

BLEEDING RISK FOLLOWING PERCUTANEOUS INTERVENTION IN PATIENTS
WITH DIABETES PRESCRIBED DUAL ANTI PLATELET THERAPY

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BLEEDING RISK FOLLOWING PERCUTANEOUS CORONARY INTERVENTION IN
PATIENTS WITH DIABETES PRESCRIBED DUAL ANTI PLATELET THERAPY

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ABSTRACT

Patients with diabetes (DM) experience higher rates of in-stent restenosis and therefore greater benefit from drug eluting stent (DES) implant at the time of percutaneous coronary intervention (PCI). DES stent implantation necessitates prolonged dual anti-platelet therapy (DAPT). While DAPT reduces the risk of ischemic events post-PCI, it also increases the risk for bleeding. Whether long-term rates of bleeding differ among patients with and without DM receiving DAPT in real-world practice is unknown.

Among patients who underwent PCI and were maintained on DAPT for 1 year in a multicenter US PCI registry, OPS/PRISM, we assessed patient-reported bleeding (defined according to the Bleeding Academic Research Consortium, BARC) over the year following PCI in patients with and without DM. Bleeding assessments were conducted by a study coordinator at index hospitalization (baseline) and at 1, 6 and 12 months following discharge. Multivariable logistic regression was used to evaluate the association of DM with bleeding during follow-up. In a sensitivity analysis, we excluded bruising from BARC-defined bleeding events. Covariates included in the model were selected *a priori* and were abstracted from the medical record by study coordinators. Covariates included demographic (e.g. age, insurance status) and clinical (e.g. medical history, procedural indication) variables.

Among 2270 PCI patients (mean age 64, 72% male, 54% ACS), 32.6% had DM. In unadjusted analyses, patients with DM had fewer BARC ≥ 1 bleeding events over the year following PCI (DM vs no DM: BARC ≥ 1 : 77.7% vs 87.6%, $p < 0.001$; BARC ≥ 2 : 4.5% vs 5.3%, $p = 0.41$). After adjusting for demographic and clinical factors, patients with DM had lower odds of BARC ≥ 1 bleeding during follow-up (odds ratio [OR] 0.52, 95% CI 0.39-0.68, $p < 0.001$ vs. no DM). This decreased odds of bleeding persisted after removing bruising from the endpoint definition (OR 0.77, 95% CI 0.62-0.96).

In a real-world PCI registry, patients with DM experienced lower bleeding on DAPT than those without DM. 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 is even more favorable in patients with DM than previously considered.

APPROVAL PAGE

The faculty listed below, appointed by the Dean of the School of Medicine, have examined a thesis titled “Bleeding Risk Following Percutaneous Intervention in Patients with Diabetes Prescribed Dual Anti Platelet Therapy,” presented by Anna Grodzinsky, candidate for the Master of Science degree, and certify that in their opinion it is worthy of acceptance.

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CHAPTER 1

INTRODUCTION

Percutaneous coronary intervention (PCI) is a cardiovascular procedure indicated for treatment of significant coronary stenosis and typically involves stent placement in a large coronary artery. This procedure may be indicated in an acute setting, such as during an acute coronary syndrome, or heart attack.¹ The procedure may also be indicated for patients with refractory angina, or cardiac-type chest pain, which has not responded to optimal medical management with cardiac medications.² The volume of PCIs has steadily risen over the past several decades.³

Bleeding events following PCI are common and are associated with an increased cost and increased short- and long-term risk of morbidity and mortality.^{4,5} The prevalence and prognosis of bleeding in the first year after PCI was recently described by Amin et al, who reported that 37.5% of patients reported nuisance bleeding, which was associated with worse quality of life.⁶

There are two stent type categories used in PCI procedures: the drug eluting (DES) and the bare metal stent (BMS) (Table 1). The DES is a more contemporary device consisting of a metallic stent backbone, antiproliferative drug, and a polymer that serves as the vehicle for drug delivery and drug release.⁷ On the other hand, the BMS is composed of a metallic design without an embedded antiproliferative drug.⁷ Prior studies exploring the efficacy of DES versus BMS have concluded that DES use is preferred because of improved ischemic outcomes and decreased need for repeat revascularization as compared to BMS use.⁸ In addition to efficacy considerations, long term bleeding risk estimation may inform whether or not a DES with prolonged DAPT (and potentially higher risk of bleeding) versus

a BMS with a need for shorter duration post procedural anti-platelet therapy (and a lower risk of bleeding) is to be preferred. However, other considerations like the likelihood of in-stent restenosis must be simultaneously considered at the time of PCI.

Diabetes mellitus (DM) may be such a factor that needs to be taken into account when choosing the stent type in PCI. Patients with DM constitute approximately thirty percent of all patients undergoing coronary revascularization, including PCI and coronary artery bypass grafting.⁹ More specifically, patients with DM constitute approximately twenty five percent of all patients undergoing PCI in large clinical trials.^{10,11} There is reason to believe that patients with diabetes, as a result of increased platelet aggregation and hyporesponse to anti platelet medication, may experience bleeding at different rates than patients without diabetes. Prior studies exploring in- stent restenosis following PCI with drug eluting stent (DES) suggest that patients with DM experience higher rates of in-stent restenosis and therefore greater net benefit from DES (as compared with BMS) implant at the time of PCI.^{10,12-14} As a result, the American Heart Association provides a Class I (highest available) recommendation that patients with DM receive prolonged DAPT following DES placement to decrease risk of late stent thrombosis.^{1,15} While DAPT reduces the risk of ischemic events post-PCI, it is known to also increase the risk for bleeding in patients undergoing elective PCI, as well as those undergoing PCI for an indication of acute coronary syndrome.¹⁶⁻¹⁸ It is unknown, however, whether this risk of bleeding would be generalizable to the subgroup of coronary artery disease patients who have DM. Having such information would help to inform clinical decisions regarding duration of DAPT prescription, in this particular risk group.

There is reason to believe that not only due to restenosis risk, but also due to bleeding risk, choosing a DES for patients with DM who undergo PCI would be beneficial. In large acute coronary syndrome clinical trials exploring ischemic outcomes of patients on DAPT following PCI, such as Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel—Thrombolysis in Myocardial Infarction (TRITON TIMI-38), pre-specified subgroup analyses of patients with DM revealed that these patients derived a greater benefit, and specifically a lower bleeding risk, from more aggressive platelet inhibition after acute coronary syndrome as compared with patients without DM.¹⁹ In TRITON TIMI-38, visits to assess clinical end points and adverse events, including bleeding, were at hospital discharge, day 30 (28-35 days), day 90 (± 2 weeks), and every 90 days (± 2 weeks) thereafter for up to 15 months.¹⁹ By 15 month follow up, patients with DM experienced all cause death, non-fatal myocardial infarction, non-fatal stroke and non-fatal major bleeding (14.6% vs. 19.2%, $p=0.001$)²⁰

This greater net benefit is hypothesized to be due to patients with DM experiencing greater platelet reactivity.²¹ While patients in these trials underwent emergent or urgent PCI for an indication of acute coronary syndrome, it is unknown whether patients with DM incur better bleeding outcomes (versus patients without DM) on prolonged DAPT following PCI for a broader set of indications. It is unknown whether or not long-term bleeding rates differ among patients with and without DM receiving prolonged DAPT (Figure 1). We aim to address this study question in the Outcomes of PCI Study-Personalized Risk Information Services Manager (OPS-PRISM) registry, a study including patients undergoing PCI for emergency and elective indications. Accordingly, our first aim is to describe the incidence of bleeding following PCI in patients with and without DM. Our second aim is to evaluate the

independent association of DM with bleeding events, adjusting for relevant clinical and socioeconomic factors. Our final aim is to examine bleeding outcomes according to indication for PCI (i.e. acute coronary syndrome [emergent or urgent] versus refractory angina management [elective]). As an exploratory analysis, we plan to examine raw rates of DAPT discontinuance in patients with and without DM to ensure that differing rates of DAPT discontinuance do not contribute to differing rates of bleeding following PCI.

