Association Between Periprocedural Bleeding and Long-Term Outcomes Following Percutaneous Coronary Intervention in Older Patients

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Objectives The authors sought to describe the association between post-procedural bleeding and long-term recurrent bleeding, major adverse cardiac events (MACE), and mortality among older patients undergoing percutaneous coronary intervention (PCI).

Background Bleeding complications after PCI are associated with an increased risk for acute morbidity and long-term mortality, but the association of these bleeding complications with other events is unknown.

Methods Patients entered into the National Cardiovascular Data Registry (NCDR) CathPCI Registry (n = 461,311; 946 sites) from January 2004 to December 2008 were linked with claims from the Centers for Medicare & Medicaid Services and grouped according to in-hospital post-PCI bleeding. The association between post-PCI bleeding and 1-, 12-, and 30-month readmission for bleeding, MACE, and all-cause mortality was examined with Cox regression that included patient and procedural characteristics using no bleeding as the reference.

Results Overall, 3.1% (n = 14,107) of patients experienced post-PCI bleeding. Patients who bled were older, more often female, had more medical comorbidities, less often received bivalirudin, and more often underwent PCI via the femoral approach. After adjustment, bleeding after the index procedure was significantly associated with readmission for bleeding (adjusted hazard ratios [95% confidence interval]: 1 month, 1.54 [1.42 to 1.67]; 12 months, 1.52 [1.40 to 1.66]; 30 months, 1.29 [1.11 to 1.50]), MACE (1 month, 1.11 [1.07 to 1.15]; 12 months, 1.17 [1.13 to 1.21]; 30 months, 1.12 [1.06 to 1.19]) and all-cause mortality (1 month, 1.32 [1.26 to 1.38]; 12 months, 1.33 [1.27 to 1.40]; 30 months, 1.22 [1.15 to 1.30]).

Conclusions Post-PCI bleeding complications are associated with an increased risk for short- and long-term recurrent bleeding, MACE, and all-cause mortality. These data underscore the prognostic importance of periprocedural bleeding and the need for identifying strategies to reduce long-term bleeding risk among patients undergoing PCI. (J Am Coll Cardiol Intv 2012;5:958–65) © 2012 by the American College of Cardiology Foundation
Bleeding complications that occur after percutaneous coronary intervention (PCI) are associated with an increased risk for morbidity and all-cause mortality (1). Mechanisms underlying this association are unclear but likely include cessation of evidence-based medical therapy (2); blood transfusion (1); the effect of comorbidities among patients who develop bleeding (3); or the effect of bleeding itself when bleeding is intracranial or retroperitoneal. Despite the lack of clarity on the pathophysiological explanations, the adverse prognostic impact of bleeding has been noted in the outpatient setting as well, with up to 11% of patients discontinuing at least 1 antiplatelet agent due to so-called “nuisance” bleeding (4). Identification of patients at high bleeding risk has been proposed as a way to selectively implement “bleeding avoidance strategies” (5,6).

Most studies examining the prognostic impact of bleeding have examined outcomes associated with either in-hospital (5) or out-of-hospital bleeding (7), but not both. In addition, these studies have primarily examined mortality or ischemic events as the outcome; few studies have assessed the relationship between acute bleeding and both recurrent bleeding and ischemic events that occur over the long term. It remains unclear whether patients who develop hemorrhagic complications after PCI continue to be at risk for bleeding complications long after the procedure. This is an important issue, given the need for prolonged antithrombotic therapy for secondary prevention (8,9) and the differential bleeding profiles of various evidence-based discharge antithrombotic therapies. Accordingly, we used a large contemporary registry of patients undergoing PCI to examine the association between post-PCI bleeding and long-term outcomes, including readmission for bleeding events.

**Methods**

**Patient population.** The National Cardiovascular Data Registry (NCDR) CathPCI Registry, which is cosponsored by the American College of Cardiology and the Society for Cardiovascular Angiography and Interventions, has been previously described (10). The CathPCI Registry collects data on patient and hospital characteristics, clinical presentation, treatments, and outcomes for PCI procedures from over 1,000 sites across the United States. Data are entered into NCDR-certified software at participating institutions, and exported in a standard format to the American College of Cardiology. There is a comprehensive data quality program, including both data quality report specifications for data capture and transmission, and an auditing program. A committee of the American College of Cardiology prospectively defined the variables, which are available at the NCDR website.

