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Clinical Features and Outcomes of Patients with Type 2 Myocardial Infarction: Insights from the Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome (TRACER) Trial

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**Clinical Features and Outcomes of Patients with Type 2 Myocardial Infarction: Insights from the
Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome
(TRACER) Trial**

Short title: Guimaraes et al.: Type 2 Myocardial Infarction

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ABSTRACT

Background: Type 2 myocardial infarction (MI) is characterized by an imbalance between myocardial blood supply and demand, leading to myocardial ischemia without coronary plaque rupture, but its diagnosis is challenging.

Methods: In the Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome (TRACER) trial, patients with non-ST-segment elevation acute coronary syndromes were included. We aimed to describe provoking factors, cardiac biomarker profiles, treatment patterns, and clinical outcomes of patients with type 2 MIs. MI events during trial follow-up were adjudicated by an independent clinical events classification committee (CEC) and were classified according to the Third Universal Definition of MI. Using available source documents retrieved as part of the CEC process, we performed a retrospective chart abstraction to collect details on the type 2 MIs. Cox regression models were used to explore the association between MI type (type 1 or type 2) and all-cause death.

Results: Overall, 10.3% (n=1327) of TRACER participants had a total of 1579 adjudicated MIs during a median follow-up of 502 days (interquartile range [IQR] 349–667). Of all MIs, 5.2% (n=82) were CEC-adjudicated type 2 MIs, occurring in 76 patients. The incidence of type 2 MI was higher in the first month following randomization, after which the distribution became more scattered. The most frequent potential provoking factors for type 2 MIs were tachyarrhythmias (38.2%), anemia/bleeding (21.1%), hypotension/shock (14.5%), and hypertensive emergencies (11.8%). Overall, 36.3% had a troponin increase $>10\times$ the upper limit of normal. Coronary angiography was performed in 22.4% (n=17) of patients during hospitalizations due to type 2 MIs. The hazard of death was numerically higher following type 2 MI (vs. no MI, adj. HR 8.25, 95% CI 4.57–14.92; $p<.0001$) than that of type 1 MI (vs. no MI, adj. HR 5.71, 95% CI 4.62–7.06; $p<.0001$).

Conclusions: Type 2 MIs were more prevalent in the first month after ACS were characterized by the presence of triggers and infrequent use of an invasive strategy, and were associated with a high risk of death. Further efforts are needed to better define the role and implications of type 2 MI in both clinical practice and research.

Key words: myocardial infarction; acute coronary syndromes; universal MI definition; type 2 myocardial infarction.

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INTRODUCTION

Type 2 myocardial infarction (MI) is defined as myocardial necrosis caused by an imbalance between myocardial blood supply and demand, without coronary plaque rupture (1). In clinical practice, type 2 MI is typically identified in the context of predisposing conditions, such as tachyarrhythmia, hypotension, sepsis, decompensate heart failure, and acute anemia, among others. While in some cases the supply-demand mismatch mechanism is clear, in other situations the diagnosis of type 2 MI is often based on subjective interpretation of the clinical context. This leads to difficulties in decision-making for these patients, especially regarding the use of antithrombotic medications and use of invasive strategies.

Uncertainties in the attribution of the correct type of MI are also reflected by the wide variation in the reported relative occurrence of type 2 MI (3–26% of all MIs) in several studies (2-8). Moreover, the availability of high-sensitivity troponin assays will likely increase the number of patients who have elevated biomarkers in a variety of clinical conditions (9). Finally, the prognostic significance of type 2 MI is not well defined.

Further description of type 2 MI characteristics may benefit both clinical practice and randomized trials. In the clinical research setting, clearer definitions may help to identify MI outcomes that are likely to be influenced by study treatment. Using the framework of the Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome (TRACER) trial, we sought to describe clinical characteristics and prognoses associated with MI identified as type 2 by a central adjudication committee.

