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Antiplatelet Therapy and Kidney Function in Non-Dialysis Chronic Kidney Disease: A Two-Centre Observational Study in Nigeria

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ABSTRACT

Antiplatelet therapy used in preventing cardiovascular events in chronic kidney disease may be associated with higher risks of bleeding, low efficacy from fewer occlusive atherosclerotic disease), attenuation of the inflammatory process, and changes in the haemogram. We prospectively determined the kidney function, the haemogram, and the lipid profile of participants with and without antiplatelet therapy. The population with a mean age of 69.21 ± 11.73 years, had more women (65.88%) (P = 0.001). Participants' age was positively correlated with the CKD stage (P < 0.001). Bleeding was more common with clopidogrel than aspirin and, less common with advancing CKD. Cardiovascular events were more common in CKD stage 5. The men had higher eGFR but lower platelet count and platelet neutrophil ratio (PNR) than the women (P = 0.004, P < 0.001, and P < 0.001, respectively). The eGFR, bicarbonate, and HDL cholesterol were higher with versus without antiplatelets (P = 0.04, P < 0.001, and P = 0.001, respectively). The platelet count and PNR were higher with antiplatelet therapy and with higher CKD stage (P < 0.001, P < 0.001, P < 0.001, and P <0.001, respectively). Higher platelet count (OR-0.410, 95% CI-0.02-1.04), lower uric acid levels (OR-0.550, 95% CI-0.271-0.948), higher HDL-C (OR-0.486, 95% CI-0.093-1.013), lower LDL-C (OR-0.572, 95% CI-0.082-1.002) and lower triglycerides (OR-1.274, 95% CI-0.755-1.493) were independently associated with antiplatelet therapy. The benefits of antiplatelet therapy in CKD are anchored on its anti-inflammatory, lipid-lowering, and kidney function-improving effects, these synergistically lead to lower cardiovascular events. The increased risk and consequences of bleeding, and reductions in leucocytes and erythrocytes population should be borne in mind to prevent heightening morbidity and mortality rates.

Keywords: *Antiplatelet therapy, Chronic kidney disease, Bleeding, Cardiovascular events, Platelet count, Kidney function*

INTRODUCTION

Chronic kidney disease (CKD) has continued to witness a rising prevalence and increasing health and socioeconomic burden globally with the most common triggers of mortality across all its stages being

cardiovascular disease (CVD) and events [1]. Epidemiological studies have shown a CKD prevalence of about 10-15%, and CKD is a known risk factor for peripheral vascular disease (PVD), atrial fibrillation (AF), ischemic heart disease (IHD), and heart failure (HF) [1-3]. The greater risk of atherosclerosis and cardiovascular events in CKD is anchored on its chronic inflammatory state [2, 3]. The release of vasogenic substances can modulate initial vasodilatation, increase permeability, fluid extravasation, and progression could lead to the release of vasoconstrictor agents secondary to the activation of the renin-angiotensin-aldosterone system (RAAS) pathway and the sympathetic nervous system (SNS) that can cause endothelial injury [4].

These vasoconstrictor agents can alter the haemogram, with derangements in platelet count and functions, such as high platelet reactivity (HPR) and angiogenic factors like platelet-derived growth factors (PDGF) [5]. CKD induces a pathophysiologic mechanism that involves platelet activation and aggregation associated with a high treatment platelet reactivity (HTPR), commonly referred to as failure (resistance) of antiplatelet therapy, is reported to be well correlated with CKD and its severity [6]. Antiplatelet therapy is useful in the management of atherosclerotic occlusive-vascular diseases, conditions that are less prevalent in CKD compared with other vasculature-associated inflammatory diseases [7]. Though antiplatelet therapy in CKD is quite common, conditions associated with a heightened risk of bleeding are common contraindications. There seems not to be a consensus yet on antiplatelet-associated treatment outcomes as higher incidences of hemorrhagic events in CKD, particularly in hemodialysis patients have been found by some researchers while others have reported a no-causal relationship between their use and hemorrhagic events [8, 9]. This has led to wide differences in the recommendations by various researchers, and bodies, on the benefits and possible adverse outcomes of antiplatelet agents in CKD [8, 9]. Platelet inhibition with clopidogrel is documented to reduce the risk of ischemia, a response that is suppressed in patients with CKD [10]. Despite this, the management of CKD with a significant risk of cardiac events has routinely included platelet inhibition as a beneficial outcome that continues to be unraveled leading to overall reductions in cardiovascular events and death [11].

