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ORIGINAL ARTICLE

A prospective randomized evaluation of a pharmacogenomic approach to antiplatelet therapy among patients with ST-elevation myocardial infarction: the RAPID STEMI study

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Treatment of carriers of the *CYP2C19*2* allele and *ABCB1 TT* genotype with clopidogrel is associated with increased ischemic complications after percutaneous coronary intervention (PCI). We sought to evaluate a pharmacogenomic strategy among patients undergoing PCI for ST-elevation myocardial infarction (STEMI), by performing a randomized trial, enrolling 102 patients. Point-of-care genetic testing for *CYP2C19*2*, *ABCB1 TT* and *CYP2C19*17* was performed with carriers of either the *CYP2C19*2* allele or *ABCB1 TT* genotype randomly assigned to a strategy of prasugrel 10 mg daily or an augmented dosing strategy of clopidogrel (150 mg daily for 6 days then 75 mg daily). The primary end point was the proportion of at-risk carriers exhibiting high on-treatment platelet reactivity (HPR), a marker associated with increased adverse cardiovascular events, after 1 month. Fifty-nine subjects (57.8%) were identified as carriers of at least one at-risk variant. Treatment with prasugrel significantly reduced HPR compared with clopidogrel by $P2Y_{12}$ reaction unit (PRU) thresholds of >234 (0 vs 24.1%, $P=0.0046$) and PRU >208 (3.3 vs 34.5%, $P=0.0025$). The sensitivity of point-of-care testing was 100% (95% CI 88.0–100), 100% (86.3–100) and 96.9% (82.0–99.8) and specificity was 97.0% (88.5–99.5), 97.1% (89.0–99.5) and 98.5% (90.9–99.9) for identifying *CYP2C19*2*, *ABCB1 TT* and *CYP2C19*17*, respectively. Logistic regression confirmed carriers as a strong predictor of HPR (OR = 6.58, 95% CI 1.24–34.92; $P=0.03$). We confirmed that concurrent identification of three separate genetic variants in patients with STEMI receiving PCI is feasible at the bedside. Among carriers of at-risk genotypes, treatment with prasugrel was superior to an augmented dosing strategy of clopidogrel in reducing HPR.

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INTRODUCTION

Inhibition of the platelet $P2Y_{12}$ receptor is an integral component of therapy for patients with ST-elevation myocardial infarction (STEMI), especially among those receiving early percutaneous coronary intervention (PCI).[1–3] Clopidogrel, the most widely studied $P2Y_{12}$ inhibitor, has established efficacy in reducing major adverse cardiovascular events (MACE).[1,2,4–6] Variability in pharmacodynamic response to clopidogrel is well described, and is associated with increased risk for MACE.[7,8] Prasugrel and ticagrelor provide potent $P2Y_{12}$ inhibition and decrease MACE in acute coronary syndrome (ACS) when compared to clopidogrel.[9,10] Despite reducing ischemic complications, there is a reluctance for universal adoption of these agents due to their increased risk for bleeding and incremental cost relative to generic clopidogrel.[11] Accordingly, there is ongoing interest in investigating the potential benefits of personalized strategies that restrict utilization of novel $P2Y_{12}$ inhibitors to those at risk for clopidogrel failure.[11]

Common genetic variants that affect intestinal uptake and biotransformation of clopidogrel alter the levels of its active metabolite and subsequent inhibition of the $P2Y_{12}$ receptor. Carriers of loss-of-function polymorphisms of the *CYP219* gene have reduced clopidogrel-mediated $P2Y_{12}$ inhibition and an increased risk for MACE after ACS and PCI.[12,13] Of these polymorphisms, the *CYP2C19*2* allele (rs4244285) is the most common with a prevalence of up to 30% among those of western European descent and nearly 50% in Asians.[14,15] The *ABCB1* gene encodes an intestinal efflux pump and influences clopidogrel absorption. Several studies have shown that patients homozygous for the *ABCB1* 3435 C→T (rs1045642) variant have an increased propensity for ischemic outcomes after ACS when treated with PCI and clopidogrel.[14,16,17] In contrast, the *CYP2C19*17* allele (rs12248560) upregulates CYP2C19 activity and has been associated with increased bleeding in patients on clopidogrel.[18]

