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Bleeding Risk Following Percutaneous Coronary Intervention in Patients with Diabetes Prescribed Dual Anti-platelet Therapy

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Abstract

Background—Patients with diabetes (DM) experience higher rates of in-stent restenosis and greater benefit from DES implant at the time of PCI, necessitating prolonged dual anti-platelet therapy (DAPT). While DAPT reduces risk of ischemic events post-PCI, it also increases risk of bleeding. Whether bleeding rates differ among patients with and without DM receiving long-term DAPT is unknown.

Methods—Among patients who underwent PCI and were maintained on DAPT for 1 year in a multicenter US registry, we assessed patient-reported bleeding over one year following PCI in patients with and without DM. Multivariable, hierarchical Poisson regression was used to evaluate the association of DM with bleeding during follow-up.

Results—Among 2334 PCI patients from 10 US hospitals (mean age 64, 54% ACS), 32.6% had DM. In unadjusted analyses, patients with DM had fewer bleeding events over the year following PCI (DM vs no DM: BARC =1: 78.0% vs 87.7%, $p<0.001$; BARC =2: 4.3% vs 5.3%, $p=0.33$). Following adjustment, patients with (vs. without DM) had a lower risk of BARC =1 bleeding during follow-up (relative risk [RR] 0.89, 95% CI 0.83–0.96). This decreased bleeding risk persisted after removing bruising from the endpoint definition.

Conclusions—In a real-world PCI registry, patients with DM experienced lower risk of bleeding risk on DAPT. As patients with DM also derive greater ischemic benefit from DES, which requires prolonged DAPT, our findings suggest that the balance between benefit and risk of this therapeutic approach may be even more favorable in patients with DM than previously considered.

Keywords

Diabetes; Dual Anti platelet therapy; Bleeding

The introduction of drug-eluting stents (DES) revolutionized percutaneous coronary interventions (PCI) by creating a more durable treatment with lower risks of restenosis compared with bare metal stents (BMS). However, achieving these benefits requires use of prolonged dual anti-platelet therapy (DAPT), which increases patients' risks of bleeding.(1–5) Recent data from the DAPT trial showed that even longer administration of DAPT, for up to 30 months as compared with 12 months, further reduces ischemic complications following DES implantation at the cost of increased bleeding.(6) Consequently, the decision to use DES vs. BMS requires carefully balancing its benefits and risks for individual patients.

Nearly one-third of all patients undergoing PCI have diabetes mellitus (DM), a group at particularly high risk for restenosis with bare metal stents and for whom the absolute reduction in the risk of restenosis with DES is particularly high.(6) Despite the advantages of DES in this population, whether or not patients with versus without DM are at increased risk for bleeding with long-term DAPT is not known. Potential mechanisms for lower risk of bleeding in this group of patients has been suggested by prior work underscoring higher

rates of clopidogrel hyporesponsiveness(7–9) and greater platelet reactivity(10,11) in patients with type 2 DM. However, this hypothesis has not been fully evaluated in clinical studies. To address this gap in knowledge, we compared bleeding outcomes over the year following index PCI in patients with and without DM in a large, contemporary, multicenter PCI registry.

METHODS

Study Design and Participants

Details regarding the OPS (Outcomes of PCI Study) and PRISM (Patient Risk Information Services Manager) prospective observational registries have been previously described. (12,13) From April 2009 to October 2011, consecutive PCI patients from 10 U.S. hospitals were prospectively approached for enrollment in OPS/PRISM (6 hospitals in PRISM, 3 hospitals in OPS, and 1 hospital with concurrent data collection [Saint Luke's Mid America Heart Institute]). The two registries had identical enrollment criteria and data structure, with the exception that PRISM patients were followed at 1, 6, and 12 months after PCI while OPS patients were followed at 6 and 12 months only.

Patients were enrolled by trained study coordinators at each site. All patients who underwent PCI, were able to complete an in-hospital interview, and agreed to participate were included. Chart abstraction was completed by trained study coordinators who entered detailed procedural data on the PCIs and information on patients' socio-demographic characteristics, comorbidities and discharge medications at the time of their initial procedure. DM was defined as a diagnosis of type 1 or type 2 DM and derived from baseline chart abstraction.

