

ORIGINAL RESEARCH

Prior Myocardial Infarction and Treatment Effect of Ticagrelor Versus Prasugrel in Patients With Acute Coronary Syndromes - A Post-hoc Analysis of the ISAR-REACT 5 Trial

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BACKGROUND: The efficacy and safety of ticagrelor versus prasugrel in patients with acute coronary syndrome and prior myocardial infarction (MI) remain unstudied. We aimed to assess the treatment effect of ticagrelor versus prasugrel according to prior MI status in patients with ACS.

METHODS AND RESULTS: Patients with acute coronary syndrome planned for an invasive strategy and randomized to ticagrelor or prasugrel in the ISAR-REACT (Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment) 5 trial were included. The primary end point was the composite of 1-year all-cause death, MI, or stroke; the secondary safety end point was the composite of 1-year Bleeding Academic Research Consortium type 3 to 5 bleeding. The study included 4015 patients (prior MI=631 patients; no prior MI=3384 patients). As compared with patients without prior MI, the primary end point occurred more frequently in patients with prior MI (12.6% versus 7.2%; hazard ratio [HR], 1.78 [95% CI, 1.38–2.29]); the secondary safety end point appears to differ little between patients with and without prior MI (5.8% versus 5.7%, respectively; HR, 1.02 [95% CI, 0.71–1.45]). With regard to the primary end point, ticagrelor versus prasugrel was associated with an HR of 1.62 (95% CI, 1.03–2.55) in patients with prior MI and an HR of 1.28 (95% CI, 0.99–1.65) in patients without prior MI ($P_{\text{int}}=0.37$). With regard to the secondary safety end point, ticagrelor versus prasugrel was associated with an HR of 1.28 (95% CI, 0.56–2.91) in patients with prior MI and an HR of 1.13 (95% CI, 0.82–1.55) in patients without prior MI ($P_{\text{int}}=0.79$).

CONCLUSIONS: Patients with acute coronary syndrome and prior MI are at higher risk for recurrent ischemic but not bleeding events. Prasugrel is superior to ticagrelor in reducing the risk of ischemic events without a tradeoff in bleeding regardless of prior MI status.

REGISTRATION: URL: <https://www.clinicaltrials.gov>; Unique identifier: NCT01944800.

Key Words: acute coronary syndrome ■ percutaneous coronary intervention ■ prasugrel ■ prior myocardial infarction ■ ticagrelor

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CLINICAL PERSPECTIVE

What Is New?

- Patients with acute coronary syndrome and prior myocardial infarction (MI) undergoing invasive management have an increased risk for recurrent ischemic events but not bleeding events compared with patients without prior MI.
- Prasugrel was superior to ticagrelor in reducing the 1-year ischemic risk in patients with and without prior MI.
- Bleeding events were similar between ticagrelor and prasugrel regardless of prior MI status.

What Are the Clinical Implications?

- The choice between prasugrel and ticagrelor in patients with acute coronary syndrome undergoing percutaneous coronary intervention should not be influenced by prior MI status.

Nonstandard Abbreviations and Acronyms

BARC	Bleeding Academic Research Consortium
ISAR-REACT	Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment

Approximately 20% of patients undergoing contemporary treatment for an acute coronary syndrome (ACS) have a history of prior myocardial infarction (MI).¹ These patients are subject to recurrent ischemic events and have worse long-term outcomes compared with patients without prior MI.^{2–4} A dual antiplatelet therapy combining aspirin and a P2Y₁₂ inhibitor is recommended for the secondary prevention of ischemic events for 6 to 12 months after an acute coronary syndrome (ACS).^{5,6} After this period, anti-thrombotic regimens should be adapted according to individual risk of recurrent ischemic events and bleeding. Ticagrelor and prasugrel, 2 newer-generation oral P2Y₁₂ inhibitors, are superior to clopidogrel for the prevention of recurrent thrombotic events in patients with ACS,^{7,8} including those with recurrent events after prior MI.^{7,9} In patients with prior MI, a therapy with ticagrelor and aspirin has proven superior anti-ischemic protection compared with aspirin alone, though in the longstanding phase of the disease.¹⁰ In contrast, the clinical performance of prasugrel in patients with prior MI remains unstudied. The ISAR-REACT (Intracoronary

Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment) 5 trial found that prasugrel is superior to ticagrelor in reducing the 12-month cumulative incidence of ischemic events without a tradeoff in bleeding in patients with ACS treated invasively.¹¹ In this context, we designed this post hoc analysis of the ISAR-REACT 5 trial to investigate whether the history of MI affects the comparative efficacy and safety of ticagrelor versus prasugrel in patients with ACS managed invasively.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Population and Treatment Groups

This study is a post hoc analysis of the ISAR-REACT 5 trial ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01944800) unique identifier: NCT01944800). The trial design and clinical outcomes have been published.^{11,12} Briefly, in the ISAR-REACT 5 trial, patients presenting with an ACS (unstable angina, ST-segment elevation myocardial infarction [STEMI], or non-STEMI) and planned to undergo an invasive treatment strategy were randomized to either ticagrelor or prasugrel in a 1:1 ratio. Patients randomized to ticagrelor received the loading dose of the drug (180 mg) as soon as possible after randomization, followed by a 90 mg maintenance dose twice daily. Patients with STEMI randomized to prasugrel received a 60 mg loading dose as soon as possible after randomization, followed by a 10 mg maintenance dose once daily. Patients randomized to prasugrel who presented with non-ST-segment elevation ACS received the 60 mg loading dose after coronary anatomy was known (but before percutaneous coronary intervention). In patients aged ≥ 75 years or those with a body weight < 60 kg, a 5 mg maintenance dose of prasugrel was recommended.¹³ A loading dose of 150 to 300 mg of intravenous or chewed aspirin and a maintenance dose of 75 to 100 mg once daily on top of the study drug were prescribed to all patients irrespective of clinical presentation. Dual antiplatelet therapy with either ticagrelor or prasugrel in addition to aspirin was recommended for at least 12 months. The study protocol was approved by the ethics committees of each participating center. The study was conducted in compliance with the Declaration of Helsinki and all patients provided written, informed consent before enrollment.

Definition of Prior MI

Prior MI was defined as at least 1 of the following: (1) documentation of prior MI in the medical history, (2) presence of pathological Q waves on the baseline ECG

in the absence of other nonischemic causes, and (3) imaging evidence of loss of regional myocardial viability. Patients were divided into 2 groups: the group with prior MI and the group without prior MI.

Definitions of Clinical Outcomes and Follow-Up Schedule

The primary (efficacy) end point was the composite of all-cause death, MI, or stroke. The secondary safety end point was the composite of Bleeding Academic Research Consortium (BARC) type 3 to 5 bleeding. Both end points were assessed at 12 months after randomization. Other end points included the individual components of the primary end point and stent thrombosis (definite or probable), all assessed at 12 months after randomization. MI was defined according to the Third Universal Definition of Myocardial Infarction.¹⁴ Cardiovascular death and definite or probable stent thrombosis were defined according to the Academic Research Consortium Criteria.¹⁵ A detailed description of end point definitions has been previously published.^{11,12} All primary and secondary end points were adjudicated in a blinded fashion by members of the event adjudication committee in the setting of the primary trial. Follow-up was performed at 30±10 days, 6±1 months, and 12±1 months. In case of potential end point-related adverse events, source data were solicited. Follow-up data of patients were obtained by telephone, structured follow-up letters, or source documentation from hospital or outpatient visits.

