

Original Research

Anti-hypertensive medicines prescribing for medical outpatients in a premier teaching hospital in Nigeria: a probable shift of paradigm

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ABSTRACT*

Background: Previous studies of anti-hypertensive medicines utilization pattern in Nigeria showed that Angiotensin converting enzyme inhibitors (ACEIs) were often the least prescribed. However, the appropriate use of ACEIs in the black population achieves good blood pressure control and provides additional long term cardio- and renovascular protection benefits.

Objective: To assess the current utilization pattern of anti-hypertensive medicines with specific emphasis on identifying possible shift in the frequency of use of ACEIs.

Methods: A prospective cross-sectional assessment of the current utilization pattern of anti-hypertensive medicines was conducted among 300 randomly selected cohort at a 900-bed premier Teaching Hospital located in Ibadan, Southwestern Nigeria. The current utilization pattern was compared with the results of a study conducted at the same site and published 10 years ago.

Results: Of the 300 random cohorts, a majority (79%) were females (237) with mean age 58.7 years (SD=2.81 years). Stage 2 hypertension was the most frequent diagnosis (54.3%). The utilization of ACEIs and long acting CCB (amlodipine) significantly increased from 8.6% and 21% (Ten years ago) to 29.93% and 36.68% respectively ($p < 0.0001$). The use of thiazide diuretic and methyl dopa declined significantly from 39.4% and 23.3% (Ten years ago) to 16.12% and 9.7% respectively ($p < 0.0001$). Adverse drug reactions due to ACEIs were documented in 1.5% (3), while laboratory monitoring of serum potassium, urea and creatinine was conducted in only 37% (111) of cohort. Potentially harmful drug-drug interactions were identified in 25% (75) of cohorts, and the most frequent were ACEIs + NSAIDs (53.3%), ACEIs + amiloride / hydrochlorothiazide (22.6%).

Conclusions: Anti-hypertensive medicines utilization has significantly shifted towards the increased use of ACEIs and long acting dihydropyridine CCBs. The use of thiazides and methyl dopa has declined significantly. Physicians appeared more cognizant of the long term cardio- and renovascular benefits inherent in using ACEIs in a high cardiovascular risk group such as black hypertensive.

Keywords: Antihypertensive Agents; Angiotensin-Converting Enzyme Inhibitors; Calcium Channel Blockers; Drug Utilization; Nigeria

INTRODUCTION

Untreated or poorly treated hypertension is a known predictor of negative coronary artery and cerebrovascular events, and increased morbidity and mortality associated with cardiovascular diseases.¹⁻³ Hence, adequate control of blood pressure levels to a defined target with appropriate, effective, safe and convenient anti-hypertensive medicines is an important determinant of cardiovascular risk reduction among hypertensive patients.⁴⁻⁶ Hypertension is an underdiagnosed chronic disease that remains a daunting public health challenge in Nigeria. Notwithstanding a reported prevalence 10% in both urban and rural settings, awareness of blood pressure status remain low, and patients who are lucky to be diagnosed in a formal health care setting often present late and with chronic complications associated with end-organ damage due to malignant hypertension.^{7,8}

Several studies including one that we conducted and published about ten years ago (June-August 2002) have documented a consistent trend in the prescribing pattern of anti-hypertensive medicines in Nigeria.⁹ The results often shows thiazide diuretics as the most prescribed anti-hypertensive medicines, followed by short-acting dihydropyridine calcium channel blockers and centrally-acting agent such as methyl dopa. Angiotensin converting enzyme inhibitors were often one of the least prescribed anti-hypertensive medicine classes¹⁰⁻¹⁴, while angiotensin receptor blockers were rarely prescribed and used for the management of hypertension in Nigeria at that period. Our previous study of anti-hypertensive medicines utilization pattern about 10 years ago showed that ACEIs and beta blockers were the least frequently prescribed.⁹ The sparse prescribing of ACEIs was associated with the reported relatively lower reduction of blood pressure by ACEIs in the black population especially as monotherapy.^{15,16} However, this view was challenged by a number of studies which showed that blood pressure response to ACEIs is probably blind to race but sensitive to patients' factors such as age, body mass index, high entry/baseline blood pressure levels and severe hypertension due to delay in seeking treatment, presence of co-morbidity such as diabetes mellitus and inequity in the access to functional health care.^{17,18} Furthermore, the appropriate use of the combination of ACEIs with thiazide diuretics in black hypertensive population have been shown to achieve good blood pressure control and improved cardio- and renovascular protection.^{19,20} Hence, ACEIs appear to provide additional long term

