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ORIGINAL RESEARCH

The Effect of Low-Dose Ticagrelor on Platelet Function Profiles in Patients With Stable Coronary Artery Disease in Trinidad: The TWIST Pilot Study

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ABSTRACT

Introduction: This prospective, pharmacodynamic study aimed to explore the potential applicability of a low-dose ticagrelor regimen in a heterogeneous Trinidadian subpopulation.
Methods: Patients with stable coronary artery disease (n = 25) who were actively treated with dual antiplatelet therapy of aspirin 81 mg daily and clopidogrel 75 mg daily were recruited. Platelet function was measured with the VerifyNow $P2Y_{12}$ assay (Accriva Diagnostics, San Diego, CA, USA) and assessed before initiation of and after 14 days of treatment with a low-dose ticagrelor 45 mg twice daily maintenance dose regimen. Results were compared with a paired t test.
Results: The mean $P2Y_{12}$ reaction units (PRU) score on ticagrelor was significantly less compared to that of clopidogrel (50.4, 95% confidence interval (CI) 29–73.9; vs. 149.6, 95% CI 129.4–169.9; p value < 0.001). Of the patients, 4% experienced Medical Research Council class 1 dyspnea, and Bleeding Academic Research Consortium class 1 bleeding on the ticagrelor regimen (one patient each).
Conclusions: Significantly attenuated platelet reactivity was seen on the low ticagrelor maintenance dose as compared to clopidogrel. This dedicated pharmacodynamic study could be applicable and informative for Trinidadian stable coronary artery disease patients. Further studies are required to confirm these exploratory findings.(Funded by the University of the West Indies, St. Augustine).
Trial Registration: ClinicalTrials.gov number NCT04206176.

Keywords: Clopidogrel; High on-treatment platelet reactivity; Ticagrelor; VerifyNow

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Key Summary Points

Why carry out this study?

Clopidogrel has been a mainstay of dual antiplatelet therapy (DAPT) for well over 20 years, whereas ticagrelor has recently emerged as a potent P2Y12 antiplatelet agent for the better part of the last decade. Low-dose ticagrelor can be considered a potential therapeutic option for some Asian patients.

The Trinidadian population is a melting pot of diverse ethnicities; some of which are known to possess characteristic atherothrombotic and bleeding risk profiles, such as the "East Asian paradox" with respect to platelet reactivity, however clinical efficacy and safety data with low-dose ticagrelor are lacking in this setting and remain virtually unknown in these racial subgroups.

What was learned from the study?

Low-dose ticagrelor significantly attenuated platelet reactivity as compared to standard-dose clopidogrel in this heterogeneous Trinidadian subpopulation.

A low-dose ticagrelor regimen could be considered in a Trinidadian setting to mitigate both atherothrombotic and bleeding risk, a population previously described to have high on-treatment platelet reactivity (HPR). Further research is required to confirm and clinically validate these exploratory findings.

INTRODUCTION

Clopidogrel has been an integral component of dual antiplatelet therapy (DAPT) for cardiovascular disease (CVD) for well over two decades, as demonstrated in several key landmark trials [1–3]. However, the pharmacodynamic (PD) effects of clopidogrel are heterogeneous and impacted by a multitude of genetic, drug interaction, and clinical factors, leading to a broad interindividual response [4, 5]. A recent study performed by Seecheran et al. in Trinidad demonstrated the estimated prevalence of high on-treatment platelet reactivity (HPR) to be considerably higher at 50%, even more so in the South Asian subpopulation at 60% [6]. Within the last decade, novel, more potent $P2Y_{12}$ inhibitors, such as ticagrelor, have gained traction as a preferred strategy to mitigate HPR [7]. Ticagrelor is an oral $P2Y_{12}$ receptor inhibitor that provides a more substantial and consistent antiplatelet effect compared to clopidogrel, notably with respect to potency, onset, and offset of action [7]. The PLATO trial (Study of Platelet Inhibition and Patient Outcomes) evaluated ticagrelor and was associated with a net clinical benefit from a significant reduction in cardiovascular events at the expense of increased bleeding events, in comparison with clopidogrel in patients with acute coronary syndromes (ACS) [8].