Statistical Analysis

The current analysis was not prespecified in the protocol of the primary trial and, therefore, it is a post hoc analysis. Continuous variables are presented as mean±SD or median with interquartile range and were compared using the Student's *t*-test or the non-parametric Wilcoxon rank sum test, as appropriate. Categorical data are presented as counts and proportions. The χ^2 or Fisher's exact tests were used to assess differences between categorical variables. The primary end point and all-cause death are presented as cumulative incidence and were analyzed using the Kaplan–Meier method. All other end points are analyzed after accounting for the competing risk of death. Competing risk analysis is used when there is an event (eg, death) whose occurrence precludes the occurrence of the other events of interest.¹⁶ Competing risk was calculated by using the R-package *cmprsk*.^{17,18}

We performed 2 types of comparisons of the adverse events: first, according to presence or absence of prior MI; second, according to the treatment group in both patients with and without prior MI separately. We used Cox proportional hazards model for both of these comparisons. The association of study drug

with the primary and secondary safety end points was adjusted for potential confounders (that showed imbalances in the monovariate analysis) using the Cox proportional hazards model. The proportional hazards assumption of the Cox model was checked and confirmed by statistical tests and graphical diagnostics (Schoenfeld residuals) for the primary end point and all secondary end points except for stroke, for which proportional hazards assumption was not met. However, because of the limited contribution of this event to the overall outcome analysis, we did not apply alternative statistical methods that are considered more appropriate in this situation. The potential statistical interaction between assigned treatment and prior MI status was studied by entering an interaction term in the Cox proportional hazards model. Hazard ratios (HRs) with 95% CIs served as summary risk estimates.

The primary end point was analyzed in an intention-to-treat population, including all patients as initially assigned, irrespective of the actual treatment received. The secondary safety end point of bleeding was analyzed in a modified intention-to-treat population (ie, including all patients who received at least 1 dose of the study drug, with bleeding assessed for up to 1 week after study drug discontinuation). A landmark analysis to address a possible time dependence of the risk for the primary end point using the 30-day time point as a landmark was performed. A sensitivity analysis, including only patients treated with percutaneous coronary intervention, was performed to assess the impact of coronary revascularization on the primary and secondary end points. The statistical analysis was performed using the R, version 3.6.0 Statistical Software (The R foundation for Statistical Computing, Vienna, Austria). A 2-tailed *P* value of <0.05 was considered to indicate statistical significance.

RESULTS

This analysis included 4015 patients enrolled in the ISAR-REACT 5 trial for whom data on prior MI status were available. Of the 4015 patients, 631 (15.7%) patients had prior MI and 3384 (84.3%) patients had not. Twelve-month follow-up was complete in all but 90 patients (2.2%; 18 patients with prior MI and 72 patients without prior MI). The study flow chart is presented in Figure S1.

Baseline and Angiographic Data According to Prior MI Status

Baseline data are shown in Table 1. Patients with prior MI were older, more likely to have diabetes, hypercholesterolemia, prior coronary revascularization, higher body mass index, and less likely to be smokers compared with patients without prior MI. Patients with prior MI presented more often with unstable angina and less often

Table 1. Baseline Data in Patients With and Without Prior Myocardial Infarction

Characteristic	Prior MI (n=631)	No prior MI (n=3384)	P value
Age, y	68.0 [58.5–76.0]	64.0 [55.0–74.0]	<0.001
Sex			<0.001
Female, no. (%)	110 (17.4)	845 (25.0)	
Male, no. (%)	521 (82.6)	2539 (75.0)	
Diabetes, no. (%)	183 (29.0)	707/3382 (20.9)	<0.001
Insulin treated, no. (%)	64 (10.1)	216/3382 (6.4)	0.001
Smoking, no. (%)	185/629 (29.4)	1164/3371 (34.5)	0.014
Arterial hypertension, no. (%)	555 (88.0)	2260/3379 (66.9)	<0.001
Hypercholesterolemia, no. (%)	531 (84.2)	1808/3377 (53.5)	<0.001
Prior PCI, no. (%)	554/629 (88.1)	361 (10.7)	<0.001
Prior CABG, no. (%)	136/630 (21.6)	109 (3.2)	<0.001
Cardiogenic shock, no. (%)	9 (1.4)	54 (1.6)	0.89
Systolic blood pressure (mmHg)	140.0 [124.0–160.0]	140 [128–160]	0.23
Diastolic blood pressure (mmHg)	80.0 [70.0–89.0]	80.0 [73.0–90.0]	<0.001
Heart rate (beats/min)	72.0 [63.0–82.0]	75.0 [66.0–86.0]	<0.001
Body mass index (kg/m ²)	27.5 [25.0–30.3]	27.2 [24.7–30.0]	0.045
Weight <60kg, no. (%)	26/627 (4.1)	176/3361 (5.2)	0.30
Creatinine (μmol/L)	88.4 [74.3–109.0]	81.3 [70.7–97.2]	<0.001
Diagnosis at admission			<0.001
Unstable angina, no. (%)	138 (21.9)	371 (11.0)	
Non-STEMI, no. (%)	305 (48.3)	1550 (45.8)	
STEMI, no. (%)	188 (29.8)	1463 (43.2)	
Coronary angiography, no. (%)	627 (99.4)	3374 (99.7)	0.26
Treatment strategy, no. (%)			0.56
PCI	523/630 (83.0)	2852/3380 (84.4)	
CABG	12/630 (1.9)	71/3380 (2.1)	
Conservative	95/630 (15.1)	457/3380 (13.5)	
Aspirin on admission	521 (82.6)	891 (26.3)	<0.001
Clopidogrel on admission	84 (13.3)	111 (3.3)	<0.001

Data are median with 25th–75th percentiles or counts (%). CABG indicates coronary artery bypass grafting; MI, myocardial infarction; PCI, percutaneous coronary intervention; and STEMI, ST-segment elevation myocardial infarction.

Missing continuous data: Prior MI: diastolic blood pressure: 2 patients, body mass index: 4 patients. No prior MI: systolic blood pressure: 3 patients, diastolic blood pressure: 14 patients, heart rate: 2 patients, body mass index: 27 patients.

with STEMI compared with patients without prior MI. Overall, 4001 patients (99.7%) underwent coronary angiography, without statistically significant difference according to prior MI status (99.4% versus 99.7%; $P=0.26$). Patients with prior MI were more likely to have multivessel disease, reduced left ventricular ejection fraction, and femoral artery used for vascular access compared with patients without prior MI (Table S1). Procedural data are presented in Table S2. Patients with prior MI were more often discharged on aspirin and clopidogrel compared with patients without prior MI (Table S3).

Clinical Outcomes According to Prior MI Status

The outcomes are shown in Table 2. The primary end point occurred in 78 patients with prior MI and 242

patients without prior MI (cumulative incidence, 12.6% versus 7.2%; HR, 1.78 [95% CI, 1.38–2.29]; Figure 1A). The statistical difference between groups was mostly owing to a higher incidence of recurrent MI in patients with prior MI as compared with patients without this condition (7.1% versus 3.3%; HR, 2.19 [95% CI, 1.54–3.10]). The risk for the primary end point according to MI history was not time dependent (Figure 1B). Patients with prior MI had a consistent higher risk for primary end point out to 30 days (HR, 1.66 [95% CI, 1.14–2.42]) and from 30 days to 12 months (HR, 1.88 [95% CI, 1.33–2.66]) as compared with patients without prior MI. BARC type 3 to 5 bleeding occurred in 36 patients with prior MI and 190 patients without prior MI (5.8% versus 5.7%; HR, 1.02 [95% CI, 0.71–1.45], $P=0.92$; Figure 2). Definite or probable stent thrombosis and stroke occurred infrequently, with no

Table 2. Clinical Outcomes in Patients With and Without Prior Myocardial Infarction

Outcome	Prior MI (n=631)	No prior MI (n=3384)	Absolute difference [95% CI]	HR [95% CI]	P value
Primary end point (death, myocardial infarction, or stroke)	78 (12.6)	242 (7.2)	5.32% [2.57%, 8.07%]	1.78 [1.38–2.29]	<0.001
Death	32 (5.2)	130 (3.9)	1.27% [–0.59%, 3.13%]	1.33 [0.90–1.96]	0.15
Myocardial infarction	44 (7.1)	111 (3.3)	3.76% [1.65%, 5.87%]	2.19 [1.54–3.10]	<0.001
Stroke	6 (1.0)	35 (1.0)	–0.07% [–0.92%, 0.77%]	0.92 [0.39–2.19]	0.85
Definite or probable stent thrombosis	10 (1.6)	35 (1.0)	0.56% [–0.49%, 1.60%]	1.55 [0.77–3.12]	0.22
Definite stent thrombosis	9 (1.4)	24 (0.7)	0.73% [–0.25%, 1.70%]	2.03 [0.94–4.37]	0.070
BARC type 3 to 5 bleeding*	36 (5.8)	190 (5.7)	0.12% [–1.87%, 2.12%]	1.02 [0.71–1.45]	0.92

Data are numbers of events with Kaplan–Meier estimates (%) for the primary end point and cumulative incidence (%) after accounting for competing risk of death for all the remaining end points. BARC indicates Bleeding Academic Research Consortium; HR, hazard ratio; and MI, myocardial infarction.