Table 1. Characteristics of BMS vs. DES stent use during PCI

Bare metal stent	Drug eluting stent
<p>DAPT duration: DAPT recommended for at least 1 month and preferably 1 year following PCI</p>	<p>DAPT duration: DAPT recommended for at least 1 year following PCI</p>
<p>Benefits: May be preferred if patient has history of bleeding problems, planned elective surgery, medication adherence issues</p> <ul style="list-style-type: none"> • Lower cost • Shorter duration of DAPT use 	<p>Benefits: May be preferred if patient able to adhere to longer duration of antiplatelet therapy and thus may therein derive greater benefit from DES (lower risk of in stent restenosis, less risk of resultant repeat revascularization)</p>
<p>Risks: Associated with higher risk of in stent restenosis</p>	<p>Risks: Associated with longer DAPT duration, thus:</p> <ul style="list-style-type: none"> • Higher cost • Associated with higher risk of bleeding

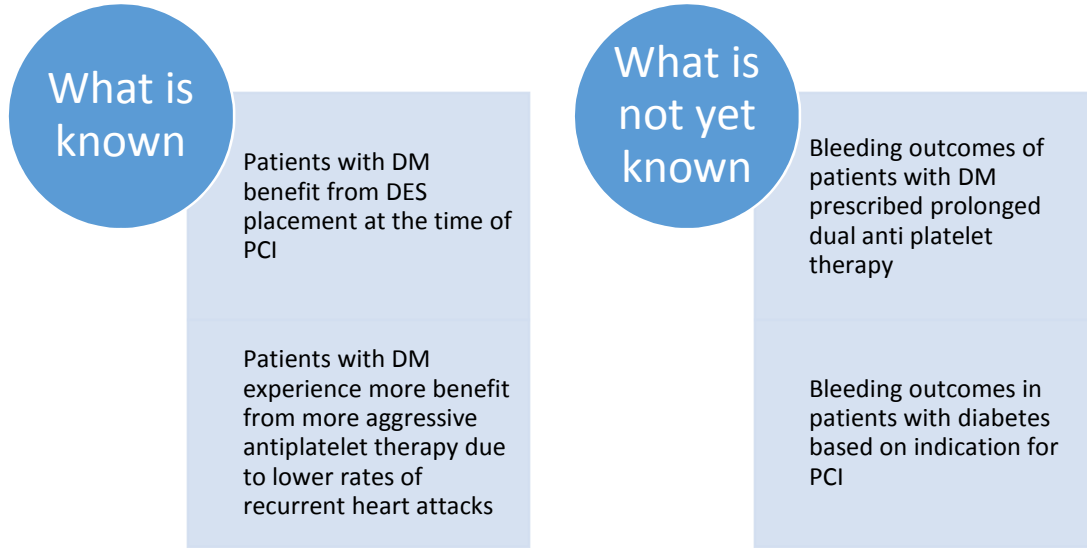


Figure 1. Knowledge Gaps Regarding Patients with Diabetes and Coronary Artery Disease Prescribed Dual Anti platelet Therapy

CHAPTER 2

METHODOLOGY

Study Design and Participants

The Patient Risk Information Services Manager (PRISM) and Outcomes of PCI Study (OPS) prospective observational registries were used as the sources of data for this study. These are ideal databases to answer our research questions as they contain de-identified data for of three thousand coronary artery disease patients available at Saint Luke's Hospital in Kansas City, MO. From May 26, 2009 to October 21, 2011. Overall, 3299 PCI patients from 10 U.S. hospitals were enrolled in PRISM (Supplemental Table 1). PRISM follow up assessments were conducted at 1,6 and 12 months following index PCI. The Outcomes of PCI Study (OPS) registry was a very similar registry to that of PRISM, with identical enrolment criteria. However, OPS enrolled 1901 patients between April 2009 and October 2011, and follow up assessments were conducted at 6 and 12 months following index PCI. The four sites participating in the OPS registry also participated in the PRISM registry (Mid America Heart Institute, Yale, Integris and the Mayo Clinic). The patients were scheduled for urgent PCI for management of acute coronary syndrome or elective PCI for persistent angina. Patients were recruited by the study coordinators at each site. Any patient who had a PCI was approached during their hospital stay post procedure. Notably, patients excluded from analysis were those not discharged on a thienopyridine or aspirin following index PCI. Patients who were not on DAPT at their 12-month assessment and those without a 12 month assessment available were also excluded from the final cohort (Figure 4). Regarding our follow up procedure, three experienced clinical research assistants at the Mid America Heart Institute made all of the follow up phone calls. Follow up interviews were largely conducted by phone

(Figure 2). Occasionally, an interview would be mailed, but these comprised a small percentage of our overall follow up responses. Data that were not derived directly from patient questionnaires, including chart-abstracted data, were obtained by study coordinators/nurses who entered abstracted data into Velos at each site. Velos is an internet-based clinical research platform used for data entry and application.

Procedural data from all PCIs performed during the study period were entered into a procedural case report form by the study coordinator at each site. The PCI case report form collected information including pre procedural medications, indication for PCI (arrhythmia management, preoperative non-cardiac surgery, congestive heart failure, staged intervention, stable coronary artery disease, unstable angina, non ST segment elevation myocardial infarction, ST segment elevation myocardial infarction), clinical evaluation pre procedurally, coronary vessel anatomy (native and graft vessel distribution), and percentage of coronary stenosis as estimated by the operator or adjunctive imaging/procedural modalities such as intravascular ultrasound or fractional flow reserve. Each participating site obtained Institutional Research Board approval, and all patients provided informed consent for baseline and follow up assessments.