Previously, our group validated the first point-of-care genetic testing device in clinical medicine and demonstrated the potential clinical utility of *CYP2C19*2* genotyping among patients undergoing PCI for stable coronary artery disease and non-ST-elevation ACS.[19] Point-of-care genetic testing may be particularly suited to STEMI, given the need for emergent treatment decisions and the prospect that personalized therapy may yield the greatest therapeutic benefit among higher-risk patients. Accordingly, we sought to expand point-of-care genotyping from detection of a single variant to three separate genetic variants and extend its use to a higher acuity population of STEMI patients. We further aimed to compare the pharmacodynamic effects of prasugrel against an augmented dosing strategy of clopidogrel, as validated in the Clopidogrel and Aspirin Optimal Dose Usage to Reduce Recurrent Events – Seventh Organization to Assess Strategies in Ischemic Syndromes (CURRENT–OASIS 7) trial,[6] among patients

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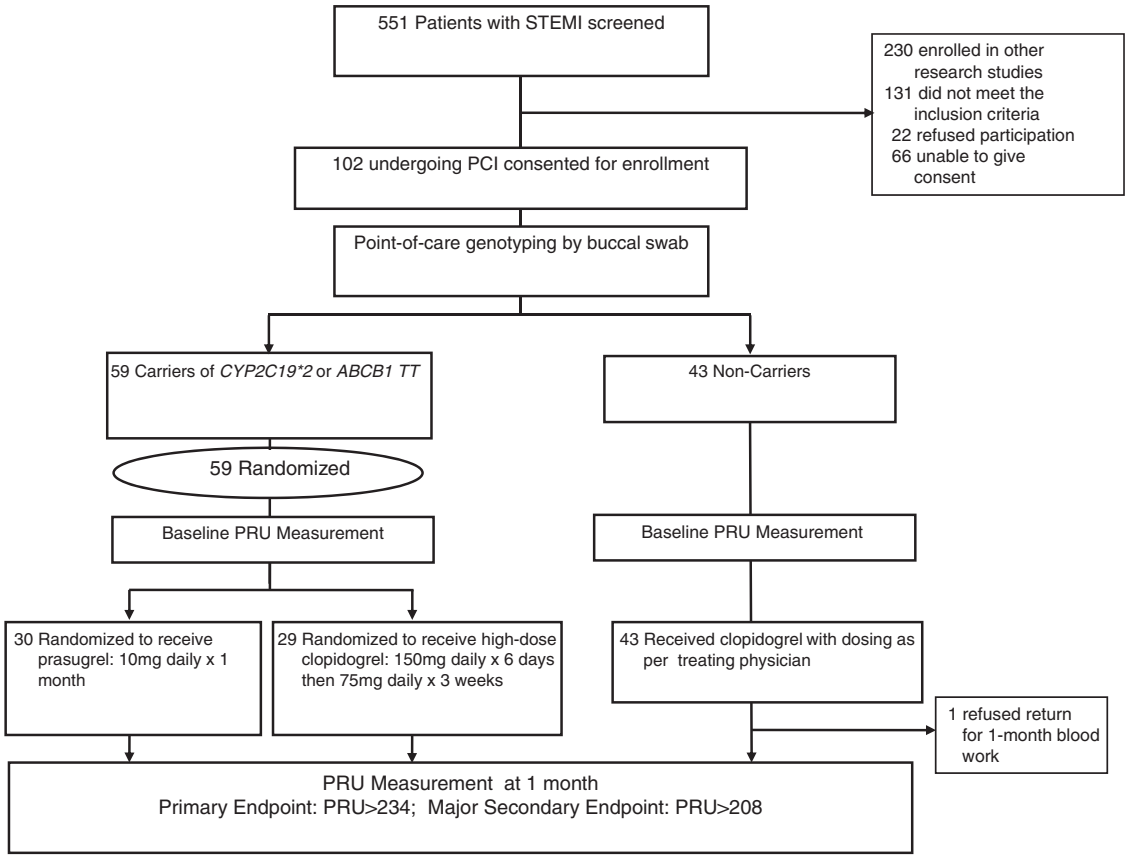

Figure 1. Study flow diagram. PCI, percutaneous coronary intervention; PRU = $P2Y_{12}$ reaction unit; STEMI = ST-elevation myocardial infarction.

identified as carriers of the *CYP2C19*2* allele and/or the *ABCB1 TT* genotype.

MATERIALS AND METHODS

The ReAssessment of antiPlatelet therapy using an InDividualized strategy in ST-elevation Myocardial Infarction (RAPID STEMI) trial was a prospective randomized study, which enrolled patients at the University of Ottawa Heart Institute. The study was conducted in accordance with the Declaration of Helsinki and approved by the local human research ethics board. The bedside genetic testing device (Spartan Rx, Spartan Biosciences, Ottawa, Canada) was approved by the Ottawa Hospital Point-of-Care Committee and Health Canada (Investigation Testing Application # 178941). The study was registered with clinicaltrials.gov (NCT01452139).

