Elderly Patients With Acute Coronary Syndromes Managed Without Revascularization

Insights Into the Safety of Long-Term Dual Antiplatelet Therapy With Reduced-Dose Prasugrel Versus Standard-Dose Clopidogrel

Matthew T. Roe, MD, MHS; Shaun G. Goodman, MD, MSc; E. Magnus Ohman, MB, ChB; Susanna R. Stevens, MS; Judith S. Hochman, MD; Shmuel Gottlieb, MD; Felipe Martinez, MD; Anthony J. Dalby, MD; William E. Boden, MD, PhD; Harvey D. White, MB, ChB, DSc; Dorairaj Prabhakaran, MD, MSc; Kenneth J. Winters, MD; Philip E. Aylward, MD; Jean-Pierre Bassand, MD; Darren K. McGuire, MD; Diego Ardissino, MD; Keith A. A. Fox, MB, ChB; Paul W. Armstrong, MD

Background—Dual antiplatelet therapy in older versus younger patients with acute coronary syndromes is understudied.

Low-dose prasugrel (5 mg/d) is recommended for younger, lower-body-weight patients and elderly patients with acute coronary syndromes to mitigate the bleeding risk of standard-dose prasugrel (10 mg/d).

Methods and Results—A total of 9326 medically managed patients with acute coronary syndromes from the Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes (TRILOGY ACS) trial (<75 years of age, n=7243; ≥75 years of age, n=2083) were randomized to prasugrel (10 mg/d; 5 mg/d for those ≥75 or <75 years of age and <60 kg in weight) or clopidogrel (75 mg/d) plus aspirin for ≤30 months. Of a total of 515 participants ≥75 years of age (25% of total elderly population) had serial platelet reactivity unit measurements in a platelet-function substudy. Cumulative risks of the primary end point (cardiovascular death/myocardial infarction/stroke) and Thrombolysis in Myocardial Infarction (TIMI) major bleeding increased progressively with age and were 2-fold higher in older participants. Among those ≥75 years of age, TIMI major bleeding (4.1% versus 3.4%; hazard ratio, 1.09; 95% confidence interval, 0.57–2.08) and the primary end point rates were similar with reduced-dose prasugrel and clopidogrel. Despite a correlation between lower 30-day on-treatment platelet reactivity unit values and lower weight only in the prasugrel group, there was a nonsignificant treatment-by-weight interaction for platelet reactivity unit values among participants ≥75 years of age in the platelet-function substudy (P=0.06). No differences in weight were seen in all participants ≥75 years of age with versus without TIMI major/minor bleeding in both treatment groups.

Conclusions—Older age is associated with substantially increased long-term cardiovascular risk and bleeding among patients with medically managed acute coronary syndromes, with no differences in ischemic or bleeding outcomes with reduced-dose prasugrel compared with clopidogrel in elderly patients. No significant interactions among weight, pharmacodynamic response, and bleeding risk were observed between reduced-dose prasugrel and clopidogrel in elderly patients.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov/ct2/home. Unique identifier: NCT0069999.

(Circulation. 2013;128:823-833.)

Key Words: aging ■ drug therapy ■ fibrinolytic agents ■ myocardial infarction ■ receptors, purinergic P2Y12

Continuing medical education (CME) credit is available for this article. Go to http://cme.ahajournals.org to take the quiz.

Received February 27, 2013; accepted June 28, 2013.

From the Duke Clinical Research Institute, Duke University Medical Center, Durham, NC (M.T.R., E.M.O., S.R.S.); Division of Cardiology, Department of Medicine, Duke University School of Medicine, Durham, NC (M.T.R., E.M.O.); Division of Cardiology, Department of Medicine, St. Michael’s Hospital, Toronto, ON, Canada (S.G.G.); Cardiovascular Clinical Research Center, Leon H. Charney Division of Cardiology, New York University School of Medicine and NYU Langone Medical Center, New York (J.S.H.); Cardiac Institute, Bikur Cholim Campus, Shaare Zedek Medical Center, Jerusalem, Israel (S.G.); Department of Cardiology, Córdoba National University, Córdoba, Argentina (F.M.); Milpark Hospital, Johannesburg, South Africa (A.J.D.); Department of Medicine, Stratton VA Medical Center/Albany Medical College, Albany, NY (W.E.B.); Auckland City Hospital, Green Lane Cardiovascular Service, Auckland, New Zealand (H.D.W.); Centre for Chronic Disease Control, New Delhi, India (D.P.); Eli Lilly and Company, Indianapolis, IN (K.J.W.); South Australian Health and Medical Research Institute, Flinders University and Medical Centre, Adelaide, South Australia, Australia (P.E.A.); Department of Cardiology, University Hospital Jean Minjoz, Besançon, France (J.-P.B.); University of Texas Southwestern Medical Center, Dallas (D.K.M.); Division of Cardiology, Azienda Ospedaliero-Universitaria di Parma, Parma, Italy (D.A.); British Heart Foundation Centre for Cardiovascular Sciences, University of Edinburgh, Edinburgh, Scotland, UK (K.A.A.F.); and Division of Cardiology, University of Alberta, Edmonton, AB, Canada (P.W.A.).

The online-only Data Supplement is available with this article at http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIRCULATIONAHA.113.002303/-/DC1.

Correspondence to Matthew T. Roe, MD, MHS, Duke Clinical Research Institute, 2400 Pratt St, Room 7035, Durham, NC 27705. E-mail matthew.roe@duke.edu

© 2013 American Heart Association, Inc.

