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ANTIHYPERTENSIVE PHARMACOTHERAPY USAGE PATTERNS FOR SECONDARY PREVENTION AND ASSOCIATED BLOOD PRESSURE OUTCOMES IN ISCHEMIC STROKE SURVIVORS AT THE TAMALE TEACHING HOSPITAL

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ABSTRACT

Background: The burden of ischemic stroke continues to increase across Sub-Saharan Africa, including Ghana. The use of pharmacological interventions for the secondary prevention of ischemic stroke, especially appropriate antihypertensive pharmacotherapy, is one of the most reliable and effective means of decreasing the recurrence of stroke. However, majority of these patients do not receive the recommended antihypertensive pharmacotherapies for secondary prevention, leading to prolonged recovery time with associated increased morbidity and mortality. **Aim:** To assess the antihypertensive Pharmacotherapy usage patterns for Secondary prevention in ischemic stroke survivors and associated outcomes at the Tamale Teaching Hospital (TTH). **Methods:** We reviewed the Hospital electronic database (LHIMS) of 200 Ischemic stroke survivors at the TTH from January 2022 to December 2023 who had documented evidence of Ischemic stroke diagnosis either through a CT scan or an MRI while those with a diagnosis of hemorrhagic stroke or Ischemic stroke with hemorrhagic transformation were excluded. . Details on patient's demographics, Classes of antihypertensive medications use patterns and Blood Pressure (BP) values at diagnosis, comorbid conditions, renal and hepatic functions, were extracted into an Excel sheet. The blood pressure control at discharge was categorized as either controlled or uncontrolled based on the 2021 AHA/ASA Guideline for the Prevention of Stroke in Patients with Stroke and Transient Ischemic Attack (BP goal of <130/80). The data was imported into Stata/SE Version 17.0 for cleaning and statistical analysis. **Results:** Ischemic Stroke diagnosis based on CT scan or MRI: 193 (96.5%), No 7 (3.5%). Diagnosis of Hypertension: Yes 172 (86%), No 28 (14%). SBP at diagnosis, mmHg (Mean SD, 153 (±29); DBP at diagnosis, mmHg (Mean (SD), 93 (±19). BP status at diagnosis: Controlled 52 (26%), Uncontrolled 148 (74%). Initiation of Antihypertensive medication before discharge: Yes 176 (88%), No 24 (12%). Class of antihypertensive medications initiated: ACEI Yes 41(20.5%), No 159 (79.5%); ARBs: Yes 68 (34%), No 132 (665); Beta Blockers: Yes 22 (11%), No l78 (89%). NDP-CCB: Yes 158 (79%), No 42 (21%). Diuretics: Yes 6 (3%), No 194 (97%).Blood pressure control at discharge: Controlled 92 (46%), Uncontrolled 108 (54%). SBP at discharge, mmHg: Mean (SD) 128 (±16). DBP at discharge, mmHg: Mean (SD) 80 (±12). **Conclusions:** Majority of Stroke Survivors at the TTH received antihypertensive Pharmacotherapy and the most prescribed were DHP-CCB, ACEIs and ARBs. Most of the patients had poorly controlled blood pressures at diagnosis and the major determinants were hypertension and renal impairment.

KEYWORDS: Secondary Prevention, Ischemic Stroke, Survivors, Antihypertensive Pharmacotherapy.