Participants

Patients were eligible for screening if they were between 18 and 75 years and underwent PCI for STEMI. Patients were excluded if they had: pre-treatment with prasugrel or ticagrelor, requirement for oral anticoagulation, history of stroke or transient ischemic attack, body weight < 60 kg, platelet count $< 100\,000\ \mu l^{-1}$, known bleeding diathesis, hematocrit $< 30\%$ or $> 52\%$, severe liver dysfunction, renal insufficiency (creatinine clearance $< 30\ ml\ min^{-1}$) or treatment with glycoprotein IIb/IIIa inhibitors in the preceding 24 h. As per the regional STEMI protocol at the time, patients triaged for reperfusion by primary PCI received a 600-mg clopidogrel bolus immediately upon confirmation of STEMI diagnosis. For patients receiving thrombolytic therapy before PCI, 300 mg of clopidogrel was given after initiation of thrombolytic therapy, with further bolus dosing dictated by the treating physician.

Procedure

Point-of-care genetic testing and core laboratory genotyping. All consented patients immediately underwent bedside genetic testing and received separate buccal swabs for each allele (*CYP2C19*2*, *ABCB1* 3435 C→T and *CYP2C19*17)*. All the three swab cartridges were inserted concurrently into the bedside genetic testing device, as per our previously described protocol.[19] Within 55 min, carrier status for all alleles was available and reported as wild type, heterozygous or homozygous for the minor allele. Blood samples were obtained at consent and underwent genetic analysis in the core laboratory to verify the accuracy of bedside testing. Genomic DNA was extracted using a commercial kit (FlexiGene, Qiagen, Hilden, Germany). Carrier status for the specified alleles was determined using TaqMan single nucleotide polymorphism (SNP) genotyping assays (Life Technologies, Carlsbad, CA, USA). Any discrepancies between point-of-care genotyping and core laboratory analysis were further investigated with direct DNA sequencing using the ABI PRISM dye terminator method (Applied Biosystems, Waltham, MA, USA).

Randomization and masking

Randomization for the study was mandated to occur after PCI in order to avoid delay in revascularization. The randomization sequence was computer generated in randomly selected block sizes of four and six. Serially numbered opaque envelopes were used for concealment. Patients identified as carriers of a *CYP2C19*2* allele or the *ABCB1 TT* genotype were considered to have an at-risk genotype and randomly assigned to either prasugrel (10 mg daily for 4 weeks) or an evidence-based augmented dosing strategy of clopidogrel (150 mg daily for 6 additional days followed by 75 mg daily for 3 weeks; Figure 1). Non-carriers continued with clopidogrel dosing as per the invasive cardiologist. The invasive cardiologists and data analysts were blinded to the genetic results and antiplatelet strategy allocation. Patients and research nurses were not masked to carrier status or $P2Y_{12}$ inhibitory drug regimen. Physicians and patients are blinded to the platelet function measurements.

Follow-up and end points

Baseline platelet function testing was conducted at consent using the VerifyNow $P2Y_{12}$ assay (Accriva, San Diego, CA, USA). Repeat

Table 1. Baseline characteristics

Clinical characteristics	*At-risk genotype[a]: randomized to prasugrel* (N = *30*)	*At-risk genotype[a]: randomized to augmented-dose clopidogrel* (N = *29*)	*Low-risk genotype* (N = *43*)	P-*value*[b]
Age (year)	57.7 ± 10.0	59.1 ± 10.0	55.6 ± 8.6	0.60
Female sex	9 (30.0)	7 (24.1)	7 (16.3)	0.61
Caucasian ethnicity	27 (90.0)	25 (86.2)	41 (95.4)	0.71
Previous MI	3 (10.0)	5 (17.2)	7 (16.3)	0.47
Body weight index (kg m^{-2})	31.7 ± 6.1	28.9 ± 5.2	28.5 ± 5.4	0.07
Anterior STEMI	10 (33.3)	15 (51.7)	15 (34.9)	0.19
Cardiac risk factors				
Family history	16 (53.3)	16 (55.2)	28 (65.1)	0.89
Hypertension	17 (56.7)	12 (41.4)	17 (39.5)	0.24
Diabetes mellitus	6 (20.0)	5 (17.2)	6 (14.0)	0.79
Hypercholesterolemia	13 (43.3)	7 (24.1)	18 (41.9)	0.12
Current smoking	12 (40.0)	17 (58.6)	24 (55.8)	0.15
Baseline medications				
Thrombolytic before PCI	13 (43.3)	14 (48.3)	31 (72.1)	0.70
Prior aspirin	6 (20.0)	10 (34.5)	11 (25.6)	0.21
Statin	9 (30.0)	4 (13.8)	9 (20.9)	0.13
Angiotensin converting enzyme (ACE) inhibitor	6 (20.0)	4 (13.8)	7 (16.3)	0.53
Beta blocker	5 (16.7)	4 (13.8)	4 (9.3)	1.00
Proton-pump inhibitor	7 (23.3)	2 (6.9)	3 (7.0)	0.15
Angiographic				
Vessels stented				
Left main artery	1 (3.3)	0 (0)	2 (4.7)	1.0
Left anterior descending artery	10 (33.3)	15 (51.7)	17 (39.5)	0.15
Circumflex artery	6 (20.0)	6 (20.7)	6 (14.0)	0.95
Right coronary artery	16 (53.3)	9 (31.0)	20 (46.5)	0.08
Drug-eluting stent use	21 (70.0)	20 (69.0)	28 (65.1)	0.93

