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Evaluation of Microvascular Injury in Revascularized Patients with ST Elevation Myocardial Infarction Treated with Ticagrelor versus Prasugrel: The REDUCE-MVI Trial

Running Title: *van Leeuwen et al.; Effect of Ticagrelor and Prasugrel on MVI*

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Abstract

Background: Despite successful restoration of epicardial vessel patency with primary percutaneous coronary intervention (pPCI), coronary microvascular injury (MVI) occurs in a large proportion of STEMI patients, adversely affecting clinical and functional outcome. Ticagrelor has been reported to increase plasma adenosine levels, which might have a protective effect on the microcirculation. We investigated if ticagrelor maintenance therapy after revascularized STEMI is associated with less MVI compared to prasugrel maintenance therapy.
Methods: A total of 110 STEMI patients received a loading dose of ticagrelor and were randomized to maintenance therapy of ticagrelor (n=56) or prasugrel (n=54) after pPCI. The primary outcome was MVI at 1 month, as determined with the index of microcirculatory resistance (IMR) in the infarct-related artery. Cardiovascular magnetic resonance imaging was performed during the acute phase and at one month.
Results: The primary outcome of IMR was not superior in ticagrelor or prasugrel treated patients (ticagrelor 21 [15-39] U, prasugrel 18 [11-29] U, p=0.08). Recovery of microcirculatory resistance over time was not better in patients with ticagrelor versus prasugrel (ticagrelor -13.9 U vs. prasugrel -13.5 U, p=0.54). Intramyocardial hemorrhage was observed less frequently in patients with ticagrelor (23% vs. 43%, p=0.04). At one month no difference in infarct size was observed (ticagrelor 7.6 [IQR 3.7-14.4] g, prasugrel 9.9 [IQR 5.7-16.6] g, p=0.17). The occurrence of microvascular obstruction was not different in patients on ticagrelor (28%) or prasugrel (41%, p=0.35). Plasma adenosine concentrations were not different during the index procedure and during maintenance therapy with ticagrelor or prasugrel.
Conclusions: In patients with STEMI, ticagrelor maintenance therapy was not superior to prasugrel in preventing MVI in the infarct-related territory as assessed by IMR and this resulted in a comparable infarct size at one month.
Clinical Trial Registration: URL: https://clinicaltrials.gov Unique identifier: NCT02422888

Key Words: microvascular injury; STEMI; ticagrelor; prasugrel

Clinical Perspective

What is new?

- This first randomized trial comparing maintenance treatment with ticagrelor or prasugrel after primary PCI showed no differential effect on the extent of microvascular injury and infarct size at one month after primary PCI.
- The attributed pleotropic benefits of ticagrelor through the adenosine metabolism could not be confirmed in a STEMI population and plasma adenosine levels were actually not increased in patients treated with ticagrelor.

What are the clinical implications?

- International guidelines provide a similar recommendation level for ticagrelor and prasugrel but randomized trials comparing the two head-to-head are lacking.
- Microvascular injury and infarct size are both predictors for long-term clinical outcome after primary PCI and are considered as important treatment targets.
- No difference was observed for ticagrelor versus prasugrel maintenance therapy regarding microvascular injury or infarct size after PCI-treated STEMI.

