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Pulse Pressure Index as a Discriminator of Predicting the Cardiovascular Events in Hypertensive Patients Treated with Drugs Acting on Angiotensinogen-Angiotensin Pathway

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ABSTRACT

Background: Pulse pressure index as a function of pulse pressure divided by systolic blood pressure served a useful predictor of cardiovascular events.
Objectives: Our aim was to assess the pulse pressure index as a discriminating variable of predicting cardiovascular events in untreated hypertensive patients and treated with one member of angiotensin converting enzyme inhibitors or angiotensin receptor blockers by using the scores of Framingham study.
Materials and methods: This observational cross-sectional study, including 140 patients who grouped into; Group I (n = 30): untreated hypertensive patients; Group II (n = 60): patients treated with angiotensin receptor blockers; and Group III (n = 50): patients treated with angiotensin converting enzyme inhibitors. Anthropometric measurements, lipid profile, and blood pressure were determined. The probability of ten-year of cardiovascular events was calculated according to the Framingham study scores using The University of Edinburgh Cardiovascular Risk Calculator (http://cvrisk.mvm.ed.ac.uk/calculator/calc.asp).
Results: There is a non-significant difference between Groups and within Groups of age, smoking habit, and the values of the cardio metabolic risk factors. Pulse pressure index as an independent risk factor found to be a significant discriminator of 10-year prediction of cardiovascular events by using the receiving operating characteristic curves.
Conclusion: The pulse pressure index is a useful discriminator of predicting cardiovascular events, and it will improve the Framingham prediction risk among hypertensive patients.

Keywords: Pulse pressure index; Hypertension; Cardiovascular Index; Angiotensin Converting Enzyme Inhibitors; Angiotensin Receptor Blockers.

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INTRODUCTION

Hypertension is a known risk factor of cardiovascular morbidity and mortality. High systolic blood pressure is one of the predominant variables in calculating the 10-year prediction of cardiovascular diseases and death in the scoring of the Framingham study. The determination of pulse pressure as a function of systolic minus diastolic blood pressure is a simple method of assessment of arterial stiffness in hypertensive patients [1]. Pulse pressure index as a function of pulse pressure divided by systolic blood pressure served as a good marker for the assessment of atherosclerosis in hypertensive patients and is a useful predictor of cardiovascular events [2].

Different groups of medicines have been used to control the high blood pressure and thereby reduced the cardiovascular complications. One of the currently applied regimens to treat hypertension is the use of angiotensin converting enzyme inhibitors (ACEIs) as a monotherapy or in combination with other antihypertensive agents. These drugs (e.g. zofenopril; ramipril) can prevent the cardiovascular events

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(CVEs)[3]. Ramipril and perindopril have a protective effect against cerebrovascular accidents and they significantly reduced the recurrence of stroke [4].

Centrally acting ACEIs (e.g., captopril, lisinopril, enalapril, ramipril) may offer a neuroprotection effect against neurodegenerative diseases. This effect is mediated by interfering with several mechanisms and pathways that ultimately associated with neuronal degeneration e.g. activation of calcium dependent enzymes, production of free radical and others [5]. Long acting ACEIs that have a tissue-penetrating selectivity (e.g., ramipril) reduce the fatal and non-fatal cardiovascular events [6, 7]. Angiotensin II receptor blockers (ARBs) show a variable effect against the CVEs. Candesartan reduces the blood pressure without reducing or preventing the CVEs [8]. Telmisartan reduces the fatal and non-fatal CVEs in both hypertensive and non-hypertensive patients, that is, the cardioprotection of telmisartan is not related to its antihypertensive effect. One meta-analysis study demonstrated that ARBs are effective antihypertensive medicines and offered neuroprotection against stroke by 21%, while they did not reduce the risk of heart failure hospitalization, myocardial infarction, or cardiovascular death [9].

The rationale of the study that the CVEs relate to multiple risk factors, including the gender, race, smoking, dyslipidemia, obesity, diabetes mellitus and hypertension in respect to the scoring of the Framingham study. Therefore, antihypertensive agents that reduce the pulse pressure via their effects on both the systolic and diastolic blood pressure can offer cardioprotection against CVEs. The aim of this cross-sectional study is the assessment of the pulse pressure index as a discriminating variable of predicting the fatal and non-fatal CVEs in hypertensive patients used one member of ACEIs or ARBs using the scores of Framingham study.