*BARC type 3 to 5 bleeding was analyzed in the intention-to-treat population.

statistically significant differences according to MI history (Table 2).

Baseline Data According to Prior MI Status and Study Drugs

In the group with prior MI, 311 patients were assigned to ticagrelor and 320 patients to prasugrel. In the group without prior MI, 1699 patients were assigned to ticagrelor and 1685 patients to prasugrel. Baseline data according to assigned treatment and MI history are shown in Table 3. In patients with prior MI, there were

no statistically significant differences regarding demographic, clinical, angiographic, and procedural data and drug therapy at discharge between patients assigned to ticagrelor and prasugrel, with the exception that patients assigned to ticagrelor were younger and more likely to have diabetes. Among patients without prior MI the baseline, angiographic, and procedural data appeared to differ little between patients assigned to ticagrelor and prasugrel. Angiographic data, procedural data, and drug therapy at discharge according to MI history and study drugs are shown in Tables S4 through S6.

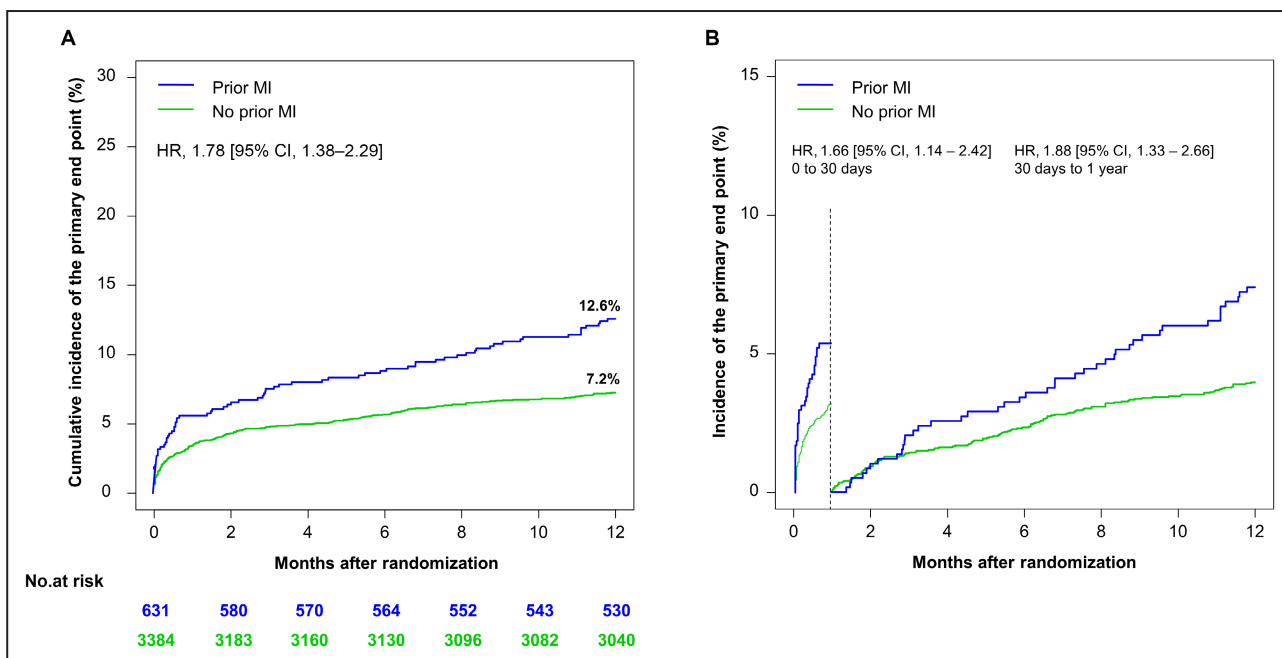


Figure 1. Cumulative incidence and landmark analysis of the primary efficacy end point.

A, Cumulative incidence of the primary end point (all-cause death, MI, or stroke) evaluated in the intention-to-treat population. **B**, Incidence of the primary end point at 30-day landmark analysis according to prior MI status. HR indicates hazard ratio; and MI, myocardial infarction.

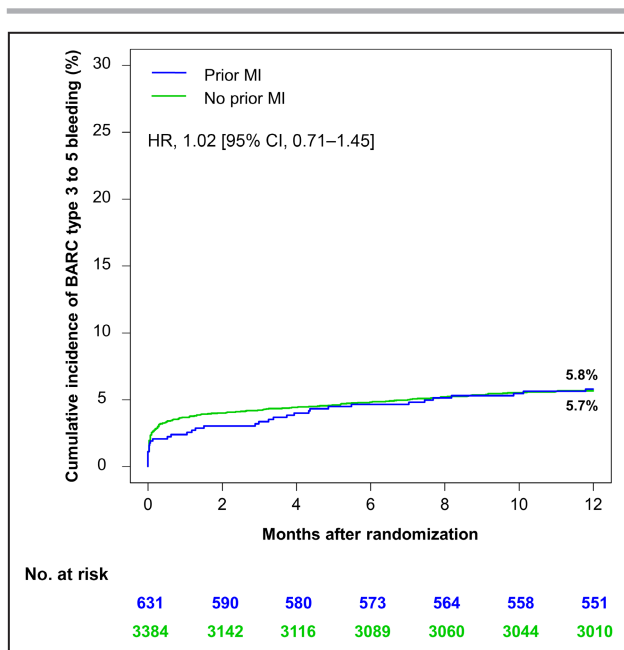


Figure 2. Cumulative incidence of the secondary safety end point.

The cumulative incidence of the secondary end point of BARC type 3 to 5 bleeding was assessed in the intention-to-treat population after accounting for the competing risk of death. BARC indicates Bleeding Academic Research Consortium type 3 to 5 bleeding; HR; hazard ratio; and MI, myocardial infarction.

Clinical Outcomes According to Prior MI Status and Study Drugs

Clinical outcomes according to prior MI status and study drugs are shown in Figure 3. In patients with prior MI, the primary end point occurred in 47 patients assigned to ticagrelor and 31 patients assigned to prasugrel (cumulative incidence, 15.4% versus 9.9%; HR, 1.62 [95% CI, 1.03–2.55]; Figure 4A). MI occurred more frequently in patients assigned to ticagrelor than prasugrel (cumulative incidence after accounting for competing risk of death, 9.1% versus 5.1%; HR, 1.88 [95% CI, 1.02–3.47]). BARC type 3 to 5 bleeding occurred in 13 patients assigned to ticagrelor and 10 patients assigned to prasugrel (cumulative incidence after accounting for competing risk of death, 5.4% versus 3.8%; HR, =1.28 [95% CI, 0.56–2.91], Figure 4B). In patients without prior MI, the primary end point occurred in 136 patients assigned to ticagrelor and 106 patients assigned to prasugrel (cumulative incidence, 8.1% versus 6.4%; HR, 1.28 [95% CI, 0.99–1.65]; Figure 4C). In this group, MI occurred more frequently in patients assigned to ticagrelor compared with patients assigned to prasugrel (cumulative incidence after accounting for competing risk, 4.0% versus 2.6%; HR, 1.52 [95% CI, 1.04–2.22]). BARC type 3 to 5 bleeding occurred in 82 patients assigned to ticagrelor and 70 patients assigned to prasugrel (cumulative incidence

after accounting for competing risk, 5.7% versus 5.1%; HR, 1.13 [95% CI, 0.82–1.55], Figure 4D). There was no statistically significant treatment arm-by-prior MI status interaction regarding the primary ($P_{\text{int}}=0.37$) and the secondary ($P_{\text{int}}=0.79$) end points. The risk for definite or probable stent thrombosis or stroke appears to differ little between patients assigned to ticagrelor or prasugrel, regardless of prior MI status.