In the South Asian, Trinidadian, and Caribbean populations, the literature is not replete with evidence comparing low versus standard doses of ticagrelor to evaluate clinical effectiveness and safety. A recent East Asian systematic review suggested that low-dose ticagrelor revealed an antiplatelet efficacy similar to that of standard-dose ticagrelor, which was faster and more potent than clopidogrel, however, required further evaluation in a large-scale randomized clinical trial [9]. These findings raised the question as to whether the current recommended dose of ticagrelor is suitable for the Trinidadian population, a population often described as multiethnic and cosmopolitan, comprising an admixture of South Asian, Caribbean Black, East Asian, Arabic, and Caucasian ancestries [6, 10]. Therefore, we conducted this exploratory pilot study to assess the antiplatelet PD effect of low-dose ticagrelor in a Trinidadian subpopulation with stable coronary artery disease (CAD).

METHODS

Study Design and Patient Population

The study complied with the Declaration of Helsinki, International Conference on Harmonization, Good Clinical Practice, and was approved by the Campus Research Ethics Committee of the University of the West Indies, St. Augustine, Trinidad [11, 12]. All participants provided written informed consent to participate in a prospective, open-label study aimed to assess the effect of low-dose ticagrelor 45 mg twice daily as compared to clopidogrel 75 mg once daily. Patients were screened and enrolled between November 2019 and December 2019 at the cardiology outpatient clinic at our institution (Eric Williams Medical Sciences Complex, Trinidad and Tobago). They were considered eligible for the study if they were above 18 years of age and awaiting elective percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) on dual antiplatelet therapy (DAPT) for at least 4 weeks with aspirin 81 mg per day maintenance dose and clopidogrel 75 mg per day maintenance dose. Exclusion criteria for this study included an acute coronary syndrome within 6 months, active bleeding, prior cerebrovascular event, clinical instability after an index event, use of an oral anticoagulation agent (warfarin derivative or other anticoagulant therapy (such as dabigatran, rivaroxaban, apixaban, edoxaban), platelet count $< 100 \times 10^6/\mu l$, hemoglobin < 10 g/dl, serum creatinine > 2.5 mg/dl, patients on concurrent CYP 2C19 inhibitors, and CYP 3A4 inducers. They were followed up for 28 days post-procedure after completing the study to assess whether they experienced any adverse events.

Blood Sampling and VerifyNow $P2Y_{12}$ Testing

Clopidogrel was held on the morning of their fasting scheduled visit (8:00–9:00 am) (18–24 h before baseline blood sampling), which ensured 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 collecting 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 $P2Y_{12}$ (VN-$P2Y_{12}$) assay (Accriva Diagnostics, San Diego, CA, USA). The assays were performed according to standard protocols, as previously described [13, 14]. The VN-$P2Y_{12}$ assay reports the results as $P2Y_{12}$ reaction units (PRU). A PRU > 208 was considered HPR according to the last consensus [2]. The enrolled patients were then treated with ticagrelor 45 mg twice daily for 2 weeks with pill accountability by the clinical research associate. The ticagrelor 90 mg tablet was attempted to be evenly divided into halves (each containing 45 mg of ticagrelor) using a standard pill-cutter, as suggested by Li et al. [15]. Ticagrelor 60 mg was not available in Trinidad. After 2 weeks of low-dose ticagrelor regimen, platelet reactivity was assessed a second time with the VN-$P2Y_{12}$ assay using the aforementioned methodology (see Fig. 1).

Patient Interview and Case Report Form

The patients' demographic data were recorded on a case report form (CRF) and included the patient's medical, procedural history, and any cardiovascular medications.

Statistical Analysis

The sample size was calculated as 25 patients based on a paired proportion sample, an alpha (α) value of 0.05, power of 80%, estimated baseline prevalence of 30% of PRU > 208, and absolute delta of 20% (expected prevalence of 30% of PRU > 208). Continuous variables were expressed as mean $\pm$ standard deviation and categorical variables as frequencies and percentages. Paired *t* tests were used for comparisons of mean differences in PRU scores and McNemar's test for comparison of paired proportions. No adjustments for multiple

