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Incidence, Predictors, and Impact of Post-Discharge Bleeding After Percutaneous Coronary Intervention

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ABSTRACT

BACKGROUND The incidence, predictors, and prognostic impact of post-discharge bleeding (PDB) after percutaneous coronary intervention (PCI) with drug-eluting stent (DES) implantation are unclear.

OBJECTIVES This study sought to characterize the determinants and consequences of PDB after PCI.

METHODS The prospective ADAPT-DES (Assessment of Dual Antiplatelet Therapy With Drug-Eluting Stents) study was used to determine the incidence and predictors of clinically relevant bleeding events occurring within 2 years after hospital discharge. The effect of PDB on subsequent 2-year all-cause mortality was estimated by time-adjusted Cox proportional hazards regression.

RESULTS Among 8,582 "all-comers" who underwent successful PCI with DES in the ADAPT-DES study, PDB occurred in 535 of 8,577 hospital survivors (6.2%) at a median time of 300 days (interquartile range: 130 to 509 days) post-discharge. Gastrointestinal bleeding (61.7%) was the most frequent source of PDB. Predictors of PDB included older age, lower baseline hemoglobin, lower platelet reactivity on clopidogrel, and use of chronic oral anticoagulation therapy. PDB was associated with higher crude rates of all-cause mortality (13.0% vs. 3.2%; $p < 0.0001$). Following multivariable adjustment, PDB was strongly associated with 2-year mortality (hazard ratio [HR]: 5.03; $p < 0.0001$), with an effect size greater than that of post-discharge myocardial infarction (PDMI) (HR: 1.92; $p = 0.009$).

CONCLUSIONS After successful PCI with DES in an unrestricted patient population, PDB is not uncommon and has a strong relationship with subsequent all-cause mortality, greater that that associated with PDMI. Efforts to reduce PDB may further improve prognosis after successful DES implantation. (Assessment of Dual Antiplatelet Therapy With Drug-Eluting Stents [ADAPT-DES]; NCT00638794) (J Am Coll Cardiol 2015;66:1036–45) © 2015 by the American College of Cardiology Foundation.

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The optimal duration of dual antiplatelet therapy (DAPT) after percutaneous coronary intervention (PCI) with drug-eluting stents (DES) remains a matter of active debate (1-3). While DAPT is effective in preventing stent-related and non-stent-related adverse ischemic events (4), prolonged DAPT use is associated with a substantial risk of bleeding and possibly increased mortality (5,6). Periprocedural bleeding after PCI has been shown to be associated with increased short-term and long-term morbidity and mortality across the entire clinical spectrum of patients with coronary artery disease treated with PCI (7-9).

SEE PAGE 1046

In contrast, the impact and contribution of nonperiprocedural bleeding events to late mortality is less certain, especially when compared to post-discharge ischemic events such as myocardial infarction (MI) (4,10). Therefore, we sought to evaluate the incidence, predictors, and impact of clinically significant bleeding occurring after hospital discharge following successful DES implantation from the large-scale ADAPT-DES (Assessment of Dual Antiplatelet Therapy With Drug-Eluting Stents) study.

METHODS

STUDY POPULATION. The ADAPT-DES study was a prospective, multicenter registry specifically designed to determine the association between platelet reactivity and stent thrombosis (ST) after DES. The design and major outcomes of the ADAPT-DES study have been previously described (11). In brief, an "all-comers" population of 8,582 patients were prospectively enrolled at 11 sites in U.S. and European hospitals. All patients successfully treated with 1 or more DES and who were adequately loaded with aspirin and clopidogrel were eligible for enrollment, regardless of clinical presentation or lesion complexity. The only major exclusion criteria were the occurrence of a major complication during the procedure or before platelet function testing, or if bypass surgery was planned after PCI. Platelet reactivity on aspirin and clopidogrel was assessed after an adequate loading period to ensure full antiplatelet effect using the VerifyNow Aspirin, $P2Y_{12}$, and IIb/IIIa assays (Accumetrics Inc., San Diego, California) (11). After PCI, patients were treated with aspirin indefinitely, and clopidogrel was recommended for at least 1 year. All other treatments were per standard of care. Clinical follow-up was scheduled at 30 days, 1 year, and 2 years. An independent clinical events committee blinded to VerifyNow results adjudicated all events using original source documents. The institutional review board at each participating center approved the study, and all eligible patients signed written informed consent prior to enrollment. For the present study, patients included in the ADAPT-DES study were compared according to the occurrence of post-discharge bleeding (PDB) at 2 years.

STUDY OBJECTIVES AND DEFINITIONS. The objectives of the present study were to: 1) determine the incidence of PDB in patients who were in-hospital event-free after PCI with DES; 2) identify risk factors associated with the occurrence of PDB; and 3) evaluate the time-dependent, multivariable adjusted effect of PDB on mortality within 2 years after the index procedure.

