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Pathophysiologically based antihypertensive pharmacotherapeutics rationality, efficacy and safety in Sub Saharan African Nations – A review

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ABSTRACT

Background: Hypertension (HT) prevalence, Uncontrolled Blood Pressure (UBP), morbidity and mortality are highest in Sub-Saharan Africa (SSA). Correlating pathophysiology of HT to pharmaco-therapy with antihypertensive drugs (AHD) may bring amelioration. *Aims:*To review peculiarities of HT in SSA, UBP causes, diagnostic modalities, AHD use, rationality and efficacy.

Methods and results: 14 published therapeutic audits in 4 SSA nations on Google Scholar or PUBMED, (total n = 6496 patients) were evaluated. Calcium Channel blockers (CCB) amlodipine, and thiazide diuretics (TD), hydrochlorothiazide (HCTZ) were the commonest AHD. Thiazide Like Diuretics (TLD) were underutilized. The % of patients on AHD were: 1 drug 5.4–55%; 2 drugs 37–82%; >/ = 3 drugs 6–50.3%. 2-drug combinations were: ACEI/ARB + TD (42%); CCB + TD (36.8%); ACEI + CCB (15.8%) of studies. Triple/quadruple therapy included Methyldopa (MTD) with ACEI + CCB or TD. The (%) attaining BP < 140/< 90 mmHg, ranged from 29 to 53.6%, median, 44%. The co-morbidities, range and median were: Diabetes Mellitus (DM): 9.8–64%, 19.2%; Chronic Kidney Disease (CKD): 5.7–7.5%, 6.9%, and Coronary artery Disease (CAD): 0.9–2.6%, 2.3%. ACEI + CCB ± TD were the preferred AHD for comorbidities.

Conclusions: Therapeutic inertia; Non-compliance; co-morbidities; refractory HT; ignorance; substandard AHD; contribute to UBP. Studies relating 24 hour ABPM to complications and mortality in SSA hypertensives; and impact of different AHD classes on ABPM, are needed. Study of ACEI + alpha-$_1$ blockers + TLD on 24 hour ABPM and personalized care, are required.

1. Introduction

Essential hypertension (HT) is the commonest cardiovascular risk factor on a global scale. 1.3 billion adults had essential or secondary hypertension globally in 2010 [1], and may reach 1.56 billion by 2025 [2]. There is a disparity in prevalence of HT (blood pressure or BP > 140/90 mmHg or taking anti-hypertensive medications) between high income (HICOM) and Low and Middle Income (LMIC) countries [1]. The global prevalence of hypertension (HT) is about 31%, and is falling in high income countries (HICOM); but rising in LMIC, and highest (40%) in Caribbean and Sub-Saharan Africa (SSA). [1,3] The global cost of HT is estimated at $ 500 billion [2], which accounts for more than 4% of the GDP in LMIC.

HT is the commonest non communicable diseases (NCD) risk factor for morbidity and mortality. Globally, 9.4 million deaths annually are hypertension -related [4]. HT is associated with 70% of heart failure (HF); 80% of strokes; 70% of acute myocardial infarction; chronic kidney disease (CKD) or end stage renal disease (ESRD) mortality [5].

Globally, about 50% of hypertensives needing treatment are aware, and less than half of these are on any treatment [1]. Drug treatment of HT reduces the incidence and mortality from: strokes, HF, ESRD and cardiac revascularization [6]. Thus, HT detection and its cost –effective treatment are paramount public health concerns, but only about 10.3% achieve adequate control, especially in SSA nations [7]. The higher and rising prevalence of HT in LMIC, the prohibitive cost of effective treatment and the defective public health systems of SSA nations poses special problems for that region of the world, with SSA having about 46% hypertension prevalence [8,9]. Analyzing causal factors of BP control and seeking cost-effective pathophysiological based –drug class intervention for HT in SSA is a priority public health policy and practice, and

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is therefore the purpose of this review.

1.1. Peculiarities of hypertension in blacks/Africans compared to whites

In SSA Africans, HT exhibits a more malignant course compared to other ethnicities. It is the commonest cardiovascular disease of Black Africans [10]. It has a higher age-adjusted prevalence and more severe target organ damage. HT in SSA is the leading non infectious cause of hospitalization [11], and the leading cause of sudden cardiac death [12]. It the commonest risk factor in black Africans for CHF [13], CKD [14], hypertensive crises and encephalopathy [15,16] cerebrovascular disease and stroke [17]. Emerging evidence also implicates HT in dementia and memory loss in the elderly [18]. In the USA, Blacks were 1.5–2.5 times at greater risk of developing HT than Whites and the onset in Blacks is a decade earlier than in whites [19]. The average prevalence of HT (>140/90 mmHg) in all Americans was about 34%, but 44% in African-Americans, and with a 4 x stroke risk of Black men compared to White women [19]..See Table 1.

Ambulatory Blood Pressure Measurement (ABPM) parameters, reflect abnormal LV geometry, severity of left ventricular hypertrophy (LVH), left ventricular mass index (LVMI) or left ventricular remodeling (LVR) indices [36–40]. The use of ABPM is now considered mandatory to diagnose and manage hypertension optimally in African- Americans [36,37], and is only gaining increasing utility in SSA blacks [39,40].

There are important interactions among (a) Hypertensive patients BP, measured by ABPM or by office measurements, (b) AHDs properties, (c) and HT patient co-morbidities, which determine efficacy and safety of pharmacotherapy, see (Fig. 1). Determinants of antihypertensive drug choice and efficacy are summarized in Fig. 1. The AHD treatment goals exceed just BP lowering, to reduction in Blood Pressure Variation (BPV), vascular endothelial protection, smooth muscle hypertrophy regression and target organ protection and repair.

