Cardiol Ther (2019) 8:229–237
https://doi.org/10.1007/s40119-019-0139-0

ORIGINAL RESEARCH

TRimetazidine as an Agent to affeCt clopidogrEl Response: The TRACER Study

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Received: May 5, 2019 / Published online: July 10, 2019

ABSTRACT

Introduction: This prospective study aimed to determine whether trimetazidine (TMZ) alters the pharmacodynamic (PD) effects of clopidogrel.

Methods: Patients with stable coronary artery disease (SCAD) (n = 24) who were actively treated with dual antiplatelet therapy (DAPT) of aspirin 81 mg daily and clopidogrel 75 mg daily were recruited. Platelet function was measured with the VerifyNow P2Y12 assay (Accriva Diagnostics, San Diego, CA, USA) and assessed before the initiation of and after 14 days of treatment with TMZ. Results were compared using a paired t test.

Results: Almost 80% of the study population were of South Asian descent and had diabetes mellitus (DM). P2Y12 reaction units (PRUs) were higher in patients on TMZ (204 ± 56 compared with 174 ± 71 before TMZ, p = 0.005). The average increase in PRU score was 29 (95% confidence interval 8.8–49.7). Before TMZ, the proportion of patients with high on-treatment platelet reactivity (PRU > 208 units) was 25%, which increased to 42% for patients on TMZ.

Conclusion: Higher platelet reactivity was seen in patients on TMZ, suggesting that TMZ attenuated the PD effects of clopidogrel in this study of a predominantly South Asian diabetic subpopulation. Alternative therapies should be considered and further research is warranted.

Trial Registration: ClinicalTrials.gov number, NCT03603249.

Keywords: Clopidogrel; Platelet reactivity; Trimetazidine

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INTRODUCTION

Clopidogrel has been a pivotal component of dual antiplatelet therapy (DAPT) in the therapeutic armamentarium for cardiovascular disease for over 20 years [1–3]. The

pharmacodynamic (PD) effects of clopidogrel are variable and influenced by a plethora of genetic, drug-interaction, and clinical factors [3–6].

Mechanistically, activation of P2Y12 inhibits adenylate cyclase (AC), causing a decrease in cyclic adenosine monophosphate (cAMP) and phosphorylated vasodilator-stimulated phosphoprotein (VASP-P) levels, and activation of P2Y1 causes an increase in intracellular ionized calcium levels. These changes promote platelet aggregation by altering the ligand-binding properties of the glycoprotein IIb/IIIa (GP IIb/IIIa) receptor. Therefore, inhibition of the P2Y12 receptor suppresses platelet activation [7].

Trimetazidine (TMZ) is a clinically effective antianginal agent without negative inotropic properties [8]. It is presently used throughout Europe and in other countries. It is cytoprotective, normalizing metabolic disturbances in ischemia via several mechanisms of action that have not been fully elucidated [9]. The major mechanism of action is its capacity to inhibit 2-oxidation of free fatty acids (FFAs) [10]. TMZ prevents a decrease in intracellular ATP levels, thereby ensuring the proper functioning of ionic pumps and transmembrane sodium–potassium flow while maintaining cellular homeostasis [11]. Several studies have assessed its clinical applicability in diabetes and ischemic cardiomyopathy to improve left ventricular and endothelial function, as an adjunctive agent in angina, in chronic heart failure with impaired myocardial energetics, and in post-percutaneous coronary intervention myocardial injury [12–16].

The 2013 European Society of Cardiology (ESC) guidelines consider TMZ to be a management option for stable coronary artery disease (SCAD); however, this is a class IIb recommendation [17]. Preliminary studies in patients with acute coronary syndromes (ACS) and hypertrophic cardiomyopathy (HCM) suggest a benefit, but efficacy is yet to be clearly established [18–25].

This study aimed to assess the effect of TMZ on the PD properties of clopidogrel in patients with stable angina.

