Research Article

Safety and Tolerability of Antihypertensive Agents in Long-term: A Literature Review

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Abstract.
Hypertension is known to affect more than one billion people globally and is estimated to increase to 1.5 billion by 2025. It is considered one of the leading causes of death and cardiovascular disease worldwide. The safety of long-term antihypertensive use is also a concern. Through a narrative or literature review, this study evaluated antihypertensive agents based on the results of various literature searches. Researchers reviewed the safety and tolerability of five classes of antihypertensive agents such as Diuretics, Angiotensin-Converting Enzyme Inhibitors (ACEI), Angiotensin Receptor Blockers (ARB), Beta-Blockers, and Calcium Channel Blockers (CCB). The use of ARB antihypertensive drugs like valsartan is well tolerated and safe. Moreover, the mortality rate associated with enalapril was 16% lower (95% CI 0.76-0.93; $P < 0.001$). Captopril and lisinopril of Angiotensin-converting Enzyme Inhibitors (ACEIs) have significant side effects (SEs) compared to any antihypertensive drug. Therefore, this study recommends using the ACEIs group, especially captopril and lisinopril, due to the minimal side effects produced compared to other antihypertensive drugs. In addition, the CCBs or Ca antagonists class like amlodipine is potentially well tolerated and safe as a first-line drug for hypertension treatment.

Keywords: antihypertensive drugs, hypertension, safety, side effect, tolerability

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1. Introduction

Hypertension is known to affect more than one billion people globally and is estimated to increase to 1.5 billion by 2025. This disease is also has the highest number of cases, which is 63,309,620 with 427,000 deaths. Symptoms of hypertension manifest in an increase in systolic and diastolic blood pressure that exceeds the limit of ≥140/90 mmHg. Thus, this condition is perceived as one of the significant risk factors for the occurrence of cardiovascular disease, as well as being the leading cause of death worldwide, especially in Indonesia [1]. Based on the National Coordinating Council for Medication Error Reporting and Prevention (NCCMERP), medication errors are defined as "Any preventable event that may cause or contribute to the inappropriate use of

a medication or harm to a patient when the medication is within the control of the health professional, patient, or consumer." Nevertheless, any medication error can be prevented before complications occur or do not harm the patient. In the recent study titled "Incidence of Medication Errors in the Intensive Care Unit", it was explained that the majority of medication errors were caused by prescribing anti-hypertensive drugs with a percentage of cases amounting to (11.21%) [2].

The treatment of hypertension aims to prevent complications of the disease and control blood pressure. In general, doctors routinely use various classes of antihypertensives, namely Angiotensin Converting Enzyme Inhibitors (ACEI), Angiotensin Receptor Blockers (ARB), Beta Blockers, Diuretics, and Calcium Channel Blockers (CCB). However, hypertension patients must control their blood pressure (BP) for high-risk complications, The application of pharmacologic therapy for hypertension is considered to have the potential to reduce disease severity and mortality. Therefore, the long-term safety aspects of various antihypertensive agents are a subject of serious concern [3]. This is supported by the high percentage of cases of errors in prescribing antihypertensive drugs by doctors to patients.

Therefore, researchers consider that the discussion of safety and tolerability of antihypertensive Agents in a long-term is needed with the aim of evaluating the prescribing of antihypertensive drugs to reduce cases of medication errors in the use of antihypertensive drugs by doctors.

2. Methods

The research method is in the form of a narrative or literature review, the comprehensive literature search performed in the MEDLINE database, Crossref, and Google Scholar equipped with a manual literature search from the bibliography of the articles retrieved. Search terms used were hypertension, cardiovascular disease, arterial hypertension, blood pressure, "antihypertensive drug, long-term safety, side effect, efficacy, captopril, lisinopril, valsartan, furosemide, amlodipine, and propranolol. As a result of this, the literature review involved 18 scientific journals in writing this literature review. After a search, the articles selected were limited to only papers published in English and without a time limit.