Abbreviations: MI, myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction. Data as *n* (%) or mean ± s.d. [a]At-risk genotype = carriers of *CYP2C19*2* or *ABCB1 TT*. [b]*P*-value for comparison between at-risk genotype carriers randomized to prasugrel or high-dose clopidogrel.

measurements were undertaken at 1-month follow-up. Validated $P2Y_{12}$ reaction unit (PRU) cutoffs of >234 and >208 were used to define high on-treatment platelet reactivity (HPR), a phenomenon characterized by inadequate $P2Y_{12}$ inhibition and strongly associated with ischemic outcomes after PCI.[8,20,21] The primary end point was the proportion of patients with at-risk genotypes assigned to prasugrel with PRU >234 at 1 month compared to those receiving clopidogrel. Secondary end points included a comparison of the two randomized at-risk genotype groups by: HPR cutoff of 208, mean PRU, percentage platelet inhibition, clinical outcomes at 1 month of cardiovascular death, myocardial infarction, urgent revascularization, stent thrombosis (Academic Research Consortium definite and probable)[22] and a safety outcome of thrombolysis in myocardial infarction (TIMI) major and minor bleeding.

Statistical analysis

The study was powered for the primary end point of the proportion of at-risk genotype carriers with HPR in the prasugrel group compared to the clopidogrel group. We projected a 40% non-response rate[23] among at-risk genotype carriers on clopidogrel and an 85% relative risk reduction with prasugrel.[19] We further estimated a 50% prevalence for carriers of either the *CYP2C19*2* allele or *ABCB1 TT* genotype.[14] For a power of 80%, 23 carriers were required per arm. Assuming 4% loss to follow-up, we projected enrollment of 96 patients for the study.

Analyses were conducted with the intention-to-treat principle. Fisher's exact or chi-squared tests were used for comparisons of categorical variables and *a t*-test was used for continuous variables. Point and 95% confidence interval (CI) estimate for sensitivity and specificity of point-of-care genetic testing were calculated with an exact binomial procedure. Multivariable analysis with logistic regression was conducted to ascertain at-risk genotypes' association to HPR. Variables in the models included diabetes, smoking status, body mass index and proton-pump inhibitor (PPI) usage. All *P*-values were two-tailed with an accepted significance level of 0.05. All analyses were performed using SAS (version 9.2).

RESULTS

A total of 102 STEMI patients were enrolled and 59 underwent subsequent randomization following point-of-care identification of an at-risk genotype. Among carriers of at-risk genotypes, 30 were randomized to prasugrel and 29 to clopidogrel. Baseline clinical characteristics did not differ between carriers and non-carriers or among subjects with at-risk genotypes randomized to prasugrel or clopidogrel (Table 1). Follow-up was complete with the exception of one patient from the low-risk genotype group who declined return for follow-up blood work; however, the patient was established to be free of MACE through a telephonic interview. The overall median time from PCI to point-of-care genotyping was 26.8 h (interquartile range: 17.6, 48.8).

Point-of-care genetic testing

The sensitivity of the point-of-care genetic testing device was 100% (95% CI 88.0–100), 100% (86.3–100) and 96.9% (82.0–99.8), and the specificity was 97.0% (88.5–99.5), 97.1% (89.0–99.5) and 98.5% (90.9–99.9) for identifying *CYP2C19*2*, *ABCB1 TT* and *CYP2C19*17* carrier status, respectively. Of the enrolled patients, 37 (36.3%) were identified as carriers of at least one copy of *CYP2C19**2 and 34 (33.7%) as homozygous for the *ABCB1 3435T* genotype. Distribution of the genetic variants was similar between the randomized groups (Table 2).

