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Prevalence of Calcium Channel Blocker Induced Ankle Edema and its Treatment in a Cohort of Newly Diagnosed Hypertensive Patients

Paul Otor Onah[1*]; Catherine Chioma Idoko[2]; Siyaka Abdulateef[3]

[1]Department of Clinical Pharmacy and Pharmacy Administration, Faculty of Pharmacy, University of Maiduguri, Borno State, Nigeria
Email: onahpaul@unimaid.edu.ng

[2]Department of Clinical Pharmacy and Pharmacy Practice, Faculty of Pharmacy, University of Benin, Benin City, Nigeria
Email: pinkjewelone@yahoo.co.uk

[3]Department of Clinical Pharmacy and Pharmacy Administration, Faculty of Pharmacy, University of Maiduguri, Borno State, Nigeria

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ABSTRACTS

Background: Calcium channel blockers are widely prescribed either as monotherapies or in combination therapies in the management of hypertension and other cardiovascular disorders. One of the major challenges with this class of drugs is their association with difficult to treat peripheral edema. There is limited literature evidence on the incidence and severity of CCB induced edema and the efficacy of management practices in developing countries. This study therefore aims to assess incidence and the common treatments.

Methods: A total of 193 eligible subjects were enrolled into an eight week study and allocated into three treatment groups for each drug [Amlodipine 10mg or Nifedipine 20mg]. One group received no intervention, while the other two groups received either Bendrofluthiazide 5mg [BDF] or Lisinopril 5mg depending on blood pressure or other patient factors. Edema was monitored every two weeks throughout the study using standard tools. The data were analyzed using students t test, one way ANOVA and descriptive statistics as appropriate. P values ≤ 0.05 was considered statistically significant.

Results/Discussion: The overall incidence of edema was about 29% at the end of the study period. Lisinopril addition to therapy resulted in significant reduction in incidence and severity of edema as opposed to other interventions. This suggests that ACEIs have a positive role in minimizing incidence of peripheral edema.

Conclusion: Peripheral edema remains a complication factor in CCB therapy and ACEIs may be considered in management of edema induced by this class of drugs

Keywords: Hypertension, Calcium channel blockers, Pedal edema, Amlodipine, Nifedipine

Corresponding author
Paul Otor Onah*
Email: onahpaul@unimaid.edu.ng
Tel: +2348038258589

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INTRODUCTION

Hypertension is among the leading causes of morbidity and mortality among adult population worldwide [Mills *et al*., 2020]. The global burden is estimated to be over a billion people, with the greatest burden occurring in low and middle income countries [Adeloye *et al*., 2015]. A number of systematic reviews and meta-analysis of published studies in Nigeria has shown an upward trend in prevalence over the last few decades [Oga *et al*., 2012, Asekun-Olarinmoye *et al*., 2013]. Hypertension among adults has been reported to range between 13 – 64% of adult population in Nigeria [Adebayo *et al*., 2013, Murthy *et al*., 2013]. While prevalence vary widely among difference population groups, the global trend indicate that hypertension is a growing public health challenge [Mills *et al*., 2016, GBD 2018].

The long term management of hypertension involve pharmacotherapy using single or combination of different classes of drugs including diuretics, CCBs and ACEIs/ARBs either alone or in combination therapy [JNC 8]. The choice of specific antihypertensive drug(s) largely depend on level of blood pressure and patient related factors. Among the most widely prescribed classes of antihypertensive drugs are the CCBs, which is largely due to their relative safety profile and low cost. This is in addition to the fact that they do not require routine monitoring of hepatic and renal organs [Mann *et al*., 2017, Li *et al*., 2014, Caballero-Gonzalez 2015]. In addition to being effective in reducing elevated systolic and diastolic blood pressure, CCBs also have several other desirable cardiovascular benefits [Whelton *et al*., 2017].