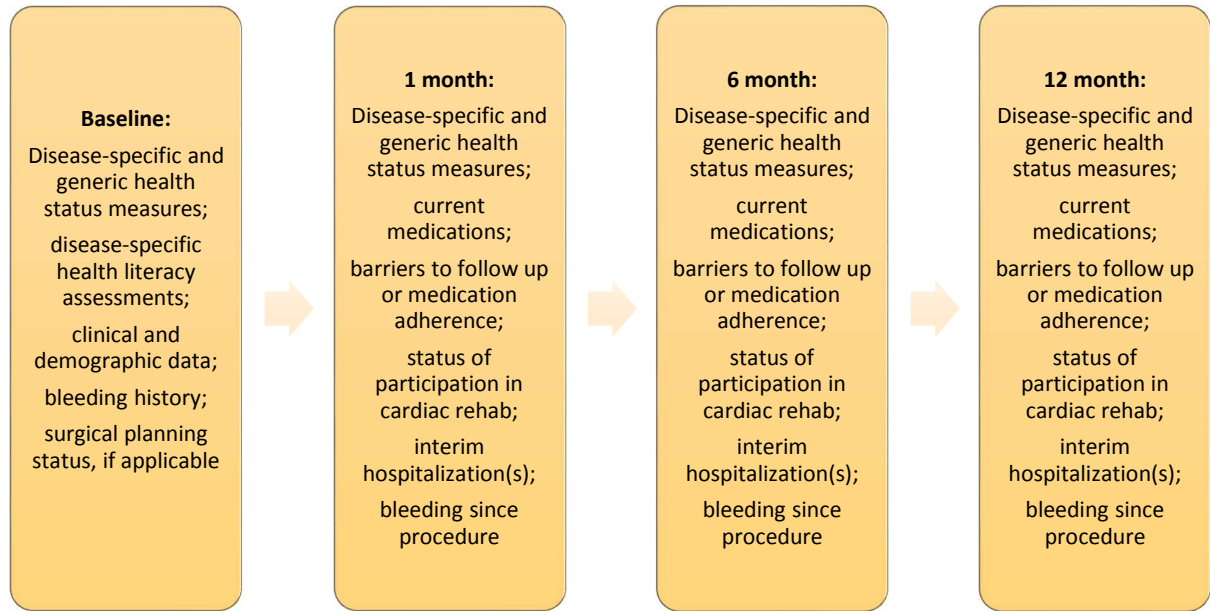


Figure 2. Data collected at baseline and at 1, 6 and 12 month follow up interviews

Measures of Follow-Up Bleeding Data

Within the OPS/PRISM registry data collection process, bleeding events were defined according to standard National Cardiovascular Data Registry definitions (access site bleeding with a hematoma >10 cm for femoral, >5 cm for brachial and >2 cm for radial access). Additionally, retroperitoneal, gastrointestinal, genitourinary bleeding requiring a transfusion, prolonged hospitalizations or hemoglobin drop of greater than 3 g/dL were prospectively collected as bleeding events. For our observational study, bleeding events were defined according to the Bleeding Academic Research Consortium (BARC) guidelines. Based on the BARC classification system, bleeding event severity is graded zero to five, with zero representing no bleeding and five representing fatal bleeding²²(Table 3). Of note, we interpreted BARC 1 bleeding events to include bruising events and subsequently did a sensitivity analysis excluding self-reported bruising events (BARC \geq 1 minus bruising).

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 each follow up interview, 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”. Patients had the option of selecting all answer choices that applied. All patients were required to have a 12-month follow up assessment for the purposes of the primary analysis. Most patients had at least one additional assessment (most commonly at 6 months post index PCI). If a particular patient reported

more than one bleeding event during the follow up period, we included the most severe self-reported bleeding episode for this analysis. Diabetes was defined as a diagnosis of type 1 or type 2 DM derived from baseline chart abstraction.

Patient characteristics, including demographic (age, gender, ethnicity), socioeconomic (insurance status [presence or absence of medication insurance, medical insurance – any vs. none], avoidance of care due to cost in the past year, level of education [high school graduate versus not], marital status [married vs. unmarried]), and clinical (body mass index, kidney disease status, platelet count before PCI procedure, history of bleeding problems, baseline and nadir hemoglobin, blood transfusion status, history of lung disease, heart failure, acute coronary syndrome status, prior PCI, anticoagulation medication status, bleeding in the hospital, drug eluting stent placement) were compared at baseline.

For multivariable adjustment, the following covariates were used: age, gender, race, body mass index, history of chronic kidney disease, acute coronary syndrome at time of presentation, heart failure and chronic lung disease, history of prior PCI, history of myocardial infarction, bleeding and/or transfusion during index hospitalization, and index PCI admission lab values including platelet count and nadir hemoglobin. We selected covariates to be included in the multivariable model *a priori*. These were based on prior literature review and clinical judgment of variables that may confound the association between bleeding and DM status, and included age²³, gender²⁴, ethnicity, platelet count, BMI, history of chronic kidney disease²⁵, history of chronic lung disease, anticoagulation at discharge, placement of drug eluting stent, anemia, bleeding, and transfusion during index hospitalization²³. We also adjusted for a history of bleeding problems, heart failure, history of PCI, and history of acute coronary syndrome²⁶.

Statistical Analysis

Baseline characteristics, including all demographic, socioeconomic, and clinical factors were compared between patients with vs. without DM using Chi square test for categorical variables and Mann-Whitney U test for continuous variables as the continuous variables were not parametrically distributed.

The incidence of bleeding over the year following index PCI, as assessed by a BARC score ≥ 1 , was compared between groups at each follow-up time point using the Chi square test. Assumptions of logistic modeling were met, including an adequate sample size, lack of multicollinearity among predictor variables, and lack of unexplained outliers. Accordingly, a multivariable logistic regression model was used to assess the independent association between DM status and bleeding outcomes over the year following index PCI.

Subsequently, we performed a sensitivity analysis to explore bleeding incidence at follow up when excluding bruising in the definition of bleeding (i.e. BARC ≥ 1 minus bruising as the primary outcome). This analysis was considered informative as healthcare providers rarely recommend antiplatelet therapy discontinuation as a consequence of bruising, which is a common patient concern while on antiplatelet therapy. Because we included bruising within our initial definition of a BARC ≥ 1 bleeding event, it was important to further explore whether removing the commonly reported bruising from outcome definition would change our primary result. Were the results to remain largely unchanged following this sensitivity analysis, this would further support the clinical actionability of our results by demonstrating that pure bleeding outcomes (without bruising included in the definition) are still different in patients with and without DM.

Further, we completed an analysis which assessed bleeding rates (BARC ≥ 1) at 1, 6 and 12 months following index PCI, including all patients discharged on DAPT. This analysis was performed because in the main model, we included patients who we required by our inclusion criteria to have reported taking 1 year of DAPT. Patients with DM are more likely to receive drug-eluting stent at time of PCI (and thus more likely to be on DAPT for 1 year). Non-diabetic and other patients who are perceived to have high bleeding risk by the PCI physician usually get bare metal stent placement, necessitating only 1 month of DAPT. Thus our main model had the potential problem of excluding those at higher risk of bleeding. To ensure that we did not dilute our results because of our methodological approach, we performed this analysis to look at rates of bleeding between patients with and without DM so as to evaluate patients who receive DAPT for less than 1 year (and may have baseline higher bleeding risk). If results of the bleeding outcomes at 1 and 6 months are similar from the results of our main model, that would further support the impact of DM on bleeding outcomes, regardless of perceived baseline bleeding risk.

Lastly, to further exclude the possibility that bleeding differences found were in part explained by different antiplatelet therapy discontinuance rates, we analyzed discontinuance between patients with and without DM who were discharged on DAPT.

In the original dataset, missing baseline data (mean number of missing items per patient=0.17) were imputed using IVEware (Imputation and Variance Estimation Software; University of Michigan's Survey Research Center, Institute for Social Research, Ann Arbor, MI). Little's MCAR test was significant, suggesting that data were not missing completely at random. Single imputation was used to account for missing variables, as the rate of missing data for any individual variable was <10%. Because the baseline characteristics of patients

who did and did not have follow up data at 12 months were statistically different, we evaluated the effect of missingness on bleeding outcomes and found that the Cohen's d was small for each of the significantly different baseline characteristics. As the effect was small (small effect size considered to be <0.1), we deferred further analyses of missingness.

All analyses were conducted using SPSS Statistics 22, and statistical significance was determined by a 2-sided p-value of <0.05 .

