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Strategies for glycemic control in nonobese and obese type 2 diabetic patients with coronary artery disease

Tetsuro Tsujimoto *, Hiroshi Kajio

Department of Diabetes, Endocrinology, and Metabolism, Center Hospital, National Center for Global Health and Medicine, Tokyo, Japan

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ABSTRACT

Background: This study aimed to assess strategies of insulin-providing (IP) or insulin-sensitizing (IS) therapy for glycemic control in nonobese diabetic patients with coronary artery disease (CAD) with possibly higher cardiovascular risk and lower insulin secretion than obese diabetic patients with CAD.
Methods: We used data from the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial to calculate hazard ratio (HR) with 95% confidence interval (95%CI) for outcome events in patients with type 2 diabetes and CAD using Cox proportional hazard models. The comparison between the IP and IS groups was performed using the randomized design of the BARI 2D trial separately for nonobese (n = 1021) and obese (n = 1319) patients. The primary outcome was a composite endpoint including all-cause death, myocardial infarction, and stroke.
Results: During the follow-up, 231 nonobese and 295 obese patients had one confirmed primary outcome event. In nonobese patients, the risk of primary outcome events was significantly higher in the IP group than the IS group (HR: 1.30, 95%CI: 1.00–1.68, $P = 0.04$), whereas that in obese patients did not differ significantly between the two groups. Moreover, in nonobese patients, the risk of primary outcome events in those without abdominal obesity was significantly higher in the IP group than that in the IS group (HR: 1.51, 95%CI: 1.05–2.19, $P = 0.02$). There were no significant interactions between the strategy for glycemic control and various subgroups of nonobese patients.
Conclusions: In nonobese patients with type 2 diabetes and CAD, the IS treatment strategy may be more beneficial than the IP treatment strategy.

1. Introduction

Type 2 diabetic patients are commonly obese. However, nonobese patients may also develop type 2 diabetes, with recent studies suggesting that approximately half of diabetic patients are nonobese [1–3]. In addition, studies have reported that nonobese diabetic patients are associated with a higher risk of cardiovascular events than obese diabetic patients [4–8]. Other studies investigating diabetic patients without known cardiovascular disease have suggested that the risk of cardiovascular events was lower in nonobese than in obese patients [9,10]. However, nonobese diabetic patients with coronary artery disease (CAD) may be at higher risk of subsequent cardiovascular events [7,8]. Thus, determining the optimal strategy for glycemic control in nonobese diabetic patients, particularly those with CAD, is essential.

Metformin is an oral antidiabetic drug recommended as first-line therapy in type 2 diabetic patients [11]. Metformin is associated with improvement in insulin sensitivity and less weight gain, thus, it is an appropriate treatment option for obese diabetic patients. The pathophysiology of nonobese diabetic patients is potentially associated with low insulin secretion rather than high insulin resistance. Therefore, insulin-providing (IP) therapy to provide more endogenous or exogenous insulin may be more effective for glycemic control than insulin-sensitizing (IS) therapy to reduce insulin resistance. However, the optimal strategy for glycemic control in nonobese diabetic patients remains unknown. The main aim of the present study was to assess the strategies of the IP and IS therapies for glycemic control in nonobese diabetic patients with CAD. Additionally, the strategies of the IP and IS therapies in obese diabetic patients with CAD were also assessed.

Abbreviations: CAD, coronary artery disease; IP, insulin-providing; IS, insulin-sensitizing; BARI 2D, Bypass Angioplasty Revascularization Investigation 2 Diabetes; HbA1c, glycated hemoglobin; BMI, body mass index; NHLBI, National Heart, Lung, and Blood Institute; HR, hazard ratio; GLP-1, glucagon-like peptide-1; SGLT2, sodium-glucose co-transporter 2.

* Corresponding author at: Department of Diabetes, Endocrinology, and Metabolism, Center Hospital, National Center for Global Health and Medicine, 1-21-1 Toyama, Shinjuku-ku, Tokyo 162-8655, Japan.
E-mail address: ttsujimoto@hosp.ncgm.go.jp (T. Tsujimoto).