PDB was defined as the occurrence of any of the following: a Thrombolysis In Myocardial Infarction (TIMI) major or minor bleed; a Global Use of Strategies to Open Occluded Arteries (GUSTO) severe or moderate bleed; an Acute Catheterization and Urgent

ABBREVIATIONS AND ACRONYMS

DAPT = dual antiplatelet therapy

DES = drug-eluting stent(s)

MACE = major adverse cardiac event(s)

MI = myocardial infarction

PCI = percutaneous coronary intervention

PDB = post-discharge bleeding

PDMI = post-discharge myocardial infarction

PRU = $P2Y_{12}$ reactivity units

ST = stent thrombosis

TVF = target vessel failure

Medicines Company. Dr. Duffy has received speaker honoraria from Volcano; and has served on the medical education advisory board for Philips. Dr. Palmerini has received speakers honoraria from Abbott Vascular. Dr. Kirtane has received institutional research grants to Columbia University from Boston Scientific, Medtronic, Abbott Vascular, Abiomed, St. Jude Medical, Vascular Dynamics, and Eli Lilly. Dr. Mehran has received research grant support from Eli Lilly, AstraZeneca, The Medicines Company, and BMS/Sanofi; served as a consultant for AstraZeneca, Bayer, CSL Behring, Janssen Pharmaceuticals, Merck & Co., Osprey Medical Inc., and Watermark Research Partners (modest <$5,000/yr); served on the scientific advisory board for Abbott Laboratories, Boston Scientific, Covidien, Janssen Pharmaceuticals, The Medicines Company, and Sanofi; given industry-sponsored lectures for Mount Sinai School of Medicine (faculty occasionally give lectures at events sponsored by industry, but only if the events are free of any marketing purposes) to PlatformQ; and has participated in other activities (including, but not limited to, committee participation and data safety monitoring board membership) for Forest Laboratories (no payment). All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. Drs. Généreux and Giustino contributed equally to this work.

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Intervention Triage Strategy (ACUITY) major bleed; or any PDB event requiring medical attention. According to its timing, PDB was defined as early (<30 days), late (30 days to <1 year), or very late (1 to 2 years). The following pre-specified categories were used to group the site of bleeding: gastrointestinal, genitourinary, central nervous system, retroperitoneal, arterial access-site (nonretroperitoneal), and other.

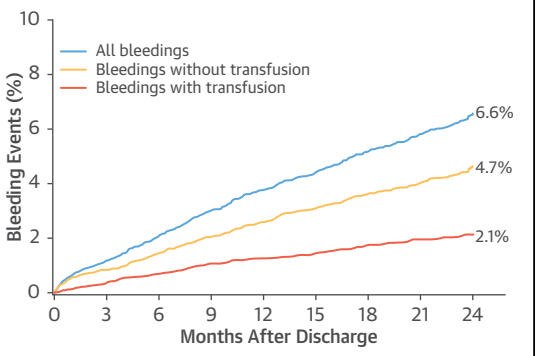
Endpoints evaluated in the present study included all-cause mortality, cardiac mortality, MI, definite or probable ST, target vessel failure (TVF), and major adverse cardiac events (MACE). MI was defined according to the ACUITY criteria (11,12). Definite or probable stent thrombosis was defined according to the Academic Research Consortium definition (13). TVF was defined as the composite of death, MI, or ischemia-driven target vessel revascularization. MACE was defined as the composite of cardiac death, MI, or ischemia-driven target lesion revascularization.

STATISTICAL ANALYSIS. Descriptive statistics are presented as mean ± SD and were compared with the Student *t* test; categorical variables are reported as percentages and were tested with the chi-square test. Event rates during follow-up were estimated by Kaplan-Meier methods. Unadjusted hazard ratios for 2-year outcomes were determined from Cox proportional hazards models with time-dependent bleeding as the only covariate. Adjusted hazard ratios were estimated from multivariable Cox models selected by a stepwise process with entry and exit thresholds set to 0.1. Both PDB and post-discharge MI (PDMI) were modeled as time-dependent covariates. All modeling assumptions were checked and addressed. The effect size of PDB and PDMI were directly compared using the Wald test, controlling for other covariates. Statistical analyses were performed in SAS version 9.4 (SAS Institute, Cary, North Carolina) and plots were constructed in R (version 3.1.2) using ggplot2 (version 1.0.0).

RESULTS

INCIDENCE AND SITES OF POST-DISCHARGE BLEEDING. Among the 8,582 patients enrolled in the ADAPT-DES study who underwent PCI with DES, 8,577 were discharged alive and included in the current analysis. Median follow-up was 729 days (interquartile range: 703 to 730 days). During follow-up, 535 patients (6.2%) had a total of 662 PDB events (Figure 1); 82 patients (15.3%) had multiple bleeding events. The most common site of PDB was gastrointestinal (Figure 2). Among those experiencing bleeding, 168 (31.4%) required a blood transfusion for treatment. Median time to first PDB was 300 days (interquartile range: 130 to 509 days). Risk of bleeding accrued constantly over time, and the rates of first bleeding at 30 days, 1 year, and 2 years were 0.7%, 3.8%, and 8.8%, respectively. The proportions of first PDB events in the early (<30 days), late (30 days to 1 year), and very late (>1 year) period were 10.5%, 48.2%, and 41.3%, respectively.