CHAPTER 3

RESULTS

Study Population

Of 3299 patients from 10 U.S. sites (Supplemental Table A-3) enrolled in the OPS/PRISM registry, we excluded 135 (4.1%) patients because they were not discharged on a thienopyridine or aspirin. We also excluded 412 patients (13.0%) who did not report taking TPD or aspirin by the one year follow up interview and 482 patients (15.2%) who did not have a 12 month follow up assessment. Our final analytic cohort consisted of 2270 patients (Figure 4). Patients who were missing 12 month outcomes data were more likely to be younger, non-white race, smokers, and of lower socioeconomic status compared with those in the analytic cohort (Supplemental Table 3) In addition, patients with missing data were less likely to be treated with drug eluting stent, had lower hemoglobin levels, and were more likely to report bleeding issues at baseline.

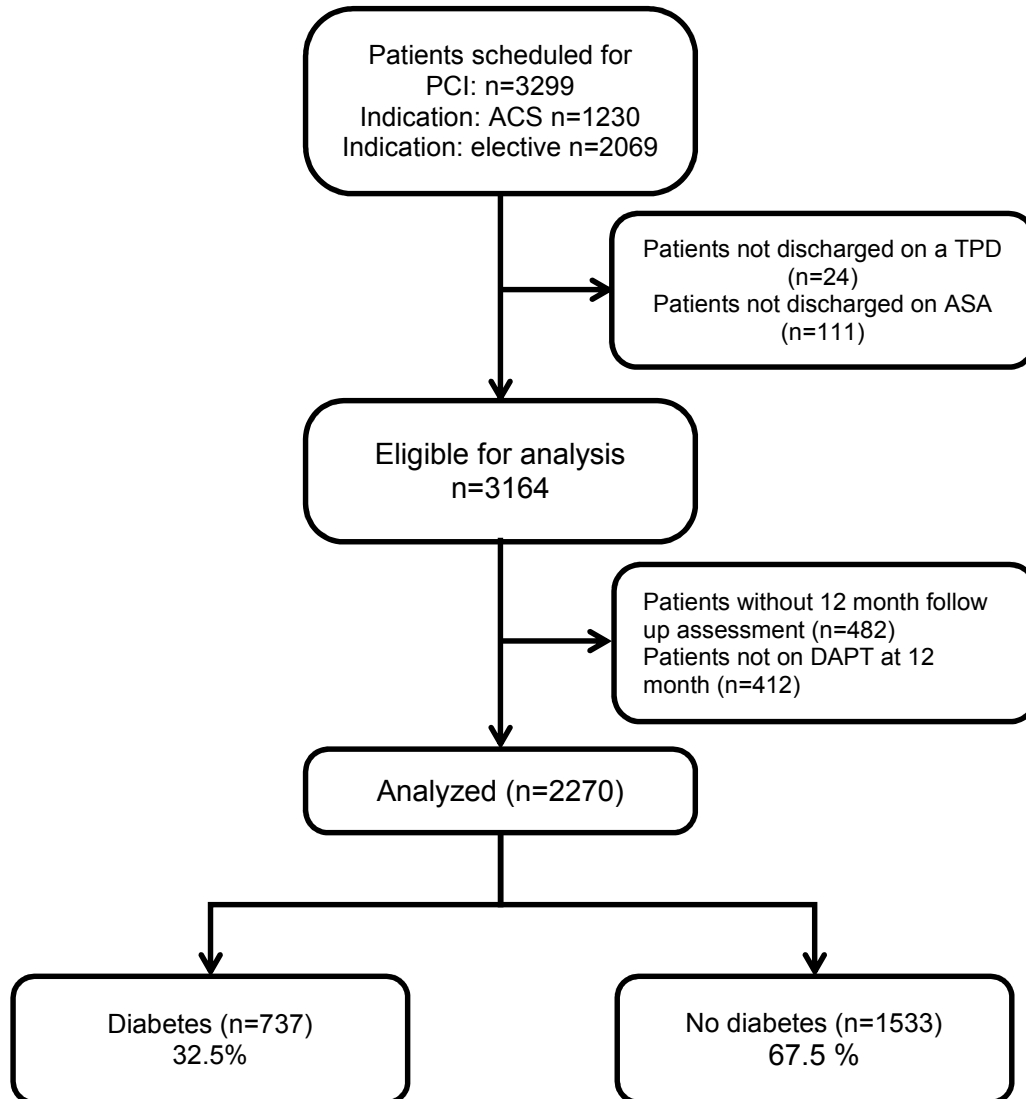


Figure 3. Flow chart of analytic cohort in the OPS-PRISM percutaneous intervention registries

Abbreviations: PCI: percutaneous intervention; ACS: acute coronary syndrome; TPD: thienopyridine; ASA: aspirin

Baseline Characteristics

Among 2270 patients (54% with acute coronary syndrome) who were discharged and maintained on DAPT for one year following index PCI, 737 (32.5%) had DM. The baseline demographic and clinical characteristics of patients with vs. without DM are shown in Table A-1. Patients with DM were more commonly female (31.9% vs. 25.7%), non-white (12.2% vs. 6.6%), have higher BMI (32.7 ± 6.9 vs. 29.3 ± 5.4), and have chronic kidney disease (13.7% vs. 4.6%), a history of heart failure (19.7% vs. 13.3%), lung disease (14.4% vs. 11.3%) and prior myocardial infarction (32.0% vs. 27.0%). They also more commonly had lower baseline (13.1 \pm 1.6 g/dL vs. 14.0 \pm 1.5 g/dL) and nadir hemoglobin (12.3 \pm 1.7 g/dL vs. 13.0 \pm 1.6 g/dL), and have undergone prior PCI (48.4% vs. 36.3%).

Bleeding Outcomes

In unadjusted analyses, patients with DM had lower reported bleeding over the year following PCI using the BARC ≥ 1 classification (DM vs. no DM: BARC ≥ 1 : 77.7% vs. 87.6%, $p < 0.001$), but not when using the BARC ≥ 2 classification (BARC ≥ 2 : 4.5% vs. 5.3%, $p = 0.375$). In adjusted analysis, patients with DM had lower odds of BARC ≥ 1 bleeding during follow-up. After adjusting for demographic and clinical factors, patients with DM had lower odds of BARC ≥ 1 bleeding during follow-up (odds ratio [OR] 0.50, 95% CI 0.38-0.66) as compared with patients who did not have DM. When excluding bruising from BARC ≥ 1 classification, the observed association persisted (OR 0.77, 95% CI 0.62-0.96; Figure 5). This decreased risk of bleeding in DM did not vary by PCI indication (ACS vs. elective; p -interaction=0.324).