The increasing westernization and sedentary lifestyle of the population is expected to heighten the risk of dyslipidemia and therefore, occlusive atherosclerotic events in the future [12]. Despite the increasing risk and adverse outcome of stroke, retinal, and cardiovascular events in CKD (more so in resource-challenged settings), Literature is still scarce in these settings regarding the use and outcome of antiplatelet drugs in CKD. In this prospective, observational study, we assessed the place of platelet inhibition on kidney function and the haemogram in CKD.

MATERIALS AND METHODS

Study design

The two-centre, cohort study was conducted at the nephrology and hypertension divisions of Babcock University Teaching Hospital, Ilishan-Remo (December 2018 to July 2022), and Bowen University Teaching Hospital, Ogbomosho (August 2022 to November 2023). Patients were recruited using a convenience sampling technique. Each participant had their blood and urine samples tested before the commencement of antiplatelet therapy (as part of their routine treatment regimen) and, was followed up for six months, at which point the blood and urine sampling were repeated.

Study population

Participants were 18 years and older, and were receiving treatment at the Nephrology and Hypertension divisions of the two hospitals. After enrolment, a detailed history, examination, and perusal of patients' medical records was conducted from where the data was generated. The participants were either newly diagnosed or had been on treatment. Women of reproductive age were instructed not to provide urine samples collected from the day preceding the onset of menses to the day after.

Exclusion criteria

Patients with CKD who declined consent or were less than 18 years old were excluded. Smokers, patients with acute illnesses, bleeding diathesis, or heightened risk of bleeding (active acid peptic disease, liver disease, infections, cancers, connective tissue diseases, heart failure, and hematologic disorders) were excluded. Patients with ultrasound-detected intra-abdominal lesions, pregnant women, current users of, antibiotics or anti-inflammatory drugs, anti-coagulant therapy, and hormone-based contraception within the preceding six months were also excluded.

Sample size

The minimum sample size was determined using the prevalence of antiplatelet usage in a CKD population (25%), and this gave a sample size of 85 [12]. One hundred and seventy CKD participants were involved in the study.

Data collection

Demographic (age, sex, weight, height, etiology of CKD) and clinical (history of body weakness, pruritus, and bone tenderness) data were entered into a data entry form. The height (m) and weight (kg) were measured without shoes or head cover, and under light clothing according to standardized protocols. Body mass index (BMI) was calculated using the Quetelet index [13]. Blood pressures were measured according to standard procedures [14].

Sample collection

About 10-12 ml of blood was obtained from a peripheral forearm vein between 8:00 and 9:00 am in the sitting position and separated into aliquots for analysis of the full blood count, serum electrolytes, creatinine, albumin, calcium, phosphate, and fasting lipids. Creatinine-based estimated glomerular filtration rate (eGFR) was calculated for each patient using the chronic kidney disease-epidemiology collaboration (CKD-EPI) formula [15]. An on-the-spot clean mid-stream urine was collected for urinalysis and urine albumin creatinine ratio. Standardized protocols had been followed in the quantitative testing for UACR with the Micra Albustix test strip [16]. One hundred and forty-six (85.88%) participants had an electrocardiogram (ECG).

Definitions of terms

Microalbuminuria: UACR > 30 mg/g [17].
Anaemia: Haematocrit < 39% in males, and < 36% in females [18].
Hypoalbuminemia: Serum albumin < 35 g/L [19].
Hyperuricemia: Serum uric acid > 0.42 mmol/L (males) and > 0.36 mmol/L (females) [20].
Platelet neutrophil ratio: The ratio of the platelet count to the neutrophil count [13].

