DIABETES RESEARCH AND CLINICAL PRACTICE 149 (2019) 69–77

Contents available at ScienceDirect

Diabetes Research and Clinical Practice

journal homepage: www.elsevier.com/locate/diabres

International Diabetes Federation

Relationships between blood pressure lowering therapy and cardiovascular events in hypertensive patients with coronary artery disease and type 2 diabetes mellitus: The HIJ-CREATE sub-study

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ARTICLE INFO

Article history:
Received 23 October 2018
Received in revised form
10 January 2019
Accepted 30 January 2019
Available online 6 February 2019

Keywords:
Coronary artery disease
Hypertension
Type 2 diabetes mellitus
Clinical trial
Pharmacotherapy

ABSTRACT

Objective: The effects of intensive blood pressure (BP) lowering for hypertensive patients with coronary artery disease (CAD) and diabetes mellitus on their clinical outcomes have not been fully evaluated. The aim was to explore the optimal systolic BP target in such patients in a substudy of a prospective, randomized trial.

Methods: Of a total of 2049 hypertensive patients with CAD who were enrolled in the HIJ-CREATE study, type 2 diabetes was diagnosed in 780 (38.1%). Titration of antihypertensive agents was performed to reach the target BP of <130/85 mmHg. The primary endpoint was the occurrence of a first major adverse cardiovascular event (MACE). Achieved BP was defined as the mean value of systolic BP in patients who did not develop MACEs and as the mean value of systolic BP prior to MACEs in those who developed MACEs during follow-up.

Results: During a median follow-up of 4.2 years, the primary outcome occurred in 259 (33.2%) diabetic patients and in 293 (23.1%) non-diabetic patients ($p < 0.0001$). The diabetic patients were divided into quartiles based on the mean systolic BP during follow-up. The relationships between achieved BP and the incidence of MACEs did not follow a J-shaped curve. Intensive systolic BP lowering to less than 120 mmHg did not correlate with an increased risk of MACEs.

Conclusions: Our results suggest that the intensive BP lowering may not impair patients' clinical courses even in a high-risk population. The establishment of an optimal management strategy for hypertensive patients with diabetes and CAD is essential.

Abbreviations: ACE, angiotensin-converting enzyme; ACCORD-BP, the Action to Control Cardiovascular Risk in Diabetes–Blood Pressure study; ARB, angiotensin receptor blocker; BP, blood pressure; CAD, coronary artery disease; HbA1c, glycosylated haemoglobin; HIJ-CREATE, The Heart Institute of Japan Candesartan Randomized Trial for Evaluation in Coronary Artery Disease; HR, hazard ratio; JNC7, the seventh report of the Joint National Committee; MACE, major adverse cardiovascular event

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https://doi.org/10.1016/j.diabres.2019.01.031
0168-8227/

1. Introduction

Most guidelines for treatment of hypertension recommend a blood pressure (BP) goal of <140/90 mmHg for hypertensive patients and a more aggressive goal of <130/80 mmHg for patients with coronary artery disease (CAD). They were not drawn from the results of prospective, randomized trials but based on expert consensus. In the seventh report of the Joint National Committee (JNC7) on prevention, detection, evaluation, and treatment of high BP, it is clearly reported that the relationship between BP and the risk of cardiovascular events is continuous, consistent, and independent of other risk factors [1]. The optimal BP target in hypertensive patients with CAD is not well defined [2,3]. Subsequently, the JNC7 statement was reviewed and updated.

Diabetes mellitus is a major cause of cardiovascular disease, chronic kidney disease, peripheral arterial disease, and strokes [4,5]. In patients with diabetes, uncontrolled blood glucose levels are associated with high cardiovascular morbidity and mortality. Sufficient attention to traditional risk factors could yield further substantive reductions in adverse events in the diabetic population [6]. In a follow-up study of Steno-2, the investigators demonstrated that intensive intervention with multiple drug combinations and behavior modification had sustained beneficial effects with respect to vascular complications and on mortality rates from any cause and from cardiovascular causes [7]. Furthermore, the coexistence of hypertension with diabetes strongly exacerbates the diabetic complications. Recent evidence [7–9] demonstrates that aggressive glucose and BP control in diabetic patients with hypertension does not provide any additional benefits with respect to cardiovascular complications compared to standard glucose and BP control, although the Action to Control Cardiovascular Risk in Diabetes–Blood Pressure (ACCORD-BP) study [10] is the only prospective clinical trial that has evaluated an intensive systolic BP target in diabetic patients. A recent meta-analysis [11] clearly demonstrated that contemporary BP lowering was associated with improved clinical outcomes. However, the authors also pointed out that the reliability of the meta-analysis was limited by the lack of sufficient data for aggressive BP lowering in the 120- to 130-mmHg range.

To date, the optimal BP target in hypertensive patients with diabetes and coronary artery disease is not well defined. However, simplification of the antihypertensive treatment regimen has been launched in the latest guideline [12,13].

The purpose of the present substudy of a randomized, controlled trial was to clarify the optimal BP target for secondary prevention in hypertensive patients with diabetes and CAD. In particular, the aim was to explore the optimal systolic BP target in hypertensive patients with CAD and type 2 diabetes in the prospective, randomized trial.

