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Periprocedural Bleeding and 1-Year Outcome After Percutaneous Coronary Interventions

Appropriateness of Including Bleeding as a Component of a Quadruple End Point

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Objectives The aim of the study was to investigate the relationship between bleeding within the 30 days after percutaneous coronary interventions (PCI) and 1-year mortality and to assess the appropriateness of inclusion of the periprocedural bleeding in a quadruple composite end point to assess PCI outcome.

Background Periprocedural bleeding is one of the most frequent complications of PCI.

Methods This study included 5,384 patients from 4 randomized placebo-controlled trials on the value of abciximab after pre-treatment with 600 mg of clopidogrel: ISAR-REACT, -SWEET, -SMART-2, and –REACT-2. Bleeding—defined according to the Thrombolysis In Myocardial Infarction criteria—included all bleeding events within 30 days after enrollment. The primary end point was 1-year mortality.

Results In the 4 trials, within the first 30 days there were 42 deaths (0.8%), 314 myocardial infarctions (MIs) (5.8%), 52 urgent revascularizations (1.0%), and 215 bleeding complications (4.0%). Mortality at 1 year was 3.6% (n = 197). A Cox proportional hazards model revealed that the 30-day occurrence of bleeding (hazard ratio [HR] 2.96, 95% confidence interval [CI] 1.96 to 4.48; $p < 0.001$), MI (HR 2.29, 95% CI 1.52 to 3.46; $p < 0.001$) and urgent revascularization (HR 2.49, 95% CI 1.16 to 5.35; $p = 0.019$) independently predicted 1-year mortality. The *c* statistic was 0.79 for bleeding, 0.78 for MI, and 0.78 for urgent revascularization, demonstrating a comparable discriminatory power of these adverse events for predicting 1-year mortality.

Conclusions Our study demonstrates a strong relationship between the 30-day frequency of bleeding and 1-year mortality after PCI and supports the inclusion of periprocedural bleeding in a 30-day quadruple end point for the assessment of outcome after PCI. (J Am Coll Cardiol 2008;51:690–7) © 2008 by the American College of Cardiology Foundation

The selection of proper end points is critical for the assessment of the efficacy and safety of drugs or interventional procedures (1). It is unanimously accepted that mortality is the most important measure of clinical outcome.

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However, in present-day interventional cardiology, total mortality has become a relatively rare event, and large numbers of patients would be required to assess the impact of an investigational therapy on mortality. Inevitably, trials with mortality as a primary end point will take longer to complete, which might delay treatment benefits to patients, and the regimen under consideration might become outdated during ongoing study, owing to potential surfacing of newly developed drugs and/or devices. Accordingly, composite end points that include not only mortality but also other adverse events that occur more frequently are used to assess the safety and efficacy of novel percutaneous coronary intervention (PCI) therapies. The choice of which nonfatal events to include in a composite end point is usually predicated on the assumption that the nonfatal adverse events are themselves associated with an increased risk of death (2). Traditionally, the composite end point of efficacy used to assess PCI procedures is the combined incidence of death, myocardial infarction (MI), and urgent repeat revascularization of the target vessel at 30 days (3–6). Recently a composite end point that includes 30-day incidence of

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death, MI, urgent revascularization, and major bleeding has been used. Termed a quadruple end point, because it includes 4 components rather than the 3 components traditionally included, this composite end point was used in the REPLACE-2 (Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events) trial to assess the outcome of patients undergoing a PCI procedure (7). A recent report from the REPLACE-2 trial has demonstrated that major hemorrhage is an independent predictor of 1-year mortality in patients undergoing elective or urgent PCI (8). Data on the predictive power of bleeding (including minor bleeding) compared with MI or urgent revascularization within 30 days after PCI, regarding 1-year mortality and the appropriateness of including bleeding in a 30-day composite primary end point for the assessment of PCI outcomes, have not previously been addressed.

The aim of the present study was to investigate the relationship between bleeding within 30 days after a PCI procedure and 1-year mortality and to assess the appropriateness of inclusion of the periprocedural bleeding in a quadruple primary composite end point to assess the PCI outcome.

