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

Running title: Roe et al.; Prasugrel vs. clopidogrel in elderly ACS patients

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Abstract:

**Background**—Dual antiplatelet therapy in older vs. younger patients with acute coronary syndromes (ACS) is under-studied. Low-dose prasugrel (5mg/d) is recommended for younger, lower-body-weight ACS patients and elderly ACS patients to mitigate bleeding risk of standard-dose prasugrel (10mg/d).

**Methods and Results**—9326 medically managed ACS patients from the TRILOGY trial (7243 <75y; 2083 ≥75y) were randomized to prasugrel (10mg/d; 5mg/d for those ≥75y or <75y and <60kg) or clopidogrel (75mg/d), plus aspirin, for ≤30 months. A total of 515 participants ≥75y (25% of total elderly population) had serial platelet reactivity unit (PRU) measurements in a platelet-function substudy (PFS). Cumulative risks of the primary endpoint (cardiovascular death/myocardial infarction/stroke) and TIMI major bleeding increased progressively with age and were ≥twofold higher in older participants. Among those ≥75y, TIMI-major bleeding (4.1% vs. 3.4%, HR=1.09, 95%CI: 0.57-2.08) and primary endpoint rates were similar with reduced-dose prasugrel vs. clopidogrel. Despite a correlation between lower 30-day on-treatment PRU values and lower weight only in the prasugrel group, there was a nonsignificant treatment-by-weight interaction for PRU values among participants ≥75y in the PFS (P=0.06). No differences in weight were seen in all participants ≥75y with vs. without TIMI-major/minor bleeding in both treatment groups.

**Conclusions**—Older age is associated with substantially increased long-term cardiovascular risk and bleeding among medically managed ACS patients, with no differences in ischemic or bleeding outcomes with reduced-dose prasugrel vs. clopidogrel in elderly patients. No significant interaction among weight, pharmacodynamic response, and bleeding risk was observed between reduced-dose prasugrel vs. clopidogrel in elderly patients.

**Clinical Trial Registration Information**—http://clinicaltrials.gov/ct2/home. Identifier: NCT00699999.

**Key words:** aging, fibrinolytic agent, medication therapy, myocardial infarction, P2Y12
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 aged ≥75 years 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 upon studies largely comprising younger patients.\(^2-7\) Finally, although age may alter the balance of risk and benefit of therapeutic strategies, trials data regarding older patients with ACS have usually been limited to subgroup analyses rather than derived from dedicated age-specific studies.\(^8-15\)

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 (PCI) with a 60-mg loading dose followed by a 10-mg/day maintenance dose.\(^16\) However, no net clinical benefit was observed with this prasugrel dose in elderly patients (≥75 years) due to an increased hazard of intracranial and fatal bleeding; also, higher bleeding rates were demonstrated in patients <75 years and <60 kg in weight.\(^16\) 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 (FDA) and the European Medicines Agency (EMA).\(^17,18\) However, recommendations for a reduced 5-mg prasugrel maintenance dose for all patients ≥75 years and those <75 years and <60 kg were based upon ancillary pharmacokinetic/pharmacodynamic data that suggested overexposure to the active metabolite with prasugrel 10 mg/day 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.\textsuperscript{21,22} TRILOGY ACS was designed to investigate the effects of prasugrel vs. clopidogrel during a longer exposure period compared with prior trials of dual antiplatelet therapy in an understudied population, with a concomitant exploration of the safety of a 5-mg prasugrel maintenance dose in elderly patients (\textgreater 75 years).\textsuperscript{22} Because superiority of prasugrel was not established in the primary cohort of 7243 participants aged <75 years (treated with prasugrel 10 mg/day, with 5 mg/day for these younger patients <60 kg), the results of the exploratory analysis in 2083 participants \textgreater 75 years have not yet been published. The present report (1) provides the first long-term data on outcomes specifically from elderly participants in TRILOGY ACS, (2) assesses the incidence and distribution of ischemic and bleeding endpoints by age, (3) evaluates the safety of reduced-dose prasugrel compared with clopidogrel in this elderly population, and (4) assesses the association between body weight, bleeding risk, and pharmacodynamic response with reduced-dose prasugrel vs. clopidogrel in elderly patients.