The SPSS version 22 was used for data analysis. Student t-test was conducted to compare means (SD), but with more than two groups, a one-way ANOVA was used. Proportions and frequencies, as categorical variables were compared using the Chi-square or Fisher's exact test. In the logistic regression analysis, the unadjusted odds ratios (ORs) were calculated to determine the correlates of the outcome variables. Adjustment variables with $P < 0.025$ were entered from the univariate analysis into the multivariate model to determine independent associates of antiplatelet therapy. This study was approved by the ethics committees of Babcock University (NHREC/24/01/2018 and BUHREC501/19) and Bowen University Teaching Hospital, Ogbomosho (NHREC/12/04/2012 and BUTH/REC-678).

RESULTS AND DISCUSSION

Quality of research data

A total of 206 participants with CKD) were enrolled for this study. Of the 206 patients, 21 were excluded on account of commencing dialysis during the follow-up period, and 15 patients were excluded on account of conditions that can alter platelet count and function, with or without bleeding diathesis. The study population had 170 participants with CKD.

Demographic and laboratory findings

At presentation, the mean age of the population was 69.21 ± 11.73 years, and women made up 65.88% of the CKD cohorts ($P = 0.001$) **(Table 1)**. The mean platelet count and urine ACR were 404.57 ± 13.77, and 35.84 ± 10.36, respectively. One hundred and fifty-eight (92.94%) participants were receiving Atorvastatin, 132 (77.65%) participants received thiazides, 126 (74.18%) received a calcium channel blocker, 69 (40.59%) participants received a beta-adrenergic antagonist, 38 (22.35%) participants received an alpha-adrenergic antagonist. Participants were initially commenced on Febuxostat 40mg or 80mg but with improvements in the uric acid levels, all were maintained on 40 mg from the third month of antiplatelet therapy. 109 (74.66%) participants had left ventricular hypertrophy (LVH).

Table 1. Participants' characteristics at presentation and with antiplatelets

Variables	Presentation	Follow up ASA	Follow up CLOP	P-value
	N = 170	N = 78	N = 92	
Age, years (mean ± SD)	69.21 ± 11.73	67.98 ± 8.31	70.25 ± 10.09	0.03
18-39 (n, %)	16 (9.41%)	8 (10.26%)	4 (4.35%)	0.002
40-64 (n, %)	66 (38.82%)	32 (41.02%)	32 (34.78%)	
> 65 (n, %)	88 (51.77%)	38 (48.72%)	56 (60.87%)	
Gender				
Male (n, %)	58 (34.12%)	26 (33.33%)	32 (34.78%)	0.08
Females (n, %)	112 (65.88%)	52 (66.67%)	60 (65.22%)	
WHR (mean ± SD)	1.10 ± 0.29	1.03 ± 0.20	1.07 ± 0.21	0.06
SBP, mmHg (mean±SD)	149.33 ± 8.42	143.33 ± 12.47	148.48 ± 39.67	0.02
DBP, mmHg (mean±SD)	94.84 ± 5.25	92.54 ± 6.74	91.96 ± 6.05	0.03
Hematocrit, % (mean±SD)	33.87 ± 7.49	31.44 ± 6.38	31.95 ± 11.95	0.04
ANC, $x10^9$ (mean±SD)	5128.96 ± 24.17	4834.51 ± 74.11	4766.67 ± 58.39	< 0.001
ALC, $x10^9$ (mean±SD)	1166.69 ± 12.06	1097.15 ± 31.45	1022.26 ± 38.92	0.001
Platelet, $x10^9$ (mean±SD)	404.57 ± 13.77	456.63 ± 56.89	431.28 ± 47.82	< 0.001
PNR (x1000) (mean±SD)	78.88 ± 7.93	94.45 ± 11.78	90.47 ± 8.25	< 0.001
UACR (mean±SD)	35.84 ± 10.36	29.42 ± 10.67	32.75 ± 11.19	< 0.001
eGFR, median (IQR)	37.2 (20.8-58.2)	37.8(19.7-57.9)	38.3 (22.1-58.4)	0.002
Albumin, mg/dL (mean±SD)	34.19 ± 9.84	35.55 ± 10.74	34.05 ± 7.73	0.07
Elevated TC, mg/dL (n, %)	29 (34.12%)	16 (20.51%)	10 (10.87%)	< 0.001
Low HDL, mg/dL (n, %)	27 (31.76%)	10 (12.82%)	12 (13.04%)	< 0.001
Elevated LDL, mg/dL (n, %)	34 (40.00%)	12 (15.38%)	16 (17.39%)	< 0.001
Elevated TG, mg/dL (n, %)	34 (40.40%)	13 (18.66%)	17 (18.48%)	< 0.001

