

# Platelet Inhibition, Endothelial Function, and Clinical Outcome in Patients Presenting With ST-Segment–Elevation Myocardial Infarction Randomized to Ticagrelor Versus Prasugrel Maintenance Therapy: Long-Term Follow-Up of the REDUCE-MVI Trial

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**Background**—Off-target properties of ticagrelor might reduce microvascular injury and improve clinical outcome in patients with ST-segment–elevation myocardial infarction. The REDUCE-MVI (Evaluation of Microvascular Injury in Revascularized Patients with ST-Segment–Elevation Myocardial Infarction Treated With Ticagrelor Versus Prasugrel) trial reported no benefit of ticagrelor regarding microvascular function at 1 month. We now present the follow-up data up to 1.5 years.

**Methods and Results**—We randomized 110 patients with ST-segment–elevation myocardial infarction to either ticagrelor 90 mg twice daily or prasugrel 10 mg once a day. Platelet inhibition and peripheral endothelial function measurements including calculation of the reactive hyperemia index and clinical follow-up were obtained up to 1.5 years. Major adverse clinical events and bleedings were scored. An intention to treat and a per-protocol analysis were performed. There were no between-group differences in platelet inhibition and endothelial function. At 1 year the reactive hyperemia index in the ticagrelor group was  $0.66 \pm 0.26$  versus  $0.61 \pm 0.28$  in the prasugrel group ( $P=0.31$ ). Platelet inhibition was lower at 1 month versus 1 year in the total study population (61% [42%–81%] versus 83% [61%–95%];  $P<0.001$ ), and per-protocol platelet inhibition was higher in patients randomized to ticagrelor versus prasugrel at 1 year (91% [83%–97%] versus 82% [65%–92%];  $P=0.002$ ). There was an improvement in intention to treat endothelial function in patients randomized to ticagrelor ( $P=0.03$ ) but not in patients randomized to prasugrel ( $P=0.88$ ). Major adverse clinical events (10% versus 14%;  $P=0.54$ ) and bleedings (47% versus 63%;  $P=0.10$ ) were similar in the intention-to-treat analysis in both groups.

**Conclusions**—Platelet inhibition at 1 year was higher in the ticagrelor group, without an accompanying increase in bleedings. Endothelial function improved over time in ticagrelor patients, while it did not change in the prasugrel group.

**Clinical Trial Registration**—URL: <https://www.clinicaltrials.gov/>. Unique Identifier: NCT02422888. (*J Am Heart Assoc.* 2020;9:e014411. DOI: 10.1161/JAHA.119.014411.)

**Key Words:** endothelial function • microvascular injury • platelet inhibition • prasugrel • ST-segment–elevation myocardial infarction • ticagrelor

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Accompanying Data S1 through S3, Tables S1 through S8 and Figures S1 through S3 are available at <https://www.ahajournals.org/doi/suppl/10.1161/JAHA.119.014411>

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## Clinical Perspective

### What Is New?

- This study reports the long-term follow-up of patients with ST-segment–elevation myocardial infarction randomized to ticagrelor versus prasugrel maintenance therapy and demonstrated a higher platelet inhibition at 1 year with an improvement in peripheral endothelial function in the ticagrelor group. Interestingly, platelet inhibition was significantly lower at 1-month versus 1-year follow-up.

### What Are the Clinical Implications?

- In patients with ST-segment–elevation myocardial infarction on P2Y<sub>12</sub> inhibitor maintenance therapy, it is clinically of great importance to seek for an optimal balance in the benefit–risk ratio of platelet inhibition.
- The lower platelet inhibition at 1 month could be explained either by a hampered platelet inhibition in the subacute phase after ST-segment–elevation myocardial infarction (with an associated increased risk of ischemic events) or by an exceedingly amplified platelet inhibition after 1 year of P2Y<sub>12</sub> inhibitor treatment (with an associated increased bleeding risk).

In patients with ST-segment–elevation myocardial infarction (STEMI), the preferred treatment is immediate percutaneous coronary intervention of the culprit coronary artery with antiplatelet therapy. Currently, the P2Y<sub>12</sub> inhibitors ticagrelor and prasugrel are recommended as antiplatelet therapy both in the acute setting and as maintenance therapy.<sup>1</sup> Despite successful revascularization, microvascular injury occurs in about half of patients with STEMI,<sup>2</sup> and its presence is associated with poor outcome.<sup>3</sup> It has been proposed that equilibrative nucleoside transporter-1 inhibition of ticagrelor could cause elevated adenosine levels and thereby may preserve endothelial function and prevent microvascular injury in STEMI with potentially better clinical outcome.<sup>4–7</sup> The REDUCE-MVI (Evaluation of Microvascular Injury in Revascularized Patients with ST-Segment–Elevation Myocardial Infarction Treated With Ticagrelor Versus Prasugrel) trial, was the first randomized trial that investigated the potential effect of ticagrelor versus prasugrel maintenance therapy on microvascular injury in patients with STEMI assessed by the index of microcirculatory resistance (IMR).<sup>8</sup> Ticagrelor as compared with prasugrel did not show a beneficial effect with regard to the IMR in the culprit vessel 1 month after the index event.

Recently, it was reported that ticagrelor treatment at steady state improves peripheral endothelial function assessed by reactive hyperemic peripheral arterial tonometry (RH-PAT) (EndoPAT, Itamar Medical Ltd., Caesarea, Israel) in

patients with a previous myocardial infarction.<sup>9</sup> However, whether ticagrelor maintenance therapy provides benefit over prasugrel with regard to long-term peripheral endothelial function is unknown. Also, comparative randomized data on platelet inhibition with either ticagrelor or prasugrel maintenance therapy are currently not available.

Here, we present the 1.5-year clinical follow-up of the REDUCE-MVI trial, including serial measurements of platelet inhibition and peripheral endothelial function as assessed by means of RH-PAT.

## Methods

### Study Design and Outcome Measures

The current study is the predefined long-term clinical follow-up of the REDUCE-MVI Trial.<sup>8</sup> This investigator-initiated, randomized, multicenter trial compared the potential effects of ticagrelor versus prasugrel maintenance therapy on microvascular injury in patients with STEMI. The study trial design<sup>10</sup> and the short-term primary outcome with IMR at 1 month and cardiac magnetic resonance imaging parameters as secondary outcomes were previously published.<sup>8</sup> In the present study, we describe patient characteristics, platelet inhibition, patient symptoms, and clinical outcome (including bleeding) at 1- and 1.5-year follow-up. Furthermore, we present the serial peripheral endothelial function measurements by means of RH-PAT. The study protocol complies with the Declaration of Helsinki, was approved by the institutional review board (local ethics committee), and conforms to the International Conference on Harmonization/Good Clinical Practice standards. The trial is registered at URL: <https://clinicaltrials.gov>, with the unique identifier: NCT02422888. The data that support the findings of this study are available from the corresponding author upon reasonable request.

The trial was conducted at 6 centers in the Netherlands and Spain. In short, patients with a STEMI presenting <12 hours after onset of symptoms were considered eligible. All patients had multivessel disease, were <75 years old, and received a loading dose of ticagrelor (180 mg). Table S1 includes a complete overview of the inclusion and exclusion criteria. After providing written informed consent, patients were randomized in a 1:1 fashion to either ticagrelor 90 mg twice daily or prasugrel 10 mg once daily as maintenance therapy for 1 year using a secure web-based electronic case report form system (Castor EDC, Amsterdam, the Netherlands). When the physician responsible for the clinical care of the patient decided that the randomized study drug was contraindicated, the patient could stop or switch their P2Y<sub>12</sub> inhibitor before 1 year and continued follow-up for the further duration of the study. Concomitant medical therapy after 1 year was left to the discretion of the treating physician and was based on current

guidelines.<sup>1</sup> Follow-up at 1 year was performed before cessation of the P2Y<sub>12</sub> inhibitor and at 1.5 years was performed to examine patient outcomes after cessation of the P2Y<sub>12</sub> inhibitor. We assessed medication compliance each visit with a questionnaire.

## Laboratory Measurements and Platelet Inhibition

Blood samples were collected in the acute setting and at all follow-up visits and were subsequently sent to the local laboratory to assess standard clinical parameters (eg, blood count, lipid spectrum, and inflammatory status). In addition, in the acute setting during the index procedure, at 1 month during the follow-up coronary angiogram, and at 1-year follow-up, we quantified platelet aggregation by percentage of inhibition by analysis of the collected blood samples with the VerifyNow System (Accumetrics, San Diego, CA). Blood was collected in a citrate-coated tube, and the first 2 to 4 mL of blood was discarded to prevent spontaneous platelet activation. The percentage of platelet inhibition was calculated as follows:  $([BASE-PRU]/BASE) \times 100$  as previously described.<sup>11</sup> We assumed a high platelet reactivity when the P2Y<sub>12</sub> reaction units (PRU) exceeded 208<sup>12,13</sup> and a low platelet reactivity when PRU was below 85.<sup>14</sup> As an alternative threshold we also described PRU <95, as this cutoff value is known to be associated with an increased bleeding risk.<sup>15</sup>

## Peripheral Endothelial Function Measurements

To assess peripheral endothelial function, RH-PAT using the EndoPAT device was performed in the acute setting (<24 hours after presentation), at 1 month, at 1 year, and at 1.5-year follow-up. The EndoPAT device measures the endothelium-mediated changes in vascular tone with each arterial pulsation by 2 plethysmographic probes placed on the index fingers. RH-PAT measurements were performed in the contralateral arm used for coronary angiographic access: (1) under resting conditions for 5 minutes; (2) after inflation of a blood cuff on the study arm, while the contralateral (angiographic access site) arm served as control for 5 minutes; and finally (3) after deflation of the blood cuff to induce reactive hyperemia for an additional 5 minutes.

The reactive hyperemia index (RHI) was calculated as a measure of reactive hyperemia by the ratio of the post- over preocclusive average amplitude of the RH-PAT signal, normalized for the control arm to compensate for possible concurrent nonendothelial-dependent systemic alterations in vascular tone. An exact description of the RH-PAT measurements was previously published.<sup>16</sup> Because of skewness of the data, we described the natural logarithm of RHI.<sup>17</sup> A decreased endothelial function was defined as RHI <1.67,<sup>18</sup> which resulted in a logarithmic RHI <0.51.

## Patient Symptoms and Clinical Follow-Up

A complete overview of the methods used to assess the occurrence and severity of angina (Seattle Angina Questionnaire and Canadian Cardiovascular Society grading), dyspnea (Borg Dyspnea Scale), and heart failure (New York Heart Association Functional class) is described in Data S1.

Major adverse clinical events (MACE) were prospectively collected between the index event and 1.5-year follow-up. MACE was defined as death and recurrent myocardial infarction. As a safety objective, we compared the occurrence and severity of bleedings between both groups. The severity of bleeding was classified by the Bleeding Academic Research Consortium criteria.<sup>19</sup> A blinded clinical study investigator performed the adjudication of events.

## Statistical Analysis

The REDUCE-MVI trial had a superiority design with a power of 80% to detect a between-group difference in IMR of 7 (arbitrary unit) with an SD of 12 in favor of the ticagrelor group at 1-month follow-up. Details of the sample size calculation are provided in Data S2. SPSS Statistics, version 22 (IBM Corp, Armonk, NY) was used to perform statistical analyses. For the current study, an intention-to-treat (ITT) analysis was used to assess the difference in outcome measures in patients randomized to ticagrelor versus prasugrel maintenance therapy. We prespecified the per-protocol (PP) analysis for secondary outcomes in the original protocol. PP analyses for all end points during 1-year follow-up were performed in those patients who did not switch or stop their randomized P2Y<sub>12</sub> therapy before 1 year. PP analyses for 1.5-year follow-up involved the subgroup of patients included in the 1-year follow-up PP analysis that no longer received a P2Y<sub>12</sub> inhibitor at 1.5-year follow-up.

A complete overview of the statistical analysis methods can be found in Data S3. Continuous normally distributed data were reported as mean±SD and non-normally distributed data as median (interquartile range). Dichotomous data were described as number (%). To assess between-group differences in continuous variables, an independent t test or Mann–Whitney *U* test was used as appropriate. Paired analyses were performed with the paired sample t test or Wilcoxon signed-rank test as appropriate. To assess between-group differences in categorical variables, a Pearson chi-square test was used, and results were summarized as numbers (%). Paired analyses with dichotomous variables were performed by the McNemar test. A linear mixed-model analysis was used to compare changes in mean RHI over time between treatment groups. Generalized estimating equations were used to compare changes in proportion of patients with decreased RHI value over time between treatment groups. Time to MACE was visualized by Kaplan–Meier curve and compared between groups using the log-rank test. A hazard ratio was calculated,

with prasugrel as the reference group. Statistical significance was assumed when 2-sided  $P$  was  $<0.05$ .

