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Research Article

Effectiveness of combination of perindopril and indapamide on ambulatory arterial stiffness index in Vietnamese patients with primary hypertension

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ABSTRACT

Arterial stiffness is an independent prognostic factor for predicting adverse cardiovascular outcomes in hypertensive patients. This study aimed to investigate the rate of increase in arterial stiffness index and the relationship between the ambulatory arterial stiffness index (AASI) with some cardiovascular risks and the change of AASI after 3 months of treatment with perindopril/indapamide (PER/IND). We conducted this research on 75 untreated hypertensive patients at Can Tho University of medicine and pharmacy, Viet Nam. AASI and pulse pressure (PP) were calculated from 24-hour ambulatory blood pressure results. Our study showed that the mean AASI is 0.44±0.14. Female's increased AASI is capable of 4.38 times as much as the male. Left ventricular hypertrophy (LVH) can increase arterial stiffness index about 3.93 times as much as the non-hypertrophy group (p<0.05). AASI is positively correlated with mean pulse pressure and age with r=0.37 and r=0.3 (p<0.05). After 3 months of treatment, results analysis of the subgroup revealed that AASI decreased 0.06±0.15 in women (p<0.05). AASI reduced significantly in the group of people aged 65 or more with a mean change to 0.11±0.12 (p<0.05). Moreover, the group of patients with grade 2 hypertension also indicated that AASI reduced 0.05±0.14 in post-treatment. In conclusion, AASI has been associated with several cardiovascular risk factors such as female, age, nocturnal non-dipper blood pressure, left ventricular hypertrophy, and increased mean pulse pressure. PER/IND has effectively reduced arterial stiffness in Vietnamese patients with primary hypertension, especially women, the elderly, and grade 2 hypertension.

Keywords:
Ambulatory arterial stiffness index, Hypertension, Perindopril, Indapamide

1. INTRODUCTION

Hypertension is a common disease in clinical practice in many countries worldwide. There are currently about 1 billion people with hypertension, and it is estimated that by 2025, this number will reach 1.5 billion[1]. Hypertension is a deteriorative illness owing to its complications that damage target organs such as the heart, eyes, brain, and kidney, in which cardiovascular events are of particular concern. Many evidence show that arterial stiffness is an independent prognostic factor for predicting adverse cardiovascular outcomes in hypertensive patients[2]. The gold standard for determining arterial stiffness is to measure pulse wave velocity. Still, this method requires high-technology equipment, making it unavailable to be performed in some medical facilities, especially in the primary health care systems. Another method that correlates with the standard measurement is to evaluate by 24-hour ambulatory blood pressure monitoring. Although it is not a new method, it has adequacy of accessible opportunity, non-invasive feature, and does not require high-technical equipment. As a result, this

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procedure is easily performed in the clinical setting to analyze the arterial stiffness index[3].

Many studies have been conducted to investigate the impact of antihypertensive drugs on reducing arterial stiffness, such as Angiotensin-converting enzyme inhibitors (ACEI), Angiotensin II receptor blockers (ARBs), calcium channel blockers. ACE-inhibitors have shown the most remarkable ability to improve arterial stiffness[4]. Furthermore, the combination of perindopril and indapamide has shown benefits not only on blood pressure control but also in reducing arterial stiffness, risk of recurrent stroke, and major cardiovascular events in hypertensive patients[5-6]. Stemming from the above issues, we conducted this study with two objectives: (i) To investigate the increase in arterial stiffness index and the relationship between the ambulatory arterial stiffness index with some cardiovascular risks. (ii) To evaluate the effectiveness of perindopril plus indapamide on the change of ambulatory arterial stiffness index in patients with primary hypertension after 3 months of treatment.

2. MATERIALS AND METHODS

2.1. Study population

2.1.1. Materials

We selected 75 patients who have already been diagnosed with primary hypertension at Can Tho University of Medicine and Pharmacy hospital during a period from May 2019 to March 2021.

2.1.2. Inclusion criteria

All patients have already been diagnosed with primary hypertension.

