Pooled analysis of adverse event collection from 4 acute coronary syndrome trials

André Zimerman [a] Renato D. Lopes, MD, PhD, [a] Amanda L. Stebbins, MS, [a] Patrícia O. Guimarães, MD, [a] Ghazala Haque, MBBS, [a] Chiara Melloni, MD, [a] Kathleen Trollinger, MSN, [a] Stefan K. James, MD, PhD, [b] John H. Alexander, MD, MHS, [a] Pierluigi Tricoci, MD, PhD, MHS, [a] Matthew T. Roe, MD, MHS, [a] Erik Magnus Ohman, MD, [a] Kenneth W. Mahaffey, MD, [c] Claes Held, MD, PhD, [b] Brian Tinga, MS, [a] Karen S. Pieper, MS, [a] and Karen P. Alexander, MD [a] *Durham, NC; Uppsala, Sweden; and Stanford, CA*

Background Adverse event collection in randomized clinical trials establishes drug safety. Although costly and regulated, it is rarely studied.

Methods Adverse event data from 4 clinical trials (APPRAISE-2, PLATO, TRACER, TRILOGY ACS) comprising 48,118 participants with acute coronary syndromes were pooled to compare patterns and determinants of reporting. Events were classified as serious (SAE) or nonserious (AE) from hospital discharge to 1 year; study end points were excluded.

Results In total, 84,901 events were reported. Of those, 12,266 (14.4%) were SAEs and 72,635 (85.6%) were AEs. Of all participants, 7,823 (16.3%) had SAEs, 18,124 (37.7%) had only AEs, and 22,171 (46.1%) had neither. Nonserious adverse events were distributed across system organ classes: general disorders (11%), infection (10%), gastrointestinal (10%), respiratory (9%), cardiovascular (8.4%), and other (35%). Serious adverse events had a higher proportion of cardiovascular causes (14.0%). Event reporting was highest after hospital discharge, decreasing rapidly during the following 3 months. In a Cox proportional hazards model, chronic obstructive pulmonary disease (hazard ratio 1.58, 95% CI 1.44-1.74), heart failure (1.55, 1.40-1.70), older age, and female sex were independent predictors of more SAEs, whereas enrollment in Eastern Europe (0.63, 0.58-0.69) or Asia (0.84, 0.75-0.94) were independent predictors of fewer SAEs.

Conclusions Half of all participants reported adverse events in the year after acute coronary syndrome; most were AEs and occurred within 3 months. The high volume of events, as well as the variation in SAE reporting by characteristics and enrollment region, indicates that efforts to refine event collection in large trials are warranted. (Am Heart J 2016;174:60-7.)

Safety event collection is a pillar of clinical trial research for investigational products and devices, and it forms the basis for approval by regulatory authorities.[1–3] Adverse events in clinical trials may lead to interruption of study drug, are viewed as important medical events, and may result in hospital admission.[4] Serious adverse events (SAEs), particularly if unanticipated in the disease state and/or unlisted in the investigator brochure, inform the safety profile of the drug or device.[5] Adverse reactions from clinical trials are a key component of the drug label, which lists adverse events that occur above a certain rate and are possibly drug related.[6] Substantial resources are spent on ensuring timely and complete reporting of adverse events during all preapproval stages of development. However, the reporting of nonserious adverse events (AEs) that are common regardless of exposure to study drug—such as arthritis, influenza, headaches, dental caries, and constipation—may add little clinically meaningful information to the safety profile of a drug at phase III. The proportion of SAE to AEs may also be influenced by the disease under study, and reporting may vary over time, across demographics, and by region of enrollment.

Therefore, we sought to better understand the collection of adverse events in clinical research, which informs clinical practice. Using pooled adverse event data from 4 recent clinical trials in acute coronary syndromes (ACS), the patterns of serious and nonserious safety events from hospital discharge to 1 year in more than 45,000 participants are described. The patterns, frequency, and determinants of postdischarge reporting may inform future safety event collection in multinational trials and provide insight into the use of adverse event information in clinical practice.

From the [a]Duke Clinical Research Institute, Duke Medicine, Durham, NC, [b]Uppsala Clinical Research Center, UCR, Uppsala University, Uppsala, Sweden, and [c]Department of Medicine, Stanford University, Stanford, CA.

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Reprint requests: Karen P. Alexander, MD, Duke Clinical Research Institute, Room 0311 Terrace Level, 2400 Pratt St, Durham, NC 27705.

