Identifying Medication-Related Problem in Secondary Stroke Prevention Therapy: A Cross-Sectional Study in Central Java, Indonesia

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Abstract. Stroke is the second leading cause of death globally after ischemic heart disease. Patients who survive the first stroke have a possibility to get a recurrent stroke. American Heart Association and the Indonesian Neurologist Association recommend secondary stroke prevention to minimize recurrent stroke. This study aims to evaluate the use of secondary stroke prevention, which includes antiplatelet, antihypertensive, and lipid-lowering agents on discharged patients after stroke events. This study applied the purposive sampling method by comparing patient medications with the guidelines. Data of medications from medical records were evaluated for an appropriate indication, contraindication, appropriate drug of choice, including combination, and appropriate dosage regimens. The number of samples in this study was 74 patients. The inclusion criteria were discharged patients who survived the first stroke. Patients diagnosed with hemorrhagic or transient ischemic attack and pregnant patients were excluded. Of 74 patients, 69 patients received antiplatelet, 73 patients received antihypertensive, and 18 patients received lipid-lowering agents. Based on the guideline, 74, 73, and 21 patients should get antiplatelet, antihypertensive, and lipid-lowering agents, respectively. Antiplatelet agents prescribed to 69 (93.24%) patients were appropriate. Antihypertensive therapy was prescribed to 73 patients: 59 (80.82%) patients were appropriate, while 19.18% were not appropriate. A lipid-lowering agent therapy prescribed to 18 (85.71%) patients was appropriate. Secondary stroke prevention medications were not prescribed to all stroke survivors. Untreated indications and inappropriate combinations of drugs are medication-related problems identified in secondary stroke prevention therapy.

Keywords: secondary stroke prevention · ischemic · stroke · antiplatelet · antihypertensive · a lipid-lowering agent

1   Introduction

Ischemic stroke is caused by reduced blood flow to some or all of the brain caused by a blockage in the brain's blood vessels [1]. Stroke leads to high morbidity and mortality.

According to the *Centers for Disease Control and Prevention* (CDC), of 100,000 stroke patients in the United States, 50–100 die each year. Stroke is a disease-causing the world's highest defects and multiple diseases after heart disease. Stroke was responsible for one out of every six deaths caused by cardiovascular disease in 2018 [2]. The highest incidence rate of stroke in Indonesia was in East Kalimantan (14.7 ‰), Yogyakarta (14.6 ‰), North Sulawesi (14,2 ‰), and Riau (12,9 ‰). The prevalence of stroke was similar between men and women [3].

Patients who survive the first stroke can have a recurrent stroke. Ninety-one out of 500 (18%) stroke patients had a recurrent ischemic stroke [4]. On average, patients with recurrent stroke have poorer outcomes than those with the first stroke. The survival level from the first stroke is consistently higher than that for recurrent stroke, with the story of 25-month survival being 56.7% versus 48.3%, respectively [5]. Therefore, to minimize the incidence of recurrent stroke, American Heart Association/American Stroke Association (AHA/ASA) and Indonesian Neurologist Association/*Persatuan Dokter Syaraf Indonesia* (PERDOSSI) recommend secondary stroke prevention therapies consisting of antiplatelet, antihypertensive, and lipid-lowering agents for ischemic stroke patients [6, 7].

Pharmacological therapy that targets high blood pressure and hyperlipidemia has decreased the incidence of recurrent stroke. Providing optimal secondary prevention therapy can reduce the incidence of recurrent stroke by 80% [8]. A study proved that secondary prevention therapy could reduce the incidence of recurrent stroke. Antiplatelet administration reduced the incidence of recurrent stroke from 68% to 24%, antihypertensive therapy diminished recurrent stroke from 69% to 23%, and lipid-lowering agent therapy decreased recurrent stroke from 54% to 29% [9]. Another study also mentioned that stroke patients with increased systolic blood pressure every ten mmHg will increase the risk of stroke by 1.6 times. [10]. Secondary stroke prevention therapies should comply with rational medicine use (appropriate indication, not contraindicated to the patients, right drugs, and proper dosage regimens). Inappropriate medications lead to failure of therapeutic goals or therapeutic outcomes. This research aimed to evaluate medication-related problems using secondary stroke prevention therapy in ischemic stroke patients in a Teaching Hospital in Central Java, Indonesia.