Among the most widely prescribed CCBs are Amlodipine and Nifedipine, their pharmacokinetic and pharmacodynamic profiles allow single daily dosage regimen, however they are often associated with peripheral edema which is common to all the drugs in this class [Khadka *et al*., 2019]. The dose dependent vasodilatory edema reported vary widely in incidence and severity between individual drugs [Messerli 2002, Sica 2003]. Literature evidence of CCB associated peripheral edema range between 5 – 70%, particularly when high doses are used [Messerli 2002], though other reviews have reported lower incidence [Blankfield 2005, Andresdottir *et al*., 2000, Per Lund-Johansen *et al*., 2003]. The wide variation in prevalence may be due to different methods of edema assessment, inter and intra subject variability and severity rating tools employed in studies.

Peripheral edema is reported to occur mainly in the lower extremities within weeks of initiation of treatment and rises with increasing doses and duration of therapy. It is relatively more common among women, elderly, chronic kidney disease and patients with congestive heart failure [Sangam *et al*., 2016, Yale *et al*., 2001]. The mechanism of edema formation is believed to be largely due to arteriolar and precapillary dilatation without commensurate dilation in the venous or post capillary circulation [Malacco *et al*., 2003]. Unlike other types, peripheral edema caused by CCBs is due to the redistribution of fluids into interstitial spaces resulting in pooling, which is thought to be the reason why it is largely unaffected by diuretic therapy [Sica 2003, Sirker *et al*., 2001].

Many studies in low and middle income countries indicate that CCB prescription prevalence ranged from 13 – 55% of antihypertensive drug monotherapies or combination therapies [Lamsal *et al*., 2020, Ibrahim *et al*., 2017, Akande-Sholabi *et al*., 2019, Adejumo *et al*., 2017]. They have demonstrated benefits in not only lowing elevated blood pressure, they have proven effective in stroke reduction and also lowering the risk of cardiovascular mortality associated with other diseases. There is however limited report of incidence of CCB induced peripheral edema and management practices in developing countries [Makani *et al*., 2011]. This study therefore aims to investigate the prevalence and severity of Amlodipine and Nifedipine induced edema as well as evaluate effectiveness of its treatment.

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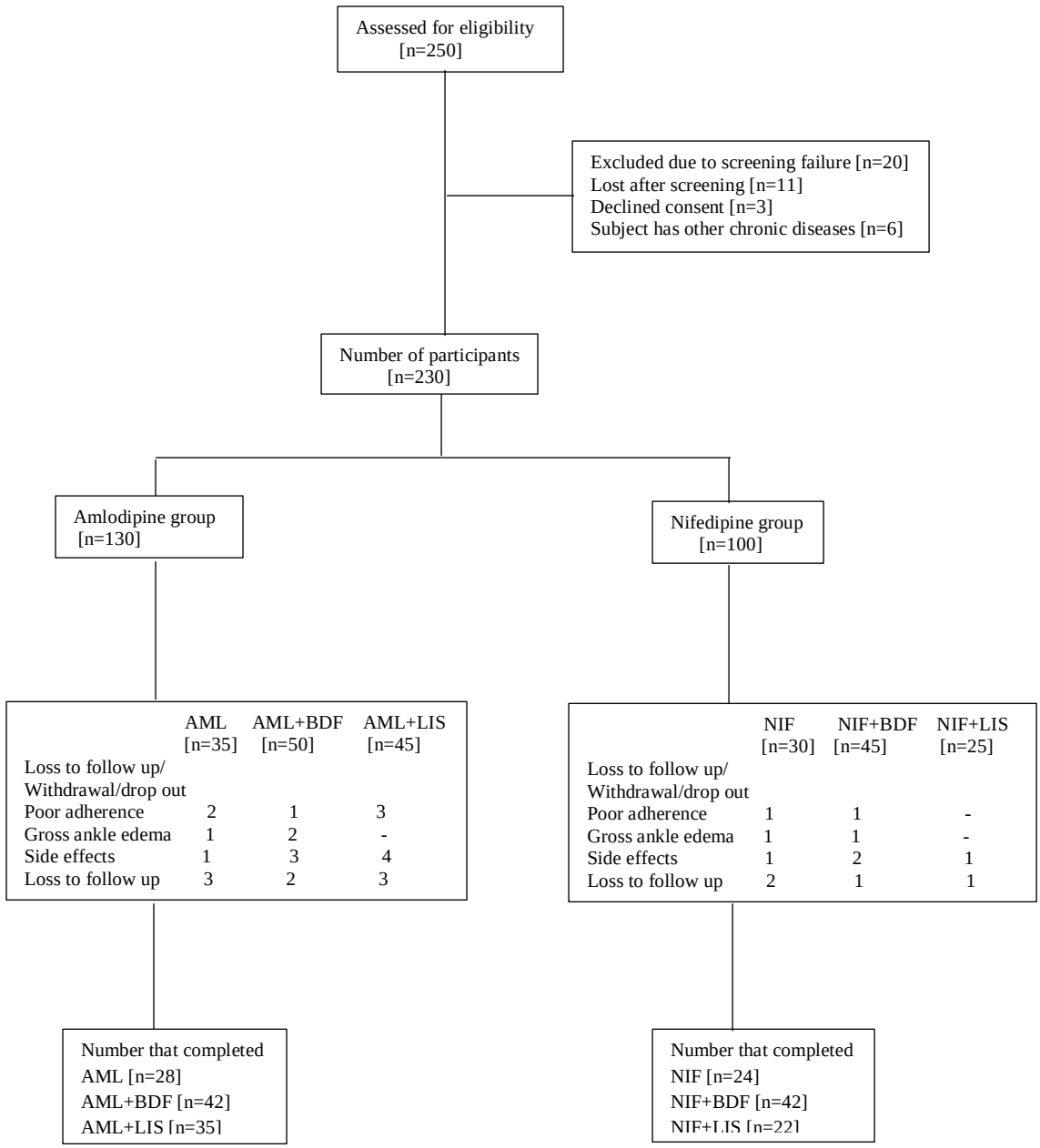
Diagram of flow of participants



