ORIGINAL ARTICLE

Can prasugrel decrease the extent of periprocedural myocardial injury during elective percutaneous coronary intervention?

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KEY WORDS

antiplatelet therapy, percutaneous coronary intervention, periprocedural myocardial injury, pharmacotherapy, prasugrel

ABSTRACT

INTRODUCTION Periprocedural myocardial injury may be associated with an increased risk of cardiovascular events. There is limited evidence on the safety and efficacy of more potent $P2Y_{12}$ antagonists in the reduction of the incidence of periprocedural myocardial injury among patients undergoing elective percutaneous coronary intervention (PCI) with inadequate response to clopidogrel.

OBJECTIVES The aim of the study was to evaluate the impact of prasugrel on the incidence of periprocedural myocardial injury among patients undergoing elective PCI with inadequate response to clopidogrel, diagnosed by point-of-care genotyping and platelet function testing (PFT).

PATIENTS AND METHODS This was a prespecified interim analysis of the randomized, open-label ONSIDE TEST study. Patients with stable coronary artery disease (CAD) scheduled for PCI were randomized to one of the following study arms: 1) genotyping, 2) PFT, or 3) control, and evaluated by the *CYP2C19* allele genotyping and PFT with the $P2Y_{12}$ assay. Patients with poor response to clopidogrel by genotyping or PFT were loaded with 60 mg of prasugrel before PCI. The incidence of periprocedural myocardial injury was analyzed.

RESULTS A total of 94 patients (genotyping, 34; PFT, 34; control, 26) were analyzed. Of the 25 patients (26.6%) with inadequate response to clopidogrel, 13 were switched to prasugrel while 12 continued dual antiplatelet therapy with clopidogrel. While similar rates of any periprocedural myocardial injury were found in the genotyping, PFG, and control arms (76.5%, 73.5%, and 73.1%, respectively), the incidence of periprocedural myocardial injury tended to be lower in the subset of patients with poor response to clopidogrel who were treated with prasugrel (61.5% vs 91.7%, $P = 0.078$).

CONCLUSIONS Guided early prasugrel administration may decrease the extent of periprocedural myocardial injury during PCI in patients with stable CAD.

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INTRODUCTION Periprocedural myocardial injury during percutaneous coronary intervention (PCI) may be associated with an increased risk of adverse cardiovascular events.[1-3] Apart from the most common causes of cardiomyocyte injury, such as side-branch occlusion and distal embolization of atheromatous debris and thrombotic elements, it has been demonstrated that the extent of injury may also be augmented by such processes as oxidative stress and platelet activation with microvascular plugging of platelets and neutrophils.[1,4]

Dual antiplatelet therapy (DAPT) with aspirin and clopidogrel decreases the risk of ischemic events; however, the response to clopidogrel is subject to substantial interpatient variability, with inadequate response to this antiplatelet agent found in up to 40% of the population.[5-7] Although *CYP2C19* genotyping and platelet function testing (PFT) allow identification of patients who do not adequately respond to DAPT with clopidogrel[5,8] and have a potentially increased risk of major adverse cardiovascular events, including stent thrombosis,[9-11] previous studies that compared clinical outcomes in patients with stable

coronary artery disease (CAD) undergoing PFT had been stopped for futility owing to a low incidence of clinical events.[12]

On the other hand, it has been demonstrated that poor responders to DAPT have a higher incidence of periprocedural myocardial injury.[13] Although more potent $P2Y_{12}$ antagonists have been available in clinical practice since 2009, the evidence on their safety and efficacy in reducing the incidence of periprocedural myocardial injury among patients undergoing elective PCI is limited. The approach to evaluate the impact of phenotyping- and genotyping-based antiplatelet therapy modification on the surrogate endpoint of elevation in peak periprocedural troponin I (TnI) levels might allow an identification of patients with stable CAD that could potentially benefit from intensified $P2Y_{12}$ inhibition.

Given this background, we report the results of a prespecified interim analysis of the ONSIDE TEST trial,[14] which aimed to evaluate the association between the incidence of periprocedural myocardial injury and the intensification of $P2Y_{12}$ inhibition with prasugrel among patients with inadequate platelet inhibition and to detect any sign of major adverse events and bleedings. The analysis was scheduled after the enrollment of the first 25% of the planned patient population.[14] The ONSIDE TEST study is currently ongoing (recruiting patients) with the estimated final data collection date in March 2019.

PATIENTS AND METHODS

Study population

ONSIDE TEST is an investigator-initiated, phase IV, multicenter, prospective, open-label, randomized controlled clinical trial conducted in academic centers in Poland, Hungary, and Lithuania (ClinicalTrials.gov; NCT01930773). Here we report the outcomes of the prespecified interim study analysis including patients enrolled at the First Department of Cardiology of the Medical University of Warsaw, Poland. Consecutive patients with stable CAD scheduled for an elective PCI with stent implantation were screened for eligibility. The inclusion and exclusion criteria were described in detail previously.[14] In brief, the inclusion criteria were presentation with stable CAD and the age between 18 and 75 years, while the main exclusion criteria were abnormal levels of myocardial necrosis enzymes at baseline, chronic oral anticoagulation, history of stroke or transient ischemic attack, coronary artery bypass surgery within the 3 months preceding randomization, weight below 60 kg, known bleeding diathesis, low platelet count (<70 000 platelets/μl), hematocrit of less than 30% or more than 52%, severe chronic renal failure (estimated glomerular filtration rate <30 ml/min/1.73 m^2), and pregnancy. The angiographic and procedural exclusion criteria involved the anticipated administration of glycoprotein IIb/IIIa inhibitors, employment of rotational atherectomy, and intervention in chronic total occlusion.

