ScientificScholar®
Knowledge is power
Publisher of Scientific Journals

www.jhas-bhs.com

Journal of Hematology and Allied Sciences

Original Research

Antiplatelet resistance among a cohort of patients at risk of atherosclerotic cardiovascular diseases in Jos, Nigeria

Basil Nwaneri Okeahialam[1], Emmanuel Akor[2], Gabriel Shut[1], Ogo Ifeacho[1], Bangalu Dauda[2], Anil Sirisena[3], Ganiyu Adeniyi Amusa[1]

Departments of [1]Medicine, [2]Haematology, [3]Radiology, Jos University Teaching Hospital, Jos, Plateau, Nigeria.

***Corresponding author:**
Basil Nwaneri Okeahialam, Department of Medicine, Jos University Teaching Hospital, Jos, Plateau, Nigeria.

basokeam@yahoo.com

Received: 12 May 2023
Accepted: 20 December 2023
Published: 07 February 2024

DOI
10.25259/JHAS_13_2023

Quick Response Code:

ABSTRACT

Objectives: Patients with atherosclerotic cardiovascular diseases (ASCVDs) are predisposed to atherothrombosis and ischemic phenomena. Antiplatelets mitigate this but not consistently, as these ischemic events still occur despite their administration. This is called antiplatelet resistance. We sought to see how much of this occurs in our patients since its rate is bound to differ from place to place. The burden of antiplatelet resistance has not been determined in our environment.

Material and Methods: Patients at risk of ASCVD who were receiving antiplatelet treatments were invited to participate in this study. They were enrolled first into a two week wash out phase, after which baseline aggregometry and full blood count were done. They were then given either Aspirin or Clopidogrel for four weeks and had the same blood work-up repeated. The Aggregometer was used to determine the platelet aggregability at these different times. If the second set showed >10% reduction from baseline, such patients were adjudged sensitive. A reduction <10% of the first value defined resistance.

Results: Twenty patients (15 F/5 M) were in Group 1 and received a low dose of Aspirin (75 mg), the age range of 42–76 years, with a mean (standard deviation [SD]) of 60.75 (10.45). Twenty-six were in Group 2 (18 F/8 M) and received low dose clopidogrel (75 mg), with an age range of 23–87 years and a mean (SD) of 58.08 (14.18). Fifteen (75%) were sensitive in Group 1 (Aspirin) with 25% resistant. For Clopidogrel, 14 (53.85%) were sensitive and 12 (46.15%) resistant. In a few cases, the aggregability actually increased paradoxically on treatment.

Conclusion: Antiplatelet resistance also occurs in our environment; it is worse for Clopidogrel than for Aspirin. These are people who, despite being on antiplatelets, would go on to develop these atherothrombotic ischemic phenomena. Efforts to identify the predictors of this phenomenon of resistance and work out effective counteractions should be encouraged.

Keywords: Antiplatelets, Aspirin, Clopidogrel, Resistance, Aggregability

INTRODUCTION

In the face of atherosclerotic cardiovascular diseases (ASCVD), individuals are at risk of atherothrombosis.[1] Atherosclerotic plaque disruption is usually involved in the initiation of atherothrombotic events. Whether it is thrombotic occlusion or thrombosis progression that heralds the critical events, platelet activation is the initiating step. The implication is that it is the development of platelet-rich thrombi that triggers the acute ischemic phenomenon.[2] Stroke ranks high in the causes of death and disability worldwide, with Aspirin as the most common antiplatelet utilized for primary and secondary prevention of ASCVD.[3] In general, not only

Aspirin but other antiplatelets are key drugs in the treatment of ASCVD,[4] the former being the benchmark while the others, like Clopidogrel, are considered alternatives, especially when Aspirin is contraindicated or not tolerated.[5]

Aspirin resistance is said to occur when, despite aspirin treatment, patients go on to develop atherothrombotic events.[6] Resistance to Clopidogrel is also known to occur.[7] Resistance to antiplatelets, to the knowledge of the authors, has not been documented in native Africans living in sub-Saharan Africa. Among Caucasians in South Africa, a prevalence of 8% was documented in a study by Bernstein *et al*.[8] There is bound to be a difference among blacks, given the involvement of genetic polymorphism.[9] Since we encounter, at times, patients who, despite being on antiplatelet drugs, go on to develop ischemic phenomena, we decided to explore the phenomenon in our patients at risk of ASCVD.