The sensitivity analysis, including only patients treated with percutaneous coronary intervention, showed no change in the direction of risk estimates for primary and secondary safety end points, according to prior MI status or assigned antiplatelet treatment, compared with the whole study data (Tables S7 and S8).

The association of study drug with the primary and secondary safety end points in the prior MI group was adjusted for age and diabetic status as potential confounders. After adjustment, ticagrelor increased the risk for the primary (adjusted HR, 1.65 [95% CI, 1.05–2.61], $P=0.031$) but not for the secondary safety end point (adjusted HR, 1.46 [95% CI, 0.64–3.35], $P=0.37$).

DISCUSSION

In this study we investigated the efficacy and safety of ticagrelor versus prasugrel in patients with ACS included in the ISAR-REACT 5 trial according to prior MI status. The main findings of this analysis are as follows:

1. Compared to patients with ACS without prior MI, patients with ACS and prior MI have an increased risk for recurrent ischemic but not bleeding events at 12-month follow-up.
2. Prasugrel appears to be superior to ticagrelor in reducing the risk for ischemic events (primary outcome) both in patients with and without prior MI. Prasugrel reduced the risk for recurrent MI compared with ticagrelor irrespective of prior MI status.
3. The relative bleeding risk of ticagrelor and prasugrel was not dependent on prior MI status.

In the present study, patients with ACS and prior MI displayed an increased risk for ischemic events compared with patients without prior MI. Previous studies have reported that prior MI was independently associated with worse clinical outcomes over the long term.^{19,20} The baseline features of patients with and without prior MI included in our study differed significantly, with patients with prior MI being older, having a worse cardiovascular risk profile and higher rates of previous revascularization compared with patients without prior MI. The imbalance of baseline features could be at least in part accountable for the higher incidence of ischemic events observed in the prior MI group. Patients with prior MI presented more often with non-ST-segment elevation ACS, a condition

Table 3. Baseline Data According to Assigned Treatment in Patients With and Without Prior Myocardial Infarction

Characteristic	Prior MI (n=631)			No prior MI (n=3384)		
	Ticagrelor (n=311)	Prasugrel (n=320)	P value	Ticagrelor (n=1699)	Prasugrel (n=1685)	P value
Age, y	67.0 [57.0–75.0]	70.0 [59.0–77.0]	0.021	65.0 [55.0–74.0]	64.0 [55.0–74.0]	0.47
Sex			>0.99			0.71
Female, no. (%)	58 (18.6)	52 (16.2)		419 (24.7)	426 (25.3)	
Diabetes, no. (%)	102 (32.8)	81 (25.3)	0.047	360/1698 (21.2)	347/1684 (20.6)	0.70
Insulin treated, no. (%)	40 (12.9)	24 (7.5)	0.036	103/1698 (6.1)	113/1684 (6.7)	0.49
Smoking, no. (%)	93 (29.9)	92/318 (28.9)	0.86	589/1695 (34.9)	575/1676 (34.2)	0.72
Arterial hypertension, no. (%)	275 (88.4)	280 (87.5)	0.82	1156/1696 (68.2)	1104/1683 (65.6)	0.12
Hypercholesterolemia, no. (%)	258 (83.0)	273 (85.3)	0.48	919/1695 (54.2)	889/1682 (52.9)	0.45
Prior PCI, no. (%)	276 (88.7)	278/318 (87.4)	0.70	176 (10.4)	185 (11)	0.60
Prior CABG, no. (%)	65 (20.9)	71/319 (22.3)	0.75	50 (2.9)	59 (3.5)	0.41
Cardiogenic shock, no. (%)	5 (1.6)	4 (1.2)	0.75	25 (1.5)	29 (1.7)	0.66
Systolic blood pressure (mmHg)	140 [122–160]	142 [125–160]	0.92	140 [130–160]	140 [126–160]	0.34
Diastolic blood pressure (mmHg)	80.0 [70.0–88.0]	80.0 [70.0–89.5]	0.19	80.0 [74.0–90.0]	80.0 [73.0–90.0]	0.47
Heart rate (beats/min)	72.0 [64.0–82.0]	73.0 [63.0–81.2]	0.95	75.0 [66.0–87.0]	75.0 [66.0–85.0]	0.088
Body mass index (kg/m ²)	27.3 [24.8–30.1]	27.7 [25.2–30.4]	0.44	27.2 [24.7–30.0]	27.1 [24.8–30.0]	0.97
Weight <60kg, no. (%)	12/310 (3.9)	14/317 (4.4)	0.89	96/1691 (5.7)	80/1670 (4.8)	0.28
Creatinine (μmol/L)	88.4 [74.3–107]	89.3 [74.3–111]	0.28	82.2 [70.7–97.2]	81.3 [70.7–96.4]	0.49
Diagnosis at admission			0.39			0.99
Unstable angina, no. (%)	62 (19.9)	76 (23.8)		186 (10.9)	185 (11.0)	
Non-STEMI, no. (%)	150 (48.2)	155 (48.4)		780 (45.9)	770 (45.7)	
STEMI, no. (%)	99 (31.8)	89 (27.8)		733 (43.1)	730 (43.3)	
Coronary angiography, no. (%)	310 (99.7)	317 (99.1)	0.62	1691 (99.5)	1683 (99.9)	0.11
Treatment strategy, no. (%)			0.23			0.26
PCI	261/310 (84.2)	262 (81.9)		1414/1696 (83.4)	1438/1684 (85.4)	
CABG	8/310 (2.6)	4 (1.2)		39/1696 (2.3)	32/1684 (1.9)	
Conservative	41/310 (13.2)	54 (16.9)		243/1696 (14.3)	214/1684 (12.7)	
Aspirin on admission	257 (82.6)	264 (82.5)	>0.99	440 (25.9)	451 (26.8)	0.59
Clopidogrel on admission	46 (14.8)	38 (11.9)	0.34	54 (3.2)	57 (3.4)	0.81

Data are shown as counts (proportion; %) or median with 25th–75th percentiles. CABG indicates coronary artery bypass grafting; MI, myocardial infarction; PCI, percutaneous coronary intervention; and STEMI, ST-segment elevation myocardial infarction.

