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FREQUENCY AND FACTORS LINKED TO REFRACTORY HYPERTENSION AMONG STROKE SURVIVORS IN GHANA

Fred Stephen Sarfo[1,2,*], **John Akassi**[1,2], **Sheila Adamu**[2], **Vida Obese**[2], **Manolo Agbenorku**[2], **Bruce Ovbiagele**[3]

[1]Kwame Nkrumah University of Science and Technology, Kumasi, Ghana

[2]Komfo Anokye Teaching Hospital, Kumasi, Ghana

[3]Department of Neurology, University of California, San Francisco, USA

Abstract

Background: Refractory hypertension (RfH) is a rare, severe phenotype of resistant hypertension, linked to higher risk of adverse cardiovascular outcomes. Little is known about the association of RfH with stroke type and subtype.

Objective: To determine the prevalence and predictors of RfH among stroke survivors in Ghana.

Methods: We interrogated the dataset of a prospectively collected registry of hypertensive patients seen between July 2015 and June 2019, at five hospitals in Ghana. We compared stroke survivors to stroke-free controls. Clinic-based blood pressure was measured using a standardized protocol and antihypertensive medications were assessed via review of medical records and inspection of pills. Refractory hypertension was defined as office BP ≥140/90mmHg on ≥5 classes of antihypertensive medications. Multivariate logistic regression models were constructed to assess factors associated with RfH.

Results: Of 3,927 hypertensive patients (1169 stroke survivors, 2758 controls), 86 had RfH for an overall prevalence of 2.2% (95% CI: 1.8–2.7%). Among patients with RfH, 5.8% (4.5 – 7.3%) were stroke survivors vs. 0.7% (0.4–1.0%) were stroke-free (p<0.0001). Adjusted odds ratio (95% CI) for factors associated with RfH were being male (1.81, 1.15–2.85), age <60 years (2.64, 1.59–4.40), chronic kidney disease (2.09, 1.21–3.60), and known stroke (7.53, 4.35–13.04). RfH was associated with intracerebral hemorrhage, (11.43, 5.65–23.14), ischemic stroke (9.76, 5.47–17.42), lacunar stroke (13.58, 6.45–28.61), and non-lacunar ischemic stroke (3.67, 1.04–13.02).

Conclusion: Presence of RfH is significantly accentuated among stroke survivors. Intensified efforts are warranted to identify and aggressively address barriers to control in these patients to avert subsequent vascular events.

*Corresponding author at: Kwame Nkrumah University of Science and Technology, School of Medical Sciences, Department of Medicine, Private Mail Bag, Kumasi, Ghana, stephensarfo78@gmail.com.

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Keywords

Refractory Hypertension; Stroke types; Africa; risk factors

INTRODUCTION

Refractory hypertension is a rare phenotype of severe resistant hypertension characterized by failure to control blood pressure with five (5) or more antihypertensive agents of different classes at maximal or near-maximal therapy.[1–3] The prevalence of refractory hypertension among 14,800 participants on antihypertensive therapy in the US-based Reasons for Geographic and Racial Differences in Stroke (REGARDS) study was 0.5%.[4] Risk factors for refractory hypertension overlap with those for resistant hypertension and include black race, obesity, diabetes mellitus, and chronic kidney disease.[4]

Several studies have demonstrated strong associations between severe uncontrolled hypertension and occurrence of specific stroke types, namely intracerebral hemorrhage, intracranial atherosclerotic ischemic stroke and small vessel occlusive ischemic stroke particularly among Blacks than Caucasians. [5–7] However, we are unaware of any published studies evaluating the associations of refractory hypertension with stroke and its sub-types. As such it remains to be determined whether difficult-to-control phenotypes of hypertension such as refractory hypertension are more frequently associated with specific stroke types or not. Moreover, there is a paucity of published studies assessing the nature of the links between severe uncontrolled hypertension and stroke in Africa. In this study, we sought to assess the prevalence and predictors of refractory hypertension among stroke survivors in Ghana.