3. Antihypertensive Agent

3.1. Angiotensin-converting Enzyme Inhibitors (ACEIs)

Angiotensin-converting enzyme inhibitors (ACEIs) have become a highly desirable option in the treatment of hypertension. It is due to their function of not only regulating blood pressure by inhibiting angiotensin-converting enzyme (ACE) to convert angiotensin (AT) I into AT II, which also maintains sodium and water homeostasis in the body. In addition, ACEIs have also shown efficacy in the prevention of renal damage in patients with diabetic nephropathy and non-diabetic renal failure, by the mechanism of modification from AT I to AT II [4].

Captopril and lisinopril are two examples of drugs in the ACEI group. Of 7,103 hypertensive patients receiving captopril medication for 3 months-4 years, 627 patients decided to discontinue, with 230 patients due to failure to maintain adequate blood pressure reduction and 397 patients due to Side Effects (SEs), Historically, the condition has been associated with increased disease severity and mortality in patients suffering from aortic stenosis [5].

The main side effect of using ACE inhibitors is mainly related to the risk of hyperkalemia, with a percentage of patients around 2% to 6%, which is due to the mechanism of action of ACE inhibitors in the body. Angiotensin II blockade inhibits downstream aldosterone secretion. Aldosterone affects the reabsorption of sodium and, therefore, water, which in turn causes the secretion of protons and potassium into the urine. Because potassium secretion is inhibited by aldosterone inhibition, potassium levels may increase significantly in patients taking ACE inhibitors. Commonly, patients taking lisinopril, a type of ACE inhibitor, often develop dry cough between one week to six months after the start of treatment, with an incidence of about 10% to 20% of total patients. Angioedema, although rare, is a potentially life-threatening side effect of taking ACE inhibitors, with incidence rates ranging from 1% to 2%. Angioedema is an adverse drug response characterized by episodic swelling of the face, lips, and upper airway region. Extensive accumulation of bradykinin in a given individual causes angioedema. Hypotension is one of the side effects, with a percentage of patients around 7% to 11%, which causes intolerance to therapy and discontinuation of treatment in a small percentage of patients using lisinopril or other antihypertensive agents. Dizziness is a reaction to drug use that is considered typical in ACE inhibitor therapy, around 12% to 19%. Once treatment is started, it is expected that the glomerular filtration rate (GFR)

will drop slightly. Discontinuation of ACE-Inhibitor therapy may be required in patients with renal insufficiency of 2% to 11%, chronic kidney disease, and bilateral renal artery stenosis with poor renal perfusion [6].

Lisinopril-type drugs have low bioavailability ranging from 10-30% after being taken orally. This side effect occurs more frequently in patients with conditions such as autoimmune, kidney disease or collagen vascular disease. Based on the latest 2017 American College of Cardiology (ACC) guidelines for the Prevention, Detection, Evaluation, and Related Management of High Blood Pressure in Adults, among patients requiring pharmacologic therapy, ACE inhibitors are the first recommended choice for hypertension management globally. However, captopril has minimal side effects that can potentially reduce disease severity and mortality [7, 8].

3.2. Angiotensin Receptor Blockers (ARBs)

Angiotensin Receptor Blockers (ARBs) these antihypertensive agents have a mechanism of action similar to ACEi. ARB-class drugs will reduce the likelihood of recurrent stroke in patients who have previously experienced a stroke or transient ischemic attack. This mechanism was accomplished by acting as an antagonist at the AT I receptor, which results in blocking the Renin-Angiotensin Aldosterone System (RAAS) and resulting in vasoconstriction. One example of a drug in the ARB class, In long-term studies, Valsartan is usually well tolerated. Serious adverse event (EDS) reports did not include any deaths in patients. The incidence of serious adverse events (SAEs) tended to be higher in the use of valsartan in combination with other groups of antihypertensive agents (19.5%) compared to the use of single valsartan (6.4%). However, treatment discontinuation due to SEs was remarkably lower in valsartan than in enalapril (ACEIs) (10.7% vs. 12.3%; P = 0.03) [9–11].