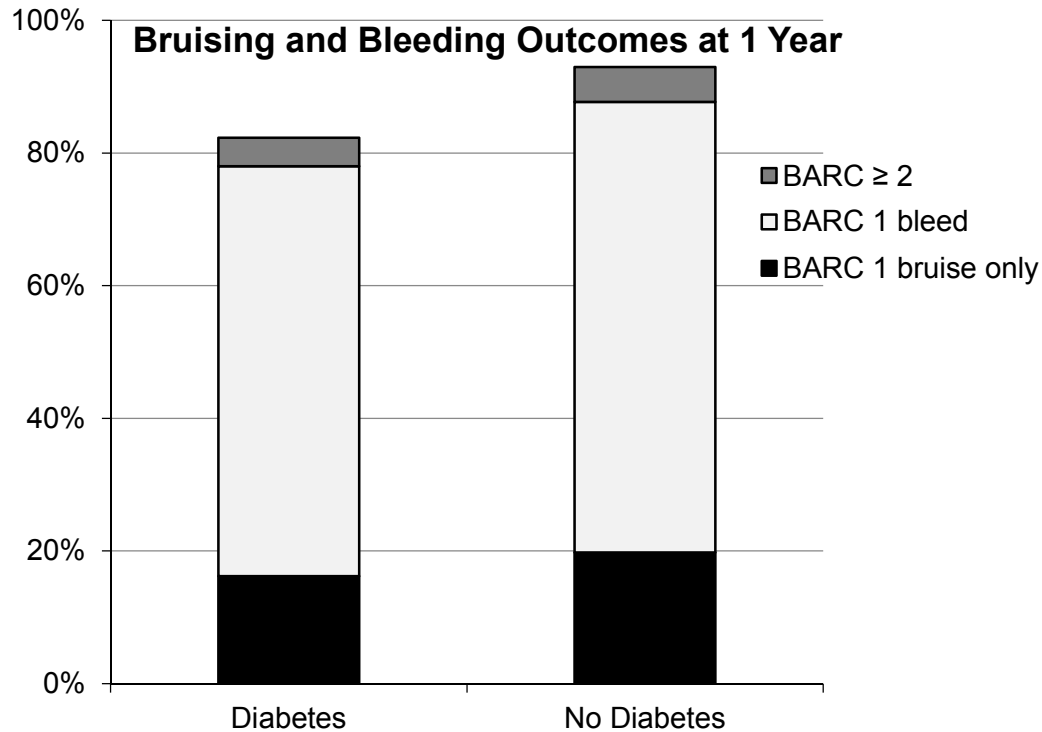
Subsequently, we performed a sensitivity analysis to explore bleeding incidence at follow up after excluding bruising from the definition of bleeding (i.e. BARC ≥ 1 minus

bruising as the primary outcome). This analysis yielded lower bleeding outcomes in patients with DM, as compared with without DM (OR 0.77, 95% CI 0.62-0.96; Figure 5).

We completed a second sensitivity analysis assessing crude bleeding rates (BARC \geq 1 including bruising) at 1,6 and 12 months, including all patients discharged on DAPT, without excluding patients who were not on DAPT at 12 month follow up. In patients with DM, there was no difference in the odds of reporting bleeding at 1 month. However, patients with DM had lower odds of reporting bleeding at 6 months (OR 0.53, 95% CI 0.42-0.67) and 12 months (OR 0.65, 95% CI 0.52-0.81). The crude bleeding rates were not statistically different at 1-month follow up between patients with and without DM, but they were lower at 6 and 12-month follow up (65.1% vs. 73.4%, $p < 0.001$ and 77.7% vs. 87.6%, $p < 0.001$ in patients with vs. without DM at 6 and 12 months, respectively).

Table 2. Adjusted odds of \geq BARC 1 bleeding in patients with diabetes on long term dual anti platelet therapy during the year following percutaneous coronary intervention

	Odds Ratio (95% Confidence Interval)	
	\geq BARC 1 bleeding	BARC \geq 1, excluding bruising
Diabetes (vs. no DM)	0.50 (0.38-0.66)	0.77 (0.62-0.96)



* Most severe level of bleeding reported

* For multivariable adjustment, the following covariates were used: Age, gender, race, BMI, history of CKD, acute coronary syndrome at time of presentation, heart failure and chronic lung disease, history of prior PCI and/or MI, bleeding and/or transfusion during index hospitalization, and index PCI admission lab values including platelets and nadir hemoglobin

Abbreviations: BMI: body mass index; CKD: chronic kidney disease; PCI: percutaneous intervention; MI: myocardial infarction

Figure 4. Bleeding outcomes over the year following PCI in patients with and without diabetes mellitus

Dual Anti platelet Therapy Discontinuance

The rate of DAPT discontinuation was similar between patients with and without DM at one-year follow up (13.6% vs. 14.2% respectively, p=0.719). For patients not on a thienopyridine or aspirin at follow up, a follow up question regarding reason for

discontinuance of the medication was asked. The reasons provided by patients for discontinuance are referenced in Supplemental Table 2.

All statistical analyses performed using SPSS version 22 and syntax is referenced in Supplemental Figure 1.

CHAPTER 4

DISCUSSION

In the multicenter, contemporary PRISM registry, among patients who underwent PCI and were discharged and maintained on DAPT, we found that patients with DM had lower bleeding rates over the year following PCI when compared with patients who did not have DM. To our knowledge, this is the first study to compare the incidence of bleeding following PCI in patients with and without DM and to examine the independent association of DM with bleeding events, adjusting for relevant clinical and socioeconomic factors. In addition, we examined bleeding outcomes according to indication for PCI (i.e. acute coronary syndrome [emergent or urgent] versus elective indication) and found that results were consistent regardless of the bleeding definition and persisted despite adjustment for multiple potential confounders and in multiple sensitivity analyses.

Prior Studies

Our study supports and extends the prior literature, which has been primarily limited to sub-studies of clinical trials.^{18,19} These results advance knowledge by highlighting the independent association of DM with bleeding outcomes, an area that was not previously explored. The OPS/PRISM registry provided a unique cohort for investigation of our research questions by including rich documentation of patient characteristics and clinical variables from representative US centers, promoting the external generalizability of our findings. Our results 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 in this group of patients.

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 subjects 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 bleeding outcomes among patients without DM.²⁰ As a result, the net clinical benefit of prasugrel compared with clopidogrel was greater in patients with DM, compared with patients without DM.²⁰ In contrast to the results of TRITON-TIMI 38, the results of the PLATelet inhibition and patient Outcomes (PLATO) study, which randomized patients following acute coronary syndrome to DAPT with ticagrelor vs. clopidogrel, showed that the rates of major bleeding not related to bypass surgery 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. Both of these large clinical trials examined bleeding outcomes in patients admitted for acute coronary syndrome, while our study enrolled a broader range of indications for PCI, including, but not limited to, acute coronary syndrome.

Some of the differences between our results and those from the 2 trials above, likely result from the bleeding definitions used (TRITON and PLATO trials classified bleeding events within major and minor categories), as we found no difference between rates of BARC ≥ 2 bleeding between groups. Another important distinction lies in that our study represented a real-world cohort, including patients who otherwise are not eligible for or choose to participate in clinical trials. As such, we believe that our study substantially

expands the current understanding of the bleeding outcomes, and the risk-benefit balance, of long-term DAPT in this important patient group.

Potential Mechanisms for Lower Bleeding Outcomes

The results of lower bleeding rates with DAPT use in PCI patients with DM vs. those who did not have DM could be explained by increased platelet reactivity in the setting of hyperglycemia and insulin resistance,^{27,28} thereby exposing patients with DM to a higher risk of ischemic events and a lower risk of bleeding while receiving long-term DAPT.

Additionally, although we adjusted for body mass index in our multivariable model, obesity has been described to attenuate bleeding,²⁹ and could therefore in part explain improved bleeding outcomes in patients with DM (who are more commonly overweight or obese).

Future studies are therefore needed to elucidate whether or not bleeding outcomes are related in a “dose-dependent” fashion to level of glycemic control in patients with DM. This information could further our understanding of the level of platelet inhibition in diabetic patients with suboptimal glycemic control, as compared with those who are euglycemic.