Key: AML – *Amlodipine*, NIF – *Nifedipine*, BDF – *Bendrofluthiazide*, LIS - *Lisinopril*

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METHODS

Study design: This was a prospective open label interventional study of CCB induced peripheral edema and efficacy of treatment. The study was carried out in a public [General Hospital north bank, Makurdi] and privately owned [Bethesda Hospital Ikachi, Oju] secondary health facilities in Benue State

Inclusion criteria:

- Newly diagnosed patients with hypertension [≥ 140/90 mm/Hg]
- Patients who need to be taken off diuretic monotherapy
- Patients with no pre-existing chronic diseases
- Age ≥ 30 years
- Women must not be pregnant
- Subjects with no chronic kidney disease, diabetes mellitus and liver diseases

Sample size: A total of 250 newly diagnosed hypertensive patients were enrolled into the study after preliminary eligibility screening, out of which 57[22.8%] either dropped out or were lost to follow up. The number of subjects who completed the study was 193[77.2%] and their data used for final analysis.

Study subjects: Patients who visited the outpatient department of the hospitals for physician consultation were recruited following diagnosis of essential hypertension, obtain informed consent and meet eligibility criteria.

Allocation to treatment groups: A total of six antihypertensive regimens were used in the study involving four drugs namely: - Amlodipine [AML], Nifedipine [NIF], Bendrofluthiazide [BDF] and Lisinopril [LIS]. Enrolled patients were alternately allocated to three Amlodipine 10mg [AML, AML+BDF, AML+LIS] and three Nifedipine 20mg [NIF, NIF+BDF, NIF+LIS] treatment groups. They were monitored for blood pressure, ankle size and sign of pitting edema at every follow up clinic visit. At the second week of therapy, subjects were observed for evidence of ankle edema in all the treatment groups. The monotherapy group of each arm continued their treatment without add on medication until end of study. Evaluation of effect of BDF and Lisinopril add on therapy on pedal size and pitting edema was assessed from differences in the rate and severity of edema at the end of the study.

Anthropometric measurements: These include height, weight, waist circumference, hip circumference, Waist/hip ration, body mass index [BMI] and ankle size using standard instruments and procedures.

Measurement of ankle edema: A thumb was pressed behind the ankle bone, over the top mid portion and over shins for 20 – 30 seconds. If an indentation occurred, the time taken to rebound is noted and compared with edema grading scale of +1 to +4 and recorded as presence or absence of edema as well as its severity [+1 – *barely detectable impression on the skin*, +2 – *slight indentation that takes 15 seconds to rebound*, +3 – *deeper indentation that takes 30 seconds to rebound*, +4 – *indentation takes greater than 30 seconds to rebound*].. Pitting edema score was recorded as the average of the total score of all 3 points.

