

# Relationship Between Peak Troponin Values and Long-Term Ischemic Events Among Medically Managed Patients With Acute Coronary Syndromes

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**Background**—The relationship between troponin level and outcomes among patients with non-ST-segment elevation ACS is established, but the relationship of troponin level with long-term outcomes among medically managed non-ST-segment elevation ACS patients receiving contemporary antiplatelet therapy is inadequately defined.

**Methods and Results**—In 6763 medically managed non-ST-segment elevation ACS patients randomized in TRILOGY ACS (Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes) (prasugrel versus clopidogrel), we examined relationships between categories of peak troponin/upper limit of normal (ULN) ratio within 48 hours of the index ACS event ( $\approx 4.5$  days before randomization) and 30-month outcomes (cardiovascular death, myocardial infarction, or stroke; cardiovascular death or myocardial infarction; and all-cause death). Patients with peak troponin levels  $< 1 \times$  ULN were younger, were more often women, and had lower GRACE risk scores than those in other troponin groups. Those with ratios  $\geq 5 \times$  ULN were more frequently smokers but less often had prior myocardial infarction or percutaneous coronary intervention. Diabetes mellitus prevalence, body mass index, serum creatinine, and hemoglobin were similar across groups. For all end points, statistically significant differences in 30-month event rates were observed between peak troponin categories. The relationship was linear for 30-month mortality ( $< 1 \times$  ULN,  $n=1849$  [6.2%];  $1$  to  $< 3 \times$  ULN,  $n=1203$  [9.6%];  $3$  to  $< 5 \times$  ULN,  $n=581$  [10.8%]; and  $\geq 5 \times$  ULN,  $n=3405$  [12.8%]) but plateaued for composite end points beyond peak troponin values  $\geq 3 \times$  ULN. There was no statistically significant heterogeneity in treatment effect by peak troponin ratio for any end point.

**Conclusions**—Among medically managed non-ST-segment elevation ACS patients selected for medical management, there was a graded relationship between increasing peak troponin and long-term ischemic events but no heterogeneity of treatment effect for prasugrel versus clopidogrel according to peak troponin.

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The relationship between baseline levels of troponin or creatine kinase-MB and outcomes among patients with non-ST-segment elevation acute coronary syndromes (NSTEMI ACS) is established.<sup>1</sup> This relationship has not been well studied in medically managed NSTEMI ACS populations in the era of modern antithrombotic therapy that includes

systematic use of more potent P2Y<sub>12</sub> inhibition as a component of dual antiplatelet therapy. In addition, whether the effect of treatment with a more potent P2Y<sub>12</sub> antagonist (eg, prasugrel versus clopidogrel) is influenced by degree of biomarker elevation, particularly among medically managed patients, is unknown. Although the relationship of troponin

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Accompanying Data S1, Tables S1 through S6 and Figures S1, S2 are available at <http://jaha.ahajournals.org/content/6/4/e005334/DC1/embed/inline-supplementary-material-1.pdf>

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elevation at baseline with outcome is strong over the first 30 days post-ACS, it becomes weaker over longer durations of follow-up.<sup>2,3</sup> The TRILOGY ACS (Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes) trial database provided the opportunity to explore these important issues in a medically managed NSTEMI ACS population treated with long-term dual antiplatelet therapy.

In a substudy of TRILOGY ACS, the Platelet Function Substudy, evaluation of platelet reactivity measured by serial P2Y<sub>12</sub> reaction unit (PRU) assessment showed more potent platelet inhibition with prasugrel compared with clopidogrel.<sup>4</sup> There was no relationship between platelet reactivity and ischemic outcomes or differential treatment effect according to platelet reactivity. The relationship between peak troponin level, platelet reactivity, outcomes, and treatment effect has not been explored. The Platelet Function Substudy provided an opportunity to examine these relationships.

## Methods

### Data Source

The study design and primary results of TRILOGY ACS were previously published.<sup>5</sup> Briefly, TRILOGY ACS was a multinational, double-blind, double-dummy, randomized active controlled trial that compared the effects of prasugrel versus clopidogrel among patients with NSTEMI ACS who were medically managed without revascularization. The trial was conducted between June 2008 and September 2011 at 966 centers worldwide. The primary end point was a composite of death from cardiovascular causes, nonfatal myocardial infarction (MI), or nonfatal stroke at 30-month follow-up. The trial was approved by the institutional review board or ethics committee of all participating sites, and all participants provided written informed consent prior to enrollment. The current analyses were approved by the Duke University Medical Center Institutional Review Board with waiver of informed consent and HIPAA (Health Insurance Portability and Accountability Act of 1996) authorization.

### Patient Characteristics and Study Definitions

TRILOGY ACS randomized 9326 patients. For this secondary analysis, we identified 6763 patients (72.5% of the intention-to-treat population) for whom peak troponin (T or I) data were available within 48 hours of the index event. Troponin I was used twice as often as troponin T. Patients were excluded if they had recurrent MI, bypass surgery, or percutaneous coronary intervention between the index event presentation and the reported peak cardiac troponin value. The analysis of platelet function included only patients enrolled in the Platelet

Function Substudy who had peak troponin data available (n=1810/2564 [70.6%]).

### End Points

Efficacy outcomes of interest in this secondary analysis were the following: (1) 30-month cardiovascular death, MI, or stroke (primary efficacy end point of TRILOGY ACS); (2) 30-month cardiovascular death or MI; (3) 30-month rates of the individual components cardiovascular death, MI, and stroke; and (4) 30-month all-cause death.

### Statistical Methods

Because multiple troponin assays were used across the 966 sites in TRILOGY ACS, we normalized site-laboratory-based peak troponin values as a ratio of the site-reported upper limit of normal (ULN) for the assay used. Patients were grouped by categories of peak troponin/ULN ratio (<1×ULN; 1 to <3×ULN; 3 to <5×ULN; ≥5×ULN). Peak troponin ratios were truncated to the 98th percentile for statistical analysis. For this study, peak troponin was the highest value measured within 48 hours of the index event.

Baseline patient characteristics, including demographics, clinical characteristics, GRACE (Global Registry of Acute Coronary Events) risk score, and concomitant medications at randomization, were summarized according to peak troponin ratio. The GRACE score is a risk-stratification tool developed to estimate the risk of in-hospital and 6-month mortality among all patients hospitalized with ACS. The risk score was created from a risk-prediction model developed using an international ACS registry database.<sup>6</sup> Continuous variables are presented as medians (25th, 75th percentiles), and differences were compared using the Kruskal–Wallis test. Categorical variables are presented as counts (percentages), and differences were compared using the Pearson  $\chi^2$  or Fisher exact test if cell frequencies were not sufficient.

For each ischemic outcome, the total number of events and Kaplan–Meier event rates at 30 months after randomization (95% CI) were presented according to peak troponin category. Time-to-event is defined as the time from randomization to the onset of the end point. Time-to-first-event for a composite end point is defined as the time from randomization to the occurrence of the first event of the composite end point. Censoring rules are defined in Tables S1 and S2. Event rates across the follow-up period were compared using the log-rank test.

To examine the relationship between peak troponin level and clinical outcomes, unadjusted and adjusted Cox proportional hazards regression models were developed to test the univariable and multivariable associations of continuous peak troponin ratios with each clinical outcome. TRILOGY ACS

models previously built for each ischemic outcome were used to adjust for baseline characteristics and risk factors. The proportional hazards assumption was checked for each variable, and the linearity assumption was checked for each continuous variable. If the proportional hazards assumption was violated, an interaction of the variable with log-transformed time was included in the model. If the linearity assumption was violated, a linear or restricted cubic spline was used to approximate the nonlinear relationship of the variable with the outcome.<sup>7</sup> In cases where the peak troponin ratio was found to have a nonlinear relationship with a given end point, it was modeled using a linear spline with a knot point at  $3.0 \times \text{ULN}$ , which was determined via numerical simulation across the range of all peak troponin ratios. For further details, please see Table S3. A full description of the TRILOGY ACS adjustment models used in this analysis is provided in Data S1 and Table S4.

The interaction between peak troponin level, study treatment (prasugrel versus clopidogrel), and ischemic outcomes was also computed. Further assessment of this relationship was completed in a subgroup of patients who underwent coronary angiography prior to randomization, eliminating those without angiographically proven coronary disease (lesion causing  $>50\%$  stenosis).

Baseline characteristics of patients in the Platelet Function Substudy sample were summarized according to peak troponin ratio category. For these patients, the unadjusted and adjusted associations of peak troponin ratio with 30-day PRU values and the interaction with study treatment were evaluated. To gauge the strength of the linear relationship between peak troponin ratio and 30-day PRU values, the Pearson correlation coefficient was computed and the null hypothesis of zero correlation was tested.

All analyses were conducted using SAS statistical software version 9.4 (SAS Institute, Cary, NC). A  $P$  value of  $<0.05$  (2-sided) was considered statistically significant. No adjustments were made for multiple comparisons.

## Results

### Overall Study Sample

Baseline characteristics of the 6763 patients who had sufficient laboratory data reported to determine the peak troponin ratio at 48 hours compared with the 2563 patients who were excluded are provided in Table S5. Baseline characteristics of the 6763 patients included are shown by peak troponin ratio categories in Table 1. Patients with peak troponin ratios  $<1 \times \text{ULN}$  were younger, more often women, more often from Central/Eastern Europe, and had lower GRACE risk scores than patients in other troponin groups. Patients with ratios  $\geq 5 \times \text{ULN}$  more frequently smoked but

less often had prior MI or percutaneous coronary intervention. Diabetes mellitus prevalence, body mass index, and hemoglobin were similar across groups. Although there was a statistically significant difference in serum creatinine across troponin groups, absolute differences were small and unlikely to be clinically relevant.

### Ischemic Outcomes According to Peak Troponin

Table 2 shows the number of 30-month ischemic outcome events and Kaplan–Meier event rates across peak troponin categories. Figure 1 displays corresponding Kaplan–Meier event rate curves. Trends for increasing event rates with increasing peak troponin ratios were statistically significant for all end points. The relationship was linear for 30-month all-cause mortality but appeared to increase and then plateau at peak troponin ratios  $\geq 3 \times \text{ULN}$  for the composite end points. The greatest difference in event rates was between peak troponin ratios  $<1 \times \text{ULN}$  and any peak troponin ratio  $\geq 1 \times \text{ULN}$  during early follow-up. Through 30 months, event rates for patients with peak troponin ratios  $\geq 5 \times \text{ULN}$  were more than twice as high as rates for patients with peak troponin ratios  $<1 \times \text{ULN}$ .