Some studies consider that valsartan is well-tolerated in this long-term study. In the article on achieving maximum dose over time, valsartan was titrated to a dose of 97/103 mg twice daily in approximately 35% of patients (95% confidence interval: 23-47), and there was no significant association with age or gender. Based on the analysis of the nine studies reviewed, the proportion of subjects who discontinued valsartan was 12.8% (95% confidence interval: 7.4-18.3). One of the adverse effects of use was hyperkalemia, assessed in six investigations (a total of 1076 people), where cases occurred in approximately 12 (95% CI 5-19)/100 person-years. In the literature, 16 selected articles evaluated the renal function of the patients. Still, of the 16 articles,

only 6 reported worsening renal function, defined in two types (an increase in serum creatinine ≥0.3 mg/dL in 18 articles and a case of a decrease in glomerular filtration rate ≥30% in 24 articles). Hence, these studies reported a reduction of renal function in 5.1% (95% CI 2.8-7.4) of treated patients who were CKD patients and were not drug related [12].

Five studies reported all-cause mortality due to the use of valsartan that included approximately 684 subjects, with the incidence rate of death being 8 (95% CI 4-12)/100 person-years. As concluded by 3 studies with a total of approximately 390 patients, the hospitalization rate was 24 (95% CI 5-42)/100 person-years experiencing hospitalization. Valsartan was well-tolerated in this long-term study [10, 12].

3.3. Beta Blockers (B-Blockers)

β-Blockers are a class of hypertension drugs recommended by the Joint National Committee 7 (JNC 7) as a particular choice of medications for essential hypertension. This drug works by inhibiting beta-adrenergic receptors, which could reduce the body's response to adrenaline and noradrenaline, thus helping to lower blood pressure. However, research for β-Blockers is still considered vague and inconclusive. Propranolol, a type of antihypertensive drug in the β-Blockers class regarded as non-cardioselective, exhibits membrane stabilizing properties in the absence of intrinsic sympathomimetic activity, as presented in the study [11].

Propranolol has shown effectiveness in controlling various medical conditions, such as hypertension, pheochromocytoma, myocardial infarction, cardiac arrhythmias, angina pectoris, and hypertrophic cardiomyopathy. Propranolol also has benefits in reducing symptoms of sympathetic overactivity in the treatment of hyperthyroidism, anxiety disorders, and tremors. Additional indications include prevention of migraine and upper gastrointestinal bleeding in patients with portal hypertension. It is still a concern that in the experience of one of the researchers, there was a patient who experienced severe hypotension during exercise and experienced sinoatrial block causing syncope after using beta-blockers for >15 years [13, 14].

Along with the required effects, the drug may also cause unwanted effects. In a meta-analysis conducted in the journal, researchers identified 26 patients (2.1%) who experienced (SEs) related to the treatment process with propranolol. More than 73% of adverse events occurred within the first 30 days of propranolol use. One of the adverse events was severe sleep disturbance that led to the discontinuation of propranolol,

representing 65.4% (17/26 patients), with 3 patients (11.5%) experiencing extreme agitation. 4 patients (approximately 15.4%) experienced severe respiratory distress. 2 of them developed significant bronchial hyperreactivity within 10 days of initiation of propranolol therapy. Bronchial hyperreactivity can be life-threatening, leading to permanent discontinuation of propranolol treatment due to its severe symptoms. Meanwhile, the other two patients experienced bronchospasm associated with viral infections but experienced rapid recovery after discontinuation of propranolol [15].

3.4. Diuretic

Diuretics are a class of hypertension drugs used for decades. Several prospective studies have shown that the use of thiazide diuretics is safe and effective in reducing disease severity and mortality in patients with hypertension. However, the use of diuretics in patients with diabetes poses a 3.8 times higher risk of cardiovascular death compared to patients not receiving such treatment [11, 16].