Measurement of ankle size: Clinical assessment of pitting edema at three anatomical sites: - 7 cm proximal to the midpoint of the medial malleolus, behind medial malleolus and dorsum of the foot. Measuring tape was placed at the extremity of designated site and measurement taken; this process was repeated at the other extremity. The measurements was carried out upon enrolment (baseline) and thereafter at every two weeks until the end of study.

Medication counseling: Participants received medicine information on possible occurrence of edema, common side effects and adherence and medication counseling was provided at each medication refill. All the clinical assessment and medicines were provided free of charge to all participants

Adherence assessment: During fortnight clinic visits, subjects came along with unused medications and manual count was carried out to determine the level of adherence before refill of prescription. Data from patients with less than 90% adherence was not included in the final analysis.

Outcome variables: The primary outcome is the number of patients who experienced ankle edema within the study period. The severity of peripheral edema was assessed every two weeks using changes in ankle size and degree of pitting edema. Antihypertensive efficacy was assessed using standard procedure and changes in systolic blood pressure [SBP] and diastolic blood pressure [DBP] was determined every two weeks until the end of the study.

Analysis: The Mean SBP and DBP was calculated as mean [SD] and comparison was made between baseline and end of study data using Students t test. A comparison of anthropometric values of subjects in different groups was done using one way ANOVA. Incidence of edema associated with Amlodipine and Nifedipine treatment groups was assessed using ankle size measurements, which is then compared with baseline values. The severity of edema was carried out using pitting edema grading scale [0= no edema, +1 to +4]. The efficacy of add on medications on edema

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was evaluated by comparing ankle size data at the fourth week and end of study [Students t test], while severity of edema was expressed using descriptive statistics. P values ≤ 0.05 was considered statistically significant.

ETHICAL APPROVAL: This was obtained from health research ethics committee of Benue State, Ministry of Health, Makurdi [*MOH/STA/204/vol.1/118*].

RESULTS

The demographic data showed that males accounted for almost two thirds of subjects [62.3%]. Majority of subjects had no formal education [38.7%] and only about a quarter had tertiary level education [21.7%]. The major occupations were business [45.1%], farming {29.5%] and civil service [25.4%]. The mean age of participants was 54.5 ± 10.9 years [**Table 1**]

Table 1: Demographic data

Variable	N (%)
Gender	
Male	105 (54.4)
Female	88 (45.6)
Marital status	
Married	126 (65.3)
Single	37 (19.2)
Divorced	18 (9.3)
Widowed	12 (6.2)
Education	
Illiterate	75 (38.9)
Primary	28 (14.5)
Secondary	49 (25.4)
Tertiary	41 (21.2)
Occupation	
Farming	57 (29.5)
Civil service	49 (25.4)
Business	87 (45.1)
Age (yrs.)	
30 - 40	21 (10.9)
41 – 50	47 (24.4)
51 – 60	67 (34.7)
61 – 70	45 (23.3)
≥ 71	13 (6.7)
Mean age	54.5 ± 10.9

A comparison of anthropometric data among treatment groups showed statistically significant differences with the exception of weight [P = 0.364]. The body mass index [BMI], waist size, hip size, height and waist hip ration all showed significant differences [P≤0.05] [**Table 2**].

Table 2: Comparison of Anthropometric data

Drugs	Age (yrs.) Mean [SD]	Height [M]	Weight [Kg]	Waist size [cm] Mean [SD]	Hip size [cm] Mean [SD]	Waist/Hip ratio	BMI
AML	50.9 [10.2]	1.7	65.6 [10.9]	126.2 [17.1]	181.6 [7.9]	0.69	22.7
NIF	50.5 [9.9]	1.5	65.4 [11.4]	137.2 [15.7]	173.2 [7.9]	0.79	29.1
AML+BDF	52.3 [7.3]	1.6	68.9 [10.8]	150.1 [8.4]	176.8 [5.8]	0.85	26.9
NIF+BDF	68.4 [6.5]	1.7	70.1 [8.6]	141.9 [6.9]	160.3 [5.8]	0.89	24.2