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benefits beyond adequate control of blood pressures to a defined target. This is important for the black hypertensive patients that are usually at the highest risk of poor prognosis associated with adverse cardiovascular and cerebrovascular events, and higher prevalence of malignant hypertension, chronic kidney disease, left ventricular hypertrophy, congestive heart failure, ischemic heart disease and myocardial infarction.^{21,22} Despite the documented evidence of therapeutic benefits associated with the use of ACEIs in black hypertensive patients, studies continue to show that they are one of the least frequently prescribed in Nigeria. The objective of the study was to assess the current utilization of anti-hypertensive medicines with a specific emphasis on identifying possible shift in the frequency of use of ACEIs

METHODS

A cross-sectional assessment of the antihypertensive medicines utilization was conducted between 1st June and 31st June 2012 among 300 randomly selected hypertensive patients diagnosed and managed at the Medical Outpatient Clinic of the University College Hospital (UCH), Ibadan. This is a 900-bed premier Teaching Hospital with medical residents located in Ibadan, Southwestern Nigeria. It is affiliated with the University of Ibadan and serves as a major tertiary referral center in Nigeria. UCH has fifty-two service and clinical departments and runs seventy-five consultative outpatient clinics per week in forty-five specialties and sub-specialties. Ibadan, where the study site is located, is one of the largest cities in sub-Saharan Africa and consisted of 11 local government areas. It has an estimated population of 2.5 million consisting of varied backgrounds and ethnicities. Ethical clearance and approval of the study protocols was granted by the Joint University of Ibadan/University College Hospital Research and Ethics Committee. All the patients who presented at the Hypertension unit of the Medical Outpatient Clinics at the study site within the study period were included and constituted the sample frame. The average number of patients seen at the weekly Hypertension clinic was 90. Patient selection was done after clinic appointment cards had been collected and patients were seated in the waiting area. Seventy-five clinic appointment cards were randomly drawn weekly from the collected pool. The case notes of the selected seventy five patients were retrieved for data extraction after physicians' consultation.

Data were extracted from the case notes of the randomly selected 300 patients using pre-tested data collection instruments. The first draft of the instrument was pre-tested with the case notes of ten patients at the study site to assess completeness and relevance of data capture. The final draft of the instrument was modified based on the results of pre-testing, but the data collected during pre-testing was not included in the final result. The data collected from patients' case notes were:

- i) Patients' hospital number, Age and Gender

- ii) Systolic and diastolic blood pressure readings at first clinic attendance.
- iii) Systolic and diastolic blood pressure readings at last clinic attendance
- iv) Hypertension diagnosis and co-existing diseases.
- v) Antihypertensive drugs prescribed with specific focus on ACEIs and ARBs.
- vi) Documentation of adverse drug reactions associated with ACEIs /ARBs
- vii) Baseline and follow-up laboratory monitoring for serum potassium, urea and creatinine
- viii) Monthly cost of antihypertensive drugs and Monthly cost of ACE inhibitors and ARBs.
- ix) Potential Drug-drug interactions and contra-indications

The classification of hypertension diagnosis was based on the Seventh report of the Joint National Committee for the prevention, detection, evaluation and treatment of hypertension, and the average systolic / diastolic blood pressure reading recorded at the first clinic attendance were used for the hypertension diagnosis. The documented systolic and diastolic blood pressure levels at the last clinic attendance was adjudged as adequately controlled if they are less than 140/90 mmHg.²³ The appropriateness of the antihypertensive drug doses, dosing interval and potentially harmful drug interactions were assessed using the British National Formulary (March, 2010).²⁴ Data analysis was carried out with descriptive and chi-square statistics using Statistical Program for the Social Sciences (SPSS) version 15.0 with $p < 0.05$ considered significant.