Methods

The 4 trials included in this pooled analysis are the ISAR-REACT (Intracoronary Stenting and Antithrombotic Regimen-Rapid Early Action for Coronary Treatment) (9), the ISAR-SWEET (Intracoronary Stenting and Antithrombotic Regimen: Is Abciximab a Superior Way to Eliminate Elevated Thrombotic Risk in Diabetics) (10), the ISAR-SMART (Intracoronary Stenting to Abrogate Restenosis in Small Arteries)-2 (11), and the ISAR-REACT-2 (12). The 4 trials were performed between June 2000 and December 2005.

These trials were considered together because of similarities in the protocols regarding, among others, the antithrombotic regimens used and the use of PCI. The inclusion and exclusion criteria for the 4 trials have previously been published in full (9–12). Briefly, all 4 ISAR trials were randomized, placebo-controlled trials addressing whether an added benefit exists from the glycoprotein IIb/IIIa inhibitor abciximab in patients undergoing PCI after pretreatment with a 600-mg loading dose of clopidogrel. The inclusion criteria common to all 4 trials were the presence of coronary artery disease requiring a PCI procedure and treatment with 600 mg of clopidogrel at least 2 h before the coronary intervention. The ISAR-REACT trial recruited patients at low-to-intermediate risk who underwent elective PCI. The ISAR-SMART-2 assessed the anti-restenotic effect of phosphorylcholine-coated stents and abciximab in patients with small coronary artery disease (vessel size <2.5 mm). The ISAR-SWEET trial enrolled diabetic patients who underwent an elective PCI, and the ISAR-REACT-2 trial recruited high-risk patients with non–ST-segment elevation acute coronary syndromes with or without an elevated troponin T. Excluded from the studies were patients presenting with: an ST-segment elevation acute MI, hemodynamic instability, in-stent restenosis, malignancies, increased risk of bleeding (stroke within the previous 3 months, active bleeding or bleeding diathesis, recent trauma or major surgery in the last month, suspected aortic dissection), oral anticoagulation within 7 days, receipt of a glycoprotein IIb/IIIa inhibitor within 14 days, high blood pressure (≥180 mm Hg) unresponsive to therapy, a hemoglobin level <100 g/l or hematocrit <34% or platelet count <100 × 10^9/l or >600 × 10^9/l, known allergy to the study medication, pregnancy (present or suspected), and reduced left ventricular function with an ejection fraction <30%.

Abbreviations and Acronyms

CI = confidence interval
HR = hazard ratio
MI = myocardial infarction
OR = odds ratio
PCI = percutaneous coronary intervention

In all 4 trials, written informed consent was required for participation, and an institutional review board approved each study at all participating hospitals.

Study protocol(s). Patients were randomized after the decision to perform a PCI was made but before the guide wire had crossed the lesion in a double-blind manner with sealed opaque envelopes containing the block randomization sequence for each participating center. Patients in the abciximab group received a bolus of abciximab 0.25 mg/kg weight followed by an infusion of 0.125 μg/kg/min (a maximum of 10 μg/min) for 12 h and a 70-U/kg bolus of heparin intravenously. Patients in the placebo group received a bolus and a 12-h continuous infusion of placebo as well as a 140-U/kg bolus of intravenous heparin. Double-blinding was achieved by using similarly appearing vials in the 2 groups of all 4 trials. No patients in any of the 4 trials required unblinding, and there were no crossovers.

Postinterventional antithrombotic therapy consisted of aspirin 100 to 325 mg indefinitely and clopidogrel 75 mg twice daily for the remainder of the hospital stay up to 3 days, followed by a recommendation of 75 mg/day for at least 6 months. Other cardiac medications were prescribed at the discretion of the patient's physician. The local research coordinators collected the data and forwarded them to the data coordinating center. The quality of data collection was assessed by checking source documentation in random samples. Angiographic data were analyzed with the same Quantitative Angiographic Core Laboratory.