2.1.3. Exclusion criteria

Patients who met the following criteria were excluded from the study: history of hypertension, currently on antihypertensive drug therapy, secondary hypertension, hypertensive emergency, stroke or acute coronary syndrome within the last 6 months, heart failure, diabetes, chronic kidney disease, chronic infection, cancer, intolerance to PER/IND, drug allergy or history of severe side effects such as progressive angioedema, persistent cough, severe hyperkalemia, renal failure, in need of adding other drugs to control blood pressure.

2.2. Methods

2.2.1. Study design

Cross-sectional descriptive research method.

2.2.2. Sample size

All prescriptions met the inclusion criteria and had no exclusion criteria.

2.2.3. Data collection

All patients who satisfied the inclusion criteria would be fitted with 24-hour Holter for blood pressure monitoring and be assessed for a number of their cardiovascular risk factors such as age, sex, and family history with premature cardiovascular disease, smoking, exercise, dipper, left ventricular hypertrophy and pulse pressure. These patients were then treated with PER/IND for 3 months according to the European Society of Cardiology's 2018 recommendation on the diagnosis and treatment of hypertension with perindopril 5 mg plus indapamide 1.25 mg (recommended level IA), then followed up every month if blood pressure goal is in the target range of systolic blood pressure (SBP) <140 mmHg and diastolic blood pressure (DBP) <90 mmHg, subsequently continue to maintain the upper dose[1]. If the target is not achieved, increase the dose to perindopril 10mg plus indapamide 2.5 mg[1]. After 3 months, the results were evaluated by re-measurement of a 24-hour ambulatory blood pressure monitor to assess the ambulatory arterial stiffness index change.

2.2.4. Data analysis

The ambulatory arterial stiffness index (AASI) is calculated by a regression coefficient of DBP/SBP, in which DBP and SBP are obtained from a 24-hour ambulatory blood pressure monitor. AASI is conventionally increased when AASI≥0.43[7-8]. Classification of hypertension into 3 degrees is based on ESC 2018[1]. A family history with premature (early) cardiovascular disease is defined when a family male <55 years old or a female <65 years old has had cardiovascular disease. According to the COMMIT (Community Intervention Trial) criteria, smoking is defined when the patient is a current smoker and has smoked at least 100 cigarettes until now. Non-smoking determination is when the patient has never smoked or used to smoke but has stopped for at least the last 5 years[9]. Exercise is when doing physical activity regularly, i.e., regular daily exercise (≥5 days/week for more than 30 minutes each), including walking or playing a sport. A sedentary lifestyle or regular physical inactivity, that is, subjects do not exercise or exercise irregularly (<5 days/week)[10]. Confirming the occurrence of the nocturnal dipper is when SBP or DBP during sleep decreases by at least 10% compared to daytime[1]. Left ventricular hypertrophy is determined if LVMI >115 g/m^2 for men or >95 g/m^2 for women[11].

2.2.5. Measurements

Blood pressure data were taken in the clinic using a sphygmomanometer with a standardized watch and stethoscope. The patient rested for 15 minutes and did not use stimulants or talk during the evaluation. The SBP was determined to correspond to the first beating (Korokoff's phase I) and DBP, which corresponded to the disappearrance of the beating (Korokoff's phase V). The results were read and measured 3 times, at least 1-minute intervals (2 times if the blood pressure results are within the normal range), then the average was calculated. According to the European Society of Cardiology in 2018, hypertension was diagnosed when the SBP ≥140 mmHg and/or DBP ≥90 mmHg[12].

24-hour Holter blood pressure measurement was performed by utilization of Spacelabs 90217 ABP. The cuff was wrapped around the arm so that the length (within the cuff) was satisfied at least 80%, with a width of at least 40% of the arm circumference. The cuff was made sure to wrap tightly enough. The lower edge of the sheath was 2 cm above the elbow crease. The measurement time was set during the day from 6 h to 22 h, assessed once every 20 minutes, similarly at night from 22 h to 6 h with a frequency of measuring once every 30 minutes remeasure if the results were displayed on the meter with <20 valid measurements during the day or <7 those during sleep[12].