**Methods**

The design and primary results of TRILOGY ACS have been previously published.\textsuperscript{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: (1) their treating physician
decided upon a final treatment strategy of medical management without revascularization within 10 days of presentation with their index event; (2) they had at least 1 of 4 risk criteria (age ≥60 years, diabetes mellitus, prior myocardial infarction [MI], and/or prior revascularization with PCI or coronary artery bypass grafting [CABG]); and (3) 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 pre-randomization clopidogrel treatment; clopidogrel treatment started in-hospital for the index UA/NSTEMI event and continued until day of randomization; and home clopidogrel treatment continued until day of randomization). From June 2008-September 2011, 9326 participants (7243 <75 years; 2083 ≥75 years) were enrolled within 8 geographic regions comprising 52 countries.

All participants randomized to prasugrel who were ≥75 years or <75 years and <60 kg received a 5-mg/day maintenance dose; all participants randomized to clopidogrel received a 75-mg/day maintenance dose. Concomitant aspirin treatment was required, with ≤100-mg/day 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 endpoint 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 vs. clopidogrel in the primary analysis cohort aged <75 years. The exploration of the 5-mg prasugrel maintenance dose in participants ≥75 years 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 enrollment of a minimum of 2000 participants ≥75 years in order to provide a reasonable sample of patients to assess the safety of reduced-dose prasugrel vs. 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, and \(n=2083\) for patients ≥75 years). As previously detailed, bleeding endpoints (bleeding unrelated to CABG by TIMI and 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 and \(n=2060\) for patients ≥75 years).  

The effect of age on the primary efficacy composite endpoint, component endpoints, all-cause mortality, and bleeding endpoints was tested using Cox proportional hazards regression models, including an indicator for participants ≥75 years 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, data are presented similarly for the treatment comparison (prasugrel vs. clopidogrel). We also tested the interactions between age <75 years vs. age ≥75 years and randomized treatment assignment.

For the primary efficacy composite and non-CABG-related TIMI major bleeding endpoints, the relationship between age as a continuous variable and the endpoint was plotted using a linear spline. Predicted event rates at 2 years (y-axis) were plotted by age (x-axis), where event rates come from proportional hazards regression modeling. Kaplan-Meier event curves were plotted for the primary efficacy composite and non-CABG-related TIMI-major bleeding
endpoint rates during the 30 months of follow-up using 4 age strata (<75, 75-79, 80-84, and ≥85 years). Within the cohort aged ≥75 years, Kaplan-Meier event curves during the 30 months of follow-up were also compared between prasugrel and clopidogrel groups. Histograms were used to show the proportion of time-to-first-event primary efficacy endpoints 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 (e.g., 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 prior 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 vs. clopidogrel in participants ≥75 years with 2 approaches.16,23 First, among the 515 participants ≥75 years (25% of the total elderly population) who were included in the TRILOGY ACS platelet function substudy, the continuous relationship of body weight with 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.23 We then tested the hypothesis that weight modifies the treatment effect on 30-day PRU values using an ANCOVA model. Second, the relationship of weight with the occurrence of non-CABG-related TIMI major or minor bleeding events was assessed in the entire sample of participants ≥75 years (n=2038) by comparing the weight of participants with vs. without a bleeding event separately by treatment, as well as with the treatment by weight interaction.