Introduction

The recommended treatment of ST-elevation myocardial infarction (STEMI) by clinical guidelines includes prompt mechanical reperfusion with primary percutaneous intervention (pPCI) and concomitant antithrombotic therapy with a $P2Y_{12}$ inhibitor plus aspirin[1]. Based on two landmark trials, ticagrelor and prasugrel are recommended over clopidogrel because of stronger and more rapid platelet inhibition and superior efficacy[2, 3]. Comparisons between ticagrelor and prasugrel are scarce and primarily based on observational data[4, 5], with the exception of the Prague-18 randomized trial that compared the efficacy and safety of both thienopyridines in patients undergoing pPCI for acute MI, and failed to show any differences in patient outcomes at short-term[6]. Of note, these studies have focused on the antithrombotic potency of both drugs, and not on other (off-target) specific pharmacological effects that might have a salutary effect on reperfused myocardium. One of such off-target properties is the unique ability of ticagrelor to block the equilibrative nucleoside transporter (ENT) -1 receptor, increasing local extracellular adenosine levels, particularly at sites of increased adenosine formation such as ischemia and tissue injury[7]. Adenosine is a microcirculatory vasodilator and thus ticagrelor mediated increased plasmatic adenosine levels might reduce coronary microvascular injury (MVI) caused by reperfusion damage in revascularized STEMI, which was previously documented in experimental studies[8]. It was demonstrated that adenosine-induced coronary blood flow could be enhanced by ticagrelor[9] and resulted in improved peripheral microvascular function, which could not be observed with prasugrel or clopidogrel[10]. The high incidence of MVI and the associated important prognostic implications makes this condition a key treatment target in STEMI[11, 12]. MVI may be quantified with either the index of microcirculatory resistance (IMR), a thermodilution derived intracoronary physiology index, or

with late gadolinium enhancement (LGE) cardiovascular magnetic resonance (CMR), which is strongly associated with mortality in revascularized STEMI[13].

We have conducted a randomized clinical trial to determine whether after an initial loading dose with ticagrelor, ticagrelor maintenance therapy following pPCI in STEMI reduces MVI, compared to maintenance therapy with prasugrel. The study also aimed to establish the effect of ticagrelor and prasugrel therapy on microvascular obstruction (MVO), intramyocardial haemorrhage (IMH) and infarct size as determined with CMR.

Methods

Study design, participant selection and outcome measurements

The REDUCE-MVI trial [NCT02422888] is a multicenter superiority trial with a Prospective Randomized Open Blinded Endpoint (PROBE) design. The study complies with the Declaration of Helsinki and the study was approved by the institutional review board (local medical ethics committee). Upon request, the analytic methods will be made available to other researchers for purposes of reproducing the results or replicating the procedure, the data and study materials will not be made available. The trial was conducted in 6 centres in the Netherlands and Spain and the study design has been published previously[14]. In brief, patients were eligible for study participation when they presented with STEMI[1] <12 hours after onset of symptoms, received a loading dose of ticagrelor (180mg), underwent successful pPCI of the infarct-related artery with a drug eluting stent and had a concomitant intermediate lesion in the non-infarct related vessel(s). This inclusion criteria was introduced to avoid repeat invasive procedures solely for study purposes. When all in- and exclusion criteria were fulfilled (Supplemental Methods 1) and witnessed oral informed consent was obtained, patients were subjected to intracoronary

physiology measurements during the index procedure. After the index procedure patients were asked to confirm study participation by written informed consent. Subsequently, patients were randomized to ticagrelor or prasugrel maintenance therapy (permuted block randomization with randomly selected block sizes, stratified according to study centre). All patients received a loading dose of ticagrelor pre PPCI. Patients randomized to ticagrelor continued with ticagrelor 90 mg BID whereas patients randomized to prasugrel received a loading dose of 60 mg and then continued with prasugrel 10 mg SID to mitigate increased platelet reactivity after switching from ticagrelor to prasugrel as earlier reported[15].

The primary aim was to determine if ticagrelor maintenance therapy as compared to prasugrel maintenance therapy is associated with less MVI as assessed by IMR in the infarct-related artery at one month follow-up. IMR assessment was performed simultaneously with FFR measurement at one month follow-up. CMR derived MVO and IMH at the acute phase and infarct size and LVEF at 1 month were considered as secondary outcome measures. As a safety objective, we compared the occurrence of bleeding complications between patients on ticagrelor or prasugrel maintenance therapy during one month follow-up, classified by the BARC criteria[16]. Major adverse clinical events were prospectively collected between the index event and one month follow-up and included death, myocardial infarction, stent thrombosis and coronary revascularization[17, 18].