End points, definitions, and follow-up. The primary end point of this analysis was 1-year mortality. The frequency of major and minor bleeding both during the first 30 days was defined with the Thrombolysis In Myocardial Infarction (TIMI) criteria (13). A bleeding complication was defined as major if it was intracranial or if clinically overt signs of hemorrhage were associated with a drop in hemoglobin concentration of more than 5.0 g/dl (or, when a hemoglobin value was not available, an absolute drop in the hematocrit of at least 15%). Minor bleeding was defined as a clinically

overt hemorrhage (including that seen on imaging) associated with a fall in hemoglobin concentration of 3.0 to 5.0 g/dl (or, when a hemoglobin value was not available, a fall in the hematocrit of 9 percentage points to <15 percentage points). A diagnosis of MI was based on the development of new abnormal Q waves in >2 contiguous precordial or >2 adjacent limb leads or an elevation of creatine kinase-myocardial band (CK-MB) (or total CK if CK-MB was not available) >3 times the upper limit of normal. If the pre-PCI CK-MB (or total CK) was higher than the upper limit of normal, both an increase by at least 50% over the previous value and documentation that CK-MB (or total CK) had been decreasing before the suspected MI was necessary. If falling enzyme levels were not documented before the procedure, recurrent anginal symptoms or new electrocardiographic changes compatible with MI and a CK-MB elevation >50% above the peak level before randomization for patients was required. In patients undergoing coronary bypass surgery, a CK-MB >10 times the upper limit of normal for patients was required to make a diagnosis of procedural MI. Target vessel revascularization was defined as coronary bypass surgery or repeat PCI involving the target vessel performed in the presence of symptoms or signs of myocardial ischemia. All events were adjudicated and classified by an adjudication committee blinded to the assigned treatment.

All patients were either seen by their physician or interviewed by phone at 30 days, 6 months, and 1 year after the procedure; patients with cardiac complaints underwent a complete clinical, electrocardiographic, and laboratory check-up.

Statistical analysis. The data are presented as median [25th, 75th percentiles] or as counts. The normality of distribution was assessed with the 1-sample Kolmogorov-Smirnov test. Continuous data were compared with the Wilcoxon rank-sum test. Categorical data were compared with the chi-square test. One-year survival was estimated by applying the Kaplan-Meier method and log-rank test, which allowed the calculation of odds ratios (ORs) (95% confidence intervals [CIs]) associated with the 30-day occurrence of MI, urgent revascularization, or bleeding. The Cox proportional hazards model was used to test the association between bleeding, MI, and urgent revascularization rates within 30 days after the PCI and 1-year mortality while adjusting for other confounding variables including age, gender, diabetes, arterial hypertension, hypercholesterolemia, smoking, prior MI, prior coronary artery bypass surgery, multivessel disease, duration of pre-treatment with clopidogrel, elevated troponin (elevated or not), lesion complexity, left ventricular ejection fraction, baseline creatinine, and abciximab therapy. Sensitivity, specificity, and accuracy with respect to 1-year mortality were calculated for MI, urgent revascularization, and bleeding within 30 days and compared by the McNemar test. Discriminatory power of the model with MI, urgent revascularization, or bleeding within 30 days included for 1-year mortality was assessed by the *c* statistic (a *c* statistic of 0.5 indicates random prediction, whereas a *c* of 1.0 indicates a perfectly discriminating model). All analyses were performed with the S-PLUS statistical package (Insightful Corp., Seattle, Washington). A p value <0.05 was considered to indicate statistical significance.

Results

Baseline characteristics. A total of 5,384 patients from 4 ISAR trials were included in this study. There were 197 deaths (3.6%) within the first year after PCI. Table 1 shows the baseline characteristics of patients who survived the first year after the PCI procedure and those who died during this period. Patients who died had a worse cardiovascular risk profile than patients who survived the first year after the PCI procedure (Table 1), as would be expected. The 12-h infusion of abciximab was prematurely discontinued in 3 patients in the group of nonsurvivors (1.5%) and in 53 patients in the group of survivors (1.0%), p = 0.50. Clopidogrel was prematurely discontinued within 30 days in 2 patients in the group of nonsurvivors (1.0 %) and in 25 patients in the group of survivors (0.5%); p = 0.30.