Missing continuous data: Prior MI: diastolic blood pressure, 2 patients (1 in each group); body mass index, 4 patients (1 in the ticagrelor group, 3 in the prasugrel group). No prior MI: systolic blood pressure, 3 patients (1 in the ticagrelor group, 2 in the prasugrel group); diastolic blood pressure, 14 patients (6 in the ticagrelor group, 8 in the prasugrel group); heart rate, 2 patients (1 in each group), body mass index, 27 patients (11 in the ticagrelor group, 16 in the prasugrel group). The remaining continuous data were complete.

associated with a worse cardiovascular risk profile,²¹ recurrent thrombotic events,²² and higher long-term mortality²³ compared with STEMI. Furthermore, compared with patients without prior MI, the majority of patients with prior MI were on aspirin and/or clopidogrel therapy at admission.²⁴ The observation of recurrence of ischemic events despite ongoing antiplatelet therapy highlights the failure of pharmacological secondary prevention strategies and is likely attributable to an ineffective antithrombotic protection owing to drug hyporesponsiveness or adherence issues.^{25–27} Currently, aspirin represents the drug of choice for secondary prevention in patients with established CAD, particularly in those with prior MI and revascularization, whereas clopidogrel serves as an

alternative in patients with aspirin intolerance or high risk of bleeding. Efforts to either replace aspirin with newer P2Y₁₂ inhibitors²⁸ or improve on its efficacy by intensifying or prolonging dual antiplatelet therapy regimens²⁹ or by adding a low-dose anticoagulant³⁰ have not produced convincing results to change current practice. In this regard, the complex interplay between baseline risk, adherence or hyporesponsiveness to antiplatelet regimens, unfavorable vascular pathobiology and the risk for recurrent ischemic events in patients with prior MI remains a matter of future investigation.

Previous evidence supports the clinical superiority of ticagrelor over clopidogrel for prevention of recurrent ischemic events in patients with ACS and previous

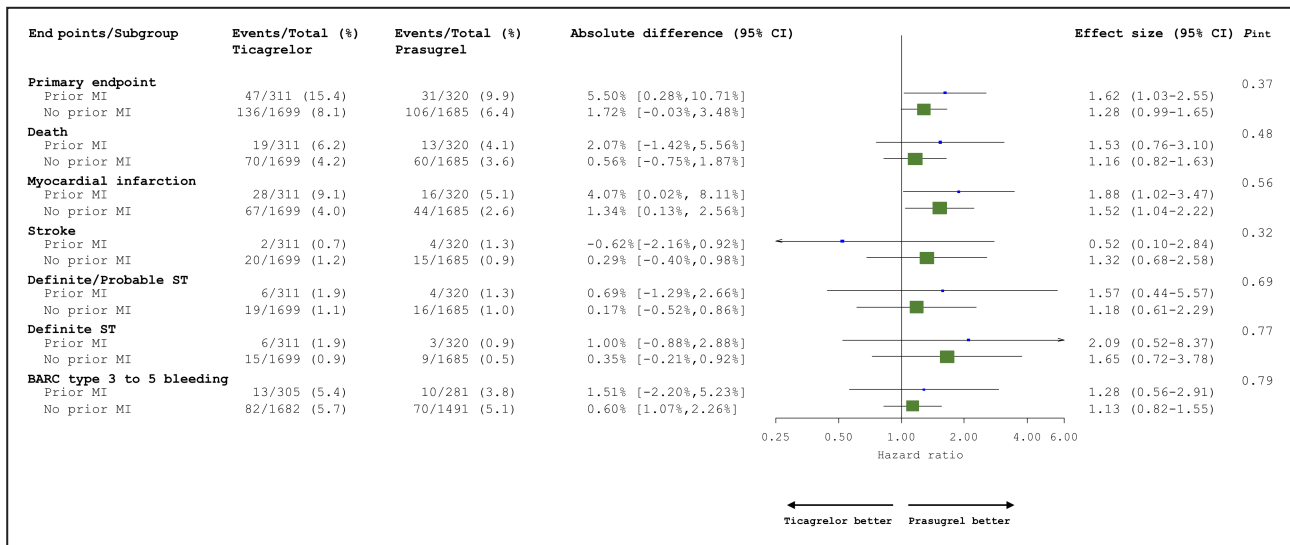


Figure 3. One-year incidences of the primary and secondary end points according to assigned treatment. The cumulative incidence of BARC type 3 to 5 bleeding was assessed in the modified intention-to-treat population. BARC indicates Bleeding Academic Research Consortium type 3 to 5 bleeding; MI, myocardial infarction; P_{int} , P for interaction; and ST, stent thrombosis.

MI, including those receiving invasive management.⁷ Similarly, prasugrel has proven superior antithrombotic protection compared with clopidogrel for secondary prevention of recurrent events in patients with ACS managed conservatively,⁹ whereas no evidence is available for prasugrel versus clopidogrel in patients with ACS and prior MI managed invasively. Of note, investigators of TRITON-TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction 38) provided no data with respect to clinical performance of prasugrel versus clopidogrel according to prior MI status.⁸ Our study for the first time compared the efficacy and safety of ticagrelor versus prasugrel in patients with ACS and prior MI undergoing invasive management. We found no significant statistical interaction between the assigned treatment and prior MI status with respect to the primary end point, a composite of all-cause death, MI, or stroke. In particular, patients with ACS treated with ticagrelor as compared with prasugrel had an excess risk of recurrent MI at 1 year of 52% and 88%, depending on prior MI status. The risk reduction for MI was the main driver for the lower risk of primary end point in patients treated with prasugrel in this study.

Patients with ACS with and without prior MI included in this study did not show statistically significant differences in the risk of major bleeding up to 12-month follow-up and the prior MI status did not influence the bleeding risk in patients assigned to ticagrelor or prasugrel. Patients with recurrent atherothrombotic events, such as those with ACS and prior MI, have enhanced systemic vascular inflammation and a higher

thrombotic burden.³¹ Previous studies have suggested that patients with prior MI might benefit from intensified antiplatelet regimens although at a collateral cost of an increased bleeding risk.^{29,32-34} For this reason, guideline-writing authorities recommend intensified antiplatelet regimens after ACS in patients at increased ischemic risk, as those with a prior MI, without concomitant high risk for bleeding.⁶ In this regard, a dual antiplatelet therapy regimen with prasugrel in patients with ACS and prior MI may provide superior protection, because of a more potent and irreversible platelet inhibition by prasugrel as compared with ticagrelor,³⁵ without excess bleeding complications because of the age- and weight-adjusted dose regimen and the strategy of no pretreatment in prasugrel-assigned patients presenting with non-ST-segment elevation ACS.^{13,36} In line with these considerations, although the present study expands previous findings by providing a head-to-head comparison of newer-generation oral P2Y₁₂ inhibitors in the high-risk cohort of patients with ACS and prior MI, it lacks the sufficient statistical power to provide definitive evidence regarding the comparative efficacy and safety of prasugrel and ticagrelor in this clinical setting.

Study Limitations

Our study is a post hoc analysis of a randomized controlled trial, which makes it liable to limitations associated with post hoc analyses in general. In this regard, our findings should be considered as hypothesis generating without causative association. Another limitation is that patients were not randomized according to