2   Methods

2.1   Research Design

This study was a descriptive observational study, and data were taken retrospectively. This study was conducted from July to August 2017. The population of this study was patients who survived the first stroke. Data were taken from patients' medical records. Guideline of the Indonesian Neurologist Association (PERDOSSI) and AHA/ASA was used to evaluate the appropriate use of secondary stroke prevention therapies. Sampling was conducted by purposive sampling. The inclusion criteria were outpatients who survived the first stroke with sufficient data in their medical records. The exclusion criteria were hemorrhagic stroke or transient ischemic attack and pregnant patients. The total population of ischemic stroke outpatients in the Teaching Hospital from January to September 2017 was 74 patients, while the total stroke population in 2016 was

129 patients. Based on the calculations with the Slovin formula, the minimum number of samples is 64 respondents, and the samples of this were 74 patients (patients from 2016–2017).

2.2 Procedure of Research

Ethics approval of the study was obtained from the Health Research Ethics Committee General Hospital/School of Universitas Sebelas Maret Surakarta number 649/VII/HREC/2017 before the beginning of the research. Seventy-four patients' medical records met inclusion and exclusion criteria during the research period. Data on patients' demographics, secondary prevention therapies (name of drugs and dosage regiment), blood pressure, laboratory test (total cholesterol, LDL, HDL, Triglycerides), SGOT, SGPT, and creatinine serum were recorded. The rational use of secondary stroke prevention was evaluated based on the guideline of the Indonesian Neurologist Association (PERDOSSI) and AHA/ASA. The data were analyzed descriptively.

3 Results

During the study, 74 patients met inclusion and exclusion criteria. The patient characteristic can be seen in Table 1.

Based on Table 1, most ischemic strokes of age characteristics were 55–64 years, with 35 patients (47.29%). It is probably because of an increase in the formation of atherosclerosis and blood vessel degenerative changes due to advancing age that interferes with blood flow [11]. The number of male patients was slightly higher than females. According to PERDOSSI, male patients are more than women because women have estrogen that protects them from atherosclerosis [7].

Profile of antiplatelet, antihypertensive, and lipid-lowering agents as secondary stroke prevention can be seen in Tables 2, 3, and 4, respectively. Of 74 patients, 69 patients (93.24%) received antiplatelet agents, 73 patients (98.63%) received antihypertensive therapy, and 18 patients (85.71%) received lipid-lowering agents.

and 18 patients (85.37%) received lipid-lowering agents.

A medication-related problem was identified in the antiplatelet agent as secondary stroke prevention in category untreated indication. Five (6.75%) patients did not receive

Table 1. Characteristics of discharged patients from the hospital because of ischemic stroke

Age (year)	Sex		Number	(%) (n = 74)
	Male	Female		
35 - 44	0	2	2	2.7
45 - 54	4	9	13	17.6
55 - 64	19	16	35	47.3
65–74	12	5	17	22.9
≥75	3	4	7	9.5

Table 2. Profile of antiplatelet administered to discharged ischemic stroke patients in the Teaching Hospital

Secondary prevention	Drugs	Number (n = 74)	%
Patients received antiplatelet agents	Clopidogrel	41	55,40
	Aspirin	28	37,83
	Total Patients received antiplatelet agents	69	93,24

Table 3. Profile of Antihypertensive administered to discharged Ischemic Stroke patients in the Teaching Hospital

Secondary prevention	Class	Drugs	Number n = 74	%
Patients received antihypertensive	ACEIs	Captopril	1	1,36
	ARBs	Valsartan	29	39,72
		Telmisartan	24	32,87
		Candesartan	7	9,58
	Diuretics	Furosemide	4	5,47
		Spironolactone	1	1,36
		Hydrochlorothiazide	1	1,36
	CCBs	Amlodipine	31	42,46
	BBs	Bisoprolol	2	2,73
	CCBs & ARBs	Amlodipine & Valsartan	7	9,58
		Amlodipin & Telmisartan	2	2,73
		Amlodipin & Candesartan	2	2,73
	ARBs & BBs	Candesartan & Bisoprolol	4	5,47
	CCBs & diuretics	Amlodipin & Furosemide	1	1,36
	Combination of 2 ARBs	Telmisartan & Candesartan	1	1,36
	Diuretik & BB	Furosemid & Bisoprolol	1	1,36
	Combination of 3 antihypertensive agents	Amlodipine, Valsartan & Bisoprolol	2	2,73
		Candesartan, Bisoprolol & Furosemid	1	1,36
		Valsartan, Bisopropol & Furosemid	1	1,36
		Candesartan, Amlodipin & Furosemid	1	1,36
	Antihypertensive		73	98.63

antiplatelets. Based on the guideline, these five patients should receive antiplatelets. Antiplatelet agents prescribed to sixty-nine (93.24%) patients were appropriate or met the rational use of drug criteria.