ABPM peculiarities in Blacks, makes pharmacokinetic-dynamic modeling profile of the AHD monotherapy or combinations important [41]. The AHDs should ensure a 24 hour duration of effective plasma concentration, during multiple dosing at steady state (Cp_{ss}), low trough to peak drug concentration ratio, to reduce BPV [41], and to ensure smooth 24 hour BP control. This is done by assessment of smoothness index or the trough to peak ratio, of corrected BP fall on treatment [41, 42]. Single daily dosing, or single fixed drug combinations (FDC) or single pill combinations (SPC) may confer 24 hour BP control, whilst enhancing compliance with regimen.

1.2. Assessment of hypertension treatment goals in SSA: deciding which drug to which patient ?

The major classes of (AHD) used increasingly in SSA nations are; Angiotensin Converting Enzyme inhibitors (ACE I)/Angiotensin Receptor Blockers (ARB) which separately are RAAS Inhibitors (**Class A**), β Blockers (**Class B**), Calcium Channel Blockers (CCB) (**Class C**) or Diuretics (Thiazides TD, Thiazide Like Diuretics -TLD) or **Class D**. are reviewed.

Other AHD, such as Methyldopa, post-junctional α-$_1$ adrenergic antagonists such as prazosin/doxazosin, direct vasodilators hydralazine which form the bulk of the older antihypertensive medication in SSA [43], are in the therapeutic HT audits (Table 2).

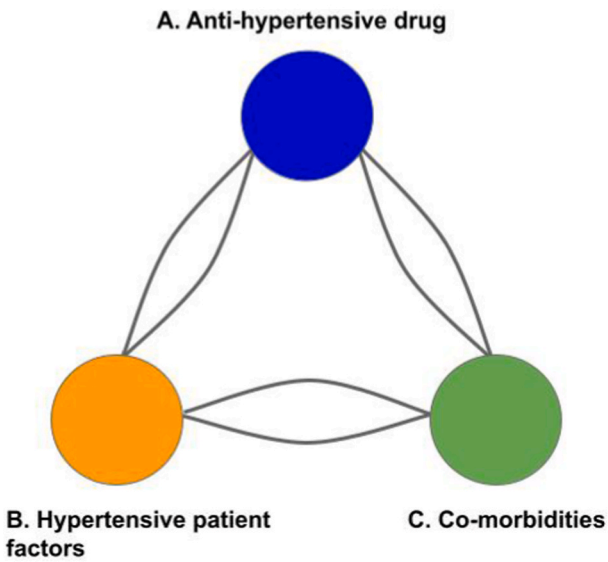
1.3. Drug class and efficacy as monotherapy

ACEI/ARB. Enalapril and propranolol comparison showed no antihypertensive action of either drug [58]. A double blind comparison of enalapril and hydrochlorothiazide (HCTZ) showed a poor hypotensive efficacy of enalapril compared to the efficacy of HCTZ [59]. In Ethiopians, a blunted antihypertensive action of enalapril and timolol, compared to significant effect of HCTZ was shown [60]. There was a lack of efficacy, both of enalapril and prazosin in dose escalation studies in

Table 1
Black -White Differences in Hypertension (HT) pathophysiology. [15,16, 20-40].

Parameters	Black- White Differences	Implications
Epidemiology	Blacks have 1.5–2.5 x the risk of developing HT compared to Whites. HT onset a decade earlier in blacks than whites. HT prevalence is 34% in Whites, but 44% in Blacks. Blacks have 4× risk of strokes than whites.	Higher incidence, prevalence, BP load and complications burden at an earlier age in Blacks.
Genetic factors	ATP1A, AQP2 gene deregulation in blacks associated with HT. Higher salt sensitivity in blacks related to adaptation to local temperature	Genetic predisposition to HT in Blacks, related to ambient temperature and thermoregulation in Africa.
Biochemical differences	Blacks have higher intra-erythrocyte Na + concentration, lower Vmax of RBC -Na + -K + ATPase, Higher Platelet and lymphocyte Ca++ compared to Whites	Higher vasoconstrictor tone in blacks, and efficacy of Thiazides and CCB drugs.
Renin Angiotensin Aldosterone System (RAAS) *ACE gene Insertion I/Deletion D polymorphism*	Blacks have low PRA/ aldosterone, 50% of the value in whites.No correlations between Plasma Na+ and PRA or BP in blacks. Higher frequency of deleterious D allele in blacks than whites.D allele confers 1.49 × risk of HT, and DD: II odds ratio for HT is 2.17.	Inhibition of RAAS leading to Na + retention. AHD which are natriuretic: Thiazides/CCB, more effective in blacks than whites. Blacks have additional genetic route to HT
Endothelial function, vasodilator/ vasoconstrictor balance	Blacks have blunted response to NO-cGMP effects and ↓Isoproterenol β-2 -cGMP vasodilation). ↑ Sympathetic vascular tone by microneurography	Blacks have ↑vascular muscular hypertrophy, ↑aortic stiffness, higher central and aortic BP
Sympathetic function	Blacks have higher BP and heart rate response to cold pressor test measured by microneurography than Whites.	Higher HT prevalence and target organ damage in Blacks at a given BP.
Alpha vasoconstrictor tone	α $_1$adrenergic (ADR1A) receptor associated genes and SNPs contribute to SBP, DBP and HT in pathway focused analysis in Nigerians.	Synergistic effects of α1 antagonists and ACEI in healthy, HT crises, and hypertensive pulmonary edema
Vascular stiffness and remodeling	Carotid-femoral pulse wave velocity (cf-PWV) higher in Blacks than Whites (46). ↓ Peak ischemic reactive hyperemia by Doppler fluximetry in skin blood vessels in Blacks	Blacks have higher aortic and proximal large elastic vessels stiffness, and abnormal microvascular remodeling of smaller blood vessel and organ damage.
24 hour Ambulatory Blood Pressure Monitoring (ABPM)	Blacks have ↑day time BP, ↑Night time and 24 hour BP, ↑Nocturnal HT prevalence, ↓ Nocturnal dipping (more Non-dippers), Greater morning surge, ↑ *Blood Pressure Variability* or BPV and clinic -to clinic BP variability.	Higher prevalence of *masked hypertension* in Blacks leading to *Therapeutic Inertia* more in Blacks. BPV is associated with endothelial dysfunction, greater target organ damage and mortality from HT) Long acting AHD exerts better HT control and AHD combinations may be more effective round the clock.