For the purpose of this analysis, we included the first PCI procedure performed in any individual patient during a qualifying hospitalization between January 2004 and December 2008. The dataset comprised 1,725,600 admissions from 967 sites. Patients who died during hospitalization (n = 22,029) and patients for whom bleeding data were missing (n = 61; 1 site) were excluded. The study was approved by the institutional review board of Duke University Medical Center, which determined that the study met the definition of research not requiring informed consent.

**Linkage to claims data.** The CathPCI Registry only contains data on in-hospital outcomes. In order to determine the association between in-hospital bleeding complications and longer-term outcomes, we linked CathPCI Registry patients over the age of 65 years with the Medicare 100% Part A claims file (11). Percutaneous coronary intervention procedure codes (International Classification of Diseases-Ninth Revision-Clinical Modification [ICD-9-CM], 00.66, 36.0x, 37.22, 37.23, and 88.5x, except 88.59) were used to identify index procedures in the Medicare files, which were then linked to the CathPCI Registry using indirect identifiers (non-unique fields that when used in combination may identify unique hospitalizations). Linking rules used a hierarchy of evidence approach such that rules with the greatest specificity were applied first. Once a match was achieved for a patient, no further rules were applied. The linking rules contained combinations of information denoting the index PCI procedure site, patient date of birth or age, admission, discharge date, and sex. If a single CathPCI Registry record matched with multiple Medicare records using the same rules, then no linking occurred. Unidentified longitudinal profiles were obtained with up to 30 months of patient follow-up. Sites that did not match to Medicare records and patients whose index PCI procedure did not occur during a period of fee-for-service enrollment were excluded. This study included all Medicare-linked patients ≥65 years of age undergoing PCI who were enrolled in the CathPCI Registry from January 1, 2004, to December 31, 2008.

**Endpoints and definitions.** The outcomes for this analysis were readmission for bleeding, major adverse cardiac events (MACE) (defined as the composite of death, myocardial infarction [MI], or revascularization), and all-cause mortality. Outcomes were evaluated at 1 month, 12 months, and 30 months. We also examined the use of evidence-based medications at hospital discharge (defined as the prescription of aspirin, clopidogrel, beta-blockers, statins, and angiotensin-converting enzyme inhibitors) between patients who bled versus those who did not, and compared length of stay between the 2 groups.

**Abbreviations and Acronyms**

- **MACE** = major adverse cardiac event(s)
- **MI** = myocardial infarction
- **PCI** = percutaneous coronary intervention
- **STEMI** = ST-segment elevation myocardial infarction
To identify patients who experienced post-PCI bleeding, we used the definition of bleeding in the CathPCI Registry (i.e., access site bleeding, retroperitoneal bleeding, gastrointestinal bleeding, genitourinary bleeding, or other). All bleeding events in the registry are further defined as requiring transfusion and/or prolonging the hospital stay, and/or causing a drop in hemoglobin >3.0 g/dl. Hematomas >10 cm for femoral access or >2 cm for radial access qualify as access site bleeding. We also grouped patients according to access site bleeding, defined as overt access site bleeding or retroperitoneal bleeding, and non-access site bleeding, defined as all other bleeding events. Readmissions for bleeding were identified from claims data using the ICD-9-CM diagnosis codes: Bleeding 430 to 432, 578.X, 719.1X, 423.0, 599.7, 626.2, 626.6, 626.8, 627.0, 627.1, 786.3, 784.7, or 459.0. Myocardial infarction and revascularization events that occurred during follow-up were obtained from claims data using the ICD-9-CM diagnosis code 410.X1 (MI) and ICD-9-CM procedure codes 36.00, 36.06, 36.07, 36.09, and 36.10 to 36.19 (revascularization). Only revascularizations occurring after discharge from the index hospital stay were included for the MACE endpoint. All-cause mortality was obtained from the claims data file.

Statistical analysis. Patients were grouped according to whether they experienced a post-procedure bleeding event. For descriptive analyses, baseline characteristics and treatment strategies were compared between patients who bled versus those who did not. Continuous variables are presented as medians with interquartile percentiles, and categorical variables are presented as percentages. Differences between patient groups were compared using chi-square tests for categorical variables and the Wilcoxon rank sum test for continuous variables, respectively.