METHODS

Patients and Study Design

The design and main results of the TRACER trial have been published (10). In summary, it was a randomized, multinational, double-blinded clinical trial that included high-risk patients with non-ST-segment elevation acute coronary syndromes (ACS). To be included, participants had to present with symptoms of ischemia within 24 hours prior to hospitalization in addition to troponin or CK-MB elevation or high-risk electrocardiogram changes, and at least one of the following: age ≥ 55 years,

diabetes, peripheral arterial disease, previous MI, percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG). Key exclusion criteria were: use of anticoagulants or inducers/inhibitors of CYP3A4 isoenzymes, history of bleeding diathesis, any previous intracranial bleeding, and severe valve heart disease. Participants were randomized in a 1:1 ratio to receive a loading dose of vorapaxar (40 mg at least 1 hour before any revascularization procedure), followed by 2.5 mg daily, or placebo, on top of standard antiplatelet therapy. The study treatment was to be given for at least 1 year. All patients provided informed consent to participate in the TRACER trial. The authors are solely responsible for the design and conduct of this study, all study analysis, the drafting and editing of the paper, and its final contents. The TRACER trial was supported by Merck & Co., Inc.

Type 2 MI Event Data Collection

MI events were prospectively adjudicated by an independent clinical events classification committee (CEC) blinded to treatment assignment, and were classified in MI types according to the Third Universal Definition of MI (1). The definitions of MI used in the TRACER trial have been previously published (11). Type 2 MIs were defined as events likely caused by supply/demand mismatch and in which the mechanism of ischemia was thought to be something other than acute coronary plaque flow-limiting events. Using available source documents retrieved as part of the CEC adjudication process, we performed a retrospective chart abstraction (abstractor P.O.G.) to collect additional details on clinical scenarios surrounding the MI presentation and the management of CEC-defined type 2 MIs. We searched the event case report form to identify event characteristics such as the presence and type of symptoms, biomarker values with respective local lab normal range values, coronary angiogram and PCI reports, and additional information in the narrative that highlighted the predisposing condition that led the adjudicator to classify the MI as type 2. This assessment was blinded to treatment assignment and clinical outcomes. We integrated the information retrieved with these ad-hoc abstractions with other data collected as part of

the main trial database such as biomarker patterns, concomitant treatments, use of coronary angiogram and revascularization procedures, and clinical outcomes.

Statistical Analysis

Baseline characteristics are presented for patients with no MI during trial follow-up, type 1 MI, and type 2 MI. Continuous variables are presented as medians with 25th and 75th percentiles, and categorical variables are presented as counts with associated percentages.

Cox proportional hazards models were used to examine the association between first MI type (type 1 or type 2) versus no MI and all-cause death. Occurrences of MIs post-randomization were treated as a time-varying covariate. The model was adjusted for important baseline factors, including demographic characteristics (age, sex, race, weight, region), medical history (smoking, hypertension, diabetes, hyperlipidemia, prior peripheral arterial disease, MI, stroke, PCI, CABG), features on presentation (ST-segment deviation, new T wave, Killip class, renal insufficiency), and treatments received during index stay (cardiac catheterization, PCI, CABG, clopidogrel, aspirin, glycoprotein IIb/IIIa inhibitors, study treatment). We performed two sensitivity analyses: a) one considering the last MI before the death event, and b) one excluding patients with multiple MI events. Results are presented as hazard ratios (HRs) with 95% confidence intervals (CIs). Analyses were performed using SAS software, version 9.3 (SAS Institute, Inc., Cary, NC). All tests were 2-sided, and a p-value <0.05 was considered statistically significant. No adjustment was made for multiple comparisons. All analyses were performed at the Duke Clinical Research Institute, Durham, NC.

RESULTS

Patient Characteristics

Overall, 1327 TRACER participants experienced a total of 1579 CEC-confirmed MIs during a median follow-up of 502 days (interquartile range [IQR] 349–667). A total of 82 MIs (5.2% of all MIs) were classified by the CEC as type 2 and occurred in 76 TRACER participants. A total of 20 patients had both

type 1 and type 2 MIs during trial follow-up. The timing of first type 1 MI and type 2 MI since randomization is shown in **Figure 1**. We observed that the occurrence of type 1 MI was more frequent in the first months after randomization and decreased and became more homogenous throughout follow-up. For type 2 MI, the incidence was higher in the first month, after which the distribution became more scattered. The distributions of type 2 MIs were not different among those who received PCI at index hospitalization vs. those who did not. Among the 57 subjects who had type 2 MI after 30 days of randomization, 84.2% had MI as the index event. Among those who had type 2 MIs within 30 days of randomization (n=19), 36.8% underwent PCI at index hospitalization.

