Flinders
UNIVERSITY

Outcomes of Patients Receiving Downstream Revascularization after Initial Medical Management for Non–ST-Segment Elevation Acute Coronary Syndromes (From the TRILOGY ACS Trial)

Tomoya T. Hinohara MD , Matthew T. Roe MD, MHS , Harvey D. White DSc , Keith A.A. Fox MB, ChB , Deepak L. Bhatt MD, MPH , Christian Hamm MD , Paul A. Gurbel MD , Philip E. Aylward MB, ChB, PhD , Stephen D. Wiviott MD , Kurt Huber MD , Megan L. Neely PhD , E. Magnus Ohman MB, ChB

PII: S0002-9149(18)31419-X
DOI: 10.1016/j.amjcard.2018.06.052
Reference: AJC 23411

To appear in: *The American Journal of Cardiology*

Received date: 26 March 2018
Revised date: 20 June 2018
Accepted date: 26 June 2018

Please cite this article as: Tomoya T. Hinohara MD , Matthew T. Roe MD, MHS , Harvey D. White DSc , Keith A.A. Fox MB, ChB , Deepak L. Bhatt MD, MPH , Christian Hamm MD , Paul A. Gurbel MD , Philip E. Aylward MB, ChB, PhD , Stephen D. Wiviott MD , Kurt Huber MD , Megan L. Neely PhD , E. Magnus Ohman MB, ChB , Outcomes of Patients Receiving Downstream Revascularization after Initial Medical Management for Non–ST-Segment Elevation Acute Coronary Syndromes (From the TRILOGY ACS Trial), *The American Journal of Cardiology* (2018), doi: 10.1016/j.amjcard.2018.06.052

Outcomes of Patients Receiving Downstream Revascularization after Initial Medical Management for Non–ST-Segment Elevation Acute Coronary Syndromes (From the TRILOGY ACS Trial)

Tomoya T. Hinohara, MD,[a] Matthew T. Roe, MD, MHS,[b,c] Harvey D. White, DSc,[d] Keith A.A. Fox, MB, ChB,[e] Deepak L. Bhatt, MD, MPH,[f,g] Christian Hamm, MD,[h] Paul A. Gurbel, MD,[i] Philip E. Aylward, MB, ChB, PhD,[j] Stephen D. Wiviott, MD,[f] Kurt Huber, MD,[k] Megan L. Neely, PhD,[c] E. Magnus Ohman, MB, ChB[b,c]

[a]Division of General Internal Medicine, [b]Division of Cardiology, Department of Medicine, [c]Duke Clinical Research Institute, Duke University School of Medicine, Durham, NC; [d]Green Lane Cardiovascular Service, Auckland City Hospital, New Zealand; [e]Centre for Cardiovascular Science, University of Edinburgh, Edinburgh, UK; [f]Cardiovascular Division, Brigham and Women's Hospital, Harvard Medical School, Boston, MA; [g]VA Boston Healthcare System, Boston, MA; [h]Kerckhoff Heart and Thoraxcenter, Bad Nauheim, Germany; [i]Sinai Center for Thrombosis Research, Sinai Hospital of Baltimore, Baltimore, MD; [j]South Australian Health and Medical Research Institute, Flinders University Medical Centre, Adelaide, SA, Australia; [k]Third Department of Medicine, Cardiology and Intensive Care Medicine, Wilhelminenhospital, and Sigmund Freud University, Medical School, Vienna, Austria.

Running head: Downstream revascularization in medically managed NSTE ACS

Corresponding Author: E. Magnus Ohman, Duke University Medical Center, Box 3126 DUMC, Durham, NC 27710. Phone: (919)-681-2069; Fax: (919)-681-6443. Email: ohman001@mc.duke.edu.