Consenting patients completed an in-person interview during their index admission that quantified their limitations in activities of daily living, angina frequency, generic and disease-specific quality of life (14), adherence to cardiac medications, access to care limitation due to cost and cigarette smoking status. Centralized phone follow-up interviews at 1 (PRISM sites only), 6, and 12 months following index PCI were performed by a specialized team at the coordinating center. Several attempts to reach the patient by phone were pursued, and, if unsuccessful, follow-up interviews were mailed to the patients with a pre-paid envelope. Each participating site obtained Institutional Research Board approval, and all patients provided informed consent for baseline and follow up assessments. For the present analysis, we excluded patients if they were not discharged on DAPT (i.e. a thienopyridine or aspirin; Figure 1).

Bleeding Outcomes

As part of the OPS-PRISM study, patients were asked to report interval hospitalizations since their last study contact during the follow-up interviews at 1, 6, and 12 months follow-up. In addition, patients were asked whether they had experienced easy bruising, easy bleeding, occasional nose or gum bleed or serious bleeding since their last interview. If any of these bruising or bleeding outcomes were reported, a follow-up question asked patients what they did about this bruising or bleeding. Choices included “didn't tell any doctor”, “told doctor, but no treatment”, “doctor stopped a medicine or switched to another

medicine”, “treated with transfusion” or “treated by hospitalization”, with the option to select all answer choices that applied (Supplemental Table 1).

The severity of bleeding events was then categorized according to the Bleeding Academic Research Consortium (BARC) guidelines, in which each bleeding event is graded from one to five, with one representing nuisance bleeding and five representing fatal bleeding.(15) The primary outcome for our study was BARC 1 bleeding over the 12 months following index PCI, defined as answering in the affirmative to the question, “Have you had easy bruising, easy bleeding, occasional nose or gum bleed or serious bleeding” since the last interview. If a patient responded “no” to serious bleed, and they either took no action or reported that they “told doctor, but no treatment [was pursued]”, the event was considered a BARC 1 bleed. The secondary outcome was BARC 2 bleeding, defined as any bleeding event that either required medical intervention by a healthcare professional or lead to hospitalization, increased level of care, or further evaluation. Specifically, patient responses were classified as a BARC 2 bleeding event as follows: If patient reported a serious bleeding but selected “told doctor, but no treatment” or “doctor stopped a medicine or switched to another medicine.” BARC 3 events were defined as those requiring blood transfusion or hospitalization. For patients with multiple bleeding events, only the most severe bleeding event was included in the analysis. This study excluded patients undergoing coronary artery bypass grafting. In addition, there were no fatal bleeds in our study (BARC 5 bleeds). Therefore, only BARC 1, 2 and 3 categories were evaluated in this analysis.

Statistical Analysis

Baseline characteristics, including demographic, socioeconomic, and clinical factors at baseline were compared between patients with and without DM using chi-square test for categorical variables and *t*-test for continuous variables. The incidence of bleeding over the year following index PCI, as assessed by a BARC score 1, was compared between patients with and without DM at each follow-up time point using the chi-square test. We also compared BARC 2 bleeding outcomes between patients with and without DM at each time point using the chi-square test. A multivariable, repeated measures logistic regression model was used to assess the independent association between DM status and BARC 1 bleeding outcomes over the year following index PCI. Covariates for the multivariable model were selected *a priori* based on prior literature review and clinical judgment and included baseline age(16), sex(16), race, platelet count, body mass index, history of chronic kidney disease(17), history of chronic lung disease, anticoagulation at discharge, baseline hemoglobin, and bleeding/transfusion during index hospitalization(18). We also adjusted for a history of bleeding problems, history of heart failure, and history of previous percutaneous intervention; and for acute coronary syndrome (ACS) as the indication for index PCI(19). We also examined the interaction between DM and indication for PCI (ACS vs. elective) to assess whether the association between DM and bleeding varied by PCI indication.

In addition to the primary model, we performed a number of sensitivity analyses. First, we excluded bruising from the definition of bleeding (i.e. BARC 1 excluding bruising as the outcome). Second, we performed an “on-treatment analysis” in which patients were required to have a 12-month assessment at which they were on DAPT. Third, because only patients

from the PRISM registry had 1 month follow up, we conducted a secondary analysis evaluating the independent association of DM with bleeding at 1 month following index PCI only among patients enrolled in the PRISM registry. Finally, we examined DAPT discontinuation rates between patients with and without DM using chi-square tests, to examine the possibility that the observed differences in bleeding rates were explained by differing DAPT discontinuation rates.

