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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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