AS-aspirin, CLOP-clopidogrel, CKD-chronic kidney disease, WHR-waist hip ratio, BP-blood pressure, ANC-absolute neutrophil count, ALC-absolute lymphocyte count, UACR-urine albumin creatinine ratio, GFR-glomerular filtration rate, TC-total cholesterol, HDL-high density lipoprotein, LDL-low density lipoprotein, TG-triglyceride.

There was an improvement in metabolic acidosis and eGFR with antiplatelet therapy, P < 0.001 and P = 0.04 respectively **(Table 2)**. There were reductions in the CaPo4 product and microalbuminuria with antiplatelet therapy.

Table 2. Prevalence of markers of chronic kidney disease at presentation and follow-up

Variables	Presentation	Antiplatelet	P-value
	N = 170	N = 170	
Hyponatremia (n, %)	49 (28.82%)	54 (31.76%)	0.09
Hypochloremia (n, %)	48 (28.23%)	34 (20.00%)	0.05
Hyperkalemia (n, %)	17 (10.00%)	6 (3.53%)	0.08
Hypobicarbonatemia (n, %)	58 (34.12%)	20 (11.76%)	< 0.001
Elevated urea (n, %)	92 (54.12%)	75 (44.12%)	0.04
Creatinine (M >1.4 mg/dL; F > 1.2 mg/dL) (n, %)	124 (72.94%)	109 (64.12%)	0.05
eGFR < 30 mL/min (n, %)	132 (77.64%)	114 (67.06%)	0.04
Uric acid (M > 4.20 mmol/l; F > 3.6 mmol/l) (n, %)	97 (57.06%)	41 (24.12%)	< 0.001
Hypocalcemia (n, %)	47 (27.65%)	22 (12.94%)	0.001

Hyperphosphatemia (n, %)	68 (40.00%)	44 (25.88%)	< 0.001
CaPo4 product (< 55 mg^2/dL^2) (n, %)	49 (28.82%)	27 (15.88%)	0.001
Hypoalbuminemia (n, %)	78 (45.88%)	42 (24.70%)	< 0.001
Anaemia (M < 39%; F < 36%) (n, %)	56 (32.94%)	58 (34.12%)	0.09
Hypoalphalipoproteiemia (n, %)	63 (37.06%)	43 (25.29%)	0.001
Microalbumiuria (n, %)	63 (37.06%)	28 (16.47%)	< 0.001

eGFR-glomerular filtration rate, CaPo4-calcium phosphate product

The urine albumin creatinine ratio and the platelet count were lower in men than the women (P = 0.03 and P < 0.001, respectively) **(Table 3)**. The platelet neutrophil ratio was lower in men than women (P < 0.001).

