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Time-Dependent Associations Between Actionable Bleeding, Coronary Thrombotic Events, and Mortality Following Percutaneous Coronary Intervention

Results From the PARIS Registry

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ABSTRACT

OBJECTIVES The aim of this study was to examine the independent associations between actionable bleeding (AB) and coronary thrombotic events (CTE) on mortality risk after percutaneous coronary intervention (PCI).

BACKGROUND The independent impact of AB and CTE on mortality risk after PCI remains poorly characterized.

METHODS A post hoc analysis was conducted of the PARIS (Patterns of Non-Adherence to Dual Antiplatelet Therapy in Stented Patients) registry, a real-world cohort of 5,018 patients undergoing PCI with stent implantation. CTE included definite or probable stent thrombosis or myocardial infarction. AB was defined as Bleeding Academic Research Consortium type 2 or 3. Associations between CTE and AB, both of which were modeled as time-dependent covariates, and 2-year mortality risk were examined using extended Cox regression.

RESULTS Over 2 years, the cumulative incidence of CTE, AB, and all-cause mortality was 5.9% (n = 289), 8.1% (n = 391), and 4.7% (n = 227), respectively. Adjusted hazard ratios for mortality associated with CTE and AB were 3.3 (95% confidence interval: 2.2 to 4.9) and 3.5 (95% confidence interval: 2.3 to 5.4), respectively. Temporal gradients in risk after either event were highest in the first 30 days and declined rapidly thereafter. Thrombotic events occurring while patients were on versus off dual-antiplatelet therapy were associated with a higher mortality risk, whereas risk related to AB was not influenced by dual-antiplatelet therapy status at the time of bleeding.

CONCLUSIONS Intracoronary thrombosis and AB are associated with mortality risks of comparable magnitude over a 2-year period after PCI, findings that might inform risk/benefit calculations for extension versus discontinuation of dual-antiplatelet therapy. (J Am Coll Cardiol Intv 2016;9:1349–57) © 2016 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

AB = actionable bleeding

BARC = Bleeding Academic Research Consortium

CI = confidence interval

CTE = coronary thrombotic event(s)

DAPT = dual-antiplatelet therapy

HR = hazard ratio

MI = myocardial infarction

PCI = percutaneous coronary intervention

ST = stent thrombosis

Thrombotic complications following percutaneous coronary intervention (PCI), such as stent thrombosis (ST) and myocardial infarction (MI), are associated with a markedly increased risk for subsequent adverse events, including mortality (1-3). Mitigating such risk requires dual-antiplatelet therapy (DAPT), the length of which may vary by a patient's clinical presentation, risk factors, or stent platform. The unavoidable corollary to such therapy is bleeding, however, which also is associated with increased risk for both short- and long-term mortality (2,4). As a result, identifying the optimal duration of DAPT that minimizes bleeding risk without compromising antithrombotic efficacy has become a highly relevant area of clinical investigation. Although multiple randomized trials have examined the impact of different durations of DAPT after PCI, results thus far have been somewhat inconsistent, further complicating decision making in this regard (5-7).

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However, because intracoronary thrombosis and bleeding represent the gains and costs from extension of DAPT, weighing the relative impact of each event on post-PCI mortality may provide a more nuanced appraisal of the risks and benefits of such a strategy. Although several studies have examined such associations, some evaluated bleeding and thrombosis separately, with limited data reported after mutual adjustment for both types of events (8-10). This is a clinically relevant distinction, as frequently observed contributors to bleeding, such as older age, renal dysfunction, and ST-segment deviation (11), are also linked with increased risks for thrombosis (12,13), suggesting that many patients may be at high and comparable risk for both events. Accordingly, we sought to examine the association between both bleeding and thrombotic complications, on subsequent mortality risk in a large and contemporary cohort of patients undergoing PCI.

METHODS

STUDY DESIGN AND POPULATION. The details of the PARIS (Patterns of Non-Adherence to Dual Antiplatelet Therapy in Stented Patients) registry have been previously reported in detail (14). In brief, the PARIS registry was a prospective observational study of patients undergoing PCI with stent implantation at 15 clinical sites in the United States and Europe between July 1, 2009, and December 2, 2010. Adult patients (18 years of age or older) undergoing stent implantation in at least 1 native coronary artery and discharged on DAPT were eligible for enrollment. All patients provided written informed consent.

DEFINITIONS. ST was defined according to the Academic Research Consortium criteria (15). MI was defined in accordance with the universal definition (16). For the present analysis, coronary thrombotic events (CTE) were defined as definite or probable ST or MI. Bleeding was classified using the Bleeding Academic Research Consortium (BARC) criteria (17). We classified actionable bleeding (AB) as BARC type 2 or 3. BARC type 2 is defined as clinically overt hemorrhage requiring medical attention, whereas BARC type 3 includes bleeds with a hemoglobin decrease of at least 3 g/dl, requiring transfusion or surgical intervention. Death was classified as cardiac or noncardiac per the Academic Research Consortium definitions (15). Our primary intent was to examine mortality risk related to nonfatal CTE and bleeding, as both of these events were either reduced or increased by a prolonged DAPT strategy (6). As a result, we did not model associations for events that

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