MATERIAL AND METHODS

Patient methods

Patients attending our Cardiology Clinic in Jos University Teaching Hospital were approached to join the study if they had risk factors for ASCVD such as hypertension, diabetes, dyslipidemia, and overweight/obesity singly or in combination and on antiplatelets. The procedure was explained to them, and they signed an informed consent form. The protocol was approved by the hospital Research and Ethics Committee, and the study adhered to the tenets of the Helsinki Protocol. Patients were grouped into two based on the antiplatelet they were previously on. They were then asked to discontinue whichever antiplatelet they were on and undergo a two week washout. Blood was then taken after washout for baseline aggregometry. After four weeks on either drug, blood was taken again for a repeat aggregometry. Group 1 was given a vasoprin brand of Aspirin 75 mg (Juhel Pharmaceuticals, Enugu, Nigeria) to be taken once daily after dinner, while Group 2 received a plagerine brand of Clopidogrel 75 mg (Micro Labs Limited. 92, SIPCOT, HOSUR - 635 126 India) also to be taken once daily after dinner. It was proposed that each group would include 35 patients each, but for operational reasons, we were only able to recruit 29 patients into Group 1 and 33 into Group 2. Subjects for optical platelet aggregation tests were resting, fasting, and non-smoking. Subjects were told to avoid taking any prescription or over-the-counter medications known to affect platelet function for ten days to 2 weeks before the test.

Laboratory methods

Specimen collection (blood sample collection)

Each participant's arm was inspected, and an appropriate venipuncture site was selected. They were made to rest for 45 min before phlebotomy so as to prevent the effect of adrenalin on platelet function. Blood samples were taken from the antecubital vein. The tourniquet was applied above the venipuncture site, cleaned with 70% isopropyl alcohol, and allowed to dry before the sample was taken. From each participant, 13 mL of venous blood was collected.

Specimens were drawn with a minimum of trauma or stasis at the venipuncture site and anticoagulated with 3.2% sodium citrate in the ratio of one (1) part anticoagulant to nine (9) parts of blood for aggregometry. Two trisodium citrate vacutainers were each filled with 4½ mL of blood for the platelet rich plasma and platelet poor plasma (PRP and PPP) for aggregometry studies, while the remaining 4 mL were collected in a sterile dipotassium ethylene diamine tetra acetic acid (K_2 EDTA) sample bottle, for full blood count. Patient's initials, age, sex, and hospital numbers were labeled on each participant sample bottle to aid identification.

Specimen handling

Venous blood was collected in sterile citrate tubes and allowed to stand for 30 min to rest the platelet before processing for PRP/PPP. In contrast, the blood sample collected into the sterile K_2 EDTA sample bottle was stored at 6–8°C before sample processing and processed within four hours of collection.

Plastic or non-contact surfaced (siliconized) materials were used throughout to minimize activation of the platelets during sample preparation.

Handling conditions

Testing was initiated within 30 minutes to 3 hours after venipuncture. Specimens were kept at room temperature (24–27°C).

Analysis of specimen

EDTA sample was run using the Sysmex Auto-hematology analyzer KX21N for full blood count with platelet indices, while citrated blood was used for light transmission optical platelet aggregometry using the Chronolog 290D.

Platelet aggregometry

Platelets in a suspension of plasma are isolated from an anticoagulated blood sample by a relatively low centrifugal force. This material, known as PRP, is removed from the blood sample following centrifugation. The tubes are then returned to the centrifuge and spun at a higher force to prepare PPP. The Born type, or Optical Aggregometer, is a fixed wavelength spectrophotometer. A beam of infrared light shines through the PRP cuvette (the test sample), and another shines through the PPP cuvette (the reference). Pressing the

set baseline pushbutton sets the 0% (PRP) and the 100% (PPP) transmission baselines. PRP, which is turbid, is stirred in a test cuvette maintained at 37°C. The light transmittance through this turbid sample is measured relative to the PPP blank. When the agonist is added, the platelets will form increasingly larger aggregates, and the PRP will begin to clear, allowing more light to pass through. This increase in light transmittance is directly proportional to the amount of aggregation and is amplified and recorded as a signal on chart paper or digitized into a computer using AGGRO/LINK® Software.

Equipment and materials

Equipment

Chrono-log Aggregometer with Optical Mode.

