≥ *Review Article* ≤

Cardiovascular Disease in Japanese Patients with Type 2 Diabetes Mellitus

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Individuals with diabetes have a two- to four-fold increased risk of coronary artery disease (CAD) and higher mortality rates than those without diabetes. Because not only microvascular but also macrovascular disease in patients with diabetes are known to predispose patients to a lower quality of life as well as lead to higher mortality rates, identifying and managing risk factors of CAD is of clinical relevance in diabetes care. A number of antihyperglycemic drugs are currently approved for the treatment of hyperglycemia in patients with type 2 diabetes mellitus (T2DM), with several new drugs having been developed during the last decade. Diabetes-related complications have been substantially reduced worldwide. However, in view of the current situation in which both the prevalence of obesity and glucose abnormality have increased worldwide, including Japan, diet and exercise remain the crucial means of treatment for patients with diabetes. Furthermore, predicting the development of CAD is essential. This review summarizes data from recent studies on cardiovascular disease in patients with T2DM, focusing on clinical trials and big data, including studies involving Japanese individuals.

Keywords: diabetes, cardiovascular disease, coronary artery disease, stroke, antihyperglycemic drugs

Introduction

Coronary artery disease (CAD) is a major cause of morbidity and mortality in patients with type 2 diabetes mellitus (T2DM).[1] Although comprehensive and intensive

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management of multiple cardiovascular risk factors in patients with T2DM is recommended to reduce the risk of cardiovascular events, a considerable number of patients develop CAD even under intensive management.[2] A number of antihyperglycemic drugs are currently approved for the treatment of hyperglycemia in patients with T2DM, and diabetes-related complications have been substantially reduced worldwide.[3] However, in view of the current situation in which both the prevalence of obesity and glucose abnormality have increased worldwide, including Japan, diet and exercise remain the crucial means of treatment for patients with diabetes. This review summarizes data from recent epidemiological and clinical studies on cardiovascular disease (CVD) in patients with T2DM, focusing on clinical trials and big data, including studies on Japanese patients.

Characteristics of CVD in Patients with T2DM

CAD during the early stages of glucose abnormalities and in individuals with diabetes was observed to be associated with worsening of the mortality rate following acute myocardial infarction.[2,4,5] The incidence of CAD among people with diabetes in Japan is lower than that in the US and other western countries as well as among the general population[6,7] (**Table 1**). Hotta et al. showed that the frequency of CVD as a cause of death was 24.0% and 31.6% in men and women, respectively, between 1991 and 2000.[8] A more recent study conducted between 2001 and 2010 showed that the frequency of CVD as a cause of death decreased; the frequencies reported were 10.7% and 12.6% in men and women, respectively.[9]

Patients with diabetes without a previous myocardial infarction have a risk of myocardial infarction as high as that in patients without diabetes with a previous myocardial infarction.[10] Thus, the presence of diabetes and underlying systemic insulin resistance and metabolic abnormalities due to diabetes may accelerate the development of CAD. Impaired fasting glucose and glucose tolerance are also associated with modest increases in the risk of CVD.[11–16] Booth et al. revealed that diabetes confers a risk of CAD equivalent to aging 15 years in western

Table 1 Summary of the association between the incidence of or death from cardiovascular disease and glucose abnormalities