Circulation is available at http://circ.ahajournals.org

DOI: 10.1161/CIRCULATIONAHA.113.002303
Optimizing care for elderly patients with cardiovascular disease constitutes both a central priority and a formidable challenge in contemporary medicine. Given the rapid growth of an aging population worldwide, an increasing proportion of morbidity and mortality related to cardiovascular disease is likely to occur in elderly patients. Hence, whereas persons ≥75 years of age constitute <10% of the US population, they account for 35% of patients with non-ST-segment-elevation acute coronary syndromes (ACS).1 Despite these demographic realities, elderly patients remain underrepresented in randomized trials for cardiovascular disease, and current ACS treatment guidelines are based primarily on studies comprising largely younger patients.3-7 Finally, although age may alter the balance of risk and benefit of therapeutic strategies, trial data on older patients with ACS have usually been limited to subgroup analyses rather than derived from dedicated age-specific studies.8-13

Clinical Perspective on p 833

Prasugrel, a thienopyridine P2Y12 inhibitor, has been shown to reduce the risk of ischemic events compared with clopidogrel in ACS patients undergoing percutaneous coronary intervention with a 60-mg loading dose followed by a 10-mg/d maintenance dose.16 However, no net clinical benefit was observed with this prasugrel dose in elderly patients (≥75 years of age) owing to an increased hazard of intracranial and fatal bleeding; in addition, higher bleeding rates were demonstrated in patients <75 years of age who were <60 kg in weight.18 These results led to warnings concerning use of the 10-mg prasugrel dose for elderly and younger, low-body-weight patients in labeled indications developed by the US Food and Drug Administration and the European Medicines Agency.17,18 However, recommendations for a reduced 5-mg prasugrel maintenance dose for all patients ≥75 years of age and those <75 years of age and <60 kg in weight were based on ancillary pharmacokinetic/pharmacodynamic data that suggested overexposure to the active metabolite with prasugrel 10 mg/d in both populations.19,20

The Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes (TRILOGY ACS) trial (NCT00699998) was undertaken in 9326 patients with unstable angina/non-ST-segment-elevation myocardial infarction (UA/NSTEMI) managed medically without revascularization.21 From June 2008 to September 2011, 9326 participants (≥75 years of age, n=7243; ≥75 years of age, n=2083) were enrolled within 8 geographic regions comprising 52 countries.22

All participants randomized to prasugrel who were ≥75 or <75 years of age and <60 kg in weight received a 5-mg/d maintenance dose; all participants randomized to clopidogrel received a 75-mg/d maintenance dose. Concomitant aspirin treatment was required, with ≤325 mg/d recommended. Study treatments were administered for a minimum of 6 months, and the maximum duration of treatment was 30 months for all patients regardless of age.

Statistical Analysis

The primary efficacy end point for the event-driven TRILOGY ACS trial was time to first occurrence of cardiovascular death, MI, or stroke. The trial was powered to show superiority of prasugrel over clopidogrel in the primary analysis cohort ≥75 years of age.21,22 The exploration of the 5-mg prasugrel maintenance dose in participants ≥75 years of age was not powered for efficacy. Formal sample-size analyses were not possible because long-term event rates in elderly UA/NSTEMI patients managed medically without revascularization were unknown. Therefore, the protocol specified an enrollment of a minimum of 2000 participants ≥75 years of age to provide a reasonable sample of patients to assess the safety of reduced-dose prasugrel compared with clopidogrel in this population. All efficacy analyses were performed on the intention-to-treat population that included all randomized patients (n=7243 for patients <75 years of age; n=2083 for patients ≥75 years of age). As previously detailed, bleeding end points (bleeding unrelated to CABG by Thrombolysis in Myocardial Infarction [TIMI] and Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries [GUSTO] criteria) were evaluated by treatment assignment among participants who received at least 1 dose of study drug during the at-risk period of study drug treatment through 7 days after study drug discontinuation (n=7180 for patients <75 years of age; n=2060 for patients ≥75 years of age).22

The effect of age on the primary efficacy composite end point, component end points, all-cause mortality, and bleeding end points was tested with Cox proportional hazards regression models, including an indicator for participants ≥75 years of age and clopidogrel stratum at randomization. P values were determined from log-rank tests stratified by clopidogrel treatment status as described above. Event rates within each age group are presented as the total number of events, the Kaplan–Meier event rate estimate at 30 months, and the 95% confidence intervals (CIs) for the Kaplan–Meier estimate. Among participants ≥75 years of age, data are presented similarly for the treatment comparison (prasugrel versus clopidogrel).

Methods

The design and primary results of TRILOGY ACS have previously been published.21,22 The study was performed in accordance with the Declaration of Helsinki, and national and local regulatory authorities approved the trial protocol in all participating countries and at all sites. All participants provided written informed consent.

Patients with UA/NSTEMI were eligible for enrollment if their treating physician decided on a final treatment strategy of medical management without revascularization within 10 days of presentation with their index event, if they had at least 1 of 4 risk criteria (age ≥60 years, diabetes mellitus, previous myocardial infarction [MI], or previous revascularization with percutaneous coronary intervention or coronary artery bypass grafting [CABG]), and if they did not have an increased risk of major bleeding.

Randomization was stratified by treatment status with clopidogrel for the index event before randomization (no prorandomization clopidogrel treatment; clopidogrel treatment started in hospital for the index UA/NSTEMI event and continued until the day of randomization; and home clopidogrel treatment continued until the day of randomization). From June 2008 to September 2011, 9326 participants (<75 years of age, n=7243; ≥75 years of age, n=2083) were enrolled within 8 geographic regions comprising 52 countries.22

Among participants randomized to prasugrel who were ≥75 or <75 years of age and <60 kg in weight received a 5-mg/d maintenance dose; all participants randomized to clopidogrel received a 75-mg/d maintenance dose. Concomitant aspirin treatment was required, with ≤325 mg/d recommended. Study treatments were administered for a minimum of 6 months, and the maximum duration of treatment was 30 months for all patients regardless of age.

