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PULSE PRESSURE FOR PICKING THE OPTIMUM CARDIAC STRATEGY WITH TYPE2 DIABETES AND CORONARY ARTERY DISEASE PATIENTS

[1]Dr. Areesha Manzor,[2]Dr Aneeka Gulzar,[3]Dr Syeda Anbar Gilani

[1]PGT, ENT, Fauji Foundation Hospital,Rawalpindi.

[2]WMO, Civil Hospital, Daska.

[3]Ex House Officer, ABSTH, Gujrat.

Abstract:

Pulse pressure may be potentially useful for selecting effective cardiac treatment strategies. This study aimed to assess the association between the cardiac treatment strategies and risk of major adverse cardiovascular events (MACE) in patients with type 2 diabetes and coronary artery disease (CAD), based on low or high levels of pulse pressure.

We analyzed data from the Bypass Angioplasty Revascularization Investigation 2 Diabetes trial and calculated hazard ratios (HRs) for MACE with 95% confidence intervals (95%CIs) using the Cox proportional hazard model. The risk of MACE in patients with type 2 diabetes and CAD was compared between the early revascularization and medical therapy groups separately in patients with pulse pressures b 60 mmHg (n = 1378) and ≥ 60 mmHg (n= 916).

During a maximal follow-up of 6 years, 389 patients experienced MACE. In patients with pulse pressure b 60 mmHg, the risk of MACE was significantly higher in the early revascularization group (HR: 1.37, 95%CI: 1.04–1.81, P = 0.02) and was specifically and significantly higher in the percutaneous coronary intervention group (HR: 1.66, 95%CI: 1.17–2.34, P = 0.004) than in the medical therapy group. In contrast, the risk of MACE in patients with pulse pressure ≥ 60 mmHg was significantly lower in the early revascularization group (HR: 0.72, 95%CI: 0.53–0.96, P = 0.02) and was specifically lower in the coronary artery bypass graft surgery group (HR: 0.49, 95%CI: 0.30–0.82, P =0.006) than in the medical therapy group.

Pulse pressure may be used to determine optimal cardiac treatment strategies in patients with type 2 diabetes and CAD.

Keywords: *Type 2 Diabetes, Pulse pressure; Coronary Artery Disease, Revascularization, Cardiovascular events, Intensive Medical Therapy*

Corresponding author:

Dr. Areesha Manzor,

PGT, ENT, Fauji Foundation Hospital, Rawalpindi.

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INTRODUCTION:

Type 2 diabetes, is a growing public health concern worldwide, and management strategies strive to prevent diabetes-related complications. Although adequate glycemic control reduces the risk of micro-vascular diseases, such as diabetic retinopathy and nephropathy, recent large-scale trials have revealed that intensive glycemic therapy alonemay not prevent major cardiovascular events (Dsouza and Bhat, 2018).

Furthermore, the Action to Control Cardiovascular Risk in Diabetes trial has revealed that intensive glycemic therapy in patients with type 2 diabetes results in the increased risk of all-cause and cardiovascular death. A possible explanation for this increased risk in patients with type 2 diabetes undergoing intensive glycemic therapy is severe hypoglycemia, which is associated with the increased risk of death and cardiovascular events. Thus, it appears that though glycemic control is essential, it is not sufficient for the adequate management of complications associated with type 2 diabetes (End, Seliger and DeFilippi, 2013).

Type 2 diabetes is an important risk factor for coronary artery disease (CAD), and some patients with type 2 diabetes already have CAD. However, optimal strategies for patients with type 2 diabetes and CAD have not been clearly described. To date, the best available evidence regarding the optimal strategies for these patients comes from the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial, which demonstrated that the risks of all-cause death and the combination of all-cause death, myocardial infarction, or stroke did not differ significantly between early revascularization and intensive medical therapy alone (Dsouza and Bhat, 2018).