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2. Methods

2.1. Study design

The present study used data from the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial. The analysis assessed two strategies of IP and IS therapies for glycemic control in nonobese and obese type 2 diabetic patients with CAD. Detailed information regarding the study protocol and design of the BARI 2D trial has been previously reported [12–16]. Briefly, the BARI 2D trial was an international, randomized, clinical trial conducted in 49 clinical sites in the United States, Canada, Austria, Mexico, Brazil, and the Czech Republic. Following the confirmation of patient eligibility and provision of written consent, the eligible patients were enrolled from January 1, 2001, to March 31, 2005. The study included 2368 type 2 diabetic patients with CAD. Type 2 diabetes was diagnosed based on the requirement for treatment with oral hypoglycemic drugs/insulin or elevated fasting plasma glucose levels (≥126 mg/dL [7.0 mmoL/L]). The diagnosis of CAD was based on the following angiographical findings: ≥70% stenosis of a major epicardial coronary artery and classic angina or ≥50% stenosis of a major epicardial coronary artery associated with a positive stress test. Patients who had undergone revascularization within 12 months prior to their enrollment in this study, required immediate coronary revascularization, had congestive heart failure functional class III or IV (New York Heart Association), serum creatinine levels >2.0 mg/dL, hepatic disease, or ≥50% stenosis of the left main coronary artery were excluded. Patients who had glycated hemoglobin (HbA1c) levels >13.0% were also excluded because, in the patients with poorly controlled diabetes, it may be difficult to achieve the target HbA1c levels <7.0% in the BARI 2D trial. All patients were treated with intensive management for hypertension and dyslipidemia. According to current guidelines during the trial, the target levels of systolic and diastolic blood pressure were <130 mm Hg and <80 mm Hg, respectively, and that of low-density lipoprotein cholesterol was <100 mg/dL. In addition, all patients received advice on weight loss, physical exercise, and smoking cessation. Patients were randomly assigned to two treatment strategies using a 2-by-2 factorial design: Patients were assigned at random to undergo either intensive medical therapy alone or prompt revascularization combined with intensive medical therapy, and were simultaneously assigned at random to receive either IP or IS therapy [12–16]. In the IP group, the agents used included sulfonylureas, repaglinide, other approved meglitinides, and insulin. In the IS group, two classes of insulin sensitizers were used: 1) biguanides, primarily reducing the production of hepatic glucose; and 2) thiazolidinediones, primarily reducing insulin resistance in skeletal muscle and adipocytes. The management of diabetes ranged from dietary management and/or exercise to treatment with insulin prior to participating in the BARI 2D trial. Therefore, the goal of this investigation was to transfer each patient to only those interventions specified by the randomized treatment allocation of the BARI 2D protocol [12–16]. The algorithms were stratified for each glycemic strategy according to prior use of insulin [17]. The general target for the HbA1c levels was <7.0%, consistent with those indicated in the current treatment guidelines [18]. For elderly patients without diabetic neuropathy, retinopathy, or nephropathy, HbA1c levels were maintained between 7.0% and 7.4%. Sustained HbA1c levels ≥8.0% mandated the use of drugs from the opposite arm of the study; however, these crossover drugs were provided at the lowest doses required to achieve HbA1c levels <8.0%. A comprehensive program of diabetes education was provided to all patients. Patients were regularly monitored during the study for home blood glucose and HbA1c levels. In addition, the functions of the liver and kidneys were measured to assess drug toxicity. Patients lacking information on body mass index (BMI) (n = 28) were excluded, resulting in a final sample of 2340 patients.

This study was approved by the institutional review board of the National Center for Global Health and Medicine. Moreover, the National Heart, Lung, and Blood Institute (NHLBI) approved the use of the BARI 2D trial data.

2.2. Evaluation of outcomes

The detailed evaluation of outcomes in the BARI 2D trial was previously reported [12,19]. The primary outcome of the present study was a composite endpoint including all-cause death, nonfatal myocardial infarction, and nonfatal stroke. The secondary outcomes were major adverse cardiovascular events (cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke), major cardiac events (cardiac death and nonfatal myocardial infarction), fatal or nonfatal myocardial infarction, fatal or nonfatal stroke, and all-cause death. Myocardial infarction included silent, spontaneous, and procedure-related events [12,19]. The classification and adjudication of the endpoint data were performed by an independent Mortality and Morbidity Classification Committee. Until November 30, 2008, patients were evaluated on a monthly basis during the first 6 months and quarterly thereafter. Because the treatment continued until the 6-year visit or until the last visit, patients were followed up for a maximum of 6 years [12].