## Results

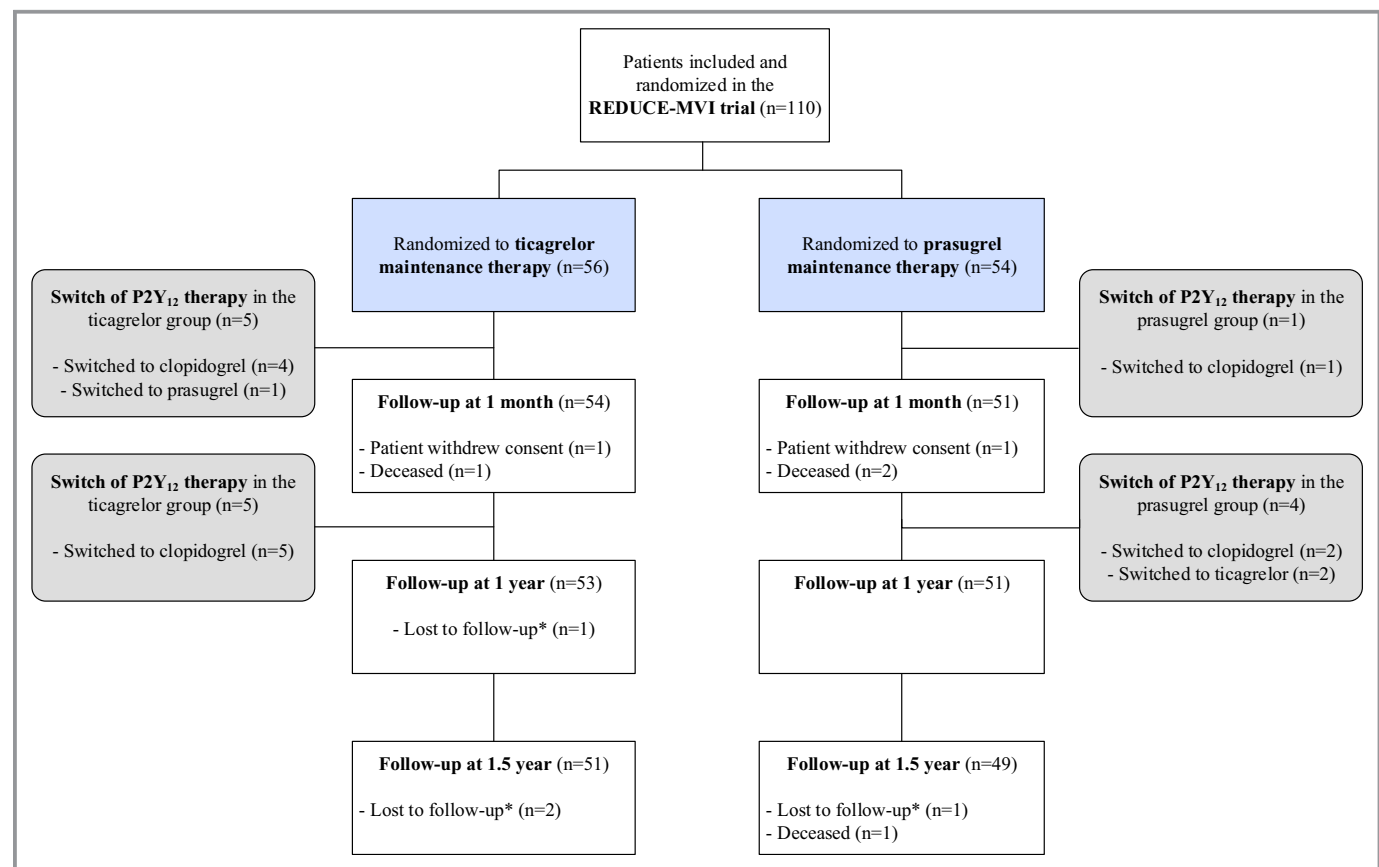
### Study Population and Treatment Strategy

Between May 2015 and October 2017 a total of 110 patients with STEMI were randomized to either ticagrelor ( $n=56$ ) or prasugrel ( $n=54$ ) maintenance therapy. Baseline and procedural characteristics of the total study population during the index procedure are described in Tables S2 and S3, respectively. Two patients withdrew informed consent before the primary end point. The total study population therefore consisted of 108 patients (ticagrelor [ $n=55$ ] versus prasugrel [ $n=53$ ]). Figure 1 represents the study flowchart during the conduct of the study. Figure S1 represents the study flowchart of the patients included in the per-protocol analysis at 1 year ( $n=84$ ) and at 1.5 years ( $n=77$ ), and Table S4 demonstrates the PP patient characteristics at 1-year follow-up. There was no difference in time between ticagrelor loading dose and the start of the index procedure (55 [39–70] minutes in the ticagrelor group versus 50 [36–71] minutes in the prasugrel group;  $P=0.55$ )

One-year follow-up was performed at  $11.8 \pm 0.5$  months and 1.5-year follow-up at  $18.6 \pm 1.4$  months. There were no relevant differences in patient characteristics, medication use or laboratory values at 1-year follow-up in patients randomized to ticagrelor versus prasugrel maintenance therapy (Table 1). During the conduct of the study, 9% of patients randomized to ticagrelor switched to either prasugrel or clopidogrel, and 5% of patients randomized to prasugrel switched to ticagrelor or clopidogrel for various reasons (Table S5). A total of 8% of patients stopped with their randomized P2Y<sub>12</sub> inhibitor before 1-year follow-up without replacement of another P2Y<sub>12</sub> inhibitor. There were no significant differences between patients initially randomized to ticagrelor versus prasugrel in cessation/switch of the initially randomized P2Y<sub>12</sub> treatment ( $P=0.44$ ). At 1.5-year follow-up, 11% of patients were still on P2Y<sub>12</sub> inhibition therapy: 4% received ticagrelor, 2% received prasugrel, and 6% received clopidogrel maintenance therapy.

### Platelet Inhibition

In the ITT analysis, there were no significant differences between the ticagrelor versus prasugrel group in platelet



**Figure 1.** Study enrollment and participation flowchart. \*In these patients we did retrieve the survival status at 1.5-year follow-up, and we therefore also included them in the final analysis.

**Table 1.** Patient Characteristics at 1-Year Follow-Up

	Ticagrelor (n=53)	Prasugrel (n=51)	P Value
Time to 1-y follow-up (d), mean±SD	359±7	360±19	0.64
Age at initial admission, y, mean±SD	60.1±10.4	61.2±8.8	0.54
Male, n (%)	46/53 (86.8)	42/51 (82.4)	0.53
Systolic blood pressure (mm Hg), mean±SD	134±16	135±17	0.78
Diastolic blood pressure (mm Hg), mean±SD	81±11	80±13	0.77
Heart rate (bpm), mean±SD	64±14	66±11	0.59
Medication at follow-up			
P2Y <sub>12</sub> inhibitor, n (%)	49/53 (92.5)	46/51 (90.2)	0.68
Acetylsalicylic acid, n (%)	51/53 (96.2)	48/51 (94.1)	0.62
Oral anticoagulants, n (%)	1/53 (1.9)	1/51 (2.0)	0.98
β-Blocker, n (%)	44/53 (83.0)	37/51 (72.5)	0.20
ACE-i, n (%)	31/53 (58.5)	29/51 (56.9)	0.87
ARB, n (%)	9/53 (17.0)	10/51 (19.6)	0.73
Lipid lowering medication, n (%)	48/53 (90.6)	47/51 (92.2)	0.77
Long acting nitrate, n (%)	2/53 (3.8)	1/51 (2.0)	0.58
CCB, n (%)	4/53 (7.5)	3/51 (5.9)	0.74
Diuretics, n (%)	2/53 (3.8)	6/51 (12.0)	0.12
Diabetes mellitus medication, n (%)	5/53 (9.4)	3/51 (5.9)	0.50
Anti-inflammatory drugs, n (%)	3/53 (5.7)	5/51 (9.8)	0.43
Laboratory values			
Hemoglobin (mmol/L), mean±SD	9.0±0.7	8.9±0.8	0.45
Hematocrit (L/L), mean±SD	0.43±0.04	0.43±0.04	0.84
Platelet count (×10 <sup>9</sup> /L), mean±SD	242.5±61.9	235.0±50.1	0.51
Total leukocyte count (×10 <sup>9</sup> /L), median (IQR)	6.4 (5.7–7.9)	7.0 (5.8–8.1)	0.42
Total cholesterol (mmol/L), mean±SD	3.4±0.9	3.7±1.1	0.18
HDL (mmol/L), mean±SD	1.2±0.4	1.3±0.4	0.35
LDL (mmol/L), median (IQR)	1.7 (1.2–2.0)	1.6 (1.1–2.2)	0.75
Triglycerides (mmol/L), median (IQR)	1.4 (2.1–0.9)	1.4 (1.0–2.0)	>0.99
CRP (mg/L), median (IQR)	2.5 (2.5–2.5)	2.5 (2.5–2.5)	0.88
LDH (U/L), median (IQR)	197 (182–220)	194 (182–228)	0.99
Glucose (mmol/L), median (IQR)	5.5 (5.0–6.5)	5.3 (4.9–6.1)	0.61
NT-proBNP (ng/L), median (IQR)	90 (43–340)	97 (49–243)	0.81

ACE-i indicates angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker; CRP, C-reactive protein; HDL, high-density lipoprotein; IQR, interquartile range; LDH, lactate dehydrogenase; LDL, low-density lipoprotein; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

inhibition or reactivity during the index procedure, at 1 month or at 1 year (Table 2, Figure 2A and 2B). In the total study population, platelet inhibition was lower (61 [42–81] versus 83 [61–95];  $P<0.001$ ) and PRU was higher (84 [44–132] versus 38 [12–84];  $P<0.001$ ) at 1 month compared with 1 year (Figure 3A and 3B). At 1-year follow-up, 79% of patients randomized to ticagrelor had low platelet reactivity (<85) versus 71% in the prasugrel group ( $P=0.39$ ). A total of 7% of patients randomized to

ticagrelor had high platelet reactivity (>208) versus 7% in the prasugrel group ( $P=0.95$ ).

In the PP analysis, platelet inhibition at 1-year follow-up was significantly higher in patients randomized to ticagrelor compared with prasugrel (Table 3, Figure 2C and 2D). Fewer patients had PRU <95 at 1-month versus 1-year follow-up (53% versus 91%;  $P<0.001$ ). Figure 3C and 3D demonstrates the PP platelet inhibition in the total study population from the index procedure to 1-year follow-up.



**Table 2.** ITT Platelet Inhibition and Platelet Reactivity

	Ticagrelor (n=55)	Prasugrel (n=53)	P Value
PRU, median (IQR)			
Index procedure	185 (87–227)	176 (102–236)	0.72
30 d	91 (43–145)	76 (51–119)	0.63
1 y	31 (10–66)	44 (20–97)	0.20
Inhibition (%), median (IQR)			
Index procedure	3 (0–51)	0 (0–39)	0.30
30 d	59 (30–83)	63 (46–78)	0.75
1 y	87 (68–96)	79 (59–92)	0.13
LPR (<85), n (%)			
Index procedure*	10 (22.2%)	9 (18.8%)	0.68
30 d <sup>†</sup>	22 (45.8%)	26 (54.2%)	0.41
1 y <sup>‡</sup>	34 (79.1%)	32 (71.1%)	0.39
HPR (>208), n (%)			
Index procedure*	19 (41.3%)	19 (39.6%)	0.87
30 d <sup>†</sup>	4 (8.3%)	0 (0.0%)	0.04
1 y <sup>‡</sup>	3 (7.0%)	3 (6.7%)	0.95

ITT analysis in the total study population of 108 patients. HPR indicates high platelet reactivity; IQR, interquartile range; ITT, intention-to-treat; LPR, low platelet reactivity; PRU, platelet reactivity unit.

\*ITT analysis; ticagrelor n=45 and prasugrel n=48.

<sup>†</sup>ITT analysis; ticagrelor n=48 and prasugrel n=48.

<sup>‡</sup>ITT analysis; Ticagrelor n=43 and Prasugrel n=45.

## Peripheral Endothelial Function

In the ITT analysis, there were no significant differences in mean RHI between patients randomized to ticagrelor versus prasugrel at individual time points (Figure 4). At 1-year follow-up, RHI in the ticagrelor group was  $0.66 \pm 0.26$  versus  $0.61 \pm 0.28$  in the prasugrel group ( $P=0.31$ ). In patients with ticagrelor maintenance therapy, average RHI significantly improved ( $P=0.03$ ), while in patients with prasugrel maintenance therapy, RHI did not change ( $P=0.88$ ) over time. However, slopes were not found to differ between groups ( $P=0.16$ ). There was no difference in the number of patients with decreased RHI between patients randomized to ticagrelor versus prasugrel in the acute setting (43% versus 48%;  $P=0.58$ ), at 1-month (41% versus 29%;  $P=0.23$ ), at 1-year (26% versus 31%;  $P=0.57$ ) or at 1.5-year follow-up (33% versus 30%;  $P=0.76$ ). The number of patients with impaired RHI values decreased from acute to 1 year ( $P=0.05$ ) in the ticagrelor group, while in the prasugrel group it did not change ( $P=0.30$ ). In the total study population, RHI was significantly lower in the acute setting compared with 1.5-year follow-up ( $0.54 \pm 0.33$  versus  $0.64 \pm 0.30$ ;  $P=0.03$ ). There were significantly more patients with lower RHI in the acute setting versus 1-year (47% versus 39%;  $P=0.03$ ) and 1.5-year (47% versus 42%;  $P=0.04$ ) follow-

up. The improvement in RHI over time ( $P=0.098$ ) in the total study population was described in Figure S2.

In the PP analysis, there were no significant between-group differences in mean RHI at all time points, but as in ITT analysis, RHI significantly improved over time in patients randomized to ticagrelor ( $P=0.04$ ), while it did not in patients randomized to prasugrel ( $P=0.56$ ) (Figure S3). RHI did not significantly change after cessation of the P2Y<sub>12</sub> inhibitor in patients randomized to ticagrelor ( $0.62 \pm 0.31$  at 1 year versus  $0.62 \pm 0.38$  at 1.5-year;  $P=0.90$ ) or prasugrel ( $0.67 \pm 0.27$  at 1 year versus  $0.68 \pm 0.29$  at 1.5 year;  $P=0.86$ ). The improvement in RHI over time in the total study population was described in Figure S2.