All P values are two-sided with alpha <0.05 to denote statistical significance. Analyses were performed using SAS software, version 9.2 (SAS Institute).
Results

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

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

Age-Related Outcomes

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

The cumulative risks of both the primary efficacy endpoint as well as non-CABG-related TIMI major bleeding through 30 months rose progressively from the lowest to the highest pre-specified age categories (Figures 2a-2b). The Kaplan-Meier estimate of the primary efficacy endpoint through 30 months was more than 2.5-fold higher in participants aged ≥75 years vs. those aged <75 years (35.7% vs. 14.9%, HR=2.65, 95% CI: 2.37-2.97) (Table 2a). Similar
differences were noted in the risk of MI and stroke between older vs. 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 endpoints within the time-to-first-event analyses of the primary efficacy endpoint was evaluated across the pre-specified age categories, the proportion of first events accounted for in the primary endpoint 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%-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 twofold to threefold higher with older age (Table 2b). Fatal bleeding events (n=8 [1.1%] vs. n=8 [0.3%]; HR=4.31 [95% CI: 1.61-11.5]) and intracranial hemorrhage (n=13 [1.2%] vs. n=20 [0.6%]; HR=2.67 [95% CI: 1.33-5.37]) were infrequent, but the risk was threefold to fourfold higher in older vs. younger participants, respectively.

**Treatment Comparisons in Elderly Participants**

The cumulative risk of the primary efficacy endpoint and non-CABG-related TIMI major bleeding through 30 months among participants ≥75 years was not significantly different with reduced-dose prasugrel vs. clopidogrel treatment, with overlapping event curves for both endpoints (Figure 4a-b). Similar results by treatment were demonstrated for all efficacy and bleeding endpoints (Table 2a-b). The age*treatment interaction P value for stroke was 0.052 and for TIMI major/minor bleeding was 0.098. All other interaction P values for the outcomes listed
in Table 2a-b were >0.1. Rates of intracranial hemorrhage (n=6 [0.9%] vs. n=7 [1.5%]; HR=0.90 [95% CI: 0.30-2.67]) and fatal bleeding (n=3 [1.0%] vs. n=5 [1.1%]; HR=0.62 [95% CI: 0.15-2.59]) were not significantly different between prasugrel and clopidogrel groups, respectively.

**Impact of Weight on Antiplatelet Response and Bleeding Events in Elderly Participants**

Among 515 participants ≥75 years 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) (Supplemental Figure S1). However, weight did not significantly modify the treatment effect on 30-day PRU values using an ANOVA model (interaction P=0.06). Among all participants ≥75 years (n=2083), median body weight was similar for patients with vs. without a non-CABG-related TIMI major/minor bleeding event in the prasugrel group (68 kg [25th, 75th percentiles: 60, 78 kg] vs. 70 kg [61, 80 kg]) and in the clopidogrel group (65 kg [55-81] vs. 70 kg [61-80]); interaction P=0.922 (Supplemental Figure S2).

**Discussion**

Our contemporary evaluation of ACS patients managed medically without planned revascularization provides several novel findings regarding 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 endpoint attributed to cardiovascular death during 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/day) vs. clopidogrel 75 mg/day 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 difference in weight by occurrence of major bleeding events with either reduced-dose prasugrel or clopidogrel among participants ≥75 years.