High on-treatment platelet reactivity

Baseline platelet function testing revealed that carriers of at-risk genotypes had a higher mean PRU compared to non-carriers (183.5 ± 90.6 vs 147.3 ± 84.7, $P = 0.040$). PRU values among subjects with at-risk genotypes randomized to prasugrel and

Table 2. Allelic frequencies of SNPs by point-of-care genotyping among randomized patients

Genotype	*At-risk genotype[a]: randomized to prasugrel (N = 30)*	*At-risk genotype[a]: randomized to augmented-dose clopidogrel (N = 29)*	P-*value*
*CYP2C19*2 (rs4244285)*			
Wild type/wild type	12 (40.0)	10 (34.5)	
*2/Wild type	17 (56.7)	16 (55.2)	0.66
*2/*2	1 (3.3)	3 (10.3)	
ABCB1 C3435T (rs1045642)			
TT, *n* (%)	17 (56.7)	16 (57.1)	
CC, *n* (%)	3 (10.0)	3 (10.7)	1.00[b]
CT, *n* (%)	10 (33.3)	9 (32.1)	
*CYP2C19*17 (rs12248560)*			
Wild type/wild type	25 (83.3)	18 (62.0)	
*17/Wild type	4 (13.3)	9 (31.0)	0.15
*17/*17	1 (3.3)	2 (6.9)	

Abbreviation: SNP, single nucleotide polymorphism. Data as *n* (%). [a]At-risk genotype = carriers of *CYP2C19*2* or *ABCB1 TT*. [b]One inconclusive result in *ABCB1* point-of-care genotyping.

Table 3. Primary and secondary platelet function outcomes according to assigned groups

	At-risk genotype[a]: randomized to prasugrel (N = 30)	*At-risk genotype[a]: randomized to augmented-dose clopidogrel (N = 29)*	P-*value*
Primary outcome			
Patients with PRU > 234 at day 30	0	7 (24.1)	0.0046
Patients with PRU > 208 at day 30	1 (3.3)	10 (34.5)	0.0025
Secondary outcomes			
Baseline PRU	192.6 ± 100.5	174.1 ± 80.6	0.4405
PRU at day 30	53.8 ± 60.3	157.1 ± 94.7	< 0.0001
% Platelet inhibition at day 30	80.0 ± 21.6	42.3 ± 31.9	< 0.0001
Change in PRU from baseline to day 30	− 53.4 ± 60.1	− 156.9 ±94.6	< 0.0001

Abbreviation: PRU, $P2Y_{12}$ reaction unit. Data as *n* (%) and mean ± s.d. [a]At-risk genotype = carriers of *CYP2C19*2* or *ABCB1 TT*.

Table 4. Primary platelet function outcomes by at-risk genotype carrier status and according to assigned groups

	Randomized to prasugrel	*Randomized to augmented-dose clopidogrel*	P-*value*
HPR cutoff at PRU > 234			
*CYP2C19 *2* carriers with HPR at day 30[a]	0 (*N* = 18)	5 (27.8; *N* = 18)	0.0455
ABCB1TT carriers with HPR at day 30[a]	0 (*N* = 17)	5 (29.4; *N* = 17)	0.0455
HPR cutoff at PRU > 208			
*CYP2C19 *2* carriers with HPR at day 30[a]	1 (5.6; *N* = 18)	8 (44.4; *N* = 18)	0.0178
ABCB1TT carriers with HPR at day 30[a]	1 (5.9; *N* = 17)	5 (29.4; *N* = 17)	0.1748

Abbreviations: HPR, high on-treatment platelet reactivity; PRU, $P2Y_{12}$ reaction unit. Data as *n* (%). [a]Among patients included in each group, there are individuals who are concurrent carriers of other at-risk alleles.

augmented-dose clopidogrel were similar at baseline (192.6 ± 100.5 vs 174.1 ± 80.6, $P = 0.4405$). Analysis of the primary outcome identified a statistically significant reduction in the proportion of HPR among subjects with at-risk genotypes randomized to prasugrel (0%) compared to clopidogrel (24.1%; $P = 0.0046$). When defined by PRU > 208, 3.3% of subjects assigned to prasugrel had HPR compared with 34.5% in the clopidogrel group ($P = 0.0025$). Other measures of platelet inhibition were also increased among prasugrel-treated patients relative to clopidogrel (Table 3). Prasugrel demonstrated consistent trends for reduction in HPR irrespective of the at-risk genotype (Table 4). Among non-carriers treated with clopidogrel, the mean PRU at 1 month was 110.4 ± 85.1, while 4.8 and 9.5% of these subjects had HPR defined by PRU > 234 and > 208, respectively. Prasugrel-treated carriers, when compared with non-carriers on clopidogrel, did not have an increased risk for HPR at 1 month ($P = 0.5070$ and 0.3932 for PRU > 234 and > 208, respectively). Patients homozygous for *CYP2C19*17* had a 1-month mean PRU value of 87.5 ± 73.2 and had no cases of HPR by either cutoff. The PRU values of carriers of *CYP2C19*17* by treatment groups are shown in the Supplementary Table S1.