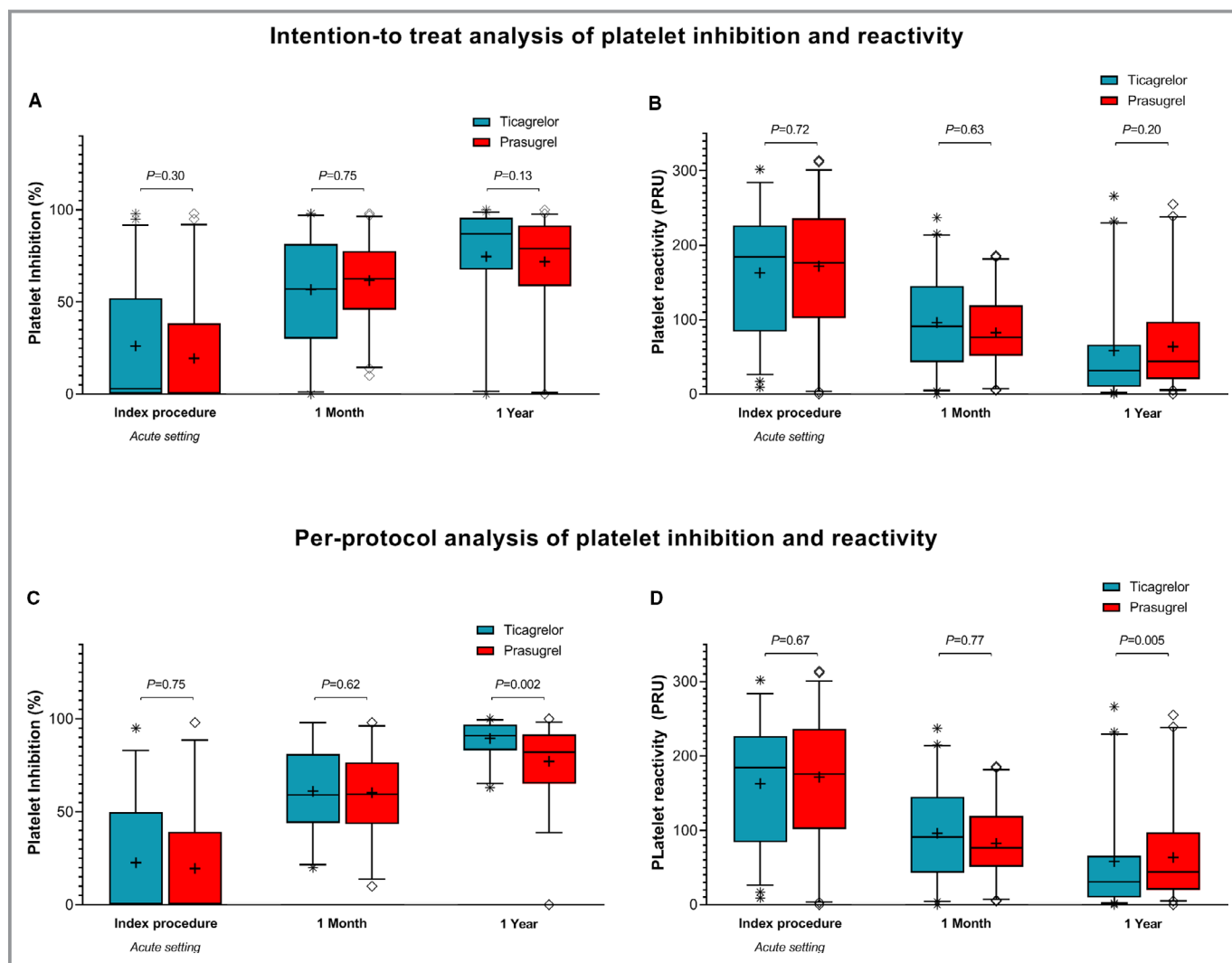
## Clinical and Patient Reported Outcome

In the ITT analysis, there were no between-group differences in the occurrence or severity of dyspnea or angina pectoris at follow-up (Tables 4 and 5). The number of patients with an increased New York Heart Association Functional score (New York Heart Association Functional score >1) at 1.5-year follow-up did not differ between patients randomized to ticagrelor versus prasugrel (13 [26%] versus 13 [27%];  $P=0.91$ ). There were no patients with stroke and 8 patients with myocardial infarction (7.8% in the ticagrelor group versus 8.2% in the prasugrel group;  $P=0.95$ ). There were 22 patients hospitalized during our study (17.0% in the ticagrelor group versus 21.6% in the prasugrel group;  $P=0.55$ ; reasons for hospitalization are described in Table S6). The combined end point of MACE at 1.5 years was not significantly different in patients randomized to ticagrelor versus prasugrel (10% versus 14%;  $P=0.54$ ; Table 5). The hazard ratio for MACE at 1.5-year follow-up with prasugrel as reference group was 0.80 (0.25–2.62), with  $P=0.72$  (Figure 5). During the conduct of the study, 50% of patients had either an actionable minor or major bleeding (Bleeding Academic Research Consortium >2). There was no significant between-group difference in bleedings in patients randomized to ticagrelor versus prasugrel (47% versus 63%,  $P=0.10$ ). The majority of bleedings were nonactionable Bleeding Academic Research Consortium 1 bleedings, and there was no significant difference in Bleeding Academic Research Consortium >1 bleeding score between patients randomized to ticagrelor versus prasugrel maintenance therapy (Tables 4 and 5).

Also in the PP analysis, there were no significant between-group differences in patient symptoms, MACE or bleedings (Table S7). The between-group relative difference (%) and risk (ratio) for clinical discrete outcomes is demonstrated in Table S8.

## Discussion

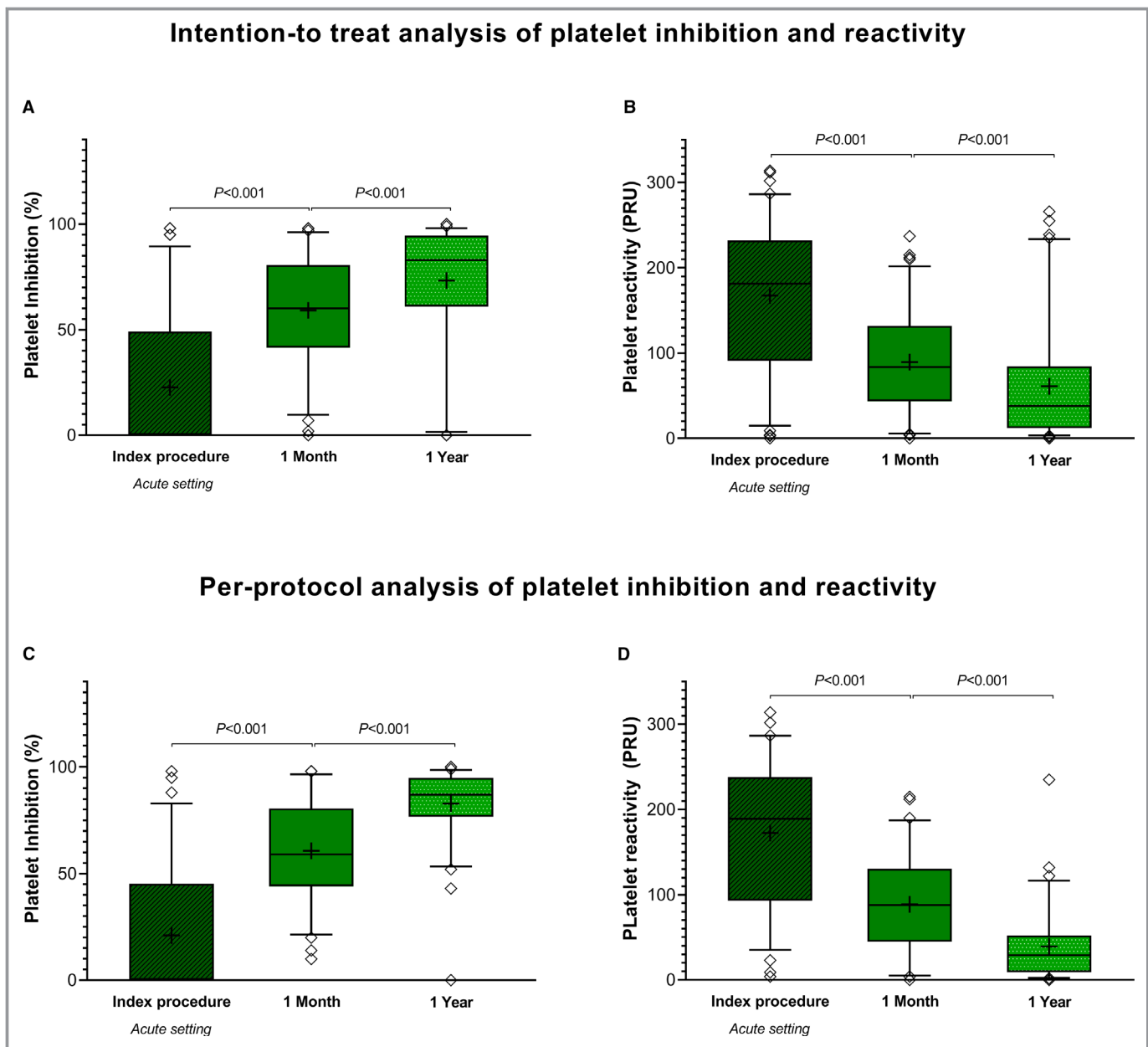
The current long-term follow-up study of the REDUCE-MVI trial reports platelet inhibition, peripheral endothelial function, and



**Figure 2.** Platelet inhibition and reactivity in patients randomized to ticagrelor vs prasugrel. In the intention to treat analysis (**A** and **B**), we included the total study population of 108 patients. The per-protocol analysis (**C** and **D**) was performed in 84 patients who did not switch or stop their randomized P2Y<sub>12</sub> therapy before 1-year follow-up. 3A (ITT) and C (PP) indicate the platelet inhibition, and 3B (ITT) and D (PP) indicate the platelet reactivity in patients randomized to ticagrelor vs prasugrel maintenance therapy at 3 different time points. The line in the boxplots indicates the median, and the cross indicates the mean. PP indicates per-protocol; PRU, platelet reactivity unit; ITT, intention to treat.

clinical outcome up to 1.5 years in patients with STEMI randomized to ticagrelor versus prasugrel maintenance therapy. While the ITT analyses did not reveal between-group differences in platelet inhibition, peripheral endothelial function, the occurrence of patient reported symptoms, bleedings, or MACE up to 1.5 years, the PP analysis revealed a significantly higher platelet inhibition at 1-year follow-up in patients randomized to ticagrelor versus prasugrel; an increase in platelet inhibition from 1-month to 1-year follow-up; a significant improvement in peripheral endothelial function from acute to long-term follow-up in patients randomized to ticagrelor, which persisted after cessation, and which did not occur in patients randomized to prasugrel; and a significantly lower peripheral endothelial function in the acute setting versus 1.5-year follow-up.

The multicenter PRAGUE-18 (Comparison of Prasugrel and Ticagrelor in the Treatment of Acute Myocardial Infarction) trial randomized patients with an acute coronary syndrome (ACS) to either ticagrelor or prasugrel maintenance therapy in the first month following primary percutaneous coronary intervention and reported an equivalent efficacy and safety between both P2Y<sub>12</sub> inhibitors.<sup>20</sup> Present guidelines therefore recommend using either ticagrelor or prasugrel as maintenance therapy in patients presenting with STEMI.<sup>1</sup> It has been suggested that ticagrelor may increase adenosine levels, predominantly at sites of ischemia and tissue injury, by blockage of the equilibrative nucleoside transporter-1 transporter and thus inhibiting adenosine uptake by red blood cells,<sup>4,5</sup> which we could not confirm in the acute setting and up to 1 month in the REDUCE-MVI trial.<sup>8</sup> Below, we discuss



**Figure 3.** Platelet inhibition and reactivity in the total study population. In the intention-to-treat analysis (A and B), we included the total study population of 108 patients. The per-protocol analysis (C and D) was performed in 84 patients who did not switch or stop their randomized P2Y<sub>12</sub> therapy before 1-year follow-up. A-C indicates the platelet inhibition, and B-D indicates the platelet reactivity in the total study population at 3 different time points. The line in the boxplots indicates the median, and the cross indicates the mean. PRU indicates platelet reactivity unit.

the long-term effects of ticagrelor versus prasugrel maintenance therapy on platelet inhibition, endothelial function, and clinical outcome.

### Platelet Inhibition

The REDUCE-MVI trial reported no significant difference in platelet inhibition from the index event to 1-month follow-up between patients randomized to ticagrelor compared with prasugrel maintenance therapy.<sup>8</sup> The loading dose of ticagrelor

given to all patients in the acute setting could have led to a similar platelet inhibition in the acute phase, and because platelet inhibition in the acute and subacute setting was impaired, this could have diluted between-group differences.