Study	Country	Glucose tolerance status	Age (years), mean or range	BMI (kg/m²), mean	% Men	No. participants total	Covariate	Endpoint	Hazard ratios
Funagata Study Tominaga et al. (1999)	Japan	IGT/DM	IGT: 63 DM: 66	ND	44	2,534	Age	CVD death	IGT, 2.22 (1.08–4.58); DM, 2.27 (1.07–4.84)
JPHC study Saito et al. (2009)	Japan	IFG/DM	IFG: 52 DM: 53	23.9	36	31,192	Age, sex, BMI, hypertension, fasting status, community, dyslipidemia, smoking, regular alcohol drinking, sports and exercise	CHD incidence	IFG, 1.61 (1.01–2.57); DM, 4.05 (2.16–7.56)
JPHC study Cui et al. (2009)	Japan	Borderline/DM	Borderline: 55 DM: 56	23.9	37	22,528	Age, BMI, SBP, fasting status, community, LDLC, HDLC, TG, smoking, regular alcohol drinking, and use antihypertensive medication	All types of stroke incidence	Borderline, 1.01 (0.76–1.34) in men and 1.26 (0.88–1.81) in women; DM, 1.64 (1.21–2.23) and 2.19 (1.53–3.12)
Hisayama Study Doi et al. (2010)	Japan	IGT/DM	58	23.0	43	2,421	Age, BMI, SBP, ECG abnormality, LDLC, HDLC, smoking, alcohol intake, and regular exercise	Ischemic stroke incidence	IGT, 0.91 (0.44–1.89) in men and 0.88 (0.46–1.70) in women; DM, 2.54 (1.40–4.63) and 2.02 (1.07–3.81)
								CHD incidence	IGT, 1.11 (0.62–2.00) in men and 0.82 (0.31–2.15) in women; DM, 1.26 (0.67–2.35) in women and 3.46 (1.59–7.54) in men
Suita Study Kokubo et al. (2010)	Japan	IFG/DM	IFG: 58 DM: 60	22.5	47	5,321	Age, BMI, hypertension, dyslipidemia, smoking, and drinking status	All types of stroke incidence	IFG, 0.97 (0.64–1.46) in men and 1.36 (0.84–2.19) in women; DM, 1.78 (1.00–3.12) in women and 2.66 (1.22–5.80) in men
								CHD incidence	IFG, 1.31 (0.87–1.96) in men and 1.83 (1.01–3.32) in women; DM, 1.69 (0.86–3.31) in women and 4.32 (1.81–10.3) in men
Large claim data Fujihara et al. (2017)	Japan	Prediabetes/ DM	31–60	23.6	100	111,621	BMI, SBP, LDLC, HDLC, and current smoking	CAD incidence	Age 31–40 years (males); prediabetes, 2.89 (1.02–8.19); DM 17.3 (6.36–47.0) Age 41–50 years (males); prediabetes, 0.88 (0.61–1.28); DM 2.74 (1.85–4.05); Age 51–60 years (males); prediabetes 1.62 (1.16–2.32); DM, 2.47 (1.69–3.58)

BMI: body mass index; CAD: coronary artery disease; CHD: coronary heart disease; CVD: cardiovascular disease; DM: diabetes mellitus; ECG: electrocardiogram; HDLC: high-density lipoprotein cholesterol; IFG: impaired fasting glucose; IGT: impaired glucose tolerance; JPHC: Japan Public Health Center-based Prospective Study; LDLC: low-density lipoprotein cholesterol; ND: not described; SBP: systolic blood pressure; TG: triglycerides

populations.[17] Similarly, diabetes confers a risk of CAD equivalent to aging 20 years in Japanese men.[12] These findings suggest that the metabolic abnormalities reflecting underlying systemic insulin resistance, which include unfavorable lipid parameter levels and other metabolic abnormalities, contribute to the development of atherosclerosis.

A meta-analysis of 102 prospective studies that included approximately 700,000 patients showed that independent of other conventional risk factors, diabetes was associated with a two-fold increase in the risk of CVD [CAD, 2.00 (95% confidence interval, 1.83–2.19); ischemic stroke, 2.27 (1.95–2.65); and hemorrhagic stroke, 1.56 (1.19–2.15)].[18] Fox et al. showed that a 50% reduction in the rate of CVD events was observed among adults with diabetes in the late 1900s compared with that in the middle 1900s.[19] However, the absolute risk of CVD remained two-fold higher among persons with diabetes than that among those without diabetes, as shown in previous western and Japanese studies.[19–21] In the Hisayama study, diabetes was shown to be an independent risk factor of ischemic stroke in both sexes and

Table 2 Incidence rate of cardiovascular disease per 1,000 person-years based on overall and glucose tolerance status