Left ventricular muscle mass was evaluated by Siemen X500 ultrasound machine, using the axial parasternal section with M-mode and based on the principle of taking a left ventricular muscle volume (which was the difference in total left ventricular volume and left ventricular chamber volume) multiplied by myocardial density (1.04-1.05 g/cm^3). Left ventricular size (for volume determination) measured at the end of diastole on echocardiography: corresponds to the peak of the R wave (on electrocardiogram (ECG)) according to Penn rule or the beginning of the QRS complex as recommended by the American Society of Echocardiography[11]. The formula to calculate LVM (g) = 0.8(1.04(LVDd +IVSd + PWLVd)^3 - LVDd^3))+0.6. Note: LVDd (Left Ventricular end Diastolic diameter). IVSd (Inter Ventricular Septal Thickness end-diastolic). PWLVd (Left Ventricular end Diastolic Post Wall). Left ventricular muscle index (LVMI) was assessed by echocardiography and was calculated based on left ventricular mass (LVM) per body skin area (BSA), according to the formula LVMI = LVM/BSA[11].

2.2.6. Statistical analysis

The data processing method was performed using SPSS 20.0 software; qualitative variables were presented by frequency and percentage. Continuous quantitative variables were expressed as mean±standard deviation, minimum and maximum value. The relationship between several cardiovascular risk factors and the degree of increased arterial stiffness was analyzed by binary logistic regression. The X^2 test was applied to investigate the correlation between ratios (using Extract's Fisher when the 2x2 table has at least one cell with an expected value less than 5). Paired T-test was applied to scrutinize whether there was a significant discrepancy in the mean values after treatment between the groups. P was evaluated as follows: p>0.05: the difference is not statistically significant; p<0.05: the difference is statistically significant; p<0.01: the difference is much statistically significant.

3. RESULTS

3.1. Baseline subject characteristics

This study was conducted on 75 patients in Can Tho University of Medicine and Pharmacy hospital that recorded male and female account for 57.3% and 42.7% respectively; the mean age of study subjects is 52.61± 12.84 and the under 60 aged group is majority with 76% among the participants. In addition, the mean body mass index is 24.89±2.99. Of the patients who joined this study, 37.3% were smoking, 57.3% had a family history of early cardiovascular disease, and 50.7% had physical activity

Table 1. Baseline characteristics of the study population.

Characteristics	Mean±SD or n (%)
Male	43(57.3)
≥60	18(24.0)
Age (years)	52.61±12.84
Body mass index (kg/m^2)	24.28± 2.99
Past or current smoker	28(37.3)
Family history	43(57.3)
Exercise	38(50.7)
Grade 1 hypertension	30(40.0)
Grade 2 hypertension	45(60.0)
AASI	0.44± 0.14
Dipping	33(44.0)
LVH	26(34.7)

Table 2. The relationship of cardiovascular risk factors and ambulatory arterial stiffness index.

Cardiovascular Risk Factors		Total	AASI increased N (%)	No AASI increased N (%)	OR	95% CI	*p*
Sex	Female	32	24(75.0)	8(25.0)	4.38	1.20-16.06	0.026
	Male	43	15(34.9)	28(65.1)	1		
Family history	Yes	43	20(46.5)	23(53.5)	1.03	0.30-3.58	0.966
	No	32	16(50.0)	16(50.0)	1		
Past or current smoker	Yes	28	13(46.4)	15(53.6)	1.02	0.27-3.85	0.981
	No	47	26(55.3)	21(44.7)	1		
Exercise	Yes	38	20(52.6)	18(47.4)	1.09	0.33-3.63	0.889
	No	37	19(51.4)	18(48.6)	1		
Dipping	Yes	33	9(27.3)	24(72.7)	0.28	0.09-0.93	0.038
	No	42	30(71.4)	12(28.6)	1		
LVH	Yes	26	20(76.9)	6(23.1)	3.93	1.15-13.39	0.029
	No	49	19(38.8)	30(61.2)	1		

Binary logistic analysis using Ambulatory Arterial Stiffness Index as a dependent variable

habits. Patients with grade 1 and 2 hypertension account for 40% and 60%, respectively. In the study, the mean AASI is 0.44±0.14. The percentage of dipping (nocturnal blood pressure) is 44%, and left ventricular hypertrophy is 34.7% (Table 1).