Table 3 displays unadjusted and adjusted hazard ratios for 30-month ischemic outcomes per unit increase in peak troponin ratio, modeled as a linear spline. The graphic representation of this relationship for the primary efficacy end point is displayed in Figure S1A and S1B. In unadjusted analyses, increases in peak troponin ratio were strongly associated with each outcome up to  $3 \times \text{ULN}$ ; beyond this, the risk of ischemic events remained relatively constant as peak troponin ratios increased. Results were consistent after adjustment for baseline characteristics, except that the association with cardiovascular death was no longer significant. Note, the upper segment of the troponin linear spline (ratios  $>3 \times \text{ULN}$ ) is not presented in Table 3 as all associations with outcomes are nonsignificant.

Table 3 also shows that there were no statistically significant interactions between peak troponin ratio and study treatment for any of the ischemic outcomes. The graphic representation of this relationship is displayed in Figure S2. In a subgroup analysis assessing this relationship among patients with angiographically proven coronary disease, the interaction between peak troponin ratio, study treatment, and either combined end point or all-cause mortality also lacked statistical significance. These results remained unchanged after adjustment for time from patient presentation to administration of study drug.

### Peak Troponin and Platelet Function

Among patients enrolled in the TRILOGY ACS Platelet Function Substudy, 1810 (70.6%) had necessary measurements to

**Table 1.** Baseline Characteristics According to 48-Hour Peak Troponin Level

|  | Peak Troponin Level as Ratio of ULN |                     |                     |                     | P Value |
|--|-------------------------------------|---------------------|---------------------|---------------------|---------|
|  | <1x (N=1574)                        | 1x to <3x (N=1203)  | 3x to <5x (N=581)   | ≥5x (N=3405)        |         |
| <b>Demographics</b>                            |                                     |                     |                     |                     |         |
| Age, y   | 65.0 (58.0, 72.0)                   | 67.0 (58.0, 75.0)   | 67.0 (60.0, 75.0)   | 67.0 (60.0, 76.0)   | <0.001  |
| Age ≥75 y                                      | 285/1574 (18.1%)                    | 301/1203 (25.0%)    | 156/581 (26.9%)     | 954/3405 (28.0%)    | <0.001  |
| Weight, kg                                     | 75.0 (65.0, 86.0)                   | 75.0 (65.0, 89.0)   | 75.0 (65.0, 86.0)   | 77.0 (66.0, 89.0)   | 0.008   |
| Weight <60 kg                                  | 211/1573 (13.4%)                    | 191/1201 (15.9%)    | 78/581 (13.4%)      | 426/3401 (12.5%)    | 0.033   |
| Sex  |                                     |                     |                     |                     | 0.004   |
| Female   | 648/1574 (41.2%)                    | 466/1203 (38.7%)    | 223/581 (38.4%)     | 1221/3405 (35.9%)   |         |
| Male   | 926/1574 (58.8%)                    | 737/1203 (61.3%)    | 358/581 (61.6%)     | 2184/3405 (64.1%)   |         |
| Region   |                                     |                     |                     |                     | <0.001  |
| Central/Eastern Europe                         | 714/1574 (45.4%)                    | 354/1203 (29.4%)    | 195/581 (33.6%)     | 798/3405 (23.4%)    |         |
| East Asia                                      | 180/1574 (11.4%)                    | 110/1203 (9.1%)     | 42/581 (7.2%)       | 246/3405 (7.2%)     |         |
| Indian subcontinent                            | 147/1574 (9.3%)                     | 140/1203 (11.6%)    | 43/581 (7.4%)       | 149/3405 (4.4%)     |         |
| Latin America                                  | 175/1574 (11.1%)                    | 142/1203 (11.8%)    | 61/581 (10.5%)      | 381/3405 (11.2%)    |         |
| Mediterranean basin                            | 103/1574 (6.5%)                     | 86/1203 (7.1%)      | 32/581 (5.5%)       | 318/3405 (9.3%)     |         |
| North America                                  | 132/1574 (8.4%)                     | 190/1203 (15.8%)    | 99/581 (17.0%)      | 821/3405 (24.1%)    |         |
| Western Europe/Scandinavia                     | 112/1574 (7.1%)                     | 158/1203 (13.1%)    | 95/581 (16.4%)      | 604/3405 (17.7%)    |         |
| Rest of world                                  | 11/1574 (0.7%)                      | 23/1203 (1.9%)      | 14/581 (2.4%)       | 88/3405 (2.6%)      |         |
| <b>Presentation characteristics</b>            |                                     |                     |                     |                     |         |
| Hours from presentation to start of study drug | 83.3 (45.5, 141.4)                  | 109.0 (64.8, 159.2) | 109.7 (69.2, 158.4) | 118.0 (72.3, 165.8) | <0.001  |
| Killip class II–IV on presentation             | 129/1572 (8.2%)                     | 148/1202 (12.3%)    | 81/581 (13.9%)      | 467/3404 (13.7%)    | <0.001  |
| Disease classification                         |                                     |                     |                     |                     | <0.001  |
| Unstable angina/unknown                        | 1291/1574 (82.0%)                   | 165/1203 (13.7%)    | 0/581 (0.0%)        | 0/3405 (0.0%)       |         |
| NSTEMI   | 283/1574 (18.0%)                    | 1038/1203 (86.3%)   | 581/581 (100.0%)    | 3405/3405 (100.0%)  |         |
| <b>Medical history</b>                         |                                     |                     |                     |                     |         |
| Family history of CAD                          | 421/1402 (30.0%)                    | 361/1070 (33.7%)    | 162/522 (31.0%)     | 1064/2984 (35.7%)   | 0.002   |
| Hypertension                                   | 1347/1570 (85.8%)                   | 991/1201 (82.5%)    | 491/581 (84.5%)     | 2720/3393 (80.2%)   | <0.001  |
| Hyperlipidemia                                 | 925/1482 (62.4%)                    | 711/1164 (61.1%)    | 334/565 (59.1%)     | 2175/3304 (65.8%)   | 0.001   |
| Diabetes mellitus                              | 598/1574 (38.0%)                    | 488/1201 (40.6%)    | 244/581 (42.0%)     | 1309/3396 (38.5%)   | 0.214   |
| Current/recent smoking*                        | 268/1558 (17.2%)                    | 231/1192 (19.4%)    | 119/573 (20.8%)     | 826/3363 (24.6%)    | <0.001  |
| Prior MI                                       | 697/1566 (44.5%)                    | 559/1194 (46.8%)    | 260/576 (45.1%)     | 1408/3366 (41.8%)   | 0.016   |
| Prior PCI                                      | 521/1569 (33.2%)                    | 422/1196 (35.3%)    | 176/578 (30.4%)     | 795/3372 (23.6%)    | <0.001  |
| Prior CABG                                     | 261/1572 (16.6%)                    | 218/1203 (18.1%)    | 90/580 (15.5%)      | 632/3390 (18.6%)    | 0.149   |
| Prior PAD                                      | 92/1552 (5.9%)                      | 89/1175 (7.6%)      | 43/572 (7.5%)       | 302/3333 (9.1%)     | 0.002   |
| Prior atrial fibrillation                      | 126/1533 (8.2%)                     | 106/1175 (9.0%)     | 50/565 (8.8%)       | 263/3296 (8.0%)     | 0.685   |
| Prior heart failure                            | 304/1565 (19.4%)                    | 178/1194 (14.9%)    | 98/576 (17.0%)      | 400/3376 (11.8%)    | <0.001  |
| Prior stroke                                   | 7/1571 (0.4%)                       | 4/1198 (0.3%)       | 4/578 (0.7%)        | 24/3385 (0.7%)      | 0.414   |

Continued

Table 1. Continued

|   | Peak Troponin Level as Ratio of ULN |                      |                      |                      | P Value |
|---|-------------------------------------|----------------------|----------------------|----------------------|---------|
|   | <1x (N=1574)                        | 1x to <3x (N=1203)   | 3x to <5x (N=581)    | ≥5x (N=3405)         |         |
| <b>Baseline risk assessment</b>                 |                                     |                      |                      |                      |         |
| GRACE risk score                                | 116.0 (101.0, 130.0)                | 122.0 (106.0, 141.0) | 128.0 (112.0, 147.0) | 124.0 (108.0, 144.0) | <0.001  |
| Body mass index, kg/m <sup>2</sup>              | 27.0 (24.5, 30.5)                   | 27.2 (24.2, 31.0)    | 27.2 (24.6, 30.8)    | 27.3 (24.4, 30.8)    | 0.485   |
| Systolic blood pressure, mm Hg                  | 130.0 (120.0, 140.0)                | 130.0 (117.0, 140.0) | 126.0 (118.0, 138.0) | 125.0 (115.0, 138.0) | <0.001  |
| Heart rate, bpm                                 | 68.5 (62.0, 76.0)                   | 69.0 (62.0, 76.0)    | 68.0 (60.0, 76.0)    | 69.0 (62.0, 76.0)    | 0.491   |
| Hemoglobin, g/dL                                | 13.6 (12.6, 14.6)                   | 13.4 (12.3, 14.5)    | 13.6 (12.4, 14.7)    | 13.5 (12.4, 14.7)    | 0.104   |
| Serum creatinine, mg/dL                         | 1.0 (0.8, 1.1)                      | 1.0 (0.8, 1.2)       | 1.0 (0.9, 1.2)       | 1.0 (0.8, 1.2)       | <0.001  |
| <b>At randomization</b>                         |                                     |                      |                      |                      |         |
| Treatment                                       |                                     |                      |                      |                      | 0.323   |
| Prasugrel                                       | 767/1574 (48.7%)                    | 585/1203 (48.6%)     | 276/581 (47.5%)      | 1725/3405 (50.7%)    |         |
| Clopidogrel                                     | 807/1574 (51.3%)                    | 618/1203 (51.4%)     | 305/581 (52.5%)      | 1680/3405 (49.3%)    |         |
| Clopidogrel strata                              |                                     |                      |                      |                      | <0.001  |
| No clopidogrel                                  | 123/1574 (7.8%)                     | 36/1203 (3.0%)       | 22/581 (3.8%)        | 92/3405 (2.7%)       |         |
| Clopidogrel started in hospital ≤72 hours       | 905/1574 (57.5%)                    | 798/1203 (66.3%)     | 421/581 (72.5%)      | 2759/3405 (81.0%)    |         |
| Home clopidogrel                                | 546/1574 (34.7%)                    | 369/1203 (30.7%)     | 138/581 (23.8%)      | 554/3405 (16.3%)     |         |
| <b>Prerandomization procedures</b>              |                                     |                      |                      |                      |         |
| Angiography performed                           | 555/1574 (35.3%)                    | 568/1203 (47.2%)     | 256/581 (44.1%)      | 1941/3405 (57.0%)    | <0.001  |
| <b>Concomitant medications at randomization</b> |                                     |                      |                      |                      |         |
| <b>Aspirin daily dose</b>                       |                                     |                      |                      |                      |         |
| <100 mg   | 470/1574 (29.9%)                    | 406/1203 (33.7%)     | 182/581 (31.3%)      | 1116/3405 (32.8%)    | 0.112   |
| 100 to 250 mg                                   | 943/1574 (59.9%)                    | 628/1203 (52.2%)     | 308/581 (53.0%)      | 1658/3405 (48.7%)    | <0.001  |
| >250 mg   | 86/1574 (5.5%)                      | 89/1203 (7.4%)       | 56/581 (9.6%)        | 396/3405 (11.6%)     | <0.001  |
| β-Blocker                                       | 1248/1574 (79.3%)                   | 947/1203 (78.7%)     | 468/581 (80.6%)      | 2753/3405 (80.9%)    | 0.339   |
| ACE-I/ARB                                       | 1173/1574 (74.5%)                   | 883/1203 (73.4%)     | 446/581 (76.8%)      | 2635/3405 (77.4%)    | 0.018   |
| Statin  | 1287/1574 (81.8%)                   | 1016/1203 (84.5%)    | 482/581 (83.0%)      | 2945/3405 (86.5%)    | <0.001  |
| Proton pump inhibitor                           | 355/1574 (22.6%)                    | 308/1203 (25.6%)     | 185/581 (31.8%)      | 982/3405 (28.8%)     | <0.001  |

