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THE EFFECT OF ANGIOTENSIN CONVERTING ENZYME INHIBITORS AND/OR ANGIOTENSIN RECEPTOR BLOCKERS VERSUS CALCIUM CHANNEL BLOCKERS ON FREQUENCY OF CARDIOVASCULAR EVENTS IN PATIENTS WITH HYPERTENSION AND CHRONIC KIDNEY DISEASE IN SUDAN

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ABSTRACT

Background: Patients with chronic kidney disease (CKD) have an elevated risk for major cardiovascular (CV) morbidity and mortality above that anticipated from their other accompanying risk factors. Reports from cumulative data suggest treatment of hypertension (HTN) would reduce the incidence of stroke by 35% -40%, myocardial infarction by 20%-24%, and heart failure>50%. The aim of this study was to compare the effect of angiotensin converting enzyme inhibitors (ACEIs) and/or angiotensin receptor blockers (ARBs) versus calcium channel blockers (CCBs) as used by physicians treating CKD patients who also had hypertension, on the degree of control of blood pressure and the frequency of occurrence of CV events over a span of about one year. **Methods:** The current study is a prospective study of 240 adult patients with CKD and HTN who were treated by their respective physicians in three major hospitals in Khartoum, Sudan. The patients were divided into two groups according to their medical records: those who were treated with ACEIs and/ or ARBs were designated as Group 1 (n=130) and those treated with CCBs designated as Group 2, (n = 110). Both groups were comparable in

demographic characteristics. The patients were reviewed in detail on two separate occasions about one year apart and labeled as 'Presentation 1 and 2' (P1 and P2); all the relevant medical data were recorded and the patients examined clinically. The response of the blood pressure to medical treatment was recorded and the renal and CV complications documented. The effects on the kidney functions were reported previously and in this communication we concentrate on the CV effects over one year of follow up (FU). **Results:** Overall the effects of ACEIs /ARBs on the degree of control of BP were comparable to those of CCBs up to one year of FU, there being no statistically significant differences between the mean systolic blood pressure (SBP) and mean of diastolic blood pressure (DBP) in P1 and P2. In the span of about one year, 36 of all the 240 (15%) patients in the study developed CV events. The CV events recorded were acute coronary syndrome (ACS), heart failure, atrial fibrillation and cerebrovascular accidents. The total of these events were 14 in Group 1 and 22 in Group 2 (p =0.023). Of special note was the observation that ischemic stroke occurred more often in Group 2 compared to Group 1 (7:2), (p=0.028). Ten of the 240 patients (4.2%) died due to causes attributed to CV events. Although there were more cases in Group 2 compared to Group 1 (7:3), the statistical difference was not significant (p = 0.832). **Conclusions:** We conclude that the use of ACEIs and/or ARBs resulted in comparable degree of control of blood pressure to the use of CCBs in patients with CKD and hypertension. However, CV events occurred more commonly in the group treated with CCBs compared to the group treated with ACEIs/ARBs in a FU period of just over one year.

KEYWORDS: angiotensin converting enzyme inhibitors, angiotensin receptor blockers, calcium chennal blockers, Hypertension, chronic kidney disease, cardiovascular complication.

INTRODUCTION

Chronic kidney disease (CKD) is defined as either measured estimated glomerular filtration rate (eGFR) abnormality or evidence of kidney damage such as, albuminuria, or both, for a minimum of three months.[1] In the United States, CKD affects more than 1 in 10 individuals and there is an increasing incidence and prevalence of renal failure with poor outcome and high costs and an even higher prevalence of earlier stages of CKD (approximately 80 times greater than end-stage kidney disease (ESKD) prevalence).[2] Unfortunately, there are no reliable statistics on CKD from most African countries. However, there is a general impression that it is at least three to four times more frequent than in developed countries.[3]

In Sudan there is no national registry for renal patients and the knowledge about epidemiology of CKD is very limited.[3] World Health Organization (WHO) estimated that in Sudan hypertension (HTN) affects 1 in 4 people suffering from non-communicable diseases (NCDs) such as cardiovascular disease, cancers, diabetes, and chronic respiratory diseases.[4] Hypertension has the highest prevalence among the major NCDs in Sudan, with a prevalence rate of 23.6 in Khartoum state.[4] Also WHO estimated NCDs account for 52% of all deaths in Sudan, with a distribution of 28% cardiovascular diseases, 6% cancers, 12% other NCDs, 3% chronic respiratory diseases, and 2% diabetes.[5] Patients with advanced CKD have an elevated risk for major cardiovascular (CV) morbidity and mortality above that anticipated from their other accompanying risk factors. Reports from cumulative data suggest treatment of HTN would reduce the incidence of stroke by 35% -40%, myocardial infarction by 20%-24%, and heart failure>50%.[6]

