Postdischarge Bleeding After Percutaneous Coronary Intervention and Subsequent Mortality and Myocardial Infarction: Insights From the HMO Research Network-Stent Registry

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Background—Bleeding after hospital discharge from percutaneous coronary intervention (PCI) is associated with increased risk of subsequent myocardial infarction (MI) and death; however, the timing of adverse events after these bleeding events is poorly understood. Defining this relationship may help clinicians identify critical periods when patients are at highest risk.

Methods and Results—All patients undergoing PCI from 2004 to 2007 who survived to hospital discharge without a bleeding event were identified from the HMO Research Network-Stent (HMORN-Stent) Registry. Postdischarge rates and timing of bleeding-related hospitalizations, MI, and death were defined. We then assessed the association between postdischarge bleeding–related hospitalizations with death and MI using Cox proportional hazards models. Among 8137 post-PCI patients surviving to hospital discharge without in-hospital bleeding, 391 (4.8%) had bleeding-related hospitalization after discharge, with the highest incidence of bleeding-related hospitalizations occurring within 30 days of discharge (n=79, 20.2%). Postdischarge bleeding–related hospitalization after PCI was associated with subsequent death or MI (hazard ratio, 3.09; 95% confidence interval, 2.41–3.96), with the highest risk for death or MI occurring in the first 60 days after bleeding-related hospitalization (hazard ratio, 7.16; confidence interval, 3.93–13.05).

Conclusions—Approximately 1 in 20 post-PCI patients are readmitted for bleeding, with the highest incidence occurring within 30 days of discharge. Patients having postdischarge bleeding are at increased risk for subsequent death or MI, with the highest risk occurring within the first 60 days after a bleeding-related hospitalization. These findings suggest a critical period after bleeding events when patients are most vulnerable for further adverse events. (Circ Cardiovasc Interv. 2016;9:e003519. DOI: 10.1161/CIRCINTERVENTIONS.115.003519.)

Key Words: hemorrhage • myocardial infarction • percutaneous coronary intervention • stent • survival

Aggressive antithrombotic regimens have led to significant reductions in thrombotic complications after percutaneous coronary intervention (PCI), but they have exposed patients to an increased risk of bleeding. Bleeding remains one of the most common complications after PCI, with ≤5% of patients experiencing a major bleeding event. Study of post-PCI bleeding has demonstrated that these events are not benign, with an association between bleeding and increased risk of death and myocardial infarction (MI). Recent data suggest that bleeding after hospital discharge carries similar risks to inpatient bleeding. Although inpatient post-PCI bleeding has been well characterized, comparatively little is known about the timing and prognostic impact of postdischarge bleeding events.

Significant gaps remain in the understanding of postdischarge bleeding. First, the sources and the timing of postdischarge bleeding after PCI are not well characterized. Establishing the highest risk periods for postdischarge bleeding after PCI can inform efforts to appropriately focus preventive measures. Second, the timing of death and MI after postdischarge bleeding remains unknown. Understanding the temporal relationship between postdischarge bleeding and subsequent adverse events could identify critical periods of patient risk after bleeding events. Finally, although risk factors for inpatient bleeding are well established, they may not overlap with risk factors for postdischarge bleeding. The identification of distinct risk factors for postdischarge bleeding may provide opportunities to further tailor post-PCI care for those at highest risk for events.

Accordingly, we studied patients undergoing PCI in 3 large integrated United States healthcare systems. First, we described the timing and the sources of bleeding events after

Coronary Interventions

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WHAT IS KNOWN

- Bleeding after percutaneous coronary intervention is associated with increased risk of adverse events.
- This increased risk is present for both in-hospital and postdischarge bleeding.

WHAT THE STUDY ADDS

- The risk of bleeding-related hospitalization after discharge from percutaneous coronary intervention is highest within 30 days of discharge.
- The risk of death or myocardial infarction after a bleeding-related hospitalization is highest within the first 60 days of the bleeding event.
- Risk factors for postdischarge bleeding are distinct from those traditionally associated with inpatient bleeding events.

hospital discharge from PCI. Second, we assessed the association between postdischarge bleeding and subsequent death or MI. Finally, we identified risk factors associated with postdischarge bleeding. The results of this analysis may assist clinicians in identifying intervals after PCI when patients are at highest risk for adverse events.