Baseline characteristics of patients with any type 1 MI, any type 2 MI, and no MIs are presented in **Table 1**. Among patients with type 2 MIs, the median age was 71 years, and 30.3% were female. Patients with type 2 MIs were older, more likely to be smokers, have hyperlipidemia, and have a history of prior MI or CABG than those with no MIs. Additionally, creatinine clearance <30 mL/min was more frequent among patients with type 2 MIs, in comparison with those with no MIs, and hemoglobin levels at baseline were lower among those with type 2 MIs. Hypertension and diabetes were more common among patients with type 1 MIs, in comparison with those with no MIs. More patients with type 1 or type 2 MIs had ≥ 4 comorbidities in comparison with those with no MIs. During index hospitalization, coronary angiography, PCI, and the use of glycoprotein IIb/IIIa inhibitors were less common among patients with type 2 MIs, compared with those with type 1 MIs or no MIs.

Type 2 MI Event Characteristics and Management

Of all patients experiencing type 2 MIs, 65.8% (n=50) had chest pain or typical angina-like symptoms, 11.8% (n=9) had atypical chest discomfort, and 21.1% (n=16) did not have symptoms clearly attributable to ischemia. The most common associated condition considered to be provocative of the supply/demand mismatch were tachyarrhythmia, anemia or bleeding, hypotension or shock, sepsis or infection, hypertension, heart failure, and non-cardiac surgery (**Table 2**). In some patients (n=16), more than one

potential causal condition was present. Of all patients with type 2 MI due to anemia/bleeding, 84.6% (n=16) had GUSTO moderate/severe bleeding from a gastrointestinal source.

One-third of patients with type 2 MI had troponin peak between 1–3× the upper limit of normal (ULN), while 36.3% had a troponin increase >10× ULN (**Supplemental Figure 1**). The median (25th, 75th percentiles) ratio of peak troponin and ULN was 10.7 (3.2, 40.8) for type 1 MI and 4.3 (1.9, 26.5) for type 2 MI.

During the acute treatment of type 2 MI, 72.4% of patients received aspirin, 51.3% received clopidogrel, and 13.7% received heparin. Coronary angiography during the hospitalization for type 2 MI was performed in 22.4% (n=17) of patients. Among those who received angiography, 9 had coronary stenosis ≥70%, and 3 of them underwent PCI.

All-cause Death Following MI Events

Estimated cumulative cardiovascular death rates following type 1 MI and type 2 MI are shown in **Figure 2**. Type 2 MI was associated with a 12-fold increase in the hazard of cardiovascular death (HR 11.82, 95% CI 5.71–24.46; p<.001) compared with no MI (**Table 3**). For patients with type 1 MI, the HR for cardiovascular death was 8.90 (95% CI 6.93–11.43; p<.0001) compared with no MI. In the analysis accounting only for the last MI prior to the cardiovascular death event, type 2 MI was associated with a 19-fold increase in the hazard of death (HR 19.15, 95% CI 10.22–35.88; p<.0001), compared with no MI. When patients with multiple MIs were excluded, the HR for cardiovascular death following type 2 MI was 14.62 (95% CI 7.04–30.34; p<.0001).

When considering the hazard of all-cause death, the HR following type 2 MI was 8.25 (95% CI 4.57–14.92; p<.001) vs. no MI. The HR for all-cause death following type 1 MI was 5.71 (95% CI 4.62–7.06; p<.0001) vs. no MI. When accounting only for the last MI prior to the death event, type 2 MI was associated with a 12-fold increase in the hazard of all-cause death (HR 12.54, 95% CI 7.47–21.06; p<.0001) compared with no MI. In the analysis excluding patients with multiple MIs, the HR for all-cause death following type 2 MI was 9.29 (95% CI 5.00–17.24; p<.0001).

Of the deaths following type 2 MI (n=19), the majority were cardiovascular (68.4%), 21.1% were non-cardiovascular, and 10.5% had unknown causes. Among deaths following type 1 MI (n=156), 75.0% were cardiovascular, 22.4% were non-cardiovascular, and 2.6% had unknown causes.

DISCUSSION

In a large clinical trial database of non-ST-segment elevation ACS patients with central adjudication of events and independent classification of MI type, we described presentation, treatments, and prognosis of type 2 MI. Our key findings are the following. First, type 2 MI was a relatively infrequent event, comprising only about 5% of all MIs. The incidence of type 2 MI was higher in the first month following randomization, after which the distribution became more scattered. Second, a variety of different triggers were thought to have provoked supply and demand mismatch, with tachyarrhythmias and anemia or bleeding among the most common mechanisms. Third, contrary to the common perception that type 2 MIs are characterized by small biomarker leaks, we observed that one-third of patients had major troponin elevation. Fourth, type 2 MI tended to be managed conservatively; yet about one-quarter of patients received a coronary angiography during type 2 MI hospitalization, with only 3 patients having undergone PCI. Finally, type 2 MIs were associated with a high risk of death, and the majority of deaths following type 2 MIs were from cardiovascular causes.

