INTRODUCTION
Hypertension is a frequently occurring cardiovascular disease [1]. The American Heart Association estimates that it affects 80 million adults in the United States alone. In Indonesia, hypertension is also a prevalent non-communicable disease, which affected 25.8% of the population in 2013 [2]. Angiotensin-converting enzyme (ACE) inhibitors are a key class of antihypertensive and are the first-line option in certain instances, such as in patients with diabetes or chronic renal failure. These drugs may be administered alone or with other hypertensives for improving efficacy, and they typically need to be taken for long periods [1,3]. Combined with the fact that patients treated with ACE inhibitors frequently have comorbidities that also require treatment, these factors increase the potential for drug interactions that can harm the patient. According to the Micromedex® Interaction Checker, which can be used to check for potential drug interactions, ACE inhibitors have major interactions with 21 other drugs and moderate interactions with 16 other drugs. In some instances of major interactions, medical treatment can be required if they are life-threatening or risk causing permanent damage. Similarly, moderate interactions may require additional therapy for preventing a patient’s clinical status from worsening. The following four major factors influence drug interactions: Age, polypharmacy, disease status, and genetics. Literature reviews are required for clarifying the frequency of possible interactions caused by the use of ACE inhibitors and other drugs in patients with hypertension because there is a lack of current data. At Bhakti Pratiwi Hospital, hypertension is among the top 10 most frequently treated diseases, resulting in antihypertensive being prescribed in large quantities.

In this research, we aimed to clarify the rates of major and moderate interactions between ACE inhibitors and other drugs.

METHODS
We conducted descriptive research using a retrospective cross-sectional study design. All data were obtained from prescription and medical records for the period from July to December 2016. The study population comprised all inpatients of Bhakti Pratiwi Hospital who received ACE inhibitors. Data were included if patients were prescribed an ACE inhibitor with one or more other drugs (including other antihypertensives), were aged ≥18 years, and were diagnosed with hypertension. We excluded any data for prescriptions with unclear, incomplete, or untraceable medical records.

After the data were collected, researchers screened the ACE inhibitors against other drugs in the same prescription using the 2017 Micromedex Solution application from Truven Health Analytic, Stockley’s Drug Interaction 8th Edition textbook, Drug Interaction Textbook Facts, and related journals. Data were initially analyzed using univariate analysis of age, sex, polypharmacy, and potential interaction data. Subsequently, bivariate analysis was used for determining whether age, gender, polypharmacy, and pathophysiology affected the potential for drug interactions. These four factors were then hypothetically tested using IBM SPSS for Windows, Version 20 (IBM Corp., Armonk, NY, USA). A value of p<0.05 indicated that there was a significant difference between the two variables.

RESULTS AND DISCUSSION
A total of 155 prescriptions met our inclusion criteria, of which 35 also met the exclusion criteria. Ultimately, 120 prescriptions from
Major interactions

Captopril and allopurinol
We identified three cases of interaction between captopril and allopurinol (2.16%). Two patients did not experience hypersensitivity symptoms, but one suffered kidney failure. This result was not comparable to that in other studies, in which eight cases (35.25%) of such interaction was shown [4]. The mechanism of interaction between captopril and allopurinol is unknown, and it should be considered that allopurinol use alone can cause severe hypersensitivity reactions, especially if the patient has renal failure. Studies conducted by Halevy et al. showed that the using ACE inhibitors and allopurinol were not associated with an increased risk of Stevens-Johnson syndrome and toxic epidermal necrolysis [5].

Captopril and digoxin
In this study, we identified six cases (4.32%) of interaction between captopril and digoxin. The use of digoxin with other drugs requires special attention because digoxin has a narrow therapeutic window of approximately 0.5–2.0 ng/mL; however, this figure is not absolute and varies with individual differences [6]. The interaction of these drugs typically increases plasma digoxin levels because captopril can lead decreases in the glomerular filtration rate and reduced tubular secretion [7]. However, research by Iraz et al. failed to show that a combination of these drugs can increase plasma digoxin levels [6].

Captopril and angiotensin receptor blockers (ARB)
Two cases were prescribed an ARB and an ACE inhibitor, with one case each (0.72%) of interactions for captopril-candesartan and captopril-valsartan. This may happen probably because doctors and pharmacists already knew that a combination of these two drugs can harm patients. Hyperkalemia can occur when ACE inhibitors are combined with ARBs. The effect is presumed to occur through each binding to adrenal receptors, interfering with the effects of angiotensin II on aldosterone secretion, and thereby decreasing potassium excretion by the kidney. In a meta-analysis of 33 randomized trials comparing the safety of ACE inhibitors and ARBs alone or in combination, it was reported that concurrent use increased the incidence of hyperkalemia, hypotension events, renal failure, and drug withdrawal by 55%, 66%, 41%, and 27%, respectively [8]. Interaction between ACE inhibitors and ARBs is rarely identified in studies of drug interactions, making it difficult to find previous research data for comparison with our own.