Statistical Analysis

The primary efficacy end point for the event-driven TRILOGY ACS trial was time to first occurrence of cardiovascular death, MI, or stroke. The trial was powered to show superiority of prasugrel over clopidogrel in the primary analysis cohort ≥75 years of age.21,22 The exploration of the 5-mg prasugrel maintenance dose in participants ≥75 years of age was not powered for efficacy. Formal sample-size analyses were not possible because long-term event rates in elderly UA/NSTEMI patients managed medically without revascularization were unknown. Therefore, the protocol specified an enrollment of a minimum of 2000 participants ≥75 years of age to provide a reasonable sample of patients to assess the safety of reduced-dose prasugrel compared with clopidogrel in this population. All efficacy analyses were performed on the intention-to-treat population that included all randomized patients (n=7243 for patients <75 years of age; n=2083 for patients ≥75 years of age). As previously detailed, bleeding end points (bleeding unrelated to CABG by Thrombolysis in Myocardial Infarction [TIMI] and Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries [GUSTO] criteria) were evaluated by treatment assignment among participants who received at least 1 dose of study drug during the at-risk period of study drug treatment through 7 days after study drug discontinuation (n=7180 for patients <75 years of age; n=2060 for patients ≥75 years of age).22

The effect of age on the primary efficacy composite end point, component end points, all-cause mortality, and bleeding end points was tested with Cox proportional hazards regression models, including an indicator for participants ≥75 years of age and clopidogrel stratum at randomization. P values were determined from log-rank tests stratified by clopidogrel treatment status as described above. Event rates within each age group are presented as the total number of events, the Kaplan–Meier event rate estimate at 30 months, and the 95% confidence intervals (CIs) for the Kaplan–Meier estimate. Among participants ≥75 years of age, data are presented similarly for the treatment comparison (prasugrel versus clopidogrel).
tested the interactions between age <75 years versus age ≥75 years and randomized treatment assignment.

For the primary efficacy composite and non–CABG-related TIMI major bleeding end points, the relationship between age as a continuous variable and the end point was plotted with a linear spline. Predicted event rates at 2 years (y axis) were plotted by age (x axis); event rates came from proportional hazards regression modeling. Kaplan–Meier event curves were plotted for the primary efficacy composite and non–CABG-related TIMI major bleeding end-point rates during the 30 months of follow-up using 4 age strata (<75, 75–79, 80–84, and ≥85 years). Within the cohort ≥75 years of age, Kaplan–Meier event curves during the 30 months of follow-up were also compared between the prasugrel and clopidogrel groups. Histograms were used to show the proportion of time-to-first-event primary efficacy end points attributed to cardiovascular death, MI, or stroke in each age stratum. When patients had >1 primary endpoint component event, the event was categorized according to the first event (eg, MI followed by death was categorized as MI).

Given the observations that both age and lower body weight contributed to higher bleeding risk with standard-dose prasugrel (10 mg/d) in previous studies, we leveraged the data from the concomitant TRILOGY ACS platelet-function substudy for this analysis by exploring the impact of body weight on antiplatelet response and the safety of reduced-dose prasugrel versus clopidogrel in participants ≥75 years of age with 2 approaches. First, among the 515 participants ≥75 years of age (25% of the total elderly population) who were included in the TRILOGY ACS platelet-function substudy, the continuous relationship between body weight and on-treatment platelet reactivity unit (PRU) values measured at 30 days was evaluated within each randomized treatment group by assessing the correlation between weight and PRU. We then tested the hypothesis that weight modifies the treatment effect on 30-day PRU values using an ANCOVA model. Second, the relationship between weight and the occurrence of non–CABG-related TIMI major or minor bleeding events was assessed in the entire sample of participants ≥75 years of age (n=2038) by comparing the weight of participants with and those

Table 1. Baseline Characteristics of Study Participants

<table>
<thead>
<tr>
<th>All Participants</th>
<th>Participants ≥75 y of Age</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Age &lt;75 y (n=7243)</td>
</tr>
<tr>
<td>Age &lt;75 y (n=7243)</td>
<td>62.0 (56.0, 68.0)</td>
</tr>
<tr>
<td>Female sex, n (%)</td>
<td>2599/7243 (35.9)</td>
</tr>
<tr>
<td>Weight &lt;60 kg, n (%)</td>
<td>939/7239 (13.0)</td>
</tr>
<tr>
<td>ACS classification, n (%)</td>
<td>2356/7243 (32.5)</td>
</tr>
<tr>
<td>NSTE MI</td>
<td>4887/7243 (67.5)</td>
</tr>
<tr>
<td>Kilip class II–IV</td>
<td>719/7237 (9.9)</td>
</tr>
<tr>
<td>Medical history, n (%)</td>
<td>5809/7226 (80.4)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>4055/6879 (58.9)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>2811/7225 (38.9)</td>
</tr>
<tr>
<td>Current/recent smoking</td>
<td>1684/7180 (23.5)</td>
</tr>
<tr>
<td>Previous MI</td>
<td>3168/7191 (44.1)</td>
</tr>
<tr>
<td>Previous PCI</td>
<td>2022/7211 (28.0)</td>
</tr>
<tr>
<td>Previous CABG</td>
<td>1115/7228 (15.4)</td>
</tr>
<tr>
<td>Previous PAD</td>
<td>472/7129 (6.6)</td>
</tr>
<tr>
<td>Previous AF</td>
<td>428/7101 (6.0)</td>
</tr>
<tr>
<td>Previous HF</td>
<td>1232/7205 (17.1)</td>
</tr>
<tr>
<td>Baseline risk assessment</td>
<td>114.0 (102.0, 128.0)</td>
</tr>
<tr>
<td>Median GRACE risk score (25th, 75th percentiles)</td>
<td>80.7 (62.5, 103.0)</td>
</tr>
<tr>
<td>Median creatinine clearance (25th, 75th percentiles), mL/min</td>
<td>80.7 (62.5, 103.0)</td>
</tr>
<tr>
<td>Angiography performed before randomization, n (%)</td>
<td>3085/7243 (42.6)</td>
</tr>
<tr>
<td>Concomitant medications at randomization, n (%)</td>
<td>5636/7243 (77.8)</td>
</tr>
<tr>
<td>ACE-I/ARB</td>
<td>5433/7243 (75.0)</td>
</tr>
<tr>
<td>Statin</td>
<td>6079/7243 (83.9)</td>
</tr>
<tr>
<td>Proton pump inhibitor</td>
<td>1666/7243 (23.0)</td>
</tr>
</tbody>
</table>