3.2. The proportion of increased index of arterial stiffness and the relationship of some cardiovascular risk factors and ambulatory arterial stiffness index

Based on our study results, there is an association between gender and increased arterial stiffness index. Females have the proportion of increased AASI higher than males (75% compared to 34.9%), and females' increased AASI is capable of 4.38 times as much as male; the difference is statistically significant (p<0.05). Family history of early cardiovascular disease, smoking, and physical activity habits are not associated with increased arterial stiffness index (p>0.05). Besides, when study data was analyzed, we found that left ventricular hypertrophy can increase arterial stiffness index, which is about 3.93 times as much as the non-hypertrophy group (p<0.05). Moreover, our study also indicated that AASI is positively (Table 2) correlated with mean pulse pressure by the equation y=0.01x+0.11 with r=0.37 and p<0.05 (Figure 1). There is a moderately positive correlation between AASI and age according to the equation y= 0.003x+0.27 with r=0.3 and p=0.01 (Figure 2). In addition, some other factors such as smoking, physical activity, lifestyle, and family history of early cardiovascular disease were not shown an association with increased AASI.

3.3. The variation of arterial stiffness index after 3 months treatment by PER/IND

Patients were set up Holter to monitor the change of AASI after 3 months of treatment by PER/IND, and we recorded the following results (Table 3). After 3 months, AASI decreased 0.017 compared to pre-treatment, but this variation was not statistically significant (p>0.05). Results analysis of the subgroup revealed that AASI decreased statistically significantly in women (decrease 0.06±0.15, with p<0.05). Analysis of AASI change by age group showed that AASI reduced significantly in people aged 65 or older with a mean change to 0.11±0.12 (p<0.05). Moreover, the group of patients with grade 2 hypertension also indicated that AASI reduced post-treatment (reduce 0.05±0.14). The change of AASI in post-treatment was a strong positive correlation with baseline AASI, which is statistically significant (r=0.75, p<0.001) (Figure 3). On the other hand, our study results did not show a statistically significant change in the smoking group, and physical activity lifestyle with the change in post-treatment is -0.02±0.14 and -0.02±0.16 respectively (p>0.05).

4. DISCUSSION

Our study showed that the average age was 52.61± 12.84, in which the group <60 years old accounted for the majority of 76%. Because we selected patients with newly diagnosed hypertension, the mean age is relatively low. Regarding gender, men and women have approximately the same ratio, similar to the NHANES 2017-2018 study[13]. The sample population had an average body mass index of 24.28±2.99 in our research, lower than the results in the study of author Berni A et al., 26±4. This difference in BMI may be due to hypertensive subjects in Italy selected in the research of Berni et al., whose stature is larger than that of Asians. The mean AASI in our study was 0.44±0.14, similar to the result of Jin study on 201 hypertensive patients (0.43±0.16)[14], higher than that of Jekell et al. study performed on 77 ongoing treatment of hypertensive patients (0.36±0.18)[15] and lower than in the research of Litvin et al. on 44 subjects with hypertension and paroxysmal nocturnal dyspnea (0.55±0.17)[16].

The rate of increase in AASI in women was higher than in men. Women had a risk of increasing AASI 4.38 times higher than men, with a statistical significance of p<0.05. This may be related to the female menopause process that changes several important hormones, especially estrogen drop. Estrogen plays a fundamental role

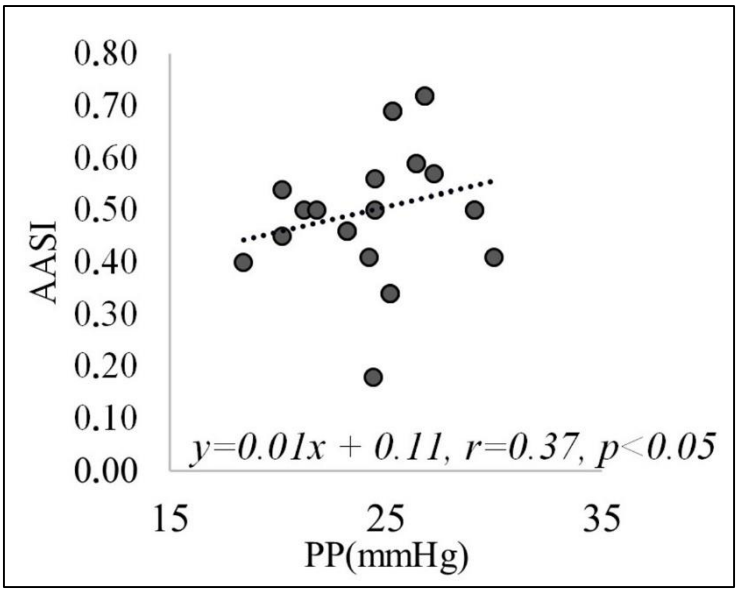

Figure 1. Linear Regression Analysis on relationship between pulse pressure and ambulatory arterial stiffness index.

