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Bedside testing of CYP2C19 vs. conventional clopidogrel treatment to guide antiplatelet therapy in ST-segment elevation myocardial infarction patients

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ABSTRACT

Background: ST-segment elevation myocardial infarction (STEMI) patients are treated with dual antiplatelet therapy comprising aspirin and a $P2Y_{12}$ inhibitor. Clopidogrel is widely used in these patients in several areas worldwide, such as Middle East, but is associated to sub-optimal platelet inhibition in up to 1/3 of treated patients. We investigated a CYP2C19 genotype-guided strategy to select the optimal $P2Y_{12}$ inhibitor.

Methods: This prospective randomized clinical trial included STEMI patients. The standard-treatment group received clopidogrel, while the genotype-guided group were genotyped for *CYP2C19* loss-of-function alleles and carriers were prescribed ticagrelor and noncarriers were prescribed clopidogrel. Primary outcome was a combined ischemic and bleeding outcome, comprising myocardial infarction, non-fatal stroke, cardiovascular death, or Platelet Inhibition and Patient Outcomes major bleeding one year after STEMI.

Results: STEMI patients (755) were randomized into a genotype-guided- (383) and standard-treatment group (372). In the genotype-guided group, 31 patients carrying a loss-of-function allele were treated with ticagrelor, while all other patients in both groups were treated with clopidogrel. Patients in the genotype-guided group had a significantly lower risk of primary outcome (odds ratio (OR) 0.34, 95% confidence interval (CI) 0.20–0.59,), recurrent myocardial infarction (OR 0.25, 95%CI 0.11–0.53), cardiovascular death (OR 0.16, 95%CI0.06–0.42) and major bleeding (OR 0.49, 95%CI 0.32–0.74). There was no significant difference in the rate of stent thrombosis (OR 0.85, 95%CI 0.43–1.71).

Conclusion: A genotype-guided escalation of P2Y12 inhibitor strategy is feasible in STEMI patients treated with clopidogrel and undergoing PCI and is associated with a reduction of primary outcomes compared to conventional antiplatelet therapy.

1. Introduction

Dual antiplatelet therapy (DAPT) in the form of a $P2Y_{12}$ inhibitor (e.g. clopidogrel, ticagrelor or prasugrel) and acetylsalicylic acid is prescribed to ST-segment elevation myocardial infarction (STEMI) patients who undergo percutaneous coronary intervention (PCI) to decrease the risk of atherothrombotic complications [1–3]. The cytochrome P450 enzyme, encoded by the *CYP2C19* gene, in the liver is the most important enzyme that converts clopidogrel into its active metabolite [4]. These active metabolites inhibit the $P2Y_{12}$ receptors on platelets leading to inhibition of platelet aggregation. Previously, clopidogrel was the standard $P2Y_{12}$ receptor inhibitor of choice to treat STEMI patients

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[5,6]. However, approximately 20–30% of the population carry loss-of-function (LoF) alleles, of which the *CYP2C19**2 allele is the most common [7–10]. Carrying LoF alleles while being treated with clopidogrel is associated with high on-treatment platelet reactivity and an increased risk of adverse clinical outcomes [11,12].

Prasugrel and ticagrelor are two $P2Y_{12}$ inhibitors, and unlike clopidogrel, platelet reactivity in treated patients is more predictable and not influenced by *CYP2C19* alleles [13,14]. In the Platelet Inhibition and Patient Outcomes (PLATO) and the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction (TRITON-TIMI 38), ticagrelor and prasugrel proved to reduce ischemic event rates compared to clopidogrel [15,16].

Due to its lower costs, clopidogrel is still widely prescribed in STEMI patients in the Middle East and other less developed areas in the world. Cardiovascular disease is highly prevalent in the Eastern Province of Saudi Arabia due to improvements in wealth standards in the past decades [17–20]. It is therefore of interest to see, whether a *CYP2C19* genotype-guided strategy in STEMI patients undergoing PCI is feasible and improves patient outcomes in this setting. The primary objective of which was to assess the efficacy, complication free survival and safety of the *CYP2C19* genotype-guided antiplatelet treatment strategy compared to conventional clopidogrel treatment.

2. Materials and methods

2.1. Trial design

The trial design has been published previously [21]. Patients were recruited from King Fahd Hospital of the University and King Fahd Military Medical Complex (KFMMC) in the Eastern Province of Saudi Arabia. The trial protocol was approved by the Ethical Committee of Imam Abdulrahman Bin Faisal University. All patients signed a written informed consent. An independent data and safety monitoring board monitored the trial and had full access to all data. A second independent committee reviewed and adjudicated all cardiovascular-related end points. The trial was supported by King Abdulaziz City for Science and Technology (KACST).