RESULTS

The clinico-demographic profile of the random 300 cohort studied is as shown in Table 1. The majority (79%) of the cohort were females (237) with mean age of 58.66 (SD=2.81) years (minimum-maximum, 33-97 years). Stage 2 hypertension was the most frequent diagnosis (54.3%) followed by stage 1 hypertension (27.7%) and isolated systolic hypertension (18%). The most frequently diagnosed co-existing diseases were osteoarthritis (38.2%), malaria (22.92%) and diabetes mellitus (20.14%). Overall, blood pressure control was documented as adequate in 33% (96) of cohort.

Calcium channel blockers (36.68%) and Angiotensin converting enzyme inhibitors (ACEIs) (29.93%) were the most frequently prescribed antihypertensive medicine classes. Diuretics, centrally acting agents, and angiotensin II receptor blockers (ARBs) were prescribed in 16.12%, 9.7% and 3.13% of cohort respectively (Table 2).

Amlodipine (78.5%) and ramipril (55.5%) were the most frequently prescribed calcium channel blocker and ACEIs respectively. Amloride/hydrochlorothiazide combination accounted for 86.73% of prescribed thiazide diuretics, while losartan accounted for 94.74% of the ARBs prescribed. Methyl dopa, atenolol and spironolactone were the only centrally acting agent, beta blocker and aldosterone antagonist prescribed

Table 1. Clinic and demographic profile of hypertensive patients.			
Age (years) (n = 300)	Mean age male		66.06 (SD=3.11)
	Mean age female		58.66 (SD=2.81)
		n	%
Gender (n = 300)	Female	237	79
	Male	63	21
Hypertension diagnoses	Stage 2 hypertension	163	54.3
	Stage 1 hypertension	83	27.7
	Isolated systolic hypertension	54	18.0
Co-morbidity (n = 144)	Osteoarthritis	55	38.2
	Malaria	33	22.92
	Diabetes mellitus	29	20.10
	Peptic ulcer disease	9	6.25
	Congestive heart failure	8	5.6
	Asthma	2	1.39
	Psychosis	2	1.39
	Impaired vision	2	1.39
	Renal dysfunction	1	0.69
	Stroke	1	0.69
	Left ventricular hypertrophy	1	0.69
	Benign prostatic hyperplasia	1	0.69
Laboratory Monitoring Tests (n = 300) (Electrolytes, urea and creatinine levels)	None	189	63
	Baseline only	104	34.7
	Baseline & follow up	7	2.3
Cost of anti-hypertensive medicines	Mean monthly cost of anti-hypertensive medicines		N 1,784.71
	Mean monthly cost of ACE inhibitors		N 1,114.53

in their respective classes (Table 2). Aspirin (25.2%), clopidogrel (12.5%) and Non-steroidal Anti-inflammatory Drugs (NSAIDs) were the most frequently non-anti-hypertensive medicines (Table 2). All patients made out of pocket payments for their medicines. The mean monthly cost of antihypertensive medicines was NGN1,784.71 ((USD11.09), while the mean monthly cost of ACEIs and ARBs were NGN1,114.5 (USD6.92) and NGN1,376.47 (USD8.55) respectively. The antihypertensive and non-antihypertensive medicines' doses and dosing interval, as documented, were adequate and no contraindication was identified among the cohort studied.