Abbreviations: ACEI- Angiotensin Converting Enzyme Inhibitors, AHD-antihypertensive drugs, CCB - Calcium channel blockers, HT – Hypertension, PRA-Plasma Renin Activity. SNP – Single Nucleotide Polymorphism. Numbers represent relevant references.



A. Anti-hypertensive drug

- Pharmacokinetics: Metabolism and Excretion route.
- Pharmacogenetic metabolism: Cyp 2D6, 3A4.
- N Acetylation
- Pharmacodynamics
- Onset, duration of action: 24 hour ABPM control
- peak : through ratio , Smoothness index
- Effect on BP Variation
- Chronopharmacology: Day / Night dosing efficacy.
- Endothelial effects
- Effects on aortic stiffness
- Effect on HOMA - IR
- Insulin resistance
- Influence of PRA /Aldo.
- Adverse effects and HRQoL
- Single or Combination
- Cost & Cost effectiveness

B. Hypertensive patient factors

- Therapeutic Inertia
- ABPM profile: Dipper,nocturnal HT, BP Variability
- Masked Hypertension
- Clinic to clinic BPV
- Ethnicity, Age, Gender
- Renin / Aldo profile, Uric acid .
- Literacy/ Health literacy
- Adherence/ Compliance
- Primary / secondary hypertension.
- Pregnancy hypertension
- Hypertensive crises
- Hepatic/ Renal function
- Drug Drug interaction

C. Co-morbidities

- Benign Prostate Hypertrophy
- Type 2 DM, Met - S, Obesity
- Sleep apnea, Dementia,
- LVH/ Valvular Regurgitation/ Arrhythmias/ AF.
- CKD, CAD, COPD / Asthma
- Reynaud phenomenon
- Arthritis, Peptic ulcer Disease, Stroke / TIA.

Fig. 1. Interacting factors influencing both the efficacy and safety of antihypertensive drugs in the individual hypertensive patient, and personalized factors which should guide the choice of combination therapy of all grades of hypertension.
Abbreviations: HOMA−1R Homeostatic Model Assessment, Insulin Resistance, PRA− Plasma Renin Activity, Aldo− Aldosterone, HRQoL− Health related Quality of Life, DM −Diabetes Mellitus, Met−S- Metabolic Syndrome, LVH – Left Ventricular Hypertrophy, CKD−Chronic Kidney Disease, CAD− Coronary Artery Disease, COPD− Chronic Obstructive Pulmonary Disease, RAAS – Renin Angiotensin Aldosterone System, TIA – Transient Ischemic Attacks.

South Africans [61], and of low doses of prazosin in Nigerians [62]. ARB monotherapy in Black South Africans was not effective, in a similar manner to ACEI [63]. More recent studies in Whites and African-Americans using 24 hour ABPM, confirm the poorer hypotensive efficacy of ARB valsartan, in Black essential hypertensives [63]. Thus, AHD inhibitors of RAAS: ACEI, ARB; β-blockers; prazosin, are unsuitable as monotherapy in SSA and should be combined with TD or calcium antagonists as in 2- drug guideline recommendations [64]. Mono-therapeutic efficacy of β adrenoceptor blockers, may manifest in malignant HT when the PRA is elevated [43,64]. CCBs, especially amlodipine [44,65,66], thiazide diuretics and Thiazide-like Diuretics (TLD) such as indapamide [67–69], have established mono-therapeutic and 2- AHDs combination efficacy in SSA.

1.4. Differential efficacy of antihypertensive diuretics: hydrochlorothiazide versus Thiazide Like Diuretics:indapamide and chlorthalidone

There are differences in efficacy and safety profile within the diuretic drug class for HT therapy. Comparison of indapamide and HCTZ using 24 hour ABPM, showed a higher anti-hypertensive response rate to indapamide 2.5 mg compared to HCTZ 12.5 mg [69]. A higher efficacy and BP normalization rate of indapamide 1.5 mg SR (75.3%) over HCTZ 25 mg (67.3%) or amlodipine 5 mg (66.9%) monotherapy, was demonstrated in elderly patients [70].

A recent meta-analysis of head to head comparisons of HCTZ with TLDs, showed that indapamide and chlorthalidone lowered systolic BP more than HCTZ, but with no difference in hypokalemia risk [71]. Meta-analysis of double –blinded studies, showed that TLD or CHIP diuretics [CHlorthalidone, Indapamide, Potassium sparing diuretic/HCTZ] exhibited a greater regression of LVH, by reducing Left ventricular Mass (LVM) and End Diastolic Left Ventricular Internal Dimension

Table2
Therapeutic Audits in SSA hypertension.