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.³⁰ Ideally, patients who are selected for prolonged DAPT should be those at higher risk of 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 general ischemic events, such as stent thrombosis and myocardial infarction. 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 by also defining a lower risk of bleeding, the adverse consequence of using DES and prolonged DAPT.

Our findings are also meaningful in the context of patient counseling as they may inform shared decision making choices between patient and provider ahead of the PCI procedure. Given this information, patients with DM may better understand their odds of adverse events following a common and necessary therapy.

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. Accordingly, future studies are needed to replicate these findings in an acute coronary syndrome and elective PCI cohort. In addition, future investigations should be conducted to elucidate the impact of glycemic control on bleeding outcomes in patients with DM. Lastly, examining the type of anti platelet medication prescribed would allow us to examine the association of use of particular anti platelet agents with bleeding with more granularity.

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. Lastly, due to the observational nature of our study, there is the possibility of residual confounding despite extensive adjustment. Such potential confounders may include markers of DM control, which were not collected in our registry. Measurement of hemoglobin A1c (a marker of average DM) control over the 2-3 months preceding A1c analysis), insulin use and presence of microalbuminuria may have informed our understanding of the gradation of bleeding outcomes based on strata of DM control. Another potential confounder that was not captured in our database was hemoglobin measurement at follow up. This value could have potentially extended our ability to validate patient self-report of bleeding events during the follow up period. Last, there is a potential that patients may have discontinued DAPT or dropped out of the study due to bleeding episodes. Differential DAPT discontinuance between patients with and without DM due to bleeding events may have skewed our observed bleeding rates to over- or under- estimate bleeding outcomes.

Conclusions

In this real-world PCI registry, patients with DM experienced significantly lower risk of bleeding on long-term DAPT 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 described.

APPENDIX

Table A-1: Baseline characteristics of patients with and without diabetes in the OPS/PRISM registry

	Overall n=2270	Diabetes n=737	No Diabetes n=1533	P -Value
Mean age (years)	64.3 ± 10.5	64.9±9.8	64.1±10.9	0.099
Male gender	72.3%	68.1%	74.3%	0.002
White race	91.6%	87.8%	93.4%	<0.001
No insurance	2.6%	1.9%	2.9%	0.187
Completed high school	91.8%	90.6%	92.3%	0.152
Married	68.2%	64.0%	70.1%	0.004
Never smoker	45.8%	46.0%	45.8%	0.007
Insurance for medication	97.4%	98.1%	97.1%	0.187
Avoided care due to cost (past 12M)	20.2%	21.4%	19.6%	0.860
Mean BMI	30.4 ± 6.1	32.7±6.9	29.3±5.4	<0.001
Chronic kidney disease	7.6%	13.7%	4.6%	<0.001
Mean platelet count pre-PCI (x1000)	217.4 ± 63.2	216.7±63.2	217.7±63.3	0.723
Thrombocytopenia**	0.8%	1.6%	0.5%	0.010
Bleeding problems* (BL)	5.7%	5.5%	5.8%	0.743
Mean Hemoglobin	13.7 ± 1.6	13.1±1.6	14.0±1.5	<0.001
Mean Hemoglobin nadir	12.8 ± 1.7	12.3±1.7	13.0±1.6	<0.001
Prior heart failure	13.3%	19.7%	10.2%	<0.001
RBC/ Whole Blood	1.5%	1.9%	1.3%	0.324
Chronic lung disease	11.3%	14.4%	9.8%	0.001
Prior PCI	40.2%	48.4%	36.3%	<0.001
Prior MI	27.0%	32.0%	24.5%	<0.001
Anticoagulation	5.2%	6.0%	4.8%	0.223
In hospital bleed [†]	2.1%	1.8%	2.2%	0.477

Abbreviations: BMI: body mass index; BL: baseline; RBC: red blood cell; PCI: percutaneous intervention; MI: myocardial infarction

*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 <100

[†]Defined as greater than or equal to a 2 g/dL drop in hemoglobin

Table A-2: The Bleeding Academic Research Consortium definition for bleeding

BARC 0	<ul style="list-style-type: none"> No bleeding
BARC 1	<ul style="list-style-type: none"> Bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment by a healthcare professional May include episodes leading to self-discontinuation of medical therapy by the patient without consulting a healthcare professional
BARC 2	<ul style="list-style-type: none"> Any overt, actionable sign of hemorrhage (eg, more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for type 3, 4, or 5 but does meet at least one of the following criteria: <ul style="list-style-type: none"> requires nonsurgical, medical intervention by a healthcare professional leads to hospitalization/increased level of care/prompting evaluation
BARC 3	<ul style="list-style-type: none"> 3a: Overt bleeding plus hemoglobin drop of 3 to <5 g/dL* (provided hemoglobin drop is related to bleed); any transfusion with overt bleeding 3b: Overt bleeding plus hemoglobin drop ≥ 5 g/dL* (provided hemoglobin drop is related to bleed); cardiac tamponade; bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid); bleeding requiring intravenous vasoactive agents 3c: Intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation, does include intraspinal); subcategories confirmed by autopsy or imaging or lumbar puncture; intraocular bleed compromising vision
BARC 4	<ul style="list-style-type: none"> Perioperative intracranial bleeding within 48 h Reoperation after closure of sternotomy for the purpose of controlling bleeding Transfusion of ≥ 5 U whole blood or packed red blood cells within a 48-h period† Chest tube output ≥ 2L within a 24-h period
BARC 5	<ul style="list-style-type: none"> 5a: Probable fatal bleeding; no autopsy or imaging confirmation but clinically suspicious 5b: Definite fatal bleeding; overt bleeding or autopsy or imaging confirmation

Table A-3. Sites participating in the OPS-PRISM registries

Medical Center	Location	Principal Investigator
*Mid America Heart Institute	Kansas City, MO	John Spertus, MD
Kaiser Permanente	San Francisco, CA	Ed McNulty, MD
*Integrus Heart Hospital	Oklahoma City, OK	Charles Bethea, MD
*Mayo Clinic	Rochester, MN	Henry Ting, MD
Henry Ford Hospital	Detroit, MI	Mayra Guerrero, MD
Baylor Health Plano Heart Hospital	Plano, TX	Bradley Leonard, MD
Bay State Medical Center	Springfield, MA	Aaron Kugelmass, MD
*Yale New Haven Hospital	New Haven, CT	Jeptha Curtis, MD
Prairie Heart St. John's Hospital	Springfield, IL	Mark Shelton, MD
Washington University Barnes-Jewish Hospital	Saint Louis, MO	Richard Bach, MD

*Sites that participated in both OPS and PRISM registries

Table A-4. List of reasons for DAPT discontinuance

"I was never told to take it"
"I was told to take it only for a specified time"
"My doctor told me to stop"
"I stopped on my own because of cost"
"I stopped on my own because of side effects"

Table A-5. Baseline characteristics of patients missing vs. not missing 12-month data