Estimates of the event rates for clinical endpoints at 1 month, 12 months, and 30 months post-intervention were determined on the basis of weights that were functions of Kaplan-Meier censoring estimates (12). The cumulative incidence rates for time-to-event clinical outcomes were estimated by using Gray’s method (13). Both the unadjusted and adjusted hazard ratios were estimated for in-hospital bleeding versus no bleeding along with a 95% confidence interval on the basis of the sandwich-estimated standard errors. The adjusted analysis include the variables adopted in the CathPCI Registry in-hospital all-cause mortality model as covariates, which consist of age, body mass index, glomerular filtration rate, ST-segment elevation myocardial infarction (STEMI), cardiogenic shock at admission, medical history (i.e., congestive heart failure, valvular surgery, cerebrovascular disease, peripheral vascular disease, chronic lung disease, diabetes, dialysis, PCI), highest-risk lesion characteristics (segment category), New York Heart Association functional class, pre-procedure intra-aortic balloon pump, coronary lesion ≥50%, and PCI status (14). In addition, we used landmark analysis to determine the 30-month component of the in-hospital bleeding effect after excluding events between 30 days and 12 months. The entire analysis was repeated to examine the relationship

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**Figure 1. Study Sample Selection Flow Diagram**

Displays initial study population through the final study population, exclusions included. ACC = American College of Cardiology; CMS = Centers for Medicare & Medicaid Services; FFS = fee for service; NCDR = National Cardiovascular Data Registry; PCI = percutaneous coronary intervention.
between access site and non-access site bleeding and the outcomes, using no bleeding as the reference. A p value <0.05 was considered significant for all tests. The Duke Clinical Research Institute performed all statistical analyses using SAS software (version 9.2, SAS Institute, Cary, North Carolina).

Results

Patient sample and baseline characteristics. The final study sample included 837,733 patients from 964 sites. After matching to Medicare claims, the analysis dataset included 461,311 patients from 946 sites (Fig. 1), 14,107 (3.1%) of whom experienced bleeding. Among patients who bled, 48.6% had access site bleeding. The rate of blood transfusion was 5.5%. Baseline characteristics of the patients who did and did not develop bleeding are listed in Table 1. Patients who bled were older and more often female. They also had a lower body mass index, and more often had comorbidities, such as chronic kidney disease, peripheral arterial disease, cerebrovascular disease, and congestive heart failure. By contrast, there was a similar prevalence of diabetes mellitus and hypertension between the 2 groups.

With respect to presenting symptoms, patients who bled more often presented with acute coronary syndrome (either non-STEMI or STEMI) rather than stable angina. In addition, there was a higher proportion of urgent, emergent,

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Table 1. Baseline Characteristics of Patients Who Did and Did Not Develop In-Hospital Bleeding

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Overall (n = 461,311)</th>
<th>Bleeding (n = 14,107)</th>
<th>No Bleeding (n = 447,204)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, yrs</td>
<td>74.0 (69.0–80.0)</td>
<td>76.0 (71.0–81.0)</td>
<td>74.0 (69.0–80.0)</td>
<td>&lt;0.001</td>
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<tr>
<td>Female</td>
<td>42.0</td>
<td>57.5</td>
<td>42.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>27.7 (24.7–31.5)</td>
<td>27.3 (24.0–31.3)</td>
<td>27.7 (24.7–31.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Medical comorbidities</td>
<td></td>
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<tr>
<td>Diabetes mellitus</td>
<td>33.5</td>
<td>33.7</td>
<td>33.5</td>
<td>0.593</td>
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<tr>
<td>Hypertension</td>
<td>82.0</td>
<td>82.5</td>
<td>82.0</td>
<td>0.145</td>
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<tr>
<td>Peripheral arterial disease</td>
<td>15.3</td>
<td>17.9</td>
<td>15.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>7.0</td>
<td>10.1</td>
<td>6.9</td>
<td>&lt;0.001</td>
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<tr>
<td>Prior CHF</td>
<td>72.7</td>
<td>81.1</td>
<td>72.5</td>
<td>&lt;0.001</td>
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<tr>
<td>Prior PCI</td>
<td>29.6</td>
<td>20.6</td>
<td>29.9</td>
<td>&lt;0.001</td>
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<tr>
<td>Prior CABG</td>
<td>23.1</td>
<td>17.4</td>
<td>23.3</td>
<td>&lt;0.001</td>
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<td>Procedure characteristics</td>
<td></td>
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<tr>
<td>Procedure indication</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stable angina/atypical chest pain/asymptomatic</td>
<td>37.3</td>
<td>23.0</td>
<td>37.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Non–ST-segment ACS</td>
<td>51.3</td>
<td>50.5</td>
<td>51.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>STEMI</td>
<td>11.5</td>
<td>26.5</td>
<td>11.0</td>
<td>&lt;0.001</td>
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<tr>
<td>Procedure status</td>
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<tr>
<td>Elective</td>
<td>48.4</td>
<td>29.1</td>
<td>49.0</td>
<td>&lt;0.001</td>
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<td>Urgent</td>
<td>38.5</td>
<td>40.5</td>
<td>38.5</td>
<td>&lt;0.001</td>
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<tr>
<td>Emergency</td>
<td>12.9</td>
<td>29.8</td>
<td>12.4</td>
<td>&lt;0.001</td>
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<td>Medications*</td>
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<tr>
<td>Aspirin</td>
<td>90.2</td>
<td>91.2</td>
<td>90.1</td>
<td>&lt;0.001</td>
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<td>Clopidogrel</td>
<td>76.5</td>
<td>73.6</td>
<td>76.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Unfractionated heparin</td>
<td>53.8</td>
<td>69.4</td>
<td>53.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LMWH</td>
<td>16.7</td>
<td>20.6</td>
<td>16.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Bivalirudin</td>
<td>40.8</td>
<td>27.5</td>
<td>41.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Any GP IIb/IIIa</td>
<td>38.2</td>
<td>61.3</td>
<td>37.4</td>
<td>&lt;0.001</td>
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<tr>
<td>Vascular access site</td>
<td></td>
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<td></td>
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<tr>
<td>Radial</td>
<td>1.2</td>
<td>0.8</td>
<td>1.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Femoral</td>
<td>97.9</td>
<td>97.9</td>
<td>97.9</td>
<td>0.863</td>
</tr>
<tr>
<td>Brachial</td>
<td>0.4</td>
<td>0.7</td>
<td>0.4</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Values are median (interquartile range) or percentages. *Includes medications given at the time of admission through the catheterization lab visit.