In the current long-term follow-up study, we demonstrated higher platelet inhibition at 1 year in the ticagrelor versus prasugrel group, which is in line with a large meta-analysis.<sup>21</sup> A possible mechanism that could explain the higher platelet inhibition in the ticagrelor group is the 24-hour systemic exposure of a direct active compound of ticagrelor versus the



**Table 3.** PP Platelet Inhibition and Platelet Reactivity

	Ticagrelor (n=41)	Prasugrel (n=43)	P Value
PRU, median (IQR)			
Index procedure	189 (84–239)	188 (114–237)	0.67
30 d	93 (45–138)	84 (53–122)	0.77
1 y	19 (7–38)	39 (20–73)	0.005
Inhibition (%), median (IQR)			
Index procedure	0 (0–50)	0 (0–39)	0.75
30 d	61 (44–82)	60 (44–77)	0.62
1 y	91 (83–97)	82 (65–92)	0.002
LPR (<85), n (%)			
Index procedure*	8 (23.5%)	6 (15.8%)	0.41
30 d <sup>†</sup>	15 (44.1%)	19 (50.0%)	0.62
1 y <sup>‡</sup>	29 (96.7%)	29 (78.4%)	0.03
HPR (>208), n (%)			
Index procedure*	15 (44.1%)	16 (42.1%)	0.86
30 d <sup>†</sup>	2 (5.9%)	0 (0%)	0.13
1 y <sup>‡</sup>	0 (0%)	1 (2.7%)	0.36

The PP analysis was performed in 84 patients who did not switch or stop their randomized P2Y<sub>12</sub> therapy before 1-year follow-up. HPR indicates high platelet reactivity; IQR, interquartile range; LPR, low platelet reactivity; PP, per-protocol; PRU, platelet reactivity unit.

\*PP analysis; ticagrelor n=34 and prasugrel n=38.

<sup>†</sup>PP analysis; ticagrelor n=34 and prasugrel n=38.

<sup>‡</sup>PP analysis; ticagrelor n=30 and prasugrel n=38.

short plasma exposure (2–4 hours) of the active metabolite of thienopyridines.<sup>22</sup> Furthermore, ticagrelor is a direct-acting drug that binds reversibly to the P2Y<sub>12</sub> receptor, while prasugrel is a prodrug that binds irreversibly to the P2Y<sub>12</sub> receptor.<sup>23</sup> In addition, ticagrelor inhibits platelet aggregation not only by P2Y<sub>12</sub> antagonism but also via adenosine.<sup>24</sup> In line with our findings, Perl et al<sup>25</sup> demonstrated an increased platelet reactivity in patients with STEMI randomized to prasugrel compared with ticagrelor in the acute setting and up to 1 month, which was confirmed in a randomized crossover pharmacodynamics study in stable patients.<sup>26</sup> Consequently, one might speculate that ticagrelor, in comparison with prasugrel maintenance therapy, reduces the occurrence of ischemic cardiovascular events at the expense of an increased bleeding risk. The recently published ISAR-REACT-5 (Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment 5) trial, however, demonstrated the opposite with an increased occurrence of the primary composite end point of death, myocardial infarction, or stroke at 1-year follow-up in the ticagrelor versus prasugrel group (9.3% versus 6.9%) in 4018 patients with ACS, without a between-group difference in the occurrence of major bleeding.<sup>27</sup>

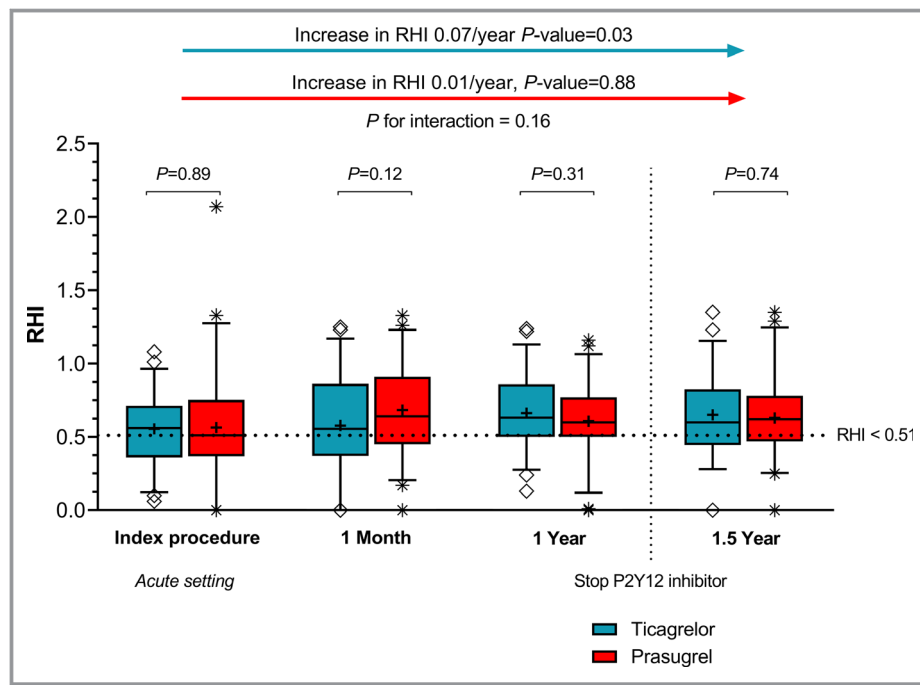
Additionally, for the first time to our knowledge, we report a lower platelet inhibition at 1 month compared with 1 year in our

total STEMI population. This could be explained either by a hampered platelet inhibition in the subacute phase after STEMI (with an associated increased risk of ischemic events) or by an exceedingly amplified platelet inhibition after 1 year of P2Y<sub>12</sub> inhibitor treatment (with an associated increased bleeding risk). It has been proposed that in the acute setting of STEMI, increased levels of reticulated (immature) platelets could increase platelet reactivity in patients on P2Y<sub>12</sub> inhibitor maintenance therapy.<sup>28</sup> Alternatively, increased reactive oxygen species and lipoperoxidation following STEMI are also predictors for increased platelet reactivity.<sup>29</sup> In patients with stable CAD undergoing elective coronary angiogram, there was a large interindividual variability in platelet inhibition that was dependent on pretreatment platelet reactivity,<sup>30</sup> which is increased after STEMI. We hypothesize that in the subacute phase, these mechanisms are not fully normalized yet and contribute to the lower platelet inhibition at 1 month and may furthermore explain the increased risk of ischemic events following STEMI.<sup>31,32</sup> Results by Lynch et al<sup>33</sup> support this hypothesis, demonstrating an increased platelet aggregation up to 3 months after the ACS index event. In patients with STEMI, a PRU  $\geq 282$  was associated with the occurrence of ischemic events and death.<sup>34</sup> Our study was not powered to detect a difference in ischemic events or death. On the contrary, a PRU <95 was associated with a 1.7-fold higher risk of bleeding.<sup>15</sup> Interestingly, we found more patients with a PRU <95 at 1-year versus 1-month follow-up, which could indicate an excessive platelet inhibition at 1 year. Concomitantly, it is clinically of great importance to seek for an optimal balance in the benefit–risk ratio of platelet inhibition in patients with STEMI receiving P2Y<sub>12</sub> inhibitor maintenance therapy.

## Peripheral Endothelial Function

Endothelial dysfunction is not limited to the coronary arteries,<sup>35</sup> and consequently RH-PAT is able to measure the status of peripheral endothelial function, which correlates with coronary endothelial function.<sup>16</sup> In the acute setting of STEMI, circulating markers for endothelial injury in peripheral blood samples are elevated,<sup>36</sup> which supports our finding of an impaired peripheral endothelial function shortly after the index event.

We demonstrate an improvement in endothelial function in patients randomized to ticagrelor, while in patients randomized to prasugrel, endothelial function did not significantly improve over time, although it must be noted that the improvement over time was not significantly different between both groups. Similar to our results, Torngren et al<sup>9</sup> also reported an improvement in peripheral endothelial function in patients with ACS treated with ticagrelor versus prasugrel. In patients with ACS, ticagrelor improved endothelial function, reduced inflammatory cytokines, and increased



**Figure 4.** Peripheral endothelial function and improvement in peripheral endothelial function in patients randomized to ticagrelor vs. prasugrel maintenance therapy. The dashed line represents the established cutoff value for decreased peripheral endothelial function (RHI <1.67 equals the natural logarithm RHI <0.51). The line in the boxplots indicates the median and the cross indicates the mean. The increase in RHI over time was calculated using a mixed-model analysis including time as main effect. RHI indicates reactive hyperemia index.

circulating progenitor cells.<sup>37</sup> The recently published randomized crossover HI-TECH (Hunting for the Off-Target Properties of Ticagrelor on Endothelial Function in Humans) trial reported no beneficial effect of ticagrelor over prasugrel or clopidogrel treatment with regard to peripheral endothelial function, but they did not assess the potential effects of ticagrelor on endothelial function over a prolonged time period.<sup>38</sup> The statistical insignificance between slopes of both groups could have been attributable to the limited statistical power to reveal an interaction.

Although we could not demonstrate increased adenosine plasma levels in the acute and subacute phase in patients randomized to ticagrelor in the REDUCE-MVI trial,<sup>8</sup> this does not exclude possible stimulation of the endothelium by adenosine on a local level, resulting in a release of microcirculatory vasodilators such as nitric oxide, endothelial hyperpolarizing factor, and prostacyclins.<sup>39,40</sup> Endothelial hyperpolarizing factor induces endothelium-dependent microcirculatory vasodilation by activation of the potassium channels<sup>41</sup> and hence remains an interesting target for future studies investigating potential effects of ticagrelor on endothelial function. Additionally, an increase in local concentrations of adenosine may lead to microcirculatory vasodilation by activation of the membrane-bound  $\alpha_{2A}$ -adenosine receptors.<sup>42</sup> We hypothesize that these combined

effects of ticagrelor are accountable for the improvement in endothelial function. Further research is necessary to explore the potential mechanisms by which ticagrelor augments peripheral endothelial function.

## Patient Symptoms and Clinical Outcome

A well-known drug-specific side effect of ticagrelor unrelated to pulmonary function is the manifestation of dyspnea.<sup>43,44</sup> We demonstrated a 42% occurrence of dyspnea in the ticagrelor group versus 35% in the prasugrel group (nonsignificant relative difference of 17%) and a similar severity of dyspnea at 1 year. Although most patients in our study were revascularized at 1-month follow-up, we know that (microvascular) angina still occurs in about 40%.<sup>45</sup> We hypothesized that ticagrelor could improve (microvascular) angina by its previously discussed off-target properties. In our study, we did not observe between-group differences in the presence or severity of angina pectoris or heart failure.

In our study, despite limited statistical power, MACE (9% in the ticagrelor group versus 14% in the prasugrel group) and the occurrence of bleeding (47% in the ticagrelor group versus 63% in the prasugrel group) at long-term follow-up were not statistically different in patients randomized to ticagrelor versus prasugrel. This was in line with a previous

**Table 4.** Patient Symptoms and Clinical Outcome at 1 Year

	Ticagrelor (n=53*)	Prasugrel (n=51 <sup>†</sup> )	P Value
Angina pectoris, n (%)	11/52 (21.2)	9/51 (17.6)	0.65
CCS class, n (%)			
1	9/11 (81.8)	5/9 (55.6)	0.19
2	2/11 (18.2)	3/9 (33.3)	
3	0/11 (0.0)	1/9 (11.1)	
4	0/11 (0.0)	0/9 (0.0)	
SAQ, median (IQR)			
Angina frequency	100 (100–100)	100 (100–100)	0.99
Physical limitation	92 (83–100)	100 (75–100)	0.52
Quality of life	71 (58–89)	83 (67–100)	0.10
Angina stability	100 (100–100)	100 (100–100)	0.84
Treatment satisfaction	94 (81–100)	94 (81–100)	0.25
Dyspnea, n (%)	22/52 (42.3)	18/51 (35.3)	0.47
MBS>3, n (%)	6/22 (27.3)	5/18 (27.8)	0.97
Total number of bleedings, n (%)	23/51 (45.1)	30/51 (58.8)	0.17
BARC score, n (%)			
0	28/51 (54.9)	21/51 (41.2)	0.33
1	19/51 (37.3)	27/51 (52.9)	
2	3/51 (5.9)	2/51 (3.9)	
3	0/51 (0.0)	0/51 (0.0)	
4	1/51 (2.0)	1/51 (2.0)	
5	0/51 (0.0)	0/51 (0.0)	
Death, n (%)	1/55 (1.8)	2/53 (3.8)	0.54
Recurrent myocardial infarction, n (%)	4/53 (7.5)	3/51 (5.9)	0.74
Stroke, n (%)	0 (0.0)	0 (0.0)	NA
Stent thrombosis, n (%)	0 (0.0)	0 (0.0)	NA
Hospitalization, n (%)	6/53 (11.3)	9/51 (17.6)	0.36
Malignant arrhythmia, n (%) <sup>‡</sup>	0/52 (0.0)	1/51 (2.0)	0.31
Intercurrent CAG (without the need for PCI), n (%) <sup>‡</sup>	3/52 (5.8)	0/51 (0.0)	0.08
PCI, n (%) <sup>‡</sup>	3/52 (5.8)	1/51 (2.0)	0.32
Cardiac surgery, n (%) <sup>‡</sup>	0/52 (0.0)	0/51 (0.0)	NA
MACE, n (%)	5/54 (9.3)	5/53 (9.4)	0.98

We included them in the final analysis regarding the occurrence of events (MACE) because we retrieved their survival status at 1 year, except for 1 patient in the prasugrel group for whom we did not have information regarding recurrent myocardial infarction. BARC indicates Bleeding Academic Research Consortium; CAG, coronary angiography; CCS, Canadian Cardiovascular Society; IQR, interquartile range; MACE, major adverse clinical events including death and recurrent myocardial infarction; MBS, Modified Borg Dyspnea Scale; NA, not applicable; PCI, percutaneous coronary intervention; SAQ, Seattle Angina Questionnaire.