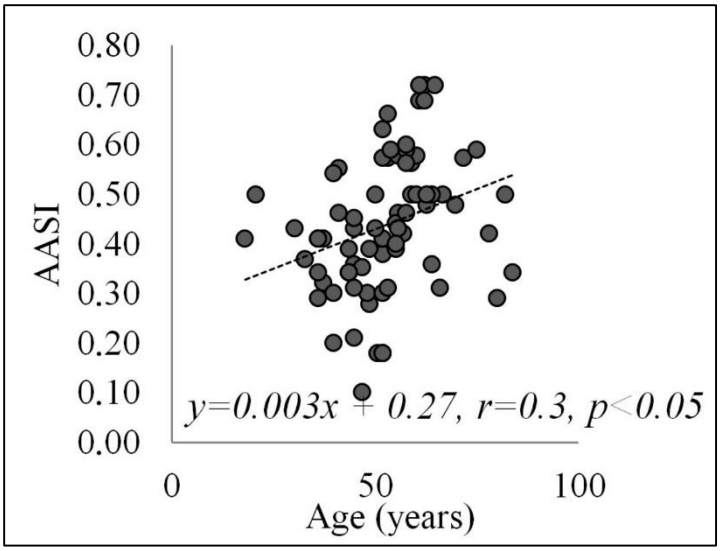

Figure 2. Linear Regression Analysis on relationship between age and ambulatory arterial stiffness index.

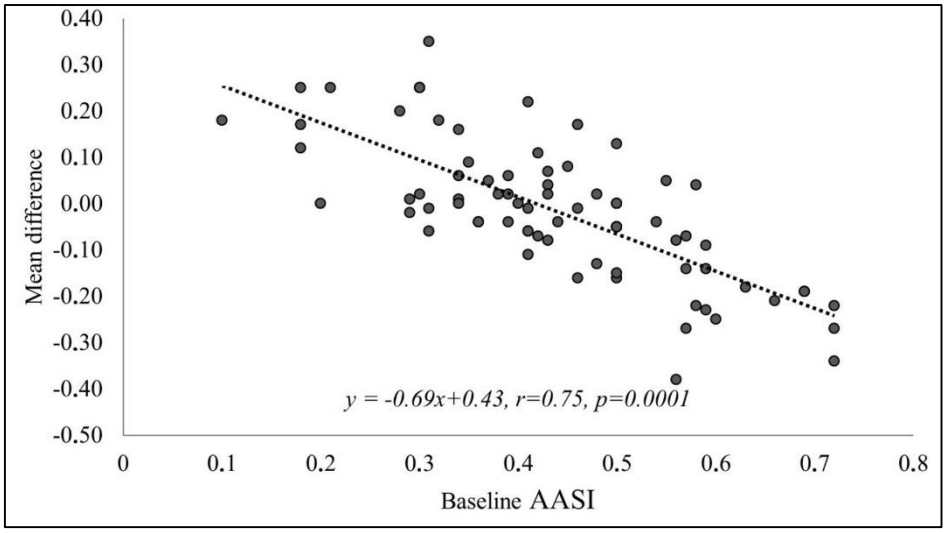

Figure 3. Linear Regression Analysis on the relationship between baseline ambulatory arterial stiffness index values and change with perindopril combined indapamide treatment.

Table 3. Ambulatory arterial stiffness index at baseline and at the end of the follow-up.