ACE-I indicates angiotensin-converting enzyme inhibitor; ACS, acute coronary syndromes; AF, atrial fibrillation; ARB, angiotensin receptor blocker; CABG, coronary artery bypass grafting; HF, heart failure; MI, myocardial infarction; NSTEMI, non–ST-segment–elevation myocardial infarction; PAD, peripheral arterial disease; and PCI, percutaneous coronary intervention.
without a bleeding event separately by treatment, as well as with the treatment-by-weight interaction.

All \( P \) values are 2 sided with a value of \( \alpha < 0.05 \) denoting statistical significance. Analyses were performed with SAS software, version 9.2 (SAS Institute).

**Results**

The largest proportion of participants \( \geq 75 \) years of age were \(< 80 \) years of age (1052 of 2083, 50.5%) at randomization, followed by those 80 to 84 years of age (n=656 of 2083, 31.5%) and those \( \geq 85 \) years of age (n=375 of 2083, 18%). Compared with participants \(< 75 \) years of age, elderly participants were more likely to be female and weigh \(< 60 \) kg, to have NSTEMI rather than UA, to present with Killip class 2 or greater, and to have higher Global Registry of Acute Coronary Events (GRACE) risk scores and lower creatinine clearance values at baseline, and they were less likely to undergo angiography before randomization (Table 1).

The median duration of follow-up was 532 days (25th and 75th percentiles, 335 and 737 days) for participants \(< 75 \) years of age versus 450 days (25th and 75th percentiles, 243 and 720 days) for those \( \geq 75 \) years of age. The median duration of study drug treatment was 453 days (25th and 75th percentiles, 267 and 716 days) for younger participants compared with 364 days (25th and 75th percentiles, 179 and 642 days) for elderly participants.

**Age-Related Outcomes**

When evaluated continuously with a linear spline function, the predicted risk of the primary efficacy end point of cardiovascular death, MI, or stroke at 2 years increased in linear fashion until 70 years of age; thereafter, a sharp increase in risk of this end point was observed with increasing age (Figure 1A). In contrast, although the predicted risk of non–CABG-related TIMI major bleeding at 2 years increased in a linear fashion until \( \approx 80 \) years of age; thereafter, the risk of this end point rose sharply with increasing age but with wide confidence bounds (Figure 1B).

The cumulative risks of both the primary efficacy end point and non–CABG-related TIMI major bleeding through 30 months rose progressively from the lowest to the highest prespecified age categories (Figure 2A and 2B). The Kaplan–Meier estimate of the primary efficacy end point through 30 months was \( > 2.5 \) -fold higher in participants \( \geq 75 \) years of age compared with those \( < 75 \) years of age (35.7% versus 14.9%; hazard ratio [HR], 2.65; 95% CI, 2.37–2.97; Table 2). Similar differences were noted in the risk of MI and stroke between older and younger patients, but there was a proportionally higher age-related risk of both cardiovascular death (HR, 3.25) and all-cause death (HR, 3.27) compared with MI and stroke.

When the distribution of each of the component end points within the time-to-first-event analyses of the primary efficacy end point was evaluated across the prespecified age categories, the proportion of first events accounted for in the primary end-point ascertainment that were attributed to cardiovascular death appeared to rise only modestly (31% to 41%) from the lowest to the highest age categories (Figure 3). In turn, the proportion of first events that were attributed to nonfatal MI declined modestly (60% to 51%) from the lowest to the highest age categories, with a relatively constant 9% to 10% of the first events attributed to nonfatal stroke across all age categories.

The risk of non–CABG-related bleeding assessed with both GUSTO and TIMI bleeding scales was \( 2 \) - to \( 3 \) -fold higher with older age (Table 3). Fatal bleeding events (n=8 [1.1%] versus n=8 [0.3%]; HR, 4.31; 95% CI, 1.61–11.5) and intracranial hemorrhage (n=13 [1.2%]) versus n=20 [0.6%]; HR, 2.67; 95% CI, 1.33–5.37) were infrequent, but the risk was \( 3 \)- to \( 4 \)-fold higher in older and younger participants, respectively.

**Treatment Comparisons in Elderly Participants**

The cumulative risk of the primary efficacy end point and non–CABG-related TIMI major bleeding through 30 months among participants \( \geq 75 \) years of age was not significantly different with reduced-dose prasugrel compared with clopidogrel treatment, with overlapping event curves for both end points (Figure 4A and 4B). Similar results by treatment were demonstrated for all efficacy and bleeding end points (Tables 2 and 3). The age-by-treatment interaction
Impact of Weight on Antiplatelet Response and Bleeding Events in Elderly Participants

Among 515 participants ≥75 years of age included in the platelet-function substudy, there was a significant positive correlation between lower 30-day on-treatment PRU values and lower body weight in the prasugrel treatment group (r=0.16, P=0.04), but no such correlation was observed in the clopidogrel treatment group (r=−0.04, P=0.58; Figure I in the online-only Data Supplement). However, weight did not significantly modify the treatment effect on 30-day PRU values in an ANOVA model (interaction P=0.06). Among all participants ≥75 years of age (n=2083), median body weight was similar for patients both with and without a non-CABG related TIMI major/minor bleeding event in the prasugrel group (68 kg [25th and 75th percentiles, 60 and 78 kg] versus 70 kg [25th and 75th percentiles, 61 and 80 kg]) and in the clopidogrel group (65 kg [25th and 75th percentiles, 55 and 81 kg] versus 70 kg [25th and 75th percentiles, 61 and 80 kg]; interaction P=0.922; Figure II in the online-only Data Supplement).