Intracoronary hemodynamic physiology indices

Coronary flow reserve (CFR), IMR, baseline microcirculatory resistance (BMR) and FFR were measured with a coronary pressure/temperature wire (Certus, Abbott, Minnesota, USA). All measurements were extracted from the RadiAnalyzer™ Xpress, QUANTIEN™ console and all traces were analyzed offline by an independent blinded expert locally with RadiView™ Software

(Abbott, St. Paul, Minnesota, USA). A second independent operator in our hospital checked all analyzed traces and if there was a discordance, both operators discussed the discordance and adjusted the values as appropriate. BMR in our study was calculated by multiplying the resting distal pressure by the mean resting transit time[19].

CMR imaging

Cardiovascular magnetic resonance (CMR) imaging was performed between 2 to 7 days and 1 month after pPCI using a 1.5-T clinical scanner (Siemens Healthcare, Erlangen, Germany). Scanning protocol included cine imaging, T2-weighted imaging and LGE. Left ventricular (LV) volumes and function were calculated from the short-axis cine images. T2-weighted images were used to identify IMH. LGE images were used for calculation of infarct size and identification of MVO. Infarct size is expressed in grams, as well as % of LV mass. A detailed description on acquisition techniques, CMR parameters and post-processing is provided in Supplemental Methods 2.

Ticagrelor, adenosine and $P2Y_{12}$-inhibition levels

At the index event, at day 3 and at one month follow-up, blood samples were collected for measurement of levels of ticagrelor, its active metabolite AR-C124910XX and adenosine plasma concentrations (APC). The samples were sent to specialized laboratories blinded for analysis (Bioanalytical Covance Laboratory, Indianapolis, United States and Q&Q labs AB, Gothenburg, Sweden, respectively (measurement details in supplement). Furthermore, platelet aggregation was quantified from the same blood samples (VerifyNow System, Accumetrics, San Diego, CA, USA). High platelet reactivity (HPR) was defined as $P2Y_{12}$ reaction units (PRU) > 235[20] and low platelet reactivity (LPR) was present when PRU < 85[21]. A detailed description is provided in Supplemental Methods 3.

Sample size calculation and statistical analyses

The sample size calculation is based on a superiority design with the null hypothesis that IMR at 30 days is equal in patients with ticagrelor- compared to prasugrel maintenance therapy. A between-group difference in mean IMR of 7 in favor of ticagrelor was considered clinically relevant. We required 47 subjects in each treatment group to detect this difference with a power of 80% (two-sided testing at α=0.05) assuming a standard deviation of 12 in both groups. We increased the sample size by 15% to account for patients being lost to follow-up, which resulted in a total sample size of 110 patients. A blinded interim analysis at 50% of inclusion was planned and the results including the decision of the data safety monitoring board are described in the Supplemental Methods 4. Our study was not powered for specific differences in secondary endpoints. To assess a difference in dichotomous and/or categorical variables Chi-square test or Fisher's exact test was used. To assess the difference in continuous variables between both treatment groups, we used the independent samples t-test for normally distributed variables and the Mann-Whitney U test in case the variable was not normally distributed. To investigate the association between continuous variables we used Pearson's correlation for pairs of normally distributed variables and Spearman's correlation in case of skewness or extreme outliers on variables. We considered a p-value of <0.05 as statistically significant.

Results

Study population characteristics

In total 56 patients were randomized to ticagrelor 90 mg BID and 54 patients to prasugrel 10 mg SID (Figure 1). We have provided a screenings log during the inclusion period with accompanying in- and exclusion criteria in the supplemental Figure 1. During the complete

follow-up period, the allocated therapy was received by 51 patients in the ticagrelor group and 53 patients in the prasugrel group. A switch to triple therapy with clopidogrel occurred in 4 patients randomized to ticagrelor and in 1 patient randomized to prasugrel because of either new onset atrial fibrillation (clopidogrel and new oral anticoagulants (NOAC)) or left ventricular thrombus (clopidogrel and acenocoumarol). In the ticagrelor group, 1 patient switched to prasugrel because of dyspnea associated with ticagrelor. Lost to follow-up was equally present in both groups (n=3 vs. n=3) and IMR could not be obtained or analyzed in 2 patients in the ticagrelor group and 3 patients in the prasugrel group. Primary endpoint analysis could thus be performed in 99 patients (ticagrelor n=51, prasugrel n=48). Clinical and procedural characteristics were well balanced between the two treatment groups (Table 1 and Table 2). IMR and blood sampling during the index procedure was performed at 96±36 minutes after ticagrelor loading.