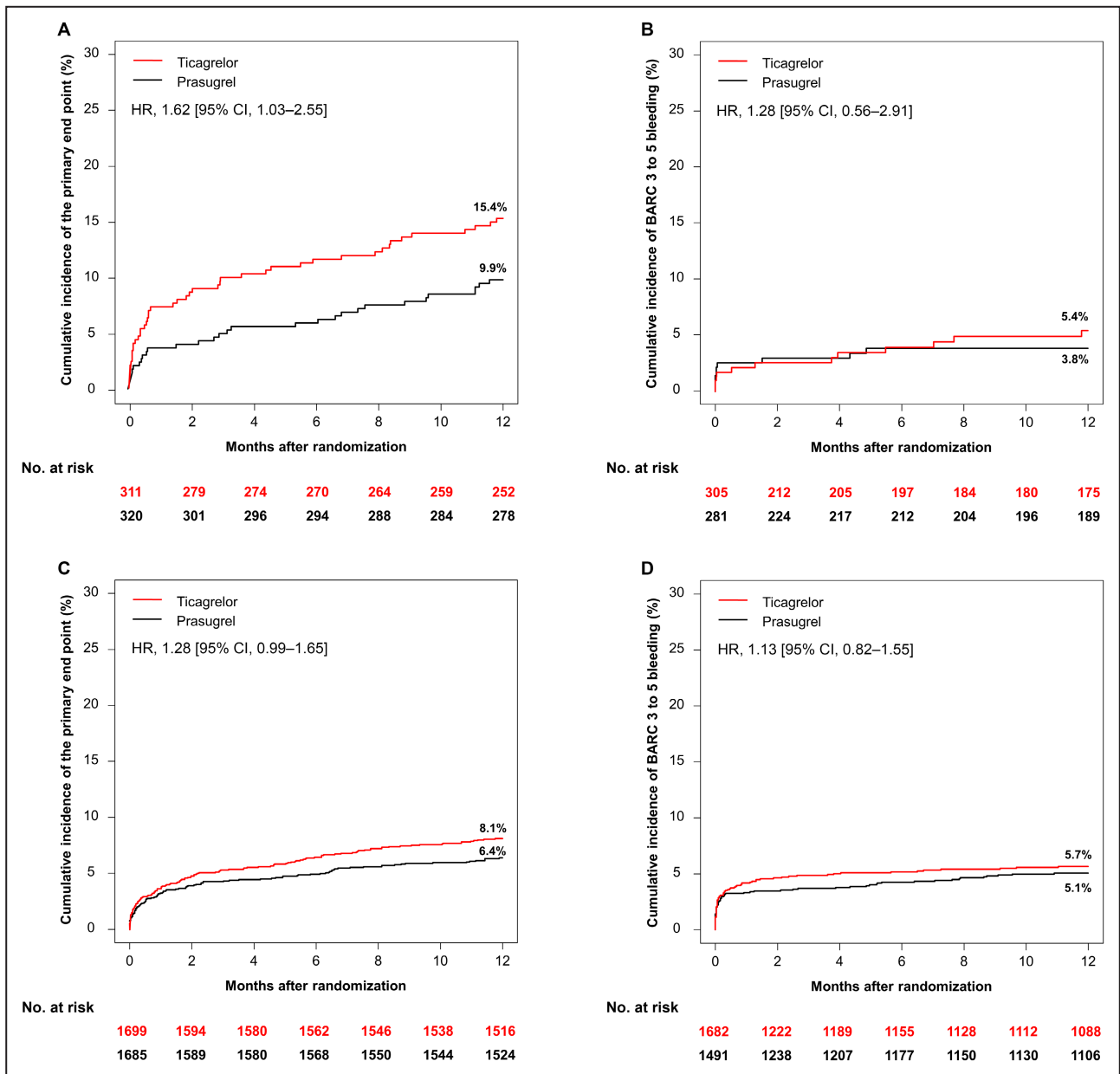


Figure 4. Cumulative incidence of the primary and secondary safety end points according to assigned treatment at 12 months.

A, Cumulative incidence of the primary end point in the Prior MI group. **B**, Cumulative incidence of BARC type 3 to 5 bleeding in the Prior MI group. **C**, Cumulative incidence of the primary end point in the No prior MI group. **D**, Cumulative incidence of BARC type 3 to 5 bleeding in the No prior MI group. The cumulative incidence of BARC type 3 to 5 bleeding was assessed in the modified intention-to-treat population. BARC indicates Bleeding Academic Research Consortium type 3 to 5 bleeding; HR; hazard ratio; and MI, myocardial infarction.

prior MI status and the impact of hidden confounders cannot be ruled out in this context. The categorization of patients according to prior MI status and treatment allocation considerably reduced the statistical power of the present analysis. Complete information about time, extent, type, or localization of previous MI was not available, which may have contributed to underreporting or underestimation of prior MI events. Finally, the study had an open-label design, albeit with

adjudication of adverse events performed in a blinded fashion.

CONCLUSIONS

Patients with ACS and prior MI managed invasively have a significantly higher risk of recurrent ischemic but not bleeding events compared with patients

without prior MI. Prasugrel appears to be superior to ticagrelor in reducing the risk for ischemic events without a tradeoff in bleeding regardless of prior MI status. These data need corroboration from randomized trials specifically focused on patients with ACS and prior MI.

ARTICLE INFORMATION

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Supplemental Material

Table S1–S8

Figure S1

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Supplemental Material

Table S1. Angiographic data in patients with and without prior myocardial infarction*

Characteristic	Prior MI (n=627)	No prior MI (n=3,374)	P value
Access site			0.045
Femoral artery	415 (66.2)	2,087 (61.9)	
Radial artery	207 (33.0)	1,272 (37.7)	
Other	5 (0.8)	15 (0.4)	
Number of diseased coronary arteries			<0.001
No obstructive CAD	15 (2.4)	319 (9.4)	
One-vessel disease	85 (13.6)	1,098 (32.5)	
Two-vessel disease	163 (26.0)	912 (27.0)	
Three-vessel disease	364 (58.1)	1,045 (31.0)	
Multivessel disease	527 (84.1)	1,957 (58.0)	<0.001
Left ventricular ejection fraction[†]	48.8 ± 11.8	52.4 ± 11.0	<0.001

Data are shown as counts (proportion; %) or mean ± standard deviation. CAD, coronary artery disease, MI, myocardial infarction. * Angiographic data were not available for 4 patients with prior MI and 10 patients without prior MI. [†]Left ventricular ejection fraction was not available in 34 patients with prior MI and 189 patients without prior MI.

Table S2. Procedural data in patients with and without prior myocardial infarction

Characteristic	Prior MI (n=631)	No prior MI (n=3,384)	P value
Target vessel			<0.001
Left main coronary artery	12 (2.3)	62 (2.2)	
LAD coronary artery	179 (34.2)	1,285 (45.0)	
Left circumflex coronary artery	118 (22.6)	573 (20.1)	
Right coronary artery	178 (34.0)	910 (31.9)	
Bypass graft	36 (6.9)	23 (0.8)	
Complex lesion (type B2/C)	332 (63.5)	1,654 (58.0)	0.021
More than 1 lesion treated	176 (27.9)	995 (29.4)	0.47
TIMI flow grade before the intervention			<0.001
0	148 (28.3)	1027 (36.0)	
1	30 (5.7)	252 (8.8)	
2	129 (24.7)	618 (21.7)	
3	216 (41.3)	957 (33.5)	
TIMI flow grade after the intervention			0.12
0	7 (1.3)	26 (0.9)	
1	5 (1.0)	11 (0.4)	
2	18 (3.4)	69 (2.4)	
3	493 (94.3)	2,748 (96.3)	
Type of intervention			
Drug-eluting stent	440 (84.1)	2,598 (91.0)	<0.001
Bare-metal stent	5 (1.0)	7 (0.3)	0.030
Bioresorbable vascular scaffold	19 (3.6)	176 (6.2)	0.029
Drug-eluting balloon	35 (6.7)	28 (1.0)	<0.001

Plain balloon angioplasty	42 (8.0)	61 (2.1)	<0.001
Maximal stent diameter (mm)	3.20 ± 0.51	3.19 ± 0.50	0.62
Total stented length (mm)	30.8 ± 17.9	30.5 ± 16.7	0.67
Successful PCI	505 (96.6)	2,795 (98.0)	0.058
Periprocedural antithrombotic medication			
Aspirin	503 (79.7)	3,005 (88.8)	<0.001
Unfractionated heparin	543 (86.1)	2,991 (88.4)	0.11
Low molecular weight heparin	25 (4.0)	152 (4.5)	0.62
Bivalirudin	33 (5.2)	235 (6.9)	0.13
GPIIb/IIIa inhibitor	52 (8.2)	366 (10.8)	0.061

Data are shown as counts (proportions; %) or mean ± standard deviation. GPIIb/IIIa, glycoprotein IIb/IIIa; LAD, left anterior descending; MI, myocardial infarction; PCI, percutaneous coronary intervention; TIMI, Thrombolysis in Myocardial Infarction.