ABSTRACT

Patients with non–ST-segment elevation acute coronary syndromes (NSTE ACS) are sometimes treated with medical management alone rather than an invasive strategy. Among those medically managed without revascularization and discharged, a proportion will require revascularization later on, but little is known about this population. In TRILOGY ACS, 9326 patients with NSTE ACS who were selected for medical management alone were randomized to treatment with prasugrel or clopidogrel and discharged without revascularization. Patient characteristics and ischemic and bleeding outcomes through 30 months were compared between patients who underwent downstream revascularization after the index hospitalization and those who did not. A total of 662 patients (7.1%) underwent later revascularization by percutaneous coronary intervention (73.1%), coronary artery bypass graft surgery (26.4%), or both (0.5%). Median time to revascularization was 121 days (25^{th}, 75^{th} percentiles: 41, 326). Revascularized patients were younger, more likely to be male, and had higher rates of hyperlipidemia, diabetes mellitus, prior myocardial infarction (MI), and prior revascularization compared with those not revascularized. Europe and North America had the highest rates of revascularization. During the follow-up period, those who underwent revascularization had a higher rate of the composite outcome of cardiovascular death, MI, or stroke occurring after revascularization compared with those not revascularized (hazard ratio [HR] 2.73 [95% confidence interval (CI) 2.21-3.38], p<0.001) as well as a higher rate of each of the individual outcomes. Major bleeding was also higher among those who underwent revascularization (GUSTO severe or life-threatening: HR 2.61 [95% CI 1.02-6.67], p=0.045; TIMI major: HR 2.24 [95% CI 1.12-4.48], p=0.022). There was no evidence that bleeding and ischemic outcomes varied by treatment with clopidogrel versus prasugrel. In conclusion, among patients initially medically managed after NSTE ACS, a small proportion later require revascularization and have a high rate of ischemic and major bleeding outcomes compared with those not requiring downstream revascularization.

Key words: acute coronary syndrome; dual antiplatelet therapy; revascularization

INTRODUCTION

Up to one-third of patients with non–ST-segment elevation acute coronary syndromes (NSTE ACS) are managed medically.[1] Very little is known, however, about patients who are initially medically managed, discharged, and subsequently require revascularization. A substudy of the PLATO trial that examined patients planned for non-invasive management found that patients receiving ticagrelor and clopidogrel had similar rates of downstream percutaneous coronary intervention (PCI) (ticagrelor 28.4% vs. clopidogrel 29.7%). Furthermore, the incidence of the composite outcome of cardiovascular death, myocardial infarction (MI), and stroke was lower with ticagrelor than with clopidogrel (12.0% vs. 14.3%, p=0.04).[2] TRILOGY ACS was a prospective randomized trial that evaluated the use of either clopidogrel or prasugrel for patients with NSTE ACS who were treated with medical management alone and did not undergo revascularization during the index hospitalization. The study showed no difference in the primary outcome of cardiovascular death, MI, or stroke up to a median of 17 months after the initial ACS event with either therapy.[3] Among patients medically managed for NSTE ACS with either prasugrel or clopidogrel and discharged without revascularization during the enrollment hospitalization, we sought to describe differences in clinical characteristics and outcomes between those who received downstream revascularization with either PCI or CABG compared with those who did not.

METHODS

This descriptive post-hoc analysis utilized data collected as part of the TRILOGY ACS study. TRILOGY ACS was a randomized, double-blind trial conducted at >800 sites worldwide and included 9326 patients. The study design has been described previously.[4] Briefly, patients presenting with NSTE ACS were eligible if they were selected for a treatment strategy of medical management alone without revascularization. Participants were randomly assigned to receive either prasugrel or clopidogrel in addition to aspirin. None of the patients underwent revascularization during the enrollment hospitalization. The primary ischemic end point was a composite of cardiovascular death, nonfatal MI, or nonfatal stroke at 30 months. Bleeding outcomes included bleeding defined by the Global Use of

Strategies to Open Occluded Coronary Arteries (GUSTO) not related to CABG and Thrombolysis In Myocardial Infarction (TIMI) criteria not related to CABG. The current study analyzed the subset of patients who underwent revascularization after the index hospitalization (n=662) as well as those who never underwent revascularization during the follow-up period (n=8664).

