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The Correlation between Various Types of Antihypertensive Drugs and the Incidence of Acute Stroke

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Abstract: Stroke is the second leading cause of death and the third leading cause of disability, whose incidence increase with hypertension. Various antihypertensives are used as secondary therapy for stroke. However, the effectiveness of each drug is still debated. This study aims to determine the correlation between various types of antihypertensive drugs on the incidence of acute stroke. This research is a cross-sectional study. Inclusion criteria included hypertensive patients who had used antihypertensive drugs for at least a year and were aged > 36. We included 78 subjects, 47 men and 31 women. The drugs were ACEI + CCB (13), ARB (8), ARB + CCB (22), and CCB (35). The subject had an ischemic stroke (8) and a hemorrhagic stroke (1). The logistic regression test showed ACEI + CCB as a reference category. The result consecutively showed ARB (OR, 4.95; CI, 0.72 to 33.89; p = 0.103), CCB (OR, 2.61; CI, 0.39 to 17.01; p = 0.317), and ARB + CCB (OR, 2.36; CI, 0.19 to 29.75; p = 0.507). The antihypertensive drugs had no significant correlation with the incidence of acute stroke. It indicated that stroke risk was not triggered by antihypertensive and could effectively control hypertension and protect patients against stroke.

Keywords: antihypertensive; hypertension; stroke

INTRODUCTION

Stroke is the second leading cause of death and the third leading cause of disability worldwide. A stroke occurs when brain cells do not work suddenly due to reduced oxygen supply and blockage or rupture in a brain artery.[1] Hypertension increases the risk of stroke through various mechanisms. The endothelium and smooth muscle function in the intracerebral arteries will change as intraluminal pressure rises. Increased permeability through the blood-brain barrier as a result of endothelial stress, resulting in local or multifocal edema. Endothelial damage and altered endothelial blood cell interactions can result in ischemic lesions or localized thrombus development. Fibrinoid necrosis can cause stenosis and localized occlusion, leading to lacunar infarction. Intracerebral bleeding is caused by degenerative alterations in smooth muscle and endothelial cells. It can hasten the arteriosclerosis process and make cerebral lesions more likely.[2]

The study published by JAMA showed that stroke could be treated with antihypertension.[3] ACEI, ARB, and CCB are the most frequently used antihypertension. It achieves the minimum target sample in this study. Antihypertensive treatment is believed to prevent stroke, but the correlation between types of antihypertension and stroke risk is still debatable.[4] Some studies had contradictory results. One showed that ACEI and CCB could reduce the risk of acute stroke and the other showed that antihypertensive ACEI or ARB had no significant correlation in reducing the risk of acute stroke.[5] The previous cohort study showed that ARBs and β-blockers consistently increased the risk of an incident stroke. β-blocker increased stroke risk by 41% to 43%, while ARBs increased stroke risk by 56% and 61%.[6] This study aims to determine the correlation between antihypertensive drug types on the incidence of acute stroke.

MATERIAL AND METHOD

This study was observational and analytical with a cross-sectional approach. The sample was measured descriptively to identify the characteristics of our subjects. The independent variable was antihypertensive drugs, and the dependent variable was the incidence of acute stroke. The population of this study included 488 subjects with essential (primary) hypertension. Inclusion criteria were subjects with a minimum of 36 years and diagnosed with essential (primary) hypertension who received antihypertensive therapy for at least one year. Samples were calculated with the Lemeshow formula and sorted by purposive sampling. We included 78 subjects. Nominal data antihypertensive (ACEI, ARB, CCB) were analyzed using SPSS with univariate and logistic regression. This study has received ethical clearance approval, 192/EC-KEPK FKIK UMY/VI/2021. This research was conducted at PKU Muhammadiyah Yogyakarta and PKU Muhammadiyah Gamping from August to October 2021.

RESULT

The data were collected from patients' medical records to obtain the correlation between patients with stroke incidence and without stroke incidence. The data were analyzed descriptively using SPSS to identify the frequencies and percentages, as shown in Table 1.

