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Prevalence of clOpidogrel 'resIstaNce' in a selected population of patients undergoing elective percutaneous coronary intervention at a tertiary cardiovascular centre in Trinidad: the POINT pilot study

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ABSTRACT

Objectives This novel, pilot study aimed to assess the estimated prevalence of high on-treatment platelet reactivity (HPR) in Trinidad and Tobago.

Methods Patients (n=40) who were awaiting elective percutaneous coronary intervention on maintenance dual antiplatelet therapy (DAPT) with aspirin 81 mg daily and clopidogrel 75 mg or loaded at least 48 hours prior were recruited. Platelet reactivity with the VerifyNow P2Y12 assay (Accriva Diagnostics, San Diego, California, USA) was assessed prior to cardiac catheterisation.

Results 60.7% (17/28) of the South Asian (Indo-Trinidadians) patients had HPR, whereas 14.3% (1/7) of Africans and 40% (2/5) of mixed ethnicity had HPR. There was a significant association between HPR (P2Y12 reaction units >208) and ethnicity with South Asians (Indo-Trinidadians) (OR 5.4; 95% CI 1.18 to 24.66, p=0.029).

Conclusions This pilot study serves to introduce the preliminary observation that the estimated prevalence of HPR is considerably higher within the heterogeneous population in Trinidad at 50% as compared with predominantly Caucasian studies. Furthermore, the HPR is significantly higher in South Asians (Indo-Trinidadians) (>60% of patients) which has severe clinical repercussions considering the cardiovascular disease pandemic. Clopidogrel may not be a satisfactory or optimal antiplatelet agent in this subgroup, and therefore, another more potent antiplatelet such as ticagrelor should be used instead. Further large-scale studies are imperative to confirm these findings. (Funded by the University of the West Indies, St. Augustine; POINT ClinicalTrials.gov number, NCT03667066.)

Key questions

What is already known about this subject?

- Clopidogrel, a second-generation oral thienopyridine, remains an integral component of dual antiplatelet therapy in the management of cardiovascular disease. Several studies underscore the importance of high on-treatment platelet reactivity (HPR) as a prognosticator for cardiovascular events, including stent thrombosis.
- Clopidogrel resistance is a significant clinical entity that has potentially devastating implications including cardiovascular mortality, however has not yet been described in Trinidad, an island with the highest reported prevalence of cardiovascular disease in the Caribbean.

What does this study add?

- This pilot study serves to introduce the preliminary observation that the estimated prevalence of HPR is considerably higher within the heterogeneous population in Trinidad at 50% as compared with predominantly Caucasian studies based in the USA and Western Europe. Furthermore, the HPR is significantly higher in the subgroup of South Asians (Indo-Trinidadians) (>60% of patients), a population in which there is a long recognised, but incompletely understood very high burden of cardiovascular disease.

How might this impact on clinical practice?

- Clopidogrel may not be a satisfactory or optimal antiplatelet agent in this subgroup, and therefore, another more potent antiplatelet such as ticagrelor should be used instead.

INTRODUCTION

Clopidogrel, a second-generation oral thienopyridine, remains an integral component of dual antiplatelet therapy (DAPT) in the management of cardiovascular disease (CVD) for almost two decades. Several studies underscore the importance of high on-treatment platelet reactivity (HPR) as a

prognosticator for cardiovascular events, including stent thrombosis.[1–3] This phenomenon is often alluded to as 'clopidogrel resistance' and yet to be clearly defined. Generally, it reflects the failure to achieve its antiaggregatory effect. Clopidogrel response is both complex and multifactorial, determined by a multitude of intrinsic and extrinsic mechanisms, including genetic polymorphisms of the P2Y12 receptor, drug–drug interactions, and clinical factors such as suboptimal dosing regimens, acute coronary syndromes (ACS),[4] diabetes mellitus[5] and possibly smoking.[6]

High pretreatment platelet reactivity may lead to mitigated clopidogrel-induced antiplatelet effects[7–9] and are more commonly observed in specific clinical scenarios such as ACS, increased body mass index and diabetes mellitus, in particular, insulin-dependent diabetes mellitus.[5 10] Matetzky *et al* also surmised that nearly one-quarter of patients with ST-segment elevation ACS would incur stent thrombosis due to this phenomenon.[3]

Overall, HPR prevalence in various studies is estimated at 5%–44%[11]; however, these are based on largely Caucasian populations and yet to be ascertained in a Caribbean subpopulation. Trinidad and Tobago has an ethnically diverse population with approximately one-third South Asian (Indo-Trinidadian), one-third Caribbean Black (Afro-Trinidadian) and the remaining one-third, mostly interracial and mixed.[12–14] CVD is currently the leading cause of mortality in Trinidad and Tobago, accounting for up to 60% of all deaths annually.[15]