2.3. Statistical analysis

Demographic data are shown as means ± standard deviations or proportions. Continuous variables were compared using the *t*-test and categorical variables were compared using the chi-squared test. Kaplan–Meier survival curves for primary outcome were constructed and the event rates of primary and secondary outcomes were calculated in the IP and IS groups. Cox proportional hazard models were used to calculate hazard ratios (HRs) for primary and secondary outcomes with 95% CI. Comparison between the IP and IS groups was performed using the randomized design of the BARI 2D trial separately for nonobese and obese patients. The BMI was calculated dividing the weight (in kilograms) by the squared height (in meters), and obesity was defined as a BMI ≥30 kg/m^2. In nonobese patients, similar analyses were performed in those with normal weight (BMI 18.5–24.9 kg/m^2) or overweight (BMI 25.0–29.9 kg/m^2), and in those with or without abdominal obesity. Abdominal obesity was defined as a waist circumference of ≥102 cm in males and ≥88 cm in females [20]. Because the number of obese patients without abdominal obesity was very small (n = 36), obese patients could not be divided into two groups with and without abdominal obesity.

The primary outcome was further compared between clinically relevant subgroups, such as age (<70 or ≥70 years), sex (male or female), race (non-white or white), duration of diabetes (<10 or ≥10 years), HbA1c levels (<7.0 or ≥7.0%), estimated glomerular filtration rate (<60 or ≥60 mL/min/1.73 m^2), use of insulin (nonuser or user), and strategy for cardiac treatment (intensive medical therapy or prompt revascularization). Interactions between the strategy for glycemic control and these subgroups were investigated.

In the present study, the association between obesity and risk of cardiovascular events was analyzed to confirm the cardiovascular risk in nonobese type 2 diabetic patients with CAD. Cox proportional hazard models were used to calculate the unadjusted and multivariable-adjusted HRs for primary outcome events. These analyses were performed using the following two classifications: 1) no obesity and obesity or 2) normal weight, overweight, and obesity. For the adjustment of model 1, age, sex, race, educational attainment, smoking status, HbA1c levels, duration of diabetes, and waist circumference were included. For the adjustment of model 2, hypertension, hypercholesterolemia, previous history of myocardial infarction and stroke/transient ischemic attack, physical activity, low-density lipoprotein cholesterol levels, estimated glomerular filtration rate, and systolic blood pressure were included to the variables of model 1. For the adjustment of model 3, the use of angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, calcium channel blockers, beta blockers, diuretics, statins, aspirin, insulin, biguanides, and sulfonylureas, along with assignment of glycemic treatment (IP or IS) and cardiac treatment (prompt revascularization or medical therapy) were included to the variables of model 2.

The null hypothesis was rejected for values of $P < 0.05$. All statistical analyses were performed using the Stata software (version 14.1; Stata Corp., College Station, Texas, USA).

3. Results

3.1. Baseline characteristics

The baseline characteristics of nonobese (n = 1021) and obese (n = 1319) patients are shown in Table 1. In both nonobese and obese patients, baseline characteristics did not differ significantly between the IP and IS groups.