Two analyses examining ischemic and bleeding outcomes by post-index revascularization status were performed. The first was descriptive and reported the occurrence of outcomes in patients who underwent revascularization and those who never underwent revascularization; and among those who did undergo revascularization, we also reported the number of outcomes occurring on/before versus after the revascularization. In order to examine the association between revascularization status and outcomes, survival analysis was performed using a Cox proportional hazards regression model with a time-dependent binary indicator for the occurrence of post-index revascularization. Specifically, the time-dependent indicator turns from 0 to 1 at the time of the revascularization and remains 1 for the duration of the patient's follow-up. As such, only first events occurring after revascularization were attributed to the revascularization group. For example, if a patient's first MI occurred after revascularization, the MI event would be included in the revascularization group. On the other hand, if a patient's first MI occurred before revascularization, the MI event would not be included in the revascularization group. Thus, this analysis examined the event risk after revascularization in those who had not yet experienced the event and were therefore still at risk for the event. The Kaplan-Meier method was used to provide a visual description of the relationship between post-index revascularization and the primary trial end point. For the no revascularization group, the Kaplan-Meier curve starts at the time of randomization. For the revascularization group, the curve starts at the time of revascularization, which is the risk period of interest.

All statistical tests were conducted at the nominal 0.05 significance level. Statistical analyses were performed with SAS version 9.2 or higher (SAS Institute Inc, Cary, NC).

RESULTS

Of 9326 patients, 662 (7.1%) received downstream revascularization (Table 1). The baseline characteristics of the revascularization and no revascularization groups are shown in Table 2. Among those who underwent revascularization, 484 (73.1%) patients received PCI, 175 (26.4%) received CABG, and 3 (0.5%) received both (Table 1). The distribution of time to revascularization is shown in Figure 1.

Patients who later underwent revascularization (Table 2) were more likely to be male, younger, and have higher rates of hyperlipidemia, diabetes mellitus, tobacco use, prior MI, and prior revascularization compared with those not revascularized. The index event leading to inclusion into the trial was more likely non–ST-segment elevation MI for those in revascularization group as compared to the no revascularization group (77.2% vs. 69.4%; p<0.001). Among the geographic regions, Europe and North America had the highest rates of downstream revascularization.

Approximately 40% of the total population (n=3851) had baseline angiography performed during the index event prior to randomization. The revascularization group had more extensive coronary artery disease, including 2-vessel (29.4% vs. 21.5%; p<0.001) and 3-vessel (32.3% vs. 21.6%; p<0.001) disease compared with the no revascularization group.

The rates of ischemic and bleeding end points relative to the revascularization status and treatment arm are shown in Table 3. The revascularization group had a higher rate of the composite ischemic end point of cardiovascular death, nonfatal MI, or nonfatal stroke compared with the no revascularization group (41.1% vs. 11.5%). In the revascularization group, the composite ischemic end point occurred on or before revascularization in 65.4% of patients and after revascularization in 34.6%. The difference in the composite end point was predominantly due to a higher rate of MI in the revascularization group (40.0% vs. 10.7%), while the rates of cardiovascular death, all-cause death, and stroke were similar between the 2 groups. Of those who had an MI, 66.8% of the MIs occurred on or before revascularization. The revascularization group had a higher rate of GUSTO severe, life-threatening, or moderate bleeding compared to the no revascularization group (2.9% vs. 1.6%). In the

revascularization group, >60% of the bleeding events occurred after revascularization. The differences in ischemic and bleeding outcomes by revascularization status did not vary by treatment arm.

In order to better assess the association of revascularization with ischemic and bleeding outcomes, analysis was performed to compare outcomes occurring only after revascularization (Table 4). During the 30-month follow-up period, the revascularization group had a higher rate of the composite ischemic end point compared with the no revascularization group (hazard ratio [HR] 2.73 [95% confidence interval (CI) 2.21-3.38], p<0.001). The revascularization group had a higher rate of myocardial infarction (HR 2.70 [2.17-3.37], p<0.001), all-cause death (HR 1.71 [1.31-2.23], p<0.001), cardiovascular death (HR 1.64 [1.21-2.23], p=0.001), and nonfatal stroke (HR 2.00 [1.07-3.75], p=0.030) compared with the no revascularization group. A Kaplan-Meier curve for the primary composite ischemic end point during the follow-up period is shown in Figure 2.