FIGURE 1 Bleeding Rates After Percutaneous Coronary Intervention



Cumulative rates of first post-discharge bleeding event increased over time in all patients; a similar pattern was seen when patients were stratified according to requirement for blood transfusion.

PREDICTORS OF BLEEDING. Per baseline clinical characteristics (Table 1), patients who had PDB within 2 years were older and more commonly female, and had a higher proportion of hypertension, hyperlipidemia, peripheral arterial disease, congestive heart failure, previous MI, and previous coronary revascularization. Patients who experienced PDB also had lower levels of baseline hemoglobin and creatinine clearance.

When comparing procedural characteristics (Table 1), patients with PDB were more likely to have multivessel and left main coronary artery disease and more frequent treatment of calcified and bifurcation lesions than those in the no-PDB group. Patients with PDB had a greater number of lesions treated, longer lesions, and longer stents. There were no significant differences in median [Q1 to Q3] baseline $P2Y_{12}$ reactivity units (PRU) on clopidogrel (PDB 188 [97 to 264] vs. 188 [114 to 260]; p = 0.83) or aspirin reactivity units (400 [387 to 432] vs. 400 [388 to 424]; p = 0.79) between the PDB and no-PDB groups, respectively.

Baseline characteristics in patients with PDB according to the need for blood transfusion are

reported in Online Table 1. Patients with PDB and blood transfusions were more commonly female, had lower baseline hemoglobin levels, and had a higher proportion of chronic kidney disease at baseline compared to patients with PDB not requiring transfusions.

In reviewing medications used in patients with and without PDB (Online Table 2), patients with PDB were more commonly treated with oral anticoagulation with warfarin and proton pump inhibitors, and less commonly on DAPT during the entire study period. Specifically, patients experiencing PDB had higher rates of DAPT disruption because of bleeding (29.0% vs. 1.6%; $p < 0.0001$). Also, statin use during 2-year follow-up was lower in patients with PDB, but there were no differences in nonsteroidal anti-inflammatory drug use between groups.

The multivariable adjusted independent predictors of PDB within 2-year follow-up were older age, peripheral artery disease, lower baseline hemoglobin levels, lower baseline PRU, and warfarin use at discharge. Treatment of heavily calcified lesions and bifurcations were also independent predictors of PDB (Table 2).

2-YEAR CLINICAL OUTCOMES AND PREDICTORS OF ALL-CAUSE MORTALITY. Unadjusted 2-year clinical outcomes according to the occurrence of PDB are reported in Table 3. Patients experiencing PDB had higher crude rates of all-cause mortality (13.0% vs. 3.2%; $p < 0.0001$) (Figure 3A) as well as higher rates of cardiac mortality (5.1% vs. 1.9%; $p < 0.0001$) (Figure 3A), MI, ST, TVF, and MACE. PDB occurring between 30 days and 1 year or 1 year and 2 years were both associated with increased mortality (Figure 3B). Patients who had PDB and received blood transfusions had the highest rates of 2-year all-cause and cardiac mortality (Figure 4).

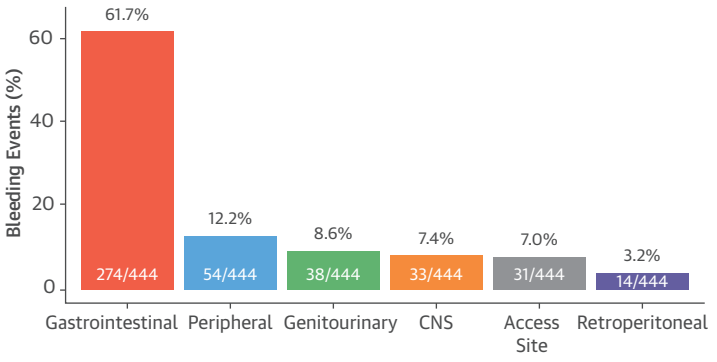
By multivariable analysis, PDB was the strongest predictor of 2-year mortality (hazard ratio: 5.03; 95% confidence interval: 3.29 to 7.66; $p < 0.0001$) (Table 4). The effect of PDB with or without transfusion on mortality was similar. The magnitude of the effect of PDB on subsequent mortality was roughly 2.6-fold greater than the effect of PDMI (hazard ratio: 1.92; 95% confidence interval: 1.18 to 3.12; $p = 0.009$) ($p = 0.008$ for the effect size of PDB vs. PDMI).

DISCUSSION

The current report, drawn from 8,577 patients undergoing successful PCI with DES, is the largest contemporary study to evaluate the incidence, predictors, and prognostic impact of PDB in an all-comers patient population (Central Illustration). The main findings of the present analysis include: 1) PDB requiring medical attention was not uncommon and increased monotonically throughout the 2-year post-PCI follow-up period; 2) clinical and pharmacologic risk factors, including lower PRU and concomitant oral anticoagulation use, were strongly associated with the risk of PDB; and 3) PDB with or without associated transfusion was strongly associated with subsequent mortality, with an adjusted hazard greater than that for PDMI.