STUDY & COUNTRY 63, 76, 99-111	n = (100%)	Commonest Drugs used	% on 1 DRUG Commonest Drugs used	% Dual Drugs Commonest Dual -therapy	% on ≥ 3 drugs	Efficacy % control BP < 140/90 mmHg	Co-morbidities	Adverse Drug Events (ADE) & Comments
Nigeria (SW) (Old Drugs) *Oyewo EA* et al. 1989	367	Diuretics −100% Thiazides – 72.7% Frusemide- 27.3% MTD-74.1% BB(propranolol)-15.8% FDC1- 18.8% FDC 2–10.6% Hydralazine – 4.9%	<5–10%	75% MTD + D −74.1% BB + D 15.8% FDC	16.9% MTD + D + Hydralaz + FDC	16–39%**	DM-12.5% CKD -7.5% LVH -86% COPD -0.81% Hypertensive Encephalopathy – 6%	FDC1 – Brinerdine FDC2-Minizide (Prazosin + HCTZ) ADE: postural dizziness Impotence Diuretics most cost effective MTD + D also cost effective MTD + D + H most effective combination. BB –effective in renal hypertension.
Ethiopia *Shukrala F* et al. 2015	400	Diuretics 55% ACEI 22% MTD 11.2% CCB 4.6%	55% Diuretics* (HCTZ) CCB.	45% ACEI + D MTD + D CCB + D		NR	DM -64.3% CHF -15.1% CAD -2.3%	NR
Ivory coast *Kramoh H* et al. 2011	2575	Diuretics 59.7% ACEI/ARB 59.6%	34% CCB*	60% ACEI/ARB + D	6%	43.7%	High added risk DM, Met S 46.7% LVH	
Kenya *Mbui JM* et al. 2017	247	ACEI Diuretics (Thiazides)		Most common ACEI + Diuretics		46%		Drug prescription was Guideline compliant. Patients on >. = 2 drugs had higher risk for uncontrolled BP
Nigeria (SW) *Adigun AQ* et al. *2003*	150	Diuretics −56% CCB -51% ACEI24% MTD-28% FDC -7% α-blocker-10% BB -5%	39% Diuretic (HCTZ) CCB* Amlodipine	52% ACEI + D CCB + D MTD + D ACEI + CCB	8–9% ACEI + CCB + D MTD + D + CCB	47%	DM -22% LVH-25% PUD -1.33% Asthma-2.67% Depression-1.33% OA-0.67% Epilepsy-0.67%	11% - ADE. CCB: headache, pedal edema. D (HCTZ); Impotence, postural hypotension ACEI: Dry cough BB: Atenolol, α-blocker-prazosin FDCs: Brinerdine, Regroton (reserpine + D)
Nigeria (SW) *Yusuff KB* et al. 2005	189	Diuretics FDC –Moduretic ACEI, CCB, MTD	27%	52.3% CCB + D ACEI + C ACEI + D MTD + D	8% MTD + CCB + D ACEI + D + MTD + BB	29%	DM; 32.7% OA: 21.8% PUD: 7.3% CKD 7.3% LVH 5.5% BPH; 5.5%	MTD: Dizziness, drowsiness, insomnia CCB (Nifedipine) throbbing headache > NSAID + Aspirin > gastritis, PUD. Lisinopril + Amiloride > hyperkalemia.
Nigeria (Lagos) *Amira CO* et al. 2006	225	CCB -28.4% ACEI-15.4% MTD-15.4% Diuretic (FDC1)-20.9%. BB-14.3%. FDC2 -2.9%, FDC3-2% α-blocker −0.9%	22.7% CCB* ACEI	52.9% ACEI + CCB FDC1 FDC 2 FDC3	24.4% MTD + FDC1 CCB + FDC1	39.6% (41.5%: monotherapy) 37.9% on multi-therapy	DM-9.8% LVH -30.2% CKD -5.7% CVD -5.7% CAD – 0.89% (2 CASES)	*FDC1* Diuretic = co-amiloride (Moduretic) *FDC2*: central agent = reserpine + clopamide + dihydroergocristine (Brinerdine). *FDC3* Atenolol + chlorthalidone (tenorretic)
Nigeria (Multicenter) Akintunde A et al., 2019	288	ACEI- 57.3% Diuretics −34% CCB- 26.4% ARB – 12.5%	20.7% ACEI D	43.9% ACEI + D ACEI + CCB ARB + D	35.4% ACEI + CCB + D, ARB + CCB + D, ARB + CCB + D + BB, ACEI + CCB + D + MTD	NR	DM Met –S HHF TIA	Multi-Center (Lagos, SW, NW) Compliance with JNC7 and JNC V8 causing conflict
Nigeria (SE) *Etuk E* et al. 2008	145	CCB 88% Diuretics (TD) 44.8%	20% CCB*	48.9% CCB + D	31.%	30.5%	NR	NR
Nigeria (SE) *Ukwe CV* et al. 2012	376	Diuretics: 46.4% ACEI/ARB: 20.3%, 5.3% CCB: 15.9% (Nifedipine = 11.3%)	10%	90% on 2 or more drugs ACEI + D (Lisinopril + HCTZ)		Estimated 40–50%**	DM: 19.2% LVH: 14.3% OA: 11.5% PUD: 4.6% CAD: 2.6%	ACEI: cough 11.3% CCB (Nifedipine) – 25.6% headache. Average drug per patient: 2.25 ± 0.77 Co-medication: Aspirin + NSAIDS for OA, headache > ulcerogenic
Nigeria (SS) *Adejumo O* et al. 2017.	224	Diuretics CCB ACEI	17.8%	82.2% ACEI/ARB + Diuretics	ACEI + CCB + D	53.6%	DM: 10.7%	Best BP control seen with patients with tertiary education, monotherapy. Guideline compliant. Still poor BP control rate.