ACS = acute coronary syndrome; BMI = body mass index; CABG = coronary artery bypass grafting; CHF = congestive heart failure; GP = glycoprotein; LMWH = low-molecular-weight heparin; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.
and salvage procedures among patients who developed bleeding. In-hospital medical therapies and procedural approaches also differed between the groups: the use of unfractionated heparin, low-molecular-weight heparins, and glycoprotein IIb/IIIa inhibitors was higher among patients who bled. In contrast, the use of bivalirudin, pre-PCI clopidogrel, and radial access was lower.

Table 2 displays the use of evidence-based medications at the time of hospital discharge among patients who bled versus those who did not. The use of antiplatelet agents and other secondary prevention medications was significantly lower among patients who bled, with the exception of beta-blockers and angiotensin-converting enzyme inhibitors, which were prescribed more often to patients who developed a bleeding complication. The hospital length of stay was significantly longer for patients who developed bleeding compared with those who did not (median length of stay: 6.0 vs. 2.0 days, \( p < 0.0001 \)).

**Outcomes.** The unadjusted rates of the outcomes are listed in Table 3. The rates of readmission for bleeding at 1 month, 12 months, and 30 months were significantly higher among patients who experienced in-hospital bleeding. Similarly, unadjusted MACE and all-cause mortality rates at 1 month, 12 months, and 30 months were also significantly higher among patients who developed in-hospital bleeding. Figures 2A to 2C show the Kaplan-Meier rates of the endpoints.

**Adjusted results.** Figure 3 displays the association between post-procedure bleeding and readmission for bleeding, all-cause mortality, and MACE after adjustment for potential confounders. Compared with patients who did not bleed, the risk for all 3 outcomes was significantly higher at all 3 time points for patients who experienced in-hospital bleeding. At the 30-month time point, the risk for recurrent bleeding and all-cause mortality attenuated slightly, but was still significantly higher for patients who bled compared with patients who did not bleed. The risk for MACE remained stable over time and was significantly higher for patients who bled compared with those who did not bleed. The relationships between access site and non-access site bleeding and outcomes are shown in Online Table 1 in the Online Appendix.
In the largest analysis of its kind involving over 400,000 older patients, we found that post-PCI bleeding is associated with an increased risk for future bleeding complications, MACE, and all-cause mortality. Although the association between bleeding and long-term mortality among patients undergoing PCI has been previously described, the present study has 2 important new findings: 1) the association between post-procedure bleeding and outcomes extends out to 30 months; and 2) patients who develop post-procedure bleeding are prone to recurrent bleeding events over the long term. Thus, post-procedure bleeding identifies a patient population that is at risk for poor net adverse clinical events.