Data presented as n/N (%) or median (25th, 75th percentile). ACE-I/ARB indicates angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; bpm, beats per minute; CABG, coronary artery bypass graft; CAD, coronary artery disease; GRACE, Global Registry of Acute Coronary Events; MI, myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; ULN, upper limit of normal.

\*Smoking within 30 days of randomization.

compute peak troponin/ULN ratios. Baseline characteristics by peak troponin ratio category are shown in Table S6. Compared with other groups, patients with peak troponin ratios <1xULN were younger, more often from Central/Eastern Europe, and less likely to be current/prior smokers or have a family history of coronary artery disease or hyperlipidemia. Additionally, they were less likely to have undergone angiography prior to randomization. Diabetes mellitus prevalence was similar across groups.

As displayed in Figure 2, there was no relationship between peak troponin and PRU among patients with angiographically proven coronary artery disease. Results remain unchanged even after adjustment for age group

(≥75 years versus <75 years), clopidogrel stratum at randomization, randomized treatment assignment, and time from patient presentation to start of study drug.

### Discussion

This analysis of TRILOGY ACS demonstrated that among NSTEMI ACS patients selected for medical management, including dual antiplatelet therapy with a P2Y12 antagonist, there was a graded relationship of increasing peak troponin with long-term ischemic events. Event rates at 30 months for patients with troponin ≥5xULN were more than twice those for patients with peak troponin <1xULN. There was no apparent

**Table 2.** Thirty-Month Ischemic Event Rates According to 48-Hour Peak Troponin Level

|                                     | Peak Troponin Level as Ratio of ULN |                    |                   |                  | P Value* |
|-------------------------------------|-------------------------------------|--------------------|-------------------|------------------|----------|
|                                     | <1x (n=1574)                        | 1x to <3x (n=1203) | 3x to <5x (n=581) | ≥5x (n=3405)     |          |
| Cardiovascular death, MI, or stroke |                                     |                    |                   |                  | <0.001   |
| No. of events                       | 118                                 | 172                | 104               | 607              |          |
| KM event rate (95% CI)              | 11.3 (9.1–13.5)                     | 18.4 (15.3–21.4)   | 26.6 (20.9–32.3)  | 25.1 (23.0–27.1) |          |
| Cardiovascular death                |                                     |                    |                   |                  | <0.001   |
| No. of events                       | 62                                  | 80                 | 41                | 297              |          |
| KM event rate (95% CI)              | 5.8 (4.2–7.3)                       | 9.6 (7.0–12.3)     | 10.8 (6.6–15.0)   | 12.8 (11.1–14.4) |          |
| Myocardial infarction               |                                     |                    |                   |                  | <0.001   |
| No. of events                       | 63                                  | 102                | 72                | 364              |          |
| KM event rate (95% CI)              | 6.4 (4.6–8.1)                       | 10.4 (8.4–12.4)    | 17.6 (13.1–22.0)  | 15.6 (13.8–17.3) |          |
| Cardiovascular death or MI          |                                     |                    |                   |                  | <0.001   |
| No. of events                       | 111                                 | 157                | 97                | 569              |          |
| KM event rate (95% CI)              | 10.6 (8.5–12.8)                     | 16.8 (13.8–19.8)   | 25.0 (19.4–30.6)  | 23.5 (21.4–25.5) |          |
| Stroke                              |                                     |                    |                   |                  | 0.005    |
| No. of events                       | 11                                  | 22                 | 8                 | 67               |          |
| KM event rate (95% CI)              | 1.2 (0.4–2.0)                       | 2.8 (1.5–4.1)      | 1.8 (0.5–3.2)     | 3.3 (2.4–4.3)    |          |
| All-cause death                     |                                     |                    |                   |                  | <0.001   |
| No. of events                       | 83                                  | 102                | 60                | 362              |          |
| KM event rate (95% CI)              | 7.3 (5.7–9.0)                       | 11.8 (9.1–14.5)    | 14.7 (10.3–19.0)  | 14.8 (13.2–16.5) |          |

KM indicates Kaplan–Meier; MI, myocardial infarction; No., number; ULN, upper limit of normal.

\*Two-sided *P* value based on the log-rank test.

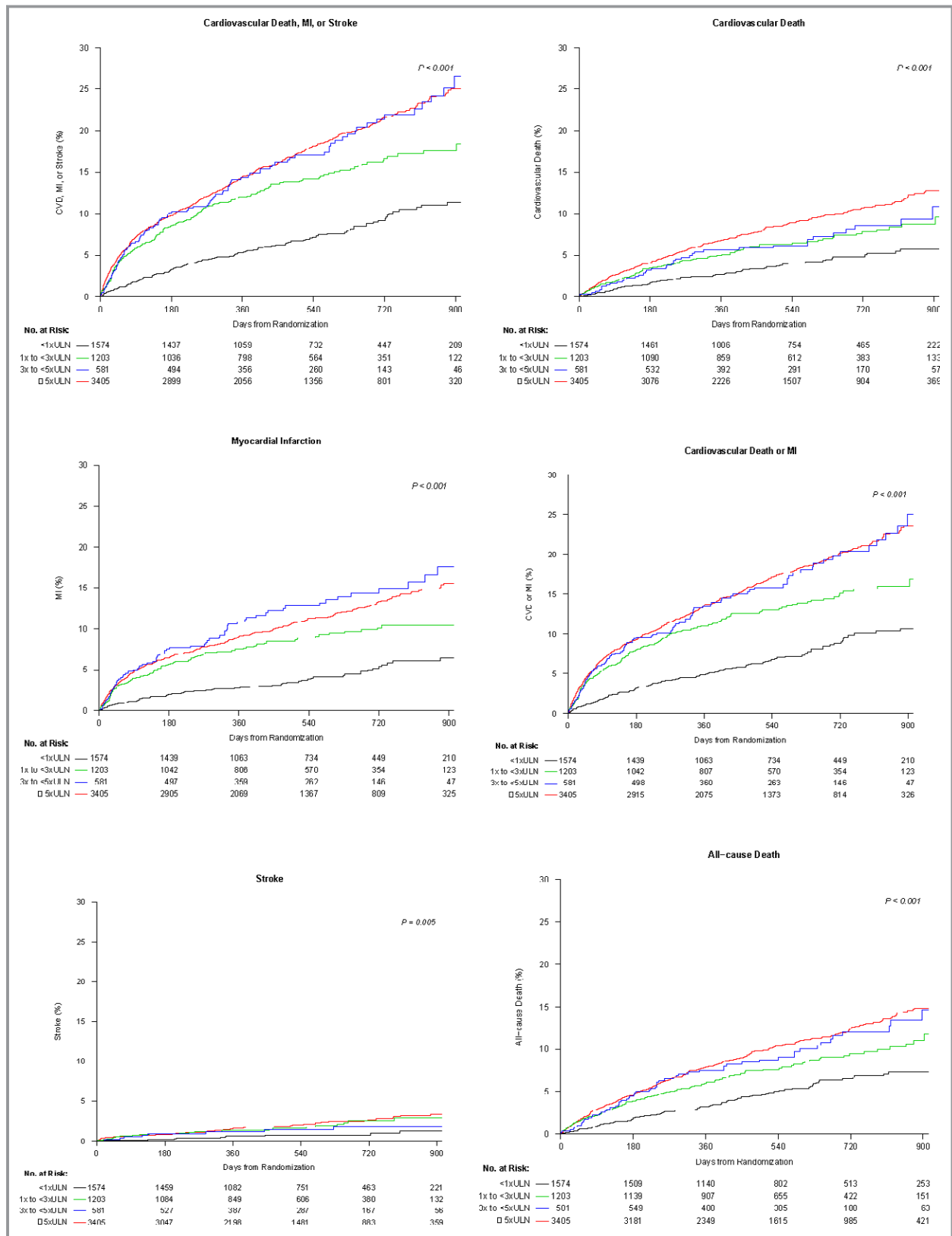
incremental benefit of treatment with prasugrel versus clopidogrel according to peak troponin ratio among medically managed patients with NSTEMI ACS.