\*In the ticagrelor group, 1 patient was deceased and 1 patient was lost to follow-up before 1-year follow-up.

<sup>†</sup>In the prasugrel group, 2 patients were deceased before 1-year follow-up.

<sup>‡</sup>There were no additional events reported between 1- and 1.5-year follow-up.

observational study in 318 patients with STEMI with the combined end point of major adverse cardiac and cerebrovascular events at 1-year follow-up.<sup>46</sup> As our study was not powered to detect differences in clinical end points, caution is needed interpreting our results. The TRITON-TIMI-38 (Trial to

Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel—Thrombolysis in Myocardial Infarction 38) showed that prasugrel compared with clopidogrel prevents ischemic events in patients with ACS, but this resulted in an accompanying increase in Thrombolysis in

**Table 5.** Patient Symptoms and Clinical Outcome at 1.5 Years

	Ticagrelor (n=51*)	Prasugrel (n=49†)	P Value
Angina pectoris, n (%)	10/51 (19.6)	4/49 (8.2)	0.10
CCS class, n (%)			
1	5 (50.0)	2/4 (50.0)	0.87
2	4 (40.0)	2/4 (50.0)	
3	1 (10.0)	0/4 (0.0)	
4	0 (0.0)	0/4 (0.0)	
SAQ, median (IQR)			
Angina frequency	100 (98–100)	100 (100–100)	0.36
Physical limitation	94 (83–100)	96 (81–100)	0.79
Quality of life	75 (66–92)	83 (67–92)	0.16
Angina stability	100 (80–100)	100 (100–100)	0.29
Treatment satisfaction	94 (81–100)	100 (88–100)	0.08
Dyspnea, n (%)	14/51 (27.5)	18/49 (36.7)	0.32
MBS>3, n (%)	6/14 (42.9)	8/18 (44.4)	0.93
Total number of bleedings, n (%)	24/51 (47.1)	31/50 (63.3)	0.10
BARC score, n (%)			
0	27/51 (52.9)	18/50 (36.7)	0.33
1	19/51 (37.3)	26/50 (53.1)	
2	4/51 (7.8)	4/50 (8.2)	
3	0/51 (0.0)	0/50 (0.0)	
4	1/51 (2.0)	1/50 (2.0)	
5	0/51 (0.0)	0/50 (0.0)	
	Ticagrelor (n=55*)	Prasugrel (n=53†)	P Value
Death, n (%)	1/55 (1.8)	3/53 (5.7)	0.29
Recurrent myocardial infarction, n (%)	4/51 (7.8)	4/49 (8.2)	0.95
Stroke, n (%)	0 (0.0)	0 (0.0)	NA
Stent thrombosis, n (%)	0 (0.0)	0 (0.0)	NA
Hospitalization, n (%)	9/53 (17.0)	11/51 (21.6)	0.55
MACE, n (%)	5/52 (9.4)	7/52 (13.5)	0.54

We included them in the final analysis regarding the occurrence of events (MACE) because we retrieved their survival status at 1 year, except for 1 patient in the prasugrel group for whom we did not have information regarding recurrent myocardial infarction. BARC indicates Bleeding Academic Research Consortium; CCS, Canadian Cardiovascular Society; IQR, interquartile range; MACE, major adverse clinical events including death and recurrent myocardial infarction; MBS, Modified Borg Dyspnea Scale; NA, not applicable; SAQ, Seattle Angina Questionnaire.

\*In the ticagrelor group, 1 patient was deceased and 3 patients were lost to follow-up (of whom 2 patients had hospitalization at 1 year follow-up, which we reported) before 1.5-year follow-up.

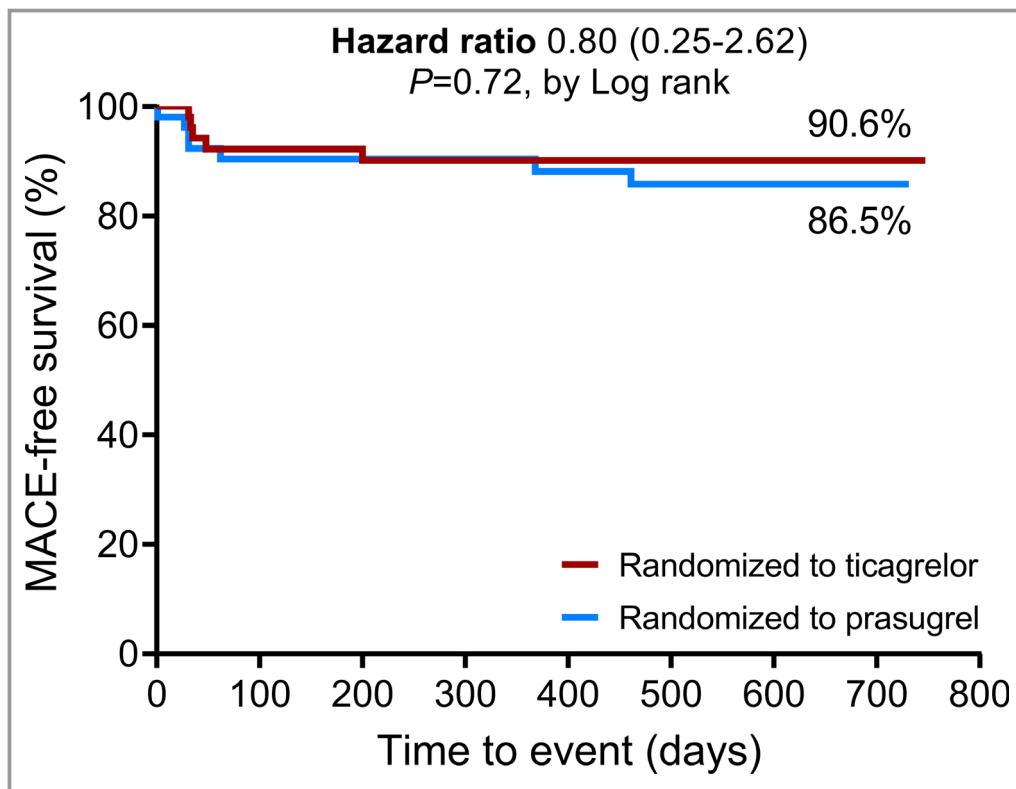
†In the prasugrel group, 3 patients were deceased and 1 patient was lost to follow-up before 1.5-year follow-up.

Myocardial Infarction major bleedings.<sup>47</sup> The PLATO (Platelet Inhibition and Patient Outcomes) trial demonstrated a similar benefit of ticagrelor over clopidogrel with regard to the occurrence of ischemic events in patients with ACS, but without an increase in Thrombolysis in Myocardial Infarction major bleeding rate.<sup>48</sup> On the other hand, it has been reported that patients with STEMI randomized to ticagrelor have an increased risk of bleeding compared with prasugrel.<sup>46</sup> The ISAR-REACT-5 trial including 41.1% STEMI, 46.2% non-ST-segment-

elevation myocardial infarction (NSTEMI), and 12.7% unstable angina patients demonstrated reduced occurrence of MACE without a difference in major bleeding in the prasugrel versus ticagrelor group in a modified intention-to-treat analysis.<sup>27</sup>

## Limitations

There are some limitations that should be considered. First of all, the current study was not powered to detect a significant



**Figure 5.** Kaplan–Meier curve for the occurrence of MACE at 1.5-year follow-up. The Kaplan–Meier curve of the MACE-free survival at 1.5-year follow-up in patients randomized to ticagrelor vs. prasugrel maintenance therapy. The hazard ratio with the 95% CI for the occurrence of MACE, with prasugrel as reference. There is no significant between-group difference in MACE. FU indicates follow-up; MACE, major adverse clinical events.

between-group difference in secondary outcomes. The sample size was determined to detect a between-group difference in the primary end point (IMR at 1 month). Including a PP analysis in our study could have led to selection bias excluding those patients who stopped or switched with their initial randomized medication, although the number of patients deviating from their randomized medication did not differ between groups. In the REDUCE-MVI trial, we reported no differences in adenosine levels in the acute setting up to 1 month in patients randomized to ticagrelor versus prasugrel maintenance therapy. Based on these findings, we hypothesized that this would not change during long-term follow-up, and thus we did not measure adenosine levels at 1- and 1.5-year follow-up. In the REDUCE-MVI main paper, we report a longer symptom-to-balloon time and a higher proportion of patients with hypertension in the ticagrelor compared with the prasugrel group. These differences were not statistically significant but could have influenced results. Furthermore, we did not test P2Y<sub>12</sub>-inhibition adherence by means of ticagrelor or prasugrel levels at follow-up, but we did assess therapy adherence at follow-up by questionnaires and platelet inhibition. Because our main results were primarily based on an ITT analysis, a potential lack in therapy adherence would not alter our main outcomes.

Furthermore, we did not mark the time of intake of the P2Y<sub>12</sub> inhibitors on follow-up days, so the time between medication intake and platelet inhibition tests could vary between patients and randomized groups. At 1 month, blood samples were collected during coronary angiography, which may have influenced platelet inhibition tests. Finally, the study participants, treating physicians, and study team were not blinded for the treatment allocation, and therefore this could have biased our results. The events, however, were adjudicated by a blinded study investigator.

## Conclusions

In this predefined 1.5-year follow-up study of the REDUCE-MVI trial, we report platelet inhibition, peripheral endothelial function, and clinical outcome in patients with STEMI randomized to ticagrelor versus prasugrel maintenance therapy. Ticagrelor maintenance therapy provided higher platelet inhibition at 1 year compared with prasugrel. Additionally, ticagrelor improved peripheral endothelial function from the acute moment to 1.5-year follow-up, albeit not statistically different compared with patients on prasugrel maintenance therapy. Patient symptoms, bleedings, and MACE rate were



not statistically different between both groups; however, our study was not powered to detect differences in clinical outcome.

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## Disclosures

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# **SUPPLEMENTAL MATERIAL**

### **Data S1. Methods and scores for patient symptom assessment.**

To assess the occurrence and severity of angina pectoris, the Seattle Angina Questionnaire (SAQ), a 19-item self-administered questionnaire was used<sup>1</sup>. We report all 5 domains of the SAQ; Physical limitation, Angina stability, Angina frequency, Treatment satisfactory and Quality of life. The domain scores range from 0-100, with higher scores indicating fewer angina, less physical limitations due to angina and an improved quality of life. Additionally, we used the Canadian Cardiovascular Society (CCS) grading to grade the severity of angina pectoris (ranging from 0 (asymptomatic) to 4 (angina at rest))<sup>2</sup>. To assess the occurrence and severity of dyspnea, the modified Borg Dyspnea scale (MDS) was used<sup>3</sup>. The dyspnea scale ranges from 0-10 where 0 is no symptoms of dyspnea and 10 is maximal symptoms of dyspnea. A MDS>3 was considered as severe dyspnea. To assess the occurrence and severity of heart failure, the New York Heart Association Functional (NYHA) classification was used<sup>4</sup>. Class I represents no symptoms, class II symptoms with moderate activity, Class III symptoms with mild activity and Class IV symptoms at rest.

3) The assumed difference of 7 might be underestimated, based on the recent results of the CV-TIME trial\* (difference in mean microcirculatory resistance was 12.2 between Ticagrelor and Clopidogrel<sup>5</sup>. In the power analysis of the study protocol, the assumed difference was based on peripheral endothelial function<sup>6</sup> and the SD was based on a study with a different pharmacological agent<sup>7</sup>. With the current evidence of the CV-TIME trial<sup>5</sup>, the expected difference in microcirculatory resistance between Ticagrelor and Prasugrel would be more than 10, which indicated that we did not have to increase the number of participants to maintain a power of 80% with the observed standard deviation of 17.2 (taking 15% loss to follow-up into account).

Decision of the data safety monitoring board (DSMB) (March 2017): The DSMB would like to state that this second Safety Review addressed the charter and protocol driven interim analysis. Based on this review, we would like to state that the interim analysis did not raise specific safety concerns. Therefore, the REDUCE-MVI study should proceed according to its design. DSMB members: Dr. Jur M. ten Berg (member), Prof. Dr. Jan G.P. Tijssen (member), Prof. dr. Freek W.A. Verheugt (Chair).



## **Data S2. Sample size calculation REDUCE-MVI trial.**

### *Initial sample size calculation*

The sample size calculation of the REDUCE-MVI trial was based on a superiority design with a null-hypothesis that microcirculatory resistance at 1-month follow-up was equal in patients randomized to ticagrelor versus prasugrel maintenance therapy. We anticipated that a mean difference in microcirculatory resistance of 7 in favour of patients randomized to ticagrelor maintenance was considered clinically relevant. To detect this mean difference with a standard deviation (SD) of 12 with a power of 80% (two-sided testing at  $\alpha=0.05$ ), 47 patients in both treatment groups were necessary. Furthermore we accounted for a lost to follow-up of patients of 15% leading to a total study population of 110 patients. We planned a blinded interim analysis with the data safety monitoring board (DSMB) at 50% (n=55) of patient inclusion (see details below). The REDUCE-MVI trial was not powered to detect differences in secondary outcomes.