Computer equipped with Chrono-log AGGRO/LINK® Interface.

Materials

1. P/N 312 Cuvettes
2. P/N 311 Disposable Siliconized Stir bars
3. P/N 331 0.5–10 µL Adjustable Pipette
4. P/N 335 Tips for P/N 331
5. P/N 332 10–100 µL Adjustable Pipette
6. P/N 337 Tips for P/N 332
7. P/N 333 100–1000 µL Adjustable Pipette
8. P/N 339 Tips for P/N 333
9. P/N 384 CHRONO-PAR® ADP (10 uM)
10. P/N 385 CHRONO-PAR® Collagen (2 ug/mL)
11. P/N 390 CHRONO-PAR® Arachidonic Acid (0.5 mM)
12. Physiological saline (0.85% w/v)
13. Bottled, sterile, and distilled water for irrigation is recommended for CHRONO-PAR® Reagent preparation.
14. 15 mL conical test tube and cap, or similar (per test subject): For diluting the specimens (for standardizing PRP)
15. Ice bucket: For maintenance of the reagents during the working day
16. Lintless wipes.

Preparation

Aggregometer

a. Turn on the unit and let it heat up for 10–15 min or until the heater block stabilizes at 37°C
b. Place P/N 311 Stir bars in P/N 312 Cuvettes
c. Put cuvettes containing stir bars in the incubation wells to warm up.

Sample

PRP

1. Centrifuge sample at 100 g for 15 min. The brake was set in the off position.
2. Take off the PRP with a polypropylene transfer pipette and put it into a polypropylene plastic tube.
3. Properly label the tube, including the patient's name and sample type. Parafilm or cap the top. Keep at room temperature (24–27°C).

Prepare the PPP

1. Centrifuge sample at approximately 2400 g for 20 min.
2. Take off the PPP with a polypropylene transfer pipette and put it into a polypropylene plastic tube.
3. Properly label the tube, including the patient's name and sample type. Parafilm or cap the top. Keep at room temperature (24–27°C).
4. A single sample of PPP per channel can be used as the reference sample for all tests run with the same patient's blood, so the amount of PPP required is only 500 µL (0.5 mL) per channel (Some instruments require only one [1] cuvette with 500 µL PPP for up to 4 channels.).

When ready to begin testing, dispense one aliquot per channel of adjusted PRP of 500 µL volume into P/N 312 cuvettes with stir bars. Warm for a minimum of 3 min.

Definition of resistance

Aspirin resistance has been defined variously; hence, the wide variation in prevalence is recorded in different studies.[10] On the contrary, with Clopidogrel, a <10% reduction in platelet aggregability with dosing defines resistance.[11] For this study, therefore, given that we had pre- and post-antiplatelet dosing aggregometry results, we decided to use a reduction of 10% or more in aggregometry values to define resistance for uniformity.

Statistics

Before this research work could be completed, we ran out of laboratory reagents, and the aggregometry data for the two months (post-antiplatelet) category could not be completed. Due to this, we had only 70% of the aggregometry data in this category. Therefore, we modeled the remaining data in this category using the linear regression method from the IBM SPSS Version 22 statistical software package. We used mean platelet volume, which we had pre- and post-antiplatelet dosing for all patients, and aggregometry data from the available 70% of the patients to determine, using linear regression equation between them and the aggregometry data, the values for the remaining 30% patients. Imputing missing data using modeled equations is permissible.[12] Categorical variables are reflected in frequencies and percentages, while continuous variables are reflected in means (standard deviation [SD]). Comparisons used that Chi-square and Student *t*-test as appropriate, and significance was set at $P < 0.05$.

RESULTS

Over the study period, 29 patients, all Nigerians, were enrolled into Group 1 (Aspirin), and 33 were enrolled into Group 2 (Clopidogrel), but 20 and 26 had complete data in the respective groups and formed the subjects of this report. Group 1 had 15 females and five males with the age range of 42–76 years and a mean (SD) of 60.75 (10.45). In Group 2, there were 18 females and eight males with the age range of 23–87 years and a mean of 58.08 (14.18). There was no statistically significant difference in gender proportion in both groups ($\chi^2 = 0.186$, df = 1, $P = 0.667$). The mean age in the two groups was also not significant statistically ($t = 0.707$, df = 44, $P = 0.483$) – [Table 1].