METHODS

Study design

Cross-sectional study of adults encountered in seven hospital-based clinics at five hospitals across Ghana. Clinics comprised four general medicine clinics, one hypertension clinic, one diabetes clinic, and one neurology clinic. Data for this study were collected between July 2015 and June 2019 from five hospitals including two tertiary care level medical centers - Komfo Anokye Teaching Hospital, (KATH) and Tamale Teaching Hospital, (TTH); two secondary care level health facilities - Agogo Presbyterian Hospital, (APH) and Atua Government Hospital, (AGH), and one primary care level hospital - Kings Medical center, (KMC).[8] The Neurology clinic at the Komfo Anokye Teaching Hospital in Kumasi was established in 2011 and runs once a week receiving referrals for adults >16 years with neurologic disorders as previously described.[9] Nearly 60% of patients encountered at this neurology clinic are stroke survivors.

Evaluation of Study Participants

Ethical approval for the study was obtained from the Committee of Human Research Publication and Ethics of the Kwame Nkrumah University of Science and Technology. We obtained written informed consent from all study participants prior to enrollment into the

registry. A Standard Operation Procedure was employed across sites to collect demographic information including age, gender, employment status and medical history. For all study participants with hypertension, information on current medications was obtained from review of medical records and inspection of pills.

Diagnosis of hypertension

All patients had been previously diagnosed with hypertension using cut-off value of ≥ 140/90 mmHg and were on antihypertensive therapy at enrollment into the study. Each site and study team was provided with an automated blood pressure device (Omron HEM-907XL) and trained on blood pressure measurement. Briefly, each study participant rested for at least 5 minutes prior to blood pressure measurements while sitting in a chair with both feet flat on the floor. Both arms were supported at the level of the heart on a table. Three consecutive blood pressure readings from the same arm were taken 2 minutes apart and the latter two readings were recorded. An average of these two latter BP readings was used for the present analysis.

Refractory hypertension was defined as having an office BP ≥140/90mmHg on ≥5 classes of antihypertensive medications.[10]

Stroke data collection

Stroke types were determined for those with cranial CT scans performed within 10 days post-stroke and were classified into ischemic stroke, intracerebral hemorrhage, sub-arachnoid hemorrhage or untyped for those without neuroimaging data. For those without neuroimaging data, stroke diagnosis was based on the World Health Organization definition[11], if participant had ever experienced sudden onset of weakness or sensory loss on one side of the body, sudden loss of vision, or sudden loss of speech. These questions were obtained from the 8-item questionnaire for verifying stroke free status (QVSFS) which have been validated locally.[12–14] QVSFS was used as neuro-imaging facilities were not available at some of the study sites at the time of the study. Based on CT scan data available, ischemic strokes were subtyped according infarct size (<1.5cm vs larger) into lacunar stroke or non-lacunar ischemic stroke. Ischemic strokes whose lesion sizes were not available were analyzed as ischemic stroke unclassified. The SMASH-U criteria were used to subtype hemorrhagic stroke etiologically.[15]

Diagnosis of diabetes mellitus

All patients had been previously diagnosed with type 2 DM using either an HBA1c reading of >6.5%, a fasting blood glucose of > 7.0 mmol/l on two occasions or a random blood glucose > 11.0 mmol/l and were on anti-glycemic therapy at enrollment into the study.

Renal impairment

Renal impairment was defined using estimated glomerular filtration rate (eGFR) calculated from baseline serum creatinine measurement using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula.[16]

Laboratory measurements

An International Organization for Standardization (ISO)-certified and quality-assured laboratory was contracted to run all biochemical panels for study participants. Samples were transported to the laboratory by trained phlebotomists on the same day of collection often within 4 hours or where not feasible (KMC and AGH sites), samples were stored in a freezer before transported to the laboratory the next day.

Statistical analysis

The Student's t-test was used to compare means of data with parametric distribution and the Mann-Whitney's U-test for comparison of medians of data which followed an non-parametric distribution. Proportions were compared using the Chi-squared tests or Fisher's exact test for proportions with subgroupings <5. Prevalence was presented with 95% confidence intervals based on normal approximation to the binomial calculation. Factors associated with refractory hypertension were assessed using a multivariable logistic regression model. Variable selection in this model was based on empirical data from bivariate analyses, and knowledge of risk factors of refractory hypertension from literature. In all analyses, two-tailed p-values <0.05 were considered statistically significant. Statistical analysis was performed using SPSS and GraphPad Prism version 7.