(*continued on next page*)

Table2 (*continued*)

STUDY & COUNTRY 63, 76, 99-111	n = (100%)	Commonest Drugs used	% on 1 DRUG Commonest Drugs used	% Dual Drugs Commonest Dual -therapy	% on ≥ 3 drugs	Efficacy % control BP < 140/90 mmHg	Co-morbidities	Adverse Drug Events (ADE) & Comments
Nigeria (NC) *Olanrewaju TO* et al. *2010*	787	Diuretics-84% CCB-66% ACEI-65% MTD-26% ARB-3.8% BB – 11.9%	9.1%	37.1% CCB + D 14.5% ACEI + D 11.4%	51.5% ACEI + CCB + D-26% ACEI + MTD + D – 9.8%	NR	CKD	NR
Nigeria (FCT) *Ojji DB* et al. 2013	590	CCB -66.9% D (TD) −54% ACEI-47.8% ARB -10.7% BB < 5%	5.4% CCB* D	44.3% 32.6% - CCB + D ACEI + CCB 17.3%: single pill combinations	50.3% ACEI + CCB + D ± BB + MTD	NR	NR	NR
Nigeria (NW) *Tamuno I* et al. *2011*	200	Diuretics: 61.5% BendroFAZ- 41.5% CCB -35% ACEI -17.6%	8.5%	42.5% ACEI/ARB + D 13% CCB + D −12% MTD + D 16.5%	30.5%	34.5%	DM -13% CKD-6.5% Obesity 6.5% PUD-4%	FDC rate 7.5% 2.57 AHD/patient
Nigeria (NC) Sanni MU et al., 2008	100	Diuretics:69% CCB-56% Central agent:38%	27%	43% CCB + D	30%	33%		BP control depended on compliance and combination treatment. AHA compliant but poor over all control

References : [43,44, 45–57].

Legend and Abbreviations: ACEI – Angiotensin Converting Enzyme Inhibitor. AHD- Anti-hypertensive drug, ARB – Angiotensin Receptor Blocker, BB- Beta-blockers, BPH- Benign Prostate Hypertrophy, CAD-coronary artery disease, CCB- Calcium Channel Blockers, CHF- Congestive Heart Failure, CKD – Chronic Kidney Disease, COPD-chronic obstructive pulmonary disease, CVD-cerebrovascular disease, D- Diuretics (TD -Thiazide Diuretics), DM -Diabetes Mellitus, FDC- Fixed Drug Combination or single pill combination (SPC), HHF- Hypertensive Heart Failure, JNC- Joint National Committee, LVH – Left Ventricular Hypertrophy, Met-S – Metabolic syndrome, MTD -Methyl-Dopa. NSAIDS – Non steroidal anti-inflammatory drugs, NR- Not reported, OA- Osteoarthritis. PUD-peptic ulcer disease, SSA- Sub-Saharan Africa, TIA- Transient Ischemic attacks.

(EDLVID) compared to HCTZ, and was more efficacious than RAAS Inhibitors [72]. There is clinical trial evidence both for chlorthalidone and indapamide for reducing cardiovascular mortality and morbidity, but no such data is available for HCTZ [72].

TLD but not HCTZ, has a pharmacodynamic effect to improve endothelial vascular function and longitudinal left ventricular performance in patients with hypertension or diabetes on ACEI [73], and cause greater BP reduction on meta-analyses [71,72]. Monotherapy comparisons, or from registry reports, uniformly suggest that CCBs, (especially amlodipine) have a superior efficacy, compared to thiazides in SSA, and should therefore be the preferred first –line AHD in the treatment of HT in SSA blacks [44,74].

Beta adrenergic antagonists showed mono-therapeutic anti-hypertensive efficacy in hypertensives with CKD [43], but have experienced diminished utility in subsequent audits [44].

1.5. Efficacy in dual (2) or multiple drug combinations

Several international guidelines suggest initiating AHD treatment with dual drug therapy [64]. These entail addition of another drug with complimentary pharmacodynamics, to either thiazide/TLDs (D) or CCBs, but there are few studies in SSA on the efficacy of dual therapies in essential hypertension, with or without co-morbidities. A summary of registry studies reporting antihypertensive prescription patterns and efficacy, in SSA countries is summarized in Table 2.

Concurrent treatment of HT-DM patients with proteinuria, with a regimen of ACEI enalapril and HCTZ caused significant BP fall, reduced proteinuria, and optimal glycemic control [75]. 63% of Nigerians receiving ACEI + Thiazide Diuretic (HCTZ) achieved normal BP (< 140/< 90 mmHg) [44].

1.6. 24 Hour ABPM studies

A 24 hour ABPM study comparing losartan 100mg/HCTZ 25 mg, with enalapril 10 mg/HCTZ25mg, showed comparable efficacy. In a 24 hour ABPM study in hypertensives with LVH, a strong correlation was found between the drug-induced reduction in BP, and the degree of regression of the left ventricular mass [71]. A recent 2-AHD combinations, 24 hour ABPM comparative study, showed that amlodipine + HCTZ or amlodipine + perindopril showed small but significantly lower 24 hour ABPM than perindopril + HCZT [65].

1.7. Role of α-$_1$ adrenergic antagonist/ACEI synergism ?

A pathway focused analysis revealed strong association between single nucleotide polymorphisms (SNP) of the α-$_1$ adrenergic receptors (ADR1A) and SBP, DBP and HT in Nigerians [30]. Consistent with this, are additive and synergistic vasodilator, antihypertensive actions of ACEI and prazosin in healthy volunteers, hypertensive urgencies or crises, and congestive heart failure [15,16,31,32]. (See Table 1).