Risk factors		AASI	n	$\bar{X}$ ±SD	Changing	*p*
AASI		Baseline	75	0.44 ± 0.14	-0.017 ± 0.15	0.331
		Follow-up	75	0.42 ± 0.10		
Sex	**Male**	Baseline	43	0.40 ± 0.13	0.015 ± 0.14	0.478
		Follow-up	43	0.42 ± 0.11		
	Female	Baseline	32	0.49 ± 0.14	-0.060 ± 0.15	0.031
		Follow-up	32	0.43 ± 0.10		
Age	**<60**	Baseline	57	0.41 ± 0.13	0.011 ± 0.15	0.541
		Follow-up	57	0.43 ± 0.11		
	≥60	Baseline	18	0.52 ± 0.14	-0.110 ± 0.12	0.001
		Follow-up	18	0.41 ± 0.09		
Hypertension	**Grade 1**	Baseline	30	0.37 ± 0.14	0.040 ± 0.15	0.153
		Follow-up	30	0.41 ± 0.11		
	Grade2	Baseline	45	0.48 ± 0.12	-0.050 ± 0.14	0.012
		Follow-up	45	0.43 ± 0.10		
Smoke	**Yes**	Baseline	28	0.42 ± 0.13	-0.020 ± 0.14	0.444
		Follow-up	28	0.40 ± 0.10		
	No	Baseline	47	0.45 ± 0.14	-0.010 ± 0.15	0.526
		Follow-up	47	0.44 ± 0.10		
Exercise	**Yes**	Baseline	38	0.45 ± 0.16	-0.020 ± 0.16	0.354
		Follow-up	38	0.43 ± 0.10		
	No	Baseline	37	0.43 ± 0.11	-0.010 ± 0.13	0.699
		Follow-up	37	0.42 ± 0.10		

in regulating endothelial function in both men and women. Several studies have shown that patients with ovarian insufficiency associated with significant endothelial dysfunction are involved in increasing arterial stiffness[17-18]. In addition, another study has indicated an effect of the menstrual cycle on arterial stiffness[19]. This suggests that the occurrence of increased arterial stiffness in women is related to hormonal changes after menopause, further supported by the study of Tolstov SN et al. performed on 2 groups: using and not using hormone replacement after menopause and finally, the result that there was a statistically significant decrease in the arterial stiffness index in the hormone group compared to the other, with AASI decreased from 0.379 to 0.264 (p<0.001)[20].

In the group of patients with nocturnal dipper, which is defined as the mean nighttime blood pressure being reduced by more than 10% compared to that of daytime, the risk of increased arterial stiffness index was 0.28 times less than in non-dipper patients' group with 95% confidence level was 0.09-0.93 and p<0.05. Many articles have also documented that nocturnal non-dipper blood pressure is associated with an increased risk of hypertension-mediated organs damage such as left ventricular hypertrophy, microalbuminuria, and renal injury[21-23]. The results of our study were similar to that of Christpher J Boos et al. performed on 508 patients aged 18-80. This study has shown the arterial stiffness index in the dipper group (0.39±0.16) was lower than the non-dipper group (0.47±0.17), and the difference was statistically significant with p=0.0001[24].

Left ventricular hypertrophy is a common complication in hypertensive patients. Our study found an association between arterial stiffness index and left ventricular hypertrophy as determined by echocardiography. Patients with increased left ventricular muscle index had a statistically significant increase in arterial stiffness index 3.93 times than the other group (p<0.05). When compared with the study of Lee et al., which was performed on 418 hypertensive patients, there was also a correlation between the arterial stiffness index and the left ventricular muscle index with r=0.192 (p<0.001)[25].

Age is considered one of the risk factors associated with the development of cardiovascular diseases. Besides, arterial stiffness is also evaluated as an independent predictor for the occurrence of cardiovascular disease. Our study showed that age was positively correlated with the increase of AASI according to the linear equation y=0.003x+0.27 with r=0.3 and p=0.01. Many pieces of evidence have proved that the structure and function of the arteries are gradually affected over time, especially the large arteries. In terms of composition, elastin components in blood vessels will be broken and abnormal collagen deposition will increase, along with an increase of vascular smooth muscle cells, all of which result in vascular stiffness. Functionally, aging contributes to enhanced systemic inflammation and loss of nitric oxide bioavailability, leading to progressive stiffening of blood vessels[7]. Pulse pressure is the difference between systolic and diastolic blood pressure, and this is one of the factors that help predict the occurrence of cardiovascular events in hypertensive patients. In the elderly, systolic blood pressure often increases, and diastolic blood pressure tends to decrease slightly after the 6th decade of life,

increasing pulse pressure. Regarding the correlation with mean pulse pressure, our study results showed a positive and moderate correspondence with r=0.37 and $p<0.05$. Higher arterial stiffness was observed in patients with higher mean 24-hour pulse pressure. In Qin et al. conducted on patients with grade 1 and grade 2 hypertension, there was a positive correlation between arterial stiffness index and 24-hour mean pulse pressure with r=0.404 and $p<0.05$[9]. Thus, in addition to aging, the increase in arterial stiffness index is also related to pulse pressure and the absence of a nocturnal dipper.