The association between bleeding and ischemic outcomes has been previously described. Kinnaird et al. (15) examined the association between Thrombolysis In Myocardial Infarction (TIMI) major and minor bleeding, as well as blood transfusion, and in-hospital and 1-year mortality among 10,974 unselected patients undergoing PCI and found that TIMI major bleeding was independently associated with in-hospital, but not 1-year, mortality. By contrast, blood transfusion was associated with increased mortality at both time points. Subsequent studies using different bleeding definitions have found that bleeding and transfusion are associated with short- and long-term mortality, MACE, target vessel revascularization, stent thrombosis, and stroke (16–18). Yet none of these studies examined the risk of recurrent bleeding. Our study, which is larger than all previous studies combined, confirms the findings of prior studies, but also extends them by demonstrating that bleeding identifies a group that is at high risk for continued bleeding events in the outpatient setting.

Putative mechanisms that underlie the association between hemorrhagic complications and ischemic outcomes include cessation of evidence-based therapy (2), the negative effects of blood transfusion (1,19), a direct effect of the bleeding itself on oxygen delivery or, rarely, exsanguination, and potentially an increased propensity for thrombosis, due to bleeding. Studies have explored these mechanisms in the inpatient setting, but little is known about the mechanisms that apply in the outpatient setting. With respect to recurrent bleeding events, it is likely that patients who are vulnerable to bleeding from acute antithrombotic therapy and invasive procedures are also susceptible to bleeding with chronic antithrombotic therapies. In the present study, patients who developed a bleeding complication were older, more often had a lower body weight, and more often had comorbidities, such as chronic kidney disease, diabetes, and peripheral arterial disease. Many of these risk factors are associated with bleeding during chronic therapy with dual antiplatelet therapy (7). This consistency in characteristics associated with bleeding across care settings underscores the
importance of monitoring these high-risk patients for both ischemic and bleeding complications from the time of PCI through long-term outpatient follow-up.

In the contemporary era of PCI, several strategies exist to reduce the risk of periprocedural bleeding (20,21). Clinical trials have shown that some of these strategies are associated with reduced all-cause mortality in specific settings (22,23). For example, the use of bivalirudin is associated with a significant reduction in both access site and non-access site bleeding (24), and is associated with reduced short- and long-term mortality among patients undergoing primary PCI (25). Similarly, the use of radial access is also associated with a significant reduction in access site bleeding and vascular complications, but is less frequently used in patients at higher risk for such complications (26). Although these strategies reduce the risk for in-hospital bleeding, neither is applicable in the outpatient setting. There are few proven approaches associated with reduced bleeding risk during chronic treatment for coronary artery disease. Reduction in aspirin dosing may be associated with lower bleeding rates during long-term therapy (27), but not within 30 days of an acute coronary syndrome episode (28). Another strategy is to avoid the use of potent thienopyridines in patients at high risk for bleeding, such as older patients, those with prior stroke or transient ischemic attack, and those with body weight <60 kg (29). Ticagrelor, a non-thienopyridine P2Y12 antagonist, has been shown to reduce ischemic events, including stent thrombosis, over the long term without an increase in major bleeding (30), and this agent may be preferred in patients at risk for bleeding.

**Study limitations.** First, we relied on linkage to administrative data to obtain long-term outcomes. This necessarily limited our population to patients who were age 65 years or older. In addition, nonmortal events, such as bleeding, revascularization, or MI were obtained from Medicare data, which may lead to missing events due to coding bias. We also could not completely account for differences in severity across events defined by the ICD-9 codes. Second, we did not have data on patient frailty, which may account, in part, for the outcomes. Third, although it is possible that some of the bleeding events that occurred during follow-up may have been associated with repeat percutaneous procedures, we minimized this possibility by limiting the bleeding outcomes to hospitalization specifically for a bleeding event. Finally, unmeasured confounders may be present. To minimize this, we used a robust statistical adjustment; however, causality cannot be inferred from our findings.

**Conclusions**

Among older patients, post-PCI bleeding complications are associated with an increased risk for short- and long-term
readmission for bleeding, MACE, and all-cause mortality. These data underscore the prognostic importance of bleeding and the need for identifying strategies to reduce both procedural and long-term bleeding risk among patients undergoing PCI.

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REFERENCES


Key Words: elderly patients ■ percutaneous coronary intervention ■ periprocedural bleeding.

APPENDIX

For a supplementary table, please see the online version of this paper.