Baseline data were infrequently missing, with a mean number of missing items per patient of 0.16 and all individual variables having a missing rate of <10%. Single imputation was used to account for missing variables using IVEware (Imputation and Variance Estimation Software; University of Michigan's Survey Research Center, Institute for Social Research, Ann Arbor, MI). In addition, to minimize the potential bias due to missing outcomes data, we calculated a non-parsimonious propensity score with successful 12-month follow-up as the dependent variable. An inversely-weighted propensity score was assigned to each patient (20), to provide greater weight to the outcomes of patients who were most like those missing follow-up data. The results of this model were consistent with the main analyses, and thus only the unweighted analyses are presented. All remaining analyses were conducted using SAS v9.3 (SAS Institute, Inc., Cary, NC), and statistical significance was determined by a 2-sided p-value of <0.05.

RESULTS

Study Participants

Of 3299 patients from 10 U.S. sites enrolled in the OPS-PRISM registry, we excluded 135 (4.1%) patients who were not discharged on a thienopyridine or aspirin. We also excluded 218 patients (6.9%) who did not have available bleeding data during any follow-up assessment. Patients who were missing outcomes data were more likely to be younger, non-white race, smokers, and lower socioeconomic status compared with those in the analytic cohort (Supplemental Table 2). In addition, patients with missing data were less likely to be treated with a DES, had lower hemoglobin levels, and were more likely to report bleeding issues at baseline.

Our final analytic cohort thus consisted of 2946 patients (55% ACS) who were discharged on DAPT following index PCI, of whom 966 (32.7%) had DM. The baseline demographic and clinical characteristics of patients with vs. without DM are shown in Table 1. Patients with DM were more likely to be female (32.7% vs. 26.5%), non-white (12.4% vs. 6.5%), have higher body mass indices (32.7 ± 6.8 vs. 29.3 ± 5.6), and chronic kidney disease (14.9% vs. 5.2%). They also had lower baseline hemoglobin levels ($13.1 \text{ g/dL} \pm 1.7$ vs. $14.0 \text{ g/dL} \pm 1.6$) and nadir hemoglobin levels ($12.2 \text{ g/dL} \pm 1.7$ vs. $13.0 \text{ g/dL} \pm 1.7$), and were more likely to have undergone prior PCI (49.2% vs. 37.1%).

Bleeding Outcomes

In unadjusted analyses, patients with DM were less likely to report a bleeding event over the year following PCI (DM vs no DM: BARC 1: 78.0% vs 87.0%, $p < 0.001$; Figure 2). Patients with DM experienced statistically lower bleeding rates vs. patients without DM at 6

and 12 months of follow-up (63.8% vs. 75.5%, $p<0.001$ at 6 months; 64.2% vs. 70.8%, $p<0.001$ at 12 months). After adjusting for demographic and clinical factors, patients with DM had lower odds of BARC 1 bleeding during follow-up (odds ratio [OR] 0.64, 95% CI 0.54–0.75 vs. no DM). This decreased risk of bleeding did not vary by PCI indication (ACS vs. elective; p -interaction=0.58) and also persisted after excluding bruising from the definition of bleeding (OR 0.83, 95% CI 0.72–0.96). BARC 2 bleeding rates were similar among patients with and without DM (5.9% vs. 5.7%, respectively, $p=0.845$).

In the secondary on-treatment analysis, patients with DM (vs. without) who were discharged and maintained on DAPT for 12 months also had a lower likelihood of BARC 1 bleeding at 6 months and 12 months (OR 0.54, 95% CI 0.42–0.69 at 6 months and OR 0.67, 95% CI 0.53–0.84 at 12 months). In the analysis of only PRISM patients ($n=2270$), the likelihood of BARC 1 bleeding was also lower at 1 month in patients with DM (OR 0.66, 95% CI 0.55–0.79 compared to patients without DM). Finally, the rates of DAPT discontinuation during the 1-year follow-up were similar between groups (DM vs. no DM: 13.6% vs. 14.2%; $p=0.72$) as were the reasons for discontinuation (Supplemental Table 3).

DISCUSSION

In this multicenter, contemporary PCI registry, we found that patients with DM experienced lower risk of BARC 1 bleeding over the year following PCI compared with patients who did not have DM. Importantly, these results persisted after adjustment for multiple potential confounders and in multiple sensitivity analyses. Collectively, these data reinforce the preferential use of DES over BMS in patients with DM by supplementing the well-known greater absolute risk reduction in restenosis in patients with DM with a lower risk of bleeding—the potential adverse consequence of using DES due to prolonged DAPT.