Discussion

Our contemporary evaluation of ACS patients managed medically without planned revascularization provides several novel findings on the long-term relationships among age and efficacy and safety outcomes with extended dual antiplatelet therapy consisting of reduced-dose prasugrel for elderly participants. First, we observed only a modest increase in the proportion of participants with the first event of the primary efficacy composite end point attributed to cardiovascular death during

Figure 2. Cumulative Kaplan–Meier estimates of key study end points during the 30-month follow-up period by age categories. A, Data for the primary efficacy end point of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke by 4 age categories (<75 years, n=7243; 75–79 years, n=1052; 80–84 years, n=656; ≥85 years, n=375). B, The key bleeding end point of Thrombolysis in Myocardial Infarction (TIMI) major bleeding unrelated to coronary artery bypass grafting by the same age categories.
prolonged follow-up with increasing age, with the majority of participants experiencing a nonfatal MI as the first event across all age categories. Second, there was a proportionally similar increased risk of both cardiovascular and major bleeding complications with increasing age. Third, we did not observe any differences in ischemic and bleeding outcomes between reduced-dose prasugrel (5 mg/d) and clopidogrel 75 mg/d in the elderly cohort. Finally, we did not observe a significant treatment-by-weight interaction when assessing 30-day on-treatment PRU values despite observing a positive correlation between lower PRU values with lower body weight only in the prasugrel group. Nonetheless, there was no

**Figure 3.** Proportional contribution of component end points to the primary efficacy end point by age categories. The proportion of component end points (cardiovascular [CV] death, myocardial infarction [MI], stroke) contributing to time-to-first-event analysis of the primary efficacy end point is shown by age categories (<75 years, n=7243; 75–79 years, n=1052; 80–84 years, n=656; ≥85 years, n=375).
Roe et al  Prasugrel vs Clopidogrel in Elderly ACS Patients

829

difference in weight by occurrence of major bleeding events with either reduced-dose prasugrel or clopidogrel among participants ≥75 years of age.

Previous data from observational studies compared with pooled historical clinical trial populations of ACS patients demonstrate both a stepwise increase in the burden of comorbidities at presentation and increases in the risk of short-term ischemic events and bleeding complications with increasing age.5,6 Our data complement and extend these observations by demonstrating a substantially increased risk of both ischemic and bleeding events in elderly versus younger participants over a longer follow-up period compared with other recent ACS trials in the understudied, high-risk population of ACS patients managed without revascularization. Importantly, as noted above, we observed only a modest increase in likelihood of cardiovascular death as the first ischemic event with increasing age, and we observed that the increased risk of the component ischemic end points (cardiovascular death, MI, stroke) observed in older versus younger participants was proportionally highest for cardiovascular death. Additionally, we have shown a similar 2- to 4-fold increase in the risk of major bleeding complications in elderly participants, with a sharp upward trajectory in the rate of bleeding events with increasing age, findings that highlight the similar increased relative risk of both ischemic and bleeding events in elderly patients.

The adverse safety findings of the 10-mg prasugrel maintenance dose in elderly ACS patients treated with percutaneous coronary intervention, coupled with our exploratory findings from TRILOGY ACS, suggest that reducing the prasugrel maintenance dose to 5 mg/d appears to have mitigated the risk of serious bleeding in the elderly with no signal of efficacy in this exploratory analysis.16 However, the absence of any increase in minor/moderate bleeding with this dose compared with clopidogrel 75 mg/d contrasts with results from the 10-mg prasugrel dose in the younger TRILOGY cohort, a finding that suggests a diminished degree of platelet inhibition with reduced-dose versus full-dose prasugrel.22 A TRILOGY platelet-function substudy and a dedicated pharmacodynamics study in stable elderly participants with coronary disease confirmed an attenuated effect on platelet reactivity for 5-mg prasugrel in elderly participants relative to the 10-mg prasugrel dose tested in both younger and older cohorts, but in both studies, the antiplatelet effect of reduced-dose prasugrel was superior to that of clopidogrel.23,24 However, the 5-mg dose of prasugrel demonstrated similar suppression of platelet reactivity in elderly patients compared with younger patients (45–65 years of age).24 Although a previous observational study showed a diminished pharmacodynamic response to both standard-dose prasugrel (10 mg/d) and clopidogrel in elderly patients undergoing percutaneous coronary intervention, the impact of