Table 3. Gender correlates in participants with chronic kidney disease on antiplatelets

Variables	**Chronic kidney disease**		**P-value**
	Males	**Females**	
	N = 58	**N = 112**	
Age years (Mean ± SD)	66.38 ± 11.43	70.67 ± 13.74	0.001
18-39 (n, %)	6 (10.34%)	10 (8.93%)	< 0.001
40-64 (n, %)	28 (48.28%)	38 (33.93%)	
> 65 (n, %)	24 (41.38%)	64 (57.14%)	
WHR (mean ± SD)	1.09 ± 0.24	1.10 ± 0.31	0.1
SBP, mmHg (mean ± SD)	145.92 ± 23.41	150.78 ± 18.68	0.03
DBP, mmHg (mean ± SD)	91.43 ± 9.39	93.45 ± 11.17	0.06
UACR, mg/g (mean ± SD)	33.38 ± 7.71	37.44 ± 11.55	0.03
Hematocrit, % (mean ± SD)	32.22 ± 6.47	30.84 ± 6.12	0.05
GFR, ml/min (mean ± SD)	31.91 ± 6.93	26.48 ± 6.02	0.004
Albumin, g/L (mean ± SD)	37.00 ± 7.88	32.35 ± 7.53	0.04
ANC, $x10^9$ (mean ± SD)	4997.51 ± 62.77	4699.86 ± 55.37	< 0.001
ALC, $x10^9$ (mean ± SD)	1254.55 ± 19.63	951.53 ± 12.84	< 0.001
Platelets 10^9/L (mean ± SD)	402.11 ± 44.29	464.04 ±71.15	< 0.001
PNR (x1000) (mean ± SD)	80.46 ± 20.70	98.73 ± 8.55	< 0.001

WHR-waist hip ratio, SBP-systolic blood pressure, DBP-diastolic blood pressure, UACR-urine albumin creatinine ratio, GFR-glomerular filtration rate, ANC-absolute neutrophil count, ALC-absolute lymphocyte count, PC-platelet count, PNR-platelet neutrophil ratio.

Forty-eight (28.24%) participants had CKD stage 3,89 (52.35%) had CKD stage 4, and 33 (19.41%) had CKD stage 5 **(Table 4)**. Cardiovascular events were more common in CKD stage 5 (P = 0.04) while bleeding episodes were more frequent in CKD stages 3 and 4 (P < 0.001).

Table 4. Relationship between antiplatelet therapy and kidney function

Variables	**CKD stage 3 N = 48 (%)**	**CKD stage 4 N = 89 (%)**	**CKD stage 5 N = 33 (%)**	**P-value**
Age, yrs (Mean±SD)	67.44 ± 74	67.91 ± 48	75.29 ± 51	< 0.001
18-39	4 (8.33%)	6 (6.74%)	6 (18.18%)	< 0.001
40-64	18 (37.50%)	39 (43.82%)	9 (27.27%)	
> 65	26 (54.17%)	44 (49.44%)	18 (54.55%)	
Sex				
Male	16 (33.33%)	32 (35.96%)	10 (30.30%)	0.06
Female	32 (66.67%)	57 (64.04%)	23 (69.70%)	

Haemogram				
ANC	5039.56 ± 15.38	4985.71 ± 30.69	4944.74 ± 31.19	< 0.001
ALC	1502.54 ± 47.83	1371.88 ± 47.45	1170 ± 31.84	< 0.001
Platelets	419.19 ± 10.22	433.96± 17.52	494.44 ± 23.73	< 0.001
PNR	68.52 ± 9.63	80.84 ± 11.67	113.85 ± 20.74	< 0.001
Lipid profile				
Elevated TC	6 (12.50%)	10 (11.23%)	10 (30.30%)	0.001
Elevated LDL-C	4 (8.33%)	7 (7.86%)	5 (15.15%)	0.002
Reduced HDLC	5 (10.42%)	6 (6.74%)	6 (18.18%)	0.003
Elevated TG	12 (25.00%)	12 (13.48%)	11 (33.33%)	< 0.001
Kidney function				
eGFR	47.76 ± 9.96	22.89 ±7.74	11.39 ± 7.12	< 0.001
Urine ACR	15.95 ± 4.72	21.79 ± 6.61	32.91 ± 8.19	< 0.001
Albumin	45.29 ± 6.90	32.04 ± 11.52	48.50 ± 18.60	0.01
CaPo4 product	44.85 ± 14.63	53.84 ± 22.39	71.86 ± 33.57	< 0.001
Haematocrit	39.04 ± 5.11	34.47 ± 21.77	25.81 ± 15.88	0.002
Cardiovascular events				
Arrhythmias	3 (6.25%)	11 (12.36%)	5 (15.15%)	0.004
Heart failure	2 (4.17%)	6 (6.74%)	2 (6.06%)	0.06
Sudden cardiac death	0 (0.00%)	2 (2.25%)	2 (6.06%)	0.02
Bleeding episodes				
Epistaxis	2 (4.17%)	3 (3.37%)	1 (3.03%)	0.05
Haematuria	1 (2.08%)	5 (5.62%)	0 (0.00%)	< 0.001
Bleeding gums	3 (6.25%)	12 (13.48%)	1 (3.03%)	< 0.001