2. Methods

2.1. Participants

The Heart Institute of Japan Candesartan Randomized Trial for Evaluation in Coronary Artery Disease (HIJ-CREATE) was a multicenter, prospective, randomized, controlled study that compared the effects of candesartan-based therapy to those of non–angiotensin receptor blocker (ARB)-based standard therapy on major adverse cardiovascular events in 2049 hypertensive patients with CAD. The study methods and main results of HIJ-CREATE have been published previously [14]. In brief, hypertensive patients with angiographically documented CAD were randomly assigned to receive either candesartan-based (n = 1024) or non–ARB-based pharmacotherapy, including angiotensin-converting enzyme (ACE) inhibitors (n = 1025). When we started the HIJ-CREATE study, candesartan was the most common once-a-day ARB prescribed as an antihypertensive in Japan. Therefore, this agent appeared to be a rational choice for the ARB-based treatment arm, and its usefulness required evaluation.

2.2. Clinical measures and follow-up

During the median follow-up period of 4.2 years (interquartile range 3.5–4.9 years), 3 patients in the candesartan arm and 5 in the non-ARB arm were lost to follow-up, resulting in a follow-up rate of 99.6%. The present trial was conducted in accordance with the principles of the Declaration of Helsinki. The institutional review board or relevant ethics committee of each participating medical center approved the protocol, and all patients provided written, informed consent before trial enrollment.

BP was measured using a standard cuff mercury sphygmomanometer after ≥5 min of rest in the sitting position. Hypertension was defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or a history of having received treatment for hypertension at the time of enrollment. Diabetes was defined as a fasting blood glucose level ≥126 mg/dL or treatment with hypoglycemic agents at the time of enrollment. Titration of antihypertensive agents was performed to reach the target blood pressure of <130/85 mmHg. Participants were followed by hospital doctors or other general practitioners. Incidence of endpoint events in addition to drug safety information was determined during the scheduled 6, 12, 24, 36, 48, and 60-month visits. In diabetic participants, glycosylated hemoglobin (HbA1c) was also measured during the scheduled 6, 12, 24, 36, 48, and 60-month visits.

All patients were followed for ≥36 months. Blood pressure values from baseline to the time of the event or to the last protocol visit were used for the analysis. The primary endpoint of HIJ-CREATE was the time to first major adverse cardiac event (MACE; a composite of cardiovascular death, non-fatal myocardial infarction, unstable angina, heart failure, stroke, and other cardiovascular events requiring hospitalization).

2.3. Statistical analysis

Participants were divided into quartiles based on their average levels of systolic and diastolic BP during follow-up. Cumulative event-free survival was measured by the method of Kaplan-Meier, and unadjusted differences were compared using the log-rank test. The relationship between achieved BP divided into quartiles and the risk of MACE was explored using a Cox proportional hazard regression model. It was desirable to include the traditional risk factors that were determined by reference to previous studies [15,16] in the proportional hazard model. Multivariate analysis using the Cox proportional hazards model was performed to assess the relationship of the following baseline characteristics to subsequent MACEs: male sex, age, number of diseased coronary arteries, estimated glomerular filtration rate, HbA1c level during the study period, and pharmacotherapy. The interaction of hypertension with the effect of antihypertensive medical therapy was analyzed using a likelihood ratio test. Adjusted hazard ratios (HRs) with 95% CIs were calculated for MACEs. Statistical analysis was conducted at an independent statistical data center (Medical TOUKEI Corporation, Tokyo, Japan) using SPSS 15.0 (SPSS Inc., Chicago, IL, USA) and SAS 9.1.3 (SAS Institute Inc., Cary, NC, USA).

3. Results

In the HIJ-CREATE study, a total of 2049 angiographically documented CAD patients with hypertension were recruited. The participants were followed-up prospectively on a regular basis to June 2007. During a median follow-up of 4.2 years, 8 patients were lost to follow-up, resulting in a follow-up rate of 99.6%. Of the 2049 participants, diabetes was diagnosed in 780 (Fig. 1). Baseline characteristics of the patients are shown in Table 1. Compared with the non-diabetic patients, the diabetic group had a higher prevalence of silent myocardial ischemia and multi-vessel coronary artery disease. Left ventricular ejection fraction was significantly lower in the diabetic group patients than that in the non-diabetic group patients (53.3% vs. 55.0%).

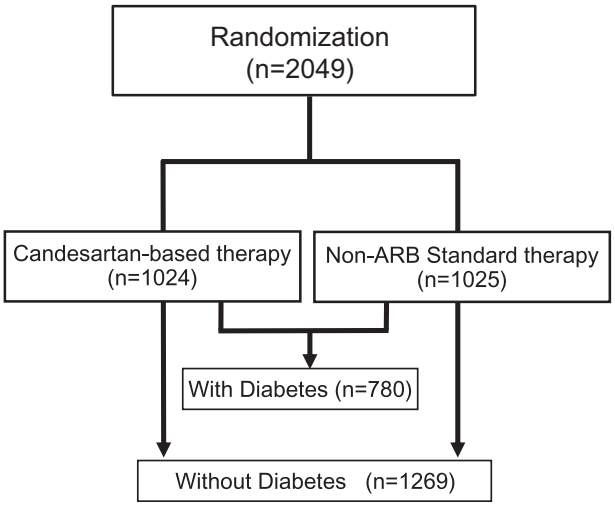

Fig. 1 – Study profile.