Study design

The protocol of the ONSIDE TEST trial was described in detail elsewhere.[14] Briefly, patients who signed a written informed consent form were randomly allocated to one of the study arms, using an electronic randomization tool (Randomizer for Clinical Trial, MEDSHARING, Fontenay-sous-Bois, France): 1) genotyping; 2) PFT; and 3) control. All the enrolled patients were on DAPT, which consisted of aspirin (75 mg/d) and clopidogrel (which was either continued at a dose of 75 mg/d or administered at a loading dose of 600 mg at least 6 hours before PFT). All participants had their platelet reactivity tested, using the point-of-care VerifyNow P2Y12 assay (Accumetrics, San Diego, California, United States) and the rapid, point-of-care Spartan RX CYP2C19 System (Spartan Bioscience Inc., Ottawa, Canada). The values above the threshold of 208 platelet reactivity units (PRUs) and identification of at least 1 copy of the loss-of-function *2 allele in the *CYP2C19* gene indicated inadequate response to antiplatelet therapy.[5,9,11,12]

Patients with poor response to clopidogrel, as identified by genotyping (group 1) or PFT with the $P2Y_{12}$ assay (group 2), received a loading dose of prasugrel (60 mg) 2 hours before PCI. Thereafter, a maintenance dose of 10 mg/d was continued for 1 week followed by therapy de-escalation to 75 mg/d of clopidogrel. Participants with adequate response to clopidogrel (group 1 or group 2) and all individuals in the control arm (group 3) remained on DAPT with clopidogrel at a dose of 75 mg/d.

Blood samples were drawn at 2, 8, and 24 hours after PCI to detect any rise in the levels of myocardial necrosis biomarkers.

Study endpoints

The primary efficacy outcome measure was the incidence of periprocedural myocardial injury defined as an elevation of TnI levels above the 1 × 99th percentile upper limit of normal (ULN), but below the 5 × 99th percentile ULN, or elevation of TnI levels above 5 × ULN in the absence of angiographic or imaging findings of ischemia.[1,15] The extent of periprocedural myocardial injury was classified as mild, moderate, or significant based on the elevation of TnI levels above the 1 × 99th percentile ULN, 3 × 99th percentile ULN, or 5 × 99th percentile ULN, respectively.

The secondary outcome measures were as follows: the maximum elevation of creatine kinase-MB (CK-MB) mass levels within 24 hours after PCI, the maximum elevation of TnI levels within 24 hours after PCI, the incidence of periprocedural myocardial infarction, and the incidence of periprocedural myocardial biomarker leak defined as any increase in the levels of myocardial necrotic enzymes above the ULN. The periprocedural myocardial infarction was defined as the elevation of TnI levels above the 5 × 99th percentile ULN and any of the following: 1) chest pain lasting longer than 20 minutes, 2) ischemic ST-segment changes or new pathological Q waves, 3) angiographic evidence of a flow-limiting complication such as dissection, or 4) imaging evidence

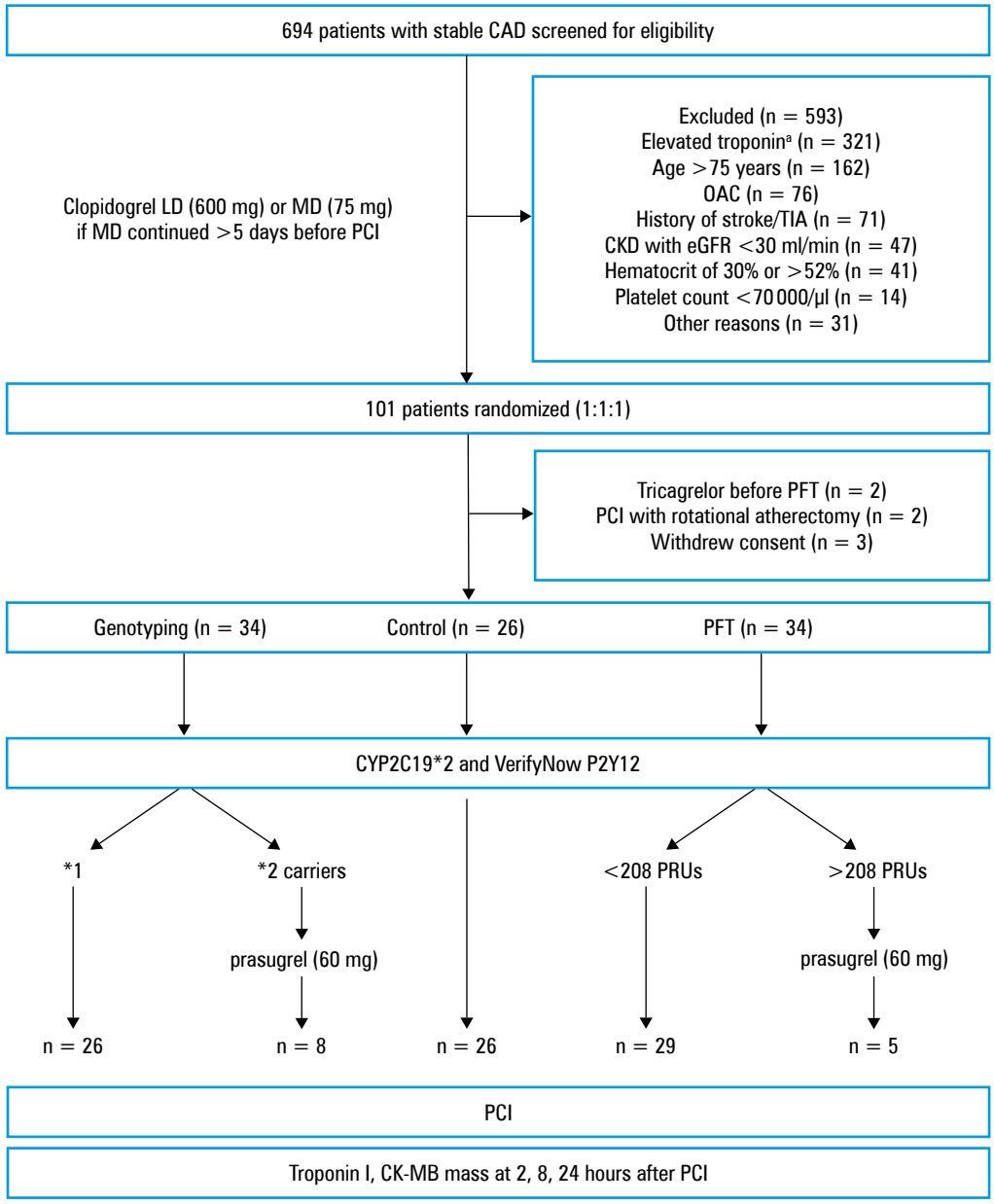

FIGURE 1 Flow chart of the study

a above the upper limit of normal

Abbreviations: CAD, coronary artery disease; CKD, chronic kidney disease; CK-MB, creatine kinase-MB; eGFR, estimated glomerular filtration rate; LD, loading dose; MD, maintenance dose; OAC, oral anticoagulation; PCI, percutaneous coronary intervention; PFT, platelet function testing; PRU, platelet reactivity unit