CKD-chronic kidney disease, ANC-absolute neutrophil count, ALC-absolute lymphocyte count, TC-total cholesterol, LDL-C-low density lipoprotein cholesterol, HDL-C-high density lipoprotein cholesterol, TG-triglyceride, eGFR-estimated glomerular filtration rate, ACR-albumin creatinine ratio.

From the multivariate logistic regression model **(Table 5)**, platelet count (OR-0.410, 95% CI-0.02-1.04), uric acid (OR-0.550, 95% CI-0.271-0.948), HDL-C (OR-0.486, 95% CI-0.093-1.013), LDL-C (OR-0.572, 95% CI-0.082-1.002) and triglycerides (OR-1.274, 95% CI-0.755-1.493) were independently related to antiplatelet therapy.

Table 5. Logistic regression for outcome of antiplatelet therapy in participants

	Univariate analysis		**Multivariate analysis**		
	Crude OR	**P-value**	**aOR**	**95% CI**	**P-value**
Age	1.584	0.046	0.99	0.85-1.57	0.06
Sex (Female)	1.24	0.051			
WHR	0.960	0.711			
Blood pressure	2.447	0.061			
ANC	4.053	< 0.001	1.52	1.43-1.79	0.37
ALC	1.692	0.073			
Platelet count	0.534	< 0.001	0.410	0.02-1.04	< 0.001
Platelet neutrophil ratio	4.552	< 0.001	0.482	0.422-0.825	0.062
Urine ACR	1.733	0.041	1.960	1.740-2.153	0.571
eGFR	4.026	< 0.001	1.093	0.917-1.732	0.054
Uric acid	1.010	< 0.001	0.550	0.271-0.948	0.03
Capo4 product	1.927	0.056			

Total cholesterol	0.932	0.768			
HDL cholesterol	0.478	< 0.001	0.486	0.093-1.013	< 0.001
LDL cholesterol	0.566	< 0.001	0.572	0.082-1.002	< 0.001
Triglycerides	1.095	< 0.001	1.274	0.755-1.493	0.042

ACR-albumin creatinine ratio, CaPo4-calcium phosphate, HDL-high density lipoprotein, LDL-low density lipoprotein WHR waist-hip ratio, BP-blood pressure, ANC-absolute neutrophil count, ALC-absolute lymphocyte count, PNR-platelet neutrophil ratio, ACR-albumin creatinine ratio, GFR-glomerular filtration rate, HDL-high density lipoprotein, LDL-low density lipoprotein.

We assessed the impact of antiplatelet therapy on the kidney function of patients with chronic kidney disease. There was an overall improvement in kidney function as evidenced by reductions in the levels of markers of chronic kidney disease in the population. Apart from higher platelet counts, the use of antiplatelet agents was associated with reductions in the leucocyte and red cell population. While the value of inflammatory markers such as urine ACR uric acid, and lipids were diminished, the levels of the platelet neutrophil ratio were elevated resulting from antiplatelet therapy.