IMR, BMR and CFR measurements

IMR during the index procedure was not lower in the ticagrelor- compared to the prasugrel group (Figure 2). After a mean follow-up of 31±7 days, the primary endpoint of IMR was not superior in the ticagrelor group (ticagrelor 21 [15-39] U, prasugrel 18 [11-29] U, p=0.08). Improvement of microvascular function over time was also non-superior between both groups (IMR ticagrelor -13.9 U vs. prasugrel -13.5 U, p=0.54). CFR, improvement of CFR over time and BMR were also not statistically different, as represented in Table 3.

Infarct size and CMR

Infarct size, as represented by creatine kinase (CK), creatine kinase-MB (CK-MB) and troponin T peak levels, were not different between treatment groups (Table 1). Baseline CMR was performed in 81 patients and follow-up CMR was performed in 96 patients. At baseline, the occurrence of MVO was not statistically different in patients on ticagrelor (28%) or prasugrel

(41%, p=0.35), but IMH was more frequently present in patients with prasugrel (ticagrelor 23% vs. prasugrel 43%, p=0.04). Total infarct size (ticagrelor 7.6 g vs. prasugrel 9.9 g, p=0.17) and LVEF (ticagrelor 53% vs. prasugrel 52%, p=0.61) was not superior in the ticagrelor- versus prasugrel group (Table 4).

Adenosine and Ticagrelor levels

APC was available for 106 patients at baseline, 77 patients at day 3 and 105 patients at one month follow-up. At baseline and at one month follow-up, APC were similar in patients randomized to ticagrelor or prasugrel, as represented in Figure 3. At day 3, similar levels of APC were found in the two groups; ticagrelor (47.1 (IQR 20.5-112.6) nM vs. prasugrel (75.4 (IQR 27.2-222.8) nM, p=0.22). The median APC at 1 month was 56.7 (IQR 28.4-298.7) nM for ticagrelor and 92.8 (IQR 23.8-422.7) nM for prasugrel (p=0.56). At the acute moment, there was no significant correlation between APC and IMR or CFR. There was a significant correlation between APC and CFR but not with IMR at 30 days (Supplemental Table 1). The levels of ticagrelor and active metabolite AR-C124910XX were obtained in 110 patients at baseline and 102 patients at one month follow-up. Ticagrelor levels are represented in a scatter plot for patients randomized to ticagrelor and prasugrel with specification of those patients who switched to a different therapy during follow-up (Figure 4). There was no significant difference in AR-C124910XX levels between the two groups during the index procedure (155.0 (IQR 0.0-356.0) ng/mL for ticagrelor vs. 50.5 (IQR 0.0-298.8) ng/mL for prasugrel, p=0.32). At 1 month, AR-C124910XX levels in the ticagrelor group were 182.5 (IQR 124.3-333.0) ng/mL vs. 0.0 (0-0) ng/mL in the prasugrel group, p<0001. There was no correlation between ticagrelor levels and IMR or CFR values (Supplemental Table 1).

Platelet inhibition

At baseline, platelet inhibition testing was performed in 94 (85%) patients and was not superior in one of both treatment groups (Table 5). After 1 month of maintenance therapy, no difference in platelet inhibition, HPR and LPR was observed between the two treatment groups.