2.2. Population

Patients between 18 and 70 years of age with STEMI and symptoms lasting between 30 min and 12 h who had undergone PCI were eligible for inclusion. Inclusion/exclusion criteria are provided in Supplementary Table S1. Clinical and demographic data were collected from the patients' medical records. In patients with the *CYP2C19*2* LoF allele, it was necessary for the therapy to be changed and therefore, the treating physicians were not blinded to group allocation.

2.3. Randomization and study procedure

Patients were randomized on a 1: 1 ratio by a schedule generated by a biostatistician. Patients were asked to participate in the trial immediately post STEMI. The choice of stent, loading dose or oral $P2Y_{12}$ inhibitors, access site and other periprocedural interventions were at the discretion of the treating physician. Patients were randomized to either a genotype-guided strategy or to the conventional therapy group. In the genotype-guided group, *CYP2C19* genotyping using a Spartan RX system (Spartan Bioscience Inc.), was carried out for all patients (Supplementary Fig. S1). Those patients who did not carry the *CYP2C19* *2 allele were given clopidogrel (75 mg once daily), while those patients who were carriers of the *CYP2C19* *2 allele were prescribed ticagrelor (90 mg twice daily) according to local protocol. In the standard-treatment group, *CYP2C19* genotyping was carried out at the end of the study period and these patients were treated with clopidogrel (75 mg once daily) according to standard care. Patients in both groups were treated with dual antiplatelet therapy for at least 12 months after STEMI. To validate the results, 10% of the samples collected were genotyped using TaqMan StepOnePlus Assay at the Department of Clinical Biochemistry at Imam Abdulrahman bin Faisal University.

2.4. End points

Study-related events were collected for 12 months after STEMI by residents. An independent committee comprising consultants from the Department of Internal Medicine, blinded to the study groups and the type of $P2Y_{12}$ inhibitor prescribed to each group, reviewed and adjudicated all cardiovascular-related end points. Definition of the end points used can be found in the supplementary appendix [22,23].

The primary outcome of the trial was the composite of cardiovascular death, recurrent myocardial infarction, non-fatal stroke and major bleeding defined according to PLATO at 12 months after STEMI (Supplementary Table S2) [24]. Secondary outcomes were the individual components of the primary outcome in addition to all strokes, stent thrombosis, all-cause death and target vessel revascularization [9,21–23].

2.5. Statistical analysis

Prior to the trial, a sample size calculation was performed. The estimated event rate of the primary outcome for the genotype-guided arm was 9%, while the estimated event rate for the standard-treatment group was 13.6% [9,23]. Using a power of 80% and an alpha level of 0.05, 1484 patients were required. Accounting for potential drop-outs, 1500 patients were scheduled to be included in the trial, equally distributed between both groups. After the trial was completed, we re-estimated the power to detect significant differences in event rates between the genotype-guided group and standard-treatment group based on the actual sample size achieved in the study. The event rates were defined by the occurrence of the events of interest within 12 months after STEMI. With the final sample size of 375 in the genotype-guided arm and 312 in the standard-treatment group, assuming event rates in the standard-treatment group of 15.5% (combined ischemic and bleeding), 8.7% (recurrent MI) 7.6% (cardiovascular death) and 3.5% (non-fatal stroke), there is 80% power at an alpha level of 0.05 to detect a reduction in event rates in the genotype-guided group, assuming events rates of 8.6% (combined ischemic and bleeding), 3.6% (Recurrent MI), 2.9% (cardiovascular death) and 0.53% (non-fatal stroke).

Comparisons of patient characteristics between the genotype-guided group and standard-treatment group were performed using two-sample *t*-test, $\chi 2$ contingency test, and Fisher's exact test where appropriate. Nonparametric methods were used to test the difference in median for variables that are not normally distributed including SBP, DBP, heart rate, weight and BMI, with the summary statistics for these variables expressed as median (interquartile range, IQR). The analysis followed the intent-to-treat principle and included all patients eligible and randomized. Logistic regression was employed to test the differences for the primary and secondary outcomes between the genotype-guided group and standard-treatment group and to calculate the odds ratio (OR) with 95% confidence intervals. Potential confounding factors, including patient characteristics and STEMI parameters that showed a statistical difference between the genotype-guided group and standard-treatment group were also included in logistic regression as covariates when testing for the main effect (randomization to genotype-guided group or standard-treatment group). Time-to-event curves were constructed with the use of the Kaplan–Meier method. Differences between the survival curves were compared with the use of the log-rank test. Cox proportional hazards model was used to calculate hazard ratios with 95% confidence intervals. All *P*-values represent the results of two-sided tests. P-values <0.05 were considered statistically significant. All data analyses were performed using NCSS version 21.0.1 software [25].