Table 2 shows mean systolic and diastolic BPs in both groups during the follow-up period. Mean systolic BP at baseline was 136.6 mmHg in the diabetic group and 134.5 mmHg in the non-diabetic group ($p = 0.01$). During follow-up after randomization, mean systolic BPs did not differ between the two groups throughout the trial ($p = 0.999$). On the other hand, mean diastolic BPs were significantly lower in patients with diabetes than in patients without diabetes throughout the entire period.

During the follow-up period, the primary outcome occurred in 259 (33.2%) diabetic patients and in 293 (23.1%) non-diabetic patients. The diabetic group showed a significantly higher incidence of MACEs than the non-diabetic group ($p < 0.0001$ by the log-rank test, Fig. 2). Table 3 shows serial changes of HbA1c in the diabetic group during the follow-up period. These results indicate that intensive hypoglycemic therapy was not conducted for the patients with diabetes during the study period.

In both diabetic and non-diabetic groups, average systolic BP levels during the study period were significantly higher in patients who experienced MACEs than in patients without MACEs (132.8 mmHg vs. 136.7 mmHg in the diabetic group, $p < 0.001$; 132.3 mmHg vs. 134.2 mmHg in the non-diabetic group, $p = 0.036$, Fig. 3). On the other hand, the mean diastolic BP levels during the study period in both groups showed no significant differences regardless of whether they experienced MACEs (74.6 mmHg vs. 74.0 mmHg in the diabetic group, $p = 0.389$; 76.4 mmHg vs. 75.6 mmHg in the non-diabetic group, $p = 0.172$, Fig. 4).

To explore the optimal BP level in hypertensive patients with CAD and diabetes, they were evaluated retrospectively. The participants were divided into quartiles based on the average systolic BPs during the study period. In hypertensive patients with CAD and diabetes, poor control of systolic BP (mean > 140 mmHg during the study period) was associated with a significantly increased incidence of MACEs compared with the well-controlled and modestly controlled groups (95% confidence interval, 1.35–2.67). On the other hand, intensive systolic BP lowering (mean $\leq$ 120 mmHg during the study period) was not correlated with an increased risk of subsequent MACEs (95% confidence interval, 0.55–1.50). The relationships between achieved systolic BP and the incidence of MACEs did not follow J-shaped curves in hypertensive patients with CAD and diabetes (Fig. 5).

The effects of systolic BP control on subsequent adverse events were evaluated in hypertensive patients with CAD and diabetes. There were 259 MACEs and 59 any-cause death cases. The participants were divided into equal quartiles based on the mean systolic BPs during the study period. There were lower risks of unstable angina, congestive heart failure, and stroke, which resulted in a good outcome, with moderate BP lowering during the study period.

In terms of the effect of the intensity of blood pressure reduction on study outcomes, well-controlled systolic BP (mean $\leq$ 134 mmHg during the study period) was associated with a 42% reduction in the odds compared with the modestly controlled group. In particular, the incidences of unstable angina, congestive heart failure, and stroke were significantly lower in the modestly controlled systolic BP group.

Table 1 – Subjects' baseline characteristics.

	With diabetes (n = 780) Number (%)	Without diabetes (n = 1269) Number (%)	p-value
Male	614 (78.7)	1030 (81.2)	0.18
Age, y (mean ± SD)	64.9±8.9	64.7 ± 9.4	0.65
Acute myocardial infarction	119 (15.3)	203 (16.0)	0.07
Stable angina	194 (24.9)	333 (26.2)	0.49
Silent myocardial ischemia	153 (19.6)	138 (10.9)	<0.0001
Acute coronary syndrome	263 (33.7)	461 (36.3)	0.23
Number of diseased vessels			
1	313 (40.1)	560 (44.1)	
2	236 (30.3)	335 (26.4)	<0.0001
3	148 (19.0)	162 (12.8)	
Percutaneous coronary intervention	664 (85.1)	1032 (81.3)	0.03
Coronary artery bypass grafting	114 (14.6)	122 (9.6)	<0.0001
Hypercholesterolemia	523 (67.1)	693 (54.6)	<0.0001
Smoker	497 (63.7)	790 (62.3)	0.51
Peripheral vascular disease	32 (4.1)	32 (2.5)	0.049
Blood pressure at enrollment, mmHg			
Systolic (mean ± SD)	136.6 ± 16.9	134.5 ± 18.6	0.010
Diastolic (mean ± SD)	74.8 ± 11.2	76.2 ± 12.3	<0.01
NYHA functional class			
I	622 (79.7)	1005 (79.2)	0.77
≥II	158 (20.3)	264 (20.8)	
LVEF (mean ± S.D., %)	53.3 ± 11.2	55.0 ± 10.7	<0.001
Body mass index (mean ± S.D.), kg/m^2	24.8 ± 3.2	24.5 ± 2.9	0.03
Estimated GFR (MDRD, mean ± S.D.), ml/min/1.73 m^2	62.3 ± 19.3	61.9 ± 17.5	0.65
Aspirin	714 (91.5)	1169 (92.1)	0.64
ARB	374 (47.9)	639 (50.4)	0.29
ACE inhibitors	308 (39.5)	423 (33.3)	0.005
Calcium-channel antagonists	410 (52.6)	621 (48.9)	0.11
Statins	385 (49.4)	521 (41.1)	<0.001
Diuretics	90 (11.5)	95 (7.5)	0.002
Beta blockers	405 (51.9)	565 (44.5)	0.001
Specific antidiabetic drugs			
Oral hypoglycemic agents	350 (44.9)		N.A.
Insulin	107 (13.7)		N.A.