Previous studies have suggested that pulse pressure is a strong predictor of cardiovascular events and that pulse pressure is an independent predictor of cardiovascular events in patients with CAD. These observations suggest that pulse pressure levels can serve as predictors in the selection of optimal management strategies in patients with type 2 diabetes and CAD. Thus, the aim of the present study was to assess the association between the cardiac treatment strategy and the risk of cardiovascular events in patients with type 2 diabetes and CAD, based on low or high levels of pulse pressure (End, Seliger and DeFilippi, 2013).

METHODS:

2.1. Study design and participants

Data from the BARI 2D trial was used to evaluate the two cardiac treatment strategies in patients with type 2 diabetes and CAD. The BARI 2D trial included 2368 patients with type 2 diabetes and CAD from 49 clinical sites who were followed from January 1, 2001, to March 31, 2005. Detailed information on the study protocol, design, and patient characteristics has been reported previously (Hamoud, 2018).

Briefly, the BARI 2D trial was an international, multicenter, randomized clinical trial in patients with type 2 diabetes and CAD. The participants were randomly assigned to one of two treatment strategies using a 2 × 2 factorial design: 1) an initial early revascularization (percutaneous coronary intervention [PCI] or coronary artery bypass graft surgery [CABG]) combined with intensive medical therapy versus an initial strategy of intensive medical therapy alone and 2) a strategy of increasing sensitivity to insulin (reducing insulin resistance) versus a strategy of providing more insulin (endogenous or exogenous), with a target glycated hemoglobin level of b 7.0% for each strategy. Randomization was stratified according to the method of revascularization (PCI or CABG), which was determined, a priori, to be the more appropriate therapy for each patient by the attending physician. Patients with type 2 diabetes aged 25 years or older and diagnosed with CAD were eligible for participation in the BARI 2D trial (Dsouza and Bhat, 2018).

Type 2 diabetes was diagnosed based on a record review, the need for treatment with oral hypoglycemic drugs or insulin, or elevated levels of fasting plasma glucose (≥ 126/mg/dL [7.0 mmoL/L]). The diagnosis of CAD was confirmed by the documentation on angiography: ≥ 50% stenosis of a major epi-cardial coronary artery associated with a positive stress test or ≥ 70% stenosis of a major epicardial coronary artery and classic angina. Patients were excluded if they had undergone revascularization within 12 months prior to study entry, required immediate coronary revascularization, had serumcreatinine N 2mg/dL, hepatic disease, HbA1c N 13.0%, congestive heart failure functional class III or IV (New York Heart Association), or stenosis ≥ 50% of the left main coronary artery. Patients were treated at least with intensive management of hypertension (blood pressure b 130/80 mmHg) and dyslipidemia (low-density lipoprotein cholesterol level b 100 mg/dL) after randomization (Hamoud, 2018).

Additionally, patients received counseling regarding weight loss, physical exercise, and smoking cessation. For the analyses in the present study, data from patients aged 80 years or older (n = 38) were trimmed and data from patients without information on pulse pressure (n = 36) were excluded from the BARI 2D trial data, resulting in a final sample size of 2294 subjects (Dsouza and Bhat, 2018).

2.2. Pulse pressure, systolic blood pressure, and diastolic blood pressure

Blood pressure was measured in a sitting position during clinic visits, and pulse pressure was defined as the difference between systolic and diastolic blood pressure. Previous studies suggested that elevated pulse pressure is associated with an increased risk of cardiovascular events and mortality. Patients in the present study were categorized into two groups based on pulse pressure b 60 mmHg or ≥ 60 mmHg (Tsujimoto and Kajio, 2018).

In addition to the pulse pressure, we assessed the association between the cardiac treatment strategy and the risk of cardiovascular events, based on low or high levels of systolic or diastolic blood pressure. Systolic and diastolic blood pressure levels of b 140/90mmHg are the recommended goals by a current guideline. Based on the current guideline, patients were also categorized as those with systolic blood pressure b 140 mmHg or ≥ 140 mmHg. Furthermore, because 90% of the patients had a diastolic blood pressure b 90mmHg, the cut-off level for high diastolic blood pressure was set at 80 mmHg, and patients were categorized as diastolic blood pressure b 80 mmHg or ≥ 80 mmHg (Tsujimoto and Kajio, 2018).