### Peak Troponin and Long-Term Outcomes

Since the introduction of troponin testing in the early 1990s, its role has evolved from MI diagnosis to include risk stratification following ACS. It is known from previous analyses, including FRISC (Fragmin during Instability in Coronary Artery Disease) and TACTICS-TIMI 18 (Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy—Thrombolysis in Myocardial Infarction 18) that patients with NSTEMI ACS who have troponin elevations above the ULN at admission are at higher risk for death and recurrent ischemic events.<sup>2,8,9</sup> Furthermore, through additional analyses of trials such as GUSTO (Global Use of Strategies to Open Occluded Coronary Arteries) IIa, there is a well-characterized relationship between the magnitude of troponin elevation and outcomes among patients with NSTEMI ACS.<sup>1</sup> Troponin elevation can also identify which patients are most likely to benefit from aggressive antithrombotic therapy and an early invasive strategy.<sup>8,9</sup>

Recently, a secondary analysis of the TRACER (Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome) trial, a study designed to examine the effect of vorapaxar (a protease-activated receptor-1 antagonist) versus placebo in NSTEMI ACS, identified a differential relationship between the magnitude of troponin elevation and 2-year mortality among patients treated with and without revascularization. In a subset of patients included in TRACER who did not undergo revascularization, increasing levels of peak cardiac troponin were associated with increasing long-term mortality ( $P=0.001$ ). This relationship was not observed in those who underwent revascularization ( $P=0.23$ ).<sup>10</sup>

The graded relationship of increasing peak troponin with ischemic events that we observed was consistent with this observation and prior studies evaluating troponin elevation as a prognostic indicator among patients with NSTEMI ACS. However, TRILOGY ACS provided the unique opportunity to establish this relationship over a long-term (30-month) follow-up period among patients who were medically managed with P2Y<sub>12</sub> inhibitor therapy. Thus, the results of this analysis extend our understanding of the relationship of troponin with risk to long-term follow-up in the important population of medically managed NSTEMI ACS patients in the contemporary



**Figure 1.** Cumulative Kaplan–Meier estimates of 30-month ischemic outcomes by 48-hour peak troponin elevation. For visualization of the numerical results presented in Table 2, Kaplan–Meier failure curves are presented for each efficacy end point. See Table 2 for relevant log-rank *P* values. MI indicates myocardial infarction; ULN, upper limit of normal.

**Table 3.** Unadjusted and Adjusted Hazard Ratios for 30-Month Ischemic Outcomes According to 48-Hour Peak Troponin Elevation

|                                  | Unadjusted HR (95% CI)* | Adjusted HR (95% CI)*            | Peak Troponin × Treatment Interaction <i>P</i> Value |
|----------------------------------|-------------------------|----------------------------------|--|
| Cardiovascular death, MI, stroke | 1.350 (1.263–1.442)     | 1.182 (1.066–1.311)              | 0.483  |
| Cardiovascular death or MI       | 1.347 (1.257–1.443)     | 1.183 (1.062–1.318)              | 0.433  |
| Cardiovascular death             | 1.291 (1.175–1.419)     | 1.090 (0.942–1.263)              | 0.371  |
| Myocardial infarction            | 1.411 (1.292–1.541)     | 1.238 (1.081–1.419)              | 0.413  |
| Stroke                           | 1.387 (1.136–1.695)     | 0.998 (0.996–1.001) <sup>†</sup> | 0.191  |
| All-cause mortality              | 1.282 (1.179–1.393)     | 1.001 (1.000–1.001) <sup>†</sup> | 0.234  |

HR indicates hazard ratio; MI, myocardial infarction.

\*Per 1 unit increase in peak troponin/upper limit of normal ratio.

<sup>†</sup>Peak troponin elevation modeled linearly as the assumption of linearity was satisfied.

era of more potent P2Y<sub>12</sub> inhibitor therapy. Our analyses demonstrate that despite advances in other medical therapy acutely and in secondary prevention, higher peak troponin values portend worse ischemic outcomes.

### Peak Troponin and Effect of More Potent Antiplatelet Therapy

Substudies of several randomized clinical trials showed that the treatment effect of glycoprotein IIb/IIIa antagonists was amplified among patients with baseline troponin elevation, but there was no evident benefit among those without.<sup>11–13</sup> These findings were consistent across studies despite significant differences in patient populations, highlighting the importance of troponin elevation in identifying high-risk patients who may benefit from more potent antiplatelet therapy.<sup>11</sup> Given these observations and our results correlating troponin and rates of adverse cardiovascular events, it might be anticipated that higher-risk medically managed patients with greater peak troponin levels would also benefit preferentially from more potent antiplatelet therapy. However, we observed no such interaction of peak troponin level with more potent dual antiplatelet therapy among patients assigned to prasugrel compared with clopidogrel. This was consistent among the subset of patients with angiographically proven coronary disease who were medically managed in TRILOGY ACS. Thus, it is unlikely that inclusion of patients with troponin elevation unrelated to atherosclerotic coronary disease significantly influenced our analysis.

A number of considerations may contribute to our observations. Because this is a secondary analysis, it was not powered to detect an effect of more potent P2Y<sub>12</sub> inhibition according to peak troponin values. Further, whereas the PARAGON-B (Platelet IIb/IIIa Antagonist for the Reduction of Acute coronary syndrome events in a Global Organization Network B) study assessed a glycoprotein IIb/IIIa inhibitor (steady-state platelet aggregation inhibition >90%) versus placebo, neither prasugrel (50%) nor clopidogrel (30%) achieve that level of platelet

aggregation inhibition, and they were compared head-to-head instead of against placebo.<sup>14,15</sup> Together these features of trial design may have contributed to the differential findings. Additionally, participants in TRILOGY ACS were randomized to prasugrel or clopidogrel ≈4.5 days after their index clinical event and could be enrolled up to 10 days after the index event.<sup>5</sup> It is possible that the benefit of more potent antiplatelet therapy may be related to the timing of therapy initiation relative to myocardial ischemia onset (which was much earlier in PARAGON-B), and particularly that patients with completed infarction by this time point may not benefit from more potent antiplatelet therapy. Additionally, prior evaluations of more potent antiplatelet therapies primarily focused on patients who underwent an invasive treatment strategy. It is possible that the benefit of more potent antiplatelet therapy seen in prior studies may have been derived from reduced periprocedural adverse ischemic outcomes. Finally, it is possible that bleeding complications may have attenuated the benefit of more potent antiplatelet therapy.

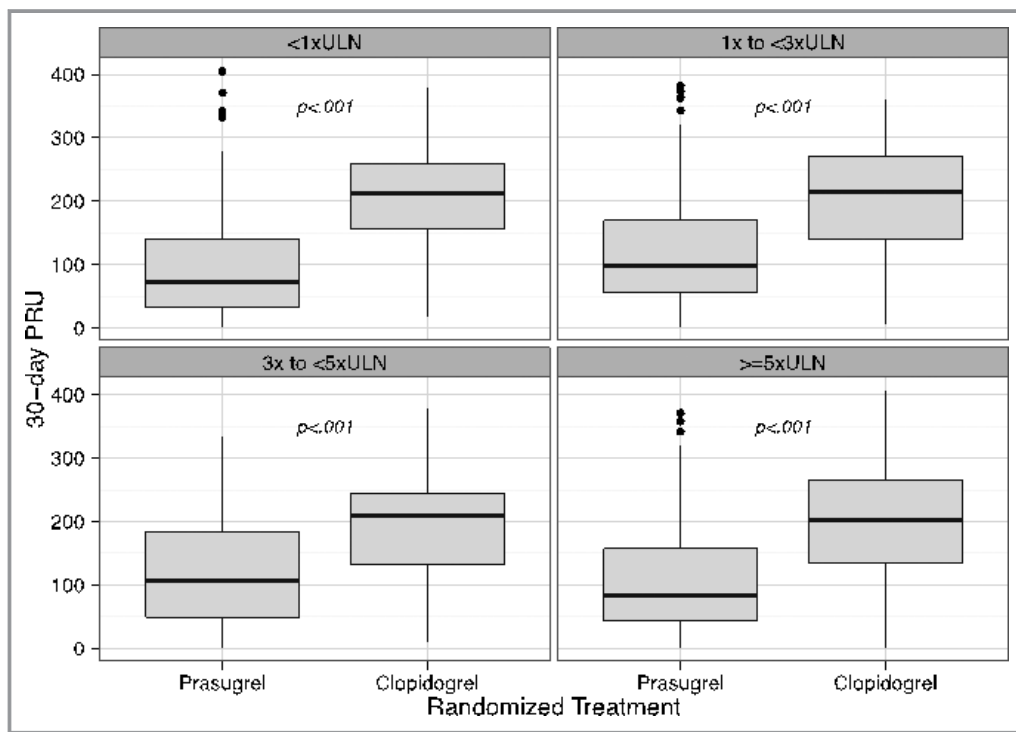
### Peak Troponin and Platelet Reactivity

A substudy of TRILOGY ACS evaluated the effects of prasugrel and clopidogrel on serial PRU assessments. This analysis revealed lower platelet reactivity with prasugrel compared with clopidogrel; however, there was no difference in ischemic outcomes by treatment assignment.<sup>4,5</sup> Our exploratory analysis of the TRILOGY ACS Platelet Function Substudy revealed that the effect of treatment on platelet inhibition (as assessed by 30-day PRU values) did not vary substantially based on peak troponin value.