Prior Studies

Our study extends the prior literature, which has been primarily limited to sub-studies of clinical trials. In the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel—Thrombolysis in Myocardial Infarction (TRITON TIMI-38), patients with a myocardial infarction treated with PCI were randomized to DAPT with prasugrel vs. clopidogrel. In pre-specified subgroup analyses, major bleeding rates (2.6% vs. 2.0%) and major or minor bleeding rates (4.8% vs. 4.2%) were similar between patients with and without DM, respectively. However, patients with DM did not experience a significant increase in bleeding with more aggressive platelet inhibition (i.e., prasugrel vs. clopidogrel), in contrast with the results among patients without DM.⁽²¹⁾ As a result, the net clinical benefit of prasugrel compared with clopidogrel was greater in patients with DM, compared with patients without DM.⁽²¹⁾ Similarly, the recently published Long-Term Use of Ticagrelor in Patients with Prior Myocardial Infarction (PEGASUS) (26) trial, which randomized patients after PCI to long-term ticagrelor and aspirin versus aspirin alone, showed no difference in bleeding between patients with and without DM. However, as patients with DM had a greater absolute risk reduction in terms of ischemic benefits with DAPT vs. those without DM, the absolute net benefit of DAPT was greater in patients with (vs. without) DM⁽¹⁾. In the Dual Antiplatelet Therapy (DAPT) trial of long-term clopidogrel

and aspirin versus aspirin alone, similar to the above studies, patients with DM had similar rates of major bleeding compared with those without DM, and all patients experienced an increased risk of bleeding with DAPT, regardless of DM status(6). In addition, in contrast to the results of TRITON-TIMI 38, PEGASUS, and DAPT, the PLATelet inhibition and patient Outcomes (PLATO) study(22), which randomized patients after ACS to DAPT with ticagrelor vs. clopidogrel, showed rates of major bleeding not related to bypass surgery that were higher in patients with vs. without DM (5.2% vs. 3.8%) with no differential effect of ticagrelor vs. clopidogrel on either ischemic or bleeding outcomes in patients with and without diabetes.

Some of the differences between our results and those from the analyses of clinical trials likely result from the bleeding definitions used. Similar to most studies, we found no difference in higher level BARC bleeds between those with and without DM; and the lower bleeding rate that we found in patients with diabetes was limited to BARC 1 events, which were not captured in the outcomes of large clinical trials. As such, it is possible that if these other studies would have expanded their definitions of minor bleeds, similar results might have been observed. We believe that the bleeding definition used in our study is more comprehensive than those used in clinical trials, and which has been shown to have substantial impact on patients' quality of life. As such, our study expands the current understanding of the bleeding outcomes, and the risk-benefit balance of long-term DAPT in this important patient group. In addition, the majority of the patients in our study were treated with clopidogrel and not the more potent anti-platelet agents, which may have contributed to some of these differences. Another important distinction lies in that our study represents a real-world clinical cohort, including patients who otherwise are not eligible for or choose not to participate in clinical trials. Nevertheless, we acknowledge the uncertainty that surrounds the decision to favor prolonged DAPT in patients with DM, as one weighs the risks and benefits in individual patients, particularly with seemingly disparate findings across studies.

Clinical Implications

Appropriate patient selection for prolonged DAPT is critically important, as one must weigh the additional ischemic benefits against the risks of bleeding that are associated with DAPT. This risk-benefit balance was recently highlighted by the Dual Antiplatelet Therapy (DAPT) trial, in which prolonged DAPT for 30 vs. 12 months after DES implantation led to reduced ischemic outcomes but more bleeding.⁶ Ideally, patients who are selected for prolonged DAPT should be those at higher risk for recurrent thrombotic events and who also have a lower risk of bleeding. In many situations, such as advanced age, the factors that increase ischemic risk also increase bleeding risk, making the decision to prescribe prolonged DAPT more challenging. In the setting of DM, the ischemic benefits of prolonged DAPT are well established—both in terms of DES use (which requires longer DAPT vs. BMS) for reduction of restenosis and for greater absolute risk reduction of ischemic events, such as myocardial infarction. Our findings of less bleeding with DAPT among those patients with DM demonstrate that the risk-benefit balance of prolonged DAPT may be even more favorable than previously recognized.