RESULTS

Demographic and clinical features of study population

This study included 3,927 patients with hypertension on antihypertensive treatment. There were 1,169 stroke survivors with hypertension and 2,758 stroke-free individuals with hypertension. Stroke survivors had had stroke for a mean (±SD) 5.0 ± 6.5 years. There were 700 (59.8%) ischemic strokes, 232 (19.7%) hemorrhagic strokes, 215 (18.4%) un-typed strokes and 22 (3.1%) with subarachnoid hemorrhage.

Blood pressure control & Number of antihypertensive medication classes

On average, patients were taking a mean ± SD of 2.3 ± 1.0 antihypertensive medications. Stroke survivors took 2.8 ± 1.2 antihypertensive medication classes compared with 2.1 ± 0.8 among stroke-free hypertensives, p<0.001. Figure 1 shows that the proportion with uncontrolled blood pressure increases with increasing number of antihypertensive drug classes prescribed (Figure 1). In total there were 110 participants on 5 or more antihypertensive medications. Across the entire study cohort, 86 out of 3,927 patients had refractory hypertension giving a prevalence of 2.2% (95% CI: 1.8 – 2.7%). The prevalence of refractory hypertension among stroke-free individuals with hypertension was 0.7% (0.4–1.0%) vs 5.8% (95% CI: 4.5–7.3%) among stroke survivors, p<0.0001. The frequency of refractory hypertension among individuals on ≥5 antihypertensive drug classes was 78.2%.

Characteristics and factors associated with refractory hypertension

Patients with refractory hypertension were significantly younger 53.3 ± 11.6 years than those without resistant hypertension 58.8 ± 12.7 years, p<0.0001. Comparing those with refractory hypertension with those without, the refractory hypertension group were

significantly more likely to be males 57.0% vs 29.7%, p<0.0001, less likely to reside in a rural location 12.8% vs 28.6%, and more likely to be employed. Those with refractory hypertension were more likely to attend a tertiary medical facility (90.7%) than secondary (9.3%) and none at primary hospitals. All antihypertensive drug classes were more frequently prescribed among those with refractory hypertension except ACE-inhibitors. (Table 1).

Factors associated with refractory hypertension in bivariate analyses were male gender, age <60 years, location of dwelling, having a stroke and chronic kidney disease. Upon adjustment for confounders, four factors which remained significantly associated with refractory hypertension reported as adjusted odds ratio (95% confidence interval) were: male gender 1.81 (1.15–2.85), age <60 years 2.64 (1.59–4.40), chronic kidney disease 2.09 (1.21–3.60) and stroke 7.53 (4.35–13.04) as shown in Table 2.

Stroke types and associations with refractory hypertension

Among 1,169 stroke survivors, 68 had refractory hypertension. In decreasing frequency by stroke type, the prevalence of refractory hypertension was 9.5% (6.0 – 14.0%) among hemorrhagic stroke survivors, 6.1% (4.5–8.2%) among ischemic stroke survivors, 1.4% (0.3 – 0.4%) among those with un-typed strokes and 0% among subarachnoid hemorrhage survivors. Correspondingly, the adjusted odds ratio (95% CI) of the major primary stroke types for refractory hypertension were: hemorrhagic stroke 11.43 (5.65–23.14), ischemic stroke 9.76 (5.47–17.42), and un-typed strokes 2.09 (0.60–7.25). Sensitivity analysis limited to ischemic stroke pathophysiologic subtypes showed lacunar stroke had aOR of 13.58 (6.45–28.61), ischemic stroke of other undetermined causes 10.55 (5.56–20.01) and non-lacunar stroke of large-infarct sizes with 3.67 (1.04–13.02). Table 3 shows a comparison of stroke survivors with refractory hypertension with those without refractory hypertension. The factors independently associated with refractory hypertension (aOR with 95% CI) among stroke survivors were male gender: 2.02 (1.12–3.65), age <60 years: 4.31 (2.06–9.05) and chronic kidney disease: 2.36 (1.30–4.30) (Table 4).

Antihypertensive classes among stroke patients with refractory hypertension

In decreasing order, calcium channel blockers 100.0%, Angiotensin receptor blockers/ACE-inhibitor 98.5%, thiazide diuretics 77.9%, beta-blockers 73.5%, direct vasodilators 73.5%, mineralocorticoid receptor antagonist 51.5%, centrally acting agents 41.2%, loop diuretics 17.6% and 0% for alpha blockers.