METHODS

Study Design and Patient Population

The study complied with the Declaration of Helsinki, the International Conference on Harmonization, and good clinical practice, and was approved by both the Research Ethics Committee of the University of the West Indies, St. Augustine, Trinidad and the Public Health Observatory of the North Central Regional Health Authority [26, 27]. All participants provided written informed consent to participate in a prospective, open-label study aimed at assessing the effect of TMZ on the PD of clopidogrel. Patients were enrolled between January 2019 and March 2019 and screened with a stratified permuted block randomization technique at the cardiology outpatient clinic at our institution (Eric Williams Medical Sciences Complex, Trinidad and Tobago) during assigned recruitment days (Fridays during routine working hours). The randomization sequence numbers were obtained from SPSS software (version 24.0; IBM SPSS Statistics, New York City, NY, USA). On average, 4–5 patients were enrolled every week for 5 weeks. They were considered eligible for the study if they were above 18 years of age, awaiting elective percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG), and were on dual antiplatelet therapy (DAPT) for at least 4 weeks with an aspirin 81 mg per day maintenance dose and a “brand name” clopidogrel 75 mg per day maintenance dose (Plavix; Sanofi SA, Gentilly, France and Bristol–Myers Squibb, New York, USA). Exclusion criteria for this study included generic (i.e., not “brand name”) clopidogrel, no recent acute coronary syndrome within 6 months, active bleeding, a prior cerebrovascular event, clinical instability after an index event, use of an oral anticoagulation agent (coumadin derivative or another anticoagulant therapy such as dabigatran, rivaroxaban, apixaban, or edoxaban), platelet count $< 100 \times 10^6$/4L, hemoglobin < 10 g/dL, and serum creatinine > 2.5 mg/dL. Patients were followed up for 28 days postprocedure to

assess whether they experienced any adverse events.

Blood Sampling and VerifyNow P2Y12 Testing

Clopidogrel was held on the morning of their fasting scheduled visit (8:00 am to 9:00 am) so that their last maintenance dose of clopidogrel was given 18–24 h before baseline blood sampling. This was done to ensure the determination of trough levels of platelet reactivity. Blood samples were obtained at rest by antecubital puncture using a 21-gauge needle and placed into Vacuette (Greiner Bio-One North America, Monroe, NC, USA) blood collection tubes containing 3.8% trisodium citrate after discarding the first 5 ml of blood to avoid artifactual platelet activation. Samples were processed by laboratory personnel blinded to ongoing study data. Platelet function assays included the VerifyNow P2Y12 (VN-P2Y12) assay (Accriva Diagnostics, San Diego, CA, USA). The assays were performed according to standard protocols, as previously described [28–30]. The VN-P2Y12 assay is a rapid whole-blood point-of-care device that reports results as P2Y12 reaction units (PRU). This assay mimics turbidimetric aggregation and utilizes disposable cartridges containing 20 mM adenosine diphosphate (ADP) and 22 nM prostaglandin E1 (PGE1). Aggregation testing using ADP as a sole agonist activates P2Y1 and P2Y12 purinergic signaling, while adding PGE1 increases the specificity of the test for P2Y12 signaling. A baseline value for platelet function is obtained in a separate channel of the cartridge in which iso-TRAP (thrombin receptor-activating peptide) is used as an agonist, enabling assessment of platelet inhibition without having to wean the patient off antiplatelet treatment. The VN-P2Y12 assay reports the results as P2Y12 reaction units (PRU). A PRU $>$ 208 was considered HPR according to the last consensus [1]. The enrolled patients were then treated with TMZ at a dosage of 35 mg twice daily for two weeks, with pill accountability assigned to the clinical research associate. After two weeks of TMZ, platelet reactivity was assessed a second time with the VerifyNow assay using the aforementioned methodology (see Fig. 1).

Patient Interview and Case Report Form

Each patient's demographic data were recorded on a case report form (CRF). This contained the patient's medical and procedural history, including any active cardiovascular medications.