of myocardial ischemia. The safety endpoints included bleeding complications occurring within 7 days, 30 days, and 1 year after PCI: Bleeding Academic Research Consortium (BARC) type 3 bleedings (clinical, laboratory, and/or imaging evidence of bleeding, with health care provider responses) and type 5 (fatal) bleedings.[16] The other endpoints included the rate of cardiac death, myocardial infarction, definite or probable stent thrombosis, or urgent repeat revascularization within 30 days and 1 year.

The study protocol, designed in compliance with the Declaration of Helsinki, was approved by the Bioethics Committee of the Medical University of Warsaw.

Statistical analysis Statistical analysis was conducted using IBM SPSS Statistics, version 21.0 (IBM, New York, New York, United States). The analysis was based on an intention-to-treat population. The Shapiro–Wilk test was applied to check for normal distribution of continuous variables. The variables were presented as mean (SD) or median and interquartile range, depending on the distribution. The study groups were compared with the *t* test or the Mann–Whitney test. Nominal variables were expressed as count and percentages, and compared using the Fisher exact test. *P* values lower than 0.05 were considered significant. Based on the results of the present interim analysis, also the efficacy sample size analysis was performed using the Fleiss method with continuity correction, assuming the 90% statistic power to detect a significant risk reduction with a 2-sided type 1 error of 5%.

RESULTS Of the 694 patients who underwent elective PCI with stent implantation between December 2012 and April 2015, a total of 101 patients were randomized. Seven patients were excluded from the final analysis, two received ticagrelor before PFT, two were eventually referred for PCI with rotational atherectomy due

to extensive calcifications, and three withdrew their consent (FIGURE 1).

There were no significant differences in the baseline clinical parameters between the study arms (TABLE 1). On admission, all patients were on aspirin, 68 patients (72.3%) received clopidogrel at a dose of 75 mg/d, and the remaining 26 patients (27.7%) were loaded with clopidogrel at a dose of 600 mg. High rates of statin therapy (>90%) were observed in all 3 arms.

The angiographic and procedural characteristics were well balanced between the 3 study groups, apart from a longer total vessel occlusion time during the intervention in the PFT arm, compared with the genotyping arm (TABLE 2). There were on average 2.3 stents implanted per patient in the overall population, with a mean (SD) stent length of 30.5 (17.4) mm and the maximum balloon inflation pressure of 19.6 (13.0) atm. Predilation and postdilation were performed in 88.3% and 73.4% of the cases, respectively (TABLE 2).

Bedside platelet testing operated by nurses or physicians was conducted in 100% of the patients, and no laboratory staff support was needed. The mean (SD) time between the clopidogrel loading dose administration and platelet testing was 450 (45) minutes. The bedside genotyping took a mean (SD) of 56.0 (11.0) minutes and PFT—a mean (SD) of 6.0 (2.0) minutes from material collection to the testing results (FIGURE 2). In 4 patients, the genotyping had to be repeated due to inconclusive results.

At baseline, the mean (SD) platelet reactivity was 158.8 (56.4) PRUs in the overall population; there were no significant differences in PRUs between the study arms. One copy of the loss-of-function (*CYP2C19*2*) allele was revealed in 12 patients (12.7%; heterozygous), whereas 2 individuals (2.13%) were identified as homozygous by genotyping. According to the prespecified cut-off value of PRUs exceeding 208, the PFT detected high on-treatment platelet reactivity in 14 patients (14.9%). The incidence of inadequate response to clopidogrel (presence of *CYP2C19* *2 allele or PRUs >208) in each randomization group is presented in TABLE 3.

On the basis of randomization and point-of-care testing, 8 patients (23.5%) in the genotyping arm and 5 patients (14.7%) in the PFT arm received protocol-mandated loading dose of prasugrel at least 2 hours before the scheduled PCI. Despite inadequate response to clopidogrel, 2 patients did not receive prasugrel: the first one because of the first episode of bleeding just after the in-hospital administration of the loading dose of clopidogrel before angioplasty; in the other patient, the referring physician decided not to administer prasugrel owing to the substantial elevation of liver enzyme levels (TABLE 3). The periprocedural platelet reactivity was lower in the genotyping arm (mean [SD], 155.7 [60.7] PRUs) and PFT arm (mean [SD], 150.5 [47.3] PRUs), as compared with the control arm (mean [SD], 177.5 [67.8] PRUs) (P = 0.011 and P = 0.032, respectively), indicating stronger platelet inhibition in the genotyping and PFT groups.

Periprocedural myocardial injury and biomarker leak The overall rate of any periprocedural myocardial injury was 74.5%. The incidence of periprocedural myocardial injury (mild, moderate, and significant) was similar between the study groups (TABLE 4). No differences were detected in the maximum elevation of postprocedural TnI and CK-MB levels between the study arms. Moreover, there were no differences in the prevalence of periprocedural myocardial biomarker leak, which was observed in 27 patients (79.4%), 26 patients (76.5%), and 19 patients (73.1%) in the genotyping, PFT, and control groups, respectively (TABLE 4).

Impact of prasugrel Among patients with poor response to clopidogrel identified either by genotyping or PFT, prasugrel tended to decrease the incidence of mild periprocedural myocardial injury compared with patients who continued clopidogrel (61.5% vs 91.7%, P = 0.078). However, no significant differences in the incidence of moderate or significant periprocedural myocardial injury were detected between the groups (TABLE 5, FIGURE 3).