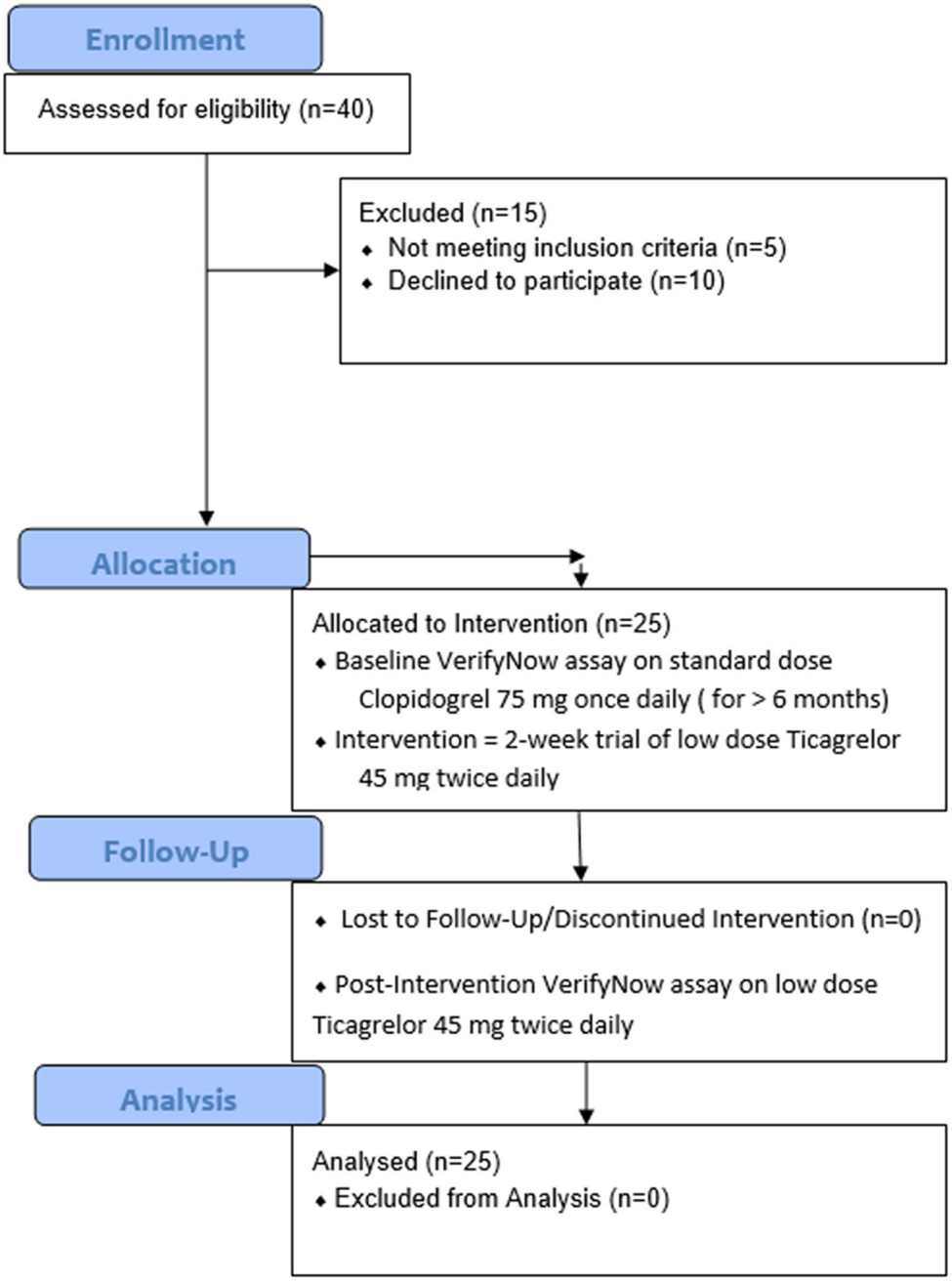

Fig. 1 Methodology outline

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 for all the analyses performed. Statistical analysis was performed using SPSS version 24.0 software (IBM SPSS Statistics, New York, NY, USA).