INTRODUCTION

Ischemic strokes can be caused by a myriad of factors, and identifying the cause is essential in effective management as well as secondary prevention.[1] Stroke remains the second leading cause of mortality and combined mortality and disability worldwide. In 2019, the global incidence of stroke was 12.2 million, and the prevalence was 101.5 million, with 77.2 million being ischemic strokes, 20.7 million being intracerebral hemorrhages, and 8.4 million being subarachnoid hemorrhages.[2] The burden of ischemic stroke and its associated mortalities is also significantly higher in developing countries compared to developed nations.[3] Survivors of ischemic strokes remain at an increased risk of various cardiovascular events including myocardial infarctions, recurrent strokes, as well as death from various vascular causes.[4] In Africa, stroke incidence keeps increasing with time, with high mortality rates recorded across several African countries. Stroke is known to account for about 40% of hypertension related complications in the University of Port Harcourt Teaching Hospital in Nigeria. In several West African countries, it is estimated to be the leading cause of adult neurological admissions, accounting for up to 65% of such hospital admissions.[5] Hypertension remains one of the most essential risk factors for the development and progression of ischemic stroke and High blood pressure may directly increase the risk of cardio embolism by having a direct activity on the heart.[6] The use of pharmacological interventions for the secondary prevention of ischemic stroke is one of the most reliable and effective means of decreasing the recurrence of stroke. This can be done using various interventions such as antiplatelet agents, lipid lowering drugs, antihypertensive agents in hypertensive patients, and anticoagulants in cardio embolic strokes.[7]

In a meta-analysis including 8 trials and 33,774 patients diagnosed with either ischemic stroke or transient ischemic attack, the use of antihypertensive drugs was associated with a 1.9% risk reduction of stroke but does not affect the risk of all-cause mortality.[8] Blood pressure lowering with appropriate antihypertensive medications is crucial in preventing stroke recurrence and improving outcomes. It is recommended that patients who are stable neurologically with cerebrovascular disorders would benefit from a blood pressure goal of less than 130/80mmHg.[9] The effect of blood pressure lowering for secondary stroke prevention is consistent, irrespective of previous hypertension and most subtypes of stroke.[10] For stroke prevention, classes of antihypertensive that have shown significant benefits include thiazide diuretics, angiotensin converting enzyme inhibitors, and angiotensin receptor antagonist.[9,11] In spite of various evidence available in understanding stroke care in Africa, there still remain some gaps in therapeutic, as well as rehabilitative stroke services in the African continent.[12]

MATERIALS AND METHODS

We reviewed the Hospital electronic database (LHIMS) of 200 Ischemic stroke survivors at the TTH from January 2022 to December 2023 who had documented evidence of Ischemic stroke diagnosis either through a CT scan or an MRI while those with a diagnosis of hemorrhagic stroke or Ischemic stroke with hemorrhagic transformation were excluded. . Details on patient's demographics, Classes of antihypertensive medications use patterns and Blood Pressure (BP) values at diagnosis, comorbid conditions, renal and hepatic functions, were extracted into an Excel sheet. The blood pressure control at discharge was categorized as either controlled or uncontrolled based on the 2021 AHA/ASA Guideline for the Prevention of Stroke in Patients with Stroke and Transient Ischemic Attack (BP goal of <130/80).

The data was imported into Stata/SE Version 17.0 for cleaning and statistical analysis. Continuous variables were assessed for normality using the Shapiro-Wilk test and visualized through Q-Q plots or histograms. Skewed continuous variables were summarized as medians with interquartile ranges (IQR), while normally distributed variables were

reported as means with standard deviations (SD). Categorical variables were described using frequencies and percentages. The associations between independent variables including demographic characteristics, clinical factors, and classes of antihypertensive medications prescribed versus good blood pressure control were assessed using Pearson's chi-squared test. Fisher's exact test was employed when the expected frequencies in any group of a categorical variable were less than five to ensure statistical robustness. For normally distributed continuous variables, associations with good blood pressure control were evaluated using the t-test, while non-parametric continuous variables were analyzed using the Wilcoxon rank-sum test.

A binary logistic regression model was applied to identify factors associated with good blood pressure control, with odds ratios (OR) and 95% confidence intervals (CI) used to quantify these associations. Variables with p-values <0.05 in the tests of association analysis were included in a backward stepwise binary logistic regression to adjust for potential confounding factors and identify independent predictors of good blood pressure control. Variables with p-values <0.05 in the multivariable model were considered significant predictors of good blood pressure control.