Table 3. Efficacy and Safety Outcomes Through 30 Months*

<table>
<thead>
<tr>
<th></th>
<th>All Participants</th>
<th></th>
<th>Participants ≥75 y of Age</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Age &lt;75 y</td>
<td>Age ≥75 y</td>
<td>P</td>
<td>Prasugrel</td>
</tr>
<tr>
<td>Events, n</td>
<td>(n=7180)</td>
<td>(n=2060)</td>
<td></td>
<td>(n=1033)</td>
</tr>
<tr>
<td>Severe/life-threatening bleeding</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Events, n</td>
<td>27</td>
<td>22</td>
<td>&lt;0.01</td>
<td>9</td>
</tr>
<tr>
<td>K-M event rate at 30 mo (95% CI)</td>
<td>0.8 (0.3–1.2)</td>
<td>2.4 (1.2–3.6)</td>
<td>2.2 (0.3–4.0)</td>
<td>2.6 (1.0–4.1)</td>
</tr>
<tr>
<td>Severe/life-threatening or moderate bleeding</td>
<td></td>
<td></td>
<td></td>
<td>3.29</td>
</tr>
<tr>
<td>Events, n</td>
<td>87</td>
<td>71</td>
<td>&lt;0.01</td>
<td>37</td>
</tr>
<tr>
<td>K-M event rate at 30 mo (95% CI)</td>
<td>2.1 (1.5–2.6)</td>
<td>7.7 (5.5–9.9)</td>
<td>8.2 (5.0–11.4)</td>
<td>7.3 (4.3–10.3)</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>2.15</td>
<td>(1.44–3.20)</td>
<td></td>
<td>1.09</td>
</tr>
<tr>
<td>Events, n</td>
<td>69</td>
<td>37</td>
<td>&lt;0.01</td>
<td>19</td>
</tr>
<tr>
<td>K-M event rate at 30 mo (95% CI)</td>
<td>1.8 (1.2–2.3)</td>
<td>3.7 (2.3–5.1)</td>
<td>4.1 (1.8–6.3)</td>
<td>3.4 (1.6–5.1)</td>
</tr>
<tr>
<td>Major/minor bleeding</td>
<td>2.00</td>
<td>(1.46–2.75)</td>
<td></td>
<td>0.90</td>
</tr>
<tr>
<td>Events, n</td>
<td>116</td>
<td>58</td>
<td>&lt;0.01</td>
<td>27</td>
</tr>
<tr>
<td>K-M event rate at 30 mo (95% CI)</td>
<td>2.7 (2.1–3.3)</td>
<td>6.7 (4.6–8.8)</td>
<td>6.4 (3.5–9.4)</td>
<td>7.0 (4.0–10.0)</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; CV, cardiovascular; GUSTO, Global Use of Strategies to Open Occluded Coronary Arteries; K-M, Kaplan–Meier; MI, myocardial infarction; and TIMI, Thrombolysis In Myocardial Infarction.

*Bleeding end points were evaluated by treatment assignment among participants who received at least 1 dose of study drug during the at-risk period of study drug treatment through 7 days after study drug discontinuation. Log-rank P values are shown for age and treatment comparisons.
Circulation
August 20, 2013

body weight on the findings was not reported. In contrast, we observed only a weak correlation between lower PRU values at 30 days and lower weight among participants ≥75 years of age treated with reduced-dose prasugrel but not with clopidogrel, but there was no significant treatment-by-weight interaction. Additionally, we showed no differences in weight by the occurrence of infrequent major bleeding events in either treatment group. Collectively, the findings from our analysis add to previous studies by demonstrating that body weight does not appear to significantly affect the antiplatelet response and bleeding risk of reduced-dose prasugrel compared with standard-dose clopidogrel in elderly patients. However, the comparative safety of dosing regimens for both agents in elderly patients requires further assessment with a study that is adequately powered to evaluate differences in infrequent major bleeding events.

Although recent large-scale trials evaluating new antithrombotic therapies for the treatment of ACS did not restrict enrollment on the basis of age, we note that the proportion of patients ≥75 years of age enrolled in these trials was low (9%–17%), whereas in our study, patients ≥75 years of age made up 29% of the total population. The proportion of elderly patients with UA/NSTEMI who underwent angiography and revascularization in these trials was substantially larger compared with studies from patients treated in routine practice. Indeed, the role of an invasive treatment strategy in elderly UA/NSTEMI patients remains uncertain and challenging to determine, as demonstrated in a trial dedicated to patients ≥80 years of age that was terminated prematurely as a result of slow enrollment. Furthermore, a recent subgroup analysis of ACS patients ≥75 years of age in a large trial comparing P2Y₁₂ inhibitors demonstrated no difference in the safety profile of standard-dose ticagrelor over clopidogrel in elderly patients over 12 months, but ≈25% of these patients had STEMI and >60% underwent revascularization during the study. In contrast, we evaluated the understudied medically managed population of UA/NSTEMI patients that was enriched with elderly patients over a prolonged (30-month) follow-up period, assessed the safety of a novel dosing regimen of prasugrel specifically designed to mitigate bleeding risks in the vulnerable elderly population, and ascertained the

Figure 4. Cumulative Kaplan–Meier estimates of key study end points among participants ≥75 years of age by treatment during the 30-month follow-up period.
A. Data for the primary efficacy end point of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke by treatment (prasugrel vs clopidogrel).
B. The key bleeding end point of Thrombolysis in Myocardial Infarction (TIMI) major bleeding unrelated to coronary artery bypass grafting by treatment (prasugrel vs clopidogrel).
impact of body weight on antiplatelet response and bleeding event occurrence to further delineate how body weight influences antithrombotic drug safety in elderly patients.

**Study Limitations**

Despite the relatively large sample of elderly participants studied in TRILOGY, some limitations should be noted. First, our study included only patients with ACS managed medically; thus, our results should not be extrapolated to patients who undergo revascularization. Second, our assessment of prasugrel versus clopidogrel in the elderly TRILOGY population was not powered for efficacy or safety, so results from this analysis should be considered exploratory and hypothesis generating. Third, study randomization typically occurred 4 to 5 days after hospital presentation, during which interval participants received open-label clopidogrel; thus, our study did not focus on the acute-care period for ACS patients. Fourth, we evaluated the relationship between body weight and antiplatelet response of reduced-dose prasugrel versus standard-dose clopidogrel, but the correlation between on-treatment PRU values and the risk of major bleeding with thienopyridine treatment has not been clearly delineated in previous studies. Finally, we assessed the impact of body weight on bleeding event occurrence by treatment group in participants ≥75 years of age, but the relatively small number of TIMI major/minor bleeding events limited the discrimination of this exploratory analysis.