The aim of this study was to determine the prevalence of clopidogrel resistance among a selected group of patients undergoing elective percutaneous coronary intervention (PCI) and to observe whether there was any South Asian (Indo-Trinidadian) predilection for HPR considering the well-established epidemiologic trends for accelerated coronary artery disease within this subgroup.[16 17]

MATERIALS AND METHODS

Study design and patient population

This is a cross-sectional, open-label (Plavix; Sanofi SA, Gentilly, France and Bristol-Myers Squibb, New York, USA) pilot study aimed to assess HPR which occurred during the period January 2017–September 2017. Patients were screened with a stratified permuted block randomisation technique at the cardiac catheterisation laboratory (cardiac bays 1–4) at our institution (Eric Williams Medical Sciences Complex, Trinidad and Tobago) during assigned recruitment days (Mondays, Tuesdays and Thursdays). The clinical research associates were blinded to the allocation assignment and randomisation sequence numbers were obtained from SPSS V.24.0 software. On average, 1–2 patients were enrolled every week for 8 months. They were considered eligible for the study if they were above 18 years of age and awaiting elective PCI on DAPT for at least 2 weeks with aspirin 81 mg per day maintenance dose and 'brand name' clopidogrel 75 mg per day maintenance dose (Plavix; Sanofi SA and Bristol-Myers Squibb) or received a loading dose of clopidogrel 600 mg at least 48 hours prior to PCI. Exclusion criteria for this study included generic clopidogrel, that is, not 'brand name', no recent ACS within 6 months, active bleeding, prior cerebrovascular event, clinical instability after an index event, use of an oral anticoagulation agent (coumadin derivative or other anticoagulant therapy (such as dabigatran, rivaroxaban or apixaban)), platelet count $<100\times10^9$/L, haemoglobin <100 g/L and serum creatinine >2.5 mg/dL. The study complied with the Declaration of Helsinki,[18] International Conference on Harmonization, Good Clinical Practice.[19] All participants provided written informed consent. Patients were followed up for 14 days postprocedure after completing the study 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 (08:00–09:00) so that their last maintenance dose of clopidogrel was 18–24 hours before baseline blood sampling. This was done to ensure 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, North Carolina, USA) blood collecting tubes containing 3.8% trisodium citrate after discarding the first 5 mL of blood to avoid spontaneous 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, California, USA). The assays were performed according to standard protocols as previously described.[20 21] 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 utilises disposable cartridges containing 20 mM ADP and 22 nM prostaglandin E1 (PGE1). Aggregation testing using ADP as a sole agonist activates P2Y1 and P2Y12 purinergic signalling, while adding PGE1 increases the specificity of the test for P2Y12 signalling. In a separate channel of the cartridge in which iso-thrombin receptor activating peptide is used as an agonist, a baseline value for platelet function is obtained, enabling assessment of platelet inhibition without having to wean the patient off antiplatelet treatment. The VN-P2Y12 assay reports the results as PRU. A PRU >208 was considered for defining HPR according to the last consensus.[1]

Patient interview and case report form

The patient's demographic and[22] anthropometric data were recorded on a case report form and included the patient's medical and procedural history including any active cardiovascular medications. Following this interview, the participant proceeded to cardiac catheterisation for which a SYNTAX score was calculated.[23 24] Echocardiography was also performed as per American College

of Cardiology, American Heart Association and American Society of Echocardiography guidelines.[25]

Statistical analysis

Continuous variables were expressed as means±SD and categorical variables as frequencies and percentages. The primary endpoint of PRU using a cut-off of >208 for HPR was used to create a dichotomous variable. Unadjusted binary logistic regression models were carried out to explore potential predictors of PRU >208. No adjustments for multiple comparisons were made. Missing data were not imputed. The arbitrary, same sample size of 40 was used for the exploratory analyses based on prior studies and in line with recommendations for pilot investigations.[23 26 27] This was also in keeping with an estimated sample size of 36 patients which was calculated based on a two-sided p-value of 0.05, power of 80%, estimated baseline prevalence of 20% of PRU >208 and absolute delta of 20% (expected prevalence of 40% of PRU >208). 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 V.24.0 software.