### Strengths and Limitations

This secondary analysis of TRILOGY ACS demonstrates a novel correlation between troponin elevation and prognosis in a study sample selected for medical management of NSTEMI ACS. One of the strengths of our analysis is that it used data





**Figure 2.** Forty-eight-hour peak troponin ratio and 30-day platelet reactivity unit (PRU). For patients enrolled in the Platelet Function Substudy, a box plot is used to assess the unadjusted association of peak troponin elevation with 30-day PRU, as well as the interaction with study treatment ( $P < 0.001$ ). ULN indicates upper limit of normal.

collected as part of a large, multinational, randomized trial, which enhances data consistency and eliminates bias in the assessment of overall treatment effects. Because of the large number of subjects, the results are statistically robust. However, because these results are drawn from a patient population selected for a randomized clinical trial, they may not be generalizable to the broader population of medically managed patients in general practice. Troponin values used for our analysis were collected up to 48 hours after presentation, consistent with contemporary clinical practice. It is possible that by limiting our analysis to values within 48 hours of presentation, a higher peak value could have been missed, but this rule was applied consistently to all patients. Peak troponin data within 48 hours were not available in about 25% of study participants, eliminating this group from our analysis. Although there were differences between those included or not, most were modest and would not be expected to alter the relationships we observed (Table S5). Troponin assays were not standardized across participating sites. Thus, they reflect a wide variety of individual assays with variable assay performance characteristics, and potentially varying site-specific ULNs for the same assay. However, this reflects the state of actual clinical practice, and we attempted to account for this by normalizing the reported values using a ratio of the reported value to the

ULN reported for the assay. This variability and resultant “noise” introduced would be expected to result in an underestimation of the relationship between increasing troponin level and outcomes. Additionally, it is possible that some patients with elevated troponin levels who were included in TRILOGY ACS did not have significant coronary artery disease. In this case, the true association of troponin with long-term ischemic outcomes may have been underestimated. Of the patients who underwent angiography, however, very few had absence of obstructive coronary disease, and when we excluded those patients from our analyses, there were no differences in our findings. Although designed to evaluate medically managed patients, a small number of patients (7.1%) underwent postindex revascularization at a median of 120.5 days after the index event. Because of the infrequency of downstream revascularization in our study sample and that it occurred late relative to the time of troponin sampling, we believe the commitment to an initial medical management strategy was met and that it is unlikely that our results were significantly affected. Finally, it is possible that because we defined peak troponin using values collected within 48 hours after the index event, the true peak troponin value was missed. However, it is important to note that the impact of missing the true peak would tend to underestimate the relationship between peak troponin level

and adverse outcomes. Despite its limitations, our analysis shows the prognostic importance of higher levels of troponin for long-term outcomes among medically managed patients with NSTEMI ACS, even in the setting of treatment with modern, potent antiplatelet agents, and the effect is not related to the degree of platelet inhibition as assessed by the P2Y12 assay.

## Conclusion

Among NSTEMI ACS patients selected for medical management, there was a graded relationship of increasing peak troponin with long-term ischemic events, but no heterogeneity of treatment effect for prasugrel versus clopidogrel (clinical or PRU-based) according to 48-hour peak troponin level.

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## Disclosures

Newby has reported all potential conflicts at <https://www.dcri.org/about-us/conflict-of-interest>. Lüscher reports grants from AstraZeneca and from Eli Lilly during the conduct of the study. White reports grants from Sanofi Aventis, Eli Lilly and Company, National Institute of Health, and Merck Sharpe & Dohm, grants and personal fees from AstraZeneca, grants from GlaxoSmithKline, Omthera Pharmaceuticals, Pfizer New Zealand, Intarcia Therapeutics Inc., Elsay Inc., DalGen Products and Services, and Daiichi Sankyo Pharma Development, outside the submitted work. Ohman reports receiving grant support and travel expenses from Daiichi Sankyo and Eli 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 support from Gilead Sciences; and lecture fees from Gilead Sciences, Boehringer Ingelheim, and The Medicines Company. Roe reports research grants from Eli Lilly and Company, Janseen Pharmaceuticals, Sanofi-Aventis, Daiichi-Sankyo, Familial Hypercholesterolemia Foundation, and Ferring Pharmaceuticals; educational activities or lectures for Amgen and Bristol-Myers Squibb; consulting or other services for AstraZeneca, Eli Lilly and Company, Merck & Co., Elsevier Publishers, Amgen, Boehringer-Ingelheim, and PriMed. All conflicts of interest are listed at <https://www.dcri.org/about-us/conflict-of-interest>. Hamm reports personal fees from GSK, during the conduct of the study; and personal fees from BRAHMS, outside the submitted work. The remaining authors have no disclosures to report.

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# **SUPPLEMENTAL MATERIAL**

## Data S1.

### TRILOGY ACS Adjustment Models

#### TRILOGY ACS Efficacy Adjustment Models

The TRILOGY ACS efficacy outcome adjustment models were constructed using a comprehensive list of patient characteristics and risk factors selected based on clinical knowledge (for a complete list, see the table below). Missing values were imputed using a multiple imputation approach that applies an MCMC method to create a monotone missing pattern and then uses a multivariate normal distribution to impute missing values. The imputation method replaces each missing value with a representative sample of plausible values by creating  $m$  complete data sets. As a result, the uncertainty due to the missingness is appropriately accounted for and analyses on the imputed data result in valid statistical inference. The  $m$  complete data sets can be analyzed using standard statistical procedures; the results are then aggregated across all simulated data sets. In this work,  $m$  was taken to be 25. Because a comparison of descriptive statistics from the first complete data set and the aggregation of the 25 complete data sets revealed negligible differences, only the first complete data set was used when fitting the adjustment for ease of computation. When fitting the adjustment model, the proportional hazards assumption was checked for each covariate and the linearity assumption was checked for each continuous covariate at alpha-level 0.05. If the proportional hazard assumption was violated, an interaction of the variable with log-transformed time was included in the model. If the linearity assumption was violated, a restricted cubic spline was used to approximate the non-linear relationship of the variable with the outcome. All analyses were performed using SAS 9.3 (SAS Institute Inc., Cary, NC) and R 2.14.1 (R Foundation for Statistical Computing, Vienna, Austria).

Table S4 details the composition of each adjustment model.

#### TRILOGY ACS Bleeding Adjustment Models

The TRILOGY ACS bleeding outcome adjustment models were constructed using a comprehensive list of patient characteristics and risk factors selected based on clinical knowledge (for a complete list, see Table S4). Missing values were imputed using a multiple imputation approach that applies an MCMC method to create a monotone missing pattern and then uses a multivariate normal distribution to impute missing values. The imputation method replaces each missing value with a representative sample of plausible values by creating  $m$  complete data sets. As a result, the uncertainty due to the missingness is appropriately accounted for and analyses on the imputed data result in valid statistical inference. The  $m$  complete data sets can be analyzed using standard statistical procedures; the results are then aggregated across all simulated data sets. In this work,  $m$  was taken to be 25. Because a comparison of descriptive statistics from the first complete data set and the aggregation of the 25 complete data sets revealed negligible differences, only the first complete data set was used when fitting the adjustment for ease of computation. When fitting the adjustment model, the proportional hazards assumption was checked for each covariate and the linearity assumption was checked for each continuous covariate at alpha-level 0.05. If the proportional hazard assumption was violated, an interaction of the variable with time was included in the model. If the linearity assumption was violated, a restricted cubic spline was used to approximate the non-linear relationship of the variable with the outcome. All analyses were performed using SAS 9.3 (SAS Institute Inc., Cary, NC) and R 3.0.2 (R Foundation for Statistical Computing, Vienna, Austria)

**Table S1.** Censoring scheme for the primary endpoint (cardiovascular death, myocardial infarction, or stroke) and for nonfatal secondary endpoints

| <b>Scenario</b>                             | <b>Censoring Rule</b>   |
|---|---|
| Completed final study visit                 | Final visit date (date of study termination / last contact on end-of-study case report form page unless type of visit = 95) |
| Death during follow-up                      | Adjudicated death date  |
| Withdrew consent                            | Date withdrew consent   |
| No final visit and did not withdraw consent | Last onsite or telephone visit date   |
| Vital status only alive                     | Last onsite or telephone visit date   |
| Vital status only died                      | Last onsite or telephone visit date   |

**Table S2.** Censoring scheme for cardiovascular death or for all-cause death

| <b>Scenario</b>  | <b>Censoring Rule</b>  |
|--|--|
| Completed final study visit                            | Final visit date (date of study termination / last contact on end-of-study page unless type of visit = 95) |
| Death during follow-up                                 | Adjudicated death date   |
| Withdrew consent                                       | Date withdrew consent  |
| No final visit and did not withdraw consent            | Last date when vital status is known   |
| Vital status only alive                                | Last date when vital status is known   |
| Vital status only died (without adjudication of a COD) | Death date (if available)  |
| Vital status only died (with adjudication of a COD)    | Adjudicated death date   |

**Table S3.** Descriptive statistics for troponin

|   | <b>Troponin I</b>      | <b>Troponin T</b>      | <b>Troponin</b>        |
|---|------------------------|------------------------|------------------------|
| N   | 4796                   | 2185                   | 6763                   |
| Median time (Q1, Q3) from initial to peak sample value* | 11.25<br>(7.00, 16.98) | 11.88<br>(7.00, 19.42) | 11.36<br>(7.00, 17.55) |
| Peak ratio percentiles                                  |                        |                        |                        |
| 100% Max  | 448222.22              | 6000.00                | 448222.22              |
| 99%   | 1082.00                | 318.18                 | 900.00                 |
| 98%   | 609.75                 | 237.86                 | 506.25                 |
| 97%   | 462.10                 | 165.00                 | 362.22                 |
| 96%   | 351.00                 | 132.14                 | 290.00                 |
| 95%   | 293.25                 | 116.00                 | 240.00                 |
| 90%   | 143.00                 | 59.46                  | 115.67                 |
| 75% Q3  | 36.45                  | 17.60                  | 28.90                  |
| 50% Median  | 5.50                   | 3.57                   | 5.00                   |
| 25% Q1  | 1.10                   | 0.90                   | 1.00                   |
| 0% Min  | <0.01                  | <0.01                  | <0.01                  |

\*Time (in hours) from initial to peak sample value within 48 hours after index presentation. Calculated from samples with non-missing initial and peak date/times.