Methods

Cohort

The HMO Research Network-Stent (HMORN-Stent) Registry captured all patients undergoing PCI with a drug-eluting stent between January 2004 and December 2007 at 3 large integrated health systems: Kaiser Permanente Northern California, Kaiser Permanente Colorado, and Health Partners (Minneapolis, MN). Each of these sites participates in the National Cardiovascular Data Registry CathPCI Registry,15 recording and submitting detailed data from the PCI procedures, including demographics, cardiac risk factors, comorbidities, cardiac history, details of admission presentation, preprocedural testing, diagnostic catheterization findings, PCI procedural details, PCI procedural complications, and admission and discharge medications. Each variable was prospectively defined by a committee of the American College of Cardiology for capture in CathPCI and captured concomitantly in the HMORN-Stent registry during the study period. Each healthcare system also maintained postdischarge data for each patient, including pharmaceutical dispensing data, rehospitalizations, and vital status. Institutional review board approval was obtained at each of the 3 sites.

All patients in the HMORN-Stent registry who underwent successful PCI with a drug-eluting stent in ≥1 coronary artery between January 2004 and December 2007 were considered for this analysis (n=8371). Patients were excluded if they did not survive to discharge (n=72), had an in-hospital bleeding event as defined by CathPCI and HMORN-Stent covariates of bleeding at access site, retroperitoneal bleeding, gastrointestinal bleeding, genitourinary bleeding, or other bleeding (n=172), or if they were missing specific data on comorbidities or admission presentation data (n=15). Patient comorbidities were obtained using HMORN-Stent recorded data. Medication and pharmacy dispensation data were obtained using specific pharmacy dispensing records, creating indicators of drug availability during the follow-up period.

Outcomes

The primary outcome for this analysis was death or MI after bleeding-related hospitalization. Deaths were derived from health plan data sources and state death certificates. Vital status data were available post discharge for all patients through December 2007. MIs were identified from administrative claims data, using International Classification of Disease, Ninth Revision, Clinical Diagnosis Codes (codes 410.XX) for events after discharge from the initial hospitalization. Hospitalizations outside of the hospital systems were similarly captured via administrative claims data as submitted for payment. Bleeding-related hospitalizations were identified by the presence of a hospital admission for a primary discharge diagnosis of a bleeding event, or a secondary discharge diagnosis of a bleeding event and evidence of blood transfusion.16 Bleeding events were obtained by review of the International Classification of Disease, Ninth Revision codes for billed diagnoses occurring after discharge from the index PCI hospitalization. International Classification of Disease, Ninth Revision bleeding diagnoses included gastrointestinal hemorrhage (International Classification of Disease, Ninth Revision codes 455–578), intracranial hemorrhage (430–432), hemarthrosis (719.2), hemopericardium (423), hematuria (599.7), hemoptysis (786.3), vaginal bleeding (623.8–626.2), epistaxis (784.7), and hemorrhage not otherwise specified or other bleeding (459). Bleeding, death, and MI events were captured for the duration of follow-up (either healthcare plan disenrollment or December 2007).

To evaluate the association between bleeding and risk of death and MI, we constructed Cox proportional hazards models17,18 with postdischarge bleeding--related hospitalization as a time-varying exposure. Covariates for adjustment were chosen from previous validated in-hospital bleeding models19 and clinical judgment to include age, sex, and medical and cardiac history (history of bleeding event, MI, cerebrovascular disease, congestive heart failure, diabetes mellitus, peripheral arterial disease, chronic lung disease, chronic kidney disease [CKD] with or without need for dialysis, hypertension, PCI, coronary artery bypass surgery, and dyslipidemia), admission history (presence of cardiogenic shock, acute coronary syndrome, and type versus stable angina or atypical chest pain syndrome), and postdischarge medications. Peripheral arterial disease and dyslipidemia were defined by the definitions used in CathPCI.19 CKD was defined in the HMORN-Stent registry using CathPCI data elements (history of renal failure requiring dialysis) as well as review of the patient record for a documented history of renal failure or serum creatinine level of ≥2.0 mg/dL. To most accurately represent outpatient medication use at the time of follow-up events, we measured postdischarge medications as time-varying covariates using pharmacy prescription and refill claims data, with methods previously described by Tsai et al.16 Specific medications were chosen based on presumed modification of bleeding risk and included clopidogrel, warfarin, proton pump inhibitors (PPI), and histamine receptor antagonists (H2 blocker). As part of a secondary analysis, prescription and refill data on 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors (statins) were also abstracted. To further evaluate the timing of death or MI from the postdischarge bleeding--related hospitalization, we estimated risk of death or MI in specific time intervals (0–60, 61–120, 121–180, 181–365, and >365 days) from the bleeding-related hospital admission.