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AML+LIS	54.3 [9.2]	1.6	68.9 [10.7]	174.2 [6.1]	198.4 [9.9]	0.89	26.9
NIF+LIS	61.7 [11.9]	1.5	69.6 [9.3]	156.5 [12.4]	189.5 [12.2]	0.83	30.9
P value	0.000	0.001	0.364	0.000	0.000	0.007	0.000

Key*: AML = Amlodipine, NIF – Nifedipine, BDF – Bendrofluthiazide, LIS – Lisinopril*

The prevalence of ankle edema among participants on Amlodipine and Nifedipine showed increased incidence from the cutoff point [4th week] and end of the study for both Amlodipine (33.2%) and Nifedipine (16.8%] monotherapies. A similar pattern of increase was also observed for BDF intervention groups (29.8 – 33.2%), however Lisinopril treatment groups showed significant reduction in the incidence of edema (37.5 – 40.1%). Lisinopril as add on medication significantly reduced the incidence of edema in contrast to diuretic therapy (BDF) **[Table 3**].

Table 3: Incidence of peripheral edema

Regimen	N [%]	Week 2 [%]	Week 4 [%]	Week 8 [%]	Change [%]
AML	28	17.8	21.4	28.5	33.2$^{\uparrow}$
NIF	24	20.8	25	29.2	16.8$^{\uparrow}$
AML + BDF	42	21.4	26.2	28.6	33.2$^{\uparrow}$
AML + LIS	35	22.9	20	14.3	37.5$^{\downarrow}$
NIF + BDF	42	23.8	26.2	30.9	29.8$^{\uparrow}$
NIF + LIS	22	22.7	18.2	13.6	40.1$^{\downarrow}$

Key: $^{\uparrow}$ *= increase,* $^{\downarrow}$ *= decrease*

The efficacy of antihypertensive drug regimens showed significant reductions in both SBP and DBP in all treatment groups [P = 0.0001]. Majority of participants achieved target blood pressure within the study period [**Table 4**]

Table 4: Comparison of antihypertensive efficacy of drugs

	Systolic blood pressure [mm/Hg]			Diastolic blood pressure [mm/Hg]		
Drugs	Pretest Mean [SD]	Posttest Mean [SD]	P value	Pretest Mean [SD]	Posttest Mean [SD]	P value
AML	178.2 [11.2]	139.3 [6.8]	0.0001	103 [8.2]	86.1 [4.2]	0.0001
NIF	168.5 [8.2]	135.2 [7.4]	0.0001	106.5 [6.9]	85.7 [3.8]	0.0001
AML + BDF	165.9 [7.4]	137.9 [5.8]	0.0001	110.2 [6.2]	88.3 [3.5]	0.0001
AML + LIS	180.3 [10.3]	140.7 [3.3]	0.0001	109.1 [4.3]	89.2 [5.7]	0.0001
NIF + BDF	159.8 [6.2]	132.7 [4.1]	0.0001	104 [5.1]	90.1 [2.7]	0.0001
NIF +LIS	179.4 [12.7]	143.2 [7.3]	0.0001	105.1 [3.2]	92.3 [1.6]	0.0001
Mean [SD]	**172.1 [9.3]**	**138.2 [5.8]**	**0.0001**	**106.3 [5.6]**	**88.6 [2.6]**	**0.0001**

The effect of the addition of Lisinopril to regimen resulted in non-significant reduction in ankle size. While monotherapies showed non-significant increase in ankle size, BDF treatment groups showed statistically significant increase in ankle size [AML+BDF (P =0.0004), NIF+BDF (P=0.0179)] [**Table 5]**.