Table 4. Profile of lipid-lowering agent administered to discharged Ischemic Stroke Patients in the Teaching hospital

Drugs	Number n = 21	%
Simvastatin	15	83,33
Gemfibrozil	2	11,11
Fenofibrate	1	5,55
Patients received a lipid-lowering agent	18	85,71

In this study, 73 patients had a blood pressure of >140/90 mmHg and received anti-hypertensive. One patient had a blood pressure of 126/76 mmHg and did not receive antihypertensive therapy. Furthermore, 73 patients (98.63%) who received antihypertensive did not show contraindication in their clinical condition. The antihypertensive class of Angiotensin-Converting Enzyme Inhibitor (ACEI) is used as captopril. Patients who were declared as inappropriate medication were 14 patients (19.18%), including patients receiving Beta-Blocker (BB) therapy, two Angiotensin Receptor Blocker (ARB) combination, diuretic, and BB combination, and a combination of three antihypertensives. Antihypertensive therapy prescribed to 59 (80.82%) patients was appropriate.

Based on the guideline, 21 patients should receive a lipid-lowering agent. Eighteen patients received a lipid-lowering agent, while three patients did not get a lipid-lowering agent. Lipid-lowering agents were simvastatin, gemfibrozil, and Fenofibrate. That 18 patients (85.71%) were receiving lipid-lowering agents was appropriate because patients had LDL $\geq$ 100 mg/dL or triglyceride $\geq$ 150 mg/dL. However, three patients (14.28%) were untreated indication medication-related problems because their LDL was $\geq$ 100 mg/dL, but they were not given lipid-lowering agents. Therefore, a lipid-lowering agent therapy and its dose prescribed to 18 (85.71%) patients was appropriate.

4 Discussion

Patients with an ischemic stroke or a transient ischemia attack are at significant risk of a recurrent stroke. Recurrent stroke can be minimized or prevented by addressing vascular risk factors, including blood pressure control, physical activity, diet, smoking cessation, and secondary stroke prevention. Antiplatelet treatment, statins, and antihypertensive are therapies for secondary stroke prevention [6, 12]. Based on the World Health Organization, rational use of drugs requires that "patients receive medications that are appropriate to their clinical needs, in doses that meet their own individual needs, for an adequate time, and at the lowest cost to them and their community [13].

All post-stroke patients should receive antiplatelet therapy [7, 14]. For patients with non-cardio embolic ischemic stroke or TIA, the use of antiplatelet agents rather than oral anticoagulation is recommended to reduce the risk of recurrent stroke and other cardiovascular events *(Class I; Level of Evidence A)* [15]. Antiplatelet administration reduced the incidence of recurrent stroke from 68% to 24% [9]. According to PERDOSSI

2011, antiplatelet should be given up to nine months after a stroke [7]. Four FDA-approved antiplatelet drugs for preventing vascular events in ischemic stroke patients are aspirin, a combination of aspirin and dipyridamole, clopidogrel, and ticlopidine. These four medications can reduce the risk of stroke, myocardial infarction, or fatality by about 22% [15]. In terms of cost, aspirin is the cheapest drug. The aspirin price is about 20 times lower than other antiplatelets [15]. Clopidogrel is used in patients with allergies or intolerance to aspirin [16]. Clopidogrel is an alternative for patients who are allergic to aspirin or patients with gastrointestinal side effects. Clopidogrel is not contraindicated in asthmatic patients [17]. Clopidogrel is contraindicated in patients with active pathologic bleeding such as peptic ulcer disease (PUD) or intracranial hemorrhage and coagulation disorders [17].

A meta-analysis of randomized trials showed that antihypertensive medications reduced the risk of recurrent stroke after stroke or TIA [18]. Blood pressure reduction is recommended to prevent recurrent stroke and other vascular events in people who have had an ischemic stroke or TIA and are beyond the first 24 h (*Class I; Level of Evidence A)* [19]. Antihypertensive therapy reduces recurrent stroke from 69% to 23% [9]. Therefore, antihypertensive treatment is one of the recommended drugs for preventing recurrent stroke. The use of antihypertensive can lower blood pressure averaging 10/5 mmHg. Blood pressure target in stroke patients is less than 140/90 mmHg. If the patient also has diabetes mellitus or chronic kidney disease, the blood pressure target is less than 130/80 mmHg [7]. Thus, antihypertensive therapy is recommended for all patients with ischemic stroke with blood pressure > 140/90 mmHg [20].