Study	Country	Glucose tolerance status	% Men	No. participants total	Endpoint	Sex	Categories	Rate per 1,000 person-years
General population								
Suita Study Okamura et al. (2009)	Japan	NA	46	4,694	MI incidence			0.14
JALS-ECC study Tanabe et al. (2009)	Japan	NA	40	22,430	AMI incidence			0.65
					Stroke incidence			3.29
According to glucose tolerance status								
JPHC study Saito et al. (2009)	Japan	IFG/DM	36	31,192	CHD incidence	Men	NGT	1.0[†]
							Borderline	1.37[†]
							DM	2.06[†]
						Women	NGT	0.30[†]
							Borderline	0.29[†]
							DM	1.02[†]
Hisayama Study Doi et al. (2010)	Japan	NGT/IGT/DM	43	2,421	Ischemic stroke incidence	Men	FPG <5.6	5.4[†]
							5.6–6.0	4.0[†]
							6.1–6.9	4.7[†]
							≥7.0	11.7[†]
						Women	FPG <5.6	3.4[†]
							5.6–6.0	3.9[†]
							6.1–6.9	7.1[†]
							≥7.0	9.6[†]
					CHD incidence	Men	FPG <5.6	7.0[†]
							5.6–6.0	4.7[†]
							6.1–6.9	7.3[†]
							≥7.0	9.9[†]
						Women	FPG <5.6	1.4[†]
							5.6–6.0	1.8[†]
							6.1–6.9	2.5[†]
							≥7.0	7.0[†]
Large claim data Fujihara et al. (2017)	Japan	Prediabetes/DM	100	123,746	CAD incidence	Men aged 31–40 years	NGT	0.06
							Prediabetes	0.23
							DM	1.91
						Men aged 41–50 years	NGT	0.52
							Prediabetes	0.62
							DM	2.52
						Men aged 51–60 years	NGT	1.12
							Prediabetes	2.24
							DM	4.14
T2DM cohort								
JDDM Yokoyama et al. (2011)	Japan	T2DM	63	2,984	CHD			4.4
					Stroke			3.1
JDCS Sone et al. (2011)	Japan	T2DM	53	1,771	MI	Men		4.95
						Women		2.62
					Stroke	Men		8.70
						Women		6.07
Western countries								
UKPDS (1998)	UK	T2DM			MI		Intensive/conventional	14.7/17.4
					Stroke incidence			5.6/5.0

[†]Age adjusted. AMI: acute myocardial infarction; CAD: coronary artery disease; CHD: coronary heart disease; DM: diabetes mellitus; FPG: fasting plasma glucose; IFG: impaired fasting glucose; IGT: impaired glucose tolerance; JDCS: Japan Diabetes Complications Study Group; JDDM: Japan Diabetes Clinical Data Management Study Group; JPHC: Japan Public Health Center-based Prospective Study; MI: myocardial infarction; NA: not applicable; NGT: normal glucose tolerance; T2DM: type 2 diabetes mellitus; UKPDS: UK Prospective Diabetes Study

of coronary heart disease (CHD) in women.[22] Also, there has been no clear change in the incidence of acute myocardial infarction.[23] Although the overall risk was lower in Japanese individuals compared with that in the western population (**Table 2**), individuals with diabetes had an approximately two- to four-fold increased risk of CVD

compared with those without diabetes in both Japan and western countries.

In the US, between 1990 and 2010, the rates of the three complications of diabetes surveyed were substantially decreased: acute myocardial infarction, stroke, and amputation decreased by 67.8% (59.3%–76.2%), 52.7% (40.9%–64.4%), and 51.4% (34.5%–68.2%).[3] Performance of health systems and production of a number of new drugs for the treatment of diabetes in the past decade might have contributed to the reduction in the rate of these complications. However, considering the pandemic of diabetes and obesity worldwide,[1] diet and exercise remain the most crucial treatment for patients with diabetes. In fact, among adults with T2DM diagnosed for <10 years, a lifestyle intervention compared with standard care resulted in a change in glycemic control that did not reach the criterion for equivalence, but was in a direction consistent with benefit.[24]

Prevalence and Risk Factors of CVD in Patients with T2DM

In the Japan Diabetes Complications Study (JDCS), the crude incidence per 1,000 patient-years of myocardial infarction in patients with diabetes was 3.84 (4.95 in men and 2.62 in women),[25] which was higher than that in the general population (0.65–1.42 per 1,000 patient-years)[26,27] (Table 2). However, the prevalence was lower compared with that in the western diabetic and general populations.[28,29] Silent infarctions were more common in individuals with diabetes compared with those without.[30] Moreover, traditional and emerging cardiac risk factors were not associated with abnormal stress tests.[31] Therefore, detecting groups at a high risk of developing CAD among patients with T2DM is difficult. In western cohorts with T2DM, elevated concentrations of low-density lipoprotein cholesterol (LDLC), decreased concentrations of high-density lipoprotein cholesterol (HDLC), hyperglycemia, hypertension, and smoking were observed to be risk factors of CAD.[32,33] In JDCS, male sex, elevated concentrations of LDLC, and hypertriglyceridemia are risk factors of CAD.[25] Moreover, hypertriglyceridemia is a useful predictor of CAD in women with diabetes.[34] No difference was observed in the prevalence of stroke between patients with T2DM in Japan and western countries (Table 2). The crude incidence per 1,000 patient-years of all strokes was 7.45 (8.70 in men and 6.07 in women); among these, the incidence of brain infarction was 6.29 (7.44 in men and 5.03 in women).[25] Similarly, in the UK Prospective Diabetes Study (UKPDS), the incidence per 1,000 patient-years of all strokes was 5.0 and 5.6 in men and women, respectively.[35] High blood pressure (BP) was shown to be the most important risk factor for stroke in patients with