Our study demonstrated that arterial stiffness index in post-treatment, after 3 months of combined treatment with perindopril and indapamide, decreased 0.017±0.15 compared to baseline level. Still, the difference was not statistically significant ($p>0.05$). At the same time, analysis of a linear correlation between mean difference (post-treatment AASI-baseline AASI) and baseline AASI indicated a positive correlation according to linear equation y=0.69x+0.43 with r=0.75, $p<0.001$. Some previous studies on the effect of antihypertensive drugs on changes in arterial stiffness index also showed similar results[26]. Furthermore, there is a meta-analysis of 8 studies (n=990) about using angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers to control blood pressure and monitoring changes in arterial stiffness by AASI from 12 to 54 weeks; these studies were conducted between 2010 and 2014, showed an overall mean decrease of 0.018 (0.003-0.033), $p=0.192$[26]. In particular, a study by Kollias et al. (2014) performed on 104 patients with hypertensive treated with irbesartan 300 mg, telmisartan 80 mg, or valsartan 320 mg once a day for 12 months showed mean AASI in post-treatment was increased 0.01±0.17, the change is not statistically significant ($p>0.05$)[26].

However, when study data was conducted subgroup analysis, we found that AASI change was significant in groups of females, people aged 60 or more, and grade 2 hypertension. These three groups of patients with a high arterial stiffness index before treatment. These results suggest that PER/IND improves AASI through blood pressure control and mechanisms that improve vascular endothelial function, improve nitric oxide bioavailability, decrease vascular remodeling and apoptosis[27-28].

4.1. Limitations

This study has several limitations that should be considered. All samples were taken from a center, and the size was likely to be small so that it may not present for the vast majority of Vietnamese patients. In addition, all 24-hour ambulatory blood pressure monitoring was set up in similar day-time and night-time periods, which led to the potential misclassification of dipping status because some patients were recorded night-time when they were still awake. Furthermore, AASI was calculated twice initially and after 3 months to reflect arterial stiffness changes. Still, this method measured peripheral arterial stiffness instead of central arterial stiffness, which may more accurately reflect the status of arterial stiffness. The time of follow-up treatment in our study is short-term, so there may be some limitations in monitoring AASI changes in post-treatment.

Therefore, we suggest that a multicenter study is needed to evaluate and compare the value of AASI with central arterial stiffness in Vietnamese patients so that AASI can be used as an alternative non-invasive tool to assess arterial stiffness.

In conclusion, study results showed that PER/IND treatment after 3 months effectively reduces arterial stiffness in increased AASI risk groups of patients such as females, elderly, and grade 2 hypertension. On the other hand, we did not see a statistically significant change in arterial stiffness index after 3 months of treatment by perindopril and indapamide based on several cardiovascular risk factors such as smoking and physical activity.

5. CONCLUSION

AASI has been associated with several cardiovascular risk factors such as female, age, nocturnal non-dipper blood pressure, left ventricular hypertrophy, and increased mean pulse pressure. In addition, perindopril/indapamide has effectively alleviated arterial stiffness in Vietnamese patients with primary hypertension, especially women, the elderly, and grade 2 hypertension.

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Conflict of interest
No conflict of interest.

Funding
None to declare.

Ethics approval
This study was approved by the Research Review Committee of the University of Medicine and Pharmacy at Can Tho City and accepted for performing at the study hospital in Vietnam in 2019 No. 332/QD-DHYDCT.

Author contribution
SKT and HTNH conceived the study and designed the study protocol. THN, TN, HTNH, ATPN organized, performed the study investigations, and supported the recruitment of the patients. HTNH, THN and TN per-

formed statistical analyses. SKT, HTNH, THN, TN, MVH wrote the manuscript.

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