The revascularization group also had a higher rate of bleeding events according to the GUSTO criteria for severe or life-threatening bleeding (HR 2.61 [95% CI 1.02-6.67], p=0.045) and severe, life-threatening, or moderate bleeding (HR 2.42 [1.39-4.23], p=0.002) as well as bleeding according to TIMI major (HR 2.24 [1.12-4.48], p=0.022) and TIMI major or minor bleeding criteria (HR 2.03 [1.15-3.60], p=0.015) compared with the no revascularization group (Table 4). The differences in ischemic and bleeding outcomes by revascularization status did not vary by treatment arm.

DISCUSSION

In the TRILOGY ACS trial, a small subset of patients medically managed for NSTE ACS later required downstream revascularization. The revascularization group differed in baseline characteristics compared with the no revascularization group and had higher rates of ischemic and major bleeding events. This study highlights the need to better identify this vulnerable population and to determine the optimal management strategy.

Among patients medically managed for NSTE ACS, the rate of downstream revascularization over time is unclear. In a meta-analysis of randomized trials including FRISC II and RITA 3 comparing

routine versus selective invasive strategies in patients with NSTE ACS, 24% of patients in the selective invasive group underwent revascularization after hospital discharge by the end of 1 year and 30.2% by the end of 3 years.[5] In a separate meta-analysis of randomized trials comparing early invasive versus conservative treatment in patients with NSTE ACS, 17.7% of patients in the conservative group underwent revascularization within 12 months after hospital discharge.[6] The rate of revascularization of 7.1% over 30 months in this study is substantially lower than rates reported from prior studies. The rate observed in this study may not mimic those in practice, as they are lower than expected; yet, the event rate is high, suggesting that we may find better approaches to manage these patients.

This study demonstrates that the revascularization group is at significantly higher risk for ischemic and bleeding events compared to the no revascularization group. The higher rate of the composite ischemic outcome in the revascularization group was primarily due to the difference in rates of MI when ischemic events were measured, regardless of its timing relative to revascularization. However, a large proportion of the ischemic outcomes, particularly MI, occurred before or at the time of revascularization. When first-onset ischemic events occurring only after revascularization were examined, the hazard rate of the composite ischemic end point as well as each of its individual components was significantly higher in the revascularization group compared to the no revascularization group. In the RITA 3 trial, the interventional strategy reduced the odds of MI or death by 56%, with the most marked reduction seen in high-risk patients.[7] It is plausible that the revascularization group would have benefited from revascularization during the index event, rather than later on. Further research to characterize this poorly studied subgroup is needed to identify patients for whom invasive management should be strongly considered despite factors that may compel physicians to opt for a conservative approach.

Angiographic data suggest greater coronary artery disease burden in the revascularization group, predisposing them to ischemic symptoms and events. Among the 40% of patients with coronary angiography prior to randomization, the revascularization group had significantly higher rates of 2- or 3-vessel coronary artery disease. However, patient characteristics and outcomes differed between those who did and did not receive angiography;[8] therefore, these angiographic findings cannot be generalized to

those without angiography. Among patients who had at least 1 lesion with >50% stenosis, the reason for not pursuing revascularization in 66% of the cases was coronary anatomy judged to be unsuitable for PCI.[8]

The rates of both minor and major bleeding events were greater in the revascularization group compared with the no revascularization group. The timing of these bleeding events suggests that they likely occurred in the setting of anticoagulation for ACS and procedure-related bleeding.

In each of the comparisons of ischemic and bleeding outcomes, there were no differences in outcomes by treatment with clopidogrel versus prasugrel, both within and between the revascularization and no revascularization groups.

Several limitations to this study should be noted. This is a secondary analysis and is limited by the biases of a non-randomized design. Additionally, the analysis comparing clopidogrel versus prasugrel by revascularization status was not powered to assess safety and efficacy; therefore, the results should be interpreted with caution and should be considered exploratory in nature. Finally, information on the indication for revascularization was not collected, which may have provided additional insights into the worse outcomes seen in the revascularization group.

