ORIGINAL INVESTIGATIONS

Long-Term Outcomes in Patients With Diabetes Mellitus Related to Prolonging Clopidogrel More Than 12 Months After Coronary Stenting

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ABSTRACT

BACKGROUND Recent large clinical trials show lower rates of late cardiovascular events by extending clopidogrel >12 months after percutaneous coronary revascularization (PCI). However, concerns of increased bleeding have elicited support for limiting prolonged treatment to high-risk patients.

OBJECTIVES The aim of this analysis was to determine the effect of prolonging clopidogrel therapy >12 months versus ≤12 months after PCI on very late outcomes in patients with diabetes mellitus (DM).

METHODS Using the Veterans Health Administration, 28,849 patients undergoing PCI between 2002 and 2006 were categorized into 3 groups: 1) 16,332 without DM; 2) 9,905 with DM treated with oral medications or diet; and 3) 2,612 with DM treated with insulin. Clinical outcomes, stratified by stent type, ≤4 years after PCI were determined from the Veterans Health Administration and Medicare databases and risk was assessed by multivariable and propensity score analyses using a landmark analysis starting 1 year after the index PCI. The primary endpoint of the study was the risk of all-cause death or myocardial infarction (MI).

RESULTS In patients with DM treated with insulin who received drug-eluting stents (DES), prolonged clopidogrel treatment was associated with a decreased risk of death (hazard ratio [HR]: 0.59; 95% confidence interval [CI]: 0.42 to 0.82) and death or MI (HR: 0.67; 95% CI: 0.49 to 0.92). Similarly, in patients with noninsulin-treated DM receiving DES, prolonged clopidogrel treatment was associated with less death (HR: 0.61; 95% CI: 0.48 to 0.77) and death or MI (HR: 0.61; 95% CI: 0.5 to 0.75). Prolonged clopidogrel treatment was not associated with a lower risk in patients without DM or in any group receiving bare-metal stents.

CONCLUSIONS Extending the duration of clopidogrel treatment >12 months may decrease very late death or MI only in patients with DM receiving first-generation DES. Future studies should address this question in patients receiving second-generation DES. (J Am Coll Cardiol 2015;66:1091–101) © 2015 by the American College of Cardiology Foundation.

ABBREVIATIONS AND ACRONYMS

BMS = bare-metal stent(s)

CABG = coronary artery bypass grafting

CI = confidence interval

DAPT = dual antiplatelet therapy

DES = drug-eluting stent(s)

DM = diabetes mellitus

HR = hazard ratio

ICD-9 = International Classification of Diseases-Ninth Revision

MI = myocardial infarction

PCI = percutaneous coronary intervention

VA = Veterans Affairs

The duration of clopidogrel therapy after percutaneous coronary intervention (PCI) remains a vexing issue. Older studies showed that discontinuing dual antiplatelet therapy (DAPT) in the first 12 months after PCI increased the risk of myocardial infarction (MI), stent thrombosis, and death and led to the current recommendations of DAPT for ≥1 year [1]. More recently, the DAPT study showed that in patients free of ischemic and major bleeding events in the first year after PCI, prolonging DAPT a further 18 months reduced recurrent ischemic events [2,3]. However, concerns of harm from increased bleeding and the results of several smaller studies supporting shorter term DAPT [4-10] have generated uncertainty, with suggestions of individualizing DAPT duration according to clinical judgment of perceived risks and benefits [11]. Exactly which patient characteristics should be used to determine prolonged DAPT remains unclear.

Diabetes mellitus (DM) is consistently identified as a risk factor for poorer outcomes after PCI [12-14]. DM could be an important determinant of DAPT duration. The aims of this analysis were to assess whether DM could serve as a clinical indicator of benefit of prolonging DAPT >12 months after PCI.

METHODS

PATIENT POPULATION. We identified all patients who received coronary stents at any Veterans Affairs (VA) facility in the United States between April 2002 and September 2006 and who were alive 12 months after their index PCI [15]. We used the International Classification of Diseases-Ninth Revision (ICD-9) procedure codes for coronary artery stent placement (36.06 for bare-metal stents [BMS] and 36.07 for drug-eluting stents [DES]) to identify patients. During this time frame, only first-generation DES were available. The index procedure was defined as the first coronary artery stent procedure between 2002 and 2006. Of 42,254 patients receiving coronary stents, 2,930 (7%) died within 12 months of their index PCI (**Figure 1**). We excluded another 10,475 patients, as outlined in **Figure 1**. Subjects free of the clinical outcomes at 1 year were followed to September 1, 2007, with a maximum follow-up of 4 years after their index PCI.

DEMOGRAPHIC DATA. Data from the time of the index procedure included the patient age, sex, race,

and presentation with an acute coronary syndrome. Comorbid conditions were defined by ICD-9 codes as those from 5 years before 12 months after the index PCI and included previous angioplasty (ICD-9: 36.01-2, 36.05-7,00.66), coronary bypass surgery (ICD-9: 36.1), smoking (ICD-9: 305.1), hypertension (ICD-9: 401), congestive heart failure (ICD-9: 428), previous stroke (ICD-9: 433.01, 433.11, 434.91, 436, V1254), peripheral arterial disease (ICD-9: 443), chronic obstructive lung disease (ICD-9: 496), anemia (ICD-9: 281-285), and chronic kidney disease (ICD-9: 585).

CLASSIFICATION OF DM. Patients were classified into 3 groups based on the ICD-9 codes for DM (250.x) and use of outpatient hypoglycemic agents in the first 12 months after the index PCI, including insulin (VA drug classification: HS501) or oral hypoglycemic agents (VA drug classification: HS502). These data were used to stratify patients into the following 3 groups: 1) no ICD-9 code for DM (no DM group); 2) ICD-9 code for DM *and* treated with oral medications or no medications (DM, no insulin group); and 3) ICD-9 code for DM *and* treated with insulin (DM and insulin).

MEDICATION USE. The VA National Pharmacy Database provided medications used at the index PCI and clopidogrel during the follow-up period. Because VA prescriptions are usually written for 90-day periods, we defined baseline cardiovascular medications as prescriptions filled within 90 days before the index procedure to up to 7 days after the index procedure. Aspirin use is a VA quality-control measure, and other studies show very high rates of outpatient aspirin use in VA patients with coronary artery disease [16]. The database tracks the dates of prescription and the amount and delivery of clopidogrel up to 4 years after their index PCI. If a clopidogrel prescription lapsed >30 days from the last day of the supply, the patient was considered to be not taking clopidogrel. We defined clopidogrel use as either prolonged (>12 months of use after the index PCI) or ≤12 months of use after the index PCI.

OUTCOMES. Clinical outcomes after the index PCI were identified from the Department of Veterans Affairs National Patient Care, VA Death Database, and the Centers for Medicaid and Medicare database using ICD-9 codes until October 2007. These included all-cause death, the combined outcome of death or MI (ICD-9: 410), admissions with a new discharge diagnosis of revascularization by PCI (ICD-9: 36.01, 36.02, 36.05, 00.66) or coronary artery bypass grafting (CABG) (ICD-9:36.1), ischemic stroke (ICD-9: 436, 433.01, 433.11, 433.21, 433.31, 433.81, 433.91, 434.01, 434.11, 434.91), and hospitalization for severe bleeding (ICD-9: rectal bleeding, 569.3; esophageal