Of the 20 in Group 1 (Aspirin), 15 (75%) recorded a drop of ≥10% of aggregometry value at base line while 5 (25%) did not. In fact, in four out of the five, aggregometry values actually went up [Table 2a and b]. This implies a sensitivity of 75% and resistance of 25%.

Of the 26 in Group 2 (Clopidogrel), 14 (53.85%) recorded a drop of ≥10% of the aggregometry value at baseline, while 12 (46.15%) did not. Like in Group 1 (Aspirin), in three out of the 12, aggregometry values actually went up [Table 3a and b]. The implication here is a clopidogrel sensitivity of 53.85% and resistance of 46.15%.

In Group 1, the mean aggregability at baseline after washout was significantly greater than after one month on the drug in those who were sensitive, but the reverse was the case in those with resistance. For patients in Group 2, the aggregability was also significantly higher at baseline compared with after one month of ingestion in the sensitive cohort, while in the resistant sub-group, the aggregability remained almost the same – [Table 4].

DISCUSSION

The need to use antiplatelets in primary and secondary prevention derives from the fact that platelet activation is the initiating step in occlusive thrombosis or the progression of thrombosis.[13] In cases where these ischemic events occur despite the use of antiplatelets, a situation of antiplatelet therapy resistance is said to exist.[9] The failure of antiplatelets to protect from these ischemic phenomena may be as a result of pharmacokinetic or pharmacodynamic issues. In the former, the concentration of the drug in the blood is insufficient for the required action, while for the latter, the drug is in adequate amounts, but genetic polymorphisms and changes in platelet structure prevent adequate antiplatelet action.[14] By whatever mechanism, antiplatelet resistance has a serious clinical implication: that of permitting the occurrence of ischemic phenomena that it was supposed to prevent. The consequences of these (stroke, myocardial infarction, blindness, and peripheral artery diseases) are huge in terms of morbidity-mortality and economic losses.

Knowledge of rates of antiplatelet efficacy in any environment will go a long way in advising on the utilization of the drugs in primary and secondary prevention of ischemic cardiovascular diseases. This is given that genetic polymorphisms and the burden of lifestyle and chronic non-communicable diseases, which could vary between regions, determine in some way the level of action of these drugs.[7,15] To the best of our knowledge, there is no report of antiplatelet resistance in native Africans living in sub-Saharan Africa, at risk of ASCVD.

Table 1: Age and gender characteristics of study population.

Characteristic	Group 1 (ASPIRIN)	Group 2 (CLOPIDOGREL)	*P*-value
Gender (M/F)	5/15	8/18	0.667
Age range (year)	42–76	23–87	
Age mean (SD)	60.75 (10.45)	58.08 (14.18)	0.483

SD: Standard deviation

Table 2a: Aggregometry values, gender, and age in Aspirin sensitive patients.

S. No.	AS1 (%)	AS2 (%)	Gender	Age (year)
1.	75.0	46.0	F	64
2.	78.0	43.0	F	70
3.	73.0	29.0	F	76
4.	67.0	54.0	F	53
5.	90.0	20.0	M	67
6.	90.0	14.0	F	42
7.	95.0	31.0	F	57
8.	80.0	45.0	F	64
9.	82.0	37.0	F	51
10.	95.0	55.0	F	70
11.	61.0	5.0	F	53
12.	77.0	65.0	F	73
13.	74.0	59.0	F	60
14.	89.0	80.0	F	56
15.	82.0	52.0	M	63

AS1 (%): Aggregometry value after washout, AS2 (%): Aggregometry value after 1 month on Aspirin, F: Female, M: Male

Table 2b: Aggregometry values, gender, and age in Aspirin resistant patients.

S. No.	AS1 (%)	AS2 (%)	Gender	Age (year)
1.	71.0	74.0	M	71
2.	75.0	71.0	F	42
3.	72.0	89.0	M	59
4.	68.0	85.0	M	76
5.	5.0	38.0	F	48

AS1 (%): Aggregometry value after washout, AS2 (%): Aggregometry value after 1 month on Aspirin, F: Female, M: Male

Table 3a: Aggregometry values, gender, and age in Clopidogrel sensitive patients.