In conclusion, among patients initially medically managed after NSTE ACS, a small proportion later require revascularization and have higher rates of ischemic and bleeding outcomes compared with those not revascularized. No differences in ischemic or bleeding outcomes were seen when stratified by treatment with either prasugrel or clopidogrel. Further studies are needed to better identify this vulnerable population and to determine the optimal management strategy.

Acknowledgments

We are indebted to Elizabeth Cook and Morgan deBlecourt for their editorial assistance and expertise.

Funding Sources

The TRILOGY ACS study was supported by Daiichi Sankyo Incorporated and Eli Lilly and Company. The study sponsors had no role in the conception or design of this manuscript, which was funded internally by the Duke Clinical Research Institute.

1. Chan MY, Mahaffey KW, Sun LJ, Pieper KS, White HD, Aylward PE, Ferguson JJ, Califf RM, Roe MT. Prevalence, predictors, and impact of conservative medical management for patients with non-ST-segment elevation acute coronary syndromes who have angiographically documented significant coronary disease. *JACC Cardiovasc Interv* 2008;1:369-378.
2. James SK, Roe MT, Cannon CP, Cornel JH, Horrow J, Husted S, Katus H, Morais J, Steg PG, Storey RF, Stevens S, Wallentin L, Harrington RA; PLATO Study Group. Ticagrelor versus clopidogrel in patients with acute coronary syndromes intended for non-invasive management: substudy from prospective randomised PLATelet inhibition and patient Outcomes (PLATO) trial. *BMJ* 2011;342:d3527.
3. Roe MT, Armstrong PW, Fox KA, White HD, Prabhakaran D, Goodman SG, Cornel JH, Bhatt DL, Clemmensen P, Martinez F, Ardissino D, Nicolau JC, Boden WE, Gurbel PA, Ruzyllo W, Dalby AJ, McGuire DK, Leiva-Pons JL, Parkhomenko A, Gottlieb S, Topacio GO, Hamm C, Pavlides G, Goudev AR, Oto A, Tseng CD, Merkely B, Gasparovic V, Corbalan R, Cinteză M, McLendon RC, Winters KJ, Brown EB, Lokhnygina Y, Aylward PE, Huber K, Hochman JS, Ohman EM; TRILOGY ACS Investigators. Prasugrel versus clopidogrel for acute coronary syndromes without revascularization. *N Engl J Med* 2012;367:1297-1309.
4. Chin CT, Roe MT, Fox KA, Prabhakaran D, Marshall DA, Petitjean H, Lokhnygina Y, Brown E, Armstrong PW, White HD, Ohman EM; TRILOGY ACS Steering Committee. Study design and rationale of a comparison of prasugrel and clopidogrel in medically managed patients with unstable angina/non-ST-segment elevation myocardial infarction: the TaRgeted platelet Inhibition to cLarify the Optimal strateGy to medicallY manage Acute Coronary Syndromes (TRILOGY ACS) trial. *Am Heart J* 2010;160:16-22.
5. Fox KA, Clayton TC, Damman P, Pocock SJ, de Winter RJ, Tijssen JG, Lagerqvist B, Wallentin L; FIR Collaboration. Long-term outcome of a routine versus selective invasive strategy in patients with non-ST-segment elevation acute coronary syndrome a meta-analysis of individual patient data. *J Am Coll Cardiol* 2010;55:2435-2345.