DISCUSSION

Refractory hypertension was found among 2.2% of a study population of nearly 3,900 subjects on antihypertensive therapy across 5 Ghanaian hospitals. However, upon dichotomizing the population into those with and without previous stroke diagnosis, we observed a much higher prevalence of 5.8% among stroke survivors compared with 0.7% among stroke free individuals with hypertension. Our data for the overall prevalence of refractory hypertension are comparable to 0.5% found among Americans in the REGARDS study highlighting the rarity of this phenotype generally.[4] However, the nearly 8-fold

difference in the prevalence of refractory hypertension among stroke survivors compared with the general population with hypertension is quite telling and may portray an underlying predisposition to stroke occurrence from severe and resistant forms of hypertension. The suggestion that refractory hypertension was more frequently observed among stroke survivors have been made by previous investigators from the US, Italy and China.[1–4]

However findings from our exploratory study extend these observations further by determining the risk of refractory hypertension among distinct stroke sub-types. On average, stroke survivors had had stroke diagnosis for five (5) years indicating that blood pressure recorded in the present study were not due to the known dramatic excursions which accompany an acute stroke. We observed profound associations between refractory hypertension and stroke sub-types that pathophysiologically emanate from small vessel disease namely intracerebral hemorrhages and lacunar infarctions in the vascular centrencephalon. These are stroke types deemed to be causally attributable to uncontrolled blood pressure.[17] Consistent with previous data[1–3], refractory hypertension was commoner among a younger age group overall, with an average age of 53 years among stroke survivors in our study. Data emerging from Africa clearly shows that the age of occurrence of stroke is about 15 years younger than that of high-income countries.[18,19] Indeed in sub-Saharan Africa with an escalating burden of stroke associated with poor outcomes[20–28], hemorrhagic stroke is estimated to contribute to 52.5% of all strokes under age 50 and the population attributable risk of hypertension for stroke in the young is a staggering 88.7%.[27,29,30]

Although resistant hypertension is commoner among blacks and thought to be due to racially determined renal mechanisms involving excess salt and water retention,[31–35] refractory hypertension may have distinctly different underlying mechanisms. Interestingly, indirect evidence suggest that antihypertensive failure in refractory hypertension may be of neurogenic origins with an exaggerated sympathetic outflow rather than via fluid retention.[36] In support of this, investigators have found that patients with refractory hypertension have persistently higher heart rates, greater vascular stiffness and greater 24-hour excretion of urinary norepinephrine levels.[36] Importantly, indicators of volume status such as renin activity, aldosterone levels, urinary sodium excretion, natriuretic peptide levels and intracardiac volumes are lower or normal in individuals with refractory hypertension compared with those with resistant hypertension with controlled blood pressure. The vascular stiffness induced by refractory hypertension could be a pivotal pathophysiologic correlate to the occurrence of small vessel hypertensive strokes. Perhaps one reason why fluid retention is not a common feature of refractory hypertension is that it is often diagnosed after addition of effective doses of a mineralocorticoid receptor antagonist or chlorthalidone to a backbone of long-acting calcium channel blocker, a thiazide-like diuretic and either ARB/ACE-inhibitor. Among our stroke cases with refractory hypertension on five or more antihypertensive medications, only half were on spironolactone and none was on chlorthalidone with approximately 73% on beta-blockers. Treatment options proposed for addressing refractory hypertension include use of agents that inhibit sympathetic output such as clonidine or device-based strategies such as carotid sinus activation or renal denervation.[37] These are therapeutic options not currently available to many hospitals across sub-Saharan Africa with a rising burden of hypertension related morbidity and mortality.[38–42]