MATERIALS AND METHODS

This observational, cross-sectional study was done in the Department of Physiology, College of Medicine, Al-Mustansiriya University, in cooperation with the Department of Pharmacology, College of Medicine, University of Anbar, from September 2016 to January 2017. The study was conducted according to the guidelines of the Declaration of Helsinki. Each participant signed a consent form prior to his/her enrollment into the study.

The patients were recruited from the private clinics in Baghdad, Iraq. The eligible patients were of both genders and aged $\geq$ 40 year. The criteria of inclusions are patients with primary (essential) hypertension; newly diagnosed; on the treatment with ACEIs or ARBs as a monotherapy of duration not less than three years. The ACEIs that received by patients were captopril, enalapril, lisinopril whereas the ARBs were valsartan, losartan, candesartan. The criteria of exclusions included secondary hypertension, diabetes mellitus, pregnancy, liver and kidney diseases. According to the above-mentioned criteria, a total number of 140 patients were enrolled into this study.

Group I(n=30): Hypertensive patients newly diagnosed without treatment. Group II(n=60): Hypertensive patients treated with angiotensin receptor-2 blockers. Group III(n=50): Hypertensive patients treated with angiotensin converting enzyme inhibitors.

The authors examined the patients thoroughly and collected the clinical and laboratory data. According to the questionnaire that designed for this purpose, demographic characteristics, medical history, and the related risk factors were obtained from each patient.

Anthropometric measurements

These included the height (m), weight (kg), and the waist circumference (cm). Body mass index (BMI) was calculated by dividing the weight (kg) by height square (m): BMI (kg/m^2). The Waist circumference was measured at the midpoint between the lowest rib and the iliac crest by metallic tape measure. The waist circumference of 88 cm (women) and 94 cm (men) is considered as discriminator value of central obesity. The waist/height ratio is calculated by dividing the waist circumference (cm) over the height (cm). A cutoff point of (0.5) is the indicator that the patients are at high risk of cardiovascular events and/or diabetes [10].

Blood pressure (BP) measurement

The mean of three readings of BP measurements was taken. The pulse pressure (PP) is the difference between the systolic and the diastolic blood pressure. The mean arterial pressure was calculated using the following formula:

$$Mean\ arterial\ pressure(mm\ Hg) = Diastolic\ BP(mm\ Hg) + 1/3(Systolic\ BP - Diastolic\ BP[mm\ Hg])$$

Pulse pressure index (PPI) was determined by using the following equation:

$$Systolic\ BP(mmHg)/PP(mmHg).$$

Biochemical measurements

Venous blood samples were obtained after a 12-hour overnight fasting and then collected into test tubes containing separator gel. Then the sera separated, within one hour after drawing of the blood, by centrifugation at 3000 rpm for 10 minutes. The samples were kept on -20^oC and analyzed within three weeks.

Fasting serum glucose and serum lipid profiles, including total triglycerides (TG), total cholesterol (TC), high-density lipoprotein-cholesterol (HDL-c), were determined by using visible spectrophotometer. Very low-density lipoprotein-cholesterol (VLDL-c) level was equal to the 0.2 multiplying by the serum triglycerides level. The low-density lipoprotein-cholesterol (LDL-c) was determined by using Friedewald's equation:

$$LDL{-}c(mg/dl) = Total\ cholesterol{-}(HDL{-}c{+}VLDL{-}c)$$

Atherogenic index was calculated by using the formula:

$$\mathrm{Log}(TG/HDL)$$

The risk factor of cardiovascular events including myocardial infarction (MI), coronary heart disease (CHD), cardiovascular disease (CVD), cardiovascular disease death (CVD death), stroke, and coronary heart disease death (CHD death) risk was assessed based on cardio metabolic risk factors and the 10-year probability of CVD. In this cross-sectional study, the following risk factors were assessed: gender, age, systolic blood pressure or known case of hypertension using antihypertensive drugs, high cholesterol level, low HDL-c levels, current

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Table 1. Characteristic features of patients enrolled in the study*