Prior 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 as well as increases in the risk of short-term ischemic events and bleeding complications with increasing age. Our data complement and extend these observations by demonstrating a substantially increased risk of both ischemic and bleeding events in elderly vs. younger patients over a longer follow-up period compared with other recent ACS trials in the under-studied, 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 endpoints (cardiovascular death, MI, stroke) observed in older vs. younger participants was proportionally highest for cardiovascular death. Additionally, we have shown a similar twofold to fourfold 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 PCI, 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. 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 vs. full-dose prasugrel. 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. 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). Although a prior observational study showed a diminished pharmacodynamic response to both standard-dose prasugrel (10 mg/d) and clopidogrel in elderly patients undergoing PCI, the impact of 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 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 prior studies by demonstrating that body weight does not appear to significantly impact the antiplatelet response.
and bleeding risk of reduced-dose prasugrel vs. 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 based upon age, we note that the proportion of patients ≥75 years enrolled in these trials was low (9%-17%), whereas in our study it was 29% of the total population.26-28 The proportion of elderly patients with UA/NSTEMI who underwent angiography and revascularization in these trials was substantially larger when compared with studies from patients treated in routine practice.1,5 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 that was terminated prematurely due to slow enrollment.29 Furthermore, a recent subgroup analysis of ACS patients ≥75 years 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 approximately 25% of these patients had STEMI and >60% underwent revascularization during the study.30 In contrast, we evaluated the under-studied, 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 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 vs. 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 4-5 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 vs. 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 prior studies. Finally, we assessed the impact of body weight on bleeding event occurrence by treatment group in participants ≥75 years, 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 vs. clopidogrel in this exploratory analysis of elderly patients. While it is encouraging that we did not observe a significant differential relationship among body weight, pharmacodynamic response, and bleeding risk with reduced-dose prasugrel vs. 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
antithrombotic therapies with adequate exposure of elderly ACS patients should be performed, potentially incorporating age-specific dosing regimens, in order to more clearly delineate optimal and safe treatment strategies for this vulnerable population.

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References:


# Table 1. Baseline Characteristics of Study Participants

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<th>Age &lt;75 y (n=7243)</th>
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<th>Prasugrel (n=1043)</th>
<th>Clopidogrel (n=1040)</th>
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<td>Median age, years (25th, 75th percentiles)</td>
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<td>Female sex</td>
<td>2599/7243 (35.9%)</td>
<td>1051/2083 (50.5%)</td>
<td>520/1043 (49.9%)</td>
<td>531/1040 (51.1%)</td>
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<td>Weight &lt;60 kg</td>
<td>939/7239 (13.0%)</td>
<td>462/2080 (22.2%)</td>
<td>233/1042 (22.4%)</td>
<td>229/1038 (22.1%)</td>
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<td>ACS classification</td>
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<td>Unstable angina</td>
<td>2356/7243 (32.5%)</td>
<td>450/2083 (21.6%)</td>
<td>214/1043 (20.5%)</td>
<td>236/1040 (22.7%)</td>
</tr>
<tr>
<td>NSTEMI</td>
<td>4887/7243 (67.5%)</td>
<td>1633/2083 (78.4%)</td>
<td>829/1043 (79.5%)</td>
<td>804/1040 (77.3%)</td>
</tr>
<tr>
<td>Killip Class II-IV</td>
<td>719/7237 (9.9%)</td>
<td>416/2081 (20.0%)</td>
<td>220/1041 (21.1%)</td>
<td>196/1040 (18.8%)</td>
</tr>
<tr>
<td>Proton-pump inhibitor</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
| ACE-I indicates angiotensin-converting enzyme inhibitor; 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; PCI=percutaneous coronary intervention
Table 2A. Efficacy and Safety Outcomes Through 30 Months*