**Conclusions**

Our findings demonstrate steeply increased trajectories in the risks of ischemic and bleeding events with increasing age among ACS patients managed without revascularization and no difference in the risks of both ischemic and bleeding outcomes with reduced-dose prasugrel versus clopidogrel in this exploratory analysis of elderly patients. Although it is encouraging that we did not observe a significant differential relationship among body weight, pharmacodynamic response, and bleeding risk with reduced-dose prasugrel versus clopidogrel in elderly patients, these exploratory findings highlight the challenges of investigating the dose selection for antiplatelet therapies in the high-risk elderly population. Therefore, large-scale clinical outcomes trials of anti-thrombotic therapies with adequate exposure of elderly ACS patients should be performed, potentially incorporating age-specific dosing regimens, to more clearly delineate optimal and safe treatment strategies for this vulnerable population.

**Acknowledgments**

We thank Yuliya Lokhnygina, PhD, and Karen Pieper, MS, of the Duke Clinical Research Institute, Durham, NC, for their input, expert guidance, and management of the statistical analyses for the TRILOGY ACS study. We also thank Jonathan McCall, MS, of the Duke Clinical Research Institute for editorial assistance in preparing this manuscript and Kerry Stenke of the Duke Clinical Research Institute for her assistance in preparing the figures. Dr Lokhnygina, K. Pieper, J. McCall, and K. Stenke received no compensation for their work other than their usual salaries.

**Sources of Funding**

The TRILOGY ACS study was funded by Eli Lilly and Daiichi Sankyo. The study sponsors had no role in the conception and design of this study or in creating the first draft of the manuscript. An employee of Eli Lilly (Dr Winters) participated as an author during subsequent drafts of the manuscript. All data analyses were performed independently by the Duke Clinical Research Institute, Durham, NC.

**Disclosures**

Dr Roe receives grant funding from Lilly, Bristol-Myers Squibb, Hoffmann-La Roche, Novartis, Schering-Plough, and KAI Pharmaceuticals; consulting fees from Lilly, Daiichi Sankyo, Bristol-Myers Squibb, GlaxoSmithKline, Merck, Janssen Pharmaceuticals, KAI Pharmaceuticals, Sanofi-Aventis, Helsinn Pharmaceuticals, Regeneron, Novartis, AstraZeneca, and Orexigen; and lecture fees from AstraZeneca and Janssen Pharmaceuticals. Dr Goodman receives grant funding from Duke Clinical Research Institute, Lilly, Sanofi-Aventis, Bristol-Myers Squibb, and AstraZeneca; travel expenses from Duke Clinical Research Institute; consulting fees from Lilly, Sanofi-Aventis, Bristol-Myers Squibb, and AstraZeneca; and payment for developing presentations and lecture fees from Lilly, Sanofi-Aventis, Bristol-Myers Squibb, and AstraZeneca. Dr Ohman receives grant funding and travel expenses from Daiichi Sankyo and Lilly; consulting fees from AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead Sciences, Janssen Pharmaceuticals, Liposcience, Merck, Pozen, Hoffmann-La Roche, Sanofi-Aventis, The Medicines Company, and Web MD; grant funding from Gilead Sciences; and lecture fees from Gilead Sciences, Boehringer Ingelheim, and The Medicines Company. Dr Hochman receives consulting fees from Lilly and GlaxoSmithKline. Dr Gottlieb receives travel expenses from Lilly and Daiichi Sankyo and consulting fees from Lilly. Dr Martinez receives consulting and travel fees from Lilly and Daiichi Sankyo. Dr Dalby receives consulting fees from Duke Clinical Research Institute; receives travel expenses from AstraZeneca, Merck Serono, Sanofi-Aventis, ICON, Astellas, Daiichi Sankyo, and Novartis; and serves as a board member for Sanofi-Aventis, Lilly, Novartis, Boehringer Ingelheim, and Aspen. Dr Boden receives travel expenses from Lilly and lecture fees from Abbott Laboratories and Gilead Sciences. Dr White receives grant funding from Sanofi-Aventis, Lilly, The Medicines Company, National Institutes of Health, Pfizer, Roche, Johnson & Johnson, Schering-Plough, Merck Sharp & Dohme, AstraZeneca, GlaxoSmithKline, Daiichi Sankyo, and Bristol-Myers Squibb; Dr White also serves as a board member for Merck Sharp & Dohme and Regado Biosciences. Dr Prabhakaran receives consulting fees from Lilly. Dr Winters is an employee and minor shareholder of Lilly. Dr Aylward receives consulting fees from Lilly, AstraZeneca, Boehringer Ingelheim, Pfizer, Sanofi-Aventis, and Bayer; and meeting expenses from AstraZeneca and Boehringer Ingelheim. Dr McGuire receives grant funding, travel expenses, and fees for review activities from Lilly and Daiichi Sankyo, as well as consulting fees from Tethys Bioscience, Daiichi Sankyo, Genentech, Pfizer, Sanofi-Aventis, Regeneron, and Johnson & Johnson. Dr Ardissino receives consulting/lecture fees from Daiichi Sankyo and Lilly. Dr Fox receives grant funding from Lilly, Bayer, Johnson & Johnson, and AstraZeneca; travel expenses from Lilly; consulting fees from Lilly, Bayer, Johnson & Johnson, and AstraZeneca; travel expenses from Lilly; consulting fees from AstraZeneca and Boehringer Ingelheim; and lecture fees from Bayer, Johnson & Johnson, AstraZeneca, Sanofi-Aventis, and Boehringer Ingelheim. Dr Armstrong receives consulting fees from Lilly, Hoffmann-La Roche, Merck, Axio Research, and Orexigen; grant funding from Boehringer Ingelheim, Hoffmann-La Roche, Sanofi-Aventis, Scios, Ortho Biotech, Johnson & Johnson, Janssen Pharmaceuticals, GlaxoSmithKline, Amylin Pharmaceuticals, and Merck; and payment for developing educational presentations from AstraZeneca and Lilly. S.R. Stevens and Dr Bassand report no conflicts.