Relationship between individual components of the primary composite end point and 1-year mortality. At 30 days, the frequency of individual components of the primary composite end point was as follows: death in 42 patients (0.8%), MI in 314 patients (5.8%), urgent revascularization in 52 patients (1.0%), and bleeding in 215 patients (4.0%). Table 2 reveals the frequency of MI, urgent revascularization, and bleeding within 30 days in patients who did or did not survive the first year. Stroke occurred in 11 patients among 1-year survivors (0.2%) and 2 patients (1.0%) among nonsurvivors (p = 0.024).

The 1-year Kaplan-Meier estimate of mortality was 11.3% (n = 35) among patients with an MI in the first 30 days after enrollment versus 3.2% (n = 162) among patients without an MI within 30 days after PCI (OR 3.72, 95% CI 2.64 to 5.22, p < 0.001) (Fig. 1). There were 38 patients with Q-wave MI and 276 patients with non–Q-wave MI. In patients with Q-wave MI, the 1-year estimate of mortality was 29.0% (n = 11) versus 3.2% (n = 162) in patients without any MI (OR 11.93, 95% CI 7.39 to 19.25; p < 0.001). In patients with non–Q-wave MI, the 1-year estimate of mortality was 8.7% (n = 24) versus 3.2% (n = 162) in patients without any MI (OR 2.83, 95% CI 1.88 to 4.26; p < 0.001). The 1-year estimate of mortality was 15.4% (n = 8) among patients who needed urgent revascularization versus 3.6% (n = 189) among patients who did not undergo urgent revascularization procedures within 30 days of the index PCI (OR 4.74, 95% CI 2.49 to 8.99, p < 0.001) (Fig. 2).

The 1-year mortality was 14.1% (n = 30) among patients in whom bleeding occurred within the 30 days after PCI

Table 1 Demographic, Clinical, and Angiographic Characteristics in 1-Year Survivors and Nonsurvivors

Characteristics	Survivors (n = 5,187)	Nonsurvivors (n = 197)	p Value
Age (yrs)	66.3 [59.3, 73.8]	74.3 [67.7, 80.8]	<0.001
Women	1,269 (24.5)	54 (27.4)	0.345
Body mass index (kg/m^2)	26.9 [24.7, 29.4]	25.7 [23.1, 29.1]	<0.001
Diabetes	1,722 (33.2)	95 (48.2)	<0.001
Arterial hypertension	3,115 (60.1)	118 (59.9)	0.965
Current smoker	973 (18.8)	34 (17.3)	0.596
Hypercholesterolemia (≥240 mg/dl)	2,946 (56.8)	97 (49.2)	0.035
Previous myocardial infarction	1,535 (29.6)	80 (40.6)	<0.001
Previous coronary artery bypass surgery	524 (10.1)	26 (13.2)	0.159
Acute coronary syndrome	1,928 (37.2)	94 (47.7)	0.002
Elevated troponin (≥0.03 μg/l)	979 (18.9)	70 (35.5)	<0.001
Elevated creatine kinase MB (>24 U/l)	429 (8.3)	26 (13.2)	0.014
Serum creatinine (mg/dl)	1.0 [0.8, 1.2]	1.2 [1.0, 1.5]	<0.001
Lesion location			<0.001
Left main coronary artery	85 (1.7)	10 (5.1)	
Left anterior descending coronary artery	2,096 (40.4)	86 (43.6)	
Left circumflex coronary artery	1,448 (27.9)	47 (23.9)	
Right coronary artery	1,463 (28.2)	43 (21.8)	
Venous bypass graft	95 (1.8)	11 (5.6)	
Multivessel disease	3,939 (75.9)	182 (92.4)	<0.001
Complex lesions	3,706 (71.4)	138 (70.1)	0.670
Left ventricular ejection fraction (%)	59.0 [50.0, 65.0]	51.0 [36.0, 62.0]	<0.001
Lesion length (mm)	11.8 [8.4, 16.6]	10.6 [6.8, 15.1]	0.001
Vessel size (mm)	2.75 [2.41, 3.14]	2.70 [2.33, 3.14]	0.187
Diameter stenosis (%)	64.4 [54.7, 75.0]	60.7 [52.7, 71.5]	0.020
Clopidogrel loading interval (h)	5.0 [2.7, 12.0]	4.8 [2.5, 10.0]	0.147
Type of intervention			0.193
Drug-eluting stent	1,118 (21.5)	53 (26.9)	
Bare-metal stent	3,698 (71.3)	132 (67.0)	
Balloon angioplasty	371 (7.2)	12 (6.1)	
Abciximab therapy	2,598 (50.1)	95 (48.2)	0.607