ACE: angiotensin-converting enzyme, ARB: angiotensin receptor blocker, GFR: glomerular filtration rate, LVEF: left ventricular ejection fraction, MDRD: Modification of Diet in Renal Disease, NYHA: New York Heart Association.

Table 2 – Blood pressure during follow-up (mean ± S.D., mmHg).

Months after randomization	Non-diabetic	Number	Diabetic	Number	*p*
Systolic blood pressure					
Baseline	134.5 ± 18.6	1268	136.6 ± 16.9	780	0.01
6	131.9 ± 17.3	1219	133.3 ± 17.4	753	N.S.
12	133.3 ± 16.5	1167	132.1 ± 16.2	724	N.S.
24	131.7 ± 16.9	1129	131.6 ± 17.5	710	N.S.
36	131.2 ± 15.6	1082	131.8 ± 17.7	682	N.S.
48	130.4 ± 15.3	765	132.1 ± 16.1	498	N.S.
60	131.5 ± 15.5	391	131.4 ± 16.7	250	N.S.
Diastolic blood pressure					
Baseline	76.2 ± 12.3	1268	74.8 ± 11.2	780	<0.01
6	75.8 ± 11.2	1218	74.4 ± 11.1	753	<0.01
12	77.1 ± 10.6	1167	73.8 ± 10.2	724	<0.001
24	76.4 ± 11.1	1129	74.0 ± 10.6	709	<0.001
36	76.1 ± 10.2	1079	74.0 ± 10.9	682	<0.001
48	75.6 ± 10.5	764	73.1 ± 10.1	493	<0.001
60	75.1 ± 10.5	389	71.7 ± 11.1	250	<0.001

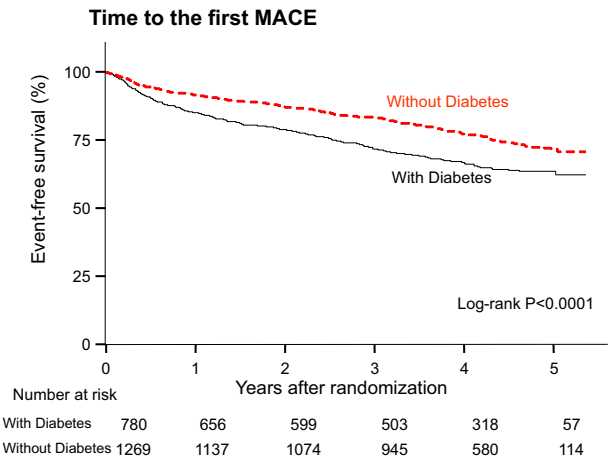

Fig. 2 – Unadjusted clinical outcomes of participants with or without diabetes Kaplan-Meier estimates demonstrate that hypertensive patients with coronary artery disease and diabetes have significantly poorer outcome than those without diabetes.

Table 3 – Glycosylated haemoglobin (HbA1c) in patients with diabetes during follow-up (mean ± S.D.).

Months after randomization	HbA1c (%)	Number
Baseline	6.98 ± 1.38	638
6	6.83 ± 1.32	681
12	6.87 ± 1.38	652
24	6.92 ± 1.23	646
36	7.03 ± 1.34	604
48	7.02 ± 1.29	432
60	7.01 ± 1.19	207

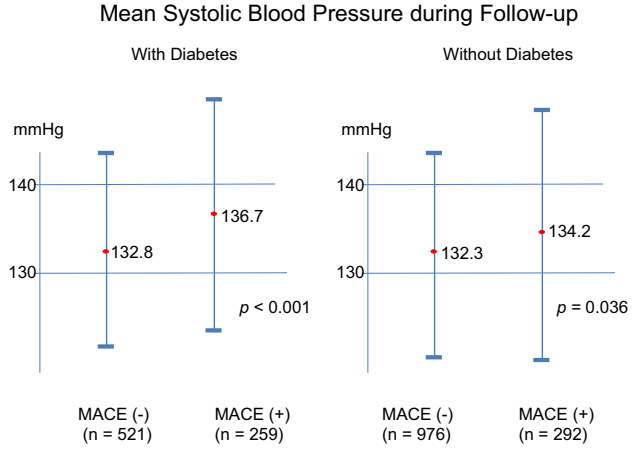

Fig. 3 – Baseline and post-baseline measurements of systolic blood pressure over time During the follow-up period, systolic blood pressures show no significant differences between the two groups.

Table 4 shows the results of a Cox proportional-hazards model. Higher achievement of the systolic BP goal was associated with a lower incidence of MACEs. On the other hand,

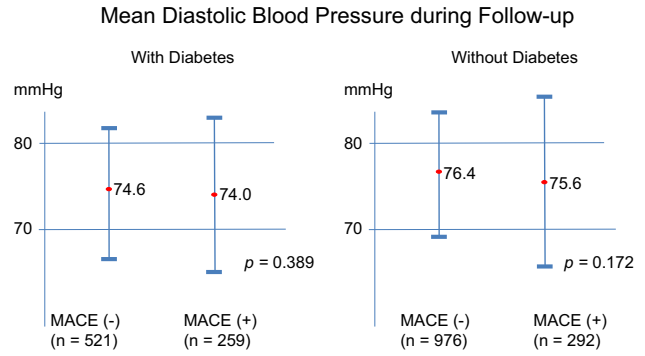

Fig. 4 – Baseline and post-baseline measurements of diastolic blood pressure over time During the follow-up period, diastolic blood pressures are significantly higher in non-diabetic patients than in diabetic patients.