1.7.1. Antihypertensive therapy and drug use with co-morbidities (compelling indications) [43,44,45–57,76]

The commonest co –morbidities or "compelling indications" in HT receiving AHDs are:Type 2 DM (T2DM) [43,44], Left Ventricular Hypertrophy (LVH), hypertensive heart failure (HHF), valvular regurgitations [13], associated cardiac arrhythmias [13], and CKD [43]. See Table 2 [43,44,45–57]. Low dose HCTZ alone, or combined with Lisinopril, in a single pill combination, did not impair Insulin sensitivity, beta cell function, or cause hyperglycemia, in HT patients whose blood potassium was unchanged [77]. In the therapeutic audit reports of hypertension and its treatment (See Table 2) in Ethiopia [45], Ivory coast [46], Kenya [47], and various parts of Nigeria, DM was the commonest co-morbidity reported. It ranged from 9.8% to 32.7% in SW Nigeria [50], with a study median of 19.2% reported in the South East Nigeria [51]. Much higher DM co-morbidity occurred in Ethiopian patients of 64.3% [45]. This was associated with a coronary artery disease (CAD) prevalence of 2.3% in Ethiopians [45]. In Nigeria [51], concurrent CAD co-morbidity of 0.89%–2.6% was reported. Osteoarthritis (OA), Peptic ulcer Disease (PUD), bronchial asthma, benign prostatic hypertrophy (BPH) obesity and depression were also reported. (Table 2).

1.8. Hypertension with concurrent Diabetes Mellitus in SSA

Diabetes Mellitus (DM) is the commonest and most lethal co-morbidity of the hypertensive patients seen this report (9.8%–64.3%). The independent prevalence of hypertensive- LVH varied from 14% to 30.2% (see Table 2). The concurrence of HT and DM causes additive cardiac systolic dysfunction, cardiac restrictive morphology and treadmill exercise limitation [78]. These predispose to protean target organ damage in SSA hypertensives, including strokes from cerebral infarction, myocardial infarction and CKD/nephropathy [78]. These results predispose to emerging complications of atherosclerotic heart disease in SSA, especially in HT-DM patients. CAD may be underdiagnosed among the SSA HT. Concurrent hypertension with diabetes, is a rising cause of sudden cardiac deaths (SCD) among Nigerians [12].

Treatment of the Hypertensive-Diabetic Patient SSA: Combined ACEI (enalapril) and HCTZ resulted significant falls in SBP and DBP, with significant reduction in proteinuria and increased plasma albumin concentration [75]. In a therapeutic audit where 33 Hypertensive diabetics were studied, 51% attained a BP of <140/< 90 mmHg control [44], 24% attained the JNCVI/ISH/WHO target BP < 130/< 85 mm Hg. AHDs used were; CCB alone; ACEI + D (FDC –Zestoretic); ACEI + CCB; or MTD + D [44]. Intense BP control using ACEI with TD or CCB over a 2 year period, caused significant mortality reduction of HT-DM from 26.6% to 12.6% [79]. A recent multinational study of the efficacy of a FDC of ACEI-Thiazide (Ramipril/HCTZ), reported a better BP control in non –diabetic hypertensives than in HT-DM [80], 13/49 patients or 26.5% attained a SBP <130 DBP <80 mmHg [80].

Hypertension chronotherapy, and hypertension in COVID 19 patients. Nocturnal (prior to sleep) dosing of AHD, results in better control of nocturnal systolic BP, nocturnal dipping, and prevention of early morning surge on 24 and 48 hour ABPM, and significantly reduced cardiovascular mortality [81]. There is at yet no study of chronotherapy in SSA hypertensives. Corona virus disease 2019 (Covid 19) disturbs the Extended Autonomic Nervous System (EAS) and causes dyshomeostasis in multiple effectors and systems. The ACE2 receptor which mediates the vasodilator (Ang 1–7) heptapeptide binding, is also the receptor for the intracellular transmembrane uptake of SARS -CoV −2 virus. It is speculated that RAAS inhibitors, by upregulation of ACE2 receptors, may enhance SAR-CoV-2 viral cell entry, in patients with frequently co-morbid COVID 19 diseases such as HT, DM, and heart disease requiring RAAS inhibitors. The preponderance of evidence, however, support the continued and safe use of ACEI/ARBs in Covid 19 disease [82].

Hypertensive Urgencies and Emergencies treatment: In 8002 hypertensive patients, the frequencies were; hypertensive urgencies (0.81% of all); emergencies/crises (1.7%) with a total of 2.5% of the patients [83]. Hypertensive encephalopathy, manifesting with confusion, headaches, were the commonest symptoms. Several oral regimes, with ACEI enalapril + α-$_1$ blocker prazosin + TD [15], captopril + prazosin therapy in hypertensive acute pulmonary edema [16], extended release nifedipine or nifedipine or atenolol in malignant hypertension [84], have demonstrated efficacy and safety in SSA.

1.9. Adverse drug events and antihypertensive drugs in SSA

Adverse drug reactions (ADR) to AHDs appear to be under reported in SSA (Table 2). A Study of ADR in 504 treated hypertensive patients reported a prevalence of 18.1% [85]. The frequency of the ADRs increased with the number of AHDs up to a maximum of ≥ 4. The AHD class ADR frequencies were; diuretics 27.9%, CCB 26.8%, and ACEI

26.8% [85], and the major ADRs reported were for diuretics; impotence and postural dizziness [43] CCBs; headaches, polyuria, pedal swelling [66,44],ACEI and dry cough [59,44]. 49.5% of patients with ADRs required medication change or substitution [85]. ACE inhibitor dry cough was reported in 27% of hypertensive recipients, with a female preponderance [44,86]. 4% of recipients receiving ACEI, all post-menopausal women, required drug discontinuation on account of severe cough, but no case of angioedema occurred [86].