3. Results

Over the period from April 2013 through December 2020, a total of 755 eligible patients, clinically diagnosed with STEMI, were selected to participate in the study. Due to duplication of randomization and providing only oral consent, 68 were excluded from the analysis. Therefore, a total of 687 patients were randomly assigned, 375 to the genotype-guided group and 312 to the standard-treatment group (Supplementary Fig. S1). All patients underwent PCI, the majority of whom were male (80.8%). The baseline characteristics, including cardiovascular risk factors and medical history, were well matched between the groups (Table 1). Patients in the genotype-guided group were slightly taller (165.38 ± 8.55) and heavier (80 [72, 90]) compared to the standard-treatment group (163.84 ± 8; 78 [70, 88]). However, no difference in BMI was detected between the two groups ($p = 0.15$).

The genotyping procedure was timed in both hospitals on the first 50 patients included in the study at each hospital. Results of genotyping were submitted to the treating cardiologist within 90–120 min from the start of the PCI procedure. The PCI characteristics were compared between the genotype-guided and standard-treatment groups (Table 2). The majority of PCI characteristics, including approaches taken, proportion of percutaneous transluminal angioplasty performed, stent implanted, Killip class, and proportion of patients with complications, were found to be similar between the two groups (Table 2). A higher proportion of patients had had trombosuction in the standard-treatment group (18.6%) compared to the genotype-guided group (12.4%) ($p = 0.03$). Bare metal stent use was found to be more frequent in the standard-treatment group (6.6%) compared to the genotype-guided group (2.2%) ($p = 0.025$). However, neither trombosuction nor bare metal stent use was found to be associated with the primary outcome ($p = 0.7$ and 0.89, respectively) and not included in later analysis as potential confounder.

In the genotype-guided group, 31.5% of patients were found to be carriers of CYP2C19 LoF polymorphisms and were intermediate or poor metabolizers of clopidogrel (Table 1). Only 31 out of 104 intermediate or poor metabolizers (28.8%) received ticagrelor as antiplatelet therapy, while 100% of patients in the standard-treatment group were prescribed clopidogrel. Despite the low rate of ticagrelor use in the genotype-guided group, CYP2C19 genotype guided therapy significantly improved both the primary and other secondary outcomes (Table 3). Compared to patients in the standard-treatment group, patients in the genotype-guided group had a significantly reduced risk of the primary outcome OR 0.34, 95% CI 0.20–0.59, recurrent MI OR 0.35 95% CI 0.17–0.70, and cardiovascular death OR 0.24 95% CI 0.10–0.58. Kaplan-Meier estimated cumulative incidence curves in the genotype-guided and standard-treatment groups for the primary outcome in KFHU patients was shown in Fig. 1. KFMC patients were excluded from this analysis due to missing follow-up event dates. The difference in incidence rate between genotype-guided and standard-treatment groups are statistically significant with HR 7.14 95% CI 4.96–10.3. Additionally, patients in the genotype-guided group also had a significantly reduced risk of target vessel revascularization (OR 0.58 95% CI 0.43–0.79), all-cause death (OR 0.24 95% CI 0.10–0.58), and the combination of all secondary end points (OR 0.54 95% CI 0.38–0.75). However, there was no significant difference in stroke risk (OR 0.41 95% CI 0.15–1.10), stent

Table 1
Baseline characteristics of patients participated in the clinical trial.

Parameter	Genotype-guided group	Standard-treatment group	p-Value
Total number of patients	375	312	
Age (Mean ± SD)	56.74 ± 11.84	55.47 ± 11.22	0.15
Male Sex, (N (%))	303 (80.8)	252 (80.8)	0.99
BMI (Median [IQR])	32.7]	29.1 [25.4, 33.5]	0.15
Cardiovascular risk factors			
Current smokers, (N (%))	157 (48.6)	127 (46.5)	0.49
Hypertension, treated, (N (%))	254 (82.7)	220 (83.3)	0.85
Hypercholesterolemia, treated, (N (%))	142 (86.1)	83 (83.8)	0.62
Sickle Cell Anemia, (N (%))	9 (3.4)	4 (1.7)	0.27
Diabetes (N (%))	262 (89.4)	200 (84.4)	0.09
Family history, 1 family members, (N (%))	75 (33.3)	65 (28.8)	0.29
Medical history			
Myocardial infarction, (N (%))	196 (54.4)	163 (54.7)	0.95
Left ventricular ejection fraction after PCI, (N (%))			
Good >50%	216 (65.7)	167 (66)	0.39
Moderate (>30% < 50%)	95 (28.9)	79 (31.2)	
Bad <30%	17 (5.2)	7 (2.8)	
Proven_PAD, (N (%))	8 (2.3)	10 (3.5)	0.40
CABG, (N (%))	20 (5.5)	21 (6.9)	0.44
Stomach ulcer, (N (%))	3 (0.8)	6 (2)	0.31
Renal failure, (N (%))[a]	10 (2.8)	9 (3)	0.85
Bleeding tendency, (N (%))	11 (3.1)	4 (1.3)	0.19
Active malignancy, (N (%))	2 (0.6)	1 (0.3)	1.00
Medication on discharge			
Clopidogrel (N (%))	338 (90.9)	309(100)	6.10E-10
Ticagrelor (N (%))	34 (9.1)	0 (0)	
Aspirin (N (%))	369 (98.4)	310 (99.4)	0.3
Statin (N (%))	375 (100)	312 (100)	1.0
Beta blockers (N (%))	375 (100)	312 (100)	1.0
ACE inhibitor (N (%))	355 (94.7)	301 (96.5)	0.26
Warfarin (N (%))	29 (7.7)	19 (6.1)	0.4
CYP2C19 metabolizer status			
Intermediate/poor metabolizers, (N (%)	104 (31)	NA	
Normal or rapid metabolizers, (N (%))	232 (69)	NA	