Characteristics	Group I (n=30)	Group II (n=60)	Group III (n=50)
Gender (Men: Women)	19:11	17:43	16:34
Age (year)	54.3±9.7	59.0±8.7	60.4±9.3
Smoking (%)	14(46.7)	30(50)	21(42)
Blood pressure measurements (mmHg)			
Systolic BP	169.3±10.5	155.0±8.7	156.6±21.4
Diastolic BP	102.1±4.7	95.0±9.5	97.3±11.0
Pulse BP	67.3±9.7	60.0±14.2	59.3±15.3
Pulse pressure index	0.4±0.04	0.383±0.058	0.374±0.061
Mean BP	124.5±5.5	115.0±11.5	116.9±13.7
Duration of hypertension (year)	–	9.2±5.4†	6.2±3.3
Anthropometric measurements			
Body mass index (kg/m^2)	30.2±6.5	29.9±7.8	30.1±5.8
Waist circumference (cm)	100.6±10.6	98.9±14.1	99.9±11.4
≥ 88 cm (women)	19 (100)	35 (81.4)	30 (88.2)
≥ 94 cm (men)	17(89.5)	10(58.8)	12(75)
Waist to height ratio	0.513±0.11	0.6±0.09	0.6±0.07
≥ 0.5	14(46.7)	55 (91.7)	47 (94)
Fasting biochemical measurements (mg/dl)			
Serum glucose	106.6±10.1	111.1±16.1	110.6±17.2
Serum cholesterol	182.0±36.6	178.6±36.7	179.1±29.3
Serum triglycerides	175.8±55.2	158.7±47.5	151.7±54.2
≥ 150	20 (66.7)	38(63.3)	28 (56)
Serum high density lipoprotein-cholesterol	50.2±9.8	45.7±8.2	48.6±7.7
≥ 50 (women)	6 (31.6)	29 (67.4)	14(41.1)
≥ 35 (men)	2 (18.2)	2 (11.8)	2 (12.5)
Serum non-high density lipoprotein-cholesterol	131.8±39.5	132.9±36.3	130.5±27.2
Atherogenic index	0.531±19	0.528±0.16	0.470±0.2

* The results are expressed as mean SD and number (%). The results analyzed using posthoc one-way ANOVA test.
† p = 0.001 significant difference in comparison with Group III.

smoking, elevated blood glucose level or known case of diabetes mellitus. The probability of a ten-year of cardiovascular disease was calculated according to the Framingham study scores using The University of Edinburgh Cardiovascular Risk Calculator (http://cvrisk.mvm.ed.ac.uk/calculator/calc.asp).

Statistical analysis

Data were expressed as a number, percent, and whenever possible as means SD. Multivariate analysis using ANOVA posthoc test for independent variable of cardio metabolic risk factors, and area under curve (asymptotic confidence interval 95%) were calculated for each cardiovascular event. For all tests, a two-tailed p ≤0.05 was considered statistically significant. All calculations were made using SPSS (version 20) program for IBM.

RESULTS

Table1 shows the characteristics of the patients enrolled in the study. There are non-significant differences between Groups and within Groups of age, smoking habit, and the values of the cardio metabolic risk factors. The mean value of duration of hypertension is significantly higher in Group II compared with Group I.

The 10-year prediction of stroke was 5.5% in Group II patients, which is significantly less than corresponding percent in Group I (Table 2).

The multivariate analysis of the data showed that the PP as an independent factor does not correlate with the prediction of the CVEs (Table 3), whereas the pulse pressure index as an independent risk factor significantly predicts the stroke and cardiovascular disease death in newly diagnosed hypertension. This indicates that patients with low pulse pressure index are vulnerable to the CVEs (Table 4).

Table 5 shows that the pulse pressure index is a significant discriminating variable that can predict cardiovascular events in Group I and II and this discrimination does not reach significant levels in hypertensive patients treated with ACEIs (Group III).

DISCUSSION

The results of this study show that the patients are in a state of uncontrolled hypertension and the PP or PPI are beyond the normal limits. The predicted of percentages of CVEs are non-significantly less than corresponding values of untreated hypertension. A wide pulse pressure that was reported in this study indicates that the elasticity of the large blood vessels is reduced, and the process of atherosclerosis is existed [11]. The values of PP and PPI of the treated hypertensive patients (Group II) or (Group III) are non-significantly less than the corresponding values of untreated hypertension (Group I). Therefore, a wide peripheral pulse pressure over 55−60 mmHg is a biomarker of increase cardiovascular morbidity [12]. There is evidence that a 10-mm Hg

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Table 2. 10-years prediction (%) of cardiovascular events*

	Group I (n=30)	Group II (n=60)	Group III (n=50)
Coronary heart disease	12.4±9.8	12.3±6.5	12.0±7.3
Myocardial infarction	7.7±7.7	7.0±5.2	6.9±5.8
Stroke	6.3±6.4	5.5±4.1†	5.7±5.3
Cardiovascular disease	22.1±14.9	22.2±11.3	21.5±12.9
Coronary heart disease death	3.4±4.9	2.9±2.8	3.2±3.6
Cardiovascular disease death	5.2±7.2	4.9±4.3	5.3±6.3

* The results are expressed as mean SD. The results were analysed using one-way posthoc ANOVA test.
† p=0.032 significant difference in comparison with Group I.

