Differential occurrence, profile, and impact of first recurrent cardiovascular events after an acute coronary syndrome

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Objective Acute coronary syndrome (ACS) trials typically use a composite primary outcome (myocardial infarction [MI], stroke, or cardiovascular death), but differential patient characteristics, timing, and consequences associated with individual component end points as first events have not been well studied. We compared patient characteristics and prognostic significance associated with first cardiovascular events in the post-ACS setting for initially stabilized patients.

Methods We combined patient-level data from 4 trials of post-ACS antithrombotic therapies (PLATO, APPRAISE-2, TRACER, and TRILOGY ACS) to characterize the timing of and characteristics associated with first cardiovascular events (MI, stroke, or cardiovascular death). Landmark analysis at 7 days after index ACS presentation was used to focus on spontaneous, postdischarge events that were not confounded by in-hospital procedural complications. Using a competing risk framework, we tested for differential associations between prespecified covariates and the occurrence of nonfatal stroke vs MI as the first event, and we examined subsequent events after the first nonfatal event.

Results Among 46,694 patients with a median follow-up of 358 (25th, 75th percentiles 262, 486) days, a first ischemic event occurred in 4,307 patients (9.2%) as follows: MI in 5.8% (n = 2,690), stroke in 1.0% (n = 477), and cardiovascular death in 2.4% (n = 1,140). Older age, prior stroke/transient ischemic attack, prior atrial fibrillation, and higher diastolic blood pressure were associated with a significantly greater risk of stroke vs MI, whereas prior percutaneous coronary intervention was associated with a greater risk of MI vs stroke. Second events occurred in 32% of those with a first nonfatal stroke at a median of 13 (3, 59) days after the first event and in 32% of those with a first nonfatal MI at a median of 35 (5, 137) days after the first event. The most common second event was a recurrent MI among those with MI as the first event and cardiovascular death among those with stroke as the first event.

Conclusions Approximately 9% of patients experienced a first cardiovascular event in the post-ACS setting during a median follow-up of 1 year. Although the profile and prognostic implications of stroke vs MI as the first nonfatal event differ substantially, approximately one-third of these patients experienced a second event, typically soon after the first event. These findings have implications for improving post-ACS care and influencing the design of future cardiovascular trials. (Am Heart J 2017;0:1-10.)

Cardiovascular (CV) disease is the leading cause of death globally, with approximately 7.4 million deaths from ischemic heart disease and 6.7 million stroke-related deaths per year.[1] Although ischemic heart disease and stroke share similar risk factors and treatments,[2-6] previous CV outcomes trials evaluating parenteral anti-

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thrombotic therapies for acute coronary syndromes (ACSs) excluded stroke as an outcome, focusing instead on a common short-term (typically 30 days) composite end point of myocardial infarction (MI) and all-cause death.[7-10] The composition of CV outcomes trial end points shifted when clopidogrel was found to significantly reduce a composite of CV death, MI, or stroke compared with aspirin for patients with stable coronary artery, cerebrovascular, and peripheral vascular disease in the Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial.[11] Thereafter, stroke was included in the primary composite end point for the first time in a large ACS CV outcomes trial, Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE).[12] Subsequent trials evaluating the long-term use of oral antithrombotic therapies post-ACS have used a similar primary composite end point of CV death, MI, or stroke and have collectively shown composite event rates of approximately 10% through 12 months.[13-18]

Although commonly incorporated into the standard primary composite end point for post-ACS trials, stroke as a unique CV event has not been well studied. Specifically, the timing, patient risk profile, and prognostic significance of post-ACS stroke compared with other CV events remain poorly characterized. We therefore analyzed combined patient-level data from the following trials evaluating post-ACS antithrombotic therapies: Platelet Inhibition and Patient Outcomes (PLATO),[13] Apixaban for Prevention of Acute Ischemic Events 2 (APPRAISE-2),[14] Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome (TRACER),[15] and Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes (TRILOGY ACS).[16] Our objectives were to (1) describe patient characteristics according to first post-ACS CV event (stroke, MI, or CV death), (2) examine the differential timing and trajectory of first CV events, and (3) compare patient characteristics and downstream outcomes by type of first nonfatal CV event (stroke vs MI).

Methods

Data sources and study population

Data were merged from 4 CV outcomes trials of post-ACS antithrombotic therapy for which we had access to patient-level data: PLATO, APPRAISE-2, TRACER, and TRILOGY ACS. Trial characteristics and major inclusion/exclusion criteria are shown in Supplementary Tables I and II, respectively.[13-16] In APPRAISE-2 and TRILOGY ACS, patients were randomized close to discharge from index hospitalization, whereas patients in PLATO and TRACER were randomized within 24 hours of index presentation.

The combined 4-trial population was 48,286 patients. A total of 1,527 patients were excluded from this analysis (Supplementary Table III) because of an ischemic event (MI, stroke, CV death; n = 1,176) or non-CV death (n = 12) occurring within 7 days of index ACS presentation or study discontinuation during this time frame without complete ascertainment of nonfatal end points during subsequent trial follow-up (n = 351). We chose a 7-day landmark time point for this analysis because of the different enrollment periods across the trials, with APPRAISE-2 and TRILOGY ACS having longer enrollment windows, and to ensure a common starting time for end point ascertainment. We designed this analysis to study the secondary prevention phase of post-ACS treatment when most CV events would be expected to be spontaneous (ie, unrelated to in-hospital ACS treatments, including medications and revascularization procedures) and therefore more likely to be comparable across the 4 trials. Accordingly, we included only patients without early (within 7 days) in-hospital events. A total of 65 patients were excluded due to inability to determine the timing of their first recurrent CV event within the merged dataset. Our final analysis population consisted of 46,694 stabilized post-ACS patients without a CV event within the first 7 days after ACS presentation. Baseline characteristics according to source trial are shown in Supplementary Table IV.

Outcomes and definitions

Primary outcomes included MI, stroke (including ischemic and hemorrhagic strokes, as per stroke end points in the 4 trials studied), and CV mortality.[13-16] All-cause mortality and stroke subtypes (ischemic and hemorrhagic) were secondary outcomes. End points were independently adjudicated and classified by clinical events committees for each trial according to similar prespecified end point definitions.[13-16] APPRAISE-2, PLATO, and TRACER classified MI end points based on the 2007 universal definition of MI as types 1-5[19]; types 1-3 MI events were considered spontaneous for this analysis. TRILOGY ACS classified MI end points as spontaneous or procedural based on an adaptation of the universal definition of MI and did not classify MI end points as types 1-5.[18]

Statistical analysis

We examined patient characteristics at randomization stratified by first event type (MI, stroke, CV death, or none). Categorical variables were presented as counts and frequencies, and continuous variables were presented as median values with interquartile ranges (IQRs). Continuous characteristics were compared using the Kruskal-Wallis test, and categorical characteristics were compared using the Pearson χ^2 test; otherwise, a Fisher exact test was used. Outcomes were assessed using landmark analyses beginning 7 days after hospitalization for the index ACS. Median times to first event and IQRs