Statistical Analysis

The sample size was calculated as 24 patients based on a two-sided p-value of 0.05, a power of 80%, an estimated baseline prevalence of 25% of PRU $>$ 208, and an absolute delta of 10% (expected prevalence of 35% of PRU $>$ 208) [30]. Continuous variables were expressed as mean ± standard deviation (SD), and categorical variables as frequencies and percentages.

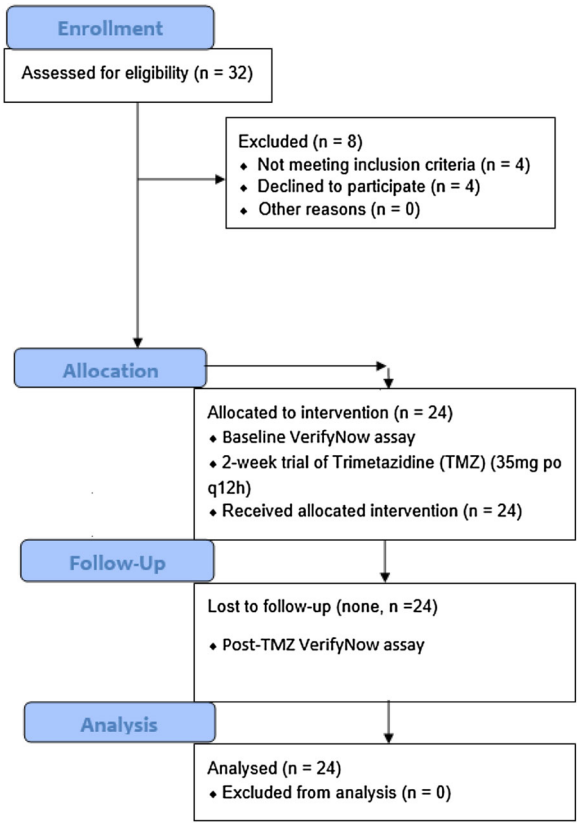

Fig. 1 Methodology outline

The primary endpoint of PRU using a cutoff of > 208 for high on-treatment platelet reactivity was used to create a dichotomous variable. No adjustments for multiple comparisons were made. Missing data were not imputed (none). A two-tailed p value of 0.05 was considered to indicate a statistically significant difference in any of the analyses performed. Statistical analysis was performed using SPSS software (version 24.0; IBM SPSS Statistics, New York City, NY, USA).

RESULTS

A total of 24 individuals with stable coronary artery disease (SCAD) who were on dual antiplatelet therapy (DAPT) with aspirin and clopidogrel were enrolled in the study. Table 1 shows the demographics of the study participants. The mean age was nearly 60 years. Slightly more than 60% of the patients were males, with over three-quarters being South Asian (Indo-Trinidadian) in ethnicity and the remainder being Caribbean Black (Afro-Caribbean), Caucasian, or interracial. The prevalence of diabetes was almost 80%, with hypertension slightly greater than 80% and dyslipidemia roughly 90%. Chronic kidney and lung diseases as well as cerebrovascular and peripheral artery diseases each accounted for less than one-fifth of all comorbidities. There was also a prevalence of at least 70% for the use of ACE inhibitors, beta-blockers, and high-intensity statins, with the prevalence of the latter surpassing 90%. No patients had been previously treated with percutaneous coronary intervention (PCI), nor with coronary artery bypass grafting (CABG). One-quarter of the patients had high baseline on-treatment platelet reactivity with P2Y12 reaction units > 208. There were no serious adverse events (SAEs).

P2Y12 reaction units (PRU) were higher in patients on TMZ (204 ± 56 compared with 174 ± 71 before TMZ, $p = 0.005$). The average increase in PRU score was 29 (95% confidence interval 49.7–8.8) (see Fig. 2). Before TMZ, the proportion of patients with high on-treatment platelet reactivity (PRU > 208 units) was 25%, which increased to 42% on TMZ ($p = 0.219$).