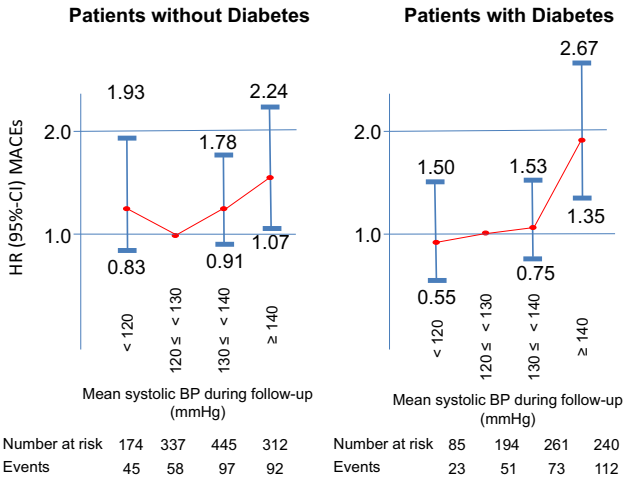

Fig. 5 – Risk of MACEs in hypertensive patients with coronary artery disease and diabetes, according to achieved systolic blood pressure expressed as the average systolic blood pressure during the study period. The relationships between achieved systolic BP and the incidence of MACEs do not follow J-shaped curves in hypertensive patients with coronary artery disease and diabetes.

glycemic control showed no relationship with the incidence of MACEs, except for poor control of diabetes, defined as mean HbA1c ≥ 7.6% during the study period.

4. Discussion

In hypertensive patients with diabetes and CAD, the results of the post hoc analysis of the prospective, randomized trial showed that the relationship between achieved systolic BP and the incidence of MACEs did not follow a J-shaped curve, and suggest that the moderate to intensive BP-lowering regimen of the contemporary era may not impair patients' clinical courses even in such a high-risk population. In addition, modest glycemic control may not increase the incidence of adverse events in such a high-risk population.

The roles of diabetes and hypertension as risk factors for cardiovascular events are well established [17–19]. A meta-

Table 4 – Univariate and multivariate analyses for major adverse cardiovascular events (patients with diabetes).

	Univariate			Multivariate		
	HR	95% CI	p	HR	95% CI	p
Male	0.97	(0.72–1.31)	0.84			
Age, 60 ≤ < 70 y	1.34	(0.97–1.86)	0.08	1.13	(0.81–1.60)	0.47
≥70 y	1.58	(1.15–2.19)	0.005	1.37	(0.98–1.91)	0.07
Number of diseased vessels						
2	2.83	(1.58–5.07)	<0.001	2.29	(1.26–4.18)	0.007
3	3.71	(2.05–6.72)	<0.001	2.75	(1.49–5.08)	0.001
Estimated GFR (MDRD)						
≥60 ml/min/1.73 m^2	0.77	(0.60–0.98)	0.034	0.90	(0.66–1.22)	0.48
Attainment of BP goals						
25% ≤ < 50%	0.36	(0.24–0.55)	<0.001	0.35	(0.22–0.53)	<0.001
≥50%	0.30	(0.21–0.43)	<0.001	0.30	(0.21–0.44)	<0.001
Hb A1c						
6.1% ≤ < 6.8%	0.91	(0.63–1.33)	0.63	0.88	(0.60–1.28)	0.50
6.8% ≤ < 7.6%	1.09	(0.75–1.59)	0.64	1.05	(0.72–1.53)	0.81
≥7.6%	1.40	(0.98–2.00)	0.06	1.24	(0.86–1.80)	0.24
Non-ARB standard therapy	1.08	(0.81–1.44)	0.57			
ACE inhibitors	1.11	(0.86–1.41)	0.43			
Beta blockers	1.36	(1.06–1.73)	0.02	1.19	(0.93–1.53)	0.17
Calcium-channel antagonists	0.91	(0.72–1.16)	0.46			
Diuretics	1.59	(1.13–2.20)	0.007	1.41	(0.98–2.02)	0.07

ACE: angiotensin-converting enzyme, ARB: angiotensin receptor blocker, BP: blood pressure, GFR: glomerular filtration rate, MDRD: Modification of Diet in Renal Disease.

analysis involving more than 1 million individuals without pre-existing cardiovascular disease indicated that deaths from cardiovascular disease increase progressively and linearly with blood pressure [20]. Consequently, "the lower, the better" theory in blood pressure lowering therapy for hypertensive patients has been widely accepted in the management of hypertension for primary prevention [21]. During the last decade, this linear theory has been challenged, especially in patients with CAD [10,22–24]. Especially, in the ACCORD trial [10], which compared a target of lower than 120 mmHg to a target lower than 140 mmHg, the investigators demonstrated no significant reduction in the composite outcome of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke. Furthermore, the investigators of ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial (ONTARGET) demonstrated that there was no benefit in the incidence of cardiovascular outcomes by aggressive BP lowering below 130 mmHg in diabetic patients with hypertension [25]. Although it is hard to explain this apparently paradoxical association in such a high-risk population, some studies have suggested that tight blood pressure control might increase cardiovascular risk by the underperfusion of vital organs [26,27]. Data on the risk of adverse events from randomized trials of intensive versus modest BP lowering regimens for secondary prevention populations are limited. In the present study, all participants underwent appropriate evaluation with coronary angiography and revascularization as needed. Consequently, the moderate to intensive BP lowering regimen might have caused no harm in the present participants. The magnitude of the increased risk associated with intensive BP lowering strategies for this high-risk population may be small in combination with adequate coronary revascularizations and modern pharmacotherapy (including aspirin and statins). Although previous studies [24,28] have demonstrated a J-shaped relationship between BP and cardiovascular events, the risk was relatively flat for systolic BPs between 110 and 140 mmHg, and excess risk was seen at systolic BPs < 110 mmHg. The results of the present study are consistent with these results.