The incidence of periprocedural biomarker leak was numerically lower among patients receiving prasugrel (69.2%), compared with those with inadequate response to clopidogrel remaining on clopidogrel (91.7%) and those with good response remaining on clopidogrel (75.4%). No significant differences in the peak TnI and CK-MB levels within 24 hours after the procedure were found between the groups (TABLE 5).

Acute and 1-year clinical outcomes There were 6 periprocedural myocardial infarctions (6.4%) noted in the overall population: 2 (5.9%) in the genotyping group, 2 (5.9%) in the PFT group, and 2 (7.7%) in the control group. One periprocedural myocardial infarction in the genotyping group led to cardiogenic shock and cardiac death within 24 hours after the procedure. No further myocardial infarctions, repeated revascularization, or deaths were reported during the 1-year follow up (TABLE 4).

At 30 days after PCI, 4 BARC type 3 bleedings occurred, all in the PFT subgroup in patients with proven adequate response to a standard dose of clopidogrel (TABLE 5). At 1 year, 1 BARC type 3 bleeding (3.4%) was reported in the genotyping group; 6 (18.2%), in the PFT group; and 0 (0.0%) in the control group.

Impact of prasugrel There was 1 periprocedural myocardial infarction (8.0%) among patients with inadequate response to clopidogrel (n = 13), compared with 2 myocardial infarctions (16.7%) among those receiving clopidogrel despite proven inadequate response (n = 12) (P = 0.490) and 3 myocardial infarctions (4.4%) in clopidogrel-treated patients with adequate response (n = 69) (P = 0.608).

TABLE 1 Baseline clinical characteristics of the intention-to-treat population (n = 101)

Parameter		Genotyping arm n = 36	PFT arm n = 35	Control arm n = 30
Age, y, mean (SD)		61.8 (10.6)	62.6 (7.1)	62.3 (7.6)
Male sex, n (%)		28 (77.8)	29 (82.9)	23 (76.7)
Cardiac risk factors, n (%)				
Symptomatic stable CAD		31 (86.1)	28 (80.0)	24 (80.0)
Stable CAD classified according to the CCS grading system	CCS 1	10 (32.3)	10 (35.7)	11 (45.8)
	CCS 2	15 (48.4)	4 (143)	9 (37.5)
	CCS 3	6 (19.4)	2 (7.1)	4 (16.7)
Hypertension, n (%)		26 (72.2)	27(77.1)	25 (83.3)
Diabetes mellitus, n (%)		13 (36.1)	12 (34.3)	15 (50.0)
Hyperlipidemia, n (%)		29 (80.6)	22 (62.9)	24 (80.0)
Heart failure (NYHA class II–III), n (%)		8 (22.2)	9 (25.7)	12 (40.0)
LVEF, %, mean (SD)		45.0 (16.9)	44.0 (5.8)	54.8 (16.4)
Chronic obstructive pulmonary disease, n (%)		2 (5.6)	3 (8.6)	3 (10.0)
Smoking history, n (%)		25 (69.4)	22 (62.9)	18 (60.0)
Current smoking, n (%)		8 (22.2)	13 (37.1)	10 (33.3)
Previous myocardial infarction, n (%)		20 (55.6)	20 (57.1)	16 (53.3)
Previous myocardial infarction, depending on location, n (%)	Anterior wall	5 (25.0)	8 (40.0)	10 (62.5)
	Lateral wall	5 (25.0)	1 (5.0)	0 (0.0)
	Inferior wall	7 (35.0)	10 (50.0)	5 (31.3)
	Posterior wall	3 (15.0)	1 (5.0)	1 (3.3)
Previous PCI, n (%)		24 (66.7)	19 (54.3)	14 (46.7)
Laboratory characteristics				
CK-MB, ng/ml, median (IQR)		0.70 (0.40–1.20)	1.00 (0.60–1.53)	1.56 (0.80–1.80)
Troponin I, ng/ml, median (IQR)		0.001 (0.000–0.006)	0.004 (0.000–0.016)	0.008 (0.000–0.020)
Creatinine, mg/dl, mean (SD)		1.01 (0.23)	1.04 (0.24)	1.09 (0.31)
Red blood cells, $10^6/\mu l$, mean (SD)		4.62 (0.36)	4.60 (0.53)	4.70 (0.41)
Hemoglobin, g/dl, mean (SD)		14.05 (1.09)	13.83 (2.02)	14.32 (1.43)
Platelet count, $10^3/\mu l$, mean (SD)		236 (63)	234 (79)	226 (75)
INR, mean (SD)		1.00 (0.08)	1.00 (0.06)	0.98 (0.07)
APTT, s, mean (SD)		28.62 (3.17)	32.41 (12.39)	28.72 (2.72)
Lipid profile, mg/dl, mean (SD)				
Total cholesterol		163.0 (48.0)	147.9 (33.9)	152.0 (41.7)
HDL cholesterol		43.7 (9.5)	41.3 (10.9)	46.0 (11.3)
LDL cholesterol		91.7 (44.8)	76.0 (26.5)	74.0 (30.2)
Triglycerides		137.3 (45.0)	129.8 (49.5)	158.5 (119.1)
Baseline pharmacotherapy, n (%)				
Aspirin		36 (100.0)	33 (94.3)	30 (100.0)
Clopidogrel		30 (83.3)	30 (85.7)	24 (80.0)
Statin		33 (92.0)	32 (91.4)	29 (96.7)
β-blocker		34 (94.4)	32 (91.4)	28 (93.3)
ACEI or ARB		33 (91.7)	30 (85.7)	27 (90.0)
Calcium channel blocker		6 (16.7)	5 (14.3)	4 (13.3)
Proton pump inhibitor		15 (41.7)	20 (57.1)	18 (60.0)

Conversion factors to SI units are as follows: for total, HDL, and LDL cholesterol, divide mg/dl by 38.67; for triglycerides, divide mg/dl by 88.57.