6. O'Donoghue M, Boden WE, Braunwald E, Cannon CP, Clayton TC, de Winter RJ, Fox KA, Lagerqvist B, McCullough PA, Murphy SA, Spacek R, Swahn E, Wallentin L, Windhausen F, Sabatine MS. Early invasive vs conservative treatment strategies in women and men with unstable angina and non-ST-segment elevation myocardial infarction: a meta-analysis. *JAMA* 2008;300:71-80.
7. Fox KA, Poole-Wilson P, Clayton TC, Henderson RA, Shaw TR, Wheatley DJ, Knight R, Pocock SJ. 5-year outcome of an interventional strategy in non-ST-elevation acute coronary syndrome: the British Heart Foundation RITA 3 randomised trial. *Lancet* 2005;366:914-920.
8. Wiviott SD, White HD, Ohman EM, Fox KA, Armstrong PW, Prabhakaran D, Hafley G, Lokhnygina Y, Boden WE, Hamm C, Clemmensen P, Nicolau JC, Menozzi A, Ruzyllo W, Widimsky P, Oto A, Leiva-Pons J, Pavlides G, Winters KJ, Roe MT, Bhatt DL. Prasugrel versus clopidogrel for patients with unstable angina or non-ST-segment elevation myocardial infarction with or without angiography: a secondary, prespecified analysis of the TRILOGY ACS trial. *Lancet* 2013;382:605-613.

Figure Legends

Figure 1. Distribution of Time to First Revascularization by Treatment Arm

Figure 2. Cumulative Kaplan-Meier Estimates of the Composite Ischemic End Points

Table 1. Frequency and Characterization of Revascularization in Overall and by Treatment Arm

Variable	Total Population (n=9326)	Prasugrel (n=4663)	Clopidogrel (n=4663)
Underwent revascularization			
At least 1	662 (7.1%)	342 (7.3%)	320 (6.9%)
Never	8664 (92.9%)	4321 (92.7%)	4343 (93.1%)
Type of first revascularization			
Percutaneous coronary intervention	484 (73.1%)	245 (71.6%)	239 (74.7%)
Coronary artery bypass grafting	175 (26.4%)	96 (28.1%)	79 (24.7%)
Both percutaneous coronary intervention and coronary artery bypass grafting	3 (0.5%)	1 (0.3%)	2 (0.6%)
Time to first revascularization, median (25^{th}, 75^{th} percentile) (days)	120.5 (41.0, 326.0)	104.5 (40.0, 307.0)	139.5 (42.0, 357.0)
Had event after revascularization*			
At least 1	289 (43.7%)	148 (43.3%)	141 (44.1%)
Never	373 (56.3%)	194 (56.7%)	179 (55.9%)

Data presented as no. (%), unless otherwise indicated.
*Events considered in this analysis: composite of cardiovascular death/myocardial infarction/stroke; cardiovascular death; all-cause death; myocardial infarction; stroke; GUSTO severe/life-threatening bleed; GUSTO severe/life-threatening/moderate bleed; TIMI major bleed; and TIMI major/minor bleed (all bleeding endpoints are non-CABG bleeds).

Table 2. Baseline Characteristics

Variable	Revascularization	P-Value

	Yes (n=662)	No (n=8664)	
Age (median 25th, 75th percentile) (years)	64.0 (58.0, 72.0)	66.0 (59.0, 74.0)	0.008
Age <70 years	541 (81.7%)	6702 (77.4%)	0.009
Women	213 (32.2%)	3437 (39.7%)	< 0.001
Weight (median, 25th, 75th percentile) (kilograms)	80.0 (70.0, 90.0)	75.0 (64.4, 86.0)	< 0.001
Weight <60 kilograms	55 (8.3%)	1346 (15.5%)	< 0.001
Unstable angina pectoris	151 (22.8%)	2655 (30.6%)	
Non-ST-segment elevation myocardial infarction	511 (77.2%)	6009 (69.4%)	
Killip class II–IV	87 (13.1%)	1048 (12.1%)	0.433
Geographic region			< 0.001
Central/Eastern Europe	236 (35.6%)	2854 (32.9%)	
East Asia	37 (5.6%)	715 (8.3%)	
Indian Subcontinent	31 (4.7%)	1110 (12.8%)	
Latin America	78 (11.8%)	1198 (13.8%)	
Mediterranean Basin	40 (6.0%)	618 (7.1%)	
North America	126 (19.0%)	1145 (13.2%)	
Western Europe/Scandinavia	104 (15.7%)	890 (10.3%)	
Rest of world	10 (1.5%)	134 (1.5%)	
Family history of coronary artery disease	224 (38.1%)	2294 (29.8%)	< 0.001
History of hypertension*	560 (84.7%)	7065 (81.8%)	0.056
History of hyperlipidemia*	453 (71.2%)	4794 (58.2%)	< 0.001
Diabetes mellitus	282 (42.7%)	3257 (37.7%)	0.011
Current or recent smoking	157 (24.0%)	1687 (19.7%)	0.008
Angiography for index event	262 (39.6%)	3589 (41.4%)	0.351
Extent of stenosis			< 0.001
Non-obstructive coronary artery disease	23 (9.0%)	566 (16.4%)	
1-vessel ≥50%	75 (29.4%)	1396 (40.5%)	
2-vessel ≥50%	75 (29.4%)	743 (21.5%)	
3-vessel ≥50%	82 (32.2%)	746 (21.6%)	
Creatinine clearance (median, 25th, 75th percentile) (milliliter per minute)	75.9 (57.8, 96.7)	72.5 (53.7, 96.1)	0.018