The Sudan Guidelines for the Management of Hypertension (SGMH) in adults recommend that the first line drug of pharmacological intervention in HTN is to start with a diuretic or one of the long-acting calcium channel blockers (CCBs)[7] This is based on the notion that African groups have low renin levels and therefore may not respond well to angiotensin converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs).[7] This notion is not based on any local studies in Sudan; rather it is adopted from the British Hypertension Society recommendations.[8] Yet, many physicians in Sudan start their hypertensive patients on ACEIs or ARBs and claim that they get good control of the HTN. The aim of this study was to compare the effect of ACEIs and/or ARBs versus CCBs as used by physicians treating CKD (stage 1-4) patients who also had HTN, on degree of control of blood pressure (BP) and the frequency of occurrence of CV events over a span of about one year.

METHODS

Study design

This is a prospective cohort study, to evaluate the effects of ACEIs and/ or ARBs versus CCBs on control of BP and frequency of CV events in CKD (stage 1-4) patients with HTN in Sudan. Patients under investigation were distributed to two groups according to the drug therapy for their HTN. Group one were patients treated by their respective physicians primarily with ACEIs and/or ARBs; while Group two were patients treated by their respective physicians primarily with CCBs. The study groups were CKD patients who were

designated for regular follow-up (FU) at three major hospitals in Khartoum: 'Ahmed Gasim Cardiac surgery and Renal Transplantation Center', 'Ibn-Sina Specialized Hospital', and Omdurman Teaching Hospital; over the period of two years (January 2018- January 2020).

Inclusion criteria

1. Adults patients (aged 18 years or more), who were diagnosed to have CKD stages 1 to 4; and who had high blood pressure (BP) that was treated by pharmaceutical agents by their respective physicians, were identified from the specialized clinics in the three hospitals named.
2. Patients on ACEIs and/or ARBs, with or without any other antihypertensive agent other than CCBs were identified as group one.
3. Patients on CCBs with or without any other antihypertensive agent other than ACEIs or ARBs were identified as group two.

Exclusion criteria

1. Patients diagnosed as having ESKD (CKD stage 5 or on a dialysis modality).
2. Patients on combination antihypertensive medications that included both ACEI/ARB and CCBs groups.
3. Patients not on regular follow-up or incomplete data records,

The main outcome points**:** To measure the effect of ACEIs and/ or ARBs versus CCBs on the control of BP; and the frequency of cardiovascular (CV) events in both groups during the follow up period.

Ethical approval

Was obtained from State Ministry of Health Research Department, and from respective hospital authorities. Recruited patients signed informed consent forms.

Sample size

The required sample size was estimated using the formula.[9]

$$(n = \frac{z^2 pq}{d^2})$$

Where (n) is sample size, (z) the normal standard deviate (z =1.96), (p) the frequency of occurrence of CKD patients on antihypertensive = 0.8, (q) the frequency of non occurrence CKD patients on antihypertensive (1- p) =1-0.8= 0.2 and (d) is level of precision (0.05).

n = 1.96x1.96x 0.8x0.2 / 0.05/ 0.05 = 245.86 ≈246

Thus, the sample size needed was 123 patients for each limb of the study (groups one and two), total estimated sample size 246 adult patients. An increment of 25% (about 60 patients) was added to account for dropouts: total required sample 300 patients (150 for each group).

Data collection and follow-up

Personal interview, checklist and review of hospital data results were used for assessment the effect of ACEIs and/or ARBs therapy on the one hand, versus patients using CCBs as antihypertensive drugs on the other hand, over the study period.

Medical history was obtained by direct interview in all patients. Cigarette smoking habits were collected by self-report (non smoker, passive smoker, slight, or moderate to heavy smoker). Measurements of height (Cm), weight (Kg), and blood pressure (BP) using a mercury sphygmomanometer after 5 min in a seated position was obtained during each clinical examination.