Clinical outcome

From randomization to follow-up, bleeding complications were more frequent in the prasugrel group as compared to the ticagrelor group (29% vs. 11%, p=0.02), primarily due to a higher number of BARC 1 bleeding complications in the prasugrel group (Supplemental Table 2). BARC ≥2 bleeding complications occurred in two patients (3.7%) randomized to ticagrelor and were not observed in the prasugrel group. There was no significant difference in ticagrelor levels in patients with or without the occurrence of bleeding at one month follow-up (Supplemental Table 2). However, in patients with elevated ticagrelor levels at one month follow-up (based on Q3: cut-off value of >811 ng/mL) there were significant more often bleedings at one month follow-up (33.3% (4 of 12) versus 5.3% (2 of 38), p=0.024). In total 3 patients died of non-cardiac causes (respiratory insufficiency due to chronic obstructive pulmonary disease (n=1), respiratory insufficiency due to interstitial pneumonitis caused by metastatic breast cancer (n=1) and complicated endoscopic retrograde cholangio- and pancreaticography with septic shock (n=1). Myocardial infarction, stent thrombosis or repeat revascularization did not occur in any of the patients during the study period.

Discussion

This is the first randomized trial that compared maintenance therapy of ticagrelor with maintenance therapy of prasugrel on coronary microvascular injury (MVI) after successful pPCI

in STEMI. Our main findings are: 1. MVI as assessed by IMR was not reduced with ticagrelor 2. At 1 month, no differences were observed regarding infarct size and LV function between the two treatment groups. 3. Plasma adenosine levels were not increased with ticagrelor during maintenance therapy. 4. In patients randomized to prasugrel, minor bleedings and IMH were slightly more frequently observed.

MVI is considered as an important treatment target in mechanically reperfused STEMI because of the high incidence and significant prognostic implications of this condition[22]. There are 3 phases following PPCI in which MVI could be attenuated to limit infarct size. The first phase directly following primary PCI consists of endothelial activation and/or injury, inflammatory cell plugging, microvascular destruction resulting in intramyocardial hemorrhage[12] and formation of microthrombi causing microvascular obstruction (no-reflow). The second phase (hours-days) is dictated by infiltrating cells. The third phase (days-months) is characterized by irreversible damage of the microcirculation. Increased levels of adenosine potentially act on all these mechanisms[8]. MVI may be assessed with non-invasive methods, such as CMR and positron emission tomography or invasively using hyperemic microcirculatory resistance and IMR[23]. A major advantage of invasive MVI assessment with IMR is that it allows for risk stratification and evaluation of adjunctive treatment strategies during the acute phase of STEMI. The normal value of IMR in non-infarct related arteries is considered to be < 25 [24, 25]. IMR in infarct-related arteries has been reported to be 31 (IQR 21-49) after primary PCI[13]. Strongly increased IMR values >40 in STEMI are associated with the extent of MVO, IMH, myocardial salvage and mortality [13, 26, 27] and recovery of microcirculatory resistance has been described as a strong predictor of functional outcome after pPCI[28]. In the present study, we did not observe superiority of ticagrelor in reduction of IMR at 1 month or IMR recovery at follow-up as

compared to prasugrel treated patients. To avoid override of endogenous adenosine by the intracoronary infused adenosine during IMR measurement we also included resting microcirculatory resistance (BMR). However, no difference in BMR between groups was observed. It should be noted though that the distribution of observed values was very large, limiting the value of this index. In our study, all patients received a loading dose of ticagrelor, which might have influenced the development of MVI. However, MVI was still present in 46% of our population, which is similar to studies with prasugrel loading dose[23].

We did observe a slightly lower incidence of CMR-derived IMH in ticagrelor treated patients, reflecting MVI with extravasation of erythrocytes during the acute phase. IMH is closely related to MVO[12] and predicts both functional and clinical outcome after STEMI. Recently, it was shown that IMH is even more closely associated with adverse outcome than MVO[29]. We did not find a significant between-group difference in CMR-derived MVO, and our study was not powered for these secondary outcomes.