PCI: percutaneous coronary intervention; ACE Inhibitor: Angiotensin-converting enzyme inhibitor.

[a] Renal Failure: defined according to Kidney Disease Outcomes Quality Initiative (KDOQI).

Table 2
PCI Characteristics and Antiplatelet Use (Class 1- No evidence of heart failure; Class 2- Findings consistent with mild to moderate heart failure; Class 3- Overt pulmonary edema; Class 4- Cardiogenic shock) (LAD-Left anterior descending artery; LCx- Left circumflex artery; RCA- Right coronary artery; RI- Ramus intermedius artery) (GP IIb/IIIa inhibitors- Glycoprotein IIb/IIIa inhibitors).

Parameter	Genotype-guided group	Standard-treatment group	p-Value
Total number of patients	375	312	
Access site, (N (%))			
Femoral, (N (%))	74 (20.2)	42 (14.3)	0.05
Radial, (N (%))	292 (79.8)	251 (85.7)	
PCI performed, (N (%))	185 (74.9)	141 (74.6)	0.94
Culprit Lesion, (N (%))			
LAD	237 (63.2)	172 (55.1)	0.001
LCx	51 (13.6)	30 (9.6)	
RCA	91 (24.3)	105 (33.6)	
RI	0 (0)	5 (1.6)	
Type of Stent implanted (N (%))	360 (98.9)	285 (99.7)	0.39
Stent Brand, (N (%))			
Drug eluting stent	267 (97.1)	198 (93.4)	0.025
Bare metal stent	6 (2.2)	14 (6.6)	
Others	2 (0.7)	0 (0)	
Killip Class, (N (%))			
Class 1 No CHF	311 (90.9)	265 (95.3)	0.13
Class 2 Rales	18 (5.3)	7 (2.5)	
Class 3 Pulmonary Edema	10 (2.9)	3 (1.1)	
Class 4 Cardiogenic Shock	3 (0.9)	3 (1.1)	
Trombosuction, (N (%))	42 (12.4)	54 (18.6)	0.03
GP IIb/IIIa inhibitors, (N (%))	152 (44.3)	150 (52.1)	0.06
Complications, (N (%))	14 (3.7)	9 (2.9)	0.54

Table 3
Effects of CYP2C19 Directed Antiplatelet Use on Major Adverse Cardiovascular Events within 1-year post-PCI. All outcomes were confirmed by an independent adjudication committee. Combination of MACE included death, myocardial infarction, stent thrombosis, stroke or major bleeding defined according to Platelet Inhibition and Patient Outcomes Criteria.

Parameters	Genotype-guided group		Standard-treatment group	OR (95%CI)	p-Value
Total number of patients	375		312		
Antiplatelet therapy					
Clopidogrel	83 (70.3)	255 (99.2)	309 (100%)		
Ticagrelor	34 (28.8)	0 (0)	0 (0)		
Major Adverse Cardiovascular Events (MACE)					
Primary outcome	21 (5.9)		47 (15.5)	0.34 (0.20–0.59)	9.49E-05
Recurrent Myocardial Infarction (MI)	12 (3.2)		27 (8.7)	0.35 (0.17–0.70)	0.003
Non-fatal stroke	6 (1.6)		11 (3.5)	0.44 (0.16–1.21)	0.11
Cardiovascular death	7 (2.0)		23 (7.6)	0.24 (0.10–0.58)	0.0013
Major bleeding	0 (0)		4 (1.3)	NA	NA
Secondary end points					
Stroke	6 (1.6)		12 (3.9)	0.41 (0.15–1.10)	0.075
Stent thrombosis	18 (5.4)		16 (6.3)	0.85 (0.43–1.71)	0.65
Target vessel revascularization	145 (38.7)		162 (51.9)	0.58 (0.43–0.79)	0.0005
All-cause Death	7 (2.0)		23 (7.6)	0.24 (0.10–0.58)	0.0013
Combination of all secondary end points	128 (39.9)		137 (55.2)	0.54 (0.38–0.75)	2.90E-04