Adverse drug reactions (ADRs) due to ACE1s were documented in 1.5% (3) of cohort with dry cough being the only ADR documented. There was no documentation of ADR for ARBs. Overall, laboratory monitoring of serum potassium, urea and creatinine was conducted in 37% (111) of cohorts. Of these (111), 93.7% (104) had baseline testing of these parameters, while only 6.3% (7) had both baseline and one follow-up testing conducted. Potentially harmful drug-drug interactions were identified in 25% (75) of cohorts. The most frequent potentially-harmful interactions were ACEIs + NSAIDs (53.3%), ACEIs + amiloride / hydrochlorothiazide (22.6%), ACEIs + spironolactone (9.3%), ARBs + amiloride/hydrochlorothiazide (5.3%) and ARBs + spironolactone (5.3%) (Table 2).

DISCUSSION

The findings of our present study suggest a significant shift in anti-hypertensive prescribing

pattern with a considerable increase in the frequency of use of ACEIs and long acting dihydropyridine CCBs. On the other hand we observed a significant downward spiral in the frequency of use of thiazide diuretics (39.4%)⁹ (ten year ago) to 16.12%. These findings stand in sharp contrast to the anti-hypertensive medicine utilization pattern that we reported from the same study site about 10 years ago.⁹ The ACEIs were one of the least frequently prescribed accounting for only 8.6% of prescribed anti-hypertensive medicines 10 years ago⁹; while the present study showed that the frequency of use has significantly risen to 29.9% (p<0.0001). This is an important prescribing shift that is likely to contribute to reducing the negative cardiovascular events associated with malignant hypertension, and long term survival among hypertensive patients in Nigeria. The paradigm shift towards increased prescribing of ACEIs probably suggest that clinicians are more cognizant of the long term cardio- and renovascular benefits inherent in using ACEIs especially in a high cardiovascular risk group such as black hypertensive. However, we believe this is not readily clear and will require further studies to identify the factors underlining the significant increase in the prescribing of ACEIs. In addition, the use of thiazide diuretics as first line anti-hypertensive agents among Nigerians with documented high co-morbidities such as diabetes appeared inappropriate ab initio. This is because the landmark Anti-hypertensive and Lipid Lowering Treatment to prevent Heart Attack Trial (ALLHAT) upon which the recommendation to use thiazides as first line agent is premised reported an increased incidence of hypokalemia, hyperglycemia and new-onset diabetes mellitus with thiazides relative to other anti-hypertensive agents such as ACEIs,

Table 2. Pattern of use of antihypertensive and non-antihypertensive drugs.

Antihypertensive drugs (n = 608)	number	%
Calcium channel blockers (n=223)		36.68
Amlodipine	175	78.5
Nifedipine	48	21.5
ACE Inhibitors (n=182)		29.93
Ramipril	101	55.5
Lisinopril	59	32.4
Enalapril	22	12.1
Thiazide diuretics (n=98)		16.12
Amiloride + hydrochlorothiazide	85	86.7
Hydrochlorothiazide	13	13.3
Centrally acting agents (n=59)		9.7
Methyldopa	59	100
ARB (n=19)		3.13
Losartan	18	94.7
Valsartan	1	5.3
Beta blockers (n=15)		2.47
Atenolol	15	100
Aldosterone antagonist (n=12)		1.97
Spironolactone	12	100
Non-antihypertensive medicines (n=360)		
Aspirin	95	26.39
Clopidogrel	73	20.28
Diclofenac	37	10.28
Artemeter + lumefantrine	33	9.17
Metformin	25	6.94
Glucosamine + chondroitin	14	3.89
Glimepiride	14	3.89
Anxiolytics	11	3.06
Calcium lactate	10	2.78
Neurobion	10	2.78
Meloxicam	8	2.21
Mist.Magnesium Trisilicate	6	1.67
Glibenclamide	5	1.39
Orphenadrine	5	1.39
Pioglitazone	4	1.11
Antipsychotics	4	1.11
Omeprazole	3	0.83
Digoxin	3	0.83