Heart rate (HR) and left ventricular ejection fraction using echocardiography were measured at least once a year during the study period. Standard criteria were used to determine the development of heart failure, atrial fibrillation, acute coronary syndrome, myocardial infarction, ischemic stroke, or hemorrhagic stroke. In patients who died the cause of death was identified as far as possible. Sudden death and death after developing seizures and/or stroke were considered as death due to CV events.

Statistical analysis

Numerical data was represented as mean and standard deviation and categorical data as frequency (count) and relative frequency (percentage). To compare categorical data, we performed a chi-square test. We made comparisons between quantitative variables using the Student t-test. We considered P values less than 0.05 as statistically significant.

RESULTS

Patient's characteristics and antihypertensive drugs

Out of 320 CKD patients approached, 300 agreed to participate in the study and responded for the first follow-up interview and data collection. The second evaluation was done after completion of one year time from the first evaluation. Almost all patients were approached to respond to the second interview and data collection. By the end of 16 months from the first

visit 240 (80%) of the patients were able to attend both first and second year visits and the data was analyzed.

Of the 240 patients who completed the study, 130 (54%) were from Group 1 (treated with ACEIs and/or ARBs drugs) and 110 (46%) were from Group 2 (treated with CCBs).

The demographic characteristics of both groups are shown in Table 1. There were no significant differences between the two groups in terms of gender distribution, employment or smoking habits.

Table 1: Comparison between some demographic characteristics and smoking habits between the two study groups (Group 1: patients treated with ACEs /ARBs; Group 2 patients treated with CCBs). Statistics chi-square (n=240).

Parameters	**Subgroup**	**Group1 (n =130)**	**Group2 (n=110)**	**p-value**
		ACEIs / ARBs n (%)	**CCBs** n (%)	
Gender	Male	66 (58.4)	47 (41.6)	0.133
	Female	64 (50.4)	63 (49.6)	
Employment	Employed	47 (52.2)	43 (47.8)	0.369
	Not-employed	83 (55.3)	67 (44.7)	
Smoking habits	Non smoker	110 (54.2)	93 (45.8)	0.864
	Passive smoker	15 (51.7)	14 (48.3)	
	Smoker	5 (62.5)	3 (37.5)	

ACEIs = angiotensin converting enzyme inhibitors. **ARBs=**angiotensin receptor blockers.

CCBs = calcium channel blockers.

There were no significant differences between two groups in the mean follow-up period, age distribution, weight or height of patients in the two groups (Table 2).

Table 2: Comparison between the two groups in primary standardization variables.

Parameters	**ACEIs / ARBs Group**		**CCBs Group**		**p -value**
	Mean	SD	Mean	SD	
Follow up period (Mons)	16.05	3.03	15.39	2.69	0.081
Age (years)	54.16	16.05	54.29	14.31	0.948
Height (Cm)	166.89	10.05	165.89	7.5	0.999
Weight (Kg) P1	85.09	19.87	80.3	17	0.458
Weight (Kg) P2	81	15.2	82	13.8	0.895

Table 3 shows comparison between the two groups in measurements in various parameters during the first presentation in the study (P1) and the second presentation (P2) that occurred after at least one year from the first presentation. Values that reached statistical difference are highlighted in *italic and bold.*

Table 3: Differences between the two groups in various study variables.

Parameters	**ACEIs / ARBs Group**		**CCBs Group**		**p -value**
	Mean	**SD**	**Mean**	**SD**	
SBP P1	*138.29*	*17.96*	*146.22*	*18.45*	*0.001*
SBP P2	144	18.7	140	16	0.110
DBP P1	80.77	9.55	77	10	0.188
DBP P2	83.5	10.38	81.5	9	0.118
Serum creatinine P1	*1.98*	*0.98*	*2.42*	*1.35*	*0.005*
Serum creatinine P2	*2.37*	*1.08*	*2.89*	*1.39*	*0.001*
eGFR P1	59.82	28.66	55.73	30.59	0.287
eGFR P2	*52.11*	*27.68*	*43.75*	*27.9*	*0.021*
Serum K P1	*4.3*	*0.596*	*4.1*	*0.595*	*0.01*
Serum K P2	4.26	0.6	4.12	0.629	0.084
Total Cholesterol P1	137.05	32.43	144.28	31.28	0.08
Total Cholesterol P2	*137.74*	*33.99*	*149.24*	*34.47*	*0.01*
Urine protein (g/day) P1	*3.4*	*1.4*	*4.98*	*1.84*	*0.001*
Urine protein (g/day) P2	*3.79*	*1.49*	*5.09*	*1.69*	*0.001*