2.3. Outcome measurements

The primary outcome of the present study was major adverse cardiovascular events (MACE), which was a composite end point including cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke. The secondary outcomes were all-cause, cardiovascular or non-cardiovascular death, fatal or non-fatal myocardial infarction, and fatal or non-fatal stroke.

2.4. Statistical analysis

Demographic data are presented as means ± standard deviations (SDs) or proportions. Continuous variables were compared using the t-test, and categorical variables were compared using the chi-squared test. Kaplan–Meier survival curves were constructed, and the event rates of primary and secondary outcomes were calculated in patients with a pulse pressure b 60 mmHg or ≥ 60 mmHg (Ueda, 2018).

Using the randomized design of the BARI 2D trial, we used the Cox proportional hazard model to calculate hazard ratios (HRs) for primary and secondary outcomes with 95% confidence intervals (CIs) in the early revascularization group compared with the medical therapy group separately in patients with pulse pressure b 60 mmHg and ≥ 60 mmHg. Further analyses were performed to assess the HRs for primary outcomes in the PCI and CABG treatment groups, and these were compared with those of the medical therapy group. Similar analyses were performed in patients with systolic blood pressure b 140 mmHg or ≥ 140 mmHg and in those with diastolic blood pressure b 80 mmHg or ≥ 80 mmHg (Tsujimoto and Kajio, 2018).

The primary outcome was further analyzed according to clinically relevant subgroups: age (b 60 or ≥ 60 years), sex (male or female), race/ethnicity, obesity status (non-obese or obese), myocardial infarction (no history of myocardial infarction or prior history of myocardial infarction), glycated hemoglobin levels (b 7% or ≥ 7%), glycemic treatment assignment (insulin sensitizing or insulin providing), angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers (ACE-I/ARB) (nonuse or use), beta blockers (nonuse or use), calcium channel blockers (nonuse or use), and diuretics (nonuse or use). To explore the effect modifications, we tested for interactions between the cardiac treatment strategy (early revascularization or medical therapy) and these subgroups (Ueda, 2018).

3. RESULTS:

3.1. Characteristics of study participants

The baseline characteristics of patients, categorized as pulse pressure b 60 mmHg (n = 1378) or ≥ 60 mmHg (n = 916), are presented in Table 1. Themean ages (±SD) of patients with pulse pressures b60 mmHg and ≥ 60 mmHg were 59.7 (±8.5) and 64.5 (±7.8) years, respectively. Within patients with pulse pressure b 60 mmHg and ≥ 60mmHg, baseline characteristics were well balanced and not significantly different between the medical therapy and early revascularization groups (Ueda, 2018).

3.2. Primary and secondary outcomes

The mean follow-up periods (±SD) were 4.1 (±1.7) years in patients with pulse pressure b 60 mmHg and 3.8 (±1.8) years in those with pulse pressure ≥ 60 mmHg. The Kaplan–Meier survival curves for MACE, cardiovascular death, myocardial infarction, and stroke in patients with pulse pressure b 60 mmHg

and in those with pulse pressure ≥ 60 mmHg are shown in Figs. 1 and 2, respectively.