RESULTS

A total of 40 individuals were enrolled in the study. The table 1 shows the demographics of the study participants. The mean age was 56.9 years. Of the patients, almost 60% were males, with 70% being South Asian (Indo-Trinidadian) in ethnicity and the remainder Caribbean Black (Afro-Caribbean) and mixed. The mean body mass index was 26.47. The prevalence of diabetes was 55%, hypertension 70% and dyslipidaemia 62.5%. Chronic kidney and lung disease, together with cerebrovascular and peripheral artery disease each accounted for less than 5% comorbidity. Hundred per cent of study participants were on DAPT with aspirin and clopidogrel. There was also a prevalence of at least 80% for ACE-inhibitors, beta blockers and high-intensity statins; 60.7% (17/28) of the South Asian (Indo-Trinidadians) patients had HPR, whereas 14.3% (1/7) of Africans and 40% (2/5) of mixed ethnicity had HPR. There was a significant association between HPR (PRU >208) and ethnicity with South Asians (Indo-Trinidadians) (OR 5.4; 95% CI 1.18 to 24.66, p=0.029) (see table 2). There were no other significant interactions for HPR and gender, diabetes mellitus, statin therapy, body mass index, ejection fraction and SYNTAX score.

Table 1 Patient population

Characteristics	Frequency (%)
Age	56.9 (range 43–77)
Gender	
Female	17 (42.5)
Male	23 (57.5)
Ethnicity	
South Asian (Indo-Trinidadian)	28 (70)
Caribbean Black (Afro-Trinidadian)	7 (17.5)
Mixed/Others	5 (12.5)
Body mass index	26.47 (range 18.48–45.7)
Comorbidities	
Diabetes mellitus	22 (55)
Hypertension	28 (70)
Dyslipidaemia	25 (62.5)
Chronic kidney disease	1 (2.5)
Cerebrovascular events	2 (5.0)
Chronic obstructive pulmonary disease	1 (2.5)
Peripheral artery disease	0 (0)
Cardiovascular medications	
Aspirin	40 (100)
Clopidogrel	40 (100)
ACE inhibitor/angiotensin receptor blocker	35 (87.5)
Beta blocker	35 (87.5)
Statin	36 (90)
Calcium channel blocker	12 (30)
Nitrates	24 (60)
Trimetazidine	27 (67.5)
Mineralocorticoid receptor antagonist	0 (0)
Ivabradine	0 (0)
Insulin	12 (30)
Ejection fraction	
25–34	3 (7.5)
35–45	8 (20)
>46	29 (72.5)
Platelet reactivity units	
>208	20 (50)
<208	20 (50)
SYNTAX Score	
0–22	32 (80)
23–32	5 (12.5)
>33	3 (7.5)

DISCUSSION

This pilot study reveals a relatively high prevalence of clopidogrel resistance of 50% which is higher when compared with international studies[28] and would be unique for the Caribbean setting.

Clopidogrel activation takes place via two sequential oxidation reactions that are catalysed by the cytochrome P450 (*CYP450*) system, notably involving the *CYP2C9* and *CYP2C19*. A potential contributor to the markedly high HPR in Trinidad could be the similarly high prevalence of the *CYP2C19* genotype in the Trinidadian public, specifically the South Asian (Indo-Trinidadians) subpopulation.[29] Among persons treated with clopidogrel, carriers

Table 2 Relationship of some comparative variables with respect to high on treatment platelet reactivity (P2Y12 reaction units >208)

Comparison variables	OR	CIs (95%)	P value
Male versus female*	0.97	0.28 to 3.40	0.962
South Asian (Indo-Trinidadians) versus non-South Asian (Caribbean Blacks/Afro-Trinidadians, mixed/others)*	5.4	1.18 to 24.66	0.029
Diabetes mellitus (DM) versus non-DM*	1.81	0.51 to 6.36	0.358
Statin therapy versus no statin therapy*	0.33	0.03 to 3.51	0.361
Body mass index	0.98	0.88 to 1.10	0.770
Ejection fraction (EF) <50% versus EF >50%*	1.15	0.30 to 4.47	0.836
SYNTAX score >33 versus <33*	3.4	0.59 to 19.46	0.169

*Comparison group.