Abbreviations: ACEIs = angiotensin converting enzyme inhibitors; **ARBs**=angiotensin receptor blockers; **CCBs** = calcium channel blockers; **DBP**= diastolic blood pressure; **EF**= ejection fraction; **HR** = heart rate; **P1**= first presentation to the study; **P2**=second presentation to the study; **SBP** = systolic blood pressure.

As shown in Table 3, the mean systolic blood pressure (SBP) was significantly lower in Group 1 (ACEI/ARBs Group) compared to Group 2 (CCBs Group) in the first presentation (P1) (P=0.001); but this did not extend to the mean SBP in the second presentation period (P2) or to the mean diastolic blood pressure (DBP) in both presentation periods (P1 and P2). Thus there was no significant difference in the degree of control of BP between the two groups. The mean serum creatinine, however, was consistently lower in Group 1 compared to Group 2 in both periods of assessment, P1 and P2. The estimated glomarular filtration rate (eGFR) was not significantly different between the two groups during P1, but during P2 the eGFR was significantly higher in Group 1 (P=0.021) (see table 3). The serum potassium was

higher in Group 1 during P1 (P=0.01), but this difference was not maintained during P2 (P=0.084). The total serum cholesterol was not much different between the two groups in P1, but became significantly lower in Group 1 in P2 assessment (P=0.01). The urinary protein excretion (grams / day) was significantly lower in Group 1 during both P1 and P2 (P=0.001).

The mean of heart rate was not significantly different between two groups during P1and P2; however, the means of ejection fraction were significantly different, being consistently higher in Group 1 compared to Group 2 in both periods of assessment (Table 4).

Table 4: Differences between the heart rate (HR) and ejection fraction (EF) between the two groups.

Parameters	ACEIs / ARBs Group		CCBs Group		p -value
	Mean	SD	Mean	SD	
HR P1	78	5.4	78.5	5	0.602
HR P2	77	4	78.1	4.5	0.406
EF P1	*56.35*	*2.8*	*55.40*	*4*	*0.033*
EF P2	*56.45*	*2.6*	*55.53*	*4.5*	*0.049*

EF= ejection fraction; **HR** = heart rate; **P1**= first presentation to the study; **P2**=second presentation to the study.

Thirty six of all the 240 (15%) patients in the study developed CV events. The overall frequency of CV events during a mean follow up period of 16.05 and 15.39 months was significantly higher in Group 2 (p = 0.023). This was mostly due to the event of ischemic stroke which occurred more frequently in Group 2 at a p value of 0.028 (Table 5).

Table 5: Development of cardiovascular events in both groups after a span of about one year.

Type of cardiovascular complication detected	Antihypertensive drugs		p-value
	ACEIs -ARBs Group	CCBs Group	
	n (%)	n (%)	
Acute coronary syndrome	6 (4.6%)	10 (9%)	0.130
Heart failure	3 (2.3%)	4 (3.6%)	0.408
Atrial fibrillation	2 (1.5%)	0	0.292
Ischemic stroke	2 (1.5%)	7 (6.4%)	0.028
Hemorrhagic stroke	1 (0.8%)	1 (0.9%)	-
Total	14 (10.8%)	22 (20%)	0.023

By the end of the study 10 (4.2%) of the 240 study patients had died due to cardiovascular complications. Table 6 shows that although more patients died in the CCB group, yet the difference between the two groups was not statistically significant (p=0.832).

Table 6: Death due to cardiovascular events in the two study groups.