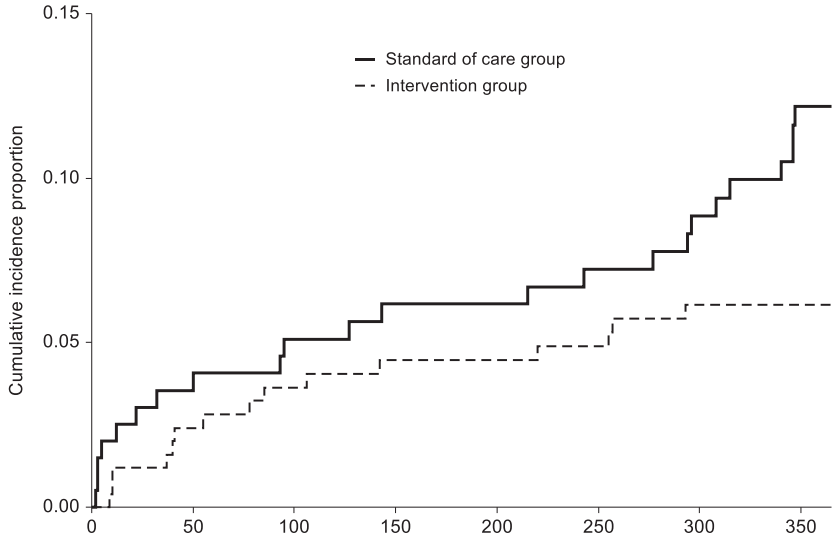
thrombosis (OR 0.85 95% CI 0.43–1.71) 0r target vessel revascularization (0.58 95% CI 0.43–0.79) between the two groups.

4. Discussion

The aim of this trial was to investigate whether a strategy using a point-of-care *CYP2C19* genotype system to guide $P2Y_{12}$ inhibitor therapy is feasible and could improve patient outcomes compared to conventional therapy with clopidogrel in patients with STEMI undergoing PCI. We found a significant reduction in the primary outcome and the individual components, such as cardiovascular death and recurrent MI, however there was no difference in the risk of stroke.

Pharmacogenetic testing is rapidly becoming a standard procedure in many hospitals as personalized medicine is now becoming widely implemented. However, there are several concerns regarding implementation of pharmacological testing, such as the feasibility of testing in a hospital set up and economic issues, which are an important limiting factor in poorer countries. For STEMI patients undergoing PCI, the current guidelines of the American College of Cardiology recommend the use of a dual antiplatelet therapy composed of a $P2Y_{12}$ inhibitor, with a preference for prasugrel or ticagrelor over clopidogrel, in combination with aspirin [26,27]. However, due to the lower costs of clopidogrel, it is still the most widely prescribed $P2Y_{12}$ inhibitor in Saudi Arabia and many other countries [28]. It has been widely reported that the use of clopidogrel is associated with a higher ischemic risk as some patients carry the *CYP2C19*2* LoF alleles which poorly metabolize clopidogrel and thus these patients have a reduced capacity for bioactivation of clopidogrel and impaired platelet inhibition [7]. In contrast, genetic variants of *CYP2C19* have no influence on the clinical effectiveness of other $P2Y_{12}$ inhibitors, such as prasugrel or ticagrelor. Despite the wealth of knowledge that we have about these variants, *CYP2C19* genotype-guided antiplatelet therapy remains controversial due to the absence of large, randomized control trials.

The present study is the first clinical trial on the use of CYP2C19 genotype-guided antiplatelet therapy in the Middle East and in in STEMI patients undergoing PCI. In addition, the present study demonstrates that rapid genotyping in a clinical setting is feasible and would allow



Number At Risk								
Standard of care group	200	193	190	188	188	186	183	177
Intervention group	251	245	242	240	240	239	236	236

Fig. 1. Kaplan-Meier estimated cumulative incidence curves and at-risk table in the genotype-guided and standard-treatment groups for combined ischemic and major bleeding events in KFHU patients.