To examine the risk factors for postdischarge bleeding, we again constructed Cox models,17,18 using time-varying medication availability and the covariates listed above in our models. All statistical analysis was performed using SAS version 9.2.

Results

There were 8371 patients who received a drug-eluting stent from January 2004 through December 2007 across the 3 sites. A total of 218 patients were excluded from the analysis because of a major in-hospital bleeding event (n=146) and in-hospital mortality (n=72). Fifteen patients were excluded for missing data on key comorbidity, admission, or presentation covariates, resulting in a final cohort of 8137 patients (Figure 1). Baseline characteristics of the study population are presented in Table 1. Mean postdischarge follow-up was 547 days (SD 218) with a median of 665 days (interquartile
Outcomes of Postdischarge Bleeding After PCI

Figure 1. Study cohort derivation.

Death or MI Related to Bleeding
After adjustment, post-PCI bleeding-related hospitalizations were significantly associated with higher rates of death or MI (adjusted hazard ratio [HR], 3.09; 95% confidence interval [CI], 2.42–3.96; Figure 4) compared with patients without bleeding events. The highest rates of death or MI were seen within the first 60 days after a bleeding-related hospitalization (Figure 3). In patients having a bleeding-related hospitalization, the HR for death or MI was 7.16 (95% CI, 3.93–13.05) within the first 60 days when compared with those patients without bleeding events. After 60 days from the bleeding-related hospitalization, the HR of death or MI decreased to between 2.87 and 3.21 (61–90 days: HR, 3.06; 95% CI, 0.74–12.64; 91–180 days: HR, 3.92; 95% CI, 1.99–7.75; 181–365 days: HR, 3.80; 95% CI, 2.39–6.04; and >365 days: HR, 3.54; 95% CI, 2.44–5.14) when compared with those patients without a bleeding-related hospitalization. Postdischarge bleeding–related hospitalization was the second most potent independent predictor of death or MI in this population, only following a history of CKD requiring dialysis (HR, 3.58; 95% CI, 2.74–4.67; Table II in the Data Supplement).

Risk Factors for Post-PCI Bleeding-Related Hospitalizations
After multivariable adjustment, the strongest risk factor associated with post-PCI bleeding-related hospitalization was filled prescriptions for warfarin (HR, 3.24; 95% CI, 2.45–4.28). Filling prescriptions for clopidogrel was also associated with a higher risk of bleeding-related hospitalization (HR, 1.28; 95% CI, 1.01–1.63). Primary historical and demographic factors associated with post-PCI bleeding-related hospitalizations included age, history of congestive heart failure, previous bleeding event within the last year, peripheral vascular disease, diabetes mellitus, and CKD with or without dialysis. Among these historical and demographic variables, history of CKD requiring dialysis (HR, 1.67; 95% CI, 1.02–2.71), congestive heart failure (HR, 1.61; 95% CI, 1.24–2.09), CKD without dialysis (HR, 1.55; 95% CI, 1.08–2.23), and peripheral vascular disease (HR, 1.48; 95% CI, 1.15–1.91) were associated with the highest rates of bleeding-related hospitalization (Table 2). Bleeding was not associated with time-varying use of PPI or H2 blocker (HR, 1.16; CI, 0.93–1.45). After adjustment, sex was not significantly associated with bleeding, nor were previous revascularization (coronary artery bypass surgery or PCI), PCI indication, or the presence of cardiogenic shock. Independent factors associated with postdischarge bleeding are shown in Table 2. Dyslipidemia was associated with a decreased event rate of postdischarge bleeding after adjustment (HR, 0.76; CI, 0.59–0.99). Because dyslipidemia is associated with statin therapy, and statin therapy has been associated with decreased rates of inpatient bleeding, a secondary analysis was performed to evaluate for association between statin use and bleeding risk. This secondary analysis of time-varying statin use did not show any significant association between statin use and risk of postdischarge bleeding (HR, 0.97; CI, 0.79–1.20).
Discussion

Patients are most likely to have bleeding-related hospitalizations during the first 30 days after PCI, with the majority of bleeding events being gastrointestinal in origin, and the incidence of bleeding-related hospitalization decreasing over time. Bleeding-related hospitalizations after PCI were significantly associated with death and MI, with a 3-fold increased hazard of death or MI during the duration of follow-up and a >7-fold hazard of death or MI within the first 60 days after the bleeding event. Independent risk factors for postdischarge bleeding differed from inpatient models, with acute coronary syndrome or cardiogenic shock presentation at the time of PCI, previous PCI, and sex not associated with risk of bleeding events. These findings suggest a risk profile for those post-PCI patients most likely to bleed after discharge, the time of greatest vulnerability for postdischarge bleeding, and should draw clinicians’ attention to the extraordinarily high risk for adverse outcomes in the 60 days after a bleeding event.