According to PERDOSSI (2011) and Dipiro *et al.* (2017), diuretics or diuretic combinations and ACEI/ARB is drugs of choice for preventing recurrent stroke [7, 20]. Furthermore, a meta-analysis study of antihypertensive CCB may reduce Systolic Blood Pressure (SBP) variability when used at high doses (single or in combination). Thus, CCB may play a role in preventing recurrent stroke [21]. CCB, namely amlodipine, and ARB, such as valsartan, are two antihypertensive drugs with the most robust supportive data for preventing stroke [22].

Thus far, there is no evidence to support the routine use of Beta-Blockers to prevent recurrent stroke [23]. Patients who received a combination of CCB and diuretics, a combination of 2 ARBs, a combination of diuretics and BB, and a combination of three antihypertensives expressed inappropriately for several reasons the drug is not a drug of choice antihypertensive to prevent recurrent stroke. As yet, no research discusses CCB combination therapy and diuretics, a combination of 2 ARBs, a combination of diuretics and BB, and a combination of three antihypertensives to prevent recurrent stroke.

A lipid-lowering agent is recommended to reduce the risk of stroke and cardiovascular events among patients with ischemic stroke or TIA. Karuniawati et al. 2015 [9] showed a significant association between lipid-lowering agent therapy and recurrent stroke with p = 0.011. Patients who did not use lipid-lowering agent therapy had a 2.925 times risk of recurrent stroke compared with those taking lipid-lowering agent therapy.

Therapy given to the patient followed the patient's clinical condition or was not contraindicated. Simvastatin is contraindicated in liver disease, elevated serum transaminases, pregnancy, and lactation [17]. Gemfibrozil and Fenofibrate are contraindicated in patients with hepatic or renal dysfunction, primary biliary cirrhosis, and pre-existing

gallbladder disease [17]. Elevated SGOT and SGPT characterize patients who experience liver damage or decline in liver function. Laboratory data of patients receiving gemfibrozil or Fenofibrate therapy showed no increase in SGOT and SGPT levels. Therefore, gemfibrozil and fenofibrate therapies were safe for these patients because they were not contraindicated.

Patients who have evidence of atherosclerosis and LDL level $\geq$ 100 mg/dL and who are diagnosed with coronary heart disease (CHD) are recommended to get statins (Class 1; Level of Evidence B) [7, 14, 19]. Statins can reduce the risk of stroke by about 30% in patients with coronary artery disease and elevated plasma lipids. In addition, statin therapy can reduce LDL levels by up to 50% for secondary stroke prevention. Other drugs used to treat dyslipidemia are fibrates. This agent can be used by stroke patients who are intolerant to statins. Patients with low HDL-C may be considered for treatment with niacin or gemfibrozil) [19, 24]. Fenofibrate may be given to patients with triglyceride levels $\geq$ 150 mg/dL [20].

5   Conclusions

The result of this study was of 74 respondents, 69 patients received antiplatelet, 73 patients received antihypertensive, and 18 patients received lipid-lowering agent. That 69 (93.24%) patients receiving antiplatelet therapy was rational (appropriate indication, patient, medicine, and dose) considering that 74 patients were supposed to get antiplatelet. Likewise, antihypertensive treatment was prescribed to 73 patients: 59 (80.82%) patients were appropriate, while 19.18% were inappropriate. Eighteen (85.71%) patients received a lipid-lowering agent therapy that was avowed reasonable, considering 21 patients were supposed to get a lipid-lowering agent.

We acknowledge that this research had a limitation. Data were based on medical records of patients and taken retrospectively. Therefore, the researchers cannot confirm why some patients did not receive secondary stroke therapies from the prescriber.

Authors' Contributions. H.K. had the idea of this study and designed the proposal. Z.C. and T.A. developed the protocol. L.N. and T.A. gathered data from medical records under H.K. and Z.C. supervision. L.N. managed the data entry while H.K. and Z.C. completed the analysis. Finally, all of the authors read and approved the manuscript.

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