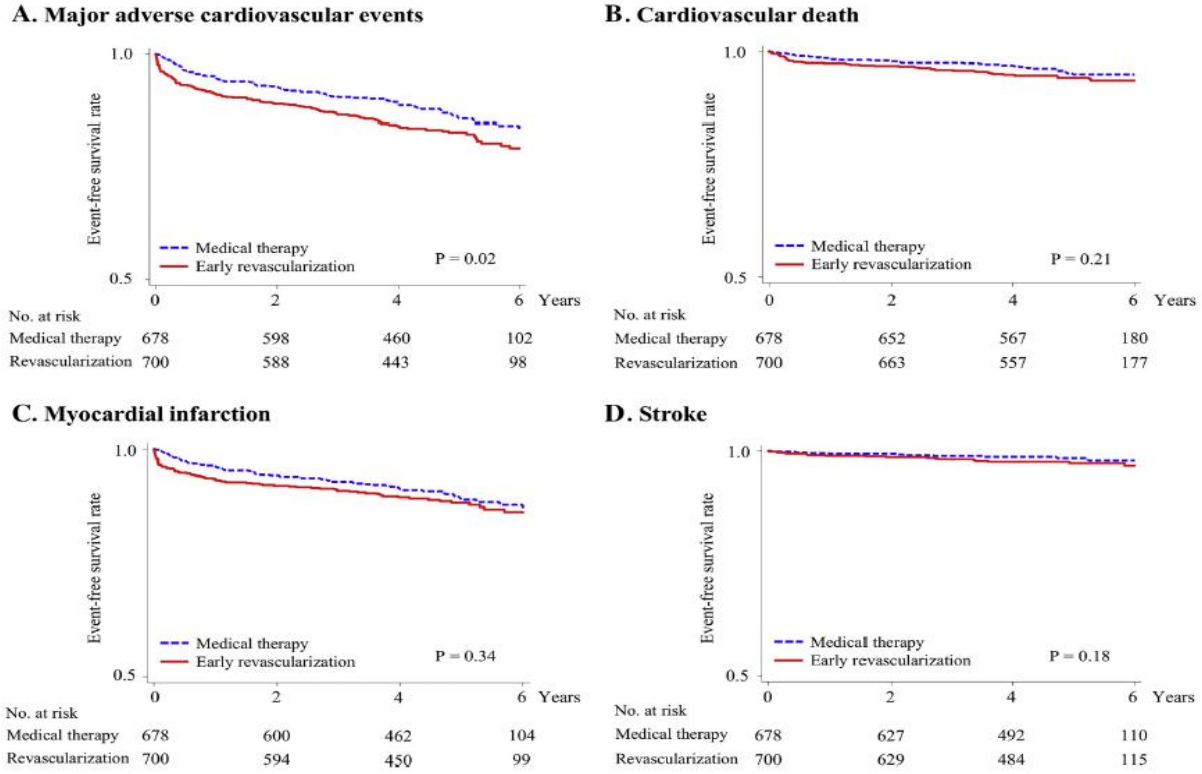

Figure 1 Source: (Dsouza and Bhat, 2018)