Previous studies, that led to the design of the present trial, reported on the potential beneficial effects of ticagrelor on MVI that were attributed to increased plasma levels of adenosine[8]. These experimental studies in animals[30-32] were corroborated in healthy volunteers and ACS patients[7,9, 33,10] showing enhanced coronary blood flow and improvement of peripheral and coronary microvascular function[34]. In contrast, the absence of a differential effect on micro- and macrovascular function and the inability to improve myocardial reperfusion with ticagrelor has also been reported [35-37]. In the present study we could not detect a difference in adenosine plasma concentrations during ticagrelor or prasugrel maintenance therapy. However, it should be noted that the measurement of endogenous plasma concentration in daily clinical practice is very cumbersome due to the extreme short half-life of adenosine and rapid cellular uptake after blood

sampling, despite the application of adequate stop solution and dedicated syringes, leading to a wide range in measured APC[38]. Also, due to active endothelial adenosine metabolism, circulating adenosine does not represent myocardial interstitial adenosine concentration, and we were not able to measure local adenosine levels at tissue level. The ongoing ISAR-REACT-5 trial (NCT01944800) currently investigates the long-term clinical outcome in ACS patients with either ticagrelor versus prasugrel maintenance therapy[39]. A substudy of this trial investigated the potential effect of reticulated platelets (RPs) on ADP mediated platelet aggregation in 124 patients with ACS treated with ticagrelor or prasugrel. They reported that RPs (increased during ACS) are less inhibited by prasugrel compared to ticagrelor, resulting in increased platelet reactivity in the prasugrel group[40]. However, in our study, platelet reactivity was equal in patients with prasugrel and ticagrelor. There was a significant correlation between ticagrelor levels and platelet inhibition at the acute moment, but not at one-month follow-up. This might be due to the fact that at follow-up a per-protocol analysis was performed in a smaller group of patients (n=53) as compared to at the acute moment.

Finally, we observed a slightly larger proportion of BARC 1 minor bleedings in patients on prasugrel, which is probably not of clinical importance[41, 42]. In patients with ticagrelor maintenance therapy, elevated ticagrelor levels were associated with a mild increase in bleeding at one month follow-up. Importantly, the current study was not designed or powered to detect differences in clinical outcome. The randomized Prague-18 trial[6], as well as a meta-analysis did not show a difference in clinical outcome and major bleedings complications between ticagrelor and prasugrel[4]. Future randomized trials with sufficient power will establish the difference in long-term clinical outcome between prasugrel and ticagrelor maintenance therapy in STEMI.

Limitations

Before pPCI all patients were loaded with ticagrelor because this is standard care in the participating centers, which might have modified microvascular injury at the index event. The sample size calculation was based on a study among patients with stable CAD[43], because at the time of protocol drafting no data were available with IMR values 1 month post PPCI in STEMI. It should be underlined that the observed standard deviation is larger than what we initially expected (SD 12), leading to a decreased power. With the increased variability, 128 additional patients would need to be included to achieve a power of 80%. However, given that the observed effect was in the opposite direction than hypothesized, it is unlikely that adding 99 extra patients to our study would yield a significant improvement of IMR in the ticagrelor group. The relatively low rates of classic risk factors, small infarct size and preserved EF could have influenced IMR values as well as the potential effects of the pharmacological intervention. We have used late gadolinium enhancement to detect MVO, which is less sensitive compared to first pass perfusion imaging or early gadolinium enhancement, however has the highest prognostic value[44]. The administration of adenosine intravenously during IMR measurements could theoretically influence MVI. However the values as observed in our cohort are comparable to other STEMI-cohorts as recently published[45]. Also, the natural recovery of microvascular dysfunction over time might have diluted the positive effects of ticagrelor, despite the fact that microcirculatory resistance is still hampered in 50% of patients at 1 month[46]. Finally, we included just a fraction of all screened STEMI patients due to the rather complex study design of our proof-of-principle study and thus it is not possible to extrapolate our results to all STEMI patients.