Table S3. Diagnosis and drug therapy at discharge in patients with and without prior myocardial infarction*

Characteristic	Prior MI (n=629)	No prior MI (n=3,378)	P value
Final diagnosis of acute coronary syndrome – no. (%)	579 (92.1)	3,062 (90.6)	0.29
Unstable angina	105/579 (18.1)	257/3,062 (8.4)	
NSTEMI	293/579 (50.6)	1,368/3,062 (44.7)	
STEMI	181/579 (31.3)	1,437/3,062 (46.9)	
Therapy at discharge – no. (%)[†]			
Aspirin	604/618 (97.7)	3,138/3,333 (94.1)	<0.001
Ticagrelor	246/618 (39.8)	1,370/3,333 (41.1)	0.58
Prasugrel	251/618 (40.6)	1,365/3,333 (41.0)	0.91
Clopidogrel	44/618 (7.1)	163/3,333 (4.9)	0.029
Oral anticoagulant drugs	33/618 (5.3)	149/3,333 (4.5)	0.40
Beta blocking agents	527/618 (85.3)	2,757/3,333 (82.7)	0.13
ACE inhibitor/ARB	547/618 (88.5)	2,800/3,333 (84.0)	0.005
Statin	582/618 (94.2)	3,057/3,333 (91.7)	0.046

Data are shown as counts (proportions; %). ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; MI, myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction. * Not available for patients who withdrew consent before discharge. † Shown for patients discharged alive, not available for patients who withdrew consent.

Table S4. Angiographic data according to assigned treatment in patients with and without prior myocardial infarction *

Characteristic	Prior MI (n=627)			No prior MI (n=3,374)		
	Ticagrelor (n= 310)	Prasugrel (n= 317)	P value	Ticagrelor (n=1,691)	Prasugrel (n=1,683)	P value
Access site			0.41			0.65
Femoral artery	203 (65.5)	212 (66.9)		1,040 (61.5)	1,047 (62.2)	
Radial artery	103 (33.2)	104 (32.8)		645 (38.1)	627 (37.3)	
Other	4 (1.3)	1 (0.3)		6 (0.4)	9 (0.5)	
Number of diseased coronary arteries			0.18			0.89
No obstructive CAD	7 (2.3)	8 (2.5)		163 (9.6)	156 (9.3)	
One-vessel disease	50 (16.1)	35 (11.0)		551 (32.6)	547 (32.5)	
Two-vessel disease	72 (23.2)	91 (28.7)		448 (26.5)	464 (27.6)	
Three-vessel disease	181 (58.4)	183 (57.7)		529 (31.3)	516 (30.7)	
Multivessel disease	253 (81.6)	274 (86.4)	0.12	977 (57.8)	980 (58.2)	0.82
Left ventricular ejection fraction[†]	48.3 ± 11.8	49.2 ± 11.8	0.33	52.2 ± 11.1	52.5 ± 11.0	0.35

Data are shown as counts (proportion; %) or mean ± standard deviation. CAD, coronary artery disease. * Angiographic data were not available for 4 patients in the Prior MI group (1 in the ticagrelor group and 3 in the prasugrel group) and 10 patients in the No prior MI group (8 in the ticagrelor group and 2 in the prasugrel group). [†] Left ventricular ejection fraction was not available in 34 patients in Prior MI group (16 in the ticagrelor group and 18 in the prasugrel group) and 189 patients in the No prior MI group (93 in the ticagrelor group and 96 in the prasugrel group).

Table S5. Procedural data according to assigned treatment in patients with and without prior myocardial infarction

Characteristic	Prior MI (n=627)			No prior MI (n=3,374)		
	Ticagrelor (n=311)	Prasugrel (n=320)	P value	Ticagrelor (n=1,699)	Prasugrel (n=1,685)	P value
Target vessel			0.46			0.47
Left main coronary artery	3 (1.2)	9 (3.4)		33 (2.3)	29 (2.0)	
LAD coronary artery	91 (34.9)	88 (33.6)		655 (46.3)	630 (43.8)	
Left circumflex coronary artery	61 (23.4)	57 (21.8)		285 (20.2)	288 (20.0)	
Right coronary artery	90 (34.5)	88 (33.6)		429 (30.3)	481 (33.4)	
Bypass graft	16 (6.1)	20 (7.6)		12 (0.9)	11 (0.8)	
Complex lesion (type B2/C)	172 (65.9)	160 (61.1)	0.29	806 (57.0)	848 (58.9)	0.30
More than 1 lesion treated	79 (25.4)	97 (30.3)	0.19	489 (28.8)	506 (30.0)	0.45
TIMI flow grade before the intervention			0.38			0.44
0	74 (28.4)	74 (28.2)		517 (36.5)	510 (35.4)	
1	14 (5.4)	16 (6.1)		113 (8.0)	139 (9.7)	
2	57 (21.8)	72 (27.5)		304 (21.5)	314 (21.8)	
3	116 (44.4)	100 (38.2)		481 (34.0)	476 (33.1)	
TIMI flow grade after the intervention			0.74			0.29
0	5 (1.9)	2 (0.8)		12 (0.9)	14 (1.0)	
1	2 (0.8)	3 (1.2)		7 (0.5)	4 (0.3)	
2	9 (3.5)	9 (3.4)		41 (2.9)	28 (2.0)	
3	245 (93.9)	248 (94.7)		1,355 (95.8)	1,393 (96.8)	
Type of intervention						
Drug-eluting stent	217 (83.1)	223 (85.1)	0.62	1,279 (90.4)	1,319 (91.7)	0.26

Bare-metal stent	1 (0.4)	4 (1.5)	0.36	3 (0.2)	4 (0.3)	>0.99
Bioresorbable vascular scaffold	8 (3.1)	11 (4.2)	0.65	91 (6.4)	85 (5.9)	0.61
Drug-eluting balloon	19 (7.3)	16 (6.1)	0.72	17 (1.2)	11 (0.8)	0.32
Plain balloon angioplasty	24 (9.2)	18 (6.9)	0.41	33 (2.3)	28 (2.0)	0.56
Maximal stent diameter (mm)	3.2 ± 0.5	3.2 ± 0.5	0.92	3.2 ± 0.5	3.2 ± 0.5	0.48
Total stented length (mm)	32.0 ± 18.6	29.7 ± 17.2	0.16	30.5 ± 16.5	30.4 ± 17.0	0.85
Successful PCI	251 (96.2)	254 (96.9)	0.80	1,388 (98.2)	1,407 (97.8)	0.64
Periprocedural antithrombotic medication						
Aspirin	240 (77.2)	263 (82.2)	0.14	1,508 (88.8)	1,497 (88.8)	0.98
Unfractionated heparin	264 (84.9)	279 (87.2)	0.47	1,490 (87.7)	1,501 (89.1)	0.23
Low molecular weight heparin	13 (4.2)	12 (3.8)	0.94	87 (5.1)	65 (3.9)	0.091
Bivalirudin	15 (4.8)	18 (5.6)	0.78	110 (6.5)	125 (7.4)	0.31
GPIIb/IIIa inhibitor	26 (8.4)	26 (8.1)	>0.99	193 (11.4)	173 (10.3)	0.33

Data are shown as counts (proportions; %) or mean ± standard deviation. GPIIb/IIIa, glycoprotein IIb/IIIa; LAD, left anterior descending; PCI, percutaneous coronary intervention; TIMI, Thrombolysis in Myocardial Infarction.