Table 1. Subject characteristics

Characteristic		Event			
		No Stroke Incidence		Stroke Incidence	
		n	%	*n*	%
Gender	Male	42	53,8	5	6,4
	Female	27	34,6	4	5,1
Age	36 – 45 years old	1	1,3	0	0,0
	46 – 55 years old	20	25,6	2	2,6
	56 – 65 years old	18	23,1	1	1,3
	65 years old and above	30	38,5	6	7,7
Blood Pressure	Normal	4	5,1	0	0,0
	High Normal	10	12,8	2	2,6
	Grade 1 Hypertension	24	30,8	3	3,8
	Grade 2 Hypertension	11	14,1	1	1,3
	Grade 3 Hypertension	20	25,6	3	3,8

A total of 78 subjects were divided into four groups of antihypertensive drugs, CCB and ARB as monotherapy, ACEI + CCB, and ARB + CCB as combination therapy. Subjects in this study were dominated by 60.3% of males while 39.7% were female. Mostly, patients with hypertension were 65 years old and above (46.2%) and on hypertension grade 1 (34.6%).

The Correlation between Antihypertensive Drugs and the Incidence of Acute Stroke

The correlation between antihypertensive drugs such as ACEI, CCB, and ARB was measured. The data were analyzed using logistic regression on SPSS to identify the correlation between each group of antihypertensive drugs, as shown in Table 2.

Table 2. The Correlation between Antihypertensive Drugs and the Incidence of Acute Stroke

OAH	Event				Total	*OR (CI 95%)*	*p*
	No Stroke		Stroke				
	n	%	n	%			
ACEI + CCB	10	12.8	3	3.8	13 (16.7%)	Ref	0.446
ARB	7	9.0	1	1.3	8 (10.3%)	4.950 (0.723 – 33.899)	0.103
ARB + CCB	19	24.4	3	3.8	22 (28.2%)	2.357 (0.187 – 29.745)	0.507
CCB	33	42.3	2	2.6	35 (44.9%)	2.605 (0.399 – 17.007)	0.317
Total	69	88.5	9	11.5	78 (100.0%)		

Abbreviations: ACEI *Angiotensin-Converting Enzyme Inhibitor; CCB Calcium Channel Blockers;* ARB *Angiotensin-II Receptor Blockers*

Calcium Channel Blocker (CCB) is the most widely used drug in hypertensive patients without stroke (*n*=33), 42.3%. Patients with the incidence of stroke mostly used Angiotensin-Converting Enzyme Inhibitor (ACEI) + Calcium Channel Blocker (CCB) (*n*=3) 3.8% and Angiotensin-II Receptor Blockers (ARB) + Calcium Channel Blocker (CCB) (*n*=3) 3.8 %. ARB is the least used drug in both patients without stroke and those with stroke.

Correlative analysis was carried out with the Wald test of significance $p<0.05$. There was no discernible link between the use of antihypertensives and the risk of stroke. The medications with the greatest effect were identified using the Odds Ratio (OR) value. The reference category was ACEI + ARB, and the results were as follows: ARB raised the incidence of acute stroke by 4,95 times, CCBs by 2,605 times, and ARB + CCB by 2,357 times; however, none of them exhibited a significant correlation ($p>0.05$).

DISCUSSION

The characteristics of subjects in this study are in accordance with previous studies where patients with hypertension mostly occur in men, 81.81%, 51.6%, 54.4%.[6-8] Smoking and overweight behavior, mostly carried out by men, will increase the risk of hypertension.[9] Data from the CDC showed that 4 out of 5 men with high blood pressure did not control their blood pressure.[10] It can affect testosterone which can cause the risk of systolic hypertension to increase by 2.71 times and diastolic by 2.5 times.[11]

Hypertension is mostly suffered in elderly patients >65 years old. This result aligns with Riskesdas 2018 that hypertension increases with age.[12] It showed that most hypertensive patients had grade 1 hypertension (n=27), 34.6%. This result is supported by previous research, which revealed that the majority of hypertensive patients came with hypertension grade 1, 61.8%, 40.3%.[13,14]

Managing vascular risk factors, especially hypertension, is important in the secondary prevention of stroke.[15] The usage of antihypertensive drugs as a treatment for blood pressure is one of the keys to preventing and reducing the risk of stroke, both ischemic stroke and hemorrhagic stroke.[16]

However, this result is not significant as the p-value>0.05. These results are similar to previous studies revealing no significant correlation between the usage of ACEIs or ARBs and stroke with an OR of 1.15 (95% CI; 0.91-1.44; *p*=0.24).[5] Another study showed no correlation between stroke incidence and the usage of ACEI (*p*=0.15).[17] Meta-analysis studies also displayed no significant difference between the use of CCBs and ACEIs on the incidence of stroke (RR, 0.96; 95% CI, 0.72 - 1.28).[18]