RESULTS

A total of 25 individuals with stable CAD on DAPT with aspirin and clopidogrel were enrolled in the study. Table 1 shows the demographics of the study participants. The mean

Table 1 Patient population

Characteristics	Frequency (%)
Age	63.3 years (mean) (range, 48–79 years)
Gender	
Female	14 (56)
Male	11 (44)
Ethnicity	
South Asian	16 (64)
Caribbean Black	5 (20)
Interracial	4 (16)
Body mass index	27.3 kg/m^2 (mean) (range, 21.4–36.1 kg/m^2)
Comorbidities	
Prior myocardial infarction	8 (32)
Diabetes mellitus	15 (60)
Hypertension	21 (84)
Dyslipidemia	18 (72)
Chronic kidney disease	2 (8)
Cerebrovascular events	11 (44)
Chronic obstructive pulmonary disease	1 (4)
Peripheral artery disease	0 (0)
Cardiovascular medications	
Aspirin	25 (100)
Clopidogrel	25 (100)
Angiotensin-converting enzyme	18 (72)
Inhibitor/angiotensin receptor blocker	23 (92)
Beta-blocker	
Statin	24 (96)
Calcium channel blocker	9 (36)
Nitrates	12 (48)
Mineralocorticoid receptor antagonist	5 (20)
Ivabradine	0 (0)
Sacubitril	0 (0)
Trimetazidine	17 (68)
Diabetic medications	
Insulins	5 (20)
Oral hypoglycemics	1 (4)
Cardiovascular procedures	
Percutaneous coronary intervention	5 (20)
Coronary artery bypass grafting	2 (8)

age was 63.3 years. Of the patients, just over half were females, with the same percentage being South Asian in ethnicity and the remainder, Caribbean Black, Caucasian, and interracial. The mean body mass index (BMI) was 27.3 kg/m^2. The prevalence of prior myocardial infarction was almost one-third; diabetes was 60%, with hypertension slightly greater than 80%, dyslipidemia roughly 70%, and cerebrovascular events, more than 40%. Chronic kidney, lung, and peripheral artery disease each accounted for less than 10% comorbidity. There was also a prevalence of at least 70% use of angiotensin-converting enzyme (ACE) inhibitors, and over 90% for both beta-blockers and high-intensity statins. One-fifth of patients had previously been treated with percutaneous coronary intervention (PCI) and less than 10% with coronary artery bypass grafting (CABG).

The mean PRU on ticagrelor was significantly less than that of clopidogrel (50.4, 95% confidence interval (CI) 29–73.9; vs. 149.6, 95% CI 129.4–169.9; p value < 0.001) (see Table 2 and Fig. 2). One patient experienced Bleeding Academic Research Consortium (BARC) class 1 bleeding during ticagrelor therapy, described as non-actionable, mild ecchymosis on her left

Table 2 Comparison of standard-dose clopidogrel 75 mg once daily versus low-dose ticagrelor 45 mg twice daily on platelet reaction units (PRU)

	Mean platelet reaction units (PRU)	Lower 95% confidence interval (CI)	Upper 95% confidence interval (CI)	*p* value
Clopidogrel	149.64	129.41	169.87	< 0.001
Ticagrelor	50.44	29.00	73.88	