In the all-comers ADAPT-DES population, PDB occurred in approximately 1 of every 15 patients within 2 years of follow-up, with more than 50% of PDB events occurring beyond 300 days. In a time-adjusted multivariable analysis (accounting for the timing of occurrence of bleeding and MI events), PDB was not only more frequent than PDMI (662 PDB events compared with 391 PDMI events), but also was associated with an approximate 2.6-fold greater risk of subsequent mortality. These data extend prior reports demonstrating that the risk of bleeding is at least as prognostically important as MI (2,4–6,10). The ongoing risk and strong association between PDMI and mortality may underlie the recent findings from randomized trials that shorter DAPT duration may result in improved survival compared to prolonged DAPT, presumably by minimizing bleeding-related complications (3,5,6). Nonetheless, some patients at high risk for thrombotic events, such as those with prior MI, might still benefit from more potent and prolonged DAPT (2,14). Choosing those patients who may benefit from shorter versus longer DAPT requires balancing the risk of future atherothrombotic events and

FIGURE 2 Site of Post-Discharge Bleeding



Among 444 patients with bleeding and specified source, gastrointestinal bleeding was the most predominant cause of post-discharge bleeding. CNS = central nervous system.

TABLE 1 Baseline Clinical and Procedural Characteristics

	PDB (n = 535)	No PDB (n = 8,042)	p Value
Clinical characteristics			
Age, yrs	67.0 ± 10.4	63.4 ± 10.8	<0.0001
Male	373 (69.7)	5,982 (74.4)	0.02
White	489 (91.4)	7,111 (88.4)	0.04
Body mass index, kg/m^2	29.0 ± 6.3	29.5 ± 5.7	0.09
Diabetes mellitus	193 (36.1)	2,588 (32.2)	0.06
Hypertension	461 (86.2)	6,368 (79.2)	0.0001
Hyperlipidemia	427 (79.8)	5,949 (74.0)	0.003
Current smoker	111 (20.7)	1,829 (22.7)	0.29
Previous MI	158 (29.5)	2,006 (24.9)	0.02
Previous PCI	267 (49.9)	3,411 (42.4)	0.0007
Previous CABG	113 (21.1)	1,354 (16.8)	0.01
Peripheral arterial disease	92 (17.2)	782 (9.7)	<0.0001
Renal insufficiency	87 (16.3)	571 (7.1)	<0.0001
Dialysis	24 (4.5)	114 (1.4)	<0.0001
Congestive heart failure	69 (12.9)	630 (7.8)	<0.0001
Ejection fraction, %	55.0 ± 13.71	54.9 ± 12.34	0.91
Ejection fraction <40%	199 (37.2)	2,376 (29.5)	0.0002
Clinical presentation			
Stable coronary artery disease	278 (52.0)	3,871 (48.1)	0.09
Acute coronary syndrome	257 (48.0)	4,171 (51.9)	0.08
Unstable angina	147 (27.5)	2,219 (27.6)	0.95
Non-ST-segment elevation MI	80 (15.0)	1,168 (14.5)	0.79
ST-segment elevation MI	30 (5.6)	784 (9.7)	0.002
Hemoglobin, g/dl	13.3 ± 1.6	14.0 ± 1.5	<0.0001
Platelet count, 10^3/dl	228.7 ± 70.4	226.6 ± 62.5	0.51
White blood cell count, 10^3/ml	8.30 ± 4.85	7.93 ± 3.05	0.08
Creatinine clearance, ml/min*	83.0 ± 40.0	94.8 ± 37.1	<0.0001
Angiographic and procedural characteristics			
Vascular access site			
Femoral	508 (95.0)	7,676 (95.4)	0.60
Radial	23 (4.3)	352 (4.4)	0.93
Brachial	4 (0.7)	14 (0.2)	0.02
Number of diseased vessels			
1	170 (31.8)	3,112 (38.7)	0.001
2	174 (32.5)	2,659 (33.1)	0.80
3	191 (35.7)	2,271 (28.2)	0.0002
Number of lesions per patient	1.6 ± 0.8	1.5 ± 0.8	0.1
Total lesion length, mm	29.2 ± 21.0	26.9 ± 20.0	0.01
Number of stents per patient	1.8 ± 1.1	1.7 ± 1.0	0.009
Total stent length, mm	35.0 ± 23.4	32.3 ± 22.3	0.006
Pre-procedural TIMI flow 0/1	40 (7.5)	748 (9.3)	0.15
Post-procedural TIMI flow 3	530 (99.1)	7,995 (99.4)	0.40
Thrombus	69 (12.9)	1,213 (15.1)	0.17
Calcified lesion	211 (39.4)	2,433 (30.2)	<0.0001
Bifurcation lesion	104 (19.4)	1,222 (15.2)	0.008
Chronic total occlusion	33 (6.2)	372 (4.6)	0.10
Location†			
Left anterior descending artery	242/658 (36.8)	3,707/9,450 (39.2)	0.21
Right coronary artery	202/658 (30.7)	2,984/9,450 (31.6)	0.63
Left main coronary artery	36/658 (5.5)	283/ 9,450 (3.0)	0.0004
Intravascular ultrasound use	208 (38.9)	3153 (39.2)	0.89

Values are n (%) or mean ± SD. *Calculated by Cockcroft-Gault formula. †Lesion-level analysis, reported as n/total lesion N (%).