Multivariate analyses for predictors of 1-month HPR, using a priori determined variables known to influence clopidogrel-

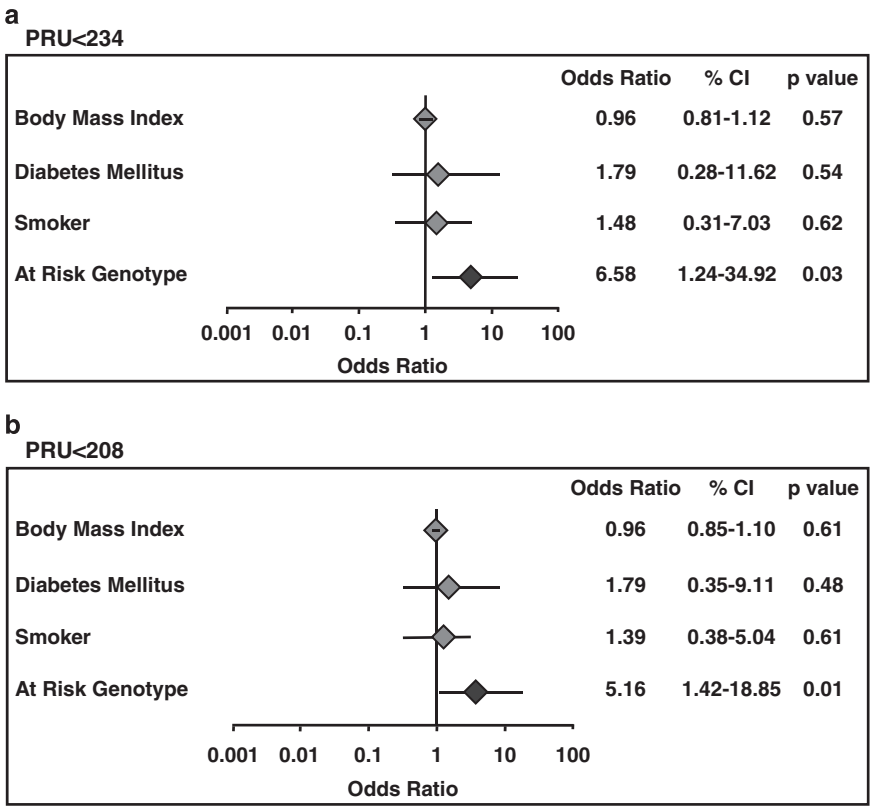

Figure 2. Multivariate analyses for predictors of high on-treatment platelet reactivity (HPR) at 1 month. Multivariate analyses by logistic regression with dependent variable as HPR at 1 month for patients on clopidogrel. HPR defined as $P2Y_{12}$ reaction unit (PRU) >234 (**a**) and >208 (**b**). Variables in the models included: carriers of at-risk genotypes, diabetes, smoking status and body mass index.

mediated platelet reactivity, revealed carrier status for an at-risk genotype to be the strongest independent predictor for HPR, irrespective of cutoffs (Figures 2a and b). PPI use was removed from the models because it perfectly predicted the outcome resulting in questionable validity of the model fit and estimates, particularly for PPI use. The estimates for the other variables in the model were not substantively different when PPI use was excluded.

Clinical outcomes and bleeding

During 1-month follow-up, no MACE was observed among randomized patients. No significant differences in bleeding were observed between randomized patients. In the prasugrel arm, 1 (3.3%) patient had a TIMI major and 1 (3.3%) had a TIMI minor bleed. One patient (3.4%) suffered a TIMI major bleed in the clopidogrel arm. In the non-carrier group on clopidogrel, there were 2 (4.7%) TIMI major and 5 (11.6%) TIMI minor bleeds.

DISCUSSION

Our results demonstrate that point-of-care genetic testing at the clinical bedside is capable of concurrent identification of multiple genetic variants. Rapid identification of at-risk genetic variants facilitated a personalized approach to antiplatelet therapy in patients receiving PCI for STEMI. Treatment of *CYP2C19*2* and *ABCB1 TT* carriers with prasugrel resulted in a significant reduction in HPR after 1 month compared to a STEMI dosing of clopidogrel.