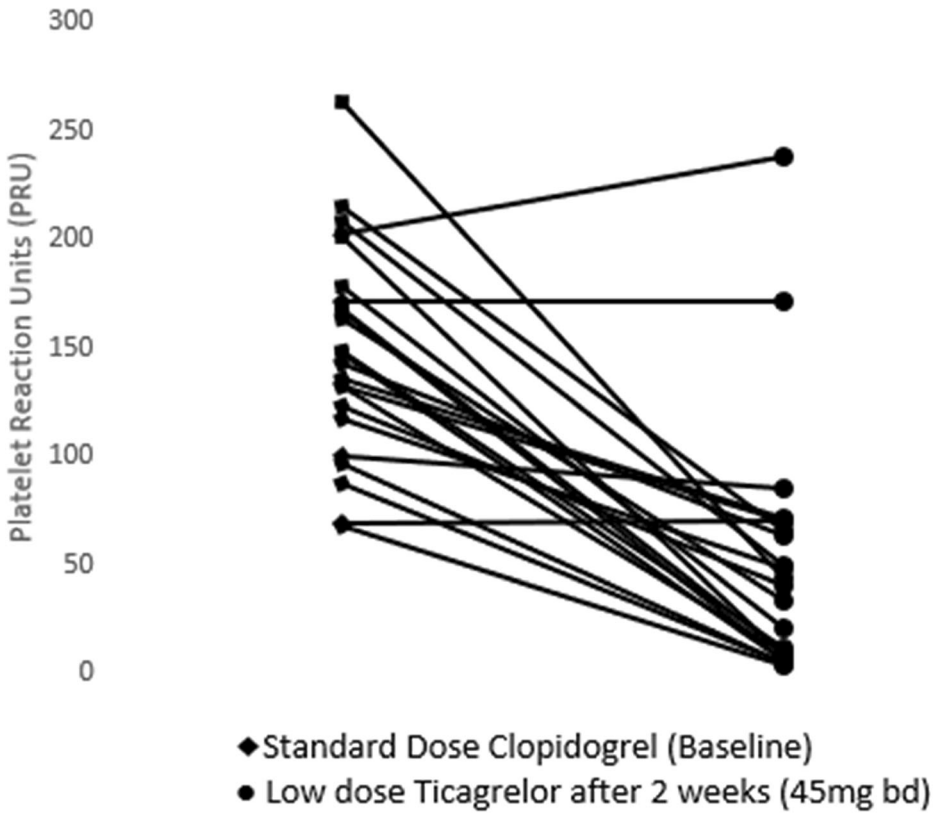

Fig. 2 Comparison of patients' $P2Y_{12}$ reaction units (PRU) on standard-dose clopidogrel 75 mg once daily versus low-dose ticagrelor 45 mg twice daily

upper extremity, while another experienced Medical Research Council (MRC) class 1 dyspnea for which they both continued the ticagrelor regimen without interruption.

DISCUSSION

This dedicated study explored the PD effects of a low-dose ticagrelor regimen in Trinidadian patients with stable CAD. Ticagrelor is an oral $P2Y_{12}$ receptor inhibitor that is biologically active (not a prodrug) and binds reversibly to the $P2Y_{12}$ receptor. Ticagrelor has been shown to provide a more powerful and consistent antiplatelet effect compared to clopidogrel. Clopidogrel is a prodrug that requires two-step metabolism by CYP enzymes to become an active metabolite, resulting in substantial variability in inter-individual response [16].

Establishing optimal antiplatelet efficacy while minimizing adverse events is pivotal to the tenet of $P2Y_{12}$ inhibition. Several mechanistic studies assess the concept of "less is more" with respect to the delicate balance of ischemic protection and bleeding. In the PEGASUS-TIMI 54 (Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin–Thrombolysis In Myocardial Infarction 54) trial, both ticagrelor doses (90 mg and 60 mg) reduced ischemic events, with the 60-mg dose demonstrating a more attractive benefit-to-risk profile with further clinical consideration of extending DAPT in patients with high ischemic and low bleeding risks [17]. The ALTIC (A Randomized, Pharmacodynamic Comparison of Low-Dose Ticagrelor to Clopidogrel) compared ticagrelor 60 mg twice daily with clopidogrel 75 mg in patients with at least one high-risk feature (age > 65 years, diabetes mellitus, prior myocardial infarction, multivessel disease, or renal dysfunction) and revealed that ticagrelor 60 mg twice daily provides greater platelet inhibition than clopidogrel 75 mg [18, 19].

However, the vast majority of mechanistic platelet function studies evaluating the PD effects of permutations of various antiplatelet strategies are based upon predominantly Caucasian populations. Trinidad is considered ethnically diverse, with the population comprising approximately one-half South Asian, one-third Caribbean Black, and the remaining one-third, mostly East Asian, Caucasian, Arabic, and interracial [20]. South Asians have higher proportional mortality rates from CAD compared with other Asian groups [21]. In a recent pilot study, the estimated prevalence of HPR was considerably higher at 50%, with HPR being more prevalent in the South Asian ethnicity [6]. To our knowledge, these novel regimens and doses remain untested in these ethnic minority subpopulations, such as Trinidad, and to a broader region, the Caribbean.