Data are expressed as median [25th, 75th percentiles] or number of patients (%).

versus 3.3% (n = 167) among patients who had no bleeding within the 30 days (OR 4.75, 95% CI 3.34 to 6.76, p < 0.001) (Fig. 3). There were 59 patients with major bleeding and 156 patients with minor bleeding. In patients with major bleeding, the 1-year estimate of mortality was 12.2% (OR 4.13, 95% CI 2.06 to 8.28; p < 0.001 compared with patients without bleeding). In patients with minor bleeding, the 1-year estimate of mortality was 14.8% (OR 5.00, 95% CI 3.38 to 7.40; p < 0.001 compared with patients without bleeding). No significant interactions were found regarding 1-year mortality between bleeding and type of trial (p = 0.45), between bleeding and abciximab use (p = 0.64), and between bleeding and age (p = 0.90).

Table 2 30-Day Ischemic and Bleeding Complications in 1-Year Survivors and Nonsurvivors

Outcome	Survivors (n = 5,187)	Nonsurvivors (n = 197)	p Value
MI	279 (5.4)	35 (17.8)	<0.001
Urgent revascularization	44 (0.8)	8 (4.1)	<0.001
Any bleeding	185 (3.6)	30 (15.2)	<0.001
Major bleeding	52 (1.0)	7 (3.6)	<0.001
Minor bleeding	133 (2.6)	23 (11.7)	<0.001

Data are expressed as number of patients (%).
MI = myocardial infarction.

At least 1 adverse event—urgent revascularization, MI, or bleeding—was encountered in 501 patients (9.3%): urgent revascularization (15 patients, 0.3%), MI (245 patients, 4.5%), bleeding (169 patients, 3.1%), and more than 1 of these events (72 patients, 1.3%). In 4,883 patients, none of these adverse events occurred in the 30 days after PCI. There were 2 deaths among patients requiring only urgent revascularization (mortality estimate 13.3%, OR 5.17, 95% CI 1.48 to 18.06; p < 0.001 compared with patients without any adverse event in the 30 days after PCI), 22 deaths among patients with only MI (mortality estimate 9.1%, OR 3.28, 95% CI 2.15 to 5.02; p < 0.001 compared with patients without events within the first 30 days after PCI), and 21 deaths among patients with only bleeding (mortality estimate 12.5%, OR 4.69, 95% CI 3.09 to 7.11;

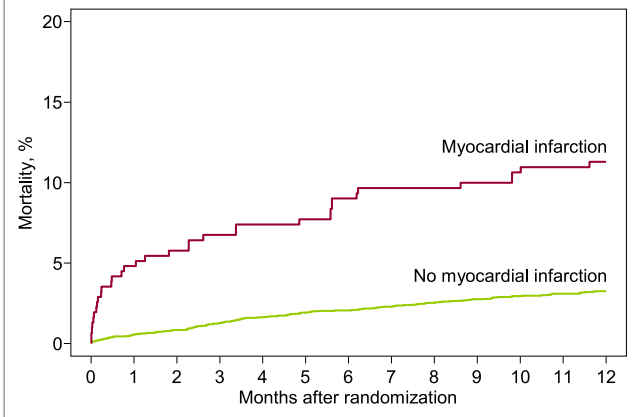

Figure 1 **Post-Procedural Myocardial Infarction and 1-Year Mortality**

Kaplan-Meier curves of 1-year mortality among patients with and without myocardial infarction within the first 30 days after the percutaneous coronary intervention.