S. No.	AS1 (%)	AS2 (%)	Gender	Age (year)
1.	92.0	82.0	F	60
2.	103.0	66.0	M	66
3.	96.0	82.0	M	59
4.	37.0	28.0	F	63
5.	89.0	70.0	M	47
6.	89.0	20.0	F	60
7.	99.0	78.0	F	31
8.	93.0	70.0	M	71
9.	90.0	75.0	F	80
10.	86.0	49.0	F	68
11.	79.0	15.0	F	55
12.	92.0	62.0	F	52
13.	87.0	73.0	F	44
14.	112.0	93.0	M	56

AS1 (%): Aggregometry value after washout, AS2 (%): Aggregometry value after 1 month on clopidogrel, F: Female, M: Male

Table 3b: Aggregometry values, gender, and age in Clopidogrel resistant patients.

S. No.	AS1 (%)	AS2 (%)	Gender	Age (year)
1.	91.0	84.0	M	65
2.	89.0	87.0	F	57
3.	81.0	73.0	F	23
4.	89.0	88.0	F	38
5.	81.0	94.0	M	87
6.	80.0	93.0	F	58
7.	87.0	86.0	M	70
8.	114.0	104.0	F	60
9.	84.0	94.0	F	72
10.	97.0	94.0	F	65
11.	79.0	78.0	F	58
12.	82.0	79.0	F	45

AS1 (%): Aggregometry value after washout, AS2 (%): Aggregometry value after 1 month on clopidogrel, F: Female, M: Male

Our study revealed a 25% aspirin resistance and 46.15% clopidogrel resistance with low doses of 75 mg each. This is within the reported range in other regions, and a higher prevalence of clopidogrel resistance seems to be the norm.[16] The range of prevalence reported for aspirin resistance is 5.5–60%,[10] while for Clopidogrel, resistance ranges from 5% to 44%,[11] with one study among people in the Caribbean islands reporting 50%.[17] It has been stated that the difficulty with comparing rates derives from the different assay methods and different disease states.[18] Whereas most of the reported studies focused on patients who already suffered these ischemic events, such as stroke and myocardial infarction, our cohort was made up of patients who have risk diseases for ASCVD but have yet to develop any thrombotic consequences.

Table 4: Comprison of aggregability in both groups between baseline and end of study.

Group	AS1 (%)	AS2 (%)	*P*-value
1 (SENSITIVE)	80.5 (9.96)	42.3 (20.09)	<0.00
(RESISTANT)	58.2 (29.8)	7.4 (20.)	0.08
2 (SENSITIVE)	88.9 (6.9)	61.6 (24.4)	0.001
(RESISTANT)	87.8 (9.8)	87.8 (8.6)	1.00
Data represent mean (SD)			
Group 1 – Aspirin, Group 2 – Clopidogrel			

AS1 (%): Aggregometry value after washout, AS2 (%): Aggregometry value after 1 month on clopidogrel, SD: Standard deviation

The implication of our finding is that a quarter of our patients at risk of ASCVD despite aspirin use and nearly half despite clopidogrel use may still go on to develop ischemic phenomena. This calls for deliberate efforts to mitigate the burden of the risk diseases for ASCVD. There would also be the need to pay attention to the diverse factors which impair responsiveness to Aspirin.[19] This is because though cytochrome c oxidase subunit I (COX1) inhibition is the main mechanism of action, multiple signaling pathways induce platelet activation; hence, platelets can still be activated despite effective COX 1 blockade.[20]

The relatively high prevalence of antiplatelet resistance in these patients demands a response to reduce rates of these thrombotic events. One of these is dose increase. The antiplatelet effects of these drugs increase with dose,[21] though at the risk of side effects, which include bleeding[22] and worse outcomes in chronic kidney disease,[23] which many ASCVD patients may have. All these call for caution. Dual antiplatelet therapy has been tried, the risk of which remains bleeding.[24] Recently, there has been a call to improve the antiplatelet effect of these drugs by synergism with nutraceuticals[25,26] as they do not increase the bleeding risk, whether given alone or with regular antiplatelets.[27] Although earlier studies made no specific recommendations in this regard,[28] struck by the rates of resistance to the regular antiplatelets, we offered those affected Nattokinase in exchange (Result not shown) as we were impressed with the report of antiplatelet effect of Nattokinase.[29] We found that those resistant to Aspirin still had high aggregability values, while 70% of those resistant to Clopidogrel recorded a significant reduction in aggregability. This is an area that would require properly designed studies, including the cases that recorded a paradoxical response to the antiplatelets.