informed antiplatelet therapy. Despite the low rate of ticagrelor use in the genotype-guided group, CYP2C19 genotype-guided therapy significantly improved both a combination of ischemic and major bleeding events and a combination of all secondary end points. Although the study included 104 patients with the LoF mutation, only 31 patients had a change in drug therapy from clopidogrel to ticagrelor due to the unforeseen unavailability of ticagrelor in one of the hospitals due to economic reasons, as mentioned previously. A number of studies in Europe and the United States have shown the use of *CYP2C19* genotype-guided antiplatelet therapy in PCI patient is associated with a lower risk of MACE in patients carrying the *CYP2C19**2 LoF allele treated with prasugrel or ticagrelor as an alternative to clopidogrel. An earlier study by Claassens et al., (2019) which included 2488 STEMI patients, has shown that a *CYP2C19* genotype-guided based therapy was non-inferior to standard treatment with ticagrelor or prasugrel in terms of thrombotic events with a lower incidence of bleeding (de-escalation strategy) [9]. On the other hand, a study by Pereira et al., (2020) showed no significant difference between the use of conventional clopidogrel therapy and ticagrelor therapy in patients carrying *CYP2C19* LoF alleles (escalation strategy) [10]. However, only 50% of the patients included in the trial were patients with MI, while the others were either stable CAD or unstable angina patients which have a lower ischemic risk. Additionally, due to a lower-than-expected event rate, they recalculated their power calculation as to not increase the number of patients needed in the trial [10]. Contrary to the trial by Pereira et al., our results are in line with a recently published meta-analysis by Galli et al., comparing guided-therapy, either by genotyping or by using platelet function testing to standard treatment [29,30]. It included 20,743 patients and concluded that guided-therapy resulted in a significant reduction in MACE (relative risk 0.78, 95% CI 0.63–0.95, $P = 0.015$). In 2019, before publication of the aforementioned trials and meta-analysis, an expert consensus paper was published on using platelet function and *CYP2C19* genetic testing to guide treatment in patients undergoing PCI [31]. Additionally, a recent review by Galli et al. presents an overview of the latest literature [32]. These recent contributions support the clinical benefit of using genetic or platelet function testing as a strategy, in combination with procedural and patient characteristics, to personalize antiplatelet selection by either escalation or de-escalation of treatment. An escalation strategy, like in our trial, could help to reduce the ischemic burden without increasing the bleeding risk in countries where clopidogrel is still standard therapy or in patients with chronic coronary syndrome. A de-escalation strategy, like the one investigated by Claassens et al., (2019) would be well suited to reduce the bleeding risk, without increasing the ischemic risk in countries where ticagrelor or prasugrel are the standard treatment. This was confirmed by results from the meta-analysis by Galli et al. (2021) [9,32]. The results of this study further strengthen the findings of this meta-analysis.

5. Limitations

The trial has several limitations. First, is the open-label design. However, in order to minimize the bias associated with this type of design, the adjudicators were blinded to patient group assignment. Another limitation was the small sample size of patients with the LoF mutation who were changed from standard care to ticagrelor. Although the study included 104 patients with the LoF mutation, only the 31 patients had a change in drug therapy from clopidogrel to ticagrelor due to economic reasons. Furthermore, follow-up was not possible for all patients, particularly during the COVID-19 pandemic which also hindered reaching the target sample size of 1500. Moreover, the exact time to event was not available for all patients, as this data could not be obtained from the hospital records. This prevented us from including these patients in the time-to-event rate analyses, but they were included in the non-time dependent analyses. The CYP2C19*3 LoF allele is present in the Saudi population, but due to its very low prevalence only the CYP2C19 *2 allele was genotyped, which is a limitation to the study [33]. Another limitation is that it was not possible to obtain follow up event date for patients from KFMMC site (our second trial site) to run survival analysis to get estimates of HRs as the follow-up time did not allow for this. After excluding KFMC patients, our study is underpowered to detect all MACE component phenotypes (death, MI, bleeding, and stroke). An anomaly of the current study is the lower rate of bleeding in the genotype-guided group. It is not possible to hypothesize on the reason for this as only 31 patients in this group were treated with ticagrelor.

Despite these limitations, our results are in line with similar studies and more importantly, this trial is the first of its kind to be conducted in STEMI patients in the Middle East who have undergone PCI. Consequently, this work provides significant information that will support physicians in providing the optimal $P2Y_{12}$ inhibitor therapy in those patients who have a LoF allele.

6. Conclusion

Among STEMI patients treated with clopidogrel and undergoing PCI, a genotype-guided escalation of P2Y12 inhibitors strategy is feasible and is associated with a reduction of the composite endpoint of cardiovascular death, non-fatal stroke, recurrent myocardial infarction and PLATO major bleeding, compared to conventional antiplatelet therapy.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2021.08.051.

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Authors' contributions

AMR, FAM, AMS, MAM, RAA, RMK, KAF, and MMS were involved in the design of the work, critically revising of protocol, patient recruitment, data acquisition, analysis, interpretation of data and drafting of the manuscript. CC, CBV, BLL and AKA were involved in the design of the work, laboratory work, analysis, interpretation of data and drafting of the manuscript. DMC and FWA were involved in the design of the work, critically revising of protocol, analysis, interpretation of data and drafting of the manuscript.

Declaration of Competing Interest

The authors declare that they have no competing interests.

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Appendix A. Appendix

Inclusion/exclusion criteria and definition of the primary and secondary end points are in Supplementary Tables S1 and S2, respectively. Randomization is shown in Supplementary Fig. S1.