Conclusions

In patients with STEMI, ticagrelor maintenance therapy was not superior to prasugrel in

preventing microvascular injury as assessed with IMR at 1 month follow-up and this resulted in a comparable infarct size at one month.

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Table 1. Baseline characteristics

	Ticagrelor (n=56) Median [IQR], Mean±SD, n [n%]	**Prasugrel (n=54)** Median [IQR], Mean±SD, n [n%]	**p-value**
Age [years]	60.2±10.1	61.0±8.8	0.69
Sex [male]	49 [87.5]	45 [83.3]	0.54
BMI [kg/m2]	27.2±3.8	27.8±3.7	0.42
Symptom-balloon time [minutes]	191 [126-340]	146 [98-322]	0.10
Loading dose ticagrelor	56 [100.0]	54 [100.0]	1.00
Loading dose-balloon time [minutes]	79±40	77±48	0.18
Loading dose-IMR time [minutes]	114±39	103±30	0.24
Medical history			
Hypertension	20 [35.7]	13 [24.1]	0.18
Diabetes mellitus	7 [12.5]	4 [7.4]	0.37
Smoking	26 [46.4]	21 [38.9]	0.47
Hypercholesterolemia	12 [21.4]	11 [20.4]	0.89
Family history of CAD	19 [33.9]	23 [42.6]	0.35
Previous PCI	3 [5.4]	1 [1.9]	0.33
Medication before PPCI			
ASA	6 [10.7]	3 [5.6]	0.30
Lipid lowering medication	12 [21.4]	9 [16.7]	0.53
ACE-i or ARB	12 [21.4]	9 [16.7]	0.53
Beta-blocker	8 [14.3]	4 [7.4]	0.25
CCB	4 [7.1]	5 [9.3]	0.68
Laboratory peak values			
CK [U/L]	1040 [441-1913]	1127 [453-2171]	0.86
CK-MB [µg/L]	86 [28-207]	102 [37-216]	0.73
Troponin T [µg/L]	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, SD: standard deviation, PCI: percutaneous coronary intervention.

Table 2. Coronary angiography and PCI parameters at the index procedure

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

cTFC: corrected TIMI frame count, 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 3. Intracoronary hemodynamic measurements at baseline and one month follow-up

Parameter	*Time*	**Ticagrelor** Mean±SD, Median [IQR]	**Prasugrel** Mean±SD, Median [IQR]	**p-value**
IMR (U)	Baseline	33 [16-48]	25 [15-50]	0.74
	Follow-up	21 [15-39]	18 [11-29]	0.08
	Δ	-13.9±39.2	-13.5±31.1	0.96
BMR (U)	Baseline	68.4 [46.0-96.6]	62.5 [34.4-119.3]	0.76
	Follow-up	95.7 [58.5-144.8]	80.9 [50.5-121.4]	0.24
	Δ	-14.5±57.9	-14.5±69.3	1.00
CFR	Baseline	2.18±1.24	2.13±1.12	0.84
	Follow-up	3.70±1.76	3.86±1.76	0.66
	Δ	1.59±1.83	1.75±1.89	0.68
FFR	Baseline	0.94±0.06	0.94±0.06	0.70
	Follow-up	0.93±0.06	0.91±0.08	0.19
	Δ	-0.01±0.07	-0.02±0.05	0.23

CFR: coronary flow reserve, FFR: fractional flow reserve, IMR: index of microcirculatory resistance, IQR: interquartile range, SD: standard deviation, Δ: delta.