The strength of our study is in trying to provide data on antiplatelet response in an understudied if not hardly studied, sub-Saharan African population. That way, the treatment approach will be tailored to population specific experience. Another strength is having a cohort of patients at risk of ASCVD but yet to develop any of the ischemic phenomena (some of which affect aggregability) and the washout period

before giving the antiplatelets. The maintenance of the same time window for the blood tests in all patients removed the diurnal variability in platelet function, which may have been introduced had they been tested at different times. Finally, each patient served as their own control, removing any bias of genetic polymorphisms, background disease, and lifestyle. It is, however, limited by small numbers, single-center experience, and the fact that we could not assay the level of drugs in the blood. The metabolism of the drugs *in vivo* could affect availability and, hence, antiplatelet effects. An additional limitation is our use of a definition of Aspirin resistance that is not universally applicable in our effort to converge it with the widely acceptable definition of resistance for Clopidogrel. This is because we had aggregability results before and after the administration of the antiplatelets used in the study. We also did not factor in comorbidities, other treatment drugs, and social habits that could impact aggregability. All the same, it could count as a pilot study on this subject in our environment.

CONCLUSION

Sub-Saharan African patients at risk of ASCVD exhibit significant antiplatelet resistance more for Clopidogrel than Aspirin. This should be borne in mind while planning primary or secondary prevention of atherothrombotic disease. While making efforts to mitigate the burden of risk diseases, dietary or nutraceutical approaches to bring about synergism are options that could also be explored.

Acknowledgment

We appreciate our study patients for their cooperation. Prof G. Imade graciously granted us access to the −70° storage facility for the reagents while his staff, especially Mr Shedrack, released the required stock as appropriate on a weekly basis. Mr. Prince Ebuka assisted with the logistics of moving patients to the laboratory for blood work, and Mr. Davou Badung provided effective services as a Research Assistant.

Ethical approval

The research/study was approved by the Institutional Review Board at JOS University Teaching Hospital, number JUTH/DCS/IREC/127/XXXI/2257, dated August 3, 2020.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

Financial support and sponsorship

Altinez Pharma Ltd, 18 Jones Street, Ebute Metta, Lagos, Nigeria (software upgrade of Aggregometer and provision of reagents and Consumables).

Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

REFERENCES

1. Asada Y, Yamashita A, Sato Y, Hatakeyama K. Pathophysiology of atherothrombosis: Mechanisms of thrombus formation on disrupted atherosclerotic plaques. Pathol Int 2020;70:309-22.
2. Nieswandt B, Kleinschnitz C, Stoll G. Ischaemic stroke: A thrombo inflammatory disease? J Physiol 2011;589:4155-23.
3. Sisodia P, Bhatia B. Aspirin resistance and stroke. J Stroke Med 2018;1:19-27.
4. Hu W, Luo Y, Yang X. Inappropriate use of proton pump inhibitor increases cardiovascular events in patients with coronary artery disease. Int J Gen Med 2022;15:8685-91.
5. Hidayat R, Rasyid A, Harris S, Harahap A, Herqutanto, Louisa M, *et al.* Correlation P2Y12 genetic polymorphism as risk factor of clopidogrel resistance in Indonesian stroke patients. Vasc Health Risk Manag 2023;19:53-61.
6. Dalen JE. Aspirin resistance: Is it real? Is it clinically significant? Am J Med 2007;120:1-4.
7. Yang J, Yu Q, Xu Z, Zheng N, Zhong J, Li J, *et al.* Clopidogrel resistance is associated with DNA methylation of genes from whole blood of humans. Front Genet 2021;11:583215.
8. Bernstein PL, Jacobson BF, Coonor MD, Becker PJ. Aspirin resistance in South African Caucasian patients with thrombotic cerebrovascular events. J Neurol Sci 2009;277:80-2.
9. Marginean A, Banescu C, Scridon A, Dobreanu M. Antiplatelet therapy resistance - concept, mechanisms and platelet function tests in intensive care facilities. J Crit Care Med (Targu Mures) 2016;2:6-15.
10. Mansou K, Tahei AT, Musalla KM, Alam S. Aspirin resistance. Adv Haematol 2009;2009:937352.
11. Ray S. Clopidogrel resistance. The way forward. Indian Heart J 2014;66:530-4.
12. White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. Stat Med 2011;30:377-99.
13. Thachil J. Antiplatelets therapy - a summary for the general physicians. Clin Med (Lond) 2016;16:152-60.
14. Khan H, Kanny O, Syed MH, Qudura M. Aspirin resistance in vascular disease. A review highlighting the critical need for improved point of care testing and personalized therapy. Int J Mol Sci 2022;23:11317.
15. Parameshwara S, Manjula B, Bhakhta G, Kallaganad G, Ranjjith Kumar GK. Clopidogrel resistance in cardiovascular disease patients and its association with gene polymorphisms: A pilot study. J Clin Prev Cardiol 2021;10:80-4.
16. Patel S, Arya V, Saraf A, Bhargawa M, Agrawal CS. Aspirin and