### *Interim analysis regarding sample size*

Interim analysis (January 2017): We performed a planned interim analysis (as reported in the study protocol) after 50% inclusion to check the assumed SD of the microcirculatory resistance at 1-month follow-up (performed by a statistician of the Amsterdam UMC). The observed SD at 1-month follow-up was 17.2. The re-calculated sample size (with 80% power) was 2 x 96 patients without loss to follow-up and 2 x 112 with 15% loss to follow-up. The re-calculated power (with the current sample size of 110 patients) was 56% without loss to follow-up and 50% with loss to follow-up. We also calculated the difference in microcirculatory resistance between patients treated with ticagrelor and prasugrel that could be detected with the observed SD and 80% power, which was 9.3 without loss to follow-up and 10 with a 15% loss to follow-up. Despite the higher SD than initially assumed, we do not recommend to increase the number of study participants because of the following aspects:

- 1) Complexity of the study with lower inclusion rate than expected
- 2) The power to detect a difference in means of 7 with the observed SD was still acceptable

### **Data S3. Complete overview of the statistical analysis methods.**

The REDUCE-MVI trial had a superiority design with a power of 80% to detect a between group difference in IMR of 7 (arbitrary unit) at 1-month follow-up. Details of the sample size calculation are provided in *Supplemental Material 3*. SPSS Statistics, version 22 (IBM Corp, Armonk, New York) was used to perform statistical analysis. For the current manuscript an intention-to-treat analysis was used to assess the difference in outcome measures in patients randomized to ticagrelor vs. prasugrel maintenance therapy. An additional per-protocol analysis at 1-year was performed in patients who did not switch or stop their randomized P2Y<sub>12</sub> therapy before 1-year and at 1.5-year including patients who did not receive a P2Y<sub>12</sub> inhibitor at 1.5-year follow-up.

Normality was visually assessed by QQ-plots. Continuous normally distributed data were described as mean  $\pm$  standard deviation (SD) and non-normally distributed data as median (interquartile range (IQR)). Dichotomous data were described as number (percentage, %). To assess between group differences in continuous variables, an independent t-test or Mann-Whitney U test were used as appropriate. Paired analyses with continuous data were performed with the paired sample t-test or Wilcoxon signed rank test as appropriate. To assess between group differences on nominal categorical variables, a Pearson Chi-Square test was used and results were summarized as numbers (%). Paired analyses with dichotomous variables were performed by the McNemar test. Mann-Whitney test was used to compare groups on ordinal categorical variables. A linear mixed model analysis was used to compare changes in mean RHI over time between treatment groups. The mixed model included a random effect for subject and fixed effects for treatment group, time and their two-way interaction. Time was included as a continuous variable in the model. Separate estimates for changes in mean RHI per year and p-value for each of the two treatment groups were obtained from this model. An additional model with the interaction term omitted was fitted in order to estimate the mean change in the whole study population. Generalized Estimating Equations (GEE) with unstructured working correlation matrix were used to compare changes in proportion of patients with decreased RHI value over time between treatment groups. The model included time, treatment group and their two-way interaction as predictors. Separate

odds ratios for the change in proportion of patients with decreased RHI value for each year increase in follow-up time and p-value for the two treatments groups were obtained from this model. An additional GEE model with the interaction term omitted was fitted in order to estimate a single odds ratio for the change in proportion of patients with decreased RHI value in the whole study population. All analyses were performed for 1 and 1.5-year follow-up and separately for the intention-to-treat and per-protocol population. Time to MACE was visualized by the Kaplan-Meier curve, with the log ranked Hazard ratio to assess the between group probability of MACE (with prasugrel as the reference group). Statistical significance was assumed when *P*-value was <0.05.

**Table S1. List of in- and exclusion criteria of the REDUCE-MVI trial.**

*Inclusion criteria:*

1. Provision of informed consent
2. Patients presenting with STEMI < 12 hours
3. Successful PCI of the culprit artery with a modern drug eluting stent (DES)
4. The presence of an intermediate stenosis in a non-culprit artery (50-90%)

*Exclusion criteria:*

1. Previous history of myocardial infarction
2. Participation in another clinical trial with an investigational product during the preceding 30 days
3. History of cerebrovascular accident (CVA) or 'transient ischaemic attack' (TIA)
4. History of intracranial haemorrhage
5. Indication or use of anticoagulant therapy (i.e. acenocoumarol)
6. Severe liver dysfunction (Child-Pughscore 10-15)
7. Congestive heart failure
8. Cardiogenic shock
9. Left ventricular ejection fraction < 35%
10. Bleeding diathesis
11. Age  $\geq 75$  or < 18
12. Body weight < 60 kg
13. Gout
14. Coagulation disorders
15. Severe pulmonary disease
16. Pregnancy and breast feeding
17. Limited life expectancy
18. Platelet count < 100.000/mm<sup>3</sup>

19. History of drug addiction or alcohol abuse in the past 2 years
20. Need for chronic anti-inflammatory drugs
21. Creatinine clearance <30 mL/min or dialysis
22. Presence of a chronic total occlusion (CTO) or left main disease
23. Allergy or contra-indication for ticagrelor or prasugrel
24. Contra-indication for adenosine
25. Patients unable to be followed on site or unable to undergo or contra-indications for MRI
26. Contra-indication for DES
27. Inability to obtain informed consent



**Table S2. Baseline characteristics of total study population at the index event.**

	<b>Ticagrelor (n=56)</b>	<b>Prasugrel (n=54)</b>	<b>P-value</b>
Age (years)	60.2±10.1	61.0±8.8	0.69
Male, n (%)	49/56 (87.5)	45/54 (83.3)	0.54
BMI (kg/m <sup>2</sup> ), mean±SD	27.2±3.8	27.8±3.7	0.42
Symptom to balloon time (min), median (IQR)	191 (126-340)	146 (98-322)	0.10
Loading dose ticagrelor received, n (%)	56/56 (100.0)	54/54 (100.0)	1.00
Loading dose-balloon time (min), mean±SD	79±40	77±48	0.18
Loading dose-IMR time (min), mean±SD	114±39	103±30	0.24
<i>Medical history</i>			
Hypertension, n (%)	20/56 (35.7)	13/54 (24.1)	0.18
Diabetes mellitus, n (%)	7/56 (12.5)	4/54 (7.4)	0.37
Smoking, n (%)	26/56 (46.4)	21/54 (38.9)	0.47
Hypercholesterolemia, n (%)	12/56 (21.4)	11/54 (20.4)	0.89
Family history of CAD, n (%)	19/56 (33.9)	23/54 (42.6)	0.35
Previous PCI, n (%)	3/56 (5.4)	1/54 (1.9)	0.33
<i>Medication before PPCI</i>			
ASA, n (%)	6/56 (10.7)	3/54 (5.6)	0.30
Lipid lowering medication, n (%)	12/56 (21.4)	9/54 (16.7)	0.53
ACE-i or ARB, n (%)	12/56 (21.4)	9/54 (16.7)	0.53
Beta-blocker, n (%)	8/56 (14.3)	4/54 (7.4)	0.25
CCB, n (%)	4/56 (7.1)	5/54 (9.3)	0.68
<i>Laboratory peak values</i>			
CK (U/L), median (IQR)	1040 (441-1913)	1127 (453-2171)	0.86
CK-MB (µg/L), median (IQR)	86 (28-207)	102 (37-216)	0.73
Troponin T (µg/L), median (IQR)	1.82 (0.58-5.04)	1.73 (0.38-4.14)	0.39

ACE-i: angiotensin converting enzyme inhibitor, ARB: angiotensin II receptor blocker, ASA: acetylsalicylic acid, BMI: body mass index, CAD: coronary artery disease, CCB: calcium channel blocker, CK: Creatine kinase, CK-MB: Creatine kinase-MB, IMR: index of microcirculatory resistance, IQR: interquartile range, SD: standard deviation, PCI: percutaneous coronary intervention.

**Table S3. Procedural characteristics of total study population at the index event.**

		<b>Ticagrelor (n=56)</b>	<b>Prasugrel (n=54)</b>	<b>P-value</b>
2-vessel disease, n (%)		42/56 (75.0)	41/54 (75.9)	0.91
3-vessel disease, n (%)		14/56 (25.0)	13/54 (24.1)	0.91
Cardiogenic shock, n (%)		0/56 (0)	0/54 (0)	1.00
Radial access, n (%)		53/56 (94.6)	52/54 (96.3)	0.43
<i>Angiographic characteristics culprit</i>				
LAD, n (%)		17/56 (30.4)	19/54 (35.2)	0.59
LCX, n (%)		15/56 (26.8)	13/54 (24.1)	0.74
RCA, n (%)		24/56 (42.9)	22/54 (40.1)	0.82
TIMI-flow pre PPCI, n (%)	0	31/56 (55.4)	31/54 (57.4)	0.96
	1	6/56 (10.7)	3/54 (5.6)	
	2	13/56 (23.2)	13/54 (24.1)	
	3	6/56 (10.7)	7/54 (13.0)	
TIMI-flow post PPCI, n (%)	0	0/56 (0)	0/54 (0)	0.34
	1	2/56 (3.6)	4/54 (7.4)	
	2	11/56 (19.6)	4/54 (7.4)	
	3	43/56 (76.8)	46/54 (85.2)	
TFC, median (IQR)		41.5 (30.5-65.3)	39.0 (29.0-54.5)	0.58
cTFC, median (IQR)		37.5 (24.3-56.0)	34.0 (21.8-50.5)	0.40
MBG, n (%)	0	1/56 (1.8)	0/54 (0)	0.98
	1	7/56 (12.5)	7/54 (13.0)	
	2	7/56 (12.5)	8/54 (14.8)	
	3	41/56 (73.2)	39/54 (72.2)	
<i>PCI characteristics culprit</i>				
Stent length (mm), mean±SD		34.07±15.03	32.07±15.6	0.50
Stent diameter (mm), mean±SD		3.56±0.57	3.66±0.50	0.35
Thrombectomy, n (%)		4/56 (7.1)	7/54 (13.0)	0.31
Pre-dilatation, n (%)		33/56 (58.9)	29/54 (53.7)	0.58
Post-dilatation, n (%)		18/56 (32.1)	13/54 (24.1)	0.35
Glycoprotein IIb/IIIa inhibitor, n (%)		7/56 (12.5)	6/54 (11.1)	0.92

cTFC: corrected TIMI frame count, IQR: interquartile range, LAD: left anterior descending artery, LCX: left circumflex artery, MBG: myocardial blush grade, PCI: percutaneous

coronary intervention, PPCI: primary percutaneous intervention, RCA: right coronary artery, SD: standard deviation, TIMI: thrombolysis in myocardial infarction, TFC: TIMI frame count.

**Table S4. Per protocol analysis of patient characteristics at 1-year follow-up.**

	<b>Ticagrelor (n=39)</b>	<b>Prasugrel (n=41)</b>	<b>P-value</b>
Time to 1-year follow-up (days), mean±SD	359±7	357±14	0.54
Male, n (%)	36/39 (92.3)	32/41 (78.0)	0.07
Systolic blood pressure (mmHg), mean±SD	135±15	135±18	0.93
Diastolic blood pressure (mmHg), mean±SD	82±10	79±14	0.33
Heart rate (beats / min), mean±SD	65±14	65±12	0.87
<i>Medication at follow-up</i>			
P2Y <sub>12</sub> inhibitor, n (%)	39/39 (100.0)	41/41 (100.0)	NA
Acetylsalicylic acid, n (%)	38/39 (97.4)	40/41 (97.6)	0.97
Oral anticoagulants, n (%)	0/39 (0)	0/41 (0)	NA
Beta-blocker, n (%)	33/39 (84.6)	30/41 (73.2)	0.21
ACE-i, n (%)	23/39 (59.0)	25/41 (61.0)	0.86
ARB, n (%)	6/39 (15.4)	7/41 (17.1)	0.84
Lipid lowering medication, n (%)	36/39 (92.3)	39/41 (95.1)	0.60
Long acting nitrate, n (%)	1/39 (2.6)	1/41 (2.4)	0.97
CCB, n (%)	3/39 (7.7)	3/41 (7.3)	0.95
Diuretics, n (%)	2/39 (5.1)	5/41 (12.2)	0.26
Diabetes mellitus medication, n (%)	4/39 (10.3)	3/41 (7.3)	0.64
Anti-inflammatory drugs, n (%)	2/39 (5.1)	5/41 (12.2)	0.26
<i>Laboratory values</i>			
Hemoglobin (mmol/L), mean±SD	9.0±0.7	8.8±0.8	0.30
Hematocrit (L/L), mean±SD	0.43±0.03	0.43±0.03	0.89
Platelet count (x 10 <sup>9</sup> /L), mean±SD	247±69	234±53	0.36
Total leukocyte count (x 10 <sup>9</sup> /L), median (IQR)	6.4 (5.4-8.6)	7.2 (5.9-8.2)	0.42
Total cholesterol (mmol/L), mean±SD	3.4±0.7	3.7±1.1	0.22

HDL (mmol/L), mean±SD	1.1±0.3	1.3±0.4	0.02
LDL (mmol/L), median (IQR)	1.7 (1.2-2.0)	1.5 (1.1-2.1)	0.52
Triglycerides (mmol/L), median (IQR)	1.5 (1.0-2.1)	1.3 (1.0-1.9)	0.72
CRP (mg/L), median (IQR)	2.5 (2.5-2.5)	2.5 (2.5-2.5)	0.73
LDH (U/L), mean±SD	195 (179-220)	195 (183-232)	0.66
Glucose (mmol/L), median (IQR)	5.6 (5.0-6.4)	5.3 (4.9-6.4)	0.80
NT-proBNP (ng/L), median (IQR)	83 (42-275)	101 (51-265)	0.58

We included the patients eligible for the per protocol analysis at 1-year, minus the deceased (n=3) and lost to follow-up (n=1) patients which resulted in a total of 80 patients (ticagrelor n=39, prasugrel n=41). ACE-i: angiotensin converting enzyme inhibitor, ARB: angiotensin II receptor blocker, CCB: calcium channel blocker, CRP: C-reactive protein, HDL: high density lipoprotein, IQR: interquartile range, LDH: lactate dehydrogenase, LDL: low density lipoprotein, NT-proBNP: N-terminal pro-brain natriuretic peptide, SD: standard deviation.