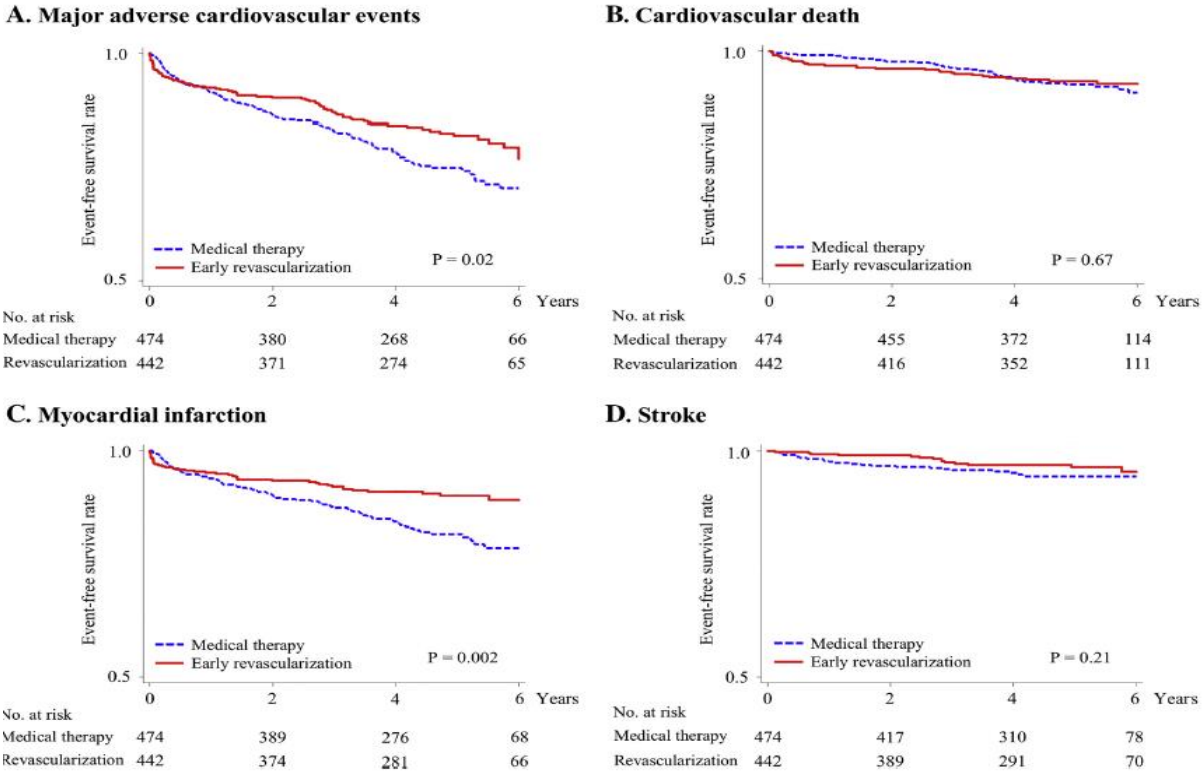

Figure 2 Source: (Dsouza and Bhat, 2018)

The cumulative event rates and HRs for these cardiovascular outcomes in both categories of patients are shown in Table 2, and those in the PCI or CABG and the medical therapy groups are shown in Tables S1 and S2, respectively.

Table 1
Baseline characteristics of patients with pulse pressure < 60 mmHg or ≥ 60 mmHg.[a]

	Pulse pressure < 60 mmHg			Pulse pressure ≥ 60 mmHg		
	Medical therapy	Revascularization	P value	Medical therapy	Revascularization	P value
	N = 678	N = 700		N = 474	N = 442	
Age (years)	59.7 (8.6)	59.6 (8.4)	0.78	64.5 (7.9)	64.7 (7.6)	0.67
Female sex (%)	26.1	25.1	0.68	34.2	36.5	0.46
Race and ethnicity (White, %)	69.9	69.7	0.93	71.3	70.1	0.69
Level of education (%)			0.59			0.26
Less than high school	35.1	36.2		39.0	39.0	
High school	20.8	22.3		24.2	20.2	
More than high school	44.1	41.5		36.8	40.8	
Physical activity (%)			0.57			0.12
Sedentary	20.1	22.2		25.1	20.7	
Mild	40.7	40.5		39.9	46.1	
Moderate/strenuous	39.2	37.3		35.0	33.2	
Smoking status (%)			0.053			0.66
Never	28.1	33.8		35.6	35.1	
Former	57.6	51.6		55.3	54.1	
Current	14.3	14.6		9.1	10.8	
Body mass index (kg/m^2)[b]	31.8 (6.0)	31.4 (5.8)	0.25	32.0 (5.4)	31.9 (5.9)	0.64
Obesity (%)	43.0	46.7	0.16	38.6	42.9	0.18
Duration of diabetes (years)	9.5 (8.7)	9.4 (8.1)	0.79	12.1 (8.8)	11.3 (8.6)	0.15
Hypertension (%)	77.2	78.2	0.65	90.0	89.6	0.83
Hypercholesterolemia (%)	79.6	83.6	0.06	83.5	81.6	0.43
History of MI (%)	37.7	36.8	0.74	25.0	24.1	0.75
History of stroke/TIA (%)	9.2	9.3	0.93	11.5	9.5	0.31
Medications						
ACE-I (%)	63.8	62.3	0.56	68.2	65.6	0.40
ARB (%)	14.5	11.3	0.08	17.2	17.0	0.94
Calcium channel blockers (%)	29.3	25.2	0.09	37.5	37.6	0.98
Beta blockers (%)	71.2	73.2	0.39	74.8	72.6	0.45
Diuretics (%)	33.1	35.1	0.44	44.9	44.6	0.92
Statin (%)	74.0	72.9	0.66	76.1	77.2	0.69
Aspirin (%)	89.6	87.8	0.27	88.1	86.2	0.39
Insulin (%)	24.9	26.7	0.44	34.3	28.8	0.07
Biguanides (%)	56.2	55.4	0.75	53.3	51.9	0.68
Sulfonylureas (%)	55.8	51.5	0.11	51.6	54.2	0.43
Glycated hemoglobin (%)	7.8 (1.7)	7.6 (1.7)	0.24	7.6 (1.5)	7.6 (1.5)	0.78
Low-density lipoprotein (mg/dL)	97.5 (35.1)	95.5 (30.9)	0.29	97.0 (35.4)	95.5 (33.2)	0.52
High-density lipoprotein (mg/dL)	37.4 (9.3)	36.9 (10.0)	0.35	39.8 (11.0)	39.4 (10.4)	0.56
Estimated GFR (ml/min/1.73m^2)	75.5 (22.8)	75.4 (36.0)	0.94	67.8 (19.9)	67.7 (19.0)	0.89
Glycemic treatment assignment						
Insulin providing (%)	49.1	50.7	0.55	50.6	49.3	0.69