CABG = coronary artery bypass graft; MI = myocardial infarction; PCI = percutaneous coronary intervention; TIMI = Thrombolysis In Myocardial Infarction.

TABLE 2 Independent Predictors of PDB Within 2 Years

Variable*	HR (95% CI)	p Value
Age (per yr increase)	1.02 (1.01–1.03)	<0.0001
Warfarin, at discharge	2.31 (1.78–2.99)	<0.0001
Peripheral artery disease	1.57 (1.25–1.98)	0.0001
Calcified lesion	1.25 (1.05–1.50)	0.01
Bifurcation lesion	1.32 (1.06–1.64)	0.01
Platelet reactivity units (per 10-unit decrease)	1.01 (1.01–1.02)	0.002
Baseline hemoglobin (per g/dl decrease)	1.28 (1.22–1.37)	<0.0001

*The candidate covariates considered for inclusion in the model were: in-hospital bleeding, age, male sex, diabetes, hypertension, hyperlipidemia, congestive heart failure, peripheral arterial disease, creatinine clearance, pervious percutaneous coronary intervention, ST-segment elevation MI, baseline hemoglobin, warfarin at discharge, triple vessel disease, left main disease, coronary calcification, bifurcation, chronic total occlusion, number of vessels treated, number of lesion treated, stents implanted, mechanical closure device used, $P2Y_{12}$ reactivity units, and aspirin reactivity units.

CI = confidence interval; HR = hazard ratio; MI = myocardial infarction; PDB = post-discharge bleeding.

bleeding risk. In this regard, some factors associated with increased risk of bleeding identified in the present report also have been associated with future ischemic events (e.g., advanced age, peripheral arterial disease, stenting of complex lesions) (15–17). Other variables, however, are uniquely associated with greater bleeding risk, such as baseline anemia and concomitant use of oral anticoagulation. Considering the individual patient's thrombotic and bleeding risk profile to personalize DAPT duration decisions should improve outcomes after DES implantation, although this decision-making process will remain challenging in some cases, and must incorporate patient preferences.

The relationship between PDB and mortality is likely multifactorial (**Central Illustration**), including: 1) decrease in circulating blood volume and oxygen-carrying capacity resulting in hypotension and propensity to ischemia and arrhythmias; 2) discontinuation of DAPT to manage bleeding, which compared to DAPT discontinuation for other reasons has been strongly associated with a higher risk of thrombotic events, especially when occurring within the first 30 days (18,19); 3) discontinuation of other life-extending medications to treat hypotension after bleeding, such as beta-blockers and angiotensin-converting enzyme inhibitors, which paradoxically often are not restarted after patient stabilization; and 4) administration of red blood cell transfusions and other blood products that have been associated with systemic vasoconstriction, activation of inflammatory pathways, apoptosis, increased platelet aggregation, and thrombosis (20). An interesting finding of the current report is that PDB without

transfusion was associated with a similar adjusted hazard for mortality as PDB with transfusion. This observation may be considered counterintuitive, as patients receiving transfusions are often sicker, with multiple comorbidities and greater extent of bleeding (21). In our study, prior to accounting for differences in baseline features, PDB with transfusion was associated with greater cardiac and all-cause mortality than PDB without transfusion. However, after multivariable adjustment, an independent detrimental effect of transfusion was no longer present in patents with PDB, suggesting that it is the deleterious effects of bleeding itself (perhaps in concert with essential medication discontinuation) rather than transfusions that may affect prognosis.

Not surprisingly, concomitant use of oral anticoagulants (22) and lower levels of PRU on clopidogrel (signifying greater inhibition of adenosine diphosphate-associated platelet activation) were strongly associated with development of PDB. This latter observation suggests a possible role for careful agent selection and/or dose modification of agents that block the platelet $P2Y_{12}$ integrin receptor in patients at high bleeding risk (e.g., the elderly, those with recent bleeding, or atrial fibrillation requiring oral anticoagulation). The association between PRU and late bleeding has been previously demonstrated (23,24), although no prospective study has yet shown clinical utility in using PRU to guide treatment decisions. Given the higher rate and prognostic impact of PDB compared to PDMI, coupled with the improved safety profile of current generation DES (19,25,26), our study suggests that future investigations might explore the role of PRU monitoring in high bleeding risk patients to ensure that $P2Y_{12}$ receptor-mediated platelet inhibition is not greater than necessary.