3.2. Primary and secondary outcomes

The overall mean follow-up period (±standard deviation) was 4.0 (±1.8) years: 3.9 (±1.8) years and 4.0 (±1.7) years for nonobese and obese patients, respectively. During the follow-up, 231 nonobese and 295 obese patients had at least one confirmed primary outcome event. The Kaplan–Meier survival curves for primary outcome events in nonobese and obese patients are shown in Fig. 1. The risk of primary outcome events in nonobese patients was significantly higher in the IP group than in the IS group (HR: 1.30, 95% CI: 1.00–1.68, $P = 0.04$, Fig. 1A), whereas that in obese patients did not differ significantly between the IP and IS groups (HR: 1.04, 95% CI: 0.83–1.31, $P = 0.72$, Fig. 1B). Similarly, a higher risk of primary outcome events in the IP group than in the IS group was observed in nonobese patients with BMI 18.5–24.9 kg/m^2 (HR: 1.46, 95% CI: 0.80–2.71, $P = 0.21$) and in those with BMI 25.0–29.9 kg/m^2 (HR: 1.26, 95% CI: 0.94–1.70, $P = 0.12$). In addition, in nonobese patients, the risk of primary outcome events in those without abdominal obesity was significantly higher in the IP group than in the IS group (HR: 1.51, 95% CI: 1.05–2.19, $P = 0.02$, Supplemental Fig. 1). The cumulative event rates and HRs for primary and secondary outcome events in nonobese patients without abdominal obesity are shown in Table 2. The risks of major adverse cardiovascular events and major cardiac events were significantly higher in the IP group than in the IS group (HR for major adverse cardiovascular events: 1.70, 95% CI: 1.12–2.57, $P = 0.01$; HR for major cardiac events: 1.70, 95% CI: 1.09–2.66, $P = 0.01$, respectively). Although there was no significant difference, the risks of fatal or nonfatal myocardial infarction, fatal or nonfatal stroke, and all-cause mortality were higher in the IP group than in the IS group. In nonobese patients with abdominal obesity, there were no significant differences in the primary and secondary outcome events between the IP and IS groups (Supplemental Table 1).

Table 1
Baseline characteristics of nonobese and obese patients.[a]

	Obesity (−)			Obesity (+)		
	n = 1021			n = 1319		
	IS	IP	*P* value	IS	IP	*P* value
	n = 510	n = 511		n = 657	n = 662	
Age			0.97			0.69
<50 y	7.7	6.9		9.4	9.2	
50–59 y	28.2	27.4		35.2	32.3	
60–69 y	39.0	40.5		35.6	40.2	
70–79 y	22.6	22.9		18.9	17.2	
≥80 y	2.5	2.3		0.9	1.1	
Female sex (%)	24.9	27.2	0.40	33.6	30.5	0.22
Race and ethnicity (White, %)	32.9	34.4	0.61	27.1	26.3	0.74
Smoking status (%)			0.54			0.06
Never	31.4	30.7		37.4	31.5	
Former	53.7	56.5		51.3	57.2	
Current	14.9	12.8		11.3	11.3	
Education level (%)			0.62			0.83
Less than high school	43.3	46.1		31.2	30.5	
High school	18.9	19.0		23.2	24.6	
More than high school	37.8	35.0		45.6	44.9	
Physical activity (%)			0.99			0.40
Sedentary	21.2	21.1		23.3	22.2	
Mild	40.0	40.0		43.5	41.0	
Moderate/strenuous	38.8	38.9		33.2	36.8	
Body mass index (kg/m^2)[b]	26.8 (2.2)	26.7 (2.3)	0.38	35.5 (4.9)	35.5 (4.5)	0.59
Duration of diabetes (years)	10.5 (8.7)	11.0 (8.6)	0.39	9.9 (8.2)	10.6 (9.1)	0.14
Hypertension (%)	74.8	79.8	0.06	86.3	86.7	0.82
Hypercholesterolemia (%)	78.2	80.7	0.31	82.9	84.3	0.51
History of myocardial infarction (%)	34.1	36.1	0.51	31.2	28.2	0.23
History of stroke/TIA (%)	10.3	10.6	0.87	9.8	8.9	0.59
History of chronic heart failure	5.1	4.7	0.77	7.9	8.1	0.88
Medications						
ACE-I (%)	64.6	65.8	0.71	63.9	64.6	0.81
ARB (%)	8.6	8.5	0.91	19.8	18.6	0.58
Calcium channel blocker (%)	26.1	27.6	0.60	32.5	37.2	0.07
Beta blockers (%)	73.7	71.7	0.47	74.7	71.2	0.15
Diuretics (%)	28.1	29.5	0.61	46.0	46.4	0.86
Statin (%)	72.7	72.6	0.96	77.4	75.8	0.48
Aspirin (%)	88.8	88.4	0.83	87.9	87.3	0.72
Biguanides (%)	54.6	52.1	0.41	54.4	54.8	0.90
Sulfonylureas (%)	58.6	58.1	0.89	50.8	48.3	0.36
Insulin (%)	21.8	23.3	0.56	32.3	32.0	0.90
Glycated hemoglobin (%)	7.7 (1.6)	7.7 (1.7)	0.61	7.6 (1.6)	7.6 (1.6)	0.84
Low-density lipoprotein (mg/dL)	96.3 (33.7)	97.3 (35.0)	0.62	94.7 (33.9)	96.6 (31.4)	0.30
High-density lipoprotein (mg/dL)	38.4 (10.1)	39.2 (10.7)	0.20	37.6 (9.9)	37.9 (10.4)	0.63
Triglyceride (mg/dL)	171.0 (135.2)	170.2 (112.9)	0.91	186.4 (129.8)	191.6 (157.2)	0.52
Estimated GFR (ml/min/1.73 m^2)	72.2 (21.5)	73.0 (21.2)	0.55	73.3 (36.6)	70.5 (21.6)	0.09
Urine albumin/creatinine (mg/gCre)	114.2 (491.9)	125.8 (444.9)	0.70	196.6 (729.2)	151.9 (462.6)	0.19
Circulating insulin (IU/mL)[c]	9.9 (11.0)	8.9 (7.9)	0.16	14.5 (13.1)	13.5 (10.1)	0.20
Systolic blood pressure (mm Hg)	130.6 (19.4)	130.7 (20.6)	0.96	132.3 (20.1)	132.8 (19.9)	0.64
Diastolic blood pressure (mm Hg)	74.2 (10.9)	74.0 (10.4)	0.86	74.8 (11.7)	74.9 (11.6)	0.90
Cardiac treatment assignment						
Early revascularization (%)	51.0	53.4	0.43	47.8	47.3	0.85