This study expands the growing body of literature evaluating post-PCI bleeding. Previous work has established a relationship between bleeding and increased major adverse cardiovascular events during the initial hospitalization for PCI, and increasing data support a similar relationship in the outpatient arena, after discharge. Our findings of a relationship between postdischarge bleeding and increased risk of death and MI are consistent with previous analyses, with an overall HR for death and MI similar to that found by Ko et al and consistent with the findings of Kazi et al. The source for these bleeding events seems to be consistent across analyses, with a majority coming from gastrointestinal sources and the highest incidence occurring in the earliest period after discharge. Finally, our study suggests that there is some overlap between traditional risk factors for inpatient bleeding of CKD, peripheral vascular disease, age, and those for postdischarge bleeding, but that factors related to presentation and sex carry less impact for risk after discharge.

Our study has several novel contributions to the literature. First, this is the first study to evaluate the timing of adverse events after a postdischarge bleeding event. We demonstrate that although post-PCI patients are at high risk for death or MI at any time after a bleeding-related hospitalization, the period of highest risk seems to be within the first 60 days after a bleed. These findings are consistent with hypotheses of major bleeding events and transfusions resulting in a prothrombotic milieu.
that can precipitate adverse events.\textsuperscript{22,23} The fact that highest risk of death and MI continues out to 60 days would suggest that the mediator for death and MI is not just the bleeding event itself (ie, hypovolemia and reduced oxygen delivery to tissues, resulting in immediate ischemia\textsuperscript{24}), but may represent continued perturbation in a patient’s hemostatic balance. These findings may also represent the higher mortality and MI risks of a sicker population, and selection bias for those patients healthy enough

Figure 2. Incidence of bleeding-related hospitalizations after discharge from percutaneous coronary intervention (PCI), overall and by bleeding source.

Figure 3. Timing of death or myocardial infarction (MI) after bleeding-related hospitalization.
to tolerate ongoing dual antiplatelet therapy after a bleeding event. However, the significant increase in risk of death or MI in the period extending from immediately after a bleeding event to 60 days raises suspicion from a pathophysiologic mechanism outside of a patient’s inherent risk. Finally, the association between ongoing clopidogrel use and decreased rates of death or MI after bleeding-related hospitalization suggests that there may still be a role for intensive antiplatelet therapy after bleeding events. These findings may represent a need for increased scrutiny and more precise tailoring of clinical decisions surrounding the discontinuation of P2Y12 antagonists after a bleed.

Another novel finding is in the review of risk factors for postdischarge bleeding–related hospitalizations. Although our study found that many inpatient risk factors were also relevant to postdischarge bleeding, we did not find sex or type of presentation for PCI to be significantly associated with bleeding risk. This is inconsistent with the literature on inpatient bleeding, which has identified female sex and acute coronary syndrome or cardiogenic shock presentation at the time of PCI as potent risk factors for inpatient bleeding. This lack of association may emphasize a difference between the evaluation of inpatient and the postdischarge bleeding events: a departure from procedural and PCI presentation factors as influential on outcome, rather focusing on intrinsic patient factors and postdischarge medications that can modulate risk. We did find an association between dyslipidemia and decreased bleeding risk that was not explained by a secondary analysis of time-varying statin use, and offers an avenue for future study. In addition, we did not find any association between H2 blocker or PPI use and bleeding events. The lack of relationship between the use of gastroprotective agents, such as PPIs and H2 blockers, is novel, especially given the majority of bleeds are from a gastrointestinal source. However, this finding may represent confounding by indication, with those patients deemed to be at highest bleeding risk receiving gastrointestinal prophylaxis.