**Table S5. Reasons for switch of initial randomized P2Y<sub>12</sub> treatment strategy.**

Randomized to	Inclusion date	Date of switch	Reason switch	Switched to
<i>Ticagrelor</i>	6-May-2015	12-May-2015	Cardiac thrombus	<i>Clopidogrel</i>
<i>Ticagrelor</i>	31-aug-2015	5-Sep-2015	Nausea after Ticagrelor	<i>Prasugrel</i>
<i>Prasugrel</i>	12-nov-2015	16-Dec-2015	Human error	<i>Ticagrelor</i>
<i>Ticagrelor</i>	12-nov-2015	3-May-2016	Hematomas and bleedings	<i>Clopidogrel</i>
<i>Ticagrelor</i>	9-dec-2015	7-Mar-2016	Surgery persistent pneumothorax	<i>Clopidogrel</i>
<i>Ticagrelor</i>	11-jan-2016	14-Jan-2016	Cardiac thrombus	<i>Clopidogrel</i>
<i>Ticagrelor</i>	26-jan-2016	29-Jan-2016	Atrial fibrillation	<i>Clopidogrel</i>
<i>Ticagrelor</i>	19-May-2016	6-Oct-2016	Hematomas	<i>Clopidogrel</i>
<i>Prasugrel</i>	21-Oct-2016	27-Jun-2017	Hemostasis	<i>Clopidogrel</i>
<i>Prasugrel</i>	31-Jan-2017	19-Jun-2017	Transient ischemic attack	<i>Clopidogrel</i>
<i>Prasugrel</i>	16-jun-2017	19-June-2017	Atrial fibrillation	<i>Clopidogrel</i>
<i>Ticagrelor</i>	27-jul-2017	9-Aug-2017	Cardiac thrombus	<i>Clopidogrel</i>
<i>Ticagrelor</i>	27-aug-2017	19-Feb-2018	Pruritis of the legs	<i>Clopidogrel</i>
<i>Ticagrelor</i>	9-jan-2016	20-Jul-2016	Percutaneous coronary intervention	<i>Clopidogrel</i>
<i>Prasugrel</i>	8-aug-2017	29-Sep-2017	Human error	<i>Ticagrelor</i>

A total of 15 patients switched their initially randomized P2Y<sub>12</sub> inhibitor to another P2Y<sub>12</sub> inhibitor during the conduct of the study (from inclusion to 1.5-year follow-up).



**Table S6. Reasons for hospitalization.**

Patient	Randomization	Reason hospitalization
1	Ticagrelor	Headache, tingling feeling in hands and feet, gastric acid
2	Ticagrelor	Maceration, lung infection
3	Ticagrelor	Chest pain
4	Prasugrel	Dyspnea
5	Ticagrelor	Chest pain
6	Prasugrel	Influenza A
7	Prasugrel	Chest pain
8	Prasugrel	Chest pain
9	Ticagrelor	Cholecystitis
10	Prasugrel	Collaps (vasovagal syncope)
11	Prasugrel	ICD implementation
12	Ticagrelor	Arthritis left shoulder
13	Prasugrel	Chest pain
14	Prasugrel	TIA
15	Ticagrelor	Colon tumor
16	Prasugrel	Hip fracture
17	Ticagrelor	Cellulitis of right groin
18	Prasugrel	Cholecystolithiasis
19	Ticagrelor	Chest pain
20	Prasugrel	Subcapital fracture of the left hip

ICD: Implantable cardioverter-defibrillator, TIA: transient ischaemic attack.

**Table S7. Per protocol analysis of patient symptoms and clinical outcome.**

<b>7A. 1-year follow-up</b>		<b>Ticagrelor (n=41*)</b>	<b>Prasugrel (n=43<sup>‡</sup>)</b>	<b>P-value</b>
Angina pectoris, n (%)		10/38 (26.3)	5/41 (12.2)	0.11
CCS class, n (%)	1	8/10 (80.0)	2/5 (40.0)	0.10
	2	2/10 (20.0)	2/5 (40.0)	
	3	0/10 (0.0)	1/5 (20.0)	
	4	0/10 (0.0)	0/10 (0.0)	
SAQ, median (IQR)	Angina Frequency	100 (90-100)	100 (100-100)	0.29
	Physical limitation	92 (85-100)	100 (75-100)	0.60
	Quality of life	67 (58-83)	83 (67-100)	0.02
	Angina Stability	100 (95-100)	100 (100-100)	0.49
	Treatment satisfaction	94 (81-100)	100 (88-100)	0.03
Dyspnea, n (%)		17/38 (44.7)	15/41 (36.6)	0.46
MBS > 3, n (%)		5/17 (29.4)	5/15 (33.3)	0.81
Total number of bleedings, n (%)		18/38 (47.4)	25/41 (61.0)	0.23
BARC score, n (%)	0	20/38 (52.6)	16/41 (39.0)	0.27
	1	16/38 (42.1)	23/41 (56.1)	
	2	2/38 (5.3)	1/41 (2.4)	
	3	0/38 (0.0)	0/41 (0.0)	
	4	0/38 (0.0)	1/41 (2.4)	
	5	0/38 (0.0)	0/41 (0.0)	
Death, n (%)		1/41 (2.4)	2/43 (4.7)	0.59
Recurrent myocardial infarction, n (%)		4/39 (10.3)	3/41 (7.3)	0.64
Stroke, n (%)		0 (0%)	0 (0%)	NA
Stent thrombosis, n (%)		0 (0%)	0 (0%)	NA
Hospitalization, n (%)		3/39 (7.7)	8/41 (19.5)	0.21

Malignant arrhythmia <sup>‡</sup> , n (%)		0/39 (0.0)	1/41 (2.4)	0.33
Intercurrent CAG (without the need for PCI) <sup>‡</sup> , n (%)		3/39 (7.7)	0/41 (0.0)	0.07
PCI <sup>‡</sup> , n (%)		2/39 (5.1)	1/41 (2.4)	0.53
Cardiac surgery <sup>‡</sup> , n (%)		0/39 (0.0)	0/41 (0.0)	NA
MACE, n (%)		5/40 (12.5)	5/43 (11.6)	0.90
<b>7B. 1.5-year follow-up</b>		<b>Ticagrelor (n=36<sup>§</sup>)</b>	<b>Prasugrel (n=41<sup>†</sup>)</b>	<b>P-value</b>
Angina pectoris, n (%)		5/33 (15.2)	3/37 (8.1)	0.36
CCS class, n (%)	1	2/5 (40.0)	1/3 (33.3)	0.86
	2	3/5 (60.0)	2/3 (66.7)	
	3	0/5 (0)	0/3 (0)	
	4	0/5 (0)	0/3 (0)	
	5	0/5 (0)	0/3 (0)	
SAQ, median (IQR)	Angina Frequency	100 (95-100)	100 (100-100)	0.49
	Physical limitation	97 (85-100)	97 (83-100)	0.96
	Quality of life	75 (67-92)	83 (67-92)	0.42
	Angina Stability	100 (80-100)	100 (100-100)	0.21
	Treatment satisfaction	94 (81-100)	100 (94-100)	0.08
Dyspnea, n (%)		6/33 (18.2)	13/37 (35.1)	0.11
MBS > 3, n (%)		3/6 (50.0)	5/13 (38.5)	0.64
Total number of bleedings, n (%)		16/33 (48.5)	25/38 (65.8)	0.14
BARC score, n (%)	0	17/33 (51.5)	13/38 (34.2)	0.22
	1	13/33 (39.4)	22/38 (57.9)	
	2	3/33 (9.1)	2/38 (5.3)	
	3	0/33 (0)	0/38 (0)	
	4	0/33 (0)	1/38 (2.6)	
<i>Events at 1.5-year follow-up</i>		<b>Ticagrelor (n=36<sup>§</sup>)</b>	<b>Prasugrel (n=41<sup>†</sup>)</b>	<b>P-value</b>
Death, n (%)		1/36 (2.8)	3/41 (7.3)	0.37

Recurrent myocardial infarction, n (%)	3/33 (9.1)	3/37 (8.1)	0.88
Stroke, n (%)	0 (0%)	0 (0%)	NA
Stent thrombosis, n (%)	0 (0%)	0 (0%)	NA
Hospitalization, n (%)	4/33 (12.1)	9/37 (24.3)	0.19
MACE, n (%)	4/34 (11.8)	6/40 (15.0)	0.69

\* In the ticagrelor group, 1 patient was deceased and 1 patient was lost to follow-up before 1-year follow-up. ‡ In the prasugrel group, 2 patients deceased before 1-year follow-up. § In the ticagrelor group, 1 patient was deceased and 3 patients were lost to follow-up before 1.5-year follow-up. † In the prasugrel group, 3 patients were deceased and 1 patient was lost to follow-up before 2-year follow-up. ‡ There were no additional events reported between 1 and 1.5 year follow-up. We included them in the final analysis because we retrieved their survival status at 1-year. BARC: bleeding academic research consortium, CAG: coronary angiography, CCS: canadian cardiovascular society, IQR: interquartile range, MACE: major adverse clinical events, MBS: modified borg dyspnea scale, PCI: percutaneous coronary intervention, SAQ: seattle angina questionnaire.

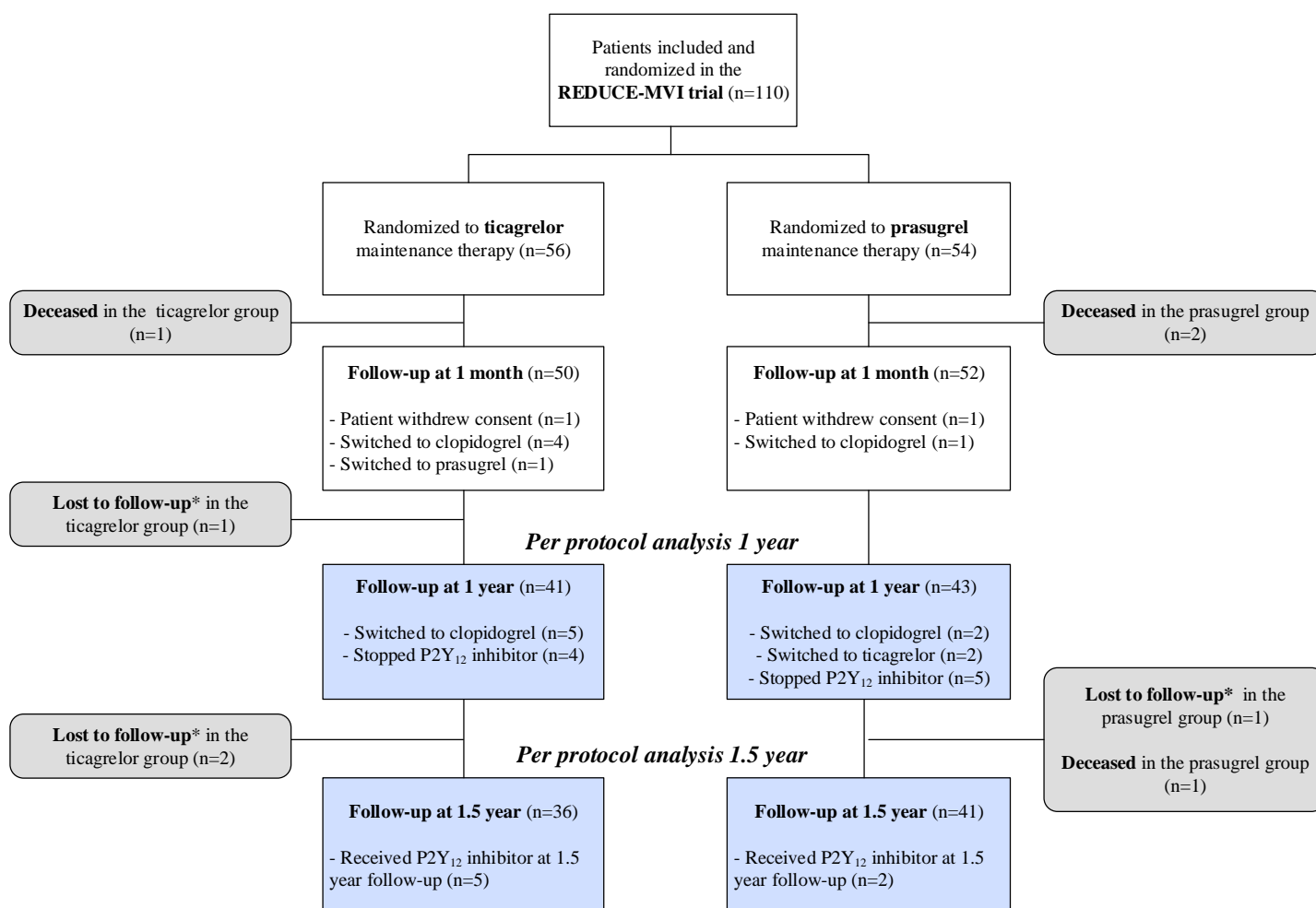
**Table S8. Relative between group difference and risk in discrete outcomes.**