ARBs and CCBs.²⁵ Furthermore, other studies have also reported that the incidence of new-onset diabetes mellitus is highest with thiazides and lowest with ACEIs, ARBs.²⁶⁻²⁹ Besides, the increased incidence of thiazide-associated hypokalemia is a known contributor to insulin resistance and poor glucose utilization by target tissues.^{30,31} The long term macro- and microvascular complications associated with this biochemical derangement though well documented are open to confounding by the duration of follow-up and thus may not be readily apparent. Therefore, the shift in anti-hypertensive medicine prescribing pattern is a significant break from the past and it appeared to be based on evidence of obtainable short and long term therapeutic benefits.

The significant prescribing shift from the short acting dihydropyridine CCBs [Nifedipine: 88.2% (past) versus 21.5% (current)] reported 10 years ago⁹ to a long acting CCBs [amlodipine: 11.8% (past) versus 78.5% (current)] ($p < 0.0001$) also suggest physicians' greater awareness of the importance of using medications with less frequent dosing regimen to improve medication adherence, smoother and better blood pressure control. This is more likely to contribute to the achievement of optimal therapeutic outcomes among patients with hypertension.³²

The decline in the frequency of use of methyldopa between 10 years ago (23.3%)⁹ and now (9.7%) is also significant ($p < 0.0001$). Indeed, the current low frequency of methyldopa's use is consistent with its widely reported low or non-usage due to poor safety profile in other countries.²³ The widespread availability and cheap acquisition cost of methyldopa, and probably prescribing dogma passed from generations of prescribers upon which the past considerable use of methyldopa was premised appeared to have waned ten years down the line. In addition, the increasing widespread availability of affordable generic version of anti-hypertensive medicine options with relatively better safety profiles appeared to contribute to the considerable decline in the use of methyldopa. Furthermore, the consideration of the negative impact of low patient adherence associated with medicines with poor ADRs profile such as methyldopa on cardiovascular outcomes in a high risk group such as Nigerian hypertensives may also be contributory.

The lack of an effective ADR monitoring, prevention, detection and documentation system which we reported ten years ago continue to be a sad phenomenon of health care delivery in Nigeria. It is thus unsurprising that ADRs associated with ACEIs and ARBs were documented in only 1.5% of cohorts. This observation is not indicative of low frequency of ADRs but suggest lack of a functional ADRs detection and documentation system. Our position is further supported by the results of the baseline and follow-up laboratory monitoring which showed that majority of patients prescribed ACEIs and ARBs were not adequately monitored with relevant laboratory parameters such serum potassium, urea and creatinine. Yet potentially harmful drug-drug interactions the impact of which could have been easily tracked with relevant laboratory parameters were identified in a majority (75%) of patients. The co-prescribing of NSAIDs and ACEIs in about half of the cohorts without close monitoring required to exclude any potential harms to patients appeared inappropriate and is potentially life-threatening.^{33,34} The reduced anti-hypertensive efficacy of medicine classes such as ACEIs and thiazide diuretics when co-prescribed on a chronic basis with NSAIDs is well documented.^{35,36} However, the depth of the contribution of this drug-drug interactions to the observed low level of blood pressure control among the cohorts studied is not readily clear. In addition, the continuing high frequency of co-prescribing of ACEIs and potassium-sparing diuretics such as amiloride + hydrochlorothiazide or aldosterone antagonist such as spironolactone may expose patients to negative cardiovascular events associated with hyperkalemia, especially with the observed poor baseline and follow-up monitoring of serum potassium and creatinine levels.