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; APTT, activated partial thromboplastin time; ARB, angiotensin receptor blocker; CCS, Canadian Cardiovascular Society; HDL, high-density lipoprotein; INR, international normalized ratio; IQR, interquartile range; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction; NYHA, New York Hear Association; others, see FIGURE 1

TABLE 2 Procedural and angiographic characteristics of the study population (n = 94)

Parameter		Genotyping arm n = 34	PFT arm n = 34	Control arm n = 26
Lesion location, n (%)				
Left main coronary artery		0 (0.00)	2 (6.06)	1 (4.17)
Left anterior descending artery		14 (41.18)	19 (55.88)	15 (57.69)
Circumflex artery		8 (24.2)	9 (27.3)	7 (29.2)
Right coronary artery		10 (30.3)	10 (30.3)	5 (20.8)
Lesion type, n (%)[a]				
Type A/B1		3 (8.8)	4 (11.7)	2 (7.7)
Type B2/C		31 (91.2)	30 (88.2)	24 (92.3)
Stent implantation				
No. of stents, n (%)	POBA	2 (5.8)	3 (9.1)	3 (11.5)
	1	28 (82.4)	18 (54.6)	15 (60.0)
	2	4 (11.7)	9 (27.3)	5 (20.0)
	3	0 (0.0)	4 (12.1)	1 (4.0)
Drug-eluting stent, n (%)		30 (88.2)	28 (84.9)	20 (76.9)
Bare metal stent, n (%)		2 (5.9)	3 (8.8)	3 (11.5)
Direct stenting, n (%)		4 (11.7)	4 (11.1)	3 (11.5)
Postdilation, n (%)		27 (79.4)	23 (67.6)	19 (73.1)
Total length of stent, mm, mean (SD)		27.0 (14.0)	24.2 (10.2)	31.77 (15.9)
Total vessel occlusion time, s, mean (SD)[b]		68.1 (36.3)	96.1 (51.3)	77.6 (38.6)
Periprocedural pain, n (%)		2 (5.9)	3 (8.8)	2 (7.7)
Contrast volume, ml, median (IQR)		140 (100–200)	200 (150–250)	150 (100–200)
Fluoroscopy exposure, mGy, median (IQR)		1466 (646–2017)	1457 (641–1424)	1201 (1010–1278)
Fractional flow reserve, n (%)		7 (20.6)	3 (8.8)	3 (11.5)
Intravascular ultrasound, n (%)		2 (5.9)	6 (17.6)	0 (0.0)
Optical coherence tomography, n (%)		2 (5.9)	1 (2.9)	0 (0.0)
Periprocedural pharmacotherapy				
Unfractionated heparin, 10^3 units, median (IQR)		8.0 (5.0–10.0)	9.0 (7.0–10.0)	8.0 (7.0–10.0)
Abciximab, n (%)		2 (6.7)	0 (0.0)	0 (0.0)
Eptifibatide, n (%)		2 (6.7)	0 (0.0)	0 (0.0)
Angiographic outcomes, n (%)				
Good angiographic result (TIMI 3 flow)		34 (94.4)	34 (94.4)	25 (96.2)
Side branch occlusion		2 (5.9)	3 (8.8)	2 (7.7)
Side branch occlusion	Marginal branch	1 (2.9)	1 (2.9)	1 (3.8)[c]
	Diagonal branch	1 (2.9)[c]	2 (5.9)[c,d]	1 (3.8)[c]
Distal embolization		1 (2.9)	0 (0.0)	1 (3.9)

a According to the American Heart Association/American College of Cardiology classification;

b $P = 0.015$ (genotyping vs PFT)

c Unsuccessful wiring of the branch artery

d Unsuccessful POBA

Abbreviations: POBA, plain old balloon angioplasty; TIMI, thrombolysis in myocardial infarction; others, see FIGURE 1 and TABLE 1

There were no BARC type 3 or 5 bleedings at 30 days and 1 BARC type 3 bleeding (3.4%) at 1 year in prasugrel-treated patients, compared with 4 bleedings (11.8%) at 30 days and 6 bleedings (18.2%) at 1 year in clopidogrel-treated patients with inadequate response to clopidogrel. Among patients receiving clopidogrel with adequate response, there were 4 BARC type 3 bleedings (6.0%) at 30 days, with no further bleeding complications at 1 year (TABLE 5).

Sample-size analysis Based on the results of the present interim analysis, assuming the prevalence of periprocedural myocardial injury of 76% in the clopidogrel-treated patients (either good or poor responders) and 61% in patients with early prasugrel therapy guided by bedside testing,

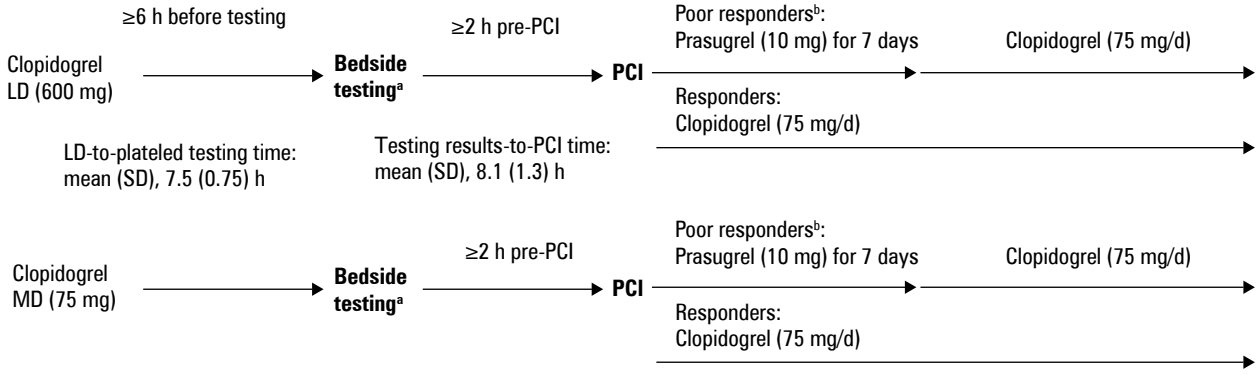

FIGURE 2 The timing of bedside testing (genotyping and platelet function testing), drug administration, and percutaneous coronary intervention in patients who were administered either a loading dose or continued the maintenance dose of clopidogrel before randomization

a Genotyping: mean (SD), 56.0 (11.0) min; PFT: mean (SD), 6.0 (2.0) min; **b** If present in the genotyping arm or PRUs >208 in the PFT arm