**Table S4.** TRILOGY ACS Efficacy and Bleeding Adjustment Models

| <b>Characteristic</b>                             | <b>CVD/MI/Stroke</b> | <b>CVD</b> | <b>MI</b> | <b>Stroke</b> | <b>All-Cause Death</b> | <b>GUSTO Severe / LT / Moderate Bleeding (non-CABG)</b> | <b>TIMI Major/ Minor Bleeding (non-CABG)</b> |
|---|----------------------|------------|-----------|---------------|------------------------|---|--|
| Randomized Treatment                              | ✓                    | ✓          | ✓         | ✓             | ✓                      | -   | -  |
| Weight (kg)                                       | ✓                    | ✓          | ✓         | ✓             | ✓                      | ✓   | ✓  |
| Age (y)   | ✓                    | ✓          | ✓         | ✓             | ✓                      | ✓*  | ✓*   |
| Female sex  | ✓                    | ✓          | ✓         | ✓             | ✓                      | ✓   | ✓  |
| NSTEMI  | ✓                    | ✓          | ✓         | ✓             | ✓                      | ✓   | ✓  |
| Killip class I on presentation                    | ✓                    | ✓          | ✓         | ✓             | ✓                      | ✓   | ✓  |
| Time from presentation to study drug start (h)    | ✓                    | ✓          | ✓         | ✓             | ✓                      | ✓   | ✓  |
| <b>Cardiovascular risk factors:</b>               |                      |            |           |               |                        |   |  |
| Family history of CAD                             | ✓                    | ✓          | ✓         | ✓             | ✓                      | -   | -  |
| Hypertension                                      | ✓                    | ✓          | ✓         | ✓             | ✓                      | -   | -  |
| Hyperlipidemia                                    | ✓                    | ✓          | ✓         | ✓             | ✓                      | -   | -  |
| Diabetes Mellitus                                 | ✓                    | ✓          | ✓         | ✓             | ✓                      | -   | -  |
| Current/recent smoke                              | ✓                    | ✓          | ✓         | ✓             | ✓                      | -   | -  |
| Previous peptic ulcer disease                     | -                    | -          | -         | -             | -                      | ✓   | ✓  |
| <b>Cardiovascular disease history:</b>            |                      |            |           |               |                        |   |  |
| Previous myocardial infarction                    | ✓                    | ✓          | ✓         | ✓             | ✓                      | -   | -  |
| Previous PCI                                      | ✓                    | ✓          | ✓         | ✓             | ✓                      | -   | -  |
| Previous CABG                                     | ✓                    | ✓          | ✓         | ✓             | ✓                      | -   | -  |
| Previous peripheral artery disease                | ✓                    | ✓          | ✓         | ✓             | ✓                      | ✓   | ✓  |
| Previous atrial fibrillation                      | ✓                    | ✓          | ✓         | ✓             | ✓                      | -   | -  |
| Previous heart failure                            | ✓                    | ✓          | ✓         | ✓             | ✓                      | -   | -  |
| <b>At randomization:</b>                          |                      |            |           |               |                        |   |  |
| Systolic blood pressure (mmHg)                    | ✓*                   | ✓          | ✓         | ✓*            | ✓                      | ✓*  | ✓  |
| Heart rate (bpm)                                  | ✓                    | ✓          | ✓         | ✓*            | ✓                      | -   | -  |
| Heart rate*log(time)                              | ✓                    | ✓          | -         | -             | ✓                      | -   | -  |
| Clopidogrel stratum 2 – Started in hospital ≤72 h | ✓                    | ✓          | ✓         | ✓             | ✓                      | ✓   | ✓  |



| <b>Characteristic</b>                    | <b>CVD/MI/Stroke</b> | <b>CVD</b> | <b>MI</b> | <b>Stroke</b> | <b>All-Cause Death</b> | <b>GUSTO Severe / LT / Moderate Bleeding (non-CABG)</b> | <b>TIMI Major/ Minor Bleeding (non-CABG)</b> |
|--|----------------------|------------|-----------|---------------|------------------------|---|--|
| Clopidogrel stratum 3 – At home          | ✓                    | ✓          | ✓         | ✓             | ✓                      | ✓   | ✓  |
| Angiography performed?                   | ✓                    | ✓          | ✓         | ✓             | ✓                      | ✓   | ✓  |
| Hemoglobin (g/dL)                        | ✓                    | ✓          | ✓         | ✓             | ✓                      | ✓   | ✓  |
| Hemoglobin (g/dL)*(time)                 | -                    | -          | -         | -             | -                      | ✓   | -  |
| Creatinine (mg/dL)                       | ✓*                   | ✓          | ✓*        | ✓             | ✓                      | ✓   | ✓  |
| <b>Baseline concomitant medications:</b> |                      |            |           |               |                        |   |  |
| Beta-blocker                             | ✓                    | ✓          | ✓         | ✓             | ✓                      | ✓   | ✓  |
| ACE/ARB                                  | ✓                    | ✓          | ✓         | ✓             | ✓                      | -   | -  |
| Statin                                   | ✓                    | ✓          | ✓         | ✓             | ✓                      | -   | -  |
| PPI                                      | ✓                    | ✓          | ✓         | ✓             | ✓                      | -   | -  |
| <b>Region:</b>                           |                      |            |           |               |                        |   |  |
| East Asia                                | ✓                    | ✓          | ✓         | ✓             | ✓                      | -   | -  |
| Indian Subcontinent                      | ✓                    | ✓          | ✓         | ✓             | ✓                      | -   | -  |
| Latin America                            | ✓                    | ✓          | ✓         | ✓             | ✓                      | -   | -  |
| Mediterranean Basin                      | ✓                    | ✓          | ✓         | ✓             | ✓                      | -   | -  |
| North America                            | ✓                    | ✓          | ✓         | ✓             | ✓                      | -   | -  |
| Rest of World                            | ✓                    | ✓          | ✓         | ✓             | ✓                      | -   | -  |
| Western Europe/Scandinavia               | ✓                    | ✓          | ✓         | ✓             | ✓                      | -   | -  |

\*A restricted cubic spline was used to account for the non-linear relationship of the variable with the outcome.

**Table S5.** Baseline characteristics of included and excluded study patients

|   | Included (N=6763)    | Excluded (N=2563)    | P-value |
|---|----------------------|----------------------|---------|
| <b>Demographics</b>                             |                      |                      |         |
| Age, yrs  | 66.0 (59.0, 75.0)    | 64.0 (57.0, 71.0)    | <0.001  |
| Age ≥75 yrs                                     | 1696/6763 (25.1%)    | 387/2563 (15.1%)     | <0.001  |
| Weight, kg                                      | 76.0 (65.0, 88.0)    | 72.1 (62.0, 83.0)    | <0.001  |
| Weight <60 kg                                   | 906/6756 (13.4%)     | 495/2563 (19.3%)     | <0.001  |
| Female sex                                      | 2558/6763 (37.8%)    | 1092/2563 (42.6%)    | <0.001  |
| <b>Region</b>                                   |                      |                      |         |
| Central/Eastern Europe                          | 2061/6763 (30.5%)    | 1029/2563 (40.1%)    |         |
| East Asia                                       | 578/6763 (8.5%)      | 174/2563 (6.8%)      |         |
| Indian Subcontinent                             | 479/6763 (7.1%)      | 662/2563 (25.8%)     |         |
| Latin America                                   | 759/6763 (11.2%)     | 517/2563 (20.2%)     |         |
| Mediterranean Basin                             | 539/6763 (8.0%)      | 119/2563 (4.6%)      |         |
| North America                                   | 1242/6763 (18.4%)    | 29/2563 (1.1%)       |         |
| Western Europe/Scandinavia                      | 969/6763 (14.3%)     | 25/2563 (1.0%)       |         |
| Rest of World                                   | 136/6763 (2.0%)      | 8/2563 (0.3%)        |         |
| <b>Presentation characteristics</b>             |                      |                      |         |
| Hours from presentation to start of study drug  | 108.5 (65.5, 159.9)  | 105.1 (53.2, 157.4)  | 0.006   |
| Killip class II–IV on presentation              | 825/6759 (12.2%)     | 310/2559 (12.1%)     | 0.904   |
| Disease classification                          |                      |                      | <0.001  |
| Unstable angina/unknown                         | 1456/6763 (21.5%)    | 1350/2563 (52.7%)    |         |
| NSTEMI  | 5307/6763 (78.5%)    | 1213/2563 (47.3%)    |         |
| <b>Medical history</b>                          |                      |                      |         |
| Family history of CAD                           | 2008/5978 (33.6%)    | 510/2303 (22.1%)     | <0.001  |
| Hypertension                                    | 5549/6745 (82.3%)    | 2076/2558 (81.2%)    | 0.213   |
| Hyperlipidemia                                  | 4145/6515 (63.6%)    | 1102/2355 (46.8%)    | <0.001  |
| Diabetes mellitus                               | 2639/6752 (39.1%)    | 900/2554 (35.2%)     | <0.001  |
| Current/recent smoking*                         | 1444/6686 (21.6%)    | 400/2542 (15.7%)     | <0.001  |
| Prior MI  | 2924/6702 (43.6%)    | 1063/2544 (41.8%)    | 0.110   |
| Prior PCI                                       | 1914/6715 (28.5%)    | 511/2555 (20.0%)     | <0.001  |
| Prior CABG                                      | 1201/6745 (17.8%)    | 253/2558 (9.9%)      | <0.001  |
| Prior PAD                                       | 526/6632 (7.9%)      | 154/2523 (6.1%)      | 0.003   |
| Prior atrial fibrillation                       | 545/6569 (8.3%)      | 165/2532 (6.5%)      | 0.005   |
| Prior heart failure                             | 980/6711 (14.6%)     | 649/2554 (25.4%)     | <0.001  |
| Prior stroke                                    | 39/6732 (0.6%)       | 8/2555 (0.3%)        | 0.106   |
| <b>Baseline risk assessment</b>                 |                      |                      |         |
| GRACE risk score                                | 122.0 (106.0, 140.0) | 119.0 (103.0, 136.0) | <0.001  |
| Body mass index, kg/m <sup>2</sup>              | 27.2 (24.4, 30.8)    | 26.7 (23.8, 29.9)    | <0.001  |
| Systolic blood pressure, mmHg                   | 128.0 (117.0, 139.0) | 130.0 (120.0, 140.0) | <0.001  |
| Heart rate, bpm                                 | 69.0 (61.0, 76.0)    | 70.0 (62.0, 78.0)    | <0.001  |
| Hemoglobin, g/dL                                | 13.5 (12.4, 14.6)    | 13.6 (12.5, 14.7)    | 0.115   |
| Serum creatinine, mg/dL                         | 1.0 (0.8, 1.2)       | 1.0 (0.8, 1.2)       | <0.001  |
| <b>At randomization</b>                         |                      |                      |         |
| Treatment                                       |                      |                      | 0.186   |
| Prasugrel                                       | 3353/6763 (49.6%)    | 1310/2563 (51.1%)    |         |
| Clopidogrel                                     | 3410/6763 (50.4%)    | 1253/2563 (48.9%)    |         |
| Clopidogrel strata                              |                      |                      | <0.001  |
| 1 - No clopidogrel                              | 273/6763 (4.0%)      | 125/2562 (4.9%)      |         |
| 2 - Clopidogrel started in-hospital ≤72 hrs     | 4883/6763 (72.2%)    | 1630/2562 (63.6%)    |         |
| 3 - Home clopidogrel                            | 1607/6763 (23.8%)    | 807/2562 (31.5%)     |         |
| <b>Pre-randomization procedures</b>             |                      |                      |         |
| Angiography performed                           | 3320/6763 (49.1%)    | 531/2562 (20.7%)     | <0.001  |
| <b>Concomitant medications at randomization</b> |                      |                      |         |
| Aspirin daily dose                              |                      |                      |         |
| <100 mg   | 2174/6763 (32.1%)    | 935/2563 (36.5%)     | <0.001  |
| 100–250 mg                                      | 3537/6763 (52.3%)    | 1419/2563 (55.4%)    | 0.008   |
| >250 mg   | 627/6763 (9.3%)      | 46/2563 (1.8%)       | <0.001  |
| Beta-blocker                                    | 5416/6763 (80.1%)    | 1835/2563 (71.6%)    | <0.001  |
| ACE-I/ARB                                       | 5137/6763 (76.0%)    | 1890/2563 (73.7%)    | 0.027   |
| Statin  | 5730/6763 (84.7%)    | 2046/2563 (79.8%)    | <0.001  |
| Proton pump inhibitor                           | 1830/6763 (27.1%)    | 514/2563 (20.1%)     | <0.001  |

\*Smoking within 30 days of randomization.