Mortality associated with cardiovascular events	Antihypertensive drugs		p-value
	ACEIs -ARBs Group n (%)	CCBs Group n (%)	
Acute coronary syndrome	1 (0.7%)	2 (1.8%)	0.694
Sudden death (Cardiac arrest)	1 (0.7%)	3 (2.7%)	0.522
Ischemic stroke	1 (0.7%)	1 (0.9%)	0.612
Heart failure	0	1 (0.9%)	0.629
Total	3 (2.3%)	7 (6.3%)	0.832

P-value less than 0.05 were considered statistically significant

DISCUSSION

A previous study in Sudanese patients for the effectiveness of ACEI/ARBs as mono therapy in controlling high blood pressure, found that 79% of the population involved in the study had a controlled blood pressure.[4] The sample size in that study consisted of 95 adult patients and no comparison was held with CCBs use.[4] We have recently published the first part of this study in which we showed that the control of blood pressure was not statistically different between patients treated with ACEs/ARBs compared to those treated primarily with CCBs up to one year of follow-up (FU); however, more patients progressed to higher classes of CKD, and proteinuria was more pronounced in the CCBs group.[10] These results are summarized in Table 3.

The results of this study show that the effects of ACEIs/ARBs compared to CCBS on CV events in both study groups within one year of FU. The data showed occurrence of more CV complications in patients treated primarily with CCBs as compared to patients treated primarily with ACEIs / ARBs over one year of FU. This was indicated by the mean of ejection fraction being consistently higher in Group 1 (ACEIs/ARBs) compared to Group 2 (CCBs) in both periods of assessment, P1 and P2.

When considering the frequency of occurrence of CV events in both groups over the FU period, only ischemic stroke occurred significantly more frequently in the CCBs group

compared to the ACEs/ARBs group (p=0.028). The overall cardiovascular mortality was higher in the CCBs group, but the difference did not reach statistical significance (Table 6).

In a meta-analysis study the pooled analysis of CKD showed a reduction in the risk for myocardial infarction, heart failure, and total CV outcomes when renin-angiotensin System (RAS) blockade compared with placebo.[11] RAS blockade decreases the risk for CV outcomes and heart failure when compared with control therapy.[11] Another study concluded that the ARB (Valsartan) had beneficial effects in patients with heart failure and CKD.[12]

Similarly, it was shown that the use of ACE inhibitors or ARBs in people with CKD reduces the risk of kidney failure and cardiovascular events, and the risk for all-cause mortality and of CV death [13]. Another meta-analysis study recommended the use of ACEIs/ARBs in patients with non dialysis-dependent CKD as it was associated with improved survival.[14]

There was more hypercholesterolemia in the CCBs group compared to the ACEIs/ARBs group by the end of this study. This may have some implications on causing more damage to the vascular system in the CCBs group over the follow-up period because of the known association of hyperlipidemia with atherosclerosis, and it has been suggested that targeting of lipoproteins may be important to decrease CVD in CKD patients,[15] This risk of side-effects associated with RAAS blockade, such as hyperkalemia, that may be exaggerated by decrease GFR[16] did not seem to be a big concern in this study as the mean serum potassium remained within the acceptable range in both groups. However, hyperkalemia is a known complication of ACEIs/ARBs treatment in CKD patients and it is recommended that potassium levels should be monitored closely in such patients.[17]

Sudanese Population has clear genetic variability.[18] There are groups who could be grouped together as populations originally from the northeastern parts of the Country (North-Nubians, mixed Arab-African decedents residing in North and Central Sudan, and the Beja tribes mostly in Eastern Sudan). Another broad group would be populations originally from Western and Southern Sudan (Nilotic tribes, Darfur and South-Kordofan populations). This ethnic differentiation is mainly caused by a large Eurasian ancestry component of the northeast populations likely driven by migration of Middle Eastern groups followed by admixture that affected the local populations in a north-to-south succession of events.[18]

Genetic evidence points to an early admixture event in the Nubians, concurrent with historical contact between North Sudanese and Arab groups.[18] Heart diseases are an important cause of morbidity and mortality in Sudan.[19] The WHO 2002 estimates for ischemic heart disease (IHD) in Sudan,[20] based on the Global Burden of Disease study [21] are an age-adjusted mortality rate of 205/100 000 and an age-adjusted DALYs of 1185/100 000 population. Such estimates need to be validated by local surveys.[21]

We conclude that ACEIs or ARBs when used to treat cardiovascular complication associated with CKD patients in all the stage 1 to 4, had comparable effect on the control of blood pressure, and in this study ACEIs/ARBs were not inferior to CCBs as far as controlling the blood pressure was concerned. However, ACEIs/ARBs seemed to have been associated with less cardiovascular complications compared to CCBs used over one year of follow-up.

It seems important to have another study on the same subject with considerations of the ethnic groups in Sudan.

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