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Table 5: Effect of diuretic and ACEI on CCB induced increase in ankle size

Drug [s]	Baseline [cm]	Week 4	Week 8	**P value**
AML [n=8]	30.2 [2.4]	32.2 [1.3]	33.4 [1.4]	0.0974$^{\uparrow}$
NIF [n=7]	29.4 [2.6]	32.9 [2.1]	33.2 [1.1]	0.7435$^{\uparrow}$
AML + BDF [n=12]	31.9 [3.2]	33.2 [1.5]	34.5 [1.2]	0.0004$^{\uparrow}$
AML + LIS [n=8]	32.5 [1.4]	34.7 [1.8]	33.8 [1.9]	0.3472$^{\downarrow}$
NIF + BDF [n=13]	28.6 [1.6]	30.4 [1.1]	31.6 [1.3]	0.0179$^{\uparrow}$
NIF + LIS [n=5]	29.1 [1.8]	31.4 [1.6]	30.3 [1.1]	0.1727$^{\downarrow}$

Key: $^{\uparrow}$ - *increase*, $^{\downarrow}$ - *decrease*

The severity of ankle edema using pitting edema grading scale indicate that between the cutoff point [4th week] and end of study [8th week] showed increase in severity in all treatment groups except for those with Lisinopril added to their regimen. The severity of edema increased from 23 – 25% among subjects on all regimens with the exception of patients on Lisinopril. However, patients who were on Lisinopril experienced decreased severity of edema from between 37 – 40% compared to baseline values [**Table 6**].

Table 6: Effect of drug intervention on severity of ankle edema

Edema severity		**+1**		**+2**		**+3**		
	Incidence N [%]	Week 4 N [%]	Week 8 N [%]	Week 4 N [%]	Week 8 N [%]	Week 4 N [%]	Week 8 N [%]	**Change [%]**
AML	8 [28.6]	3 [37.5]	3 [37.5]	2 [37.5]	3[37.5]	1 [25]	2 [25]	25$^{\uparrow}$
NIF	12 [28.6]	3 [25]	5 [41.7]	4 [25]	4 [33.3]	2 [16.7]	3 [16.7]	25$^{\uparrow}$
AML+BDF	8 [22.9]	2 [25]	2 [25]	4 [50]	2 [25]	2 [25]	1 [12.5]	37.5$^{\uparrow}$
AML+LIS	7 [29.2]	2 [28.6]	1 [14.3]	2 [28.6]	3 [42.8]	2 [28.6]	3 [42.8]	14.3$^{\downarrow}$
NIF+BDF	13 [30.9]	4 [30.8]	4 [30.8]	4 [30.8]	6 [46.1]	2 [15.4]	3 [23.1]	23.1$^{\uparrow}$
NIF+LIS	5 [22.7]	1 [20]	2 [40]	3 [60]	1 [20]	1 [20]	-----	40$^{\downarrow}$

Key: $^{\uparrow}$ = *increase*, $^{\downarrow}$ = *decrease*

DISCUSSION

Calcium channel blockers are among the most frequently prescribed antihypertensives either as monotherapies or in combination with other classes of drugs. In developing countries like Nigeria, they are widely available, cheap and preferred by physicians in management of essential hypertension. One of the major challenges of their use is the risk of peripheral edema [Sener *et al*., 2005, Leonetti *et al*., 2002]. Among the most frequently prescribed CCBs are Amlodipine and Nifedipine [Elliot *et al*., 2018, Shetty *et al*., 2017] which are known to be very effective in sustaining reduction in blood pressure [Dalal *et al*., 2015, Yavdav *et al*., 2015].

The effect of BDF and Lisinopril on incidence and severity of ankle edema showed that the latter caused a non-significant reduction in incidence and severity of edema which is consistent with earlier studies [Fogari *et al*., 2003, Oparil *et al*., 2010, Chrysant *et al*., 2008, Sangam *et al*., 2016]. The former [BDF] had no significant effect on drug induced edema which is comparable to monotherapies [Weir 2001]. The significant increase in ankle size observed in this study with BDF treatment groups may be related to the fact that diuretics have little or no effect on CCB induced peripheral edema, mainly because it's not a volume dependent edema.

This study also demonstrated that reduction in both SBP and DBP can be achieved by CCB based monotherapies and combination therapies as earlier reported in many studies [Dalal *et al*., 2022, Khan *et al*., 2020, Weycker *et al*., 2008, Ram *et al*., 2012, Bisognano *et al*., 2004]. The antihypertensive regimens used in this this study are widely prescribed for patients in the study setting, and have been found to be effective in achieving sustained blood pressure control. However, little attention has be given to incidence and severity of ankle edema experienced by patients on CCB therapies. While the underlying mechanism of ACEI/ARB ability to reduce incidence of CCB induced edema remains poorly understood, some experts have suggested that their ability to oppose circulatory changes caused by CCBs may be the primary explanation for their efficacy in reducing edema [Fogari *et al*., 2007]. The onset of edema following

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initiation of CCB therapy vary widely in studies, while some studies reported interval of two weeks similar to this study result, others indicated that it may take months to years and tend to get worse over time [Messerli *et al*., 2002].