E-mail: karen.alexander@duke.edu

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Methods

Participant population and clinical trials

The combined study cohort included all randomized participants who survived to hospital discharge in the 4 trials: (1) Apixaban for Prevention of Acute Ischemic Events 2 (APPRAISE-2), (2) Study of Platelet Inhibition and Patient Outcomes (PLATO), (3) Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome (TRACER), and (4) Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes (TRILOGY ACS).[7–10] All 4 trials were multinational, randomized, and double-blind, and tested a novel antiplatelet or anticoagulant drug in post-ACS populations from 2006 to 2011 (online Appendix Supplementary Table). Eligibility criteria differed; APPRAISE-2 and PLATO included any ACS, and TRACER and TRILOGY ACS excluded patients with ST-segment elevation myocardial infarction (MI). Trial designs have been reported elsewhere.[11,12]

Age and sex were comparable across trials, but participants enrolled in TRILOGY ACS and APPRAISE-2 had higher baseline risk, as indicated by higher rates of diabetes mellitus, prior MI, and moderate-to-severe renal insufficiency. Revascularization rates in the primary event varied from 44% to 68%, with the notable exception of TRILOGY ACS, a trial of medically managed ACS, which had a 0% revascularization rate. The median follow-up ranged from 7.9 months (APPRAISE-2, stopped early by the data safety monitoring board) to 17.1 months (TRILOGY ACS). Follow-up intervals were fairly uniform across studies, and assessments were conducted either in person or via telephone.

Adverse events

Event terminology was standardized using the Medical Dictionary for Regulatory Activities software. For event-specific analyses, equivalent event terms were combined. All trial end points were excluded from analyses (eg, MI, unstable angina, stroke, bleeding, and death). Adverse events were defined as undesirable medical occurrences, regardless of whether they were potentially drug related.[5] For an adverse event to be serious, it should result in death, be life-threatening, lead to hospitalization (or prolong current hospitalization), cause persistent or significant disability, cause a congenital anomaly, or be an important medical event, based on clinician judgment.[5] If no serious criterion was fulfilled, the adverse event was considered nonserious. The attribution of seriousness was performed by the site investigator, and all events that occurred between hospital discharge date and 1 year were included.

Statistical analysis

Participants were divided into 3 comparison groups based on their adverse event reporting: any SAE reported (any SAE), AE only reported (AE only), and the remainder reporting no adverse events (no adverse event). Discrete variables were presented as frequencies and percentages. Continuous variables were described as medians with 25th and 75th percentiles. Wilcoxon rank sum or *t* test statistics were used to analyze continuous variables, and the χ^2 test was used for discrete variables. All hypothesis tests were 2-sided. *P* values <.05 were considered significant. Missing values were excluded from statistical summaries. Baseline characteristics associated with any SAE reporting (vs no SAE reporting) were presented as row percentages among those with that characteristic. A Cox proportional hazards model was used to identify baseline factors independently associated with any SAE reporting.

A linearity test was performed for continuous variables. Missing values were uncommon (<3%) for most predictors, except for Killip class (15%), creatinine clearance (15%), and chronic obstructive pulmonary disease (COPD; 36%). Forward selection and stepwise selection were used to generate the final model. Results were stratified by trial. An instantaneous hazard was calculated for each time point in the 1-year interval for the outcomes of SAEs and AEs, separated again by cardiovascular or noncardiovascular. A smoothing function was applied to the estimates, with a smoothing parameter of 0.4. This smoothed function of hazard was plotted across the 1-year interval. Analyses were performed with SAS software (version 9.2; SAS Institute, Inc, Cary, NC) and Microsoft Excel (version 14.4.7; Microsoft Corporation, Redmond, WA).

Results

Study participants

The analysis population comprised 48,118 participants from the 4 clinical trials who survived to hospital discharge and continued in the follow-up phase: APPRAISE-2 (N = 7389), PLATO (N = 18,616), TRACER (N = 12,812), and TRILOGY ACS (N = 9301). The total number of reported adverse events was 84,901, of which 12,266 (14.4%) were SAEs and 72,635 (85.6%) were AEs. Of all participants, 7,823 (16.3%) had any SAE, 18,124 (37.7%) had AEs only, and 22,171 (46.1%) had no adverse event reported. A total of 5,285 (11.0%) participants had both SAEs and AEs. Among participants who reported an SAE, 68.5% had 1, 18.9% had 2, 6.9% had 3, and 5.7% had ≥4 SAEs. The maximum number of SAEs reported by a participant was 15. Of participants who reported AEs, 80.0% had 1 to 3 events; the most AEs reported by a single participant was 35. Nonserious adverse events were 3-fold more common in participants who experienced SAEs (mean 3.6 AEs/participant with SAE vs 1.1 AEs/participant without SAE).

Baseline characteristics

Participants who had any SAE, as compared with those with only AEs or no adverse events, were older (67 vs 64 and 63 years; $P < .0001$), more likely to be female, and had more risk factors, such as hypercholesterolemia, diabetes, prior MI, peripheral artery disease, COPD, congestive heart failure, and lower creatinine clearance (Table I). Moreover, participants who had any SAE had a higher Killip class. Participants enrolled in Eastern Europe or Asia contributed fewer adverse events as compared with participants from the United States/Canada or