<table>
<thead>
<tr>
<th></th>
<th>All Participants</th>
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<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Age &lt; 75 y</td>
<td>Age ≥75 y</td>
<td>Hazard Ratio</td>
<td>Prasugrel</td>
<td>Clopidogrel</td>
<td>Hazard Ratio</td>
<td>95% CI</td>
</tr>
<tr>
<td></td>
<td>(n=7243)</td>
<td>(n=2083)</td>
<td>(95% CI)</td>
<td>(n=1043)</td>
<td>(n=1040)</td>
<td>(95% CI)</td>
<td></td>
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</tr>
<tr>
<td>Ischemic events</td>
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<td></td>
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</tr>
<tr>
<td>CV death, MI, or stroke</td>
<td>No. of events</td>
<td>761</td>
<td>508</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(95% CI)</td>
<td>(13.6–16.3)</td>
<td>(32.5–38.8)</td>
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<tr>
<td>K-M event rate at 30 months</td>
<td></td>
<td>14.9</td>
<td>35.7</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>(95% CI)</td>
<td>(3.1–5.8)</td>
<td>(6.7–10.6)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CV death</td>
<td>No. of events</td>
<td>346</td>
<td>292</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(95% CI)</td>
<td>(5.9–7.6)</td>
<td>(16.8–21.9)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>No. of events</td>
<td>461</td>
<td>276</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(95% CI)</td>
<td>(17.6–25.8)</td>
<td>(15.3–22.7)</td>
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<td></td>
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<tr>
<td>K-M event rate at 30 months</td>
<td></td>
<td>9.4</td>
<td>19.4</td>
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<tr>
<td></td>
<td>(95% CI)</td>
<td>(5.9–7.6)</td>
<td>(16.8–21.9)</td>
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<td></td>
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<tr>
<td>Stroke</td>
<td>No. of events</td>
<td>77</td>
<td>54</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td></td>
<td>(95% CI)</td>
<td>(1.2–2.4)</td>
<td>(3.1–5.8)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>K-M event rate at 30 months</td>
<td></td>
<td>1.8</td>
<td>4.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(95% CI)</td>
<td>(1.2–2.4)</td>
<td>(3.1–5.8)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause death</td>
<td>No. of events</td>
<td>426</td>
<td>368</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(95% CI)</td>
<td>(7.1–8.8)</td>
<td>(22.8–28.2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>K-M event rate at 30 months</td>
<td></td>
<td>8.0</td>
<td>25.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(95% CI)</td>
<td>(2.9–6.9)</td>
<td>(2.1–5.9)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Log-rank P values are shown for age and treatment comparisons. CV=cardiovascular; CI=confidence interval; GUSTO=Global Use of Strategies to Open Occluded Coronary Arteries; K-M=Kaplan-Meier; MI=myocardial infarction; TIMI=Thrombolysis In Myocardial Infarction

DOI: 10.1161/CIRCULATIONAHA.113.002303
### Table 2B. Efficacy and Safety Outcomes Through 30 Months*

<table>
<thead>
<tr>
<th></th>
<th>All Participants</th>
<th>Participants ≥75 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Age &lt;75 y (n=7180)</td>
<td>Age ≥75 y (n=2060)</td>
</tr>
<tr>
<td><strong>Bleeding events – GUSTO criteria</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe/life-threatening bleeding (%)</td>
<td>3.33 (1.89–5.85)</td>
<td>0.72 (0.31–1.68)</td>
</tr>
<tr>
<td>No. of events</td>
<td>27</td>
<td>22</td>
</tr>
<tr>
<td>K-M event rate at 30 months (95% CI)</td>
<td>0.8 (0.3–1.2)</td>
<td>2.4 (1.2–3.6)</td>
</tr>
<tr>
<td>Severe/life-threatening or moderate bleeding (%)</td>
<td>3.29 (2.41–4.51)</td>
<td>1.11 (0.69–1.76)</td>
</tr>
<tr>
<td>No. of events</td>
<td>87</td>
<td>71</td>
</tr>
<tr>
<td>K-M event rate at 30 months (95% CI)</td>
<td>2.1 (1.5–2.6)</td>
<td>7.7 (5.5–9.9)</td>
</tr>
<tr>
<td><strong>Bleeding events – TIMI criteria</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major bleeding (%)</td>
<td>2.15 (1.44–3.20)</td>
<td>1.09 (0.57–2.08)</td>
</tr>
<tr>
<td>No. of events</td>
<td>69</td>
<td>37</td>
</tr>
<tr>
<td>K-M event rate at 30 months (95% CI)</td>
<td>1.8 (1.2–2.3)</td>
<td>3.7 (2.3–5.1)</td>
</tr>
<tr>
<td>Major/minor bleeding (%)</td>
<td>2.00 (1.46–2.75)</td>
<td>0.90 (0.53–1.50)</td>
</tr>
<tr>
<td>No. of events</td>
<td>116</td>
<td>58</td>
</tr>
<tr>
<td>K-M event rate at 30 months (95% CI)</td>
<td>2.7 (2.1–3.3)</td>
<td>6.7 (4.6–8.8)</td>
</tr>
</tbody>
</table>