MI, myocardial infarction; TIA, transient ischemic attack; ACE–I, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; GFR, glomerular filtration rate.
[a] Data are presented as number of participants, percent, or mean (standard deviation).
[b] Body mass index was calculated as weight in kilograms divided by the square of height in meters. Obesity was defined as body mass index ≥ 30 kg/m^2.

Table 1, Source: (Dsouza and Bhat, 2018)

In patients with pulse pressure b 60mmHg, the MACE event rate per 1000 person years was significantly higher in the early revascularization group (42.3) than in the medical therapy group (30.6) (HR: 1.37, 95% CI: 1.04–1.81, P=0.02, Fig. 1A) (Dsouza and Bhat, 2018).

The risks of cardiovascular death, myocardial infarction, and stroke were also higher in the early revascularization group than in the medical therapy group but were not significantly different (HR for cardiovascular death: 1.34, 95% CI: 0.84–2.15, P = 0.21 [Fig. 1B]; HR for myocardial infarction: 1.17, 95% CI: 0.84–1.62, P = 0.34 [Fig. 1C]; and HR for stroke: 1.69, 95% CI: 0.77–3.68, P = 0.18 [Fig. 1D], respectively) (Dsouza and Bhat, 2018).

Additionally, in patients with pulse pressure b 60 mmHg, the MACE risk was significantly higher in the PCI group than in the medical therapy group (HR: 1.66, 95% CI: 1.17–2.34, P = 0.004, Fig. S1A), whereas it was not significantly different between the CABG and medical therapy groups (HR: 0.94, 95% CI: 0.59–1.50, P = 0.80, Fig. S1B) (Table S1). Although not statistically significant, there seemed to be an interaction between the cardiac treatment strategy and revascularization procedures in patients with pulse pressure b60 mmHg (P for interaction =

0.057) (Dsouza and Bhat, 2018).
In patients with pulse pressure ≥ 60mmHg, the MACE event rate per 1000 person years was significantly lower in the early revascularization group (43.2) than in the medical therapy group (61.0) (HR: 0.72, 95% CI: 0.53–0.96, P = 0.02, Fig. 2A). In these patients with pulse pressure ≥ 60 mmHg, the risk of myocardial infarction was also significantly lower in the early revascularization group than in the medical therapy group (HR for myocardial infarction: 0.54, 95% CI: 0.37–0.79, P = 0.002, Fig. 2C), whereas the risks of cardiovascular death and stroke were not significantly different between the two groups (HR for cardiovascular death: 0.89, 95% CI: 0.55–1.47, P = 0.67 [Fig. 2B] and HR for stroke: 0.66, 95% CI: 0.34–1.28, P = 0.21 [Fig. 2D], respectively) (Dsouza and Bhat, 2018).