The prevalence of type 2 MI is between 3% and 26% in observational cohorts (3, 5, 12-14) and in clinical trials (15, 16). In our study, about 5% of MIs were deemed to be type 2 by the CEC. The assessment of type 2 MI is mostly based on subjective interpretation in determining the most likely trigger of ischemia. While in some scenarios the identification of a predisposing condition may be clear (i.e., bleeding followed by MI), in others it may be quite difficult to determine whether the MI was a cause or a consequence, such as in patients with tachyarrhythmias or heart failure (17). Moreover, differentiating between type 2 MI (i.e., ischemia) and acute myocardial injury (i.e., toxin or other mechanisms) in settings of sepsis or following non-cardiac surgeries can be controversial (18-20). Recently, it has been suggested to combine type 2 MI and non-ischemic myocardial injury into a single

category, reserving the term “MI” for coronary occlusion-related events (21, 22). This strategy could potentially reduce the heterogeneity of these definitions among clinicians and researchers, but at the same time may lead to excessive simplification and grouping of events that are different in nature.

The presence of symptoms of ischemia may be clinically helpful to distinguish ischemia-driven events from those caused by other mechanisms, although identification of symptoms may be challenging, especially in critically ill patients. In our study, we observed that more than half of the patients with type 2 MIs presented with chest pain and symptoms thought to be typical of ischemia, which is in accordance with previous studies (2, 4, 5). It has been previously observed that atypical presentation is much more common among type 2 MIs than type 1 MIs (23). With the availability of high-sensitivity troponin assays, the incidence of myocardial necrosis due to supply and demand mismatch is likely to increase (9). Because MI is an almost ubiquitous outcome used in clinical trials, the absence of clear characterization of type 2 MI may potentially jeopardize the evaluation of treatment effect of cardiovascular therapies.

In our study, 22.4% of patients with type 2 MI underwent coronary angiography during hospital admission and few of them underwent PCI. Others have shown a lower frequency of invasive procedures in patients with type 2 MIs, compared with those with type 1 MIs (2, 3, 5). However, these findings may be affected by the assessment criteria used (i.e., an MI that was not treated invasively may be more likely to be assigned to the type 2 category). The prognostic benefit of revascularization in the setting of secondary ischemia has not been investigated, and invasive procedures may be contraindicated in certain conditions. We have also observed lower rates of antithrombotic therapy among patients experiencing type 2 MIs, which may be in part explained by the fact that a substantial number of them had acute anemia or bleeding. Because of the high risk of cardiovascular events following type 2 MI, the benefit of more aggressive management, when not contraindicated, may need further assessment.

The prognosis of type 2 MI is not well established. Patients experiencing a type 2 MI in the TRITON-TIMI 38 trial were at a 3-fold increased risk of cardiovascular death over the following 180 days, in comparison with those with no recurrent MIs (15). We have observed an increased hazard of cardiovascular death among patients presenting with type 2 MIs during trial follow-up as compared with

those with no MIs— which was at least as high as observed following type 1 MIs. A recent study with 1251 patients undergoing coronary or peripheral arterial angiography showed that patients with type 2 MI had an increased risk of all-cause mortality (HR 2.96, 95% CI 2.01–4.36; $p < .001$) in comparison with those without type 2 MIs (24). Additionally, observational studies have shown similar or higher mortality rates among patients with type 2 compared with type 1 MIs (4, 5, 25). Interestingly, although the increase in mortality with type 2 MI could be due to co-existing morbidity, we observed that the majority of deaths were from cardiovascular causes. Further efforts are needed to clarify the mechanism of disease progression in patients with type 2 MI.