In the secondary analyses of ONTARGET and TRANSCEND [29], the investigators demonstrated that a diastolic BP of 70–80 mmHg was associated with the lowest event rate in patients with controlled systolic BP, whereas there was increased risk among those with both lower and higher diastolic BPs. These data suggest that cardiovascular risk may be defined by diastolic BP levels, despite optimally achieved systolic BP levels. In patients with hypertension, the Framingham Heart Study also found that the same cutoff point of diastolic BP was associated with increased cardiovascular events. Furthermore, the investigators showed that the risk was increased among those with both low diastolic BP and a wide pulse pressure [30]. The results of the present study, which showed that low diastolic BP and wide pulse pressure were associated with increased risk, were consistent with those of the previous studies.

Previous studies demonstrated the U-shaped relationship between HbA1c and subsequent cardiovascular events and mortality [31–33]. Previous studies clearly demonstrated the validity of a "sweet spot" for controlling glycemia in primary prevention [34,35]. In the present study, the results also suggest that moderate glycemic control, defined as mean HbA1c ≤ 7.5%, during the study period correlates with favorable outcomes for secondary prevention. A larger scale, prospective, randomized trial is required to elucidate the rela-

tionship between BP-lowering therapy and the incidence of adverse events in hypertensive patients with CAD and diabetes.

We previously reported that the modern pharmacotherapy with aspirin and renin-angiotensin blockers combined with acute revascularization may improve the prognosis of diabetic patients with acute myocardial infarction [36]. It has been previously demonstrated that the association of antihypertensive medications with incident diabetes was lowest for renin-angiotensin blockers, followed by calcium blockers, beta blockers, and diuretics in rank order [37]. Although renin-angiotensin receptor blocker use led to significant risk reductions in the incidence of diabetes in a high-risk population [14,38], the investigators of Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) clearly demonstrated that such pharmacotherapy did not reduce the rate of cardiovascular events [38], and sometimes it causes concerns about the increased risk of myocardial infarction [39]. In a recent network meta-analysis, although renin-angiotensin receptor blockers were the most effective agents against end-stage kidney disease for diabetic patients, the investigators showed that no BP-lowering therapeutic modality in the contemporary era improved survival in such a population [40]. The results of the present study suggest that the use of renin-angiotensin receptor blockers does not improve the outcomes of hypertensive patients with CAD and diabetes.

In the Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes (JPAD) Trial [41], the investigators demonstrated that aspirin use for type 2 diabetic patients had no clear benefit from the perspective of bleeding risk and cardiovascular event prevention. Furthermore, the investigators of the A Study of Cardiovascular Events in Diabetes (ASCEND) study [42] concluded that aspirin use is not recommended in persons with diabetes and no evident cardiovascular disease, balancing the bleeding risk and the primary prevention of cardiovascular disease. The HIJ-CREATE study was started before such evidence had been established. On the other hand, it is well established that aspirin use is beneficial for secondary prevention in patients with cardiovascular disease [43]. In the present study, because 83% of the HIJ-CREATE participants underwent coronary interventions, more than 90% of them were prescribed aspirin. Thus, the usefulness of aspirin for hypertensive patients with CAD and diabetes was not evaluated.

5. Study limitations

It must be emphasized that this was a post hoc analysis of a prospective, randomized study, the HIJ-CREATE study, which was not designed to investigate the risk of diabetic patients with CAD and hypertension as a primary outcome. Although the results were statistically significant, the wide confidence intervals for the hazard ratios prevent any firm conclusions. The present study may be still underpowered due to low event rates. This study was retrospective and based on a subgroup analysis of a prospective study, and a post hoc power calculation was not performed. The results must, therefore, be interpreted with caution. Because the sample size may have been inadequate for making any conclusions, further larger-scale, prospective, randomized studies are needed to reach any conclusions. Because it was not a predefined study objective to evaluate the effects of antidiabetic treatment, the diagnosis of diabetes was based on history obtained at enrollment. Furthermore, the details of specific antidiabetic medications and their adherence were not fully investigated. The number of study subjects was small. Furthermore, in the absence of an appropriate power calculation, the study power of the present post hoc analysis might have been insufficient.

In conclusion, the present study suggests that the excessive BP lowering regimen of the contemporary era may not impair the clinical courses of hypertensive patients with CAD and diabetes. Nonetheless, along with BP-lowering therapy, further prospective, randomized studies are needed to establish the optimal management strategy for hypertensive patients with diabetes and CAD.

Funding

This investigation was funded by the Japan Research Promotion Society for Cardiovascular Diseases, which played no role in the conduct of the study.