The severity of pedal edema in this study appeared to increase among subjects on monotherapies and BDF add on medication as opposed to Lisinopril group. This result is comparable to previous studies which clearly indicated that ACEI/ARBs tend to reduce CCB induced edema severity but not necessarily eliminate its incidence [Messerli *et al*., 2002]

While ankle edema is a common feature of all CCBs [Sica 2003, De la Sierra 2009, Malacco *et al*., 2003], the relative risk of edema occurring vary widely between individual drugs [Galapatthy *et al*., 2016, Khadka *et al*., 2019]. The overall incidence of edema observed in this study [29%] is much lower than previously reported in some studies [Galapatthy *et al*., 2016 [31.4%], Fogari *et al*., 2003 [34.4%], but higher than some previous studies such as Chrysant *et al*., 2008 [24.5%], Khadka *et al*., 2019 [15.6%], Makani *et al*., 2011 [12.3%] and Philips *et al*., 2007 [8.7%].

Literature review has reported wide disparity in incidence of edema [Fogari *et al*., 2007, Julius *et al*., 2004, Philips *et al*., 2007] in clinical trials as well as in retrospective and prospective studies from high income countries. Incidence of edema has been reported to be associated with multiple factors such as assessment method [Brodovicz *et al*., 2009], racemic form of drug [Liu *et al*., 2010], monotherapy or combination therapy [Fogari *et al*., 2007, Liu *et al*., 2010], female gender [Messerli *et al*., 2001, Oh *et al*., 2012], Obesity [Blackfield 2006], advanced age [Sica 2003], high dosage [Langman *et al*., 2002, Messerli *et al*., 2002], longer duration of therapy [Sangam *et al*., 2016], though some studies have reported that there is no gender based increased risk of edema with CCBs [Galapatthy *et al*., 2016, Khadka *et al*., 2019]. Other factors that may affect estimates of incidence of edema include method of data collection [Julius *et al*., 2004, Kloner *et al*., 2001, Julius *et al*., 2006] and definition of edema used in the study [Lund-Johansen *et al*., 2003].

In clinical settings, the incidence of CCB induced edema may by underestimated and/or under reported by patients depending on whether or not data is actively or passively obtained [Schumm 2006]. Patients on long term CCB therapy may under report their mild edema, making it difficult to recognize it as a source of distress that will ultimately lead to poor adherence and intentional withdrawal from treatment [Van *et al*., 2005, Weir 2003]. The doses of Amlodipine and Nifedipine used in this study are reflective of the most frequently prescribed dosage for patients in Nigeria [Adejumo *et al*., 2017, Bakare *et al*., 2016, Nwaka *et al*., 2015]. Interestingly, there has been little literature report of ankle edema associated with these CCBs in Nigeria, so this study represent an approach to highlight this important drug therapy problem, that is not commonly recognized by healthcare providers.

CONCLUSION: It is important that health professionals recognize pedal edema as a potential adverse drug reaction among CCBs which can potentially complicate antihypertensive therapy for many patients. There should be active focus by pharmacists on identifying signs of edema in the course of their routine pharmaceutical care interaction with patients. This will not only assist in early intervention, but also help reduce associated distress and provide information feedback to physicians and other care givers.

SIGNIFICANCE OF THE STUDY: The efficacy of ACEI in reducing incidence and severity of CCB induced ankle edema was demonstrated in this study. This finding is an important fact to be considered by physicians and other health care professionals when initiating antihypertensive therapy or managing edema that may occur in the course of treatment. While diuretics are widely prescribed along with CCBs in Nigeria and other developing countries, their role in preventing or reducing incidence of edema is limited, and therefore not a viable option in managing this type of drug induced edema.

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CONFLICT OF INTEREST. The authors declare no conflict of interest

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