Clopidogrel resistance in Indian patients with ischaemic stroke and its associations with gene polymorphism: A pilot study. An Indian Acad Neurol 2019;22:147-52.
17. Seecheran NA, Maharaj A, Boodhai B, Seecheran R, Seecheran V, Persad S, *et al.* 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. Open Heart 2019;6:e000841.
18. Lordkipanidzé M, Pharand C, Schampaert E, Turgeon J, Palisaitis DA, Diodati JG. A comparison of six major platelet function tests to determine the prevalence of aspirin resistance in patients with stable coronary artery disease. Eur Heart J 2007;28:1702-8.
19. Xu ZH, Jiao JR, Yang R, Luo BY, Wang XF, Wu F. Aspirin resistance: Clinical significance and genetic polymorphism. J Int Med Res 2012;40:282-92.
20. Tanty US, Mahla E, Gurbel PA. Aspirin resistance. Prog Cardiovasc Dis 2009;52:141-52.
21. Vivas D, Bernardo E, Garcia-Rubira JC, Azcona L, Nunez-Gil I, Gonzalez-Ferrer JJ, *et al.* Can reistance to Aspirin be reversed after an additional dose? J Thromb Thrombolysis 2011;32:356-61.
22. Lanas A, García-Rodríguez LA, Arroyo MT, Gomollón F, Feu F, González-Pérez A, *et al.* Risk of upper gastrointestinal ulcer bleeding associated with selective cyclo-oxygenase-2 inhibitors, traditional non-aspirin non-steroidal anti-inflammatory drugs, Aspirin and combinations. Gut 2006;55:1731-8.
23. Tsai MH, Liou HH, Huang YC, Lee TS, Chen M, Fang YW. Hazardous effect of low-dose Aspirin in patients with predialysis advanced chronic kidney disease assessed by machine learning method feature selection. Healthcare (Basel) 2021;9:484.
24. Awada Z, Abboud R, Nasr S. Risk of serious bleeding with antiplatelet therapy for secondary prevention post ischemic stroke in Middle East population. Cureus 2019;11:e4942.
25. Ke J, Li MT, Huo YJ, Cheng YQ, Guo SF, Wu Y, *et al.* The synergistic effect of *Gingko biloba* extract 50 and Aspirin against platelet aggregation. Drug Des Dev Ther 2021;15:3543-60.
26. Zhao Y, Yang S, Wu M. Mechanisms of improving aspirin resistance: Blood activating herbs combined with Aspirin in treatment of atherosclerotic cardiovascular diseases. Front Pharmcol 2021;12:794417.
27. Kellermann AJ, Kloft C. Is there a risk of bleeding with standardized *Gingko biloba* extract therapy? A systematic review and meta-analysis. Pharmacotherapy 2011;31:490-502.
28. Feher G, Feher A, Pusch G, Koltai K, Tibold A, Gasztonyi B, *et al.* Clinical importance of aspirin and clopidogrel resistance. World J Cardiol 2010;2:171-86.
29. Chen H, McGowan EM, Ren N, Lal S, Nassif N, Shad-Kaneez F, *et al.* Nattokinase: A promising alternative in prevention and treatment of cardiovascular diseases. Biomark Insights 2018;13.

How to cite this article: Okeahialam BN, Akor E, Shut G, Ifeacho O, Dauda B, Sirisena A, *et al.* Antiplatelet resistance among a cohort of patients at risk of atherosclerotic cardiovascular diseases in Jos, Nigeria. J Hematol Allied Sci. 2023;3:136-42. doi: 10.25259/JHAS_13_2023