Table 3. Multivariate analysis shows the impact of pulse pressure as an independent variable on the 10-year prediction of cardiovascular events

Multivariate variables	Group I (n=30)		Group II (n=60)		Group III (n=50)	
	Adjusted R^2	P*-value	Adjusted R^2	P-value	Adjusted R^2	P-value
Coronary heart disease	−0.127	0.833	0.136	0.108	−0.015	0.108
Myocardial infarction	−0.159	0.910	0.079	0.221	0.0300	0.221
Stroke	−0.033	0.359	0.088	0.200	0.2150	0.200
Cardiovascular disease	−0.074	0.677	0.124	0.127	0.0090	0.127
Coronary heart disease death	−0.113	0.794	0.041	0.330	−0.009	0.330
Cardiovascular disease death	−0.060	0.634	−0.021	0.549	−0.079	0.549

* P; probability

Table 4. Multivariate analysis shows the impact of pulse pressure index as an independent variable on the 10-year prediction of cardiovascular events

Multivariate variables	Group I (n=30)		Group II (n=60)		Group III (n=50)	
	Adjusted R^2	P*-value	Adjusted R^2	P-value	Adjusted R^2	P-value
Coronary heart disease	−0.002	0.470	−0.054	0.620	−0.039	0.581
Myocardial infarction	−0.023	0.521	−0.117	0.753	−0.041	0.401
Stroke	−0.556	0.001	−0.054	0.621	0.25200	0.075
Cardiovascular disease	−0.122	0.215	−0.075	0.667	0.02100	0.445
Coronary heart disease death	−0.131	0.201	−0.129	0.775	−0.034	0.568
Cardiovascular disease death	−0.310	0.036	−0.171	0.845	−0.209	0.887

* P; probability

Table 5. Areas under the receiver operating characteristic (ROC) curves for pulse pressure index in predicting cardiovascular events*

	Group I (n=30)	Group II (n=60)	Group III (n=50)
Coronary heart disease	0.547(0.334−0.759)	0.710(0.578−0.842)	0.469(0.306−0.632)
Myocardial infarction	0.560(0.349−0.771)	0.712(0.581−0.843)	0.478(0.316−0.641)
Stroke	0.667(0.465−0.868)	0.738(0.609−0.866)	0.574(0.413−0.735)
Cardiovascular disease	0.609(0.402−0.816)	0.698(0.564−0.832)	0.522(0.359−0.684)
Coronary heart disease death	0.573(0.361−0.786)	0.680(0.543−0.817)	0.485(0.322−0.648)
Cardiovascular disease death	0.618(0.408−0.827)	0.660(0.518−0.802)	0.498(0.334−0.661)

* The results expressed as area under the curve (95% confidence interval. Null hypothesis true =0.5 taking the cutoff of pulse pressure index of 0.394, 0.388 and 0.377 (the median value of Group I, II and III respectively) which represents the median value.

increase of PP was associated with a 12% increase in coronary heart diseases [13]. It has been found that PP is an independent risk factor of stroke in normotensive middle-aged subjects [14]. Therefore, our results highlight the importance of using ARBs in management of hypertension as the predicted percentage of future stroke is significantly less than untreated

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hypertension despite of non-significant difference in the pulse pressure between Group I and II (Table 2). Pulse pressure, as an independent risk factor of prediction the CVEs does not show a significant relation to the CVEs whereas the PPI is a significant independent risk factor in predicting stroke and death due to cardiovascular disease in Group I. This observation highlights two important remarks. The first, antihypertensive agents, including ARBs or ACEIs have cardiovascular protective effects, and the second remark is PPI has an advantage over the PP as an independent risk factor of CVEs [2, 15, 16].

Table 5 showed that PPI is a discriminating risk factor of predicting CVEs in Group I and II while in Group III was a discriminating factor for stroke and cardiovascular disease. Previous study highlighted the importance of using the PP to improve the Framingham CVEs risk prediction among middle age and elderly age group while this study adds other important information that PPI may improve the Framingham CVEs score in hypertensive patients whether they are treated or untreated [17]. Therefore, this finding sends a massage to reduce both systolic and diastolic blood pressure aiming to reduce the PPI value and this explain why PPI is not a good discriminator in Group III compared with Group I and II because the PPI in Group III patients is less than corresponding values of Group I and II. Limitations of the study including stratification the data in respect to the individual drug therapy to eliminate the bias of the antihypertensive agent that offered a cardio-protective effect.