Improvements in kidney function and lipid profile resulting from antiplatelet therapy in this study manifested in minute and, significant patterns. The more prominent impact of antiplatelet therapy on the lipids agrees with previously reported findings that antiplatelet therapy also has anti-inflammatory and lipid-lowering properties [11, 14]. The antiplatelet, antioxidant, and anti-inflammatory effects of atorvastatin could therefore have contributed to the improvements in the lipid profile thus justifying the anti-lipids properties of the antiplatelet drugs [14]. The improvements in urine ACR agree with the findings by Taji *et al.* [21] who reported the antiproteinuric and anti-inflammatory properties of antiplatelet therapy in decreasing protein trafficking across the glomerular filtration barrier and protective effects on glomerulonephritis, respectively.

The statistically insignificant improvement in kidney function of participants probably gives credence to findings by Polzin *et al.* [22] who reported that aspirin decreases kidney function, attributing it to pharmacodynamic changes associated with the drug. They also opined that the glomerular filtration rate was positively correlated with the formation of thromboxane A_2, a potent vasoconstrictor and inducer of endothelial injury [22]. The upregulation of glycoprotein IIb/IIIa expression is also reported to contribute to this pattern [6]. This partly explains the possible adverse effects of renal ischemia induced by inhibitors of angiotensin II and angiotensin-converting enzymes in conditions associated with acute kidney function decline with or without background chronic kidney disease [23].

The antiplatelet actions of statins are mediated via reductions in the levels of low-density lipoprotein cholesterol (LDL-C) and this contributes to the inhibition of platelet function. Reductions in the levels of atheroma-enhancing LDL-C play a synergistic role with the aspirin-mediated reductions in platelet-dependent thromboxane A_2, both contributing to enhanced endothelial oxygen defense [24]. The inhibitory role of antiplatelets on lipid peroxidation and the suppression of endothelial lipase expression (a pro-atherosclerotic process) further enhances its protective effect on vascular endothelium, justifying their inhibitory actions on vascular remodeling [14, 25]. The blood pressure-lowering actions of antiplatelets are in agreement with findings of higher systolic BP mediated by an inflammation-associated vascular wall calcification in chronic kidney disease [25]. The higher risk of bleeding found in the relatively milder CKD stages (3/4) compared with CKD stage 5 mirrors previous works that found an inverse relationship between the CKD stage, and both the risk of bleeding and overall antiplatelet actions of these drugs [6, 8]. Chronic kidney disease presents with a bimodal risk profile that involves higher tendencies of bleeding and thrombus formation [6, 9]. Though this study didn't compare the risk of bleeding and thrombus formation between ASA and clopidogrel, it is worth noting that several previous comparative studies involving both drugs have reported greater bleeding risk with clopidogrel than aspirin [26]. However, clopidogrel use was more common than ASA among the elderly who mostly had the latter CKD stages, and in whom, the possibility of an age-dependent defect of the clotting system exists. The bleeding pattern could correlate with the antiplatelet status of these drugs. The higher bleeding episodes associated with clopidogrel in this study reflect the higher platelet count in participants who used aspirin. Thrombocytosis plays a major contributory role in the pathogenesis and occurrence of occlusion and restenosis experienced with aspirin in patients who had coronary and other vascular surgeries [14, 21, 22]. Li *et al.* [24] reported that antiplatelet-depended bleeding is positively related to aging and, HDL-C concentrations. The higher antiplatelet effects of aspirin and clopidogrel in females than in males are evident in the higher platelet count and PNR and, lower neutrophil count and hematocrit [27].

Thrombocytosis increases platelet reactivity and attenuates the responses to antiplatelet therapy hence the higher platelet count and platelet neutrophil ratio in association with lower hematocrit in participants that received aspirin

compared to those that had clopidogrel, attesting to the greater platelet count increasing actions of the former [28]. This has remained the significant basis on which the widely reported greater antiplatelet actions (recanalization and prevention of vascular occlusion) of clopidogrel are anchored [29, 30].