RESULTS

Table 1: Demographic characteristics of ischemic stroke survivors.

Characteristics	Statistics [a] (N = 200)	Percentage (%)
Age, years		
Mean (SD)	61.2 (±15.6)	
Sex		
Male	121	60.5
Female	79	39.5
Educational status		
No formal education	135	67.5
Primary	5	2.5
Junior high school	16	8.0
Senior high school	9	4.5
Tertiary	35	17.5

a = Statistics represent frequency, mean and standard deviation, SD = Standard deviation

Table 2: Clinical characteristics of ischemic stroke survivors.

Characteristics	Statistics [a] (N = 200)	Percentage (%)
Diagnosis evidenced by CT scan or MRI		
No	7	3.5
Yes	193	96.5
Hypertensive		
No	28	14.0
Yes	172	86.0
SBP at diagnosis, mmHg		
Mean (SD)	153 (±29)	
DBP at diagnosis, mmHg		
Mean (SD)	93 (±19)	
BP status at diagnosis		
Uncontrolled	148	74.0
Controlled	52	26.0
Comorbidity		
No	107	53.5
Yes	93	46.5
Renal impairment (eGFR ≤ 30ml/ml/min/1.73m^2)		
No	184	92.0
Yes	16	8.0

Liver impairment (high ALT values)		
No	184	92.0
Yes	16	8.0
Antihypertensive initiation		
No	24	12.0
Yes	176	88.0
SBP at discharge, mmHg		
Mean (SD)	128 (±16)	
DBP at discharge, mmHg		
Mean (SD)	80 (±12)	

a = Statistics represent frequency, mean and standard deviation, SD = Standard deviation, SBP = Systolic blood pressure, DBP = Diastolic blood pressure.

Table 3: Distribution of the class of antihypertensive medication prescribed.

Antihypertensive class	Frequency (N = 200)	Percentage (%)
ACEI		
No	159	79.5
Yes	41	20.5
Aldosterone Antagonist		
No	199	99.5
Yes	1	0.5
ARB		
No	132	66.0
Yes	68	34.0
Beta Blocker		
No	178	89.0
Yes	22	11.0
DHP-CCB		
No	42	21.0
Yes	158	79.0
Diuretic		
No	194	97.0
Yes	6	3.0
TLD		
No	188	94.0
Yes	12	6.0

Table 4: Association test between patients' demographic, clinical characteristics and class of antihypertensive medication prescribed versus blood pressure control at discharge.

	Blood Pressure Control		
Characteristics	**BP Uncontrolled[1]**	**BP Controlled[1]**	**p – value[2]**
Age, years			0.216 [T]
Sex			0.100
Male	71 (65.7)	50 (54.4)	
Female	37 (34.3)	42 (45.6)	
Educational status			0.719 [F]
No formal education	74 (68.5)	61 (66.3)	
Primary	3 (2.8)	2 (2.2)	
Junior high school	10 (9.2)	6 (6.5)	
Senior high school	3 (2.8)	6 (6.5)	
Tertiary	18 (16.7)	17 (18.5)	
Diagnosis evidenced by CT scan or MRI			0.705 [F]
No	3 (2.8)	4 (4.4)	