ACE inhibitors and potassium chloride
There were 14 cases (10.07%) of interaction between captopril and potassium chloride (KCl) and five cases (3.59%) of interaction between ramipril and KCl. This differed slightly from two previous studies showing that ACE inhibitor interactions with KCl resulted in 2.2 cases (35.85%) [9] and five cases (27.78%) [10,11]. ACE inhibitors have a potent retention effect due to decreased aldosterone levels, and this is exacerbated by the addition of supplemental potassium. In practice, increased potassium levels occur clinically only if other factors are present. Retrospective studies of hyperkalemia among inpatients found that the main risk factors were potassium supplementation, severe renal dysfunction, ACE inhibitor/antagonist angiotensin II, use of potassium-sparing diuretics, and diabetes mellitus. Moreover, the presence of two or more of these risk factors was associated with the rapid development of hyperkalemia [12].

Captopril and cotrimoxazole
Based on this research, there were four cases (2.88%) of interaction between captopril and cotrimoxazole. Previous studies have shown that more than half of all patients taking ACE inhibitors were hospitalized for hyperkalemia after taking cotrimoxazole for urinary tract infection [13]. Trimethoprim, a component of cotrimoxazole, has a comparable structure and pharmacology to the potassium-sparing diuretic amiloride. This antibiotic competitively inhibits the potassium channel in the epithelium of the distal nephron, thus interfering with potassium excretion in the kidneys and can lead to hyperkalemia when given in isolation. The combination of cotrimoxazole with an ACE inhibitor significantly increases the risk of hyperkalemia: The ACE inhibitor has a potent retention effect due to decreased aldosterone levels, and this is exacerbated by the combination due to hyperkalemia [14]. Studies have shown that more than half of all patients taking ACE inhibitors were hospitalized for hyperkalemia after taking antibiotics (i.e., cotrimoxazole) to treat a urinary tract infection [13].

ACE inhibitors and spironolactone
In this study, interactions were observed between captopril and spironolactone in 16 cases (11.51%) and between ramipril and spironolactone in two cases (1.44%). The simultaneous use of these ACE inhibitors with spironolactone can cause hyperkalemia: The ACE inhibitors decrease the amount of aldosterone and cause potassium retention, while spironolactone works additively as an aldosterone antagonist to lower aldosterone levels further [12]. Given that aldosterone is a major hormonal stimulus for potassium excretion in the urine [15], hyperkalemia can occur when its levels decrease. In 2015, another study reported that 1062 patients were treated for hyperkalemia due to combination therapy with an ACE inhibitor and spironolactone [16].

Moderate interactions

Captopril and nonsteroid anti-inflammatory drugs (NSAIDs)
The total number of cases of ACE inhibitor interactions with NSAIDs was 20 (13%) in this study, which was greater than that reported previously (n=35; 4.2%) [17]. Captopril interacts with virtually all NSAIDs, which can cause the effectiveness of captopril decrease. Alone, NSAIDs can increase blood pressure in elderly patients, purportedly through the following mechanisms: (1) Inhibiting enzymes that produce prostaglandins, (2) Affecting the renin-angiotensin system by causing a decrease in renal blood flow.
resulting in decreased renal perfusion, (2) increasing sodium and water resistance, and (3) decreasing prostaclin production.

Captopril and aspirin
We identified 24 cases (17.26%) of interaction between captopril and aspirin, comparable to research on drug interactions that identified 33 cases of such interaction [18]. Aspirin may inhibit the effects of ACE inhibitors by inhibiting cyclooxygenase enzymes so that prostaglandins do not form, causing vasoconstriction, decreased cardiac output, and worsening heart failure (Baxter, 2010). The interaction between aspirin and ACE inhibitors has only been reported for high-dose aspirin (2.4 g/day), not low-dose aspirin, and to date.

Captopril and antacid
There were three cases (2.16%) of interaction between captopril and antacids in the present research. In previous research among 10 healthy subjects, antacids were shown to be capable of reducing the area under the curve of single-dose captopril (50 mg) by 40%, albeit without altering the rate of blood pressure decrease. Overall, interaction-related evidence between ACE inhibitors is limited, and the mechanism by which antacids decrease captopril absorption is unclear and needs further investigation [12].