**References**


**CLINICAL PERSPECTIVE**

The use of dual antiplatelet therapy (aspirin plus a P2Y₁₂ inhibitor) is recommended by practice guidelines for patients with acute coronary syndromes but is understudied in older compared with younger patients. Within the Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes (TRILOGY ACS) trial, a concomitant exploration of the safety of aspirin plus reduced-dose prasugrel (5 mg/d) versus aspirin plus standard-dose clopidogrel (75 mg/d) was undertaken in >2000 elderly (≥75 years of age) patients with acute coronary syndromes who were medically managed without revascularization with follow-up through 30 months. Older patients had a 2- to 3-fold increased risk of ischemic and bleeding outcomes compared with younger patients. No difference in the frequency of the primary ischemic end point and major bleeding events was observed with reduced-dose prasugrel compared with standard-dose clopidogrel in patients ≥75 years of age. These results highlight the increased risk of both ischemic and bleeding events in elderly patients with acute coronary syndromes and the challenges of optimizing the dose selection of antiplatelet therapies in this vulnerable, understudied population.

Go to [http://cme.ahajournals.org](http://cme.ahajournals.org) to take the CME quiz for this article.
Elderly Patients With Acute Coronary Syndromes Managed Without Revascularization: Insights Into the Safety of Long-Term Dual Antiplatelet Therapy With Reduced-Dose Prasugrel Versus Standard-Dose Clopidogrel


Circulation. 2013;128:823-833; originally published online July 12, 2013; doi: 10.1161/CIRCULATIONAHA.113.002303

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2013 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/128/8/823

Data Supplement (unedited) at:
http://circ.ahajournals.org/content/suppl/2013/07/12/CIRCULATIONAHA.113.002303.DC1

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org/subscriptions/
Online Supplemental Material

Elderly Patients with Acute Coronary Syndromes Managed Without Revascularization

Insights into the Safety of Long-Term Dual Antiplatelet Therapy with Reduced-Dose Prasugrel vs. Standard-Dose Clopidogrel

Matthew T. Roe, MD, MHS1,2; Shaun G. Goodman, MD, MSc3; E. Magnus Ohman, MB, ChB1,2; Susanna R. Stevens, MS1; Judith S. Hochman, MD4; Shmuel Gottlieb, MD5; Felipe Martinez, MD6; Anthony J. Dalby, MD7; William E. Boden, MD, PhD8; Harvey D. White, MB, ChB, DSc9; Dorairaj Prabhakaran, MD, MSc10; Kenneth J. Winters, MD11; Philip E. Aylward, MD12; Jean-Pierre Bassand, MD13; Darren K. McGuire, MD14; Diego Ardissino, MD15; Keith A. A. Fox, MB, ChB16; Paul W. Armstrong, MD17

From the 1Duke Clinical Research Institute, Duke University Medical Center, Durham, NC, USA; 2Division of Cardiology, Department of Medicine, Duke University School of Medicine, Durham, NC, USA; 3Division of Cardiology, Department of Medicine, St. Michael's Hospital, Toronto, Ontario, Canada; 4Cardiovascular Clinical Research Center, Leon H. Charney Division of Cardiology, New York University School of Medicine & NYU Langone Medical Center, New York, NY, USA; 5Cardiac Institute, Bikur Cholim Campus, Shaare Zedek Medical Center, Jerusalem, Israel; 6Department of Cardiology, Córdoba National University, Córdoba, Argentina; 7Milpark Hospital, Johannesburg, South Africa; 8Department of Medicine, Stratton VA Medical Center/Albany Medical College, Albany, NY, USA; 9Auckland City Hospital, Green Lane Cardiovascular Service, Auckland, New Zealand; 10Centre for Chronic Disease Control, New Delhi, India; 11Eli Lilly and Company, Indianapolis, IN, USA; 12South Australian Health and Medical Research Institute, Flinders University and Medical Centre, Adelaide, South Australia, Australia; 13Department of Cardiology, University Hospital Jean Minjoz, Besançon, France; 14University of Texas Southwestern Medical Center, Dallas, TX, USA; 15Division of Cardiology, Azienda Ospedaliero-Universitaria di Parma, Parma, Italy; 16British Heart Foundation Centre for Cardiovascular Sciences, University of Edinburgh, Edinburgh, Scotland, UK; 17Division of Cardiology, University of Alberta, Edmonton, Alberta, Canada

Contents:

Supplemental Figure S1 and figure legend

Supplemental Figure S2 and figure legend
Figure S1

PRU vs Weight (kg)

- **Clopidogrel**
- **Prasugrel**
Supplemental Figure S1. Correlation of body weight with 30-day on-treatment platelet reactivity unit (PRU) values by treatment among 515 participants ≥75 years included in the TRILOGY platelet function substudy. The correlation of body weight with PRU values is demonstrated separately by treatment, with weight by treatment interaction \( P=0.055 \).
Figure S2

Weight (kg) vs. Treatment and bleeding

- Prasugrel no bleed
- Prasugrel bleed
- Clopidogrel no bleed
- Clopidogrel bleed
Supplemental Figure S2. Distribution of body weight by occurrence of TIMI major/minor bleeding events among participants ≥75 years. Results are shown separately for each treatment group, with weight by treatment interaction $P=0.922$. 