Yes	105 (97.2)	88 (95.6)	
Hypertensive			0.036 *
No	10 (9.3)	18 (19.6)	
Yes	98 (90.7)	74 (80.4)	
SBP at diagnosis			<0.001 T*
DBP at diagnosis			0.258 T
BP status at diagnosis			0.003 *
Uncontrolled	89 (82.4)	59 (64.1)	
Controlled	19 (17.6)	33 (35.9)	
Comorbidity			0.360
No	61 (56.5)	46 (50.0)	
Yes	47 (43.5)	46 (50.0)	
Renal impairment (eGFR ≤ 30ml/ml/min/1.73m^2)			0.034 *
Renal impairment (eGFR ≤ 30ml/ml/min/1.73m^2)			0.034 *
No	95 (88.0)	89 (96.7)	
Yes	13 (12.0)	3 (3.3)	
Liver impairment (High ALT)			0.391
No	101 (93.5)	83 (90.2)	
Yes	7 (6.5)	9 (9.8)	
Antihypertensive initiation			0.002 *
No	6 (5.6)	18 (19.6)	
Yes	102 (94.4)	74 (80.4)	
SBP at discharge			<0.001 T*
DBP at discharge			<0.001 T*
ACEI			0.175
No	82 (75.9)	77 (83.7)	
Yes	26 (24.1)	15 (16.3)	
Aldosterone Antagonist			1.000 F
No	107 (99.1)	92 (100.0)	
Yes	1 (0.9)	0 (0.0)	
ARB			0.326
No	68 (63.0)	64 (69.6)	
Yes	40 (37.0)	28 (30.4)	
Beta Blocker			0.612
No	95 (88.0)	83 (90.2)	
Yes	13 (12.0)	9 (9.8)	
CCB			0.007 *
No	15 (13.9)	27 (29.4)	
Yes	93 (86.1)	65 (70.6)	
Diuretic			0.221 F
No	103 (95.4)	91 (98.9)	
Yes	5 (4.6)	1 (1.1)	
TLD			0.552 F
No	100 (92.6)	88 (95.6)	
Yes	8 (7.4)	4 (4.4)	

1 = Frequency (%), 2 = Pearson's Chi-squared test, F = Fisher's exact test, T = T test, * = p-values < 0.05

Table 5: Logistic regression for the determinants of good blood pressure control.

	Crude			Adjusted		
Characteristics	**OR [1]**	**95% CI [3]**	**p-value**	**OR [2]**	**95% CI [3]**	**p-value**
Hypertensive						
No	Ref					
Yes	0.42	0.18 - 0.96	0.040 *			
SBP at diagnosis, mmHg						
	0.98	0.97 - 0.99	0.001 *	0.98	0.97 - 0.99	0.001 *

BP status at diagnosis						
Uncontrolled	Ref					
Controlled	2.62	1.36 - 5.04	0.004 *			
Renal impairment						
No	Ref			Ref		
Yes	0.25	0.07 - 0.89	0.033 *	0.26	0.07 - 0.97	0.045 *
Antihypertensive initiation						
No	Ref					
Yes	0.24	0.09 - 0.64	0.004 *			
SBP at discharge						
	0.83	0.79 - 0.87	<0.001 *			
DBP at discharge						
	0.85	0.81 - 0.89	<0.001 *			
CCB						
No	Ref					
Yes	0.39	0.19 - 0.79	0.009 *			

1 = Crude odds ratio, 2 = Adjusted odds ratio, 3 = 95% Confidence interval, Ref = Reference group, * = Significant p-values < 0.05

DISCUSSION

Majority of the patients were females with a mean age of 63 years and no formal education (Table.1). Most of the patients were diagnosed with Ischemic Stroke via CT or MRI, had comorbidities and were hypertensive at diagnosis. (Table. 2). This confirms what has been reported by Boehme et al, that hypertension is very common and can be termed as an independent risk factor for ischemic stroke (A. Boehme, 2017 In our study, hypertension was also the most common comorbid condition among ischemic stroke survivors. This is consistent with a study conducted by Kalkonde et al, which showed about 57% of participants were hypertensive (Kalkonde et al., 2020). Controlling risk factors, including hypertension, is one of the crucial strategies for preventing secondary ischemic stroke (Choudhury et al., 2015). Certain antihypertensive classes have been extensively studied in stroke patients for their ability to effectively manage elevated blood pressures and also reduce stroke recurrence in various jurisdiction. In our study, the classes of antihypertensive agents that possess enormous evidence with respect to their secondary prevention benefits were under prescribed, with 20.5% receiving ACEIs, then 34% received ARBs and a combined 9% received thiazide and thiazide-like diuretics (Table. 3). According to Khan et al, the most commonly prescribed antihypertensive medication during their study was dihydropyridine calcium channel blockers, just like in our study (Khan et al., 2010).