Previously, we reported the first successful use of clinical point-of-care genetic testing based on *CYP2C19*2* carrier status in a proof-of-concept randomized clinical trial.[19] A limitation of this approach, however, was the use of a single genetic variant in isolation when drug response is frequently influenced by multiple variants.[14,16,24,25] Notably, in the context of antiplatelet therapy, both *CYP2C19* loss-of-function alleles and the *ABCB1 TT* genotype have been shown to be independent predictors for MACE among patients treated with clopidogrel following PCI for ACS.[12,14,16,17] The evidence supporting the clinical importance of *CYP2C19* loss-of-function alleles, particularly *CYP2C19*2*, is derived from numerous clinical trials and observational studies and has been validated by two meta-analyses, each involving ~10 000 subjects.[13,26] Though certain studies have failed to show an association with MACE, these conflicting results have generally emerged from studies which did not restrict analyses to subjects receiving PCI with stenting.[27–29] The data supporting the clinical importance of the *ABCB1 TT* genotype has been variable with several studies suggesting that carriers have an increased risk for ischemic complications,[14,16,17] while others failed to identify an association.[30,31] Of note, in the only analysis of data from a randomized controlled trial restricted solely to ACS patients undergoing PCI, both *CYP2C19* loss-of-function alleles and the *ABCB1 TT* genotype were shown to have independent associations with MACE, while carriers of both at-risk genetic variants were observed to be at even greater incremental risk.[16]

In addition to expanding the number of genetic variants that can be assessed at the bedside, extending the use of point-of-care genetic testing to higher acuity STEMI patients is particularly relevant given the increased risk for subsequent MACE and the need for decisions in an expedient manner. The failure of previous personalized studies guided by platelet function testing, not genotyping, may in part be secondary to the predominant enrollment of non-ACS patients with lower risk for MACE.[32–34] The GRAVITAS (Gauging Responsiveness with A VerifyNow Assay

—Impact on Thrombosis and Safety) study, which evaluated the benefits of high-dose clopidogrel among PCI patients with predominantly stable disease, had MACE rates of only 2.3% at 6 months.[23] Similarly, the TRIGGER-PCI (Testing platelet Reactivity In patients underGoing elective stent placement on clopidogrel to Guide alternative thErapy with pRasugrel) trial, which only enrolled elective stable patients, was prematurely terminated following only 1 (0.4%) event in 236 patients.[33] Indeed, the authors of TRIGGER-PCI attribute a key reason for the failure of the study as the exclusive enrollment of stable coronary artery disease patients, who have less incidence of MACE.[33] In contrast, the risk of MACE following ACS approximates 10% at one year, emphasizing the need to improve treatment strategies in this population.[9,10]

Several novel strategies have provided additional benefits over standard clopidogrel among patients with non-ST ACS and STEMI.[6,9,10,35,36] The CURRENT–OASIS 7 trial demonstrated that a higher clopidogrel dosing strategy decreased MACE among ACS and STEMI patients undergoing PCI.[6] In addition, novel $P2Y_{12}$ agents, prasugrel and ticagrelor, confer additional ischemic benefits over clopidogrel as shown in the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel (TRITON–TIMI-38) and the Platelet Inhibition and Patient Outcomes (PLATO) trials.[9,10] However, these strategies were associated with increased fatal and non-fatal bleeding events, which have contributed to reluctance for their universal adoption. Of note, a key finding of the ADAPT-DES study was the importance of both ischemic and hemorrhagic complications to account for all-cause mortality.[37] Although there may be proponents for the universal adoption of novel $P2Y_{12}$ agents, randomized studies of these agents against clopidogrel have consistently demonstrated increased rates of non-CABG-related major bleeding. Consequently, there is an impetus to pursue novel personalized strategies consisting of selective administration of more potent $P2Y_{12}$ inhibitors that carry the potential to reduce ischemic and hemorrhagic complications concurrently.