Several studies explored low-dose ticagrelor regimens in East Asian ethnicity [9]. East Asians are susceptible to increased bleeding events when compared to other races after the administration of antiplatelet agents [22–24]. A recent systematic review, including two clinical studies, compared and evaluated the niche of a lower dose versus standard dose of ticagrelor in East Asians, which revealed similar efficacy [9]. Generally, there was a higher incidence of adverse events observed in the standard ticagrelor dose; however, no formal conclusions could be drawn, as the studies were hindered by limited patient enrollment and outcomes, warranting larger-scale studies [9]. In the PEGASUS-TIMI 54 study, there was a caveat that an Asian subgroup analysis should be interpreted with caution, as it was likely underpowered to detect significant geographical differences [17]. The PHILO study assessed outcomes in Japanese, Korean, and Taiwanese ACS patients undergoing PCI and revealed there were no significant differences between clopidogrel and ticagrelor in clinical efficacy and major bleeding; however, a composite of major and minor bleeding occurred at a higher rate in the ticagrelor allocation, calling into question the clinical equipoise and pragmatism of this potent $P2Y_{12}$ inhibitor in East Asians [22]. As a result, there was a suggestion put forward to evaluate lower doses of ticagrelor in this population [23]. Of note, in Japan, other widely used oral $P2Y_{12}$ receptor antagonists such as clopidogrel and prasugrel have been approved at lower doses than the doses approved worldwide based on pharmacokinetic (PK) and PD studies of these agents [24]. Overall, it has been suggested that East Asians appear to possess a contrasting therapeutic window for platelet reactivity, as they tend to display HPR after antiplatelet agents with respective lower thrombotic events, dubbed the "East Asian paradox" [25, 26]. The rationale for such differences is not fully elucidated; however, attributed to genetic, cellular, plasmatic, and inflammatory factors [27]. Additionally, there has been the observance of increased risk of bleeding, including intracranial hemorrhage in East Asians, due to anthropometric differences [28, 29]. To our knowledge, these phenomena have not yet been described in the South Asian ethnicity, amongst others, and within the scope of the Caribbean.

It appeared that at low doses of ticagrelor 45 mg twice daily, potent platelet inhibition occurred, which was significantly more than

clopidogrel. By illustrating that this low-dose regimen provided a more potent and consistent antiplatelet effect, this mechanistic study can be potentially clinically relevant. In fact, because of the tolerability and safety profile in this population, larger studies are warranted to ascertain clinical outcomes on this regimen.

Study Limitations

Although the study was relatively small ($n = 25$), it was adequately powered for PD outcomes. There was a relatively high prevalence history of prior myocardial infarction, diabetes mellitus, and cerebrovascular events, approximately 32%, 60%, and 44%, alluding to a stable but albeit high-risk population [30]. Diabetes is implicated in accentuating platelet reactivity via a complex thrombotic milieu [5]. The study also had a relatively higher proportion of women (56%) as compared to prior studies performed by this group in a similar setting [6, 10]. Thus, any emerging recommendations cannot be extrapolated to other populations, such as patients with ACS. The patient population constituted almost two-thirds of South Asians, whose ethnicity has also been linked with HPR [6]. These issues may suggest an inherent selection bias. Additionally, it is possible for a temporal effect to potentially confound the study results. It would be ideal to perform other platelet function tests such as light transmittance aggregometry or multiple electrode aggregometry; however, these modalities are not currently available in Trinidad. Another potential limitation is that the 90-mg ticagrelor pill may not have been evenly divided. The study was not powered to assess clinical outcomes; therefore, no safety or efficacy conclusion on low-dose ticagrelor in stable CAD can be drawn; and, the rates of adverse events, although minimal, cannot be definitively concluded from this study from the relatively small number of patients enrolled.

CONCLUSIONS

This mechanistic study can be clinically pertinent because of improved efficacy, safety, and tolerability profile. Low-dose ticagrelor achieved a greater antiplatelet effect than clopidogrel and led to significantly lower platelet reactivity than clopidogrel, with 4% of patients experiencing high on-treatment platelet reactivity.

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Authorship Contributions. All authors contributed equally in writing the manuscript. All authors read and approved the final manuscript.

Disclosures. Naveen Seecheran, Brent Boodhai, Aarti Maharaj, Arvinash Ramdeen, Niranjan Debideen, Vishesh Ochalal, Randall Singh, Rajeev Seecheran, Valmiki Seecheran, Sangeeta Persad, Harun Abdullah, Lakshmipathi Peram, Shastri Motilal, Antonio Tello-Montoliu, and David Schneider have nothing to disclose.

Compliance with Ethics Guidelines. The study complied with the Declaration of Helsinki, International Conference on Harmonization, Good Clinical Practice, and was approved by the Campus Research Ethics Committee of the University of the West Indies, St. Augustine, Trinidad. All participants provided written informed consent.

Data Availability. All available data can be obtained by contacting the corresponding author. TWIST ClinicalTrials.gov number NCT04206176. All materials, data, code, and associated protocols will be made promptly available to the editor and readers upon request. If requested, there will not be any restrictions on the availability of materials.

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