Our study has several limitations. While the TRACER trial was large in size, the cohort of patients with type 2 MI is small, limiting the amount of information included. Many data used were not prospectively collected but retrieved by retrospective chart abstraction using clinical source documents obtained for the purpose of event adjudication. Some information was missing for some patients. Data on non-invasive coronary and myocardial imaging, which could have been helpful to understand ischemic burden in patients with type 2 MI, were not collected in the trial. Additionally, we are unable to confirm the reasons prompting measurement of cardiac biomarkers in patients without primarily ischemic symptoms. Finally, the TRACER trial included non-ST-segment elevation ACS as a criterion for eligibility; thus, our population was pre-selected and our results might not be applicable to patients without known coronary artery disease. It is important to note that 88% of the overall TRACER population underwent coronary angiography and 58% underwent PCI during index hospitalization; therefore, most of these patients had significant coronary lesions and were on secondary prevention with dual antiplatelet therapy.

CONCLUSIONS

Type 2 MIs were more prevalent in the first month after ACS, were characterized by the presence of triggers and infrequent use of an invasive strategy, and were associated with a high risk of death. Further

efforts are needed to better define the role and implications of type 2 MI in both clinical practice and research.

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Author Contributions

Dr. Guimaraes and Dr. Tricoci had full access to all data in the study and take responsibility for the integrity of the data and the accuracy of the data analyses.

PO Guimaraes: Dr. Guimaraes contributed to the conception and design of the study, data analysis, data interpretation, manuscript drafting, and critical revision of the manuscript.

S Leonardi: Dr. Leonardi contributed to the data analysis, data interpretation, manuscript drafting, and critical revision of the manuscript.

Z Huang: Ms. Huang contributed to the data analysis, data interpretation, and critical revision of the manuscript.

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C Held: Dr. Held contributed to the data analysis and critical revision of the manuscript.

RA Harrington: Dr. Harrington contributed to the data interpretation and critical revision of the manuscript.

DJ Moliterno: Dr. Moliterno contributed to data interpretation and critical revision of the manuscript.

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HD White: Dr. White contributed to the data interpretation and critical revision of the manuscript.

KP Alexander: Dr. Alexander contributed to the data interpretation, manuscript drafting, and critical revision of the manuscript.

RD Lopes: Dr. Lopes contributed to the data analysis, data interpretation, manuscript drafting, and critical revision of the manuscript.

KW Mahaffey: Dr. Mahaffey contributed to the data analysis, data interpretation, manuscript drafting, and critical revision of the manuscript.

P Tricoci: Dr. Tricoci contributed to the conception and design of the study, supervision, data acquisition, analysis and interpretation, manuscript drafting, and critical revision of the manuscript.

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Figure Legends**Figure 1. Timing of type 1 MI and type 2 MI since randomization**

Abbreviations: MI, myocardial infarction.

Figure 2. Estimated cumulative cardiovascular death rates following type 1 MI and type 2 MI

Abbreviations: MI, myocardial infarction.

Table 1. Baseline characteristics and index hospitalization treatments of patients with no MI, type 1 MI, or type 2 MI

	No MI (N=11,617)	Type 1 MI (N=847)	Type 2 MI (N=76)
Clinical characteristics			
Age, yrs ^{†‡}	64 (58-71)	66 (59-74)	71 (62-79)
Female sex [†]	3244 (27.9)	263 (31.1)	23 (30.3)
Body weight, kg	80.0 (70.0-92.0)	80.0 (69.9-94.0)	80.0 (70.0-93.7)
Hypertension [†]	8101 (69.8)	688 (81.2)	60 (78.9)
Hyperlipidemia ^{†‡}	7128 (61.4)	625 (73.8)	58 (76.3)
Diabetes [†]	3510 (30.2)	419 (49.5)	27 (35.5)
Smoking ^{†‡}	3731 (32.1)	304 (35.9)	36 (47.4)
Prior MI ^{†‡}	3221 (27.7)	416 (49.1)	37 (48.7)
Prior CABG ^{†‡}	1244 (10.7)	223 (26.3)	26 (34.2)
Number of comorbidities ^{†‡}			
0-3	10451 (90.1)	606 (71.5)	53 (69.7)
4-6	1128 (9.7)	232 (27.4)	23 (30.3)
≥7	24 (0.2)	9 (1.1)	0 (0.0)
Median hemoglobin, g/dL ^{†‡}	14.1 (13.0-15.1)	13.5 (12.1-14.8)	13.0 (11.2-14.7)
CrCl <30 mL/min ^{†‡}	142 (1.3)	38 (4.7)	7 (9.2)
Thienopyridine at baseline	10,116 (87.1)	744 (87.8)	67 (88.2)
Killip class ^{†‡}			
I	11012 (95.7)	749 (88.7)	65 (85.5)
II	405 (3.5)	64 (7.6)	6 (7.9)
III-IV	92(0.8)	31 (3.7)	5 (6.6)
Index hospitalization treatments			
Coronary angiography	10250 (88.2)	711 (83.9)	56 (73.7)
PCI	6638 (57.1)	440 (51.9)	27 (35.5)
Stenting	6292 (54.2)	399 (47.1)	26 (34.2)
CABG	1209 (10.4)	73 (8.6)	7 (9.2)
Clopidogrel	10633 (91.5)	790 (93.3)	68 (89.5)
Aspirin	11515 (99.1)	839 (99.1)	74 (97.4)