DISCUSSION

Mechanistically, the activation of P2Y12 inhibits adenylate cyclase (AC), causing a decrease in cyclic adenosine monophosphate (cAMP) and phosphorylation of vasodilator-stimulated phosphoprotein (VASP) that ultimately increases intracellular ionized calcium. These changes promote platelet activation, which includes cytoskeletal changes, release of granular products, and aggregation. ADP induces activation through interaction with both P2Y1 and P2Y12 receptors, and inhibition of the P2Y12 receptor suppresses platelet activation [7]. TMZ exerts its effects by preventing a decrease in intracellular adenosine triphosphate (ATP). This effect enhances ionic pump function and transmembrane sodium–potassium flow to maintain cellular homeostasis [31]. TMZ inhibits mitochondrial 3-ketoacyl-CoA thiolase, which increases glucose metabolism. In so doing, TMZ directs pyruvate into the mitochondria, leading to reduced proton and lactic acid production from the ischemic myocardium and more anaerobic cytosolic ATP production. High concentrations of ATP can act as an antagonist of the effects of adenosine diphosphate (ADP) at P2Y1 and P2Y12 receptors and inhibit ADP-induced platelet activation [32, 33]. In whole blood, ATP is metabolized to adenosine, which is an inhibitor of platelet activation [34–36]. It stimulates adenylate cyclase and increases the intracellular level of cAMP, which in turn inhibits calcium mobilization and other signal transduction pathways. While ATP can induce platelet activation [43], reduced activation is a consequence of very high concentrations of ATP because ATP can block interactions between ADP and the P2Y1 or P2Y12 receptors [37].

Our study results suggest that treatment with TMZ attenuated the pharmacodynamic effects of clopidogrel in a predominantly South Asian diabetic subpopulation. Mechanisms that may explain this interaction include the promotion of activation through direct effects of the high levels of ATP induced by TMZ, or through the conversion of ATP to ADP by ecto-ATPases on blood cells (platelets or leukocytes). In addition,

Table 1 Patient population

Characteristics	Frequency (%)
Age	59.9 (range 47–73)
Gender	
Female	9 (37.5)
Male	15 (62.5)
Ethnicity	
South Asian	19 (79.2)
Caribbean Black	4 (16.7)
Caucasian	1 (4.2)
Interracial	0 (0)
Comorbidities	
Diabetes mellitus	19 (79.2)
Hypertension	20 (83.3)
Dyslipidemia	22 (91.7)
Chronic kidney disease	1 (4.2)
Cerebrovascular events	2 (8.3)
Chronic obstructive pulmonary disease	0 (0)
Peripheral artery disease	3 (12.5)
Cardiovascular medications	
Aspirin	24 (100)
Clopidogrel	24 (100)
ACE inhibitor/angiotensin receptor	17 (70.8)
Blocker	
Beta-blocker	20 (83.3)
Statin	23 (95.8)
Calcium channel blocker	6 (25)
Nitrates	4 (16.7)
Mineralocorticoid receptor antagonist	0 (0)
Ivabradine	2 (8.3)
Sacubitril	0 (0)
Cardiovascular procedures	
Percutaneous coronary intervention	0 (0)
Coronary artery bypass grafting	0 (0)
P2Y12 reaction units	
> 208	6 (25)
< 208	18 (75)

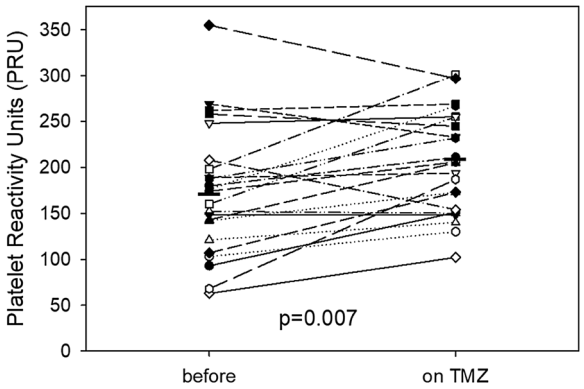

Fig. 2 Individual patient baseline P2Y12 reaction units (PRU) compared to PRU score on TMZ

the effect of TMZ on cAMP inside platelets may contribute to the observed effects [44]. Previous studies have not demonstrated that TMZ promotes platelet activation [38–40]. TMZ may interfere with the binding of the active metabolite of clopidogrel to the P2Y12 receptor.