This study has several limitations. As a cross-sectional study causal inferences between refractory hypertension and stroke occurrence cannot be drawn. Antihypertensive medication dosages, adherence and duration of use were not reported. Furthermore stroke survivors were drawn predominantly from a neurology clinic from a single tertiary center and the practices in antihypertensive medication prescriptions may not be reflective of the situation in other secondary or primary level health facilities in Ghana. Inclusion of hospital or clinical sites in our models showed significant interactions with location of residence and thus we did not include cadre of healthcare as a covariate in our final models. Nearly 90% of all refractory hypertension cases were encountered at tertiary medical centers in accord with previous data from high-income countries.[1,2,4] These limitations notwithstanding, our study is the first from sub-Saharan Africa to provide data on the burden and predictors of refractory hypertension with particular reference to stroke, its types and sub-types. Our contribution to the body of knowledge on resistant hypertension among stroke survivors in this resource-limited setting may useful for clinicians, researchers and policy makers. Clinicians managing stroke survivors with uncontrolled hypertension on multiple classes of antihypertensive medications may need to aware that refractory hypertension is a potential cause and therefore should initiate referral to specialists for appropriate management. For stroke researchers interested in secondary prevention, prospective studies are urgently required to understand the course and outcomes of difficult-to-control hypertension among stroke survivors given its relatively higher prevalence in this high-risk population.

In conclusion, the risk of refractory hypertension is significantly accentuated among stroke survivors. The associations observed between refractory hypertension and specific stroke types perhaps suggest yet-to-be identified pathophysiologic mechanisms linking difficult-to-control hypertension with stroke occurrence.

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Highlights

- Refractory hypertension (RfH) is uncontrolled BP on 5 or more classes of antihypertensive meds
- RfH is rare, severe and linked with poor CVD outcomes
- In this study 2.2% of Ghanaians had RfH
- Stroke survivors had 8-fold higher risk of RfH
- Small vessel stroke types had accentuated risks for RfH

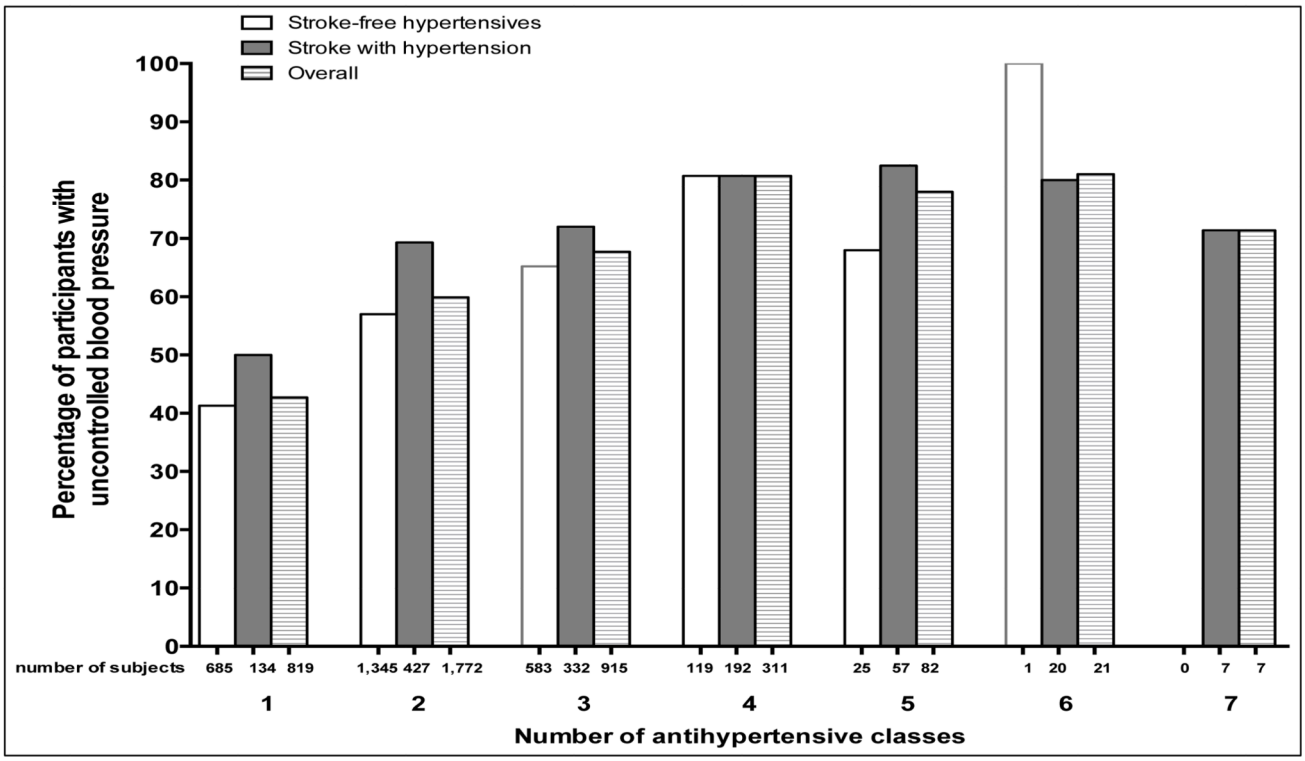

Figure 1.