Consistent with prior studies (10,27), gastrointestinal bleeding was the most frequent identifiable source of PDB. Interestingly, proton pump inhibitors were used relatively infrequently at discharge, and at 1 year their use was slightly more common in the group with PDB, likely a response to the bleed. As proton pump inhibitors have been shown to significantly reduce gastrointestinal bleeding in patients with selected risk factors (28), more liberal prophylactic use of these agents during DAPT treatment may improve patient prognosis. Moreover, the predominance of gastrointestinal bleeding highlights the need for judicious screening (e.g., careful history, selective use of gastroscopy and colonoscopy) in appropriate patients before elective PCI involving DES implantation requiring prolonged DAPT.

TABLE 3 2-Year Outcomes According to PDB Occurrence

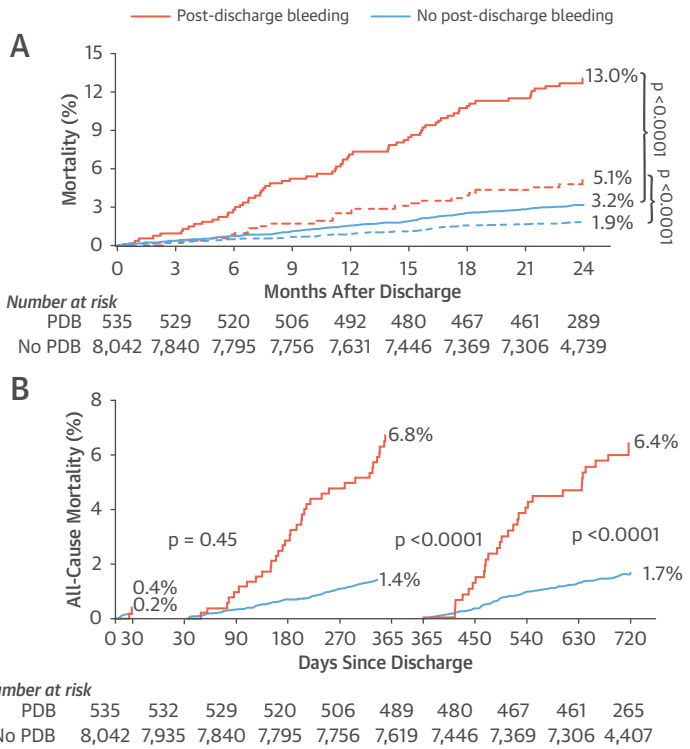
	PDB (n = 535)	No PDB (n = 8,042)	Unadjusted HR (95% CI)	p Value*
All-cause mortality	13.0 (68)	3.2 (243)	8.14 (5.53–12.00)	<0.0001
Cardiac	5.1 (25)	1.9 (144)	4.95 (2.64–9.28)	<0.0001
Noncardiac	6.1 (31)	1.2 (87)	10.52 (5.89–18.81)	<0.0001
MI	13.5 (68)	4.1 (319)	3.14 (2.02–4.90)	<0.0001
Target vessel failure	20.6 (103)	9.0 (685)	2.59 (1.83–3.68)	<0.0001
Definite/probable Stent thrombosis	1.5 (8)	1.0 (81)	3.63 (1.29–10.24)	0.02
MACE†	24.1 (123)	9.9 (758)	2.89 (2.10–3.97)	<0.0001

Event rates are Kaplan-Meier estimates reported as % (n). *Wald p value. †Composite of cardiac death, MI, or target lesion revascularization.

MACE = major adverse cardiac event(s); other abbreviations as in Table 1.

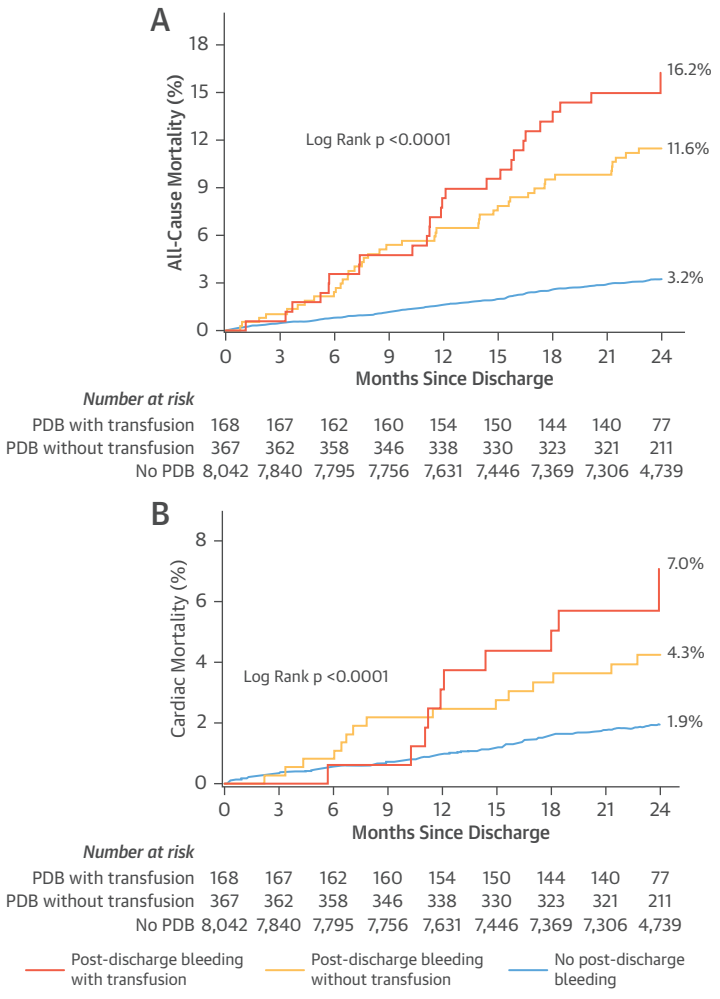
Early discontinuation of or removing aspirin entirely from the DAPT regimen may reduce bleeding in patients at high risk for hemorrhagic complications, as suggested in a recent modest-sized trial in noncomplex post-PCI patients with atrial fibrillation requiring warfarin anticoagulation (29). This is consistent with the ADAPT-DES study, which