IS, insulin-sensitizing therapy; IP, insulin-providing therapy; 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, percentage, or mean (standard deviation).

[b] Body mass index was calculated as weight in kilograms divided by the square of height in meters.

[c] Circulating insulin levels were evaluated in patients not treated with insulin.

In nonobese patients, the associations between the risk of primary outcome events and the strategy for glycemic control in the various subgroups are shown in Fig. 2. The analyses found no significant interactions between the strategy for glycemic control and the patients' age, sex, race, duration of diabetes, HbA1c levels, estimated glomerular filtration rate, use of insulin, or assignment of cardiac treatment. Although statistically significant associations were not observed in all subgroups, these results indicated that the risk of primary outcome events within these subgroups was higher in the IP group than in the IS group. In obese patients, no significant associations were observed between the risk of primary outcome events and the strategy for glycemic control in the various subgroups (Supplemental Fig. 2).

3.3. Risk of primary outcome events in nonobese and obese type 2 diabetic patients with CAD

The baseline characteristics of patients with normal weight, overweight, and obesity are shown in Supplemental Table 2, and associations between primary outcome events and the obesity status are presented in Supplemental Table 3. The risk of primary outcome events was slightly lower in obese patients than in nonobese patients; there was no significant difference between the two groups. However, the risk of primary outcome events was significantly lower in obese patients than in patients with normal weight (adjusted HR in model 1: 0.64, 95% CI: 0.43–0.94, $P = 0.02$; adjusted HR in model 2: 0.65, 95% CI: 0.43–0.99, $P = 0.04$; adjusted HR in model 3: 0.63, 95% CI: 0.41–0.96, $P = 0.03$).