In our study, carriers of at-risk genotypes had a significantly higher prevalence of HPR at baseline compared to non-carriers, supporting their classification as an at-risk group for treatment failure with clopidogrel. Moreover, treatment of non-carriers with clopidogrel resulted in only 4.6% of subjects having HPR at 1 month suggesting that clopidogrel may be adequate among the vast majority of subjects who do not possess an at-risk genotype. These findings highlight the potential of a personalized strategy to target more potent therapy to at-risk patients, while sparing the remaining patients from increased bleeding risks of more potent agents; this concept may be particularly well suited for the future development of strategies to achieve a therapeutic window, where ischemic and bleeding risks are optimized simultaneously.[38]

Within our study, treatment of at-risk genotype carriers with the OASIS-7 dosing of clopidogrel resulted in 24.1% continuing to exhibit HPR at 1 month. In contrast, carriers of at-risk genotypes assigned to prasugrel resulted in complete elimination of HPR. Both augmented-dose clopidogrel and prasugrel have been shown to decrease ischemic complications relative to standard clopidogrel dosing in STEMI patients.[6,9,35] Of note, both strategies continue to be endorsed in guidelines.[39,40] The Escalating Clopidogrel by Involving a Genetic Strategy (ELEVATE) study showed that clopidogrel dosing at 225 mg daily reduced HPR among heterozygous *CYP2C19*2* carriers; however, dosing up to 300 mg daily failed to overcome HPR in homozygotes. Our study design predated publication of ELEVATE,[41] but was based on the approach from CURRENT–OASIS 7, which showed clinical benefits when compared to standard dosing of clopidogrel.[6] Previous retrospective genetic studies comparing the effects of prasugrel to high-dose clopidogrel in elective PCI patients suggested high-dose clopidogrel was only effective in reducing HPR in non-carriers of *CYP2C19**2.[42,43] In contrast, prasugrel effectively reduced HPR irrespective of *CYP2C19 *2* status, which is consistent with our trial results. Notably, our study is the first to prospectively demonstrate in a randomized manner that treatment of STEMI patients carrying at-risk genotypes with prasugrel is superior to the OASIS-7 clopidogrel strategy for reducing HPR. These findings should draw caution to the ongoing use of higher dosing of clopidogrel among STEMI patients known to be carriers of at-risk genotypes. This is of particular significance, given that at-risk variants are prevalent and therefore use of an augmented clopidogrel dosing strategy may fail to adequately protect a substantial proportion of the population.

The third variant tested, *CYP2C19*17*, confers a gain of function.[18] Carriers of this SNP have an increased propensity toward bleeding when receiving clopidogrel[18] and current pharmacogenetic guidelines recommend standard dosing at 75 mg daily.[44] In our study, there were no homozygous carriers of *CYP2C19*17* that had HPR after treatment with clopidogrel. Larger prospective studies will be required to further investigate the impact of this SNP among individuals who also carry *CYP2C19* loss-of-function alleles and/or the *ABCB1 TT* genotype.

There are some limitations to our study. First, our study had enrolled patients treated with primary PCI and also a significant proportion of patients who initially had received thrombolytic therapy preceding PCI. However, as a major objective was to provide a proof of concept of being able to identify multiple at-risk variants in patients with STEMI, our enrollment of patients initially treated with thrombolytics should not detract from the fact that the main objective was achieved. Moreover, clopidogrel continues to be the main $P2Y_{12}$ inhibitor used in patients treated with thrombolytics due previous studies supporting its use in this context.[1,2] Accordingly, we believe that the enrollment of patients treated initially with thrombolytics should not affect the significance of our data. Second, there are other factors, apart from genetics, which may affect clopidogrel response. Consequently, among non-carriers treated with standard-dose clopidogrel in our study, there were some which had HPR at 1 month. Our study was designed to evaluate an intervention using genetics alone. Future strategies will require consideration of a multifactorial approach to address non-genetic causes for HPR.[11] Lastly, is our use of HPR as the primary end point. HPR has been extensively investigated and has been shown to be an important predictor of ischemic outcomes after PCI.[45–49] Studies involving antiplatelet agents have routinely utilized HPR to evaluate the efficacy of novel treatment strategies.[19,50] Although we have demonstrated that a gene-guided approach to selective administration of prasugrel was successful in overcoming HPR among carriers of at-risk genotypes, our study was nonetheless small and not powered to determine associations to clinical outcomes. Therefore, future studies powered for evaluation of clinical outcomes will be required to permit integration of a pharmacogenomic approach into routine clinical practice. The Tailored Antiplatelet Therapy Following PCI (TAILOR-PCI) trial, which is powered for clinical outcomes, will be recruiting more than 5000 patients to further evaluate this hypothesis (NCT01742117).

In conclusion, we have extended the use of point-of-care genetic testing to STEMI patients receiving PCI and have shown that concomitant genotyping of three separate SNPs is feasible and accurate. A pharmacogenomic approach with selective administration of prasugrel to carriers of at-risk genetic variants reduces the risk of HPR compared to an augmented dosing strategy of clopidogrel among STEMI patients. These serve as integral steps that will facilitate the execution of large clinical trials capable of definitively evaluating the use of pharmacogenomic strategies in patients with ACS.

CONFLICT OF INTEREST

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