FIGURE 3 All-Cause and Cardiac Mortality According to PDB



Kaplan-Meier estimates demonstrate higher rates of all-cause mortality **(solid line)** and cardiac mortality **(dotted line)** according to the occurrence of post-discharge bleeding (PDB) (**salmon**) compared to no PDB **(blue)** over 2 years of follow-up **(A)** as well as the landmark analysis at 30-day and 1-year follow-up **(B)**.

FIGURE 4 Mortality According to PDB and Need for Transfusion



Kaplan-Meier estimates of **(A)** all-cause mortality and **(B)** cardiac mortality according to post-discharge bleeding (PDB) occurrence and requirement (or not) of blood transfusion demonstrate that early after percutaneous coronary intervention, individuals with PDB needing blood transfusions experience lower or comparable rates of mortality compared to those with no transfusions, but those rates cross between 9 and 12 months and climb more sharply thereafter.

TABLE 4 Independent Predictors of All-Cause Mortality at 2 Years

Variable*	Adjusted HR (95% CI)	p Value
PDB†	5.03 (3.29–7.66)	<0.0001
With transfusion	4.71 (2.76–8.03)	<0.0001
Without transfusion	5.27 (3.32–8.35)	<0.0001
Post-discharge MI†	1.92 (1.18–3.12)	0.009
Current smoker	1.69 (1.25–2.29)	0.001
Age (per yr increase)	1.04 (1.02–1.05)	<0.0001
Male	1.45 (1.11–1.90)	0.007
Diabetes mellitus	1.48 (1.17–1.88)	0.001
Previous MI	1.42 (1.12–1.81)	0.004
STEMI or non-STEMI presentation	1.41 (1.10–1.83)	0.008
VerifyNow $P2Y_{12}$ reactivity units >208	1.22 (0.96–1.54)	0.10
IVUS use	0.83 (0.65–1.06)	0.13
Creatinine clearance (per ml/min increase)‡	0.99 (0.99–1.00)	0.0007
Baseline white blood cells (per 10^3/ml increase)	1.03 (1.01–1.04)	<0.0001
Baseline hemoglobin (per g/dl increase)	1.18 (1.09–1.28)	<0.0001

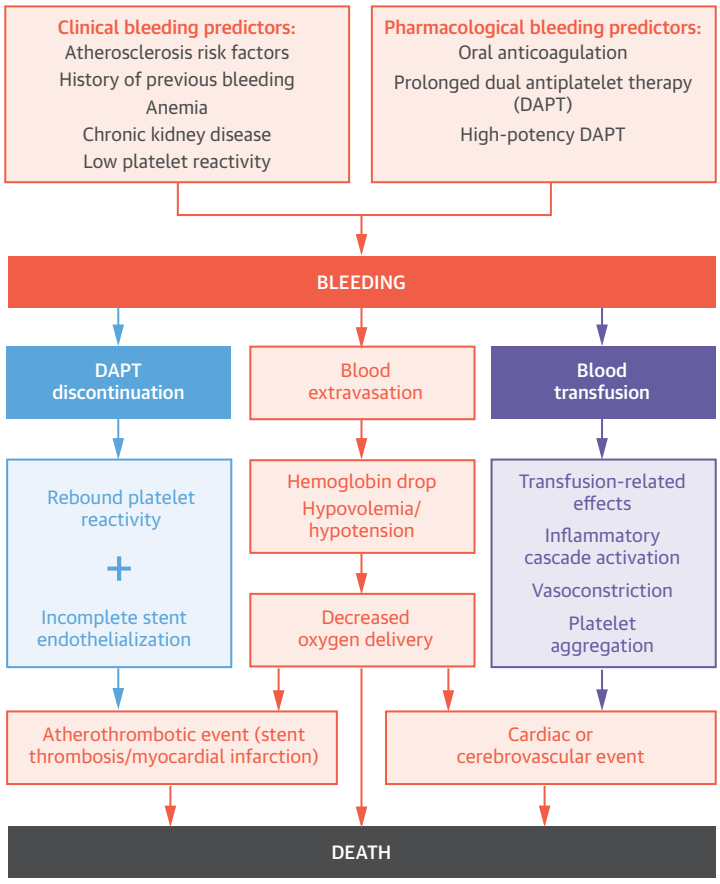
*The candidate covariates considered for inclusion in the model were: PDB, post-discharge MI, age, male, diabetes, current smoker, previous MI, baseline presentation with ST-segment elevation MI (STEMI) or non-STEMI (vs. stable coronary artery disease), hyperlipidemia, baseline hemoglobin, baseline white blood cells, baseline platelets, creatinine clearance, VerifyNow $P2Y_{12}$ reactivity units >208, and intravascular ultrasound (IVUS) guidance. †Both variables were included as time-dependent covariates. ‡Calculated by the Cockcroft-Gault formula.