of a reduced-function *CYP2C19* allele had comparatively decreased levels of the active metabolite, attenuated platelet inhibition and a higher rate of major adverse cardiovascular events than did non-carriers.[2 30] The clinical relevance of clopidogrel response variability is a double-edged sword as there is a delicate balance of the spectrum with a higher ischaemic risk for atherothrombotic events in hyporesponders versus higher bleeding risk in hyper-responders. Additionally, due to its widespread application for both vascular disease and post-cardiovascular interventions, resistance to this agent presents a dilemma in patients with atherothrombotic diseases.[31] In Trinidad, there was a high proportion (37%) of allelic frequencies for *CYP2C19*2* in South Asians (Indo-Trinidadian) than Caribbean Black (Afro-Trinidadian) or persons of mixed descent.[29] The pharmacogenetics of clopidogrel metabolism display marked ethnic variegation.[32 33] The frequency of *CYP2C19*2* mutant alleles in South Asians was higher than in Chinese and Caucasians and as a result of this poor metaboliser genotype frequency of 12.6%, this translates to at least 28 million being poor metabolisers of *CYP2C19* substrates in the southern subcontinent alone.[34 35] Several other east and southeast Asian studies also demonstrate a similar polymorphism propensity.[36–38] These patients displayed biochemical characteristics consistent with higher residual platelet reactivity with an attenuated antiplatelet response. The higher prevalence of these *CYP2C19* loss-of-function alleles may well contribute to worse cardiovascular outcomes in the Asian population as compared with the Western population as evidenced a recent meta-analysis.[39] The South Asian (Indo-Trinidadians) diaspora in Trinidad as of the national census in 2011 is approximately one-half million persons and with an alarming adult cardiovascular mortality of up to 60%,[15] this higher frequency genotype would undoubtedly phenotypically translate as an important practical aspect of management.

As a result, there have been concerns regarding the clinical efficacy and safety of antiplatelet strategies in various ethnicities.

Diabetes is also associated with heightened platelet reactivity and attributed to a complex interplay of factors including hyperglycaemia, hyperlipidaemia, both relative and absolute insulin resistance, oxidative stress, inflammation and endothelial dysfunction.[5]

According to the WHO and International Diabetes Federation, Trinidad has a particularly high burden of diabetes with an estimated prevalence of 13% and ranks 37th and 10th worldwide and the America, respectively.[40 41] This alarming diabetic pandemic can also be implicated in HPR, as the two conditions are mechanistically linked.

As the South Asian (Indo-Trinidadians) subpopulation appears to be replete with HPR, further large-scale studies are imperative to affirm these findings and as such, alternative antithrombotic regimens should be considered on the basis of one's ethnicity. Novel strategies have and are currently being investigated in the ATLAS-ACS 2-TIMI 51,[42] GEMINI-ACS 1,[43] PIONEER AF-PCI trials[44] among many others.

Study limitations

The major limitation is that the study is of a pilot design.[45] As aforementioned, this novel study's objective was to provide preliminary, exploratory observations of clopidogrel 'resistance' in Trinidad which would serve to generate hypotheses for future studies. The sample size was calculated based on speculative data; as this prevalence has not been previously described in this particular setting. It was also in keeping with the guidelines and recommendations of pilot studies, thus enrolling 40 arbitrary, randomised participants. Selection bias can be a potential issue, as all patients were screened at the cardiac catheterisation laboratory and were awaiting PCI and thus, may have an inherent predilection for HPR, although attempts were made to mitigate this by randomising enrolment and stringent selection criteria. Another limitation is that assessing platelet reactivity has many pitfalls including both interindividual and intraindividual variability being affected by smoking, alcohol, fasting and intrinsic circadian rhythms.[46–48] Generally, the inconsistent VerifyNow P2Y12 point-of-care assay results may complicate management decisions as reactivity is not a stable phenomenon and may require repetitive testing to ascertain 'clopidogrel resistance' status.[49] Another drawback is that genotyping for these polymorphisms was not performed in this cohort. As a result, we are unable to ascertain the precise relationship between HPR and allelic frequencies for *CYP2C19*2*, although this was reported previously without evaluating clinical clopidogrel resistance.[29]

CONCLUSIONS

Clopidogrel resistance is a significant clinical entity that has potentially devastating implications including

cardiovascular mortality, however has not yet been described in the Caribbean setting. This pilot study serves to introduce the preliminary observation that the estimated prevalence of HPR is considerably higher within the heterogeneous population in Trinidad at 50% as compared with predominantly Caucasian studies. Furthermore, the HPR is significantly higher in South Asians (Indo-Trinidadians) (>60% of patients) which has severe clinical repercussions considering the cardiovascular disease pandemic. Further large-scale studies are imperative to confirm these findings. Point-of-care testing may be important consideration in high-risk groups such as the South Asian ethnicity (Indo-Trinidadians) and they may require, individualised antithrombotic regimens post-PCI, post-coronary artery bypass grafting and management of ACSs.[50 51] Clopidogrel may not be a satisfactory or optimal antiplatelet agent in this subgroup, and therefore, another more potent antiplatelet such as ticagrelor should be used instead.

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Competing interests None declared.

Patient consent for publication Obtained.

Ethics approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (Research Ethics Committee of the University of the West Indies, St. Augustine, Trinidad) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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Data sharing statement All materials, data, code and associated protocols will be made promptly available to the editor and/or readers upon request. If requested, there will not be any restrictions on the availability of materials.

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