1.10. Causes of Uncontrolled Blood Pressure (UBP) and adherence in Sub Saharan Africa. Treatment resistant hypertension (TRH)

The majority of the treated hypertensive patients in SSA do not attain satisfactory Office Systolic or Diastolic BP < 140 mmHg/< 90 mmHg) (Table 2). The possible causes for this poor control or uncontrolled BP (UBP) are summarized in Table 3. Non-adherence, both with AHDs and life style changes, play a role and are discussed, as are the reasons for the non –compliance. A recent study from Morocco [87], with 73% UBP in hypertensives found that *therapeutic inertia* (TI) (adjusted odds ratio AOR 18.2) AHD non-adherence, obesity/overweight, low income, HT family history, and male sex all contributed [87].

A study of *therapeutic inertia* in HT (failure to intensify therapy as indicated, when there is no contraindication) [89], indicated that many patients prescribed initial monotherapy, fail to move to combination therapy, as guideline -suggested. 2 AHDs combination reduced cardiovascular deaths (−20%) and hospitalizations (−16%) [89]. TI arises from failure of up titration, of the daily dosages, of the active pharmacological ingredients (API), or failure to use additional AHD of different pharmacological class. Inadequate doses with the right AHD, may contribute to suboptimal HT population control. The correct defined daily dose (DDD) is an important efficacy factor with AHDs. 2-AHDs combination for HT therapy initiation, helps regimen adherence/compliance, and also reduces UBP [89]. See Table 3.

AHD adherence and its determinants have been studied in different parts of the SSA nations and African continent [90,91] (See Table 3). Patient-focused or tailored interventions, on patient specific barriers to adherence are needed [90,91]. (Table 3).Another cause of UBP in treated patients is fake/substandard medicines and AHDs in Africa [92]. Specific drugs amlodipine and captopril, were dispensed as substandard or fake products [92].

Table3
Causes of UBP in SSA nations.

1. Therapeutic/Clinical inertia: May arise from masked hypertension
2. Non Adherence/poor adherence with medications and clinic appointments and non pharmacological interventions:
   - Ethiopia. Adherence measured with Morisky medication adherence scale may be as high as 67.2% with Non adherence rate
   - Ethiopia. Non adherence rate of 39.5% with 50.3% BP control rate
   - Burkina Faso. Uncontrolled BP rate of 54.2% associated with non –compliance
   - Ghana. Non –adherence rate of 93.3%
   - Cameroon – 67.7% non adherence with medication rate, BP control 21.3%. 47% in adherent versus 8.2% in non adherent
   - Kenya. Non –adherence rate in Kenya – 37%, (63% adhered with clinic) –medication adherence 94% in clinic attendees .
   - Nigeria (North West) Morisky adherence scale used to assess pharmacological and non pharmacological therapies. Non adherence rate to medications was 91.1%, and to life style modification 94% Nigeria (South East) poor/Non-adherence rate to medication of 68.7%. Blood pressure controlled in 32.9%
3. Factors causing and contributing to non –adherence with medications and life style modifications and BP control
   - Multiple daily drug doses
   - Patient- health provider relationships
   - Co- morbidities (compelling indications)
   - Long duration of treatment
   - Cost of Medications
   - Adverse drug
   - Forgetfulness and cigarette smoking
   - Older age (>.65 years old)
   - Physical inactivity
   - Adding Salt to diet
   - Chat chewing
   - Coffee consumption
   - Low socio-econpmic status
   - Antihypertensive monotherapy
4 Fake or Substandard Antihypertensive medications
   - Poor quality amlodipine (29%) and captopril (26%) in generic versions or produced from certain global zones had <85% of the active pharmacological ingredient
5 True Resistant/Refractory Hypertension
Patient resistant to 5 antihypertensive drug combination including a diuretic and a mineralocorticoid antagonist (MRA) such as spironolactone.
References [87–95]:

UBP – Uncontrolled Blood Pressure.
References [87–95]:

1.10.1. Treatment resistant hypertension (TRH) and refractory hypertension (RfH) phenotype as causes of UBP

Resistant low renin hypertension occurs in 6% of Black African hypertensives [93]. The causes of true resistant HT in SSA or TRH (requiring 3 or more AHDs for BP control) is associated with many mutations SNPs of renal epithelial Na + channels, including (ENa + C and Sodium Channel epithelial 1 beta subunit SCNN1B) which is responsible for 5% of sodium excretion, and causes severe HT, Na + retention, low PRA and low aldosterone (Liddle Phenotype) [87]. The patients with apparent resistance or a-TRH in Ghana, had 4-fold risk association with all types of strokes, compared to treated HT with no stroke history, indicating that apparent treatment resistance (a- TRH) is a predisposition to stroke in SSA [87].

Refractory hypertension (RfH), defined as BP greater than 140/90 mmHg on 5 or more classes of AHDs is a more severe phenotype of TRH [94]. RfH is associated with male gender, age <60 years, CKD and ESRD, and very high stroke risks in SSA hypertensives [94]. Treatment, both of TRH and RfH, are challenging and are in need of further research. Physiologically personalized AHD treatment, using PRA and aldosterone profiles to guide AHD drug choice, caused a significant improvement in BP control, compared to the usual care [95].