Thrombocytopenia which was more common in clopidogrel could partly account for the reported higher risk of bleeding with it, and this agrees with previous findings of higher bleeding rates with clopidogrel than aspirin, particularly in conditions associated with elevated blood pressure [26, 31]. The RAAS inhibitors particularly angiotensin II receptor blockers are reported to improve lipid peroxidation, and reduce platelet aggregation and hypercholesterolemia, β adrenergic blockers and calcium channel blockers only inhibit platelet aggregation and, thiazides are generally associated with little or no platelet-related actions [26].

Despite the known uric acid lowering and anti-inflammatory role of febuxostat used by all participants, the synergistic action of febuxostat and atorvastatin could have contributed to the significant reductions in serum uric acid as was found in this study. This had been previously reported by Zhang *et al.* [32]. The inhibitory role of atorvastatin on the occurrence of platelet-mediated accumulation of NADPH oxidase-derived reactive oxygen species buttresses the anti-inflammatory role of antiplatelets thereby drawing in statins as a major therapeutic class with inhibitory effects on platelet functions [33]. The higher risk of platelet reactivity associated with the accumulation of polyunsaturated fatty acids in the absence of anti-lipid therapy further buttresses the benefits of dual antiplatelet and anti-lipid therapy to minimize the consequences of higher platelet reactivity such as increased morbidity and mortality [10, 11].

The higher platelet count in females mirrors previous findings, some of which also reported higher platelet reactivity in females [34-36]. The lower platelet count reported in the aging population is observed in this study as a greater majority of the elderly population was receiving clopidogrel just as the majority of the young (with higher platelet count) received aspirin [37]. This is more so because a greater proportion of the participants received clopidogrel, a $P2Y_{12}$ inhibitor with a high HTPR. The synergy between advancing age and lower platelet count is expected to result in higher bleeding, particularly in the elderly population [29, 30]. This pattern would have been more likely had a $P2Y_{12}$ inhibitor with a low HTPR like ticagrelor or prasugrel been used [38].

The higher systolic blood pressure in participants that received clopidogrel compared with aspirin agrees with findings that clopidogrel prevents the downregulation of the sodium chloride cotransporter (NCC) and sodium-potassium 2-chloride (NK2Cl) cotransporter increases serum sodium concentration and, increases renal aquaporin [31]. The combined effect of these is blood pressure elevation, unlike findings that showed that aspirin exhibits a dose-independent blood pressure lowering [25]. The higher bleeding found in this study and in earlier reported findings could at least partly be accounted for by the higher blood pressure in clopidogrel users compared to aspirin users [31].

We had limitations in this study.

The observational design of the study limited the drawing of causal inferences. We couldn't determine platelet reactivity and hence its association with CKD severity. We couldn't conduct an echocardiogram for each patient on account of cost. Information given by participants concerning atrial fibrillation and its associated symptoms, and bleeding episodes may be less reliable. Results related to clopidogrel may not be related to newer agents in the class like ticagrelor and prasugrel. The strength of the study is anchored on the following: its two-center design, the fact that the participants were followed up with second sample analysis, the use of microalbuminuria as an additive to the serum creatinine and eGFR in determining the kidney function, and, the exclusion of patients on anticoagulants.

CONCLUSION

Antiplatelet therapy in the chronic kidney has become a significant component of an optimized treatment regimen for the prevention and management of cardiovascular, cerebrovascular, and, peripheral vascular diseases. Apart from inhibiting platelet function, they also possess anti-inflammatory and atheroma-reducing effects. The effects of antiplatelet therapy correlate negatively with the stages of CKD, being less effective in non-occlusive vascular diseases and, they mediate reductions in leucocyte and erythrocyte counts with increased platelet count thereby leading to a higher platelet neutrophil ratio, more so in females. While aspirin tends to mediate higher non-bleeding antiplatelet activity, clopidogrel mediates a higher risk of bleeding. The complementary anti-inflammatory, vascular endothelium-protecting role played by antilipids, statins, and uric acid lowering therapies has a synergistic beneficial effect on the vasculature and improvement in kidney function.

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