*Bleeding endpoints 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. CV=cardiovascular; CI=confidence interval; GUSTO=Global Use of Strategies to Open Occluded Coronary Arteries; K-M=Kaplan-Meier; MI=myocardial infarction; TIMI=Thrombolysis In Myocardial Infarction.
Figure Legends:

Figure 1. Estimated event rates of the primary efficacy endpoint and the key bleeding endpoint of TIMI major bleeding unrelated to coronary artery bypass grafting at 24 months by age. The estimated event rates (95% CIs) of the primary endpoint of cardiovascular death, myocardial infarction, or stroke at 24 months (Panel A) and TIMI major bleeding unrelated to coronary artery bypass grafting (Panel B) among the entire study population (n=9326) are demonstrated by age with a linear spline function.

Figure 2. Cumulative Kaplan-Meier estimates of key study endpoints during the 30-month follow-up period by age categories. Panel A shows data for the primary efficacy endpoint of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke by four age categories (<75 years, n=7243; 75–79 years, n=1052; 80–84 years, n=656; ≥85 years, n=375). Panel B shows the key bleeding endpoint of TIMI major bleeding unrelated to coronary artery bypass grafting by the same age categories.

Figure 3. Proportional contribution of component endpoints to the primary efficacy endpoint by age categories. The proportion of component endpoints (cardiovascular death, myocardial infarction, stroke) contributing to time-to-first-event analysis of the primary efficacy endpoint is shown by age categories (<75 years, n=7243; 75–79 years, n=1052; 80–84 years, n=656; ≥85 years, n=375).

Figure 4. Cumulative Kaplan-Meier estimates of key study endpoints among participants ≥75
years by treatment during 30-month follow-up period. Panel A shows data for the primary
efficacy endpoint of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke by
treatment (prasugrel vs. clopidogrel). Panel B shows the key bleeding endpoint of TIMI major
bleeding unrelated to coronary artery bypass grafting by treatment (prasugrel vs. clopidogrel).
Figure 1B
Figure 2A

- ≥ 85 yrs: 51.8%
- 80–84 yrs: 37.3%
- 75–79 yrs: 28.7%
- < 75 yrs: 14.9%

No. at risk:
- < 75 yrs: 7243, 6492, 4749, 3207, 1899, 788
- 75–79 yrs: 1062, 856, 613, 394, 244, 104
- 80–84 yrs: 656, 525, 354, 238, 142, 44
- ≥ 85 yrs: 375, 263, 185, 123, 67, 28
Figure 2B
Figure 3
Figure 4A
Figure 4B

TIMI Major Bleeding

%

Days

Prasugrel 4.1%

Clopidogrel 3.4%

No. at risk:

<table>
<thead>
<tr>
<th>Prasugrel</th>
<th>Clopidogrel</th>
</tr>
</thead>
<tbody>
<tr>
<td>1033</td>
<td>1027</td>
</tr>
<tr>
<td>762</td>
<td>790</td>
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<tr>
<td>515</td>
<td>538</td>
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<td>337</td>
<td>351</td>
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<tr>
<td>199</td>
<td>210</td>
</tr>
<tr>
<td>93</td>
<td>85</td>
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</table>
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


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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

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Contents:

Supplemental Figure S1 and figure legend

Supplemental Figure S2 and figure legend
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: Box plots showing the distribution of weight (kg) for different treatments and bleeding statuses. The treatments are Prasugrel no bleed, Prasugrel bleed, Clopidogrel no bleed, and Clopidogrel bleed. The box plots indicate the median, interquartile range, and outliers for each group.
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 $P=0.922$. 