References

[1] N.J. Breet, J.W. van Werkum, H.J. Bouman, et al., Comparison of platelet function tests in predicting clinical outcome in patients undergoing coronary stent implantation, JAMA 303 (8) (2010) 754–762, https://doi.org/10.1001/jama.2010.181.

[2] J.P. Collet, J.S. Hulot, A. Pena, et al., Cytochrome P450 2C19 polymorphism in young patients treated with clopidogrel after myocardial infarction: a cohort study,

Lancet 373 (9660) (2009) 309–317, https://doi.org/10.1016/S0140-6736(08)61845-0 Epub 2008 Dec 26.
[3] D.E. Cutlip, S. Windecker, R. Mehran, et al., Clinical end points in coronary stent trials: a case for standardized definitions, Circulation 115 (17) (2007) 2344–2351, https://doi.org/10.1161/CIRCULATIONAHA.106.685313.
[4] M. Kazui, Y. Nishiya, T. Ishizuka, et al., Identification of the human cytochrome P450 enzymes involved in the two oxidative steps in the bioactivation of clopidogrel to its pharmacologically active metabolite, Drug Metab. Dispos. 38 (1) (2010) 92–99, https://doi.org/10.1124/dmd.109.029132.
[5] D.L. Campbell-Scherer, L.A. Green, ACC/AHA guideline update for the management of ST-segment elevation myocardial infarction, Am. Fam. Physician 79 (12) (2009 Jun 15) 1080–1086.
[6] B. Ibanez, S. James, S. Agewall, et al., 2017 ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: the task force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC), Eur. Heart J. 39 (2) (2018) 119–177, https://doi.org/10.1093/eurheartj/ehx393.
[7] J. Petrović, V. Pešić, V.M. Lauschke, Frequencies of clinically important CYP2C19 and CYP2D6 alleles are graded across Europe, Eur. J. Hum. Genet. 28 (1) (2020 Jan) 88–94, https://doi.org/10.1038/s41431-019-0480-8. Epub 2019 Jul 29, 31358955.
[8] F.I. Al-Jenoobi, K.M. Alkharfy, A.M. Alghamdi, et al., CYP2C19 genetic polymorphism in Saudi Arabians, Basic Clin. Pharmacol. Toxicol. 112 (1) (2013) 50–54, https://doi.org/10.1111/j.1742-7843.2012.00919.x.
[9] D.M.F. Claassens, G.J.A. Vos, Bergmeijer TO, et al., A genotype-guided strategy for oral P2Y, N. Engl. J. Med. 381 (2019) 1621–1631, https://doi.org/10.1056/NEJMoa1907096.
[10] N.L. Pereira, M.E. Farkouh, D. So, et al., C. effect of genotype-guided oral P2Y12 inhibitor selection vs conventional clopidogrel therapy on ischemic outcomes after percutaneous coronary intervention: the TAILOR-PCI randomized clinical trial, JAMA 324 (8) (2020 Aug 25) 761–771, https://doi.org/10.1001/jama.2020.12443.
[11] A.R. Shuldiner, J.R. O'Connell, K.P. Bliden, et al., Association of cytochrome P450 2C19 genotype with the antiplatelet effect and clinical efficacy of clopidogrel therapy, JAMA 302 (2009) 849–857.
[12] J.L. Mega, T. Simon, J.P. Collet, et al., Reduced-function CYP2C19 genotype and risk of adverse clinical outcomes among patients treated with clopidogrel predominantly for PCI: a metaanalysis, JAMA 304 (16) (2010) 1821–1830, https://doi.org/10.1001/jama.2010. 1543.
[13] J.L. Mega, S.L. Close, S.D. Wiviott, et al., Cytochrome P450 genetic polymorphisms and the response to prasugrel: relationship to pharmacokinetic, pharmacodynamic, and clinical outcomes, Circulation 119 (19) (2009) 2553–2560, https://doi.org/10.1161/CIRCULATIONAHA. 109.851949.
[14] Y.D. Wijeyeratne, S. Heptinstall, Anti-platelet therapy: ADP receptor antagonists, Br. J. Clin. Pharmacol. 72 (4) (2011 Oct) 647–657, https://doi.org/10.1111/j.1365-2125.2011.03999.x.
[15] L. Wallentin, R.C. Becker, A. Budaj, et al., Ticagrelor versus clopidogrel in patients with acute coronary syndromes, N. Engl. J. Med. 361 (2009) 1045–1057.
[16] S.D. Wiviott, E. Braunwald, C.H. McCabe, et al., Prasugrel versus clopidogrel in patients with acute coronary syndromes, N. Engl. J. Med. 357 (2007) 2001–2015.
[17] K.F. Alhabib, A.J. Kinsara, S. Alghamdi, et al., The first survey of the Saudi acute myocardial infarction registry program: main results and long-term outcomes (STARS-1 program), PLoS One 14 (5) (2019), https://doi.org/10.1371/journal.pone.0216551, 21.