Distribution of Number of antihypertensive medication classes versus percentage of participants (stroke-free hypertensives, stroke survivors with hypertension and total cohort of hypertensive subjects) with uncontrolled BP ≥ 140/90 mmHg.

Table 1.

Comparison of demographic and clinical features of subjects with and without refractory hypertension

Characteristic	Refractory Hypertension N=86	No refractory hypertension N=3,841	P-value
Age, mean ± SD	53.3 ± 11.6	58.8 ± 12.7	<0.0001
Male, n (%)	49 (57.0)	1139 (29.7)	<0.0001
Location of residence			0.004
rural	11 (12.8)	1,097 (28.6)	
Semi-urban	23 (26.7)	972 (25.3)	
urban	52 (60.5)	1772 (46.1)	
Employment status			<0.0001
Unemployed	26 (30.2)	1269 (33.0)	
Employed	49 (57.0)	2446 (63.7)	
No data	11 (12.8)	125 (3.3)	
Level of healthcare			<0.0001
Tertiary	78 (90.7)	2532 (65.9)	
Secondary	8 (9.3)	1143 (29.8)	
Primary	0 (0.0)	166 (4.3)	
Previous stroke, n (%)	68 (79.1)	1101 (28.7)	<0.0001
Diabetes mellitus, n (%)	22 (25.6)	1,329 (34.6)	0.08
Chronic kidney disease, n (%)			0.004
eGFR <60 ml/min	22 (25.6)	514 (13.4)	
eGFR ≥60 ml/min	47 (54.7)	2542 (66.2)	
No data	17 (19.8)	785 (20.4)	
Blood pressure			
Systolic BP, mean ± SD	172.7 ± 22.5	144.0 ± 22.5	<0.0001
Diastolic BP, mean ± SD	100.0 ± 18.1	83.9 ± 14.0	<0.0001
Classes of antihypertensive medications			
ACE-Inhibitors	31 (36.0)	1,600 (41.6)	0.30
Angiotensin Receptor Blocker	59 (68.6)	1,425 (37.1)	<0.0001
Beta-blocker	60 (69.8)	439 (11.4)	<0.0001
Calcium channel blocker	86 (100.0)	3,017 (78.5)	<0.0001
Diuretic	83 (96.5)	1,287 (33.5)	<0.0001
Methyldopa	45 (52.3)	536 (14.0)	<0.0001
Hydralazine	52 (60.5)	148 (3.9)	<0.0001
Mineralocorticoid receptor antagonist	35 (40.7)	40 (1.0)	<0.0001

Table 2.

Risk Factors for Refractory Hypertension among Ghanaians with hypertension on treatment

Factor	Unadjusted OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value
Male gender	3.14 (2.03–4.83)	<0.0001	1.81 (1.15–2.85)	0.01
Age <60 years	2.63 (1.58–4.35)	0.0002	2.64 (1.59–4.40)	0.0002
Location of residence				
Urban dwelling	2.93 (1.52–5.63)	0.001	1.23 (1.21–3.60)	0.55
Semi-urban dwelling	2.36 (1.14–4.87)	0.02	1.07 (0.48–2.38)	0.87
Rural dwelling	1.00		1.00	
Diabetes mellitus	0.65 (0.40–1.06)	0.08	- -	- -
Stroke	9.40 (5.57–15.88)	<0.0001	7.53 (4.35–13.04)	<0.0001
Chronic kidney disease	2.31 (1.38–3.87)	0.001	2.09 (1.21–3.60)	0.008
	Sensitivity analysis			
Stroke type				
Intracerebral hemorrhage	15.95 (8.42–30.20)	<0.0001	11.43 (5.65–23.14)	<0.0001
Ischemic stroke	9.96 (5.71–17.38)	<0.0001	9.76 (5.47–17.42)	<0.0001
Untyped stroke	2.15 (0.63–7.37)	0.22	2.09 (0.60–7.25)	0.34
Non-stroke hypertensive	1.00		1.00	
Ischemic stroke subtypes				
Lacunar stroke	14.05 (6.95–28.38)	<0.0001	13.58 (6.45–28.61)	<0.0001
Other causes	10.51 (5.68–19.45)	<0.0001	10.55 (5.56–20.01)	<0.0001
Non-lacunar ischemic stroke	3.40 (0.99–11.67)	0.05	3.67 (1.04–13.02)	0.04
Non-stroke hypertensive	1.00		1.00	