Limitations

Our findings should be considered in the context of several potential limitations. First, bleeding events were self-reported, which may have led to over- or under-estimation of bleeding events. However, the presence of DM would not be expected to lead to differential reporting bias. Second, DAPT adherence was also self-reported, as we did not have access to pharmacy data to verify the exact duration of DAPT use. Third, the majority of patients in this analysis were prescribed clopidogrel, potentially limiting our ability to examine whether there were differences in outcomes between different anti-platelet therapies, such as prasugrel and ticagrelor. Fourth, there was a paucity of DM-specific data such as differentiation of T1DM from T2DM, HbA1c, and background insulin use in our data set, limiting our ability to characterize bleeding outcomes across the spectrum of duration and control of DM. Finally, despite the extensive adjustments and multiple sensitivity analyses that demonstrated stability of our findings, due to the observational nature of our study, a possibility of residual confounding cannot be definitively excluded.

Conclusions

In this real-world PCI registry, patients with DM discharged on DAPT experienced significantly lower likelihood of bleeding than those without DM over the year following index PCI. As patients with DM also derive greater ischemic benefit from DES, which require prolonged DAPT, our findings suggest that the balance between benefit and risk of this therapeutic approach is likely even more favorable in patients with DM than previously recognized.

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Figure 1.
Flowchart of analytic cohort from the OPS & PRISM registries
*TPD=Thienopyridine

Figure 2.

Bleeding outcomes over the year following index percutaneous intervention in patients with and without diabetes mellitus

* Most severe level of bleeding reported

* For multivariable adjustment, the following covariables were used: Age, sex, race/ethnicity, BMI, history of CKD, heart failure and chronic lung disease, history of prior PCI and/or MI, use of anticoagulants during admission, bleeding and/or transfusion during index hospitalization, and index PCI admission lab values including platelets and nadir hemoglobin

Table 1

Baseline characteristics of patients with and without diabetes undergoing PCI

	Overall n=2946	Diabetes n=966	No Diabetes n=1980	P -Value
<i>Sociodemographic</i>				
Mean age (years)	64.4 ± 10.9	64.9±10.3	64.2±11.2	0.090
Male sex	71.5%	67.3%	73.5%	<0.001
White race	91.5%	87.6%	93.5%	<0.001
No insurance	2.7%	2.2%	2.9%	0.280
Completed high school	91.0%	90.2%	91.4%	0.289
Married	68.0%	63.8%	68.8%	0.008
No insurance for medication	6.9%	5.7%	7.5%	0.081
Self-reported avoided care due to cost	21.0%	21.9%	20.6%	0.724
<i>Clinical factors</i>				
Never smoker	43.5%	44.2%	43.1%	<0.001
History of hypertension	83.0%	93.3%	78.0%	<0.001
Chronic kidney disease	8.4%	14.9%	5.2%	<0.001
Prior MI	27.1%	31.2%	25.2%	<0.001
Prior PCI	41.0%	49.2%	37.1%	<0.001
Prior heart failure	14.4%	20.6%	11.4%	<0.001
Chronic lung disease	12.5%	15.0%	11.2%	0.003
<i>Bleeding/Anemia-related Variables</i>				
Body mass index (kg/m ²)	30.4 ± 6.2	32.7±6.8	29.3±5.6	<0.001
History of Bleeding problems* (BL)	6.4%	6.2%	6.6%	0.664
Anticoagulation (at discharge)	6.7%	7.5%	6.4%	0.267
Platelets (×1000/μL) (BL)	218.7 ± 64.4	217.4±64.4	219.3±64.4	0.470
Thrombocytopenia (BL) [†]	0.9%	1.4%	0.6%	0.041
Hemoglobin (BL; g/dL)	13.7 ± 1.7	13.1±1.7	14.0±1.6	<0.001
Hemoglobin (nadir; g/dL)	12.7 ± 1.7	12.2±1.7	13.0±1.7	<0.001
In-hospital blood transfusion	1.6%	2.2%	1.3%	0.079
Drug-eluting stent	82.1%	82.7%	81.8%	0.542
In-hospital bleed [‡]	2.3%	2.1%	2.4%	0.548

* Defined as answering in the affirmative to the following questionnaire question: Do you have bleeding problems, such as blood in your urine, blood in your stool, coughing up blood or vomiting blood, or an ulcer?

[†] Defined as platelet count of <100, 000/μL

[‡] Defined as 2 g/dL drop in hemoglobin

Anticoagulation variable defined as discharged on any of the following: Rivaroxaban, Dabigatran, Coumadin, or Warfarin

BL=at baseline, defined as laboratory value drawn just prior to index PCI

Data are presented as mean ± standard deviation or percentages