[18] W. Almahmeed, M.S. Arnaout, R. Chettaoui, et al., Coronary artery disease in Africa and the Middle East, Ther. Clin. Risk Manag. 8 (2012) 65–72, https://doi.org/10.2147/TCRM.S26414.
[19] M. Al-Omran, Atherosclerotic disease and risk factor modification in Saudi Arabia: a call to action, Vasc. Health Risk Manag. 8 (2012) 349–355, https://doi.org/10.2147/VHRM.S32783.
[20] A. El-Menyar, M. Zubaid, A. Shehab, et al., Prevalence and impact of cardiovascular risk factors among patients presenting with acute coronary syndrome in the middle east, Clin. Cardiol. 34 (1) (2011) 51–58, https://doi.org/10.1002/clc.20873.
[21] Abdullah M. Al-Rubaish, Fahad A. Al-Muhanna, Abdullah M. Alshehri, et al., Bedside testing of CYP2C19 gene for treatment of patients with PCI with antiplatelet therapy, BMC Cardiovasc. Disord. 20 (1) (2020) 268, 3. (PMID: 32493215 (web archive link,)).
[22] K. Thygesen, J.S. Albert, A.S. Jaffe, et al., Third universal definition of myocardial infarction, Eur. Heart J. 33 (20) (2012 Oct) 2551–2567, https://doi.org/10.1093/eurheartj/ ehs184 (Epub 2012 Aug 24).
[23] D.E. Cutlip, S. Windecker, R. Mehran, et al., Clinical end points in coronary stent trials: a case for standardized definitions. Academic Research Consortium, Circulation 115 (17) (2007 May 1) 2344–2351, https://doi.org/10.1161/CIRCULATIONAHA.106.685313 (PMID : 17470709).
[24] R. Mehran, S.V. Rao, D.L. Bhatt, et al., Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the bleeding academic research consortium, Circulation 123 (23) (2011) 2736–2747, https://doi.org/10.1161/CIRCULATIONAHA.110.009449.
[25] J. Hintze, NCSS, in: NCSS and PASS Number Cruncher Statistical System, Kaysville, Utah, USA, 2012.
[26] M.D. Klein, A.K. Williams, C.R. Lee, G.A. Stouffer, Clinical utility of CYP2C19 genotyping to guide antiplatelet therapy in patients with an acute coronary syndrome or undergoing percutaneous coronary intervention, Arterioscler. Thromb. Vasc. Biol. 39 (4) (2019 Apr) 647–652.
[27] G.N. Levine, E.R. Bates, J.A. Bittl, et al., ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: a report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines, J. Am. Coll. Cardiol. 68 (2016) 1082–1115, 2016.
[28] A.A. Almeman, Major CYP450 polymorphism among Saudi patients, Drug Metabol. Lett. 14 (1) (22 Jul 2021), https://doi.org/10.2174/1872312814666200722122232.
[29] B. Kheiri, T.F. Simpson, M. Osman, et al., Genotype-guided strategy for P2Y 12 inhibitors in coronary artery disease: a meta-analysis of randomized clinical trials, JACC Cardiovasc. Interv. 13 (5) (2020 Mar 9) 659–661, https://doi.org/10.1016/j.jcin. 2019.11.019.
[30] M. Galli, S. Benenati, D. Capodanno, et al., Guided versus standard antiplatelet therapy in patients undergoing percutaneous coronary intervention: a systematic review and meta-analysis, Lancet 397 (10283) (2021 Apr 17) 1470–1483, https://doi.org/10.1016/S0140-6736(21)00533-X. 33865495.
[31] D. Sibbing, D. Aradi, D. Alexopoulos, et al., Updated expert consensus statement on platelet function and genetic testing for guiding P2Y12 receptor inhibitor treatment in percutaneous coronary intervention, JACC Cardiovasc. Interv. 12 (16) (2019) 1521–1537, https://doi.org/10.1016/j.jcin.2019.03.034. Epub 2019 Jun 12, 31202949.
[32] M. Galli, F. Franchi, F. Rollini, L.H. Cavallari, D. Capodanno, F. Crea, D. J. Angiolillo, Genetic testing in patients undergoing percutaneous coronary intervention: rationale, evidence and practical recommendations, Expert. Rev. Clin. Pharmacol. (2021 May 15), https://doi.org/10.1080/17512433.2021.1927709 (Epub ahead of print. PMID: 33993817).
[33] Y. Ionova, J. Ashenhurst, J. Zhan, H. Nhan, C. Kosinski, B. Tamraz, et al., CYP2C19 allele frequencies in over 2.2 million direct-to-consumer genetics research participants and the potential implication for prescriptions in a large health system, Clin. Transl. Sci. 13 (6) (2020) 1298–1306.