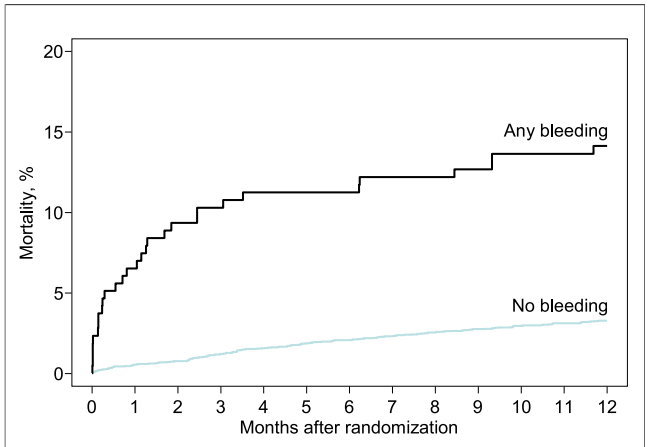

Figure 3 **Post-Procedural Bleeding and 1-Year Mortality**

Kaplan-Meier curves of 1-year mortality among patients with and without periprocedural bleeding within the first 30 days after the percutaneous coronary intervention.

$p < 0.001$ compared with patients without any adverse event in the 30 days after PCI). The remaining 13 deaths (18.0%) occurred in 72 patients who had suffered more than 1 adverse event within the first 30 days after PCI.

At 1 year, there were 58 deaths (11.6%) among patients who had suffered at least 1 of these events (n = 501) in the 30 days after PCI versus 139 deaths (2.8%) among patients who had not (OR 4.46, 95% CI 3.23 to 6.16; $p < 0.001$). At 1 year there were 37 deaths (11.1%) among patients who needed urgent revascularization or had suffered an MI within 30 days (n = 332) versus 160 deaths (n = 5,052; 3.2%) among patients who had not (OR 3.83, 95% CI 2.62 to 5.58; $p < 0.001$).

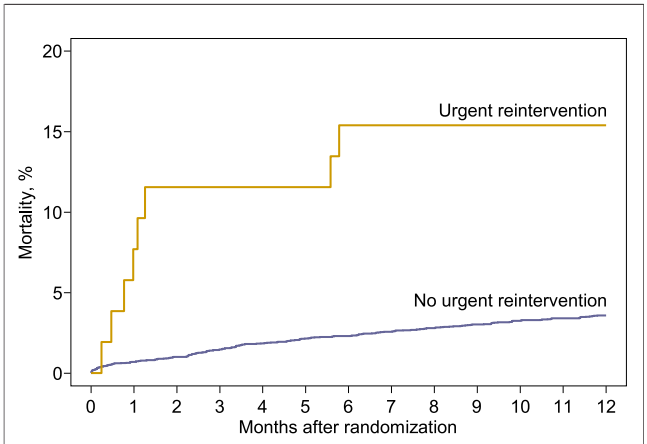

Figure 2 **Post-Procedural Urgent Reintervention and 1-Year Mortality**

Kaplan-Meier curves of 1-year mortality among patients with and without urgent reintervention within the first 30 days after the percutaneous coronary intervention.

The impact of each ischemic or hemorrhagic complication within 30 days after PCI on mortality from 30 days to 1 year was also assessed. There were 155 deaths between 30 days and 1 year (2.8%). Kaplan-Meier estimates of mortality were 6.4% (n = 20) among patients who suffered an acute MI versus 2.7% (n = 135) among patients without an MI (OR 2.58, 95% CI 1.64 to 4.05; $p > 0.001$), 7.4% (n = 16) among patients with bleeding versus 2.7% (n = 139) among patients without bleeding (OR 3.10, 95% CI 1.89 to 5.06; $p > 0.001$) and 2.8% (n = 152) among patients who needed an urgent revascularization versus 5.8% (n = 3) among those who did not undergo an urgent revascularization within first 30 days after randomization (OR 2.25, 95% CI 0.74 to 6.85; $p = 0.15$).