Abbreviations: see **FIGURE 1**

TABLE 3 The results of platelet function testing and genotyping; pharmacotherapy modifications in the study arms (per treatment analysis; n = 94)

	Genotyping arm n = 34	PFT arm n = 34	Control arm n = 26
Before testing[a]			
Baseline PRU, mean (SD)	150.5 (59.5)	159.0 (55.4)	168.9 (60.6)
High on-treatment platelet reactivity (PRU >208), n (%)	2 (5.9)	6 (17.7)	6 (23.1)
*CYP2C19**2 carrier (heterozygote), n (%)	8 (23.5)	3 (9.1)	2 (7.7)
CYP2C19 carrier (homozygote), n (%)	1 (3.0)	0 (0.0)	1 (3.9)
After testing			
Switch to prasugrel[b]	8 (23.5)	5 (14.7)	0 (0.0)

a No significant differences were found between the groups.

b Two patients did not receive prasugrel despite randomization results and identification as poor responders to clopidogrel (see the text for details)

Abbreviations: see **FIGURE 1**

given that inadequate response to clopidogrel was identified in 26.6% of the patients, of whom half were treated with prasugrel (according to platelet testing and randomization outcomes), we could confirm, using the Fleiss method with continuity correction, that within the previously estimated sample size of 362 patients for the total study population, it would be feasible to demonstrate a significant reduction in the risk of periprocedural myocardial injury with a power of 90% (assuming a 2-sided type 1 error of 5% and accounting for the potential risk of loss to follow-up and inconclusive testing results).

DISCUSSION The main findings of this prespecified interim analysis of the ONSIDE TEST study could be summarized as follows: 1) periprocedural myocardial injury was a prevalent finding in patients undergoing elective PCI and occurred with a similar frequency in patients with bedside testing (genotyping and PFT) guided DAPT and the control group managed with standard DAPT; 2) preprocedural administration of prasugrel tended to reduce the incidence of periprocedural myocardial injury among patients with inadequate response to clopidogrel identified either by genotyping or PFT; 3) preprocedural prasugrel in poor responders to clopidogrel appeared not to be associated with a higher incidence of bleeding complications after elective PCI, although it should be emphasized that the study was not powered to evaluate bleeding endpoints; 4) the approach to assess the efficacy of a more potent $P2Y_{12}$ inhibitor among patients with stable CAD with the use of a surrogate endpoint of postpostprocedural elevation in the levels of myocardial necrosis biomarkers is feasible and warrants further investigation.

Different criteria for the threshold values for defining periprocedural myocardial injury, the selection of myocardial necrosis biomarker assay, as well as the timing and frequency of blood sampling contributed to the vast diversity in the incidence of periprocedural myocardial injury reported in previous studies.[1,17] The rates of elevated biomarkers after PCI in our study (74.5% of the patients) were higher than those in a study by Christensen et al[18] and in a meta-analysis by Testa et al,[19] who reported the incidence of cardiac troponin T levels exceeding ULN after elective PCI of 37.7% and 28.7%, respectively. This could be related to the fact that in the present study the TnI concentration was evaluated at 3 time points after the procedure, thereby increasing the sensitivity for the detection of subclinical myocardial injury, compared with other studies among patients with stable CAD.[3,18,20,21] In addition, the clinical and angiographic complexity of the lesions treated in our tertiary care department of invasive cardiology needs to be highlighted, because more than 90% of the lesions were classified as type B2/C according to the American Heart Association / American College of Cardiology classification.

Moreover, invasive intravascular imaging performed in some patients in each study group, in particular the fractional flow reserve (FFR) with adenosine infusion, could have potentially

TABLE 4 The main study outcomes stratified according to the randomization outcome

Outcome	Genotyping arm n = 34	PFT arm n = 34	Control arm n = 26	*P* value		
				Genotyping vs PFT	PFT vs control	Genotyping vs control
Pharmacokinetic response 30 min after PCI, PRUs, mean (SD)	155.8 (60.7)	150.5 (47.3)	177.5 (67.8)	0.789	0.011	0.032
Periprocedural myocardial injury, cTnI >1×ULN[d], n (%)	26 (76.47)	25 (73.53)	19 (73.08)	0.779	0.969	0.764
Periprocedural myocardial injury, cTnI >3×ULN, n (%)	19 (55.88)	21 (61.76)	13 (50.00)	0.622	0.362	0.651
Periprocedural myocardial injury, cTnI >5×ULN, n (%)	15 (44.12)	16 (47.06)	9 (34.62)	0.808	0.333	0.457
Periprocedural MI, cTnI >5×ULN + symptoms, n (%)	2 (5.88)	2 (5.88)	2 (7.69)	1.00	0.781	0.781
Periprocedural myocardial biomarker leak, cTnI or CK-MB >1×ULN[d], n (%)	27 (79.41)	26 (76.47)	19 (73.08)	0.770	0.764	0.565
Peak cTnI elevation, ng/ml[d], median (IQR)	0.21 (0.07–0.80)[a]	0.21 (0.06–0.73)	0.19 (0.06–0.50)	0.907	0.541	0.665
Peak CK-MB elevation, ng/ml, median (IQR)[c]	1.60 (0.8–4.8)	1.65 (0.7–3)	1.55 (1.1–3.1)	0.512	0.916	0.760
BARC type 3 or 5 bleeding (within 7 days), n (%)	0 (0.00)	4 (11.76)[b]	0 (0.00)	0.045	0.082	1.00
BARC type 3 or 5 bleeding (within 30 days), n (%)	0 (0.00)	4 (11.76)[b]	0 (0.00)	0.045	0.082	1.00
Cardiac death, MI, stent thrombosis, revascularization (within 30 days), n (%)	2 (5.88)	2 (5.88)	2 (7.69)	1.00	0.781	0.781
BARC type 3 or 5 bleeding at 1 year, n (%)	1 (3.33)	6 (18.18)	0 (0.00)	0.061	0.027	0.366
Cardiac death, MI, stent thrombosis, revascularization at 1 year, n (%)	2 (5.88)	2 (5.88)	2 (7.69)	1.00	0.781	0.781

a Peak TnI value (ng/ml) after exclusion of the patient with periprocedural myocardial leading to subsequent cardiogenic shock and death

b All bleedings occurred among patients receiving clopidogrel who demonstrated adequate response to antiplatelet therapy.