ACE inhibitors and furosemide
Based on this research, there were 17 cases (12.23%) of captopril and furosemide interactions and four cases (2.88%) of ranipril and furosemide interactions. This was slightly different from data obtained in Iran, where interactions were only reported between ACE inhibitors and furosemide in two patients (0.98%) [19]. The coadministration of ACE inhibitors with strong diuretics or thiazide diuretics is normally safe and effective, but some patients develop a first-dose hypotensive syndrome (i.e., dizziness, head lightness, and fainting), which occurs when some patients treated for chronic renal failure and taking a high dose of a strong diuretic use an ACE inhibitor for the first time [20]. This hypotension can be aggravated by several conditions, such as heart failure, renovascular hypertension, hemodilution, high levels of renin and angiotensin, sodium intake, dehydration, diarrhea, vomiting, and hypovolemia, and/or sodium deficiency due to high-dose diuretic use. The risk of hypotension was reported to be greater at furosemide doses ≥80 mg daily, so it is recommended that ACE inhibitors should be started in these patients under strict supervision. Clinicians should consider stopping or lowering the doses of diuretics for at least 24 h before administration. If this is not possible, the response to initial ACE inhibitor administration needs to be monitored for 2 h, or until the blood pressure is stable.

Captopril and antidiabetic medications
Interactions were observed between captopril and metformin (11 cases; 7.91%), captopril and glimepiride (3 cases; 2.16%), captopril and acarbose (1 case; 0.72%), captopril and gliquidone (2 cases; 1.44%), and captopril and insulin (2 cases; 1.44%). Research, in 2015, showed less significant results with up to seven cases of interaction between captopril and insulin and four cases of interaction between captopril and metformin [21]. The mechanism by which ACE inhibitors increase insulin sensitivity remains unclear and is clinically questionable [22]. However, two mechanisms have been proposed. First, captopril may provide a vasodilatory effect which then increases the access of insulin and glucose to skeletal muscle tissue, a key site of insulin-mediated glucose uptake [23]. Second, the increased bradykinin levels associated with ACE inhibitor use may increase vascular permeability and increase the delivery of glucose and insulin to tissues. Although they provided potential mechanisms as to how captopril may improve insulin sensitivity, the researchers failed to show any significant differences between controls and dogs administered captopril and antidiabetic medications simultaneously.

Bivariate analysis
There was no relationship between sex and potential drug interactions (p=0.722, Chi-square test), consistent with research in Saudi Arabia, which also showed no association (p=0.361) [22]. However, there was a significant relationship between polypharmacy and drug interactions (p<0.05; Mann–Whitney U-test), again consistent with the research from Saudi Arabia (p<0.001) [24]. Increasing the number of drugs administered to a patient increases the potential for drug interactions. This is more common in elderly patients who usually suffer more than one disease, requiring the provision of multiple drugs and increasing the risk of polypharmacy [25].

The Chi-square test results comparing pathophysiology with potential drug interactions also showed that there was no relationship between the two factors (p>0.05). Theoretically, changes in liver and kidney function associated with age produce objective changes in drug clearance and metabolism. For example, as the body ages, blood flow through the liver decreases and the clearance of some drugs can be inhibited by as much as 30–40% [25]. Some interaction effects will also develop more rapidly if the patient has comorbid renal failure, such as when the patient develops interactions due to captopril-allopurinol, captopril-digoxin, captopril-spiroloolactone, and captopril-furosemide combinations.

Finally, we use the Kruskal–Wallis tests for assessing the relationship between age and potential drug interaction, which revealed that there was no relationship (p=0.07). Comparable results were shown in a study of 227 patients (p=0.99) [26]. However, the fact that our results approached significance (p<0.05), may have been because our age variation was not evenly distributed (e.g., one patient was aged 24 years) and because the cohort was too small to show a relationship (71 patients).

CONCLUSION
In our hospital from July to December 2016, patients treated with ACE inhibitors for hypertension tended to be female, be aged ≥60 years, have polypharmacy (5–6 drugs), and have no liver or kidney disease. ACE inhibitors were associated with potential interactions with other drugs on 75 prescriptions (53.96%), with 52 major interactions and 87 moderate interactions identified. The most common interaction was between captopril and aspirin (24 cases, 17.26%). The bivariate analyses indicated that there was a relationship between potential drug interactions and polypharmacy (p<0.05), but that there was no relationship between potential drug interactions and either sex, age, or pathophysiology (p>0.05).

CONFLICTS OF INTEREST
All authors declared that there are no conflicts of interest.

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