	No MI (N=11,617)	Type 1 MI (N=847)	Type 2 MI (N=76)
Glycoprotein IIb/IIIa inhibitors	2360 (20.3)	187 (22.1)	10 (13.2)

Data presented as median (interquartile range) or n (%).

Abbreviations: CABG, coronary artery bypass graft; CrCl, creatinine clearance; MI, myocardial infarction; PCI, percutaneous coronary intervention.

[†] P-value <0.05 for assessing the univariate relationship between a baseline characteristic and type 1 MI controlling for randomized treatment.

[‡] P-value <0.05 for assessing the univariate relationship between a baseline characteristic and type 2 MI controlling for randomized treatment.

Table 2. Triggers of type 2 MIs

Mechanisms	N (%)
Arrhythmias	29 (38.2)
Atrial fibrillation/flutter	17 (22.4)
Supraventricular tachycardia	9 (11.8)
Ventricular tachycardia	3 (4.0)
Anemia/bleeding	16 (21.1)
Hypotension/shock	11 (14.5)
Hypertension	9 (11.8)
Sepsis/infection	8 (10.5)
Heart failure	6 (7.9)
Non-cardiac surgery	6 (7.9)
Coronary spasm	3 (4.0)
Stress	3 (4.0)
Syncope	2 (2.6)
Aortic stenosis	1 (1.3)
Respiratory insufficiency	1 (1.3)

More than one mechanism per type 2 myocardial infarction was identified in 16 patients. Information was missing for 6 type 2 myocardial infarctions.

Table 3. Cardiovascular death with type 1 MI and type 2 MI versus no MI

	HR (95% CI)	P value
<i>Based on first MI event</i>		
Type 1 MI	8.90 (6.93–11.43)	<.0001
Type 2 MI	11.82 (5.71–24.46)	<.0001
<i>Based on last MI event</i>		
Type 1 MI	9.94 (7.74–12.76)	<.0001
Type 2 MI	19.15 (10.22–35.88)	<.0001
<i>Excluding patients with multiple MI events</i>		
Type 1 MI	7.59 (5.73–10.04)	<.0001
Type 2 MI	14.62 (7.04–30.34)	<.0001

Hazard ratios are adjusted for randomized treatment, age, sex, race, weight, region, smoking, hypertension, diabetes, hyperlipidemia, prior peripheral arterial disease, prior myocardial infarction, prior stroke, prior percutaneous coronary intervention, prior coronary artery bypass graft, features on presentation (ST-segment deviation, new T wave, Killip class, renal insufficiency), and treatments received during index stay (cardiac catheterization, percutaneous coronary intervention, coronary artery bypass graft, clopidogrel, aspirin, glycoprotein IIb/IIIa inhibitors).

Abbreviations: CI, confidence interval; HR, hazard ratio; MI, myocardial infarction.