Table 3.

Comparison of demographic and clinical features of stroke survivors with and without refractory hypertension

Characteristic	Refractory hypertension N= 68	No Refractory hypertension n = 1101	P-value
Age, mean ± SD	53.1 ± 11.6	59.7 ± 13.2	**<0.0001**
Male, n (%)	45 (52.3)	513 (13.4)	**0.002**
Location of residence			0.23
Rural	7 (10.3)	109 (9.9)	
Semi-urban	17 (25.0)	386 (35.1)	
urban	44 (64.7)	606 (55.0)	
Employment status			0.28
Unemployed	19 (27.9)	396 (36.0)	
Employed	38 (55.9)	580 (52.7)	
Missing data	11 (16.2)	125 (11.4)	
Level of healthcare facility			0.20
Primary	0 (0.0)	5 (0.5)	
Secondary	0 (0.0)	45 (4.1)	
Tertiary	68 (100.0)	1051 (95.5)	
Stroke types			**0.002**
Ischemic stroke	43 (63.2)	657 (59.7)	0.56
Hemorrhagic stroke	22 (32.4)	210 (19.1)	**0.008**
Subarachnoid hemorrhage	0 (0.0)	22 (2.0)	0.27
Untyped	3 (4.4)	212 (19.3)	**0.002**
Ischemic stroke subtypes			**0.02**
Lacunar	15 (83.3)	162 (54.7)	0.14
Non-lacunar	3 (16.7)	134 (45.3)	**0.03**
Duration of stroke (months) mean ± SD	56.6 ± 78.2	58.6 ± 77.6	0.84
Diabetes co-morbidity	20 (29.4)	311 (28.2)	0.84
CKD (eGFR) ml/min			**0.005**
eGFR <60ml/min	35 (51.5)	624 (56.7)	
eGFR >60ml/min	20 (29.4)	166 (15.1)	
No data	13 (19.1)	311 (28.2)	
Classes of antihypertensive			
ACE-I	19 (27.9)	352 (32.0)	0.48
ARB	48 (70.6)	636 (57.8)	0.04
Beta blockers	50 (73.5)	183 (16.6)	<0.0001
Calcium channel blockers	68 (100.0)	930 (84.5)	0.0004
Diuretics (thiazide)	53 (77.9)	422 (38.3)	<0.0001
Diuretics (loop)	12 (17.6)	39 (3.5)	<0.0001
Mineralocorticoid receptor antagonist	35 (51.5)	40 (3.6)	<0.0001
Methyldopa	28 (41.2)	136 (12.4)	<0.0001
Hydralazine	50 (73.5)	161 (14.6)	<0.0001
Other drug classes			

Characteristic	Refractory hypertension N= 68	No Refractory hypertension n = 1101	P-value
Statins, n (%)	55 (80.9)	871 (79.1)	0.73
Antiplatelets, n (%)	44 (64.7)	710 (64.5)	0.97

Table 4.

Risk Factors for Refractory Hypertension among Ghana stroke survivors

Factor	Unadjusted OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value
Male gender	2.24 (1.34–3.75)	0.002	2.02 (1.12–3.65)	0.02
Age <60 years	3.27 (1.79–5.95)	0.0001	4.31 (2.06–9.05)	0.0001
Diabetes mellitus	1.06 (0.62–1.81)	0.84	- -	- -
Chronic kidney disease	2.15 (1.21–3.82)	0.009	2.36 (1.30–4.30)	0.005