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Association of Spontaneous Bleeding and Myocardial Infarction With Long-Term Mortality After Percutaneous Coronary Intervention

Dhruv S. Kazi, MD, MSc,*†‡ Thomas K. Leong, MPH,§ Tara I. Chang, MD, MS,‖ Matthew D. Solomon, MD, PhD,§‖ Mark A. Hlatky, MD,‖¶ Alan S. Go, MD‡§¶

ABSTRACT

BACKGROUND Platelet inhibition after percutaneous coronary intervention (PCI) reduces the risk of myocardial infarction (MI) but increases the risk of bleeding. MIs and bleeds during the index hospitalization for PCI are known to negatively affect long-term outcomes. The impact of spontaneous bleeding occurring after discharge on long-term mortality is unknown.

OBJECTIVES This study sought to examine, in a real-world cohort, the association between spontaneous major bleeding or MI after PCI and long-term mortality.

METHODS We conducted a retrospective cohort study of patients ≥30 years of age who underwent a PCI between 1996 and 2008 in an integrated healthcare delivery system. We used extended Cox regression to examine the associations of spontaneous bleeding and MI with all-cause mortality, after adjustment for time-updated demographics, comorbidities, periprocedural events, and longitudinal medication exposure.

RESULTS Among 32,906 patients who had a PCI and survived the index hospitalization, 530 had bleeds and 991 had MIs between 7 and 365 days post-discharge. There were 4,048 deaths over a mean follow-up of 4.42 years. The crude annual death rate after a spontaneous bleed (9.5%) or MI (7.6%) was higher than among patients who experienced neither event (2.6%). Bleeding was associated with an increased rate of death (adjusted hazard ratio [HR]: 1.61, 95% confidence interval [CI]: 1.30 to 2.00), similar to that after an MI (HR: 1.91; 95% CI: 1.62 to 2.25). The association of bleeding with death remained significant after additional adjustment for the longitudinal use of antiplatelet agents.

CONCLUSIONS Spontaneous bleeding after a PCI was independently associated with higher long-term mortality, and conveyed a risk comparable to that of an MI during follow-up. This tradeoff between efficacy and safety bolsters the argument for personalizing antiplatelet therapy after PCI on the basis of the patient's long-term risk of both thrombotic and bleeding events. (J Am Coll Cardiol 2015;65:1411–20) © 2015 by the American College of Cardiology Foundation.

Contemporary percutaneous coronary intervention (PCI) involves arterial cannulation, periprocedural anticoagulation, and dual antiplatelet therapy. This combination of factors leads to procedure-related major bleeding in 2% to 5% of patients (1–4). An additional 1% to 5% of patients have spontaneous major bleeding in the first year after PCI, depending on the clinical definition used

From the *Division of Cardiology, San Francisco General Hospital, San Francisco, California; †Department of Medicine (Cardiology), University of California San Francisco, San Francisco, California; ‡Department of Epidemiology & Biostatistics, University of California San Francisco, San Francisco, California; §Division of Research, Kaiser Permanente Northern California, Oakland, California; ‖Department of Medicine, Stanford University, Stanford, California; and the ¶Department of Health Research and Policy, Stanford University, Stanford, California. This study was funded in part by the American Heart Association (Grant Number 0875162N), Kaiser Permanente Northern California Division of Research, Stanford University, and the University of California-San Francisco. The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; or preparation, review, and approval of the manuscript. Dr. Go has received a research grant from Genentech. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.
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ABBREVIATIONS AND ACRONYMS

CI = confidence interval

HR = hazard ratio

IQR = interquartile range

MI = myocardial infarction

PCI = percutaneous coronary intervention

(5,6). Procedural bleeding is associated with increased mortality during the index hospitalization and in the first year after discharge (1,3,7–13). The effect, if any, of spontaneous bleeds that occur after hospital discharge (i.e., nonprocedural bleeds) on long-term outcomes is unclear.

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The potential impact of spontaneous bleeding on long-term outcomes is important to assess for 2 reasons. First, although strategies to reduce periprocedural bleeding are receiving increasing attention (e.g., use of radial access for PCI), no such systematic efforts are in place to reduce bleeding that occurs after hospital discharge. Second, if spontaneous bleeding were indeed associated with higher late mortality, it would motivate careful consideration of the net clinical benefit of new antiplatelet and antithrombotic agents that reduce myocardial infarctions (MIs), but increase bleeding. This tradeoff between efficacy and safety may bolster the argument for personalizing the choice and duration of antiplatelet therapy after PCI on the basis of the patient's long-term risk of both thrombotic and bleeding events.

To address this issue, we examined the association between major spontaneous bleeding or MI and long-term risk of death in a large, community-based cohort of patients receiving PCI within usual care clinical settings. We hypothesized that spontaneous bleeds in the first year after PCI would be associated with increased all-cause mortality that is comparable to the risk associated with a spontaneous MI.

METHODS

SOURCE POPULATION. The source population was from Kaiser Permanente Northern California, a large integrated healthcare delivery system with >3.3 million members in the San Francisco and greater Bay Area. The health plan membership is representative of the regional and statewide population, apart from slightly lower representation at the extremes of income and age.

STUDY POPULATION. We used health plan electronic health records to identify all members 30 years of age and older who received PCI between January 1, 1996, and December 31, 2008. We excluded patients who had incomplete demographic data, or <12 months of continuous membership and pharmacy benefit before the index procedure. We also excluded patients who died either during the index hospitalization or within 7 days after discharge because the outcome of interest was long-term mortality. All patients were followed through December 31, 2008 (the latest date for which complete mortality data were available at the time of analysis), or until disenrollment from the health plan, defined as a continuous gap in membership of 90 days or longer.

OUTCOME. The primary outcome was death from any cause through December 31, 2008, which was identified from a combination of health plan hospitalization and administrative records, California state death certificate files, and Social Security Administration vital status files (14,15).

EXPOSURES OF INTEREST. We defined spontaneous bleeding or MI as events occurring between days 7 and 365 after discharge from the index hospitalization. We treated events occurring during the initial hospital stay for PCI or within the first 7 days after discharge as procedural events because of the limited temporal resolution of available electronic data. On the basis of previously validated methods (16–19), we used International Classification of Diseases-Ninth Edition, codes to identify subsequent hospitalizations for MI (defined as a primary discharge diagnosis of an acute MI) or bleeding (a primary or secondary discharge diagnosis of intracranial bleeding, or a primary discharge diagnosis of extracranial bleeding). This was on the basis of our previous work demonstrating a low positive predictive value of codes for extracranial bleeds in the secondary position (17). We did not evaluate the use of blood transfusions because procedure codes are not sufficiently accurate to identify them in our data (20,21).

COVARIATES. We obtained demographic and clinical data from health plan electronic health records and other associated databases. We identified comorbid conditions up to 4 years before the date of the index procedure and throughout follow-up using previously validated approaches from health plan hospitalization, ambulatory, laboratory, and pharmacy databases (22–24). We obtained a time-updated history of heart failure, diabetes mellitus, hypertension, dyslipidemia, mitral or aortic valvular heart disease, peripheral arterial disease, stroke or transient ischemic attack, dementia, systemic cancer, hypothyroidism, and chronic lung disease. We also identified previous hospitalizations for bleeding. Because kidney dysfunction and anemia are predictors of both major bleeding and mortality, we extracted baseline and longitudinal estimated glomerular filtration rates and hemoglobin concentrations from the health plan laboratory database (25–27). From health plan pharmacy