Table S6. Diagnosis and drug therapy at discharge according to prior myocardial infarction status and assigned treatment*

Characteristic	Prior MI (n=629)			No prior MI (n=3,378)		
	Ticagrelor (n=309)	Prasugrel (n=320)	P value	Ticagrelor (n=1,695)	Prasugrel (n=1,683)	P value
Final diagnosis of acute coronary syndrome – no. (%)	294 (95.1)	285 (89.1)	0.008	1,535 (90.6)	1,527 (90.7)	0.91
Unstable angina	53/294 (18.0)	52/285 (18.2)		136/1,535 (8.9)	121/1,527 (7.9)	
NSTEMI	149/294 (50.7)	144/285 (50.5)		685/1,535 (44.6)	683/1,527 (44.7)	
STEMI	92/294 (31.3)	89/285 (31.2)		714/1,535 (46.5)	723/1,527 (47.3)	
Therapy at discharge – no. (%)[†]						
Aspirin	294/302 (97.4)	310/316 (98.1)	0.72	1,571/1,672 (94.0)	1,567/1,661 (94.3)	0.69
Ticagrelor	242/302 (80.1)	4/316 (1.3)	<0.001	1,360/1,672 (81.3)	10/1,661 (0.6)	<0.001
Prasugrel	5/302 (1.7)	246/316 (77.8)	<0.001	16/1,672 (1.0)	1,349/1,661 (81.2)	<0.001
Clopidogrel	22/302 (7.3)	22/316 (7.0)	>0.99	68/1,672 (4.1)	95/1,661 (5.7)	0.033
Oral anticoagulant drugs	15/302 (5.0)	18/316 (5.7)	0.82	67/1,672 (4.0)	82/1,661 (4.9)	0.22
Beta blocking agents	259/302 (85.8)	268/316 (84.8)	0.83	1,381/1,672 (82.6)	1,376/1,661 (82.8)	0.89
ACE inhibitor/ARB	268/302 (88.7)	279/316 (88.3)	0.96	1,390/1,672 (83.1)	1,410/1,661 (84.9)	0.18
Statins	283 (93.7)	299/316 (94.6)	0.76	1,526 (91.3)	1,531/1,661 (92.2)	0.38

Data are shown as counts (proportions; %). ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; NSTEMI, non-ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction. * Not available for patients who withdrew consent before discharge. † Shown for patients discharged alive, not available for patients who withdrew consent before discharge.

Table S7. Clinical outcomes according to prior myocardial infarction status in patients treated with PCI

Outcome	Prior MI (n=523)	No prior MI (n=2,852)	HR [95% CI]	P value
Primary endpoint (death, myocardial infarction or stroke)	69 (13.4)	212 (7.5)	1.83 [1.39-2.40]	<0.001
BARC type 3 to 5 bleeding*	32 (6.2)	163 (5.8)	1.07 [0.73-1.57]	0.72

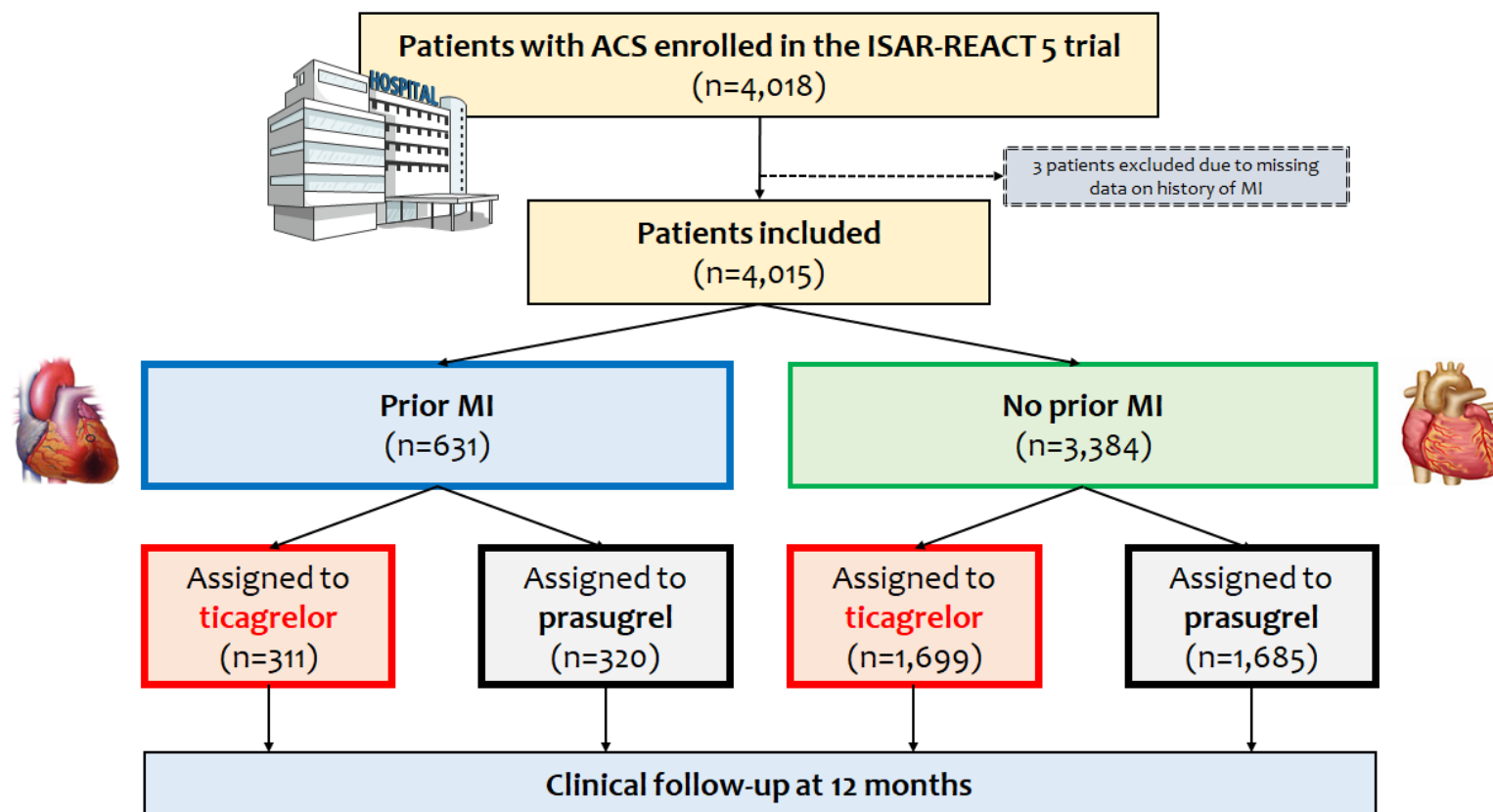
Data are numbers of events with Kaplan-Meier estimates (%) for the primary endpoint and cumulative incidence (%) after accounting for competing risk of death for the safety (bleeding) endpoint. BARC, Bleeding Academic Research Consortium; CI, confidence interval; HR, hazard ratio *BARC type 3 to 5 bleeding was analyzed in the intention-to-treat population.

Table S8. Clinical outcomes according to prior myocardial infarction status and assigned treatment in patients treated with PCI

Outcome	Prior MI (n=523)			No prior MI (n=2,852)			P for interaction
	Ticagrelor (n=261)	Prasugrel (n=262)	HR [95% CI]	Ticagrelor (n=1,414)	Prasugrel (n=1,438)	HR [95% CI]	
Primary endpoint – (death, myocardial infarction or stroke)	42 (16.3)	27 (10.4)	1.63 [1.01-2.65]	119 (8.5)	93 (6.5)	1.31 [1.00-1.71]	0.43
BARC type 3 to 5 bleeding*	13/259 (5.9)	9/257 (3.7)	1.48 [0.63-3.45]	71/1412 (5.3)	69/1422 (5.2)	1.04 [0.75-1.45]	0.45

Data are numbers of events with Kaplan-Meier estimates (%) for the primary endpoint and death or cumulative incidence (%) after accounting for the competing risk of death for the safety (bleeding) endpoint. BARC, Bleeding Academic Research Consortium; CI, confidence interval; HR, hazard ratio; STEMI, ST-segment elevation myocardial infarction. *BARC type 3 to 5 bleeding was analyzed in the modified intention-to-treat population.

Figure S1. Study flowchart.



ACS, acute coronary syndrome; ISAR-REACT, Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment; MI, myocardial infarction.