The findings of this analysis add to the data surrounding post-PCI bleeding, and again demonstrate the need for caution with patients at risk for bleeding. Post-PCI bleeding is associated with increased rates of death and MI, even if the bleeding occurs after hospital discharge. Patients at risk for bleeding merit close follow-up and evaluation, as their bleeding events occur early on and carry substantial risk. There is an opportunity for further exploration into possible targets for prevention of bleeding events after the identification and substantiation of known bleeding events. Among those patients on warfarin, it is possible that closer monitoring of international normalized ratios post-PCI may minimize time in supratherapeutic ranges that can place patients at risk for bleeding. Furthermore, data from the WOEST (What is the Optimal Antiplatelet and Anticoagulant Therapy in Patients With Oral Anticoagulation and Coronary Stenting Trial) and ISAR-TRIPLE (Duration of Triple Therapy in Patients Requiring Anticoagulation After Drug-Eluting Stent Implantation) studies offer the possibility of alternative management strategies to either redefine therapy for post-PCI anticoagulation or to at least limit the duration of risk.25,26 Ongoing evaluations with novel anticoagulants and antiplatelet agents may also offer alternatives to current practice with warfarin and clopidogrel.27,28

There are several limitations to our work. First, as with any retrospective analysis, there is risk of residual confounding and bias. Through multivariable adjustment for known bleeding risk factors, we attempted to minimize the residual confounding that may be present. We also excluded patients who had a bleeding event as inpatients or who did not survive to discharge, to accurately isolate postdischarge bleeding events. We made this decision in the belief that inpatient and outpatient bleeds are different events, which is supported by our findings of different risk profiles for inpatient and postdischarge bleeding. A second limitation is the analysis of medications as a variable. With any retrospective analysis of medication use, compliance is a concern. We performed our analysis with the medication use as a time-varying exposure based on medication prescription refills, attempting to capture as much variability in compliance as possible with retrospective data. Third, this study pre-dates the introduction of newer antiplatelet and anticoagulant options,29-33 and so our findings do not reflect the use of these agents. However, clopidogrel and warfarin remain the dominant antiplatelet and anticoagulant medications used in the United States,34,35 suggesting that our results remain applicable to a large number of patients undergoing PCI. Fourth, our analysis does not identify readily modifiable risk factors for postdischarge bleeding. Identifying such risk factors remains an area that requires further study. However, our findings can aid clinicians in
refining the profile of patients at highest risk as well as defining time periods of highest vulnerability after PCI and bleeding events. Fifth, we were unable to identify other recognized risk factors for bleeding, such as the presence of malignancy or inflammatory conditions, as these are challenging to obtain from administrative data and retrospective data sets. However, we did include a broad range of covariates for risk adjustment, chosen from established bleeding models as well as clinical judgment. Finally, the size of our cohort may be a limitation for our analysis of death or MI after bleeding events. However, despite the smaller cohort, a statistically significant relationship was still observed between postdischarge bleeding and death or MI.

In summary, bleeding-related hospitalization is a major risk for death or MI in patients after PCI. Patients at risk for bleeding-related hospitalizations tend to be older, with more comorbid conditions including CKD, diabetes mellitus, and heart failure, with higher rates of warfarin use. Bleeding-related hospitalizations occur early after PCI and are associated with higher rates of subsequent death and MI, which is most pronounced in the first 60 days after the bleeding event. Clinicians should be aware of this vulnerable period after a postdischarge bleed. It is possible that focusing resources and increasing vigilance during this critical period may improve patient outcomes.

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Disclosures

None.
References


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SUPPLEMENTAL MATERIALS

Supplemental Table Legends:

Supplemental Table 1. Incidence of Bleeding by Time Interval from Discharge

Supplemental Table 2. Cox Proportional Hazard Ratios of Demographic, Clinical and Medication Variables for Post-Discharge Death or Myocardial infarction.
Supplemental Table 1. Incidence of Bleeding by Time Interval from Discharge

<table>
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<th>Time Interval</th>
<th>Any Bleeding</th>
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<th>Genitourologic Bleeding</th>
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<th>Pulmonary Bleeding</th>
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<td>35</td>
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Supplemental Table 2. Cox Proportional Hazard Ratios of Demographic, Clinical and Medication Variables for Post-Discharge Death or Myocardial infarction.

<table>
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<tr>
<th>Variable</th>
<th>Hazard Ratio for post-discharge death or myocardial infarction</th>
<th>95% Confidence Interval</th>
<th>p value</th>
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<td>2.42</td>
<td>3.96</td>
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<tr>
<td>Cardiogenic shock</td>
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<td>Dyslipidemia</td>
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**PCI Presentation**

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</tbody>
</table>

*All table variables are categorical and binary with the exception of age and PCI presentation; †PCI = Percutaneous Coronary Intervention; ‡MI = Myocardial Infarction; §ACS = Acute Coronary Syndrome; ‖STEMI = ST-Elevation Myocardial Infarction