Data presented as n/N (%) or median (25<sup>th</sup>, 75<sup>th</sup> percentile).

ACE-I/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; CABG, coronary artery bypass graft; CAD, coronary artery disease; MI, myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; PAD, peripheral artery disease; GRACE, Global Registry of Acute Coronary Events; PCI, percutaneous coronary intervention.

**Table S6.** Baseline characteristics according to 48-hour peak troponin level in Platelet Function Substudy participants

| Characteristic                                 | Peak troponin level as ratio of ULN |                      |                      |                     | P-value |
|--|-------------------------------------|----------------------|----------------------|---------------------|---------|
|  | <1x<br>(N=468)                      | 1x to <3x<br>(N=325) | 3x to <5x<br>(N=158) | ≥5x<br>(N=856)      |         |
| <b>Demographics</b>                            |                                     |                      |                      |                     |         |
| Age, yrs                                       | 66.0 (58.5, 72.0)                   | 67.0 (59.0, 75.0)    | 67.5 (60.0, 74.0)    | 66.0 (59.0, 74.0)   | 0.089   |
| Age ≥75  | 85/468 (18.2%)                      | 86/325 (26.5%)       | 39/158 (24.7%)       | 200/856 (23.4%)     | 0.034   |
| Weight, kg                                     | 75.0 (65.0, 86.0)                   | 78.0 (65.0, 90.0)    | 77.1 (67.0, 90.0)    | 75.0 (65.0, 87.1)   | 0.188   |
| Weight <60 kg                                  | 64/468 (13.7%)                      | 50/325 (15.4%)       | 15/158 (9.5%)        | 123/856 (14.4%)     | 0.344   |
| Sex  |                                     |                      |                      |                     | 0.096   |
| Female   | 196/468 (41.9%)                     | 132/325 (40.6%)      | 60/158 (38.0%)       | 303/856 (35.4%)     |         |
| Male   | 272/468 (58.1%)                     | 193/325 (59.4%)      | 98/158 (62.0%)       | 553/856 (64.6%)     |         |
| <b>Region</b>                                  |                                     |                      |                      |                     | <0.001  |
| Central/Eastern Europe                         | 206/468 (44.0%)                     | 93/325 (28.6%)       | 49/158 (31.0%)       | 144/856 (16.8%)     |         |
| East Asia                                      | 98/468 (20.9%)                      | 53/325 (16.3%)       | 16/158 (10.1%)       | 134/856 (15.7%)     |         |
| Indian Subcontinent                            | 50/468 (10.7%)                      | 29/325 (8.9%)        | 8/158 (5.1%)         | 58/856 (6.8%)       |         |
| Latin America                                  | 23/468 (4.9%)                       | 13/325 (4.0%)        | 17/158 (10.8%)       | 77/856 (9.0%)       |         |
| Mediterranean Basin                            | 15/468 (3.2%)                       | 8/325 (2.5%)         | 2/158 (1.3%)         | 26/856 (3.0%)       |         |
| North America                                  | 46/468 (9.8%)                       | 69/325 (21.2%)       | 40/158 (25.3%)       | 284/856 (33.2%)     |         |
| Western Europe/Scandinavia                     | 29/468 (6.2%)                       | 47/325 (14.5%)       | 17/158 (10.8%)       | 83/856 (9.7%)       |         |
| Rest of World                                  | 1/468 (0.2%)                        | 13/325 (4.0%)        | 9/158 (5.7%)         | 50/856 (5.8%)       |         |
| <b>Presentation characteristics</b>            |                                     |                      |                      |                     |         |
| Hours from presentation to start of study drug | 86.9 (44.8, 144.2)                  | 102.3 (68.2, 151.6)  | 122.2 (73.5, 166.3)  | 120.2 (70.5, 169.1) | <0.001  |
| Killip class II–IV on presentation             | 40/467 (8.6%)                       | 37/325 (11.4%)       | 24/158 (15.2%)       | 117/856 (13.7%)     | 0.029   |
| Disease classification                         |                                     |                      |                      |                     | <0.001  |
| Unstable angina/unknown                        | 382/468 (81.6%)                     | 41/325 (12.6%)       | 0/158 (0.0%)         | 0/856 (0.0%)        |         |
| NSTEMI   | 86/468 (18.4%)                      | 284/325 (87.4%)      | 158/158 (100.0%)     | 856/856 (100.0%)    |         |
| <b>Medical history</b>                         |                                     |                      |                      |                     |         |
| Family history of CAD                          | 108/395 (27.3%)                     | 107/291 (36.8%)      | 58/140 (41.4%)       | 300/788 (38.1%)     | 0.001   |
| Hypertension                                   | 391/465 (84.1%)                     | 269/324 (83.0%)      | 142/158 (89.9%)      | 690/854 (80.8%)     | 0.036   |
| Hyperlipidemia                                 | 224/414 (54.1%)                     | 205/309 (66.3%)      | 96/147 (65.3%)       | 550/832 (66.1%)     | <0.001  |
| Diabetes mellitus                              | 175/468 (37.4%)                     | 136/325 (41.8%)      | 66/158 (41.8%)       | 319/855 (37.3%)     | 0.391   |
| Current/recent smoking*                        | 69/460 (15.0%)                      | 61/321 (19.0%)       | 32/156 (20.5%)       | 226/848 (26.7%)     | <0.001  |
| Prior MI                                       | 200/467 (42.8%)                     | 146/323 (45.2%)      | 69/155 (44.5%)       | 366/850 (43.1%)     | 0.897   |
| Prior PCI                                      | 141/468 (30.1%)                     | 118/323 (36.5%)      | 40/158 (25.3%)       | 202/852 (23.7%)     | <0.001  |
| Prior CABG                                     | 59/467 (12.6%)                      | 56/325 (17.2%)       | 23/158 (14.6%)       | 155/854 (18.1%)     | 0.062   |
| Prior PAD                                      | 14/463 (3.0%)                       | 25/319 (7.8%)        | 13/156 (8.3%)        | 61/834 (7.3%)       | 0.007   |
| Prior atrial fibrillation                      | 57/452 (12.6%)                      | 32/320 (10.0%)       | 12/153 (7.8%)        | 70/840 (8.3%)       | 0.078   |
| Prior heart failure                            | 117/462 (25.3%)                     | 55/319 (17.2%)       | 24/156 (15.4%)       | 115/848 (13.6%)     | <0.001  |
| Prior stroke                                   | 2/467 (0.4%)                        | 1/322 (0.3%)         | 3/157 (1.9%)         | 5/851 (0.6%)        | 0.203   |