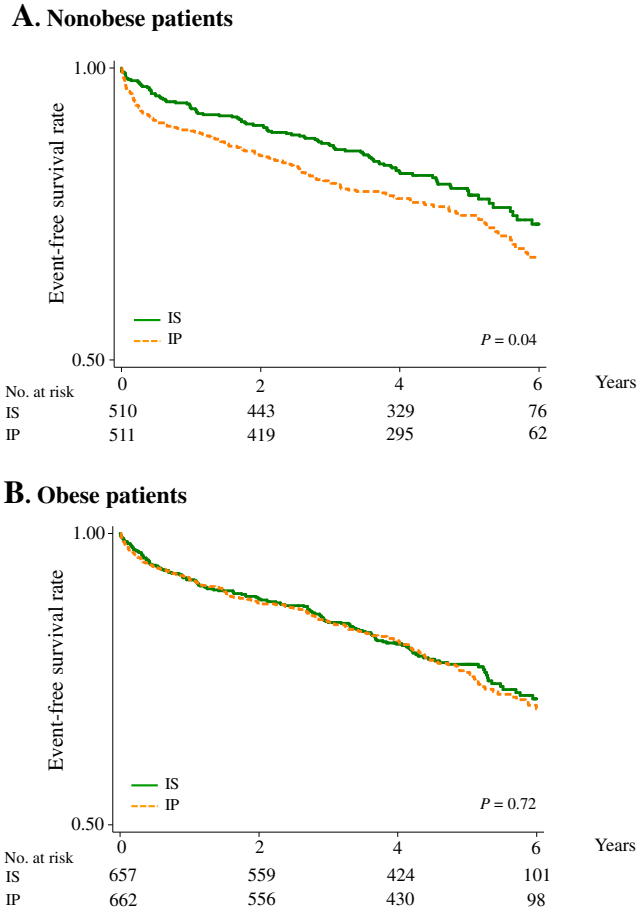

Fig. 1. Kaplan–Meier survival curves for primary outcome events in nonobese and obese patients. Rates of freedom from primary outcome events: IP vs. IS in nonobese (A) and obese (B) type 2 diabetic patients with coronary artery disease. IP, insulin-providing; IS, insulin-sensitizing.

4. Discussion

The present study revealed that, in nonobese type 2 diabetic patients with CAD, the cardiovascular risk was significantly higher in the IP group than in the IS group. The results were similar even in nonobese patients without abdominal obesity. No significant interactions were found between the strategy for glycemic control and nonobese patients' age, sex, race, diabetes duration, HbA1c levels, estimated glomerular filtration rate, insulin use, and strategy for cardiac treatment. Consistent with previous studies [7,8], nonobese type 2 diabetic patients with CAD (particularly those with normal weight) were at higher risk of cardiovascular events and death compared with obese patients. Meanwhile, the cardiovascular risk did not differ significantly between the IP and IS therapies in obese patients.

Current treatment guidelines recommend the administration of metformin as first-line pharmacological therapy following the diagnosis of type 2 diabetes, unless contraindicated [11]. Metformin is an effective and safe therapeutic option [21] and may reduce the long-term risk of cardiovascular events and death [22]. The UK Prospective Diabetes Study (UKPDS) demonstrated that intensive glycemic control using metformin reduces the risk of diabetes-related complications in overweight (>120% of ideal body weight) diabetic patients, and is associated with less weight gain and lower rates of hypoglycemic events than are insulin and sulfonylureas [21]. However, there is limited evidence on the effects of antihyperglycemic therapy in nonobese type 2 diabetic patients. Although obesity is a well-established risk factor for diabetes and common in type 2 diabetic patients, approximately half of diabetic patients in the United States are nonobese [1,2]. In China, the mean BMI levels of diabetic patients are approximately 25 kg/m^2, indicating that approximately half of diabetic patients have normal weight [3]. Thus, the optimal strategy for glycemic control in nonobese diabetic patients is essential worldwide. Studies have reported that, following the development of diabetes, nonobese patients may be at higher risk of cardiovascular events than obese patients [4–6]. Although other studies have suggested otherwise in diabetic patients without known cardiovascular disease [9,10], recent evidence indicated that in type 2 diabetic patients with CAD, those who are nonobese and those with normal weight are at higher risk of cardiovascular events and death compared with obese patients [7,8]. The results of the present study are consistent with these previous findings. However, this does not imply that weight gain in nonobese type 2 diabetic patients with CAD leads to improved outcomes. Nonobese type 2 diabetic patients with CAD, for which obesity is a common risk factor, may have other undetermined and severe risk factors for cardiovascular events. The present study suggested that IS therapy may lower the risk of cardiovascular events and death in nonobese type 2 diabetic patients with CAD compared with IP therapy. Although the pathophysiological mechanisms involved in this process remain unknown, the lower weight gain and fewer hypoglycemic events associated with the IS treatment strategy may result in improved outcome [12,21]. In addition, the antithrombotic and anti-inflammatory effects of the IS treatment strategy may lead to a decreased risk of cardiovascular events and death [23]. Further studies are warranted to clarify the pathological condition of nonobese type 2 diabetic patients with CAD and establish the optimal strategy for glycemic control in such patients.