Even though dihydropyridine calcium channel blockers are recommended for the management of hypertension in stroke patients, evidence suggesting their efficacy in secondary stroke prevention is limited. Nevertheless, the use of dihydropyridine calcium channel blockers is reasonable for stroke patients who may require additional antihypertensive medication (Kleindorfer et al., 2021). The target BP for ischemic stroke is considered to be ≤130/80mmHg , and so the average SBP and DBP obtained from our study (Table.2) can be considered suboptimal (Kleindorfer et al., 2021).

Slightly over half of hypertensive patients were also noted to have uncontrolled blood pressure despite being prescribed antihypertensive, the reasons for this are multifactorial and beyond the scope of our study. (Table. 3). This is consistent with a study by Olson et al which also confirmed that uncontrolled blood pressure is one of the most common phenomena in stroke patients. Olson and Colleagues reported that close to 57% of participants had uncontrolled BP despite initiation of antihypertensive agents. The bivariate analysis showed that for each unit increase in SBP at diagnosis, the odds of achieving good BP control decreases by 2% (Crude OR = 0.98; 95% CI: 0.97 - 0.99; p-value =

0.001). This observation was still true even after adjusting for cofounders (Adjusted OR = 0.98; 95% CI: 0.97 - 0.99; p-value = 0.001) (Table.4). These observations may be attributed to parameters that were probably not considered in our study. Another determinant observed during our study is renal impairment. Patients who presented with renal impairment had a significantly lower odds of achieving good blood pressure control compared to participants with no renal impairment (Crude OR = 0.25; 95% CI: 0.07 - 0.89; p-value = 0.033) (Table. 5) Furthermore, initiation of BP medications has shown to be associated with lower odds of achieving blood pressure control, probably due to the lack of control by a large portion of the participants of this study.

Limitations of the study

The biggest limitation of our study is that we could not establish a possible causal relationship between the adherence to the dosage regimens of the prescribed antihypertensive medications and adequacy of blood pressure control. Also the retrospective nature of our study design did not create a good opportunity for us analyse the impact of adequate blood pressure on the rate and severity of recurrent Ischemic strokes.

CONCLUSIONS

The pattern of prescribing antihypertensive medications with the highest secondary prevention potential in ischemic stroke survivors at the Tamale Teaching Hospital is substandard resulting in suboptimal blood pressure controls. The most commonly prescribed class of antihypertensive medications for ischemic stroke survivors at the Tamale Teaching Hospital were dihydropyridine calcium channel blockers, ACEIs and ARBs. The major determinants of poor blood pressure control at diagnosis were hypertension and renal impairment.

Recommendations

- Clinicians should be sensitized on the trends observed in this study, and also the need to ensure adherence to relevant clinical guidelines.
- Further research should be conducted to assess the specific prescribe-related or patient-related factors that contribute to the inability for patients to receive their pharmacological secondary prevention.
- The hospital may need to consider employing the services of more neurologists, as well as clinical pharmacists in order to improve the level of pharmaceutical care of the patients.
- The hospital should also expand the stroke unit and equip it with the requisite resources in order to ensure that stroke patients are well monitored and well taken care of.

Conflict of interest declaration

All the researchers have no conflict of interest situations to declare

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Authors Contributions

MG conceived the research idea and collected all the relevant data including the literature review under the supervision of MMDM. JKK performed the data analysis. MMDM wrote the manuscript with the help of CA. All the authors thoroughly reviewed the manuscript and approved its content for publication.

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Data Availability Statement

All the quantitative and qualitative data used in writing the article are included in this manuscript.

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