Variable	Revascularization: Yes (n=662)	Revascularization: No (n=8664)	P-Value
GRACE risk score (median, 25th, 75th percentile)	118.0 (104.0, 138.0)	122.0 (105.0, 139.0)	0.116
Prior myocardial infarction	310 (47.0%)	3677 (42.8%)	0.035
Prior percutaneous coronary intervention	240 (36.5%)	2185 (25.4%)	< 0.001
Prior coronary artery bypass grafting	240 (36.5%)	2185 (25.4%)	< 0.001
Prior heart failure	124 (18.8%)	1505 (17.5%)	0.399
Prior atrial fibrillation	34 (5.3%)	440 (5.2%)	0.956
Medications			
Clopidogrel strata			0.353
No use prior to index event	30 (4.5%)	368 (4.2%)	
Used for index event	446 (67.4%)	6067 (70.0%)	
Used prior to index event	186 (28.1%)	2228 (25.7%)	
Beta-blocker	548 (82.8%)	6703 (77.4%)	0.001
Angiotensin-converting enzyme inhibitor/angiotensin receptor blocker	515 (77.8%)	6512 (75.2%)	0.130
Statin	576 (87.0%)	7200 (83.1%)	0.009
Proton-pump inhibitor	191 (28.9%)	2153 (24.8%)	0.022
Aspirin dose (milligrams per day)			0.165
<100	196 (32.5%)	2786 (35.0%)	
100–250	350 (57.9%)	4567 (57.3%)	
>250	58 (9.6%)	615 (7.7%)	

Data presented as no. (%), unless otherwise indicated.
*Refer to TRILOGY ACS results for definitions.[4]

Table 3. First Ischemic and Bleeding Events by Revascularization Status, Timing of Event Relative to Revascularization, and Treatment Arm

	Revascularization			No Revascularization		
	Overall	**Prasugrel**	**Clopidogrel**	**Overall**	**Prasugrel**	**Clopidogrel**
	n=662	n=342	n=320	n=8664	n=4321	n=4343
Ischemic Endpoints						