The present study has several limitations. First, this was a secondary analysis of the data obtained from the BARI 2D trial. Therefore, conducting a randomized, controlled trial is necessary to confirm these results. Second, the number of patients and events of this study was relatively small, limiting the analysis. Third, nonobese diabetic patients in the present study had prior history of CAD. Thus, it remains unknown whether these findings are observed in other nonobese diabetic patients. In nonobese diabetic patients, those with CAD may be at the highest risk of cardiovascular events. Hence, the findings of the present study may contribute to the improvement of outcomes and management in this subset of patients. Fourth, the present study was unable to clarify which drugs used in IS therapy exerted benefit in nonobese diabetic patients. In patients receiving IS therapy, the use of metformin and thiazolidinedione without metformin at 3 years from randomization has been shown to be 75.6% and 13.5%, respectively. Therefore, metformin may also be administered as first-line therapy for nonobese patients [23]. In addition, the BARI 2D trial did not involve new diabetic medications such as glucagon-like peptide-1 (GLP-1) receptor agonists and sodium-glucose co-transporter 2 (SGLT2) inhibitors. GLP-1 receptor agonists stimulate the release of glucose-dependent insulin from the pancreatic islets [24] and are effective in improving glycemic control [25]. In addition, the risk of cardiovascular events is significantly lower in type 2 diabetic patients treated with GLP-1 receptor agonists than in those not treated with these agents [26,27]. SGLT2 inhibitors reduce the levels of blood glucose by increasing urinary glucose excretion [28] and have been shown to improve glycemic control [29] and cardiovascular outcome [30]. Importantly, GLP-1 receptor agonists and SGLT2 inhibitors are both associated with a low risk of hypoglycemia and do not usually cause hypoglycemia in the absence of therapies that cause hypoglycemia [26,30]. In addition, GLP-1 receptor agonists and SGLT2 inhibitors are linked to weight loss [26,30,31]. Recent studies that demonstrated the benefits of the GLP-1 receptor agonists and SGLT2 inhibitors for the prevention of cardiovascular events included many obese type 2 diabetic patients [26,30]. Although the IP and IS therapies in obese patients did not show a significant difference in cardiovascular outcomes in the present study, the GLP-1 receptor agonists and SGLT2 inhibitors are expected to lower the risk of cardiovascular events in obese type 2 diabetic patients