c No significant differences were detected between patients with and without fractional flow reserve evaluation with adenosine infusion: periprocedural MI with cTnI >1×ULN (76.9% vs 74.1%, $P = 0.889$); periprocedural myocardial biomarker leak (76.9% vs 75.3%, $P = 0.898$); peak cTnI elevation (0.20 ng/ml vs 0.21 ng/ml, $P = 0.920$); peak CK-MB elevation (1.58 ng/ml vs 1.54 ng/ml, $P = 0.770$).

Abbreviations: BARC, Bleeding Academic Research Consortium; cTnI, cardiac troponin I; MI, myocardial infarction; ULN, upper limit of normal; others, see **FIGURE1** and **TABLE 1**

influenced the risk of myocardial injury during angioplasty, given potential augmentation of the microvascular flow, attenuation of oxidative stress, and inhibition of neutrophil-mediated reperfusion injury after adenosine administration.[22] Nevertheless, no differences were observed in the incidence of periprocedural myocardial injury or myocardial necrosis biomarker leak in patients undergoing FFR-guided and non–FFR-guided PCI, which is in line with the results of some previous large randomized trials that addressed this issue.[23]

Notably, the incidence of elevated cardiac biomarker levels above 5 × ULN in our study appeared to be similar to that reported in previous prospective studies and meta-analyses.[3,18,19,21]

We selected TnI to evaluate the incidence and extent of myocardial injury because it is a more sensitive and more specific marker than CK-MB, and its prognostic significance has been demonstrated in prospective studies and meta-analyses.[3,24,25]

In our analysis, prasugrel tended to decrease the risk of periprocedural myocardial injury, apparently at no cost of increased bleeding risk, though it should be underlined that the study was not adequately powered to evaluate the bleeding events after prasugrel administration. The potential explanations of this finding might be as follows: 1) the periprocedural inhibition of platelet activation could lead to reduced platelet degranulation and secretion of agonists, chemotaxins, and clotting factors that promote platelet aggregation, thrombin generation, and vasospasm, facilitating thrombus formation over the denuded arterial endothelium during the PCI-induced plaque rupture[4,26-28]; and 2) more intensive inhibition of the formation of platelet-leukocyte aggregates with prasugrel, which was demonstrated to block platelet and leukocyte interaction better than clopidogrel,[29] might translate to less

TABLE 5 Incidence of troponin level elevation depending on the adequacy of clopidogrel response and $P2Y_{12}$ inhibition intensification with prasugrel

Outcome	Poor response to clopidogrel (switched to prasugrel) n = 13	Poor response to clopidogrel (continued on clopidogrel) n = 12	Good response to clopidogrel (continued on clopidogrel) n = 69	Poor or good response to clopidogrel (continued on clopidogrel) n = 81	*P* value[a]	*P* value[b]	*P* value[c]
Periprocedural myocardial injury, cTnI >1×ULN, n (%)	8 (61.5)	11 (91.7)	51 (73.9)	62 (76.5)	0.078	0.362	0.249
Periprocedural myocardial injury, cTnI >3×ULN, n (%)	6 (46.2)	8 (66.7)	39 (56.5)	47 (58.0)	0.302	0.491	0.423
Periprocedural myocardial injury, cTnI >5×ULN, n (%)	3 (23.1)	5 (41.7)	32 (46.4)	37 (45.9)	0.678	0.119	0.126
Periprocedural MI, cTnI >5×ULN + symptoms, n (%)	1 (8.0)	2 (16.7)	3 (4.4)	5 (6.2)	0.490	0.608	0.835
Periprocedural myocardial biomarker leak, cTnI or CK-MB >1×ULN, n (%)	9 (69.2)	11 (91.7)	52 (75.3)	63 (77.8)	0.161	0.642	0.499
Peak cTnI elevation, ng/ml, median (IQR)	0.07 (0.05–0.25)	0.21 (0.12–1.06)	0.20 (0.07–0.60)	0.20 (0.08–0.67)	0.183	0.286	0.661
Peak CK-MB elevation, ng/ml, median (IQR)	1.6 (0.7–3.3)	1.90 (1.10–3.30)	1.60 (1.00–3.30)	1.6 (0.01–3.30)	0.384	0.761	0.869
BARC 3 or 5 bleeding (within 7 days), n (%)	0 (0.0)	0 (0.0)	4 (5.97)	4 (5.06)	1.00	0.405	0.445
BARC 3 or 5 bleeding (within 30 days), n (%)	0 (0.0)	0 (0.0)	4 (5.97)	4 (5.06)	1.00	0.405	0.445
Cardiac death, MI, stent thrombosis, revascularization (within 30 days), n (%)	1 (7.69)	1 (8.33)	3 (4.35)	5 (6.17)	0.328	0.608	0.835
BARC 3 or 5 bleeding at 1 year, n (%)	1 (9.09)	0 (0.0)	4 (5.97)	6 (7.89)	0.306	0.336	0.892
Cardiac death, MI, stent thrombosis, revascularization at 1 year, n (%)	1 (7.69)	1 (8.33)	3 (4.35)	5 (6.17)	0.328	0.608	0.835

a Poor response to clopidogrel (switched to prasugrel) vs poor response to clopidogrel (continued on clopidogrel)

b Poor response to clopidogrel (continued on clopidogrel) vs good response to clopidogrel (continued on clopidogrel)

c Poor response to clopidogrel (switched to prasugrel) vs good response to clopidogrel (continued on clopidogrel)

Abbreviations: see **FIGURE 1**, **TABLE 1**, and **TABLE 4**

pronounced disturbances of the microcirculation flow and the associated cardiomyocyte injury.