	Missing 1 year data n=482	Not missing 1 year data n=2270	P -Value
Age (years)	60.9±12.8	64.3±10.5	<0.001
Male gender	69.7%	72.3%	0.253
White race	86.0%	91.6%	<0.001
No insurance	6.7%	2.6%	<0.001
Completed high school	88.5%	91.8%	0.022
Married	57.8%	68.2%	<0.001
Never smoker	33.6%	45.8%	<0.001
Insurance for medication	90.0%	93.8%	0.003
Avoided care due to cost (past 12M)	27.2%	20.2%	<0.001
BMI	31.0±7.0	30.4±6.1	0.064
Chronic kidney disease	11.8%	7.6%	0.002
Platelet count pre-PCI (x1000)	226.8±66.1	217.4±63.2	0.004
Thrombocytopenia	0.9%	0.8%	1.000
Bleeding problems* (BL)	8.4%	5.7%	0.027
Hemoglobin	13.5±1.9	13.7±1.6	0.008
Hemoglobin nadir	12.5±1.9	12.8±1.7	<0.001
Prior heart failure	9.5%	6.8%	0.034
RBC/ Whole Blood Transfusion	1.1%	1.5%	0.554
Chronic lung disease	17.0%	11.3%	<0.001
Prior PCI	45.0%	40.2%	0.052
Prior MI	32.2%	27.0%	0.021
Anticoagulation	7.1%	7.2%	0.096
In hospital bleed†	2.7%	2.1%	0.392
Drug eluting stent	71.2%	86.1%	<0.001

*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 <100

†Defined as greater than or equal to a 2 g/dL drop in hemoglobin

Figure A-1

SPSS Program Syntax delineating code for creation of baseline characteristics table, logistic regression models for primary and sensitivity analyses, and discontinuance rates stratified by diabetes status

CROSSTABS

```
/TABLES=BARC1Plus_1 BARC1Plus_6 BARC1Plus_y Barc1PlusDC_y Barc2PlusDC_y BY  
Diabetes  
/FORMAT=AVALUE TABLES  
/STATISTICS=CHISQ  
/CELLS=COUNT ROW COLUMN TOTAL  
/COUNT ROUND CELL.
```

CROSSTABS

```
/TABLES=BARC1Plus_1 BARC1Plus_6 BARC1Plus_y Barc1PlusDC_y Barc2PlusDC_y BY  
Diabetes  
/FORMAT=AVALUE TABLES  
/STATISTICS=CHISQ  
/CELLS=COUNT EXPECTED ROW COLUMN TOTAL  
/COUNT ROUND CELL.
```

T-TEST GROUPS=Diabetes(0 1)

```
/MISSING=ANALYSIS  
/VARIABLES=Age BodyMassIndex hgb_nadir Hemoglobin  
/CRITERIA=CI(.95).
```

FREQUENCIES VARIABLES=Age BodyMassIndex Hemoglobin hgb_nadir

```
/STATISTICS=MINIMUM MAXIMUM SKEWNESS SESKEW KURTOSIS SEKURT  
/HISTOGRAM NORMAL  
/ORDER=ANALYSIS.
```

EXAMINE VARIABLES=Age BodyMassIndex Hemoglobin hgb_nadir BY Diabetes

```
/PLOT BOXPLOT STEMLEAF HISTOGRAM NPLOT  
/COMPARE GROUPS  
/STATISTICS DESCRIPTIVES  
/CINTERVAL 95  
/MISSING LISTWISE  
/NOTOTAL.
```

T-TEST GROUPS=Diabetes(0 1)

```
/MISSING=ANALYSIS  
/VARIABLES=Sex Race RaceWhite InsuranceNone Married Smokingstatus PriorMI PriorPCI  
Chronicheart
```

```
Chronicckidney Chroniclung BodyMassIndex Heartfailure AspirinonDischarge Thienopyridine  
Insuranceformedications BleedingproblemsBL Avoidedcareduetocost
```


Completedhighschool education

PlateletcountprePCI Cardiogenicshockprecath DES RBCwholebloodtransfusion ACS Inhospital
HeartFailure_A BARC1Plus_1 BARC1Plus_6 BARC1Plus_y Barc1PlusDC_y Barc2PlusDC_y
Thrombocytopenia
anticoag_d
/CRITERIA=CI(.95).

*****Now going to compare nonparametrically distributed continuous variables at
baseline between patients with and without DM*****

DATASET ACTIVATE DataSet1.

*Nonparametric Tests: Independent Samples.

NPTESTS

/INDEPENDENT TEST (Age BodyMassIndex Hemoglobin hgb_nadir) GROUP (Diabetes)
/MISSING SCOPE=ANALYSIS USERMISSING=EXCLUDE
/CRITERIA ALPHA=0.05 CILEVEL=95.

*Nonparametric Tests: Independent Samples.

NPTESTS

/INDEPENDENT TEST (Age BodyMassIndex Hemoglobin hgb_nadir) GROUP (Diabetes)
/MISSING SCOPE=ANALYSIS USERMISSING=EXCLUDE
/CRITERIA ALPHA=0.05 CILEVEL=95.

DESCRIPTIVES VARIABLES=Age BodyMassIndex hgb_nadir Hemoglobin

/STATISTICS=MEAN STDDEV MIN MAX.

*****checking logistic regression initial output*****

LOGISTIC REGRESSION VARIABLES Barc1PlusDC_y

/METHOD=ENTER ACS PlateletcountprePCI Chronickidney PriorPCI Smokingstatus
/CONTRAST (ACS)=Indicator
/CONTRAST (Chronickidney)=Indicator
/CONTRAST (PriorPCI)=Indicator
/CONTRAST (Smokingstatus)=Indicator
/PRINT=CI(95)
/CRITERIA=PIN(0.05) POUT(0.10) ITERATE(20) CUT(0.5).

*****checking assumptions for logistic regression modeling (sample size is adequate,
no multicollinearity, no unexplained outliers*****

REGRESSION

/MISSING PAIRWISE
/STATISTICS COEFF OUTS R ANOVA COLLIN TOL

```
/CRITERIA=PIN(.05) POUT(.10)
/NOORIGIN
/DEPENDENT BARC1Plus_y
/METHOD=ENTER Age Sex RaceWhite BodyMassIndex Chronicheart Chronickidney
Chroniclung
BleedingproblemsBL Hemoglobin PlateletcountprePCI RBCwholebloodtransfusion Inhospital
Thrombocytopenia anticoag_d PriorPCI PriorMI
/CASEWISE PLOT(ZRESID) OUTLIERS(3).
```

REGRESSION

```
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/STATISTICS COEFF OUTS R ANOVA COLLIN TOL
/CRITERIA=PIN(.05) POUT(.10)
/NOORIGIN
/DEPENDENT BARC1Plus_y
/METHOD=ENTER Age Sex RaceWhite BodyMassIndex Chronicheart Chronickidney
Chroniclung
BleedingproblemsBL Hemoglobin PlateletcountprePCI RBCwholebloodtransfusion Inhospital
Thrombocytopenia anticoag_d PriorPCI PriorMI
/SCATTERPLOT=(*ZRESID,*ZPRED)
/RESIDUALS NORMPROB(ZRESID)
/CASEWISE PLOT(ZRESID) OUTLIERS(3).
```

*****multicollinearity not violated, sample size adequate, this is the logistic regression model looking at primary outcome at 1 year of BARC greater than or equal to 1 bleeding INCLUDING bruising*****