Furosemide is a loop diuretic approved by the Food and Drug Administration (FDA), which works by inhibiting the reabsorption of sodium and chloride in the proximal tubule, distal tubule, and ascending loop of Henle. It does this by inhibiting the sodium-chloride transporter and is used to treat conditions of volume overload and edema caused by exacerbations of congestive heart failure, liver failure, or renal failure, including nephrotic syndrome. The use of furosemide reduces costs and hospital stays. Furosemide administration in heart failure patients was considered well-tolerated and relatively safe after hospital discharge. Side effects (SEs) can be classified based on the organ system affected and ranked in order of severity. In the digestive system, hepatic encephalopathy may occur in patients with cirrhosis, pancreatitis, jaundice (intrahepatic cholestatic jaundice), elevated liver enzymes, and anorexia. Extreme hypersensitive responses, such as severe anaphylactic or anaphylactoid reactions (with possible shock), as well as systemic vasculitis, can also occur in response to sensitizing stimuli, As for metabolism, hyperglycemia, hyperuricemia, and hypokalemia may occur [17, 18].

3.5. Calcium Channel Blockers (CCBs)

Calcium Channel Blockers (CCBs) have become the primary choice as antihypertensive agents. The action binds to transmembrane sites located in L-type calcium channels,

especially in heart muscle and smooth muscle cells. interfering with the influx of calcium ions. Medicine and patients appreciate this class of drugs for their effectiveness, metabolic neutrality, and lack of side effects. However, recent studies have shown that hypertensive patients taking CCBs may have a higher risk of developing myocardial infarction and have a higher mortality rate compared to patients taking other types of antihypertensive drugs [11].

Individually, amlodipine (dihydropyridine) is generally considered safe with a low incidence rate of adverse events. Combined use of amlodipine may be a particularly appropriate option for patients with diabetes or metabolic syndrome as it does not exacerbate metabolic complications related to the cause. Most studies evaluating the safety of both monotherapy and the combination of telmisartan and amlodipine were conducted over a short period, while the most common adverse effect is peripheral edema, which is a result of the vasodilatory capacity of amlodipine [19]. Description of safety and tolerability of the antihypertensive agents in long-term use can be seen in Table 1.

TABLE 1: Description of safety and tolerability of the antihypertensive agents in long-term use.

Classes	**Antihypertensive Agents**		
	Drug's Name	**Daily Dose**	**Side Effects (SEs)**
Angiotensin Converting Enzyme Inhibitors (ACEIs)	Captopril	50-75 mg	Paroxysmal cough (1% to 10%), proteinuria (1 of 100 patients), Renal insufficiency or renal failure (found in 1 to 2 percent of every 1000 patients).
	Lisinopril	Start at 10 mg and titrate upwards to 40 mg once daily.	Dry cough (found in 10% to 20), dizziness (found in 12% to 19%), renal failure or insufficiency (2% to 11%), and hyperkale mia (2% to 6%).
Angiotensin Receptor Blockers (ARBs)	Valsartan	40-80 mg	Hyperkalaemia (5.1%) and the incidence rate of death was 8/100 person-years.
Beta Blocker	Propranolol	At first, 40 mg thrice daily	Chest tightness, cough-producing mucus, and difficulty with breathing.
Diuretic	Furosemide	20-80 mg	Electrolyte disturbances, hypokalemia, and kidney disease
Calcium Channel Blockers (CCBs)	Amlodipine	5-10 mg	Peripheral edema (18%), headache, and dizziness.

4. Conclusion

This study recommends using the ACEIs group, especially captopril, and lisinopril, due to the minimal side effects produced compared to other antihypertensive drugs. In the ARB group in the form of valsartan, administering valsartan at the time of hospital discharge was explicitly associated with decreased mortality and hospitalization after hospital discharge. In addition, the CCBs class amlodipine is potentially well tolerated and safe. Furthermore, to effectively lowering blood pressure, long-term amlodipine therapy can reduce seasonal blood pressure variations in high-risk hypertensive patients. However, the antihypertensive agents should be tailored to the patient's underlying disease; hence, the antihypertensive agent could work optimally.

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