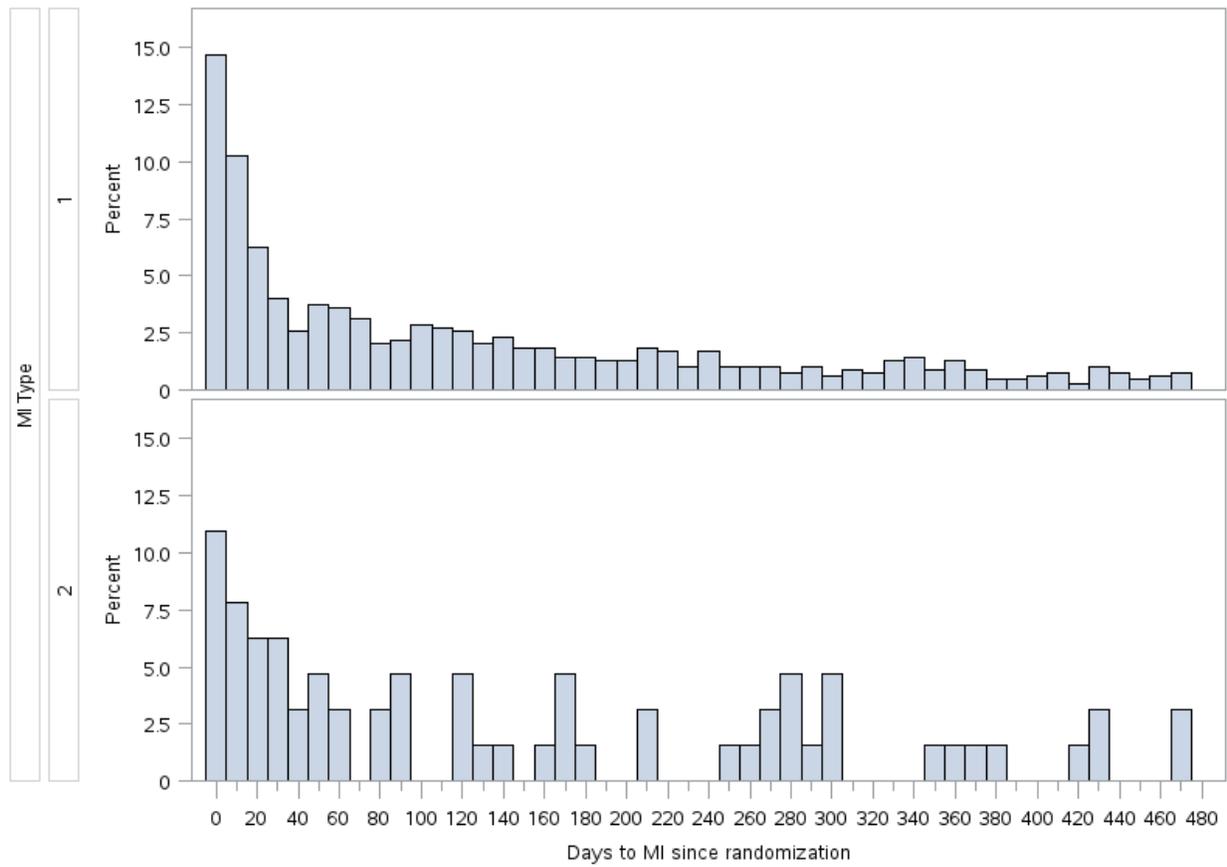
Timing of MI: distribution of days to MI since randomization

Figure 1

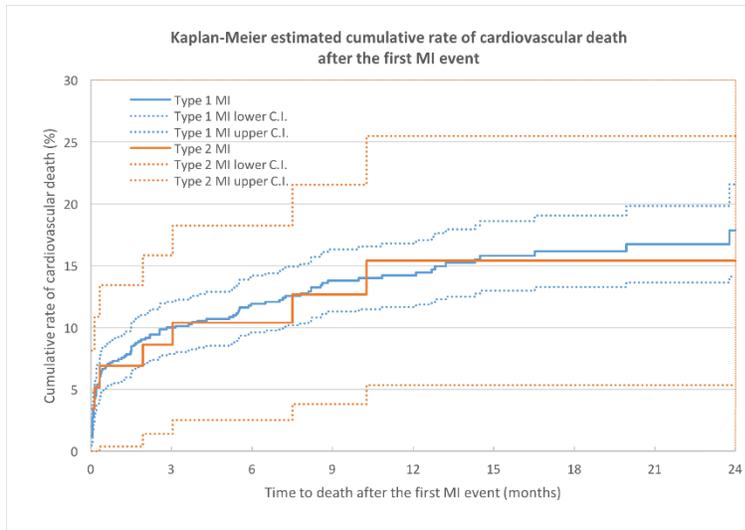


Figure 2

Highlights

- Provoking factors and clinical outcomes of patients with type 2 MIs are described.
- Type 2 MIs were more prevalent in the first month after ACS.
- Tachyarrhythmias and anemia or bleeding were the most common triggers of type 2 MIs.
- Type 2 MI tended to be managed conservatively.
- The hazard of cardiovascular death following type 2 MI was high.