This study is in contrast to others showing that using CCBs could minimize negative outcomes in this area, such as the incidence of stroke (OR of 0.78, p=0.001) and ACEI/ARB (OR of 0.6, p=0.002). This non-significant result could be due to the influence of other factors such as age, gender, drug use, and other side effects.[19] Factors that can increase the risk of stroke include age, gender, race, hypertension, smoking, diet, lack of physical activity, inflammatory diseases, infections, pollution, and atrial fibrillation.[20]

In ischemic stroke patients, the most widely used antihypertensive drugs are ACEI + CCB and ARB + CCB. Meanwhile, 100% of hemorrhagic stroke patients used CCB. CCB monotherapy and a combination of ACEI/ARB + CCB are the top two uses of antihypertensive therapy. Both are at low risk for a poor outcome of death at three months and 12 months of follow-up.[19] ARBs block the angiotensin II type 1 receptor, which has been shown to reduce and positively affect the incidence of acute stroke.[21]

The combination of ARB and amlodipine (CCB) gave results that were as effective and well tolerated as the fixed-dose combination (FDC). Secondary peripheral edema can be caused by dihydropyridine calcium antagonists, which increase arterial vasodilation at hydrostatic capillary pressure. ARB normalizes the hydrostatic pressure of capillaries by promoting the return of blood to the heart and counteracting the effects of amlodipine in most patients with edema. Previous studies have shown that adding amlodipine to the ARB showed better results in lowering hypertension than using a single drug at the same dose.[22]

Amlodipine CCB class is useful in preventing athero-thrombolytic type stroke in the large arteries in the brain.[21] The CCB is considered to have a good therapeutic effect for hypertensive patients and has been shown to reduce the incidence of stroke by 33.3% compared to placebo. However, the molecular mechanism remains unknown.[23] The CCBs are classified into phenylalkylamines, benzodiazepines, and dihydropyridines.[24] Dihydropyridines have a high affinity for calcium intermediates in smooth muscle compared with phenylalkylamines and benzodiazepines, which have high selectivity in the myocardium.[25] CCBs have an athero-protection effect by activating endothelial nitric oxide synthase, inhibiting oxidative modification of LDL and membrane lipids, and regulating membrane instability, cholesterol, and matrix deposition.[19] The mechanism of action of CCBs is related to the inhibition of Ca2+ entry into body cells by binding to L-type

calcium intermediates in liver muscle. It will cause peripheral vasodilation and inhibit the sinoatrial and atrioventricular nodes so that the contractility and conductivity of the heart decreases.[26]

Furthermore, ACE inhibitors can reduce the adverse effects caused by the binding of angiotensin II to its receptors by blocking the conversion of angiotensin I to angiotensin II. In addition, combining the reduced form of angiotensin II with the Mas receptor results in vasodilatory, anti-inflammatory, and antifibrotic effects.[27]

There are two mechanisms of ARBs and ACEIs that can reduce the risk of stroke, namely the vascular protective effect and the effect of reducing angiotensin II, which can cause vasoconstriction. Inhibition of RAA can reduce endothelial and smooth muscle proliferation and prevent plaque instability. The usage of ARB therapy is the main recommendation in the world in treating hypertension, especially in patients with high cardiovascular risk. This therapy is based on natural metabolic effects and direct protective effects in lowering blood pressure in the heart and kidneys (pleiotropic effect). ARBs protect the cardiovascular system by stimulating angiotensin II type 2 (AT2) receptors. ARBs will increase the concentration of angiotensin II, which causes binding to the AT2 receptor and has a beneficial effect in reducing the risk of cardiovascular disease.[28] A meta-analysis study revealed that ARBs are safe drugs and do not increase the risk of death, myocardial infarction, and stroke.[29]

The main goal of hypertension treatment is to control the target blood pressure. Recommended first-line therapy includes thiazide-type diuretics, calcium channel blockers (CCBs), angiotensin-converting enzyme inhibitors (ACEIs), or angiotensin receptor blockers (ARBs).[30] Giving therapy is adjusted to the physical and clinical conditions, and the patient's choice is considered. If blood pressure does not reach the target within one month of treatment, increasing the dose or adding a second-line drug may be an option. In patients with blood pressure >160/100 mmHg, a combination of antihypertensive therapy is recommended as initiation therapy.[31] Achieving blood pressure control requires combination therapy with multiple drug types.

CONCLUSION

There was no significant correlation between various types of antihypertensive drugs on the incidence of acute stroke. It indicated that the risk of either hemorrhagic stroke or ischemic stroke was not triggered by antihypertensive and antihypertensive could work quite effectively to control hypertension and protect patients against *stroke.*

CONFLICT OF INTEREST

No conflict of interest.

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