As TMZ appears to mitigate clopidogrel response, further large-scale studies are recommended to examine these findings, and alternative therapies should be considered [41–43].

Study Limitations

Although the study was adequately powered, there was a notably high prevalence of patients with diabetes mellitus—approximately 80%, as compared to 46% in a previous Trinidadian study assessing cardiovascular medication adherence [44]. Diabetes is associated with increased platelet reactivity, and involves hyperglycemia, hyperlipidemia, insulin

resistance, absolute insulin deficiency, oxidative stress, inflammation, and endothelial dysfunction [4]. Almost four-fifths of the patient population was South Asian; this ethnicity has also been implicated in high on-treatment platelet reactivity. In a recent study by Seecheran et al., there was a significant association between HPR (P2Y12 reaction units > 208) and South Asian (Indo-Trinidadian) ethnicity (OR 5.4; 95% CI 1.18 to 24.66, $p = 0.029$) [30]. These two issues suggest a selection bias, as all patients were screened at the outpatient cardiology clinic and may therefore have been at increased risk for diabetes (which Trinidadian South Asians tend to develop), although robust attempts were made to reduce this by randomizing enrollment and applying stringent selection criteria. All patients bar one were on statin therapy, which can affect platelet reactivity, with recent studies alluding to an enhanced pharmacodynamic response to clopidogrel [45, 46]. This is in stark contrast to the typical statin adherence of almost two-thirds, as illustrated by the aforementioned local study. Our study results are reflective of patients who are predominantly South Asian and have diabetes, and thus cannot be extrapolated to the general population.

CONCLUSIONS

Treatment with trimetazidine was associated with increased platelet reactivity among patients with stable coronary artery disease who were treated with clopidogrel. Alternative therapies should be considered, and further research is warranted.

ACKNOWLEDGEMENTS

We thank the participants in the study.

Funding. This study was sponsored by the Campus Research and Publication Fund (CRP.4MAR16.38) from the University of the West Indies, St. Augustine, which provided TTD 50,000. The article processing charges were funded by the authors. All authors had full access to all of the data in this study and take complete responsibility for the integrity of the data and the accuracy of the data analysis.

Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Author Contributions. Naveen Seecheran, Antonio Tello-Montoliu, and David Schneider conceived the study. Victoria Seebalack, Rajeev Seecheran, Aarti Maharaj, Brent Boodhai, Valmiki Seecheran, and Sangeeta Persad initiated the study design and Naveen Seecheran and Shastri Motilal helped with its implementation. Naveen Seecheran is the grant holder. Shastri Motilal and David Schneider provided statistical expertise in clinical trial design, and David Schneider conducted the primary statistical analysis. All authors helped to refine the study protocol and approved the final manuscript.

Disclosures. The authors Naveen Seecheran, Victoria Seebalack, Rajeev Seecheran, Aarti Maharaj, Brent Boodhai, Valmiki Seecheran, Sangeeta Persad, Shastri Motilal, Antonio Tello-Montoliu, and David Schneider have nothing to disclose.

Compliance with Ethics Guidelines. The study complied with the Declaration of Helsinki, the International Conference on Harmonization, and good clinical practice, and was approved by both the Research Ethics Committee of the University of the West Indies, St. Augustine, Trinidad and the Public Health Observatory of the North Central Regional Health Authority. All participants provided written informed consent to participate in a prospective, open-label study aimed at assessing the effect of TMZ on the PD of clopidogrel.

Data Availability. All available data can be obtained by contacting the corresponding author. ClinicalTrials.gov number for TRACER: NCT03603249. All materials, data, code, and

associated protocols will be made promptly available to the editor and to readers upon request. There are no restrictions on the availability of materials.

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