CONCLUSION

We conclude that the pulse pressure index is a useful discriminator of predicting cardiovascular events in untreated hypertension and in uncontrolled treated hypertension with ARBs or ACEIs. Therefore, using PPI in the assessment of CVEs will improve the Framingham prediction risk among hypertensive patients.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

REFERENCES

[1] A. Chugh and G. L. Bakris. Pulse pressure and arterial stiffness: an emerging renal risk predictor? *J. Hypertens*, 25:1796–1797, 2017.

[2] Y. Peng-Lin and L. Yue-Chun. Pulse pressure index (pulse pressure/systolic pressure) may be better than pulse pressure for assessment of cardiovascular outcomes. *Med. Hypotheses*, 72(6):729–731, 2009.

[3] C. Borghi et al. Zofenopril and ramipril in combination with acetyl salicylic acid in postmyocardial infarction patients with left ventricular systolic dysfunction: A retrospective analysis of the smile-4 randomized , double-blind study in diabetic patients. *Cardiovascular Therapeutics*, 34(2):76–84, 2016.

[4] A. Awada. Primary and secondary prevention of ischemic stroke. *J. Med. Liban.*, 59(4):213–219, 2011.

[5] A. Muthuraman P. Kaur and M. Kaur. The implications of angiotensin-converting enzymes and their modulators in neurodegenerative disorders: current and future perspectives. *ACS Chem. Neurosci.*, 6(4):508–521, 2015.

[6] S. G. Vijan. Angiotensin-converting enzyme inhibitors (aceis), not angiotensin receptor blockers (arbs), are preferred and effective mode of therapy in high cardiovascular risk patients. *J. Indian Med. Assoc.*, 107(3):178–182, 2009.

[7] L. Akioyamen et al. Cardiovascular and cerebrovascular outcomes of long-term angiotensin receptor blockade: meta-analyses of trials in essential hypertension. *J. Am. Soc. Hypertens.*, 10(1):55–69, 2016.

[8] C. Keller and J. Mueller-Ehmsen. Pharmacological primary prevention of myocardial infarction, stroke and death: A possible task? *Dtsch. Med. Wochenschr.*, 141(18):1330–1332, 2016.

[9] S. Foulquier et al. Impact of telmisartan on cardiovascular outcome in hypertensive patients at high risk: a telmisartan randomised assessment study in ace intolerant subjects with cardiovascular disease subanalysis. *J. Hypertens.*, 32(6):1334–1341, 2014.

[10] M. Ashwell and S. Gibson. Waist-to-height ratio as an indicator of early health risk: simpler and more predictive than using a matrixbased on bmi and waist circumference. *BMJ Open*, 32(6), e010159, 2016.

[11] K. M. Hanus et al. Relationship between gender and clinical characteristics, associated factors, and hypertension treatment in patients with resistant hypertension. *Kardiol. Pol. (Polish Hear. Journal)*, 75(5):421–431, 2017.

[12] P. Lokaj, J. Parenica, M. P. Goldbergova, K. Helenova, R. Miklik, P. Kubena, and et al. Pulse pressure in clinical practice. *Eur. J. Cardiovasc. Med.*, 2(1):66–68, 2011.

[13] V. Vaccarino, T. R. Holford, and H. M. Krumholz. Pulse pressure and risk for myocardial infarction and heart failure in the elderly. *J. Am. Coll. Cardiol.*, 36(1):130–138, 2000.

[14] K. Okada, H. Iso, R. Cui, M. Inoue, and S. Tsugane. Pulse pressure is an independent risk factor for stroke among middle-aged japanese with normal systolic blood pressure the jphc study. *J. Hypertens.*, 29(2):319–324, 2011.

[15] L. Potier et al. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in high vascular risk. *Heart*, 103(17):1339–1346, 2017.

[16] K. Miura et al. Pulse pressure compared with other blood pressure indexes in the prediction of 25-year cardiovascular and all-cause mortality rates: The chicago heart association detection project in industry study. *Hypertension*, 38(2):232–237, 2001.

[17] T. S. Nawrot et al. Should pulse pressure become part of the framingham risk score?*J. Hum. Hypertens.*, 18(4):279–286, 2004.