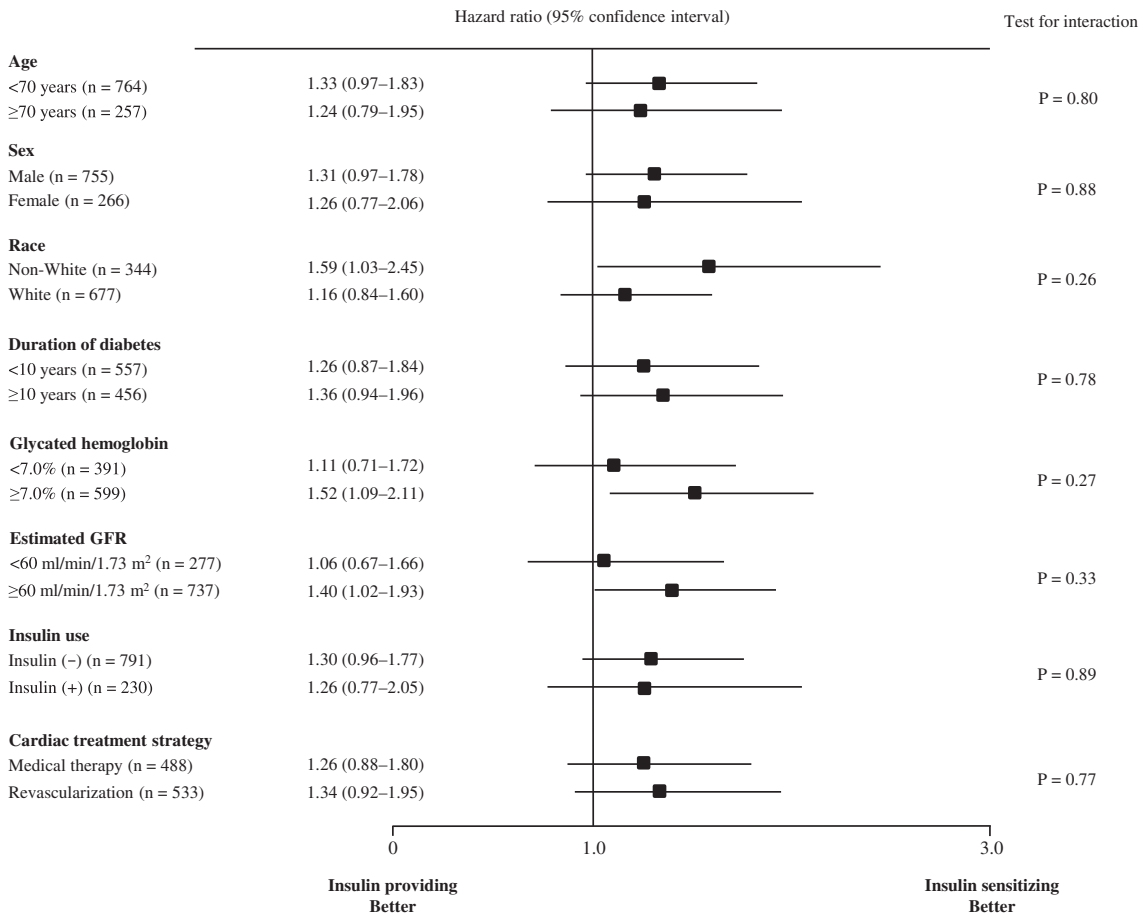

Fig. 2. Association between the strategy for glycemic control and the risk of primary outcome events in subgroups of nonobese patients.

Table 2
Primary and secondary outcomes in nonobese patients without abdominal obesity.[a]

Event	IS	IP	*P* value
	n = 275	n = 281	
Primary outcome events			
No. of patients	48	70	
Event rate (per 1000 person-year)	42.1	64.3	
Hazard ratio (95% CI)	1.00 (ref)	1.51 (1.05–2.19)	0.02
Major adverse cardiovascular events			
No. of patients	36	59	
Event rate (per 1000 person-year)	32.0	55.0	
Hazard ratio (95% CI)	1.00 (ref)	1.70 (1.12–2.57)	0.01
Major cardiac events			
No. of patients	31	51	
Event rate (per 1000 person-year)	27.2	47.4	
Hazard ratio (95% CI)	1.00 (ref)	1.70 (1.09–2.66)	0.01
Fatal or nonfatal myocardial infarction			
No. of patients	28	42	
Event rate (per 1000 person-year)	24.6	39.0	
Hazard ratio (95% CI)	1.00 (ref)	1.55 (0.96–2.50)	0.07
Fatal or nonfatal stroke			
No. of patients	4	8	
Event rate (per 1000 person-year)	3.4	6.7	
Hazard ratio (95% CI)	1.00 (ref)	2.01 (0.60–6.67)	0.25
All-cause death			
No. of patients	28	34	
Event rate (per 1000 person-year)	21.3	25.7	
Hazard ratio (95% CI)	1.00 (ref)	1.21 (0.73–2.00)	0.45

CI, confidence interval; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft surgery.
[a] Data are presented as number or hazard ratio (95% CI).

with CAD. However, the effect of further reduction of body weight in nonobese diabetic patients remains unknown. Moreover, recent trials have been carried out in very high-risk patients with type 2 diabetes, with a high proportion of obese patients, to increase the hazard rate for major cardiovascular events and complete the studies in a relatively short period of time. Because there is limited evidence on cardiovascular safety or benefits in nonobese diabetic patients, further studies are warranted to investigate the risk of cardiovascular events and determine the optimal treatment strategies in nonobese diabetic patients, particularly those with CAD.

In conclusion, the present study revealed that in type 2 diabetic patients with CAD, the risk of cardiovascular events and death in nonobese patients, particularly in patients with normal weight was equal or higher to those observed in obese patients. In nonobese patients, the IS treatment strategy was more beneficial than the IP treatment strategy. Further randomized, controlled trials are required to determine the optimal strategy for glycemic control in nonobese diabetic patients.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2019.02.008.

Acknowledgments

Author contributions

T.T. conceptualized and designed the study and acquired and statistically analyzed the data. T.T. and H.K. analyzed and interpreted data and drafted the manuscript. Dr. Tsujimoto had full access to all data in the study and takes responsibility for the integrity and accuracy of data analysis.

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Competing interests

The authors have no conflict of interest to report.

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