Conflict of interest

Nothing to declare.

Author contributions

K.K. and H.O. had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. K.K. wrote the manuscript and researched data. H.O. described the study concept and reviewed/edited the manuscript. J.Y. contributed to the statistical analyses. N.H. researched data and contributed to discussion.

Disclosures

None.

All authors have approved the final article.

This study was a sub-analysis of the HIJ-CREATE trial, which was registered as an International Standard Randomised Controlled Trial, No. UMIN000000790. http://www.umin.ac.jp/ctr/index.htm.

Participating investigators of HIJ-CREATE

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REFERENCES

[1] Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo Jr JL, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. JAMA 2003;289:2560–72.

[2] Vidal-Petiot E, Ford I, Greenlaw N, Ferrari R, Fox KM, Tardif JC, et al. Cardiovascular event rates and mortality according to achieved systolic and diastolic blood pressure in patients with stable coronary artery disease: an international cohort study. Lancet 2016;388:2142–52.

[3] Bohm M, Schumacher H, Teo KK, Lonn EM, Mahfoud F, Mann JFE, et al. Achieved blood pressure and cardiovascular outcomes in high-risk patients: results from ONTARGET and TRANSCEND trials. Lancet 2017;389:2226–37.

[4] Buse JB, Ginsberg HN, Bakris GL, Clark NG, Costa F, Eckel R, et al. Primary prevention of cardiovascular diseases in people with diabetes mellitus: a scientific statement from the American Heart Association and the American Diabetes Association. Circulation 2007;115:114–26.

[5] Engelgau MM, Geiss LS, Saaddine JB, Boyle JP, Benjamin SM, Gregg EW, et al. The evolving diabetes burden in the United States. Ann Intern Med 2004;140:945–50.

[6] Vazquez-Benitez G, Desai JR, Xu S, Goodrich GK, Schroeder EB, Nichols GA, et al. Preventable major cardiovascular events associated with uncontrolled glucose, blood pressure, and lipids and active smoking in adults with diabetes with and without cardiovascular disease: a contemporary analysis. Diabetes Care 2015;38:905–12.

[7] Gaede P, Lund-Andersen H, Parving HH, Pedersen O. Effect of a multifactorial intervention on mortality in type 2 diabetes. N Engl J Med 2008;358:580–91.

[8] Margolis KL, O'Connor PJ, Morgan TM, Buse JB, Cohen RM, Cushman WC, et al. Outcomes of combined cardiovascular risk factor management strategies in type 2 diabetes: the ACCORD randomized trial. Diabetes Care 2014;37:1721–8.

[9] Buckley LF, Dixon DL, Wohlford GFt, Wijesinghe DS, Baker WL, Van Tassell BW. Intensive versus standard blood pressure control in SPRINT-eligible participants of ACCORD-BP. Diabetes Care 2017;40:1733–8.

[10] Cushman WC, Evans GW, Byington RP, Goff Jr DC, Grimm Jr RH, Cutler JA, et al. Effects of intensive blood-pressure control in type 2 diabetes mellitus. N Engl J Med 2010;362:1575–85.

[11] Emdin CA, Rahimi K, Neal B, Callender T, Perkovic V, Patel A. Blood pressure lowering in type 2 diabetes: a systematic review and meta-analysis. JAMA 2015;313:603–15.

[12] Whelton PK, Carey RM, Aronow WS, Casey Jr DE, Collins KJ, Dennison Himmelfarb C, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation 2018;138:e426–83.

[13] Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. Eur Heart J 2018;39:3021–104.

[14] Kasanuki H, Hagiwara N, Hosoda S, Sumiyoshi T, Honda T, Haze K, et al. Angiotensin II receptor blocker-based vs. non-angiotensin II receptor blocker-based therapy in patients with angiographically documented coronary artery disease and hypertension: the Heart Institute of Japan Candesartan Randomized Trial for Evaluation in Coronary Artery Disease (HIJ-CREATE). Eur Heart J 2009;30:1203–12.

[15] D'Agostino Sr RB, Grundy S, Sullivan LM, Wilson P. Validation of the Framingham coronary heart disease prediction scores: results of a multiple ethnic groups investigation. JAMA 2001;286:180–7.

[16] Granger CB, Goldberg RJ, Dabbous O, Pieper KS, Eagle KA, Cannon CP, et al. Predictors of hospital mortality in the global registry of acute coronary events. Arch Intern Med 2003;163:2345–53.

[17] Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet 2004;364:937–52.

[18] Sarwar N, Gao P, Seshasai SR, Gobin R, Kaptoge S, Di Angelantonio E, et al. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. Lancet 2010;375:2215–22.

[19] Kasanuki H, Honda T, Haze K, Sumiyoshi T, Horie T, Yagi M, et al. A large-scale prospective cohort study on the current status of therapeutic modalities for acute myocardial infarction in Japan: rationale and initial results of the HIJAMI Registry. Am Heart J 2005;150:411–8.

[20] Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet 2002;360:1903–13.

[21] Anderson TW. Re-examination of some of the Framingham blood-pressure data. Lancet 1978;2:1139–41.

[22] Cooper-DeHoff RM, Gong Y, Handberg EM, Bavry AA, Denardo SJ, Bakris GL, et al. Tight blood pressure control and cardiovascular outcomes among hypertensive patients with diabetes and coronary artery disease. JAMA 2010;304:61–8.