<i>ITT 1 year</i>	<b>Ticagrelor (n=53)</b>	<b>Prasugrel (n=51)</b>	<b>Relative difference (%)</b>	<b>Relative risk</b>	<b>P-value</b>
Angina pectoris	21.2%	17.6%	-17.0%	1.20	0.65
Dyspnea	42.3%	35.3%	-16.5%	1.20	0.47
Bleedings	45.1%	58.8%	30.4%	0.77	0.17
Death	1.8%	3.8%	111.1%	0.47	0.54
Recurrent myocardial infarction	7.5%	5.9%	-21.3%	1.27	0.74
Stroke	0.0%	0.0%	0.0%	NA	NA
Stent thrombosis	0.0%	0.0%	0.0%	NA	NA
Hospitalization	11.3%	17.6%	55.8%	0.64	0.36
Malignant arrhythmia	0.0%	2.0%	NA	NA	0.31
Inter current CAG (without the need for PCI)	5.8%	0.0%	NA	NA	0.08
PCI	5.8%	2.0%	-65.5%	2.86	0.32
Cardiac surgery	0.0%	0.0%	0.0%	NA	NA
MACE	9.3%	9.4%	1.1%	0.99	0.98
<i>PP 1 year</i>	<b>Ticagrelor (n=41)</b>	<b>Prasugrel (n=43)</b>	<b>Relative difference (%)</b>	<b>Relative risk</b>	<b>P-value</b>
Angina pectoris	26.3%	12.2%	-53.6%	2.17	0.11
Dyspnea	44.7%	36.6%	-18.1%	1.22	0.46
Bleedings	47.4%	61.0%	28.7%	0.78	0.23
Death	2.4%	4.7%	95.8%	0.51	0.59
Recurrent myocardial infarction	10.3%	7.3%	-29.1%	1.41	0.64
Stroke	0.0%	0.0%	0.0%	NA	NA
Stent thrombosis	0.0%	0.0%	0.0%	NA	NA
Hospitalization	7.7%	19.5%	153.3%	0.40	0.21
Malignant arrhythmia	0.0%	2.4%	NA	NA	0.33
Intercurrent CAG (without the need for PCI)	7.7%	0.0%	NA	NA	0.07
PCI	5.1%	2.4%	-52.9%	2.13	0.53
Cardiac surgery	0.0%	0.0%	0.0%	NA	NA
MACE	12.5%	11.6%	-7.2%	1.08	0.90
<i>ITT 1.5 year</i>	<b>Ticagrelor (n=51)</b>	<b>Prasugrel (n=49)</b>	<b>Relative difference (%)</b>	<b>Relative risk</b>	<b>P-value</b>
Angina pectoris	19.6%	8.2%	-58.2%	2.38	0.10
Dyspnea	27.5%	36.7%	33.5%	0.75	0.32
Bleedings	47.1%	63.3%	-34.4%	1.34	0.10
Death	1.8%	5.7%	216.7%	0.32	0.29

Recurrent myocardial infarction	7.8%	8.2%	5.1%	0.95	0.95
Stroke	0.0%	0.0%	0.0%	NA	NA
Stent thrombosis	0.0%	0.0%	0.0%	NA	NA
Hospitalization	17.0%	21.6%	27.1%	0.79	0.55
MACE	9.4%	13.5%	43.6%	0.69	0.54
<i>PP 1.5 year</i>	<b>Ticagrelor (n=36)</b>	<b>Prasugrel (n=41)</b>	<b>Relative difference (%)</b>	<b>Relative risk</b>	<b>P-value</b>
Angina pectoris	15.2%	8.1%	-46.7%	1.89	0.36
Dyspnea	18.2%	35.1%	92.9%	0.52	0.11
Bleedings	48.5%	65.8%	35.7%	0.74	0.14
Death	2.8%	7.3%	160.7%	0.38	0.37
Recurrent myocardial infarction	9.1%	8.1%	-11.0%	1.12	0.88
Stroke	0.0%	0.0%	0.0%	NA	NA
Stent thrombosis	0.0%	0.0%	0.0%	NA	NA
Hospitalization	12.1%	24.3%	100.8%	0.50	0.19
MACE	11.8%	15.0%	27.1%	0.79	0.69

The relative risk/ratio is compared to the ticagrelor group. CAG: coronary angiography, ITT: intention to treat analysis, MACE: major adverse clinical events, PCI: percutaneous coronary intervention, PP: per protocol analysis, SAQ: seattle angina questionnaire.

**Figure S1. Study flow chart of patients included in the per-protocol analysis.**

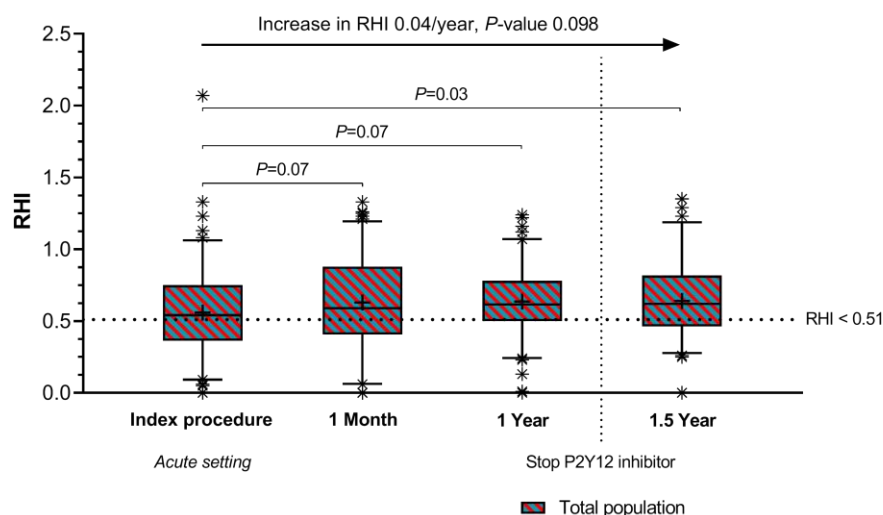


For the 1-year analysis, we included 84 patients who did not switch or stop with their initial randomized P2Y<sub>12</sub> inhibition therapy before 1-year follow-up. For the 1.5-year analysis, we included 77 patients (ticagrelor n=36 versus prasugrel n=41) who did not switch or stop with their initial randomized P2Y<sub>12</sub> inhibition therapy before 1-year follow-up and who did not receive P2Y<sub>12</sub> inhibition therapy at 1.5-year follow-up. \* In these patients we did retrieve the survival status at 1.5-year follow-up and we therefore included them in the final analysis.

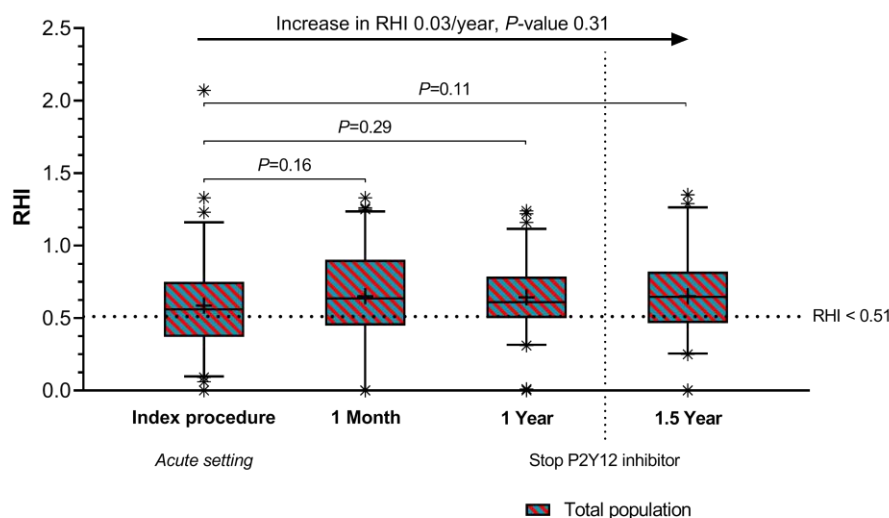


**Figure S2. Improvement in peripheral endothelial function over time in the total study population.**

**A. Peripheral endothelial function at different time points: ITT analysis**

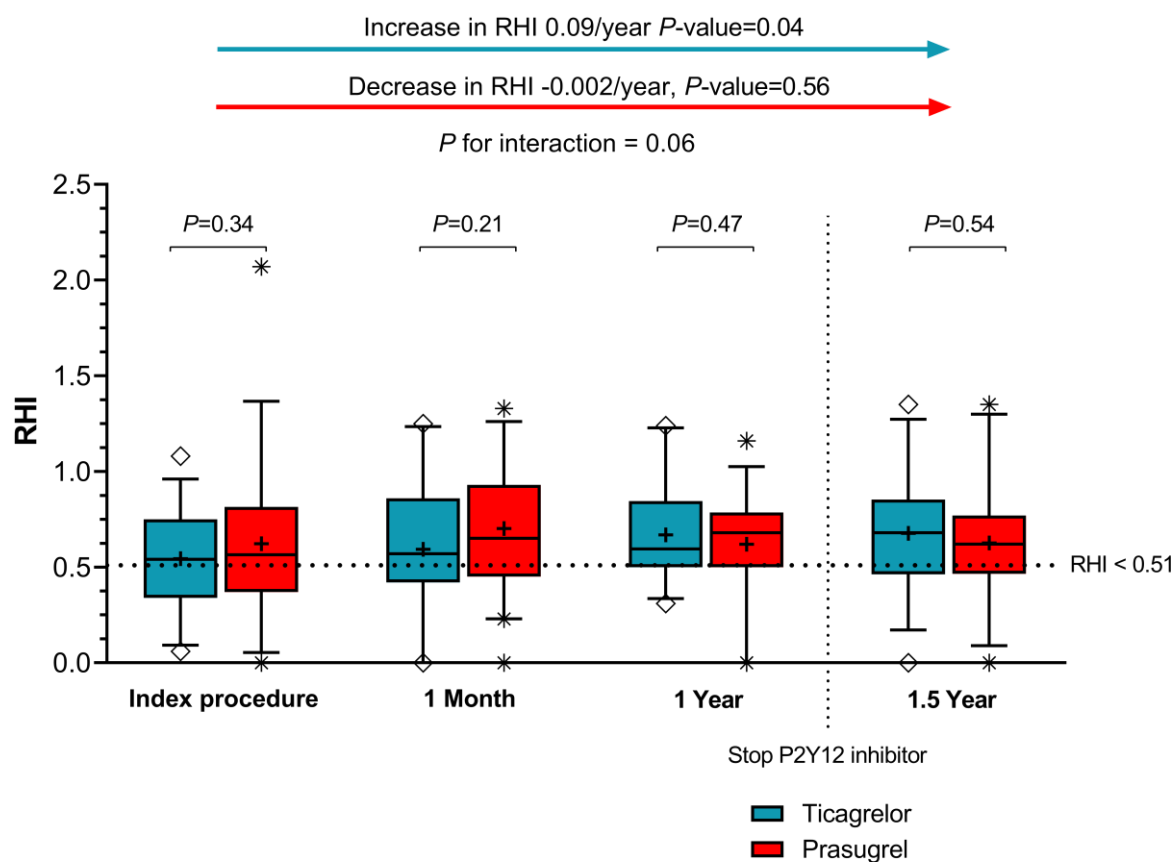


**B. Peripheral endothelial function at different time points: PP analysis**



Peripheral endothelial function and improvement in peripheral endothelial function at different time points. In the ITT analysis (A) all patients were included (n=108). In the per-protocol analysis (B) we included 77 patients (ticagrelor n=36 versus prasugrel n=41) who did not switch or stop with their initial randomized P2Y<sub>12</sub> inhibition therapy before 1-year follow-up and who additionally did not receive P2Y<sub>12</sub> inhibition therapy at 1.5-year follow-up. The dashed line represents the established cut-off value for decreased peripheral endothelial function (RHI < 1.67, equals the natural logarithm RHI < 0.51). The line in the boxplots indicates the median and the cross indicates the mean. The increase in RHI over time was calculated using a mixed model analysis including time as main effect. ITT; intention to treat, PP; per protocol, RHI; reactive hyperemia index.

**Figure S3. Per protocol analysis of peripheral endothelial function.**



Peripheral endothelial function and improvement in peripheral endothelial function in patients randomized to ticagrelor vs. prasugrel maintenance therapy. In the per-protocol analysis at we included 77 patients (ticagrelor n=36 versus prasugrel n=41) who did not switch or stop with their initial randomized P2Y<sub>12</sub> inhibition therapy before 1-year follow-up and who additionally did not receive P2Y<sub>12</sub> inhibition therapy at 1.5-year follow-up. The dashed line represents the established cut-off value for decreased peripheral endothelial function (RHI < 1.67, equals the natural logarithm RHI < 0.51). The line in the boxplots indicates the median and the cross indicates the mean. The increase in RHI over time was calculated using a mixed model analysis including time as main effect. RHI: reactive hyperemia index.

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