleeding in the combined end point would tend to bias the results in favor of bivalirudin. Interestingly, patients who were pre-treated with clopidogrel and subsequently received bivalirudin in the catheterization laboratory exhibited no excess of ischemic events but did maintain lower rates of major bleeding (4). The results of the recent ISAR-REACT 3 (Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment 3) trial confirm a reduction in major bleeding with bivalirudin but no overall impact on mortality (among patients undergoing PCI who had not presented with MI) or on the combined end point of death, MI, or target lesion revascularization (55). In this study the quadruple end point, which included major bleeding, also was nonsignificant, with the favorable effect of bivalirudin on bleeding seemingly counterbalanced by a small excess of ischemic events (55).

Data from the HORIZONS-AMI (Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction) study of patients with ST-segment elevation MI undergoing primary PCI has further enlivened the debate, whereby reduced bleeding was associated with

lower all-cause 30-day mortality in patients treated with bivalirudin (56). The publication of long-term follow-up from this cohort is eagerly awaited. Although the weight of evidence would suggest that bivalirudin is a reasonable choice for routine use in the catheterization laboratory, it appears that this agent may ultimately prove most useful for patients at increased risk of major bleeding complications.

Refinements in the use of blood transfusion. In addition to reducing the incidence of major bleeding complications, refinements in the use of blood transfusion may lead to better outcomes for patients undergoing PCI. Appropriate indications for transfusion after PCI have not yet been defined, specifically with regard to the hemoglobin level above which the risks of transfusion might outweigh any benefit. Among patients with critical illness, a randomized trial has demonstrated that those treated with the use of a restrictive transfusion policy had better outcomes (when compared with a more liberal transfusion policy) (57), although older patients with cardiac disease were highlighted as a specific group to whom the findings might not be applicable (50).

The situation is likely to be even more complex among patients undergoing PCI, because factors such as clinical presentation and completeness of revascularization will probably alter the risk/benefit ratio for transfusion. For example, observational data suggest that a more liberal approach to blood transfusion in the setting of acute MI may be beneficial, although how this strategy interacts with the approach to revascularization is not entirely clear (48). (Might early and complete revascularization offset the theoretical need to increase oxygen-carrying capacity through blood transfusion?)

Pre-emptively targeting patients with anemia may be another way to reduce transfusion requirements after PCI. Baseline anemia is associated with increased need for blood transfusion and greater mortality after PCI (58,59). Aggressive strategies to increase hemoglobin levels with the use of iron repletion, erythropoietin, or other disease-specific measures would probably reduce the need for transfusion by providing a greater window of tolerance for bleeding. It is reasonable to assume that such an approach could also improve tolerance of myocardial ischemia during long, complex cases. Although the value of postponing elective PCI to treat anemia has not yet been tested, given the frequency of this finding in routine clinical practice such a study would clearly be of tremendous interest.

There are ongoing efforts to improve the quality of transfused blood through refined harvest and storage techniques. For example, decreased deformability of stored RBCs may be ameliorated by correction of intracellular pH and restoration of adenosine triphosphate levels (36,60). Repletion of SNO-Hb levels during storage improved the vasodilatory function of RBCs in vivo (41). Reduction of the white blood cell content of stored blood (leukodepletion) also may contribute to improvements in RBC function and decrease the content of cytokines and inflammatory mediators in stored blood (61–64). The immune response to TRIM is attenuated by leukodepletion of blood products before transfusion, suggesting that either a component or byproduct of donor leukocytes elicits the recipient response (65).

The age of RBCs at the time of collection might also affect the impact of storage time on RBCs. In normal circumstances, erythrocytes have a lifespan of approximately 120 days. It would be expected therefore that a unit of blood would contain a proportion of cells that are approaching the end of their lifespan and may be more prone to storage-induced changes than younger cells. In support of this hypothesis, Sparrow et al. (66) separated old and young RBCs before storage and reported differences in the cell-surface expression of cell adhesion molecules and glycophorin A. With a growing understanding of storage-related hazards and the development of assays to measure these, it appears likely that quality criteria for RBCs will expand in the future to include functional biochemical properties in addition to current regulations based on hemolysis and hemoglobin mass (36).

On the basis of current data, it is our view that use of arbitrary cutoffs (such as a hemoglobin of <8 g/dl) to trigger transfusion after PCI should be avoided in most circumstances. Risks and potential benefits of transfusion should be weighed on clinical grounds. Among patients with low hemoglobin who exhibit evidence of ischemia despite successful revascularization, there is clear potential for blood transfusion to have a net beneficial effect. When there is clearly no evidence of ongoing ischemia, and therefore minimal potential gain, adverse effects of transfusion may be more likely to predominate (an exception to this may be the asymptomatic patient who is considered at very high risk for rebleeding from a noncompressible site, where a greater reserve of red cell mass may be desirable).

The design of a randomized trial to define the optimal use of blood transfusion for patients with bleeding after PCI would be quite complicated. Most would consider it unethical to withhold transfusion from a patient with low hemoglobin who exhibits clear evidence of ischemia. A study of transfusion versus no transfusion for post-PCI bleeding among patients who are asymptomatic, however, should not present any ethical difficulties and would certainly be of interest. The arbitrary hemoglobin threshold for enrollment would need to be set quite low (certainly <8 g/dl) to allow any potential therapeutic effect of transfusion to emerge. Recruitment of sufficient patients to complete such a trial would be a challenge, but should be possible using a multicenter collaborative approach.

Conclusions

Accumulating clinical and experimental data establish a strong association between major bleeding, blood transfusion, and the risk of death after PCI. It remains to be proven, however, that strategies to reduce bleeding and/or

blood transfusion will consistently lower all cause mortality. In addition, despite frequent use of blood transfusions in patients undergoing PCI, important questions regarding appropriate transfusion thresholds and the importance of the age of stored blood remain unanswered. These issues need to be addressed as a priority by adequately powered studies.

Acknowledgment

The authors thank Mike King for his tremendous work on the illustrations for this paper.

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Key Words: bleeding ▪ blood transfusion ▪ percutaneous intervention.