	Revascularization			No Revascularization		
	Overall	**Prasugrel**	**Clopidogrel**	**Overall**	**Prasugrel**	**Clopidogrel**
Cardiovascular death/myocardial infarction/stroke	272 (41.1%)	139 (40.6%)	133 (41.6%)	997 (11.5%)	482 (11.2%)	515 (11.9%)
On or before revascularization	178 (26.9%)	92 (26.9%)	86 (26.9%)	---	---	---
After revascularization	94 (14.2%)	47 (13.7%)	47 (14.7%)	---	---	---
Cardiovascular death	49 (7.4%)	22 (6.4%)	27 (8.4%)	589 (6.8%)	286 (6.6%)	303 (7.0%)
On or before revascularization	3 (0.5%)	2 (0.6%)	1 (0.3%)	---	---	---
After revascularization	46 (6.9%)	20 (5.8%)	26 (8.1%)	---	---	---
All-cause death	63 (9.5%)	30 (8.8%)	33 (10.3%)	731 (8.4%)	355 (8.2%)	376 (8.7%)
On or before revascularization	3 (0.5%)	2 (0.6%)	1 (0.3%)	---	---	---
After revascularization	60 (9.0%)	28 (8.2%)	32 (10.0%)	---	---	---
Myocardial infarction	265 (40.0%)	137 (40.1%)	128 (40.0%)	924 (10.7%)	446 (10.3%)	478 (11.0%)
On or before revascularization	177 (26.7%)	92 (26.9%)	85 (26.6%)	---	---	---
After revascularization	88 (13.3%)	45 (13.2%)	43 (13.4%)	---	---	---
Stroke	15 (2.3%)	6 (1.8%)	9 (2.8%)	116 (1.3%)	56 (1.3%)	60 (1.4%)
On or before revascularization	4 (0.6%)	2 (0.6%)	2 (0.6%)	---	---	---
After revascularization	11 (1.7%)	4 (1.2%)	7 (2.2%)	---	---	---

	Revascularization			No Revascularization		
	Overall	**Prasugrel**	**Clopidogrel**	**Overall**	**Prasugrel**	**Clopidogrel**
Bleeding Endpoints*						
GUSTO severe/life-threatening	5 (0.8%)	2 (0.6%)	3 (0.9%)	44 (0.5%)	20 (0.5%)	24 (0.6%)
On or before revascularization	0 (0.0%)	0 (0.0%)	0 (0.0%)	---	---	---
After revascularization	5 (0.8%)	2 (0.6%)	3 (0.9%)	---	---	---
GUSTO severe/life-threatening/moderate	19 (2.9%)	9 (2.6%)	10 (3.1%)	139 (1.6%)	80 (1.9%)	59 (1.4%)
On or before revascularization	5 (0.8%)	2 (0.6%)	3 (0.9%)	---	---	---
After revascularization	14 (2.1%)	7 (2.0%)	7 (2.2%)	---	---	---
TIMI major	11 (1.7%)	6 (1.8%)	5 (1.6%)	95 (1.1%)	52 (1.2%)	43 (1.0%)
On or before revascularization	2 (0.3%)	1 (0.3%)	1 (0.3%)	---	---	---
After revascularization	9 (1.4%)	5 (1.5%)	4 (1.3%)	---	---	---
TIMI major/minor	21 (3.2%)	12 (3.5%)	9 (2.8%)	153 (1.8%)	85 (2.0%)	68 (1.6%)
On or before revascularization	8 (1.2%)	4 (1.25%)	4 (1.3%)	---	---	---
After revascularization	13 (2.0%)	8 (2.3%)	5 (1.6%)	---	---	---

* All bleeding endpoints were prespecified as non-CABG related.
Data presented as no. (%).
GUSTO, Global Use of Strategies to Open Occluded Coronary Arteries; TIMI, Thrombolysis In Myocardial Infarction.

Table 4. Association Between the Occurrence of a Post-Index Revascularization and Outcomes

	Overall Hazard Ratio (95% Confidence Interval)	Overall P-Value	Interaction with Treatment Arm P-Value
Ischemic Endpoints			
Cardiovascular death/myocardial infarction/stroke	2.73 (2.21-3.38)	<0.001	0.945
Cardiovascular death	1.64 (1.21-2.23)	0.001	0.258
All-cause death	1.71 (1.31-2.23)	<0.001	0.397
Myocardial infarction	2.70 (2.17-3.37)	<0.001	0.891
Stroke	2.00 (1.07-3.75)	0.030	0.318
Bleeding Endpoints			
GUSTO severe/life-threatening	2.61 (1.02-6.67)	0.045	0.625
GUSTO severe/life-threatening/moderate	2.42 (1.39-4.23)	0.002	0.340
TIMI major	2.24 (1.12-4.48)	0.022	0.771
TIMI major/minor	2.03 (1.15-3.60)	0.015	0.976

GUSTO, Global Use of Strategies to Open Occluded Coronary Arteries; TIMI, Thrombolysis In Myocardial Infarction