Independent predictors of 1-year mortality. The Cox proportional hazards model was used to identify independent predictors of 1-year mortality. The model included MI, urgent revascularization, and bleeding at 30 days as well as the baseline characteristics (see Methods). Results of this analysis are shown in Table 3. It can be seen that bleeding

Table 3 **Independent Predictors of 1-Year Mortality**

Variable	Hazard Ratio (95% Confidence Interval)	p Value
Bleeding within 30 days	2.96 (1.96–4.48)	<0.001
Myocardial infarction within 30 days	2.29 (1.52–3.46)	<0.001
Urgent revascularization within 30 days	2.49 (1.16–5.35)	0.019
Age (yrs)*	2.27 (1.78–2.89)	<0.001
Diabetes	1.47 (1.11–1.96)	0.008
Multivessel coronary disease	2.72 (1.58–4.67)	<0.001
Elevated troponin	1.77 (1.27–2.47)	<0.001
Left ventricular ejection fraction	0.71 (0.60–0.85)	<0.001
Creatinine level†	1.10 (1.06–1.14)	<0.001

*Calculated for a 10-year increase in age. †Calculated for a 0.25-mg increase in concentration.

in the 30 days was 1 of the strongest independent predictors of mortality at 1 year.

The impact of ischemic or hemorrhagic complications within 30 days after PCI on 30-day to 1-year mortality was also tested in the Cox proportional hazards model, which included MI, urgent revascularization, and bleeding at 30 days as well as the baseline characteristics (see preceding text). The model showed that bleeding (hazard ratio [HR] 2.04, 95% CI 1.19 to 3.50; p = 0.009) and MI (HR 1.96, 95% CI 1.18 to 3.26; p = 0.01) but not urgent revascularization (HR 1.49, 95% CI 0.45 to 4.91; p = 0.51) independently predicted 30-day to 1 year mortality.

Sensitivity, specificity, and accuracy of MI, urgent revascularization, and bleeding within 30 days with respect to 1-year mortality are shown in Table 4. Furthermore, predictivity of the models with MI, urgent revascularization, or bleeding regarding 1-year mortality was assessed by calculating the *c* statistic in the multivariable model including each of the components. The *c* statistic was 0.78 for MI, 0.78 for urgent revascularization, and 0.79 for bleeding, demonstrating a comparable discriminatory power of each of the components. The univariate *c* statistic for a composite of MI or urgent revascularization was 0.56. The univariate *c* statistic for a composite of MI, bleeding, or urgent revascularization was 0.61. In the multivariable model, the *c* statistic was 0.78 for a composite end point of MI or urgent revascularization and 0.80 for a composite end point of urgent revascularization, MI, or bleeding.

Discussion

The main finding of this study is that bleeding in the 30 days after a PCI is strongly associated with mortality as late as 1 year after the procedure and that bleeding in the first 30 days after a PCI is comparatively as strong as the 30-day occurrence of other adverse events such as MI or urgent revascularization. This finding is particularly important, because so many of the deaths in the first year (155 of 197 deaths, 79%) occurred more than 30 days after the procedure and the time that the bleeding occurred. Importantly, our study showed that not only major but also minor bleeding was associated with late mortality.

Periprocedural bleeding is 1 of the most frequent complications of PCI. Large registries of patients with coronary artery disease treated by PCI have reported an incidence of major bleeding as high as 5.4%, close to the reported incidences of refractory ischemia, MI, or death (14). A growing body of evidence suggests that periprocedural bleeding in patients undergoing PCI is associated with an increased risk of recurrent ischemic complications and that bleeding adversely affects both short-term (15–17) and long-term (8,18) mortality. A stepwise increase in the 30-day death, 30-day death or MI, and 6-month death with increasing bleeding severity has been reported (15). The risk of bleeding seems to be particularly high among patients of older age, women, patients with lower body weight, and those with impaired renal function, receiving multiple antithrombotic drugs, and those undergoing invasive procedures (14,19–23). Advances in adjunct antithrombotic therapy have reduced the incidence of thrombotic complications, but they have increased the risk of bleeding (24,25). Despite the frequent occurrence of bleeding and the potential that bleeding might adversely affect clinical outcome and even increase mortality, traditionally the outcome of PCI procedures in patients with coronary artery disease has been assessed by using the triple end point of death, MI, and urgent repeat revascularization at 30 days (3–6). Bleeding complications have been either reported separately or analyzed as component of a secondary end point, occasionally referred to as net clinical benefit (26).