The potential effect of $P2Y_{12}$ therapy individualization and the use of more potent antiplatelet agents on the incidence of periprocedural myocardial injury is notable, as even mild injury was demonstrated to affect the prognosis.[3,19,21,30]

The short-term intervention with the use of more potent antiplatelet agents based on bedside testing of the response to standard clopidogrel regimen could potentially protect from subsequent long-term complications of PCI with concomitant subclinical myocardial injury, without the exposure to more pronounced bleeding risk associated with prasugrel in the longer term. It may be assumed that more potent prasugrel might compensate for the already reported elevated risk of periprocedural myocardial injury among patients with inadequate response to clopidogrel therapy.[13] Nevertheless, in a large randomized clinical trial, prasugrel was associated with more bleeding complications in the subset of patients with acute coronary syndrome, compared with clopidogrel.[31] Hence, caution is necessary even while administering prasugrel therapy of short duration, and larger randomized trials are needed to evaluate the clinical efficacy and safety of such pharmacological strategy among patients with stable CAD.

The study provided additional information on the incidence of periprocedural myocardial biomarker release, myocardial injury and infarction in the context of intensified $P2Y_{12}$ inhibition. Despite comparable plasma levels of myocardial injury biomarkers in all 3 study arms at the current phase of the study, our present interim analysis confirmed that within the previously estimated sample size[14] it may be feasible to demonstrate the reduction of the risk of periprocedural myocardial injury with a sufficient statistical power by employing short-term prasugrel therapy guided by bedside testing among patients undergoing elective PCI. Given the fact that we have not observed any worrying findings such as major adverse events or bleedings at this stage, the study enrollment will be continued.

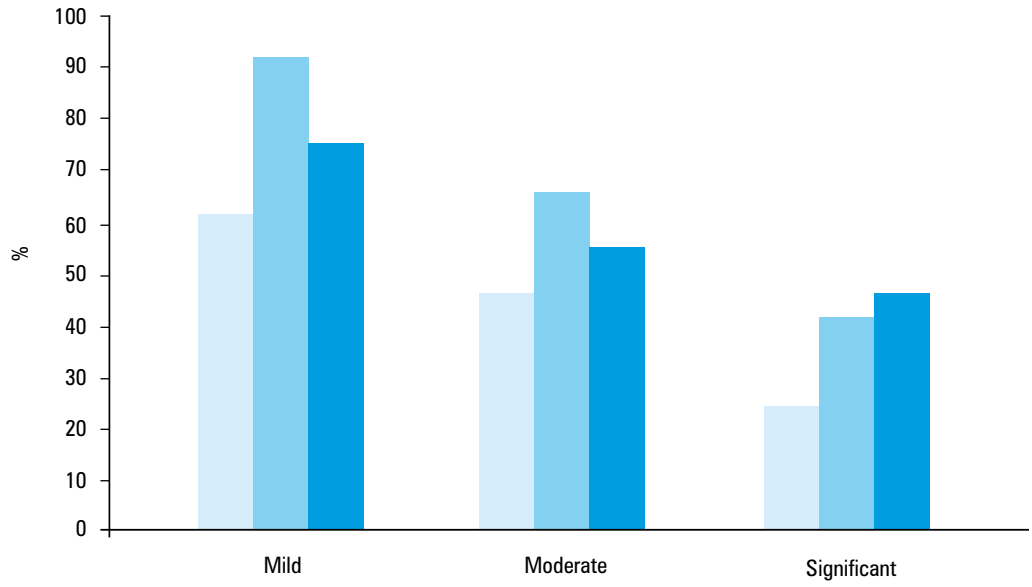

FIGURE 3 Extent of periprocedural myocardial injury (categorized into mild, moderate, and significant) stratified according to response to clopidogrel and intensification of $P2Y_{12}$ inhibition with prasugrel

	Mild	Moderate	Significant
Poor responders (prasugrel); n = 13	61.5	46.5	23.1
Poor responders (clopidogrel); n = 12	91.7	66.7	41.7
Good responders (clopidogrel); n = 69	75.9	56.5	46.4

Finally, the incidence of inadequate response to clopidogrel (defined as the presence of the *2 allele of the*CYP2C19* gene or PRUs exceeding 208) was slightly lower in our study than in the previous reports.[6,8,9,11,32-35] To address the sensitivity and specificity limitations of the current platelet testing modalities, emerging novel biomarkers of platelet activation and inhibition are under clinical evaluation, such as platelet-derived microvesicles, platelet-leukocyte aggregates, and paraoxonase activity, which may facilitate the identification of patients with poor response to clopidogrel therapy in the future.[36]

Study limitations This study was limited by the relatively small size of the study population. Therefore, the data should be considered as descriptive and hypothesis generating. The second limitation is the open-label design of the study, which was mandated by numerous interventions that were performed during the study. Furthermore, given the specific inclusion and exclusion criteria, the observed rates of periprocedural biomarker release might differ from the real-world rates of this complication of PCI. Finally, Although the study was designed to enroll consecutive eligible patients, a selection bias cannot be excluded.

Conclusions Guided early prasugrel administration may decrease the incidence of periprocedural myocardial injury during elective PCI. Further studies in larger populations are necessary to evaluate the short-term safety and efficacy of more potent antiplatelet agents in patients with stable CAD.

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Contribution statement MT contributed to study concept and design, collected the data, performed statistical analysis, discussed the results, and wrote the manuscript. LK contributed to study concept and design, collected the data, and discussed the results. JK, ZH, AR, AP, and GO discussed the results. AG and SG contributed to data collection. KJF contributed to study conception and design and discussed the results. All authors contributed to the interpretation of the data, reviewed the manuscript, and approved its final version before submission.

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