[23] Messerli FH, Mancia G, Conti CR, Hewkin AC, Kupfer S, Champion A, et al. Dogma disputed: can aggressively lowering blood pressure in hypertensive patients with coronary artery disease be dangerous? Ann Intern Med 2006;144:884–93.

[24] Bangalore S, Qin J, Sloan S, Murphy SA, Cannon CP. What is the optimal blood pressure in patients after acute coronary syndromes?: Relationship of blood pressure and cardiovascular events in the PRavastatin OR atorVastatin Evaluation and Infection Therapy-Thrombolysis In Myocardial Infarction (PROVE IT-TIMI) 22 trial. Circulation 2010;122:2142–51.

[25] Redon J, Mancia G, Sleight P, Schumacher H, Gao P, Pogue J, et al. Safety and efficacy of low blood pressures among patients with diabetes: subgroup analyses from the ONTARGET (ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial). J Am Coll Cardiol 2012;59:74–83.

[26] Mancia G, Laurent S, Agabiti-Rosei E, Ambrosioni E, Burnier M, Caulfield MJ, et al. Reappraisal of European guidelines on hypertension management: a European Society of Hypertension Task Force document. J Hypertens 2009;27:2121–58.

[27] Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Bohm M, et al. 2013 ESH/ESC Guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). J Hypertens 2013;31:1281–357.

[28] Bangalore S, Messerli FH, Wun CC, Zuckerman AL, DeMicco D, Kostis JB, et al. J-curve revisited: an analysis of blood pressure and cardiovascular events in the Treating to New Targets (TNT) Trial. Eur Heart J 2010;31:2897–908.
[29] Bohm M, Schumacher H, Teo KK, Lonn E, Mahfoud F, Mann JFE, et al. Achieved diastolic blood pressure and pulse pressure at target systolic blood pressure (120–140 mmHg) and cardiovascular outcomes in high-risk patients: results from ONTARGET and TRANSCEND trials. Eur Heart J 2018;39:3105–14.
[30] Franklin SS, Gokhale SS, Chow VH, Larson MG, Levy D, Vasan RS, et al. Does low diastolic blood pressure contribute to the risk of recurrent hypertensive cardiovascular disease events? The Framingham Heart Study. Hypertension (Dallas, Tex: 1979) 2015;65:299–305.
[31] Aguilar D, Bozkurt B, Ramasubbu K, Deswal A. Relationship of hemoglobin A1C and mortality in heart failure patients with diabetes. J Am Coll Cardiol 2009;54:422–8.
[32] Currie CJ, Peters JR, Tynan A, Evans M, Heine RJ, Bracco OL, et al. Survival as a function of HbA(1c) in people with type 2 diabetes: a retrospective cohort study. Lancet 2010;375:481–9.
[33] Colayco DC, Niu F, McCombs JS, Cheetham TC. A1C and cardiovascular outcomes in type 2 diabetes: a nested case-control study. Diabetes Care 2011;34:77–83.
[34] Weinrauch LA, Lewis EF. Aiming for the best control of glycemia in patients with heart failure and type 2 diabetes the “sweet spot”. J Am Coll Cardiol 2009;54:429–31.
[35] Nichols GA, Joshua-Gotlib S, Parasuraman S. Glycemic control and risk of cardiovascular disease hospitalization and all-cause mortality. J Am Coll Cardiol 2013;62:121–7.
[36] Takara A, Ogawa H, Endoh Y, Mori F, Yamaguchi J, Takagi A, et al. Long-term prognosis of diabetic patients with acute myocardial infarction in the era of acute revascularization. Cardiovasc Diabetol 2010;9:1.
[37] Elliott WJ, Meyer PM. Incident diabetes in clinical trials of antihypertensive drugs: a network meta-analysis. Lancet 2007;369:201–7.
[38] McMurray JJ, Holman RR, Haffner SM, Bethel MA, Holzhauer B, Hua TA, et al. Effect of valsartan on the incidence of diabetes and cardiovascular events. N Engl J Med 2010;362:1477–90.
[39] Haller H, Ito S, Izzo Jr JL, Januszewicz A, Katayama S, Menne J, et al. Olmesartan for the delay or prevention of microalbuminuria in type 2 diabetes. N Engl J Med 2011;364:907–17.
[40] Palmer SC, Mavridis D, Navarese E, Craig JC, Tonelli M, Salanti G, et al. Comparative efficacy and safety of blood pressure-lowering agents in adults with diabetes and kidney disease: a network meta-analysis. Lancet 2015;385:2047–56.
[41] Ogawa H, Nakayama M, Morimoto T, Uemura S, Kanauchi M, Doi N, et al. Low-dose aspirin for primary prevention of atherosclerotic events in patients with type 2 diabetes: a randomized controlled trial. JAMA 2008;300:2134-41.
[42] Bowman L, Mafham M, Wallendszus K, Stevens W, Buck G, Barton J, et al. Effects of aspirin for primary prevention in persons with diabetes mellitus. N Engl J Med 2018;379:1529–39.
[43] Smith Jr SC, Benjamin EJ, Bonow RO, Braun LT, Creager MA, Franklin BA, et al. AHA/ACCF Secondary Prevention and Risk Reduction Therapy for Patients with Coronary and other Atherosclerotic Vascular Disease: 2011 update: a guideline from the American Heart Association and American College of Cardiology Foundation. Circulation 2011;124:2458–73.