Table 4. Infarct size as defined by laboratory values and CMR characteristics

	Ticagrelor Median [IQR], Mean±SD, n [n%]	**Prasugrel** Median [IQR], Mean±SD, n [n%]	**p-value**
Baseline CMR	*40 CMRs* (70%)*	*42 CMRs* (78%)*	
MVO present [yes]	11 [27.5%]	17 [40.5%]	0.35
IMH present [yes]	8 [22.9%]	18 [42.9%]	0.04
Edema [g]	26.2±20.1	33.2±18.2	0.12
Infarct size [g]	10.5 [5.1-22.6]	13.6 [7.2-23.7]	0.29
MSI [%]	69.8±27.8	73.6±19.4	0.50
1 month follow-up CMR	*49 CMRs (89%)*	*47 CMRs (90%)*	
LVEDV [ml]	179.9±37.4	183.7±39.8	0.63
LVEDV [ml/m^2]	87.9±16.7	88.7±18.0	0.82
LVESV [ml]	85.2±28.0	89.7±33.6	0.48
LVESV [ml/m^2]	41.6±13.5	43.5±16.9	0.54
LVEF [%]	53.3±8.1	52.5±8.3	0.61
LVED mass [g/m^2]	52.9±11.4	52.7±9.0	0.92
Infarct size [g]	7.6 [3.7-14.4]	9.9 [5.7-16.6]	0.17
Infarct size [% of LV]	7.6 [3.4-12.5]	8.7 [5.4-13.7]	0.14

CMR: cardiac magnetic resonance imaging, IMH: intramyocardial haemorrhage, IQR: interquartile range, LV: left ventricular, LVEDV: left ventricular end-diastolic volume, LVEDVi: indexed left ventricular end-diastolic volume, LVEF: left ventricular ejection fraction, LVESV: left ventricular end-systolic volume, LVESVi: indexed left ventricular end-systolic volume, MSI: myocardial salvage index, MVI: microvascular injury, SD: standard deviation. *Not all of the baseline CMR's were eligible to assess MVO and IMH. There were 82 CMR's in which MVO (40 in ticagrelor group and 42 in prasugrel group) and 77 CMR's in which IMH (35 in ticagrelor group and 42 in prasugrel group) could be assessed.

Table 5. $P2Y_{12}$ platelet inhibition

Parameter	*Time*	**Ticagrelor** Median [IQR], Mean±SD, n [n%]	**Prasugrel** Median [IQR], Mean±SD, n [n%]	**p-value**
PRU	Baseline	162.8±83.3	171.8±87.0	0.61
	1 month	96.1±66.4	82.6±50.1	0.26
Inhibition [%]	Baseline	3 [0-52]	0 [0-39]	0.25
	1 month	59 [30-83]	63 [46-78]	0.75
LPR (<85)	Baseline	11 [55.0%]	9 [45.0%]	0.54
	1 month	22 [45.8%]	26 [54.2%]	0.41
HPR (>235)	Baseline	9 [19.6%]	12 [25.0%]	0.53
	1 month	1 [2.2%]	0 [0%]	1.00

$P2Y_{12}$ platelet inhibition was determined during the index-procedure [baseline] and one month follow-up. HPR: high on platelet reactivity, LPR: low on platelet reactivity, PRU: platelet reactivity unit, SD: standard deviation.

Figure Legends

Figure 1. Enrollment Flow Diagram

Patients were enrolled between May 2015 and October 2017. 51 patients in the ticagrelor group and 48 patients in the prasugrel group were analyzed for the primary endpoint.

Figure 2. Microcirculatory resistance in patients randomized to ticagrelor or prasugrel

No significant difference in the index of microcirculatory resistance between patients randomized to ticagrelor or prasugrel during the index-procedure (baseline) and one month follow-up. Median values are denoted and the cross marks the mean value. The whiskers represent the minimal to maximal values with in between the median.

Figure 3. Adenosine plasma concentration

No significant difference in adenosine levels between patients randomized to ticagrelor or prasugrel during the index-procedure (baseline) and one month follow-up. The whiskers indicate the 10-90 percentile range, with in between the median. The mean is marked by the cross.

Figure 4. Ticagrelor levels

Ticagrelor levels are represented in a scatter plot for patients randomized to ticagrelor and prasugrel with specification of those patients who switched to a different therapy during follow-up. The cross denotes the median and interquartile range. There were no significant differences in the ticagrelor level during the index-procedure at baseline. At one month follow-up significantly higher levels of ticagrelor were observed in the ticagrelor group