1.11. General observations and recommendations

Most patients in the audits reported (Table 2) received CCBs or Diuretics (HCTZ) as the initial AHD, consistent with guideline suggestions [64]. The over all frequency of thiazide or thiazide –like diuretic single agents use, ranged from 44.8% to 84% of all the patients. CCB alone or in combination use ranged from 4.6% in Ethiopia, to 88% in Nigeria. Reasons for variation in CCBs use are unclear, but geographic location, drug price and availability and physician preference, may contribute. Thiazides were the most prescribed AHD class, followed by CCB, but CCB are the most efficacious antihypertensive monotherapeutic class [44]. Consistent with this, CCB as first-line drugs, or in combination with TD or ACEI, was recently reported to be most efficacious antihypertensive agents in a meta -analysis in Black Africans [96].

Among the thiazide/thiazide -like diuretics used, HCTZ prescription was overwhelming. Only one audit [52], reported a 41.5% bendrofluazide prescription rate (Table 2). TLD agents, such as indapamide or chlorthalidone, which have greater 24 hour ABPM reduction, greater left ventricular remodeling reversal, more vascular protection efficacy, as well as superior survival benefits over HCTZ [72,73], were rarely utilized in the audits reported. This hiatus in evidence based practice needs to be addressed and rectified.

Most patients reported in the therapeutic audits were on at least 2 drugs. The proportion of patients on monotherapy ranged from 5.4% in Nigeria FCT to 39% in Nigeria SW, and 55% in Ethiopia. By contrast, the proportion of patients on 2 -AHDs combination ranged from 37.1% [55] to 82.2% [49]. (Table 2). The commonest non fixed dose, dual antihypertensive combinations were ACEI + D, CCB + D, ACEI + CCB, MTD + D (Table 2).

The distribution (%) of patients receiving 3 or more AHD in these

audits was bimodal. Some studies reported, less than 10% of the total, but others reported 20–45%. Time-trends in practice, the severity of HT or co-morbidities (*compelling indications for antihypertensive treatment*) may impact the population proportion of hypertensive patients receiving multiple AHDs. Audits with higher proportion of CKD, had more patients on at least 3 drugs [55]. The commonest 3 or more drugs combination, consists of ACEI, CCB, D, MTD with FDC/SPC such as (atenolol + chlorthalidone), (HCTZ + amiloride), or (reserpine + clopamide + dihydroergocristine).

The BP control rate, defined as Systolic BP < 140 mmHg/Diastolic BP < 90 mmHg in the clinic, ranged from 53.6% [49], 47% [71], 46% [53], 43.7% [52], to much lower values of 30.5% [54], 30% [57], or 29% [56]. These values represent poor control of BP, in treated hypertensives, seen in tertiary care centers in SSA. The values are lower than the 69% control of treated hypertensives in the USA, although over all, just 50% of treated and untreated US hypertensives are controlled [97].

2. Discussion

The pathophysiological attributes of HT in blacks of SSA (Table 1) are different from the European experience, but are explanatory of the worse natural history of hypertension in blacks. DM is the commonest co-morbidity of HT in SSA. 24 hour ABPM, though rarely used, is needed for optimal diagnosis and assessing pharmacotherapy of HT in SSA, to detect nocturnal HT and avoid masked hypertension. Current evidence indicates that HT treatment in SSA is guideline compliant, with the initial use of long acting AHDs; diuretic (D) or CCB drug classes used in combination therapy, either together, or with ACEI/ARB, or MTD, in 2-AHD combinations. The drug choice is rational for the low renin status of SSA hypertensives. TLD which are longer acting than HCTZ, and with evidence of cardiac and cerebrovascular mortality benefits, are under utilized, and this needs to change (Table 2). The utility of the combination of ACEI + α-$_1$ blocker, or MTD + thiazide or TLD, which demonstrated efficacy in severe hypertension, should be evaluated further with 24 hour ABPM [15,16,31]. The role α -$_1$ adrenergic receptor antagonists as adjunctive therapy in SSA hypertensives, needs to be investigated, as well as the personalized management of TRH/RfH [95], and the impact of pharmacotherapy on hypertension-related morbidity and mortality in SSA.

There are few studies of the efficacy of AHDs evaluated by 24 hour ABPM, or linking of pharmacotherapy to myocardial echocardiographic changes, or to markers of myocardial injury such as hs-cardiac troponin T or NT-Pro-BNP. Further, prognostic studies of efficacy by AHD class, in the prophylaxis of stroke and/or the prevention of cognitive impairment/dementia and mortality in SSA are needed. The rising concurrence of HT, HT-DM, with CAD, deserve urgent and comprehensive preventive strategies for acute myocardial infarction, and possibly sudden cardiac death [12].

Non compliance with AHD, which occurs in over 90% of patients, requires more research and aggressive intervention, focused on socio-economic, patient educational or packaging issues to improve and reverse non adherence. This will reduce the burden of UBP, target organ complication and mortality. (See Table 3). The interventions taken to reduce non-adherence with AHDs, and to reduce UBP and hence cardiovascular morbidity, include: patient education; use of smart phone app; or mobile phone short message system texting [98]. Dosing simplification, reduction in out of pocket costs, use of allied health professionals for intervention delivery, and self monitoring of BP [89], or use of single pill combinations (SPC) with 2 or 3 AHD combinations [89–91], all enhance compliance. The use of triple drug combinations (Amlodipine/ARB/Diuretic) appear to produce greater falls in BP in a greater population of patients than 2 –drug combinations [99,100]. Treatment intensification was shown to be more important than adherence in BP control, in a study of treatment resistant hypertension (TRH) [89,90]. The observations reported here, should guide further research inquiry, and should also be considered in revising guidelines for treating HT in SSA.

Conflict of interest statement

The authors declare no conflict of interest with regard to this submitted article to the journal.

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