3.3. Pulse pressure and risk of cardiovascular events

The baseline characteristics of patients with pulse pressure b 60 mmHg and ≥ 60 mmHg. Compared to patients with pulse pressure b 60 mmHg, those with pulse pressure ≥ 60 mmHg were significantly associated with the following variables: older age, higher proportion of females, fewer current smokers, longer duration of diabetes, higher prevalence of hypertension, lower prevalence of myocardial infarction, higher levels of high-density lipoprotein cholesterol, lower levels of estimated glomerular filtration rate and more use of ACE-I/ARB and insulin. HRs for MACE according to pulse pressure levels are shown in Table S4. The unadjusted and adjusted risks of MACE were significantly higher in patients with pulse pressure ≥ 60 mmHg than those with pulse pressure b 60 mmHg (unadjusted HR: 1.42, 95% CI: 1.16–1.73, P = 0.001; adjusted HF [model 1]: 1.32, 95% CI: 1.07–1.63, P = 0.01; adjusted HF [model 2]: 1.35, 95% CI: 1.07–1.70, P = 0.01; adjusted HF [model 3]: 1.34, 95% CI: 1.06–1.69, P = 0.01) (Dsouza and Bhat, 2018).

4.0 DISCUSSION:

The results of our analyses demonstrated that the risk of MACE in patients with pulse pressure b 60 mmHg was significantly higher in the revascularization group, and specifically in the PCI group, than in the medical therapy group (Tsujimoto and Kajio, 2018).
In contrast, in patients with pulse pressure ≥ 60 mmHg the risk for MACE was significantly lower in the revascularization group, and specifically in the CABG group, than in the medical therapy group. Interestingly, similar associations were not observed when patients were classified based on systolic and diastolic blood pressure cut-offs of 140 mmHg and 80 mmHg, respectively (Dsouza and Bhat, 2018).
Moreover, the risk of MACE in obese (but not non-obese) patients with pulse pressure b 60 mmHg was significantly higher in the early revascularization group than in the medical therapy group, whereas the risk of MACE was significantly lower in patients with pulse pressure ≥ 60 mmHg and no history of myocardial infarction (but not in those with a history of myocardial infarction) significantly lower in the early revascularization group than in the medical therapy group. Consistent with previous studies, the present study found that high pulse pressure was associated with an increased risk of MACE (Tsujimoto and Kajio, 2018).

These results may be attributed to the difference between pulse pressure and systolic or diastolic blood pressure as a predictor of future cardiovascular events. Although the exact reasons remain unclear, the risk of revascularization in patients with a low pulse pressure may be equal to or higher than the benefits of reperfusion. In contrast, in patients with a high pulse pressure, who have a very high risk of coronary events, prompt revascularization, specifically CABG, may be effective in reducing their risk of MACE and myocardial infarction (Dsouza and Bhat, 2018).

However, considering the influence of obesity and a prior history of myocardial infarction on the association between the cardiac treatment strategy and risk of MACE, further studies are warranted to validate our results. In addition, elevated pulse pressure was recognized as a risk factor for cardiovascular events in the 2013 ESH/ESC guidelines. However, the clinical significance of pulse pressure in younger patients remains controversial. A recent study has suggested that office pulse pressure is a negative predictor of MACE in young patients with hypertension. Although, the present study found that high pulse pressure was associated with an increased risk of MACE and that there was no significant interaction between the cardiac treatment strategy and age in patients with pulse pressure b 60 mmHg and those with pulse pressure ≥ 60 mmHg, further investigations are needed to assess whether these results are observed in younger patients (Tsujimoto and Kajio, 2018).

5.0 CONCLUSION:

In conclusion, the present study on patients with type 2 diabetes and CAD demonstrated that in patients with pulse pressure b 60mmHg, the risk of MACE is significantly higher in the early revascularization

than in the medical therapy, whereas in those with pulse pressure ≥ 60 mmHg, the risk of MACE was found to be significantly lower in the early revascularization. Further studies, particularly randomized controlled trials, are needed to identify optimal cardiac strategies in patients with type 2 diabetes and CAD.

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