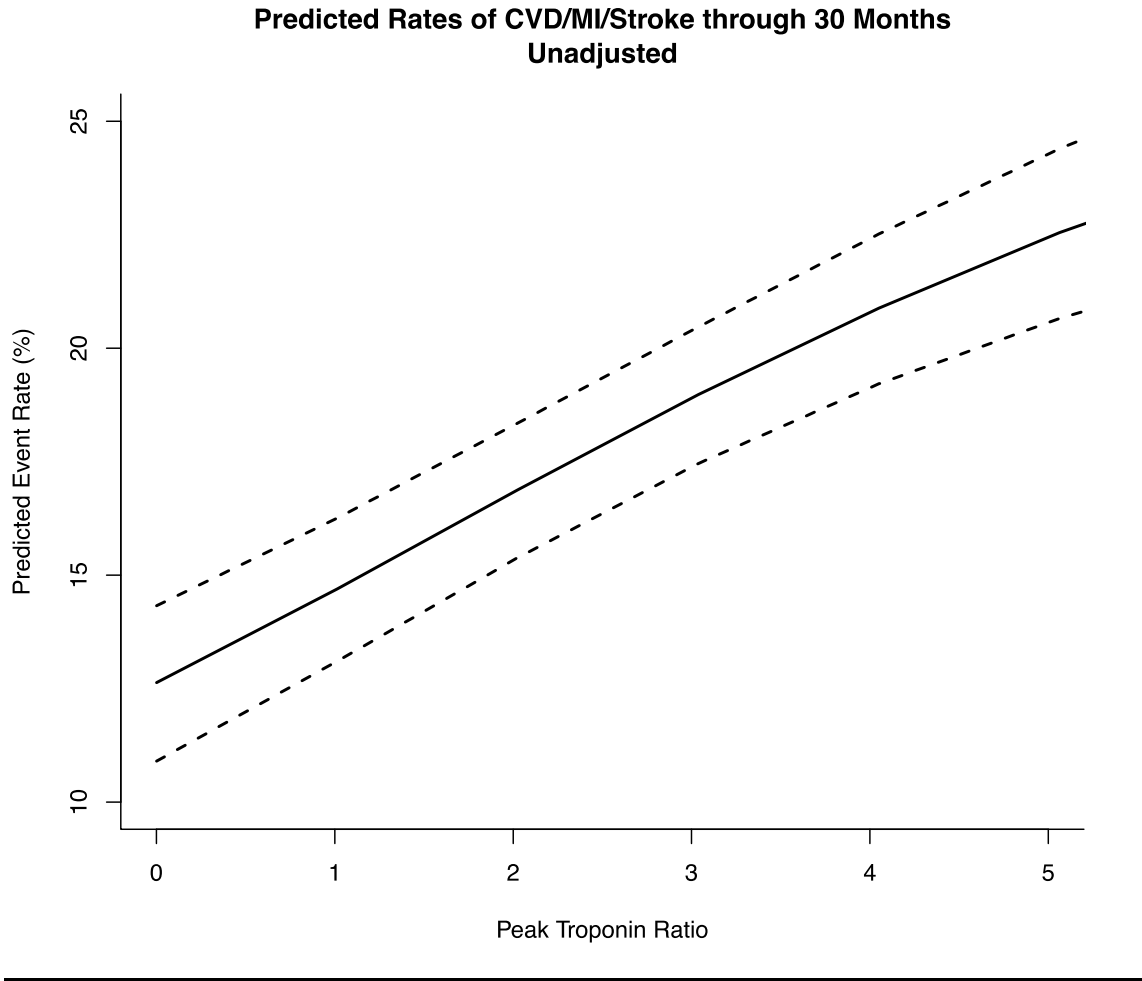
| Characteristic                                  | Peak troponin level as ratio of ULN |                      |                      |                      | P-value |
|---|-------------------------------------|----------------------|----------------------|----------------------|---------|
|   | <1x<br>(N=468)                      | 1x to <3x<br>(N=325) | 3x to <5x<br>(N=158) | ≥5x<br>(N=856)       |         |
| <b>Baseline risk assessment</b>                 |                                     |                      |                      |                      |         |
| GRACE risk score                                | 118.0 (101.0, 134.0)                | 124.0 (106.0, 143.0) | 130.0 (112.0, 144.0) | 123.0 (108.0, 143.0) | <0.001  |
| Body mass index, kg/m <sup>2</sup>              | 26.7 (24.2, 30.5)                   | 27.0 (24.1, 31.1)    | 27.5 (24.7, 32.0)    | 27.0 (24.2, 30.6)    | 0.235   |
| Systolic blood pressure, mmHg                   | 130.0 (120.0, 140.0)                | 130.0 (118.0, 140.0) | 126.5 (115.0, 136.0) | 124.0 (110.0, 135.0) | <0.001  |
| Heart rate, bpm                                 | 68.0 (61.0, 75.0)                   | 68.0 (60.0, 75.0)    | 68.0 (62.0, 77.0)    | 70.0 (62.0, 77.0)    | 0.061   |
| Hemoglobin, g/dL                                | 13.8 (12.8, 14.7)                   | 13.4 (12.4, 14.5)    | 13.6 (12.5, 14.9)    | 13.6 (12.5, 14.7)    | 0.042   |
| Serum creatinine, mg/dL                         | 1.0 (0.8, 1.1)                      | 1.0 (0.8, 1.2)       | 1.0 (0.8, 1.2)       | 1.0 (0.8, 1.2)       | 0.008   |
| <b>At randomization</b>                         |                                     |                      |                      |                      |         |
| Treatment                                       |                                     |                      |                      |                      | 0.577   |
| Prasugrel                                       | 233/468 (49.8%)                     | 158/325 (48.6%)      | 69/158 (43.7%)       | 423/856 (49.4%)      |         |
| Clopidogrel                                     | 235/468 (50.2%)                     | 167/325 (51.4%)      | 89/158 (56.3%)       | 433/856 (50.6%)      |         |
| Clopidogrel strata                              |                                     |                      |                      |                      | <0.001  |
| 1 - No clopidogrel                              | 28/468 (6.0%)                       | 9/325 (2.8%)         | 8/158 (5.1%)         | 33/856 (3.9%)        |         |
| 2 - Clopidogrel started in-hospital ≤72 hrs     | 255/468 (54.5%)                     | 217/325 (66.8%)      | 119/158 (75.3%)      | 686/856 (80.1%)      |         |
| 3 - Home clopidogrel                            | 185/468 (39.5%)                     | 99/325 (30.5%)       | 31/158 (19.6%)       | 137/856 (16.0%)      |         |
| <b>Pre-randomization procedures</b>             |                                     |                      |                      |                      |         |
| Angiography performed                           | 136/468 (29.1%)                     | 155/325 (47.7%)      | 77/158 (48.7%)       | 475/856 (55.5%)      | <0.001  |
| <b>Concomitant medications at randomization</b> |                                     |                      |                      |                      |         |
| Aspirin daily dose                              |                                     |                      |                      |                      |         |
| <100 mg   | 180/468 (38.5%)                     | 156/325 (48.0%)      | 77/158 (48.7%)       | 342/856 (40.0%)      | 0.009   |
| 100–250 mg                                      | 242/468 (51.7%)                     | 118/325 (36.3%)      | 58/158 (36.7%)       | 326/856 (38.1%)      | <0.001  |
| >250 mg   | 17/468 (3.6%)                       | 23/325 (7.1%)        | 16/158 (10.1%)       | 119/856 (13.9%)      | <0.001  |
| Beta-blocker                                    | 363/468 (77.6%)                     | 257/325 (79.1%)      | 116/158 (73.4%)      | 674/856 (78.7%)      | 0.479   |
| ACE-I/ARB                                       | 330/468 (70.5%)                     | 242/325 (74.5%)      | 118/158 (74.7%)      | 615/856 (71.8%)      | 0.566   |
| Statin  | 367/468 (78.4%)                     | 278/325 (85.5%)      | 132/158 (83.5%)      | 720/856 (84.1%)      | 0.028   |
| Proton pump inhibitor                           | 115/468 (24.6%)                     | 81/325 (24.9%)       | 43/158 (27.2%)       | 215/856 (25.1%)      | 0.930   |

\*Smoking within 30 days of randomization.

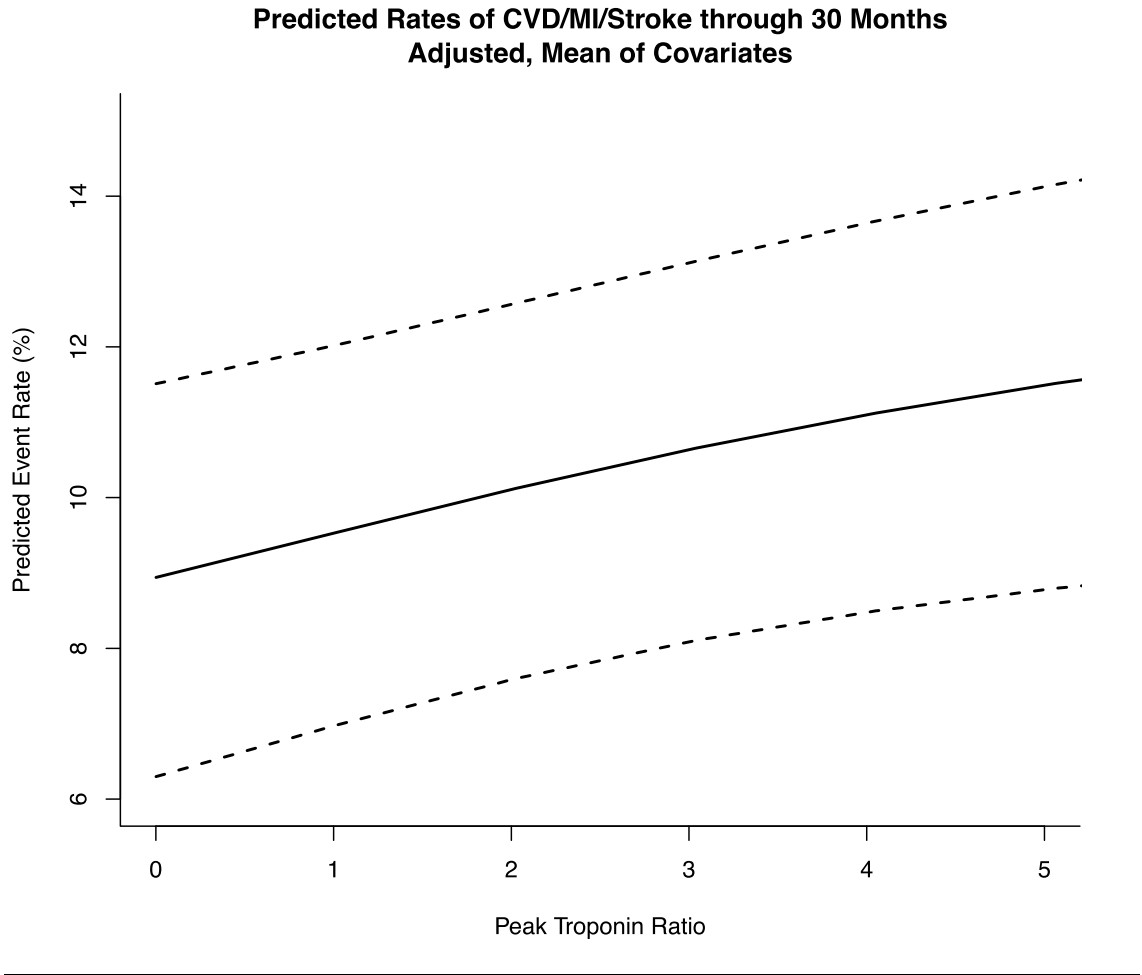
Data presented as n/N (%) or median (25th, 75th percentile).

ACE-I/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; CABG, coronary artery bypass graft; CAD, coronary artery disease; MI, myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; PAD, peripheral artery disease; GRACE, Global Registry of Acute Coronary Events; PCI, percutaneous coronary intervention.

**Figure S1A.** Estimated spline transformation and 95% confidence interval for the relationship of troponin elevation and unadjusted rates of cardiovascular death, MI, or stroke through 30 months



**Figure S1B.** Estimated spline transformation and 95% confidence interval for the relationship of troponin elevation and adjusted rates of cardiovascular death, MI, or stroke through 30 months



**Figure S2.** Estimated spline transformation and 95% confidence interval for the relationship of troponin elevation and adjusted rates of cardiovascular death, myocardial infarction, or stroke through 30 months stratified by treatment