The present pooled analysis of 4 ISAR trials captures a wide range of patients with coronary artery disease, from lower-risk patients undergoing elective PCI to higher-risk patients with non–ST-segment elevation acute coronary syndromes and MI. The analysis reveals that bleeding within 30 days—nearly all of which was periprocedural bleeding—is 1 of the strongest predictors of 1-year mortality after PCI. Importantly, this study showed that not only major bleeding but also minor bleeding was associated with increased risk of death as long as 1 year after PCI. The most important result of this study, however, is the finding that periprocedural bleeding is as strong a correlate of mortality at 1 year as the components of the most commonly used composite end point in PCI studies, a 30-day occurrence of MI and urgent revascularization. Multivariable analysis unequivocally demonstrated that periprocedural bleeding independently correlates with 1-year mortality. The *c* statistic shows that periprocedural bleeding (commonly thought of as an index of safety) and MI or urgent revascularization (commonly thought of as indexes of efficacy) have similar discriminatory power in predicting 1-year mortality.

The inclusion of any event in a structure of a composite end point is generally based on the assumption that the event is associated with the outcome of primary interest

Table 4 Predictive Accuracy of MI, Urgent Revascularization, or Bleeding Within 30 Days After PCI Regarding 1-Year Mortality

	MI	Urgent Revascularization	Bleeding	p Value*	p Value†
Sensitivity	17.8 (35/197)	4.1 (8/197)	15.2 (30/197)	0.46	<0.001
Specificity	94.6 (4,908/5,187)	99.1 (5,143/5,187)	96.4 (5,002/5,187)	<0.001	<0.001
Accuracy	91.8 (4,943/5,384)	95.7 (5,151/5,384)	93.4 (5,032/5,384)	<0.001	<0.001

Data are expressed as % (n/N). *Bleeding versus myocardial infarction (MI). †Bleeding versus urgent revascularization.
PCI = percutaneous coronary intervention.

and has a relatively frequent occurrence and a relatively equal (or only slightly less) importance than other components (1,2,27,28). Our study suggests that periprocedural bleeding fulfills the aforementioned assumptions. First, as the present study and prior studies (8,18) show, periprocedural bleeding is strongly and independently associated with 1-year mortality, even after adjustment for other components of the composite end point (i.e., 30-day MI and urgent revascularization). Periprocedural bleeding is at least as strong as MI as a prognostic factor. These data are in agreement with a recent report from the ACUITY (Acute Catheterization and Urgent Intervention Triage strategy) trial, which showed that bleeding was an even stronger correlate than MI of 30-day mortality (17). Of note, our study did not evidence any gradient of importance between bleeding and other components traditionally included in the structure of composite primary end point. Second, bleeding is a relatively common event after PCI procedures, so its inclusion in a primary end point reduces the sample size requirements and increases the statistical power of a study. The occurrence of bleeding is comparable in frequency to that of MI, which has traditionally been included in the primary composite end point to evaluate the outcome of PCI (14,19). Third, there is a cause–effect relationship between the adjunctive therapies that are being studied and bleeding complications (19,24,25).

In conclusion, our study found a strong and independent relationship between bleeding early after a PCI procedure and mortality at 1 year, independent of baseline characteristics measured and of the other components of the composite end point traditionally used in evaluation trials of novel PCI therapies. This observation supports the inclusion of bleeding in a 30-day quadruple primary end point that also includes death, MI, and urgent repeat revascularization to assess the outcome of PCI procedures. Owing to the strong and independent association between bleeding after a PCI and death, measures to reduce bleeding complications should remain an important therapeutic goal.

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