LOGISTIC REGRESSION VARIABLES BARC1Plus_y

```
/METHOD=ENTER Chronickidney PriorPCI BleedingproblemsBL Hemoglobin
RBCwholebloodtransfusion
Inhospital Thrombocytopenia anticoag_d Heartfailure Chroniclung PriorMI Age Sex RaceWhite
BodyMassIndex
/CONTRAST (Chronickidney)=Indicator(1)
/CONTRAST (PriorPCI)=Indicator(1)
/CONTRAST (BleedingproblemsBL)=Indicator(1)
/CONTRAST (Inhospital)=Indicator(1)
/CONTRAST (Thrombocytopenia)=Indicator(1)
/CONTRAST (anticoag_d)=Indicator(1)
/CONTRAST (Heartfailure)=Indicator(1)
/CONTRAST (Chroniclung)=Indicator(1)
/CONTRAST (PriorMI)=Indicator(1)
/CONTRAST (Sex)=Indicator(1)
```

```
/CONTRAST (RaceWhite)=Indicator(1)
/CLASSPLOT
/CASEWISE OUTLIER(2)
/PRINT=GOODFIT ITER(1) CI(95)
/CRITERIA=PIN(0.05) POUT(0.10) ITERATE(20) CUT(0.5).
```

*****logistic regression (producing odds ratios) for first sensitivity analysis, looking at BARC greater than or equal to 1, EXCLUDING bruising, at 1 year*****

LOGISTIC REGRESSION VARIABLES Barc1PlusDC_y

```
/METHOD=ENTER Chronickidney PriorPCI BleedingproblemsBL Hemoglobin
RBCwholebloodtransfusion
  Inhospital Thrombocytopenia anticoag_d Heartfailure Chroniclung PriorMI Age Sex RaceWhite
  BodyMassIndex Diabetes
/CONTRAST (Chronickidney)=Indicator(1)
/CONTRAST (PriorPCI)=Indicator(1)
/CONTRAST (BleedingproblemsBL)=Indicator(1)
/CONTRAST (Inhospital)=Indicator(1)
/CONTRAST (Thrombocytopenia)=Indicator(1)
/CONTRAST (anticoag_d)=Indicator(1)
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/CONTRAST (PriorMI)=Indicator(1)
/CONTRAST (Sex)=Indicator(1)
/CONTRAST (RaceWhite)=Indicator(1)
/CLASSPLOT
/CASEWISE OUTLIER(2)
/PRINT=GOODFIT ITER(1) CI(95)
/CRITERIA=PIN(0.05) POUT(0.10) ITERATE(20) CUT(0.5).
```

*****logistic regression model looking at BARC 2 or greater at 1 year*****

LOGISTIC REGRESSION VARIABLES Barc2PlusDC_y

```
/METHOD=ENTER Chronickidney PriorPCI BleedingproblemsBL Hemoglobin
RBCwholebloodtransfusion
  Inhospital Thrombocytopenia anticoag_d Heartfailure Chroniclung PriorMI Age Sex RaceWhite
  BodyMassIndex Diabetes
/CONTRAST (Chronickidney)=Indicator(1)
/CONTRAST (PriorPCI)=Indicator(1)
/CONTRAST (BleedingproblemsBL)=Indicator(1)
/CONTRAST (Inhospital)=Indicator(1)
/CONTRAST (Thrombocytopenia)=Indicator(1)
```

```
/CONTRAST (anticoag_d)=Indicator(1)
/CONTRAST (Heartfailure)=Indicator(1)
/CONTRAST (Chroniclung)=Indicator(1)
/CONTRAST (PriorMI)=Indicator(1)
/CONTRAST (Sex)=Indicator(1)
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/CLASSPLOT
/CASEWISE OUTLIER(2)
/PRINT=GOODFIT ITER(1) CI(95)
/CRITERIA=PIN(0.05) POUT(0.10) ITERATE(20) CUT(0.5).
```

*****logistic regression sensitivity analyses looking at BARC greater than or equal to 1 including bruising at 1 and 6 months, not requiring them to be on DAPT at 1 and 6 months)*****

LOGISTIC REGRESSION VARIABLES BARC1Plus_1

```
/METHOD=ENTER Chronickidney PriorPCI BleedingproblemsBL Hemoglobin
RBCwholebloodtransfusion
Inhospital Thrombocytopenia anticoag_d Heartfailure Chroniclung PriorMI Age Sex RaceWhite
BodyMassIndex Diabetes
/CONTRAST (Chronickidney)=Indicator(1)
/CONTRAST (PriorPCI)=Indicator(1)
/CONTRAST (BleedingproblemsBL)=Indicator(1)
/CONTRAST (Inhospital)=Indicator(1)
/CONTRAST (Thrombocytopenia)=Indicator(1)
/CONTRAST (anticoag_d)=Indicator(1)
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/CONTRAST (PriorMI)=Indicator(1)
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/CONTRAST (RaceWhite)=Indicator(1)
/CLASSPLOT
/CASEWISE OUTLIER(2)
/PRINT=GOODFIT ITER(1) CI(95)
/CRITERIA=PIN(0.05) POUT(0.10) ITERATE(20) CUT(0.5).
```

LOGISTIC REGRESSION VARIABLES BARC1Plus_6

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/METHOD=ENTER Chronickidney PriorPCI BleedingproblemsBL Hemoglobin
RBCwholebloodtransfusion
Inhospital Thrombocytopenia anticoag_d Heartfailure Chroniclung PriorMI Age Sex RaceWhite
BodyMassIndex Diabetes
/CONTRAST (Chronickidney)=Indicator(1)
```

```
/CONTRAST (PriorPCI)=Indicator(1)
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/CONTRAST (PriorMI)=Indicator(1)
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/CONTRAST (RaceWhite)=Indicator(1)
/CLASSPLOT
/CASEWISE OUTLIER(2)
/PRINT=GOODFIT ITER(1) CI(95)
/CRITERIA=PIN(0.05) POUT(0.10) ITERATE(20) CUT(0.5).
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*****checking DAPT discontinuance rates (by 12 months) in patients with and without DM discharged on DAPT*****

CROSSTABS

```
/TABLES=Discontinuance BY diabetes
/FORMAT=AVALUE TABLES
/STATISTICS=CHISQ
/CELLS=COUNT
/COUNT ROUND CELL.
```

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VITA

Anna Grodzinsky was born on April 21st 1984 in Lvov, Ukraine. She immigrated to Columbia, Missouri, with her parents in 1990. She was educated in the public school system in Columbia and moved in 1997 to Kansas City, where her parents began to work following their graduation from the University of Missouri-Columbia. Anna graduated from Shawnee Mission East High School in 2002. She attended the University of Missouri-Kansas City's combined baccalaureate/medical degree program and graduated in 2009.

After finishing medical school, she began internal medicine residency at Saint Luke's Hospital and Truman Medical Center in Kansas City, Missouri. She completed her residency in 2012. After completion of her residency, she completed an additional year dedicated as a chief resident of the internal medicine program at UMKC. Following completion of her chief year, Anna began her fellowship in the NIH T32 cardiovascular outcomes research program at Saint Luke's Mid America Heart Institute and the University of Missouri-Kansas City. Here she served as part-time faculty to the internal medicine residency program. During her fellowship, she elected to pursue a Master of Science through the Bioinformatics Program at the University of Missouri-Kansas City.

Upon completion of her research fellowship and her degree requirements, Dr. Grodzinsky will begin her clinical cardiology fellowship at the University of Missouri-Kansas City. Following this fellowship, Dr. Grodzinsky plans to practice general cardiology as well as to engage in cardiovascular research.

Dr. Grodzinsky is a member of the American College of Cardiology, the American Heart Association, the American Medical Association, and is certified by the American Board of Internal Medicine.