The result of this study is limited by the fact that patients were sampled at the major tertiary hospital (UCH) in Nigeria. However, the choice of UCH was because it is the premier teaching/tertiary hospital, and a major referral center for other health care centers in Nigeria. Furthermore, it is a major site for

undergraduate and post-graduate residency training of physicians. Therefore, the tutelage and practices at UCH as a determinant of clinical practices and prescribing habits of physicians in other parts, or settings, in Nigeria was strongly considered. In addition, the lack of an integrated functional monitoring and documentation system to track patients' progress and long term outcomes of medication use in chronic medical conditions such as hypertension made such long term assessment almost impossible. Furthermore, patient selection appeared skewed towards the female gender. However, the mid-year random sampling strategy, a valid procedure commonly used in epidemiological study, may mitigate probable selection bias. In addition, the observed distribution pattern may also suggest that female hypertensive patients are probably more adherent with clinic attendance or perhaps seeking medical help for the management of hypertension at the study site in relatively greater proportion. This is a probable focus for future research.

CONCLUSIONS

Physicians' prescribing of anti-hypertensive medicines in Nigeria appeared to have significantly shift towards increased use of ACEIs and long acting dihydropyridine CCBs, and decline in the use of thiazide diuretics and methyldopa. However, baseline and follow-up monitoring of relevant laboratory parameters to preclude potentially-harmful adverse events and effective detection and documentation of ADRs remain inadequate.

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CONFLICT OF INTEREST

The authors declare no conflict of interest

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PRESCRIPCIÓN DE ANTIHIPERTENSIVOS PARA PACIENTES MÉDICOS AMBULATORIOS DE UN HOSPITAL UNIVERSITARIO EN NIGERIA: PROBABLE CAMBIO DE PARADIGMA

RESUMEN

Antecedentes: anteriores estudios de patrones de utilización de antihipertensivos en Nigeria mostraron que los inhibidores de la enzima convertidora de angiotensina (IECA) eran a menudo los menos prescritos. Sin embargo, el uso apropiado de IECA en la población negra alcanza buen control de presión arterial y proporciona protección adicional cardio y renovascular a largo plazo.

Objetivo: Evaluar el patrón actual de utilización de antihipertensivos con especial énfasis en identificar potenciales cambios de frecuencia de uso de IECA.

Métodos: Se realizó una evaluación transversal prospectiva de la actual utilización de antihipertensivos entre una cohorte de 300 individuos aleatoriamente seleccionados en un hospital universitario localizado en Ibadan, Sur-Oeste de Nigeria. Se comparó el patrón actual de utilización de resultados con un estudio realizado en la misma localización hace 10 años. **Resultados:** De los 300 individuos aleatorizados, la mayoría (79%) eran mujeres (237) con una edad media de 58,7 años (DE=2,81). El diagnóstico más frecuente era la hipertensión en Estado 2 (54,3%). La utilización de IECA y bloqueantes de canales de calcio (BCC) de larga acción (amlodipina) se aumentó significativamente de 8,6% y 21% (hace 10 años) a 29,93% y 36,68% respectivamente ($p < 0.0001$). El uso de diuréticos tiazídicos y metildopa se redujo significativamente de 39,4% y 23,3% (hace 10 años) a 16,12% y 9,7% respectivamente ($p < 0.0001$). Se documentaron reacciones adversas debidas a IECA en el 1,5% (3) de los casos, mientras que se realizaron solo un 37% (111) de monitorizaciones laboratoriales de potasio sérico, urea y creatinina. Se identificaron interacciones medicamentosas potencialmente dañinas en el 25% (75) siendo las más frecuentes las de IECA + AINE (53,3%), IECA + amilorida / hidroclorotiazina (22,6%).

Conclusiones: El uso de antihipertensivos ha cambiado significativamente hacia los IECA y los BCC dihidropiridínicos de larga acción. El uso de tiazidas y metildopa ha disminuido significativamente. Parece que los médicos están más concienciados de los beneficios a largo plazo cardio y renovasculares asociados al uso de IECA en un grupo de alto riesgo cardiovascular como los hipertensos negros.

Palabras clave: Antihipertensivos; Inhibidores de la Enzima Convertidora de Angiotensina; Bloqueadores de los Canales de Calcio; Utilización de Medicamentos; Nigeria

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