Abbreviations as in Table 1.

suggested that aspirin resistance was protective from major bleeding after DES implantation without affecting MI or stent thrombosis rates (11). However, given the well-established role of aspirin in secondary prevention after acute coronary syndrome and in patients with vascular disease (30), large-scale randomized trials are required before aspirin withdrawal can be routinely recommended. Several such trials involving agents such ticagrelor and novel oral anticoagulant drugs are ongoing that might provide insight to this issue (NCT02270242; NCT01813435; NCT01830543; NCT02164864).

STUDY LIMITATIONS. Our study has several strengths relative to prior similar investigations, including its large size, prospective nature, recruitment of an all-comers population (resulting in higher PDB rates than in previous studies) (4,10), and assessment of platelet reactivity to aspirin and clopidogrel. Conversely, our study has several limitations. First, bleeding events were not independently adjudicated by a blinded clinical events committee, introducing potential reporting bias. It is possible that minor bleeding events were under-reported. Second, the source of bleeding was not obtained in all patients. Third, the present study was a post hoc analysis from the ADAPT-DES study, and as such should be considered hypothesis generating. Fourth, patients with major periprocedural complications were excluded from the ADAPT-DES study, which while representing a small proportion of contemporary cases, may represent a high-risk group for subsequent bleeding and MI. Fifth, prasugrel only became available late during the ADAPT-DES study recruitment, and ticagrelor was unavailable; as a result almost all patients were treated with clopidogrel. Use of novel, more potent antithrombotic regimens, however, would have most likely resulted in an increase in PDB and a decrease in PDMI, further reinforcing our findings

CENTRAL ILLUSTRATION **Post-Discharge Bleeding After PCI: Predictors and Impact of Clinically Significant Bleeding on Mortality**



Généreux, P. et al. J Am Coll Cardiol. 2015; 66(9):1036–45.

Pathophysiological mechanisms linking out-of-hospital clinically significant bleeding and mortality after implantation of drug-eluting stents (DES). Several clinical and pharmacological factors increase the propensity for bleeding under dual antiplatelet therapy (DAPT). Hemorrhagic events lead to mortality through a direct effect (central pathway) by reducing circulating blood volume as well as reducing blood oxygen-carrying capacity and tissue hypoxia; and through indirect effect (lateral pathways) by increasing the risk for stent thrombosis (because of sudden DAPT discontinuation with rebound in platelet reactivity while the DES is still partially endothelialized) as well as cardiac and noncardiac ischemic events associated with increased thrombogenicity after blood transfusions. Preventing out-of-hospital bleeding after DES implantation may significantly improve survival and long-term prognosis after percutaneous coronary revascularization (PCI).

(31,32). Finally, although we performed a rigorous multivariable time-adjusted analysis to characterize the relative risks of PDB and PDMI on subsequent mortality, the presence of residual confounders cannot be excluded.

CONCLUSIONS

In an unrestricted PCI population discharged after successful DES implantation, subsequent bleeding complications were not uncommon and were strongly associated with cardiac and all-cause mortality. The magnitude of the effect of PDB on 2-year mortality exceeded that of post-discharge MI, underscoring the frequency and impact of late bleeding events on prognosis after PCI and the importance of tailoring antiplatelet approaches in patients undergoing PCI with DES.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Because bleeding after hospital discharge following percutaneous coronary intervention occurs more frequently and has a greater impact on mortality than myocardial infarction, physicians should carefully consider the trade-off between risks of ischemic and bleeding events to individualize the duration and intensity of antiplatelet therapy.

TRANSLATIONAL OUTLOOK: More research is needed to develop safer antithrombotic strategies to reduce the risk of hemorrhagic complications after deployment of drug-eluting coronary stents, especially in patients at high risk of bleeding.

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KEY WORDS late bleeding, mortality, platelet reactivity

APPENDIX For supplemental tables, please see the online version of this article.