T2DM in JDCS as well in the general population.[25]

CAD among working age people is relevant and urgent not only because of its association with premature death but also because of its enormous socioeconomic impact. A largescale claims database in Japan showed that compared with men with normal glucose tolerance, diabetes was associated with a 17.3-fold, 2.74-fold, and 2.47-fold risk in men aged 31–40 years, 41–50 years, and 41–50 years, respectively[12] (Table 1). Being a prediabetic confers an approximately three-fold higher risk of CAD in men aged 31–40 years. Impact of diabetes on CAD was markedly higher in men aged 31–40 years compared with that in men aged 41–60 years, and diabetes conferred an approximately 20-fold higher risk of CAD independently of other conventional risk factors in men aged 31–40 years. That risk was equal to those aged 51–60 years with normal glucose tolerance, similar to findings by Booth et al. that diabetes confers a risk of CAD equivalent to aging 15 years in western populations.[17]

Relationship between Glucose Abnormality, Metabolic Phenotype, and CAD

Metabolically healthy and unhealthy obese individuals differ in terms of the cardiovascular risk.[36] The impact of obesity and metabolically unhealthy phenotype on the development of CAD based on the glucose tolerance status showed that nonobese persons in a metabolically unhealthy state had an approximately two- to three-fold increased risk of CAD compared with those not in a metabolically unhealthy state across all glucose tolerance categories.[37] In contrast, the presence of obesity alone showed no increase in the risk of CAD in all glucose tolerance categories. Compared with nonobese individuals with normal glucose tolerance not in a metabolically unhealthy state, the risk of CAD in obese prediabetic individuals in a metabolically unhealthy state was four-fold, which was equal to that in nonobese individuals with diabetes not in a metabolically unhealthy state.[37]

Diet, Physical Activity, and CVD in Patients with T2DM

In JDCS, increased dietary fiber, particularly soluble fiber, and intake of vegetables and fruits was associated with a lower incidence of stroke but not cerebrovascular disease in patients with T2DM.[38] After adjustment for confounders, the hazard ratio for CVD in patients in the fourth quartile of sodium intake (mean, 15.0 g/day) After adjustment for confounders, the hazard ratio for CVD in patients in the fourth quartile of sodium intake (mean 15.0 g/day) compared with the first quartile (mean 6.4 g/day) was 2.17 (1.21–3.90).[39] These results demonstrated that dietary

fiber intake and sodium restriction were important aspects of diet therapy in Japanese patients with T2DM.

Results of the JDCS showed that leisure-time physical activity of 15.4 metabolic equivalents (Mets) or more was associated with a significantly lower risk of stroke partly through ameliorating combinations of cardiovascular risk factors.[40] The amount of daily exercise in the top tertile was >2.2 Mets·h, which was equivalent to walking >30 min per day at a speed of 5.6 km/h. However, the amount of average daily exercise for this group was 5.3 Mets·h, which was reached in about 70 min of walking with quick steps. These findings were consistent with the results of a meta-analysis,[41] suggesting that starting exercise contributes to the prevention of macrovascular disease in patients with T2DM without an exercise habit.

Effects of Diabetes Treatment on CVD

Intensive glycemic control and CVD in patients with T2DM

The effect of intensive glycemic control on cardiovascular outcomes in patients with T2DM is controversial. In the Kumamoto study, 110 Japanese patients with T2DM were randomly assigned to multiple insulin injection therapy groups and administered three or more daily insulin injections or assigned to conventional insulin injection therapy and followed up for 6 years.[42] Intensive glycemic control delayed the onset and progression of the early stages of diabetic microvascular complications.[42] The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial investigated 4,733 patients with T2DM who were randomized to two different blood glucose targets (<6.0% and 7.0%–7.9%) and followed up for 3.4 years. This trial showed no significant differences between the groups in the primary endpoints nonfatal myocardial infarction, nonfatal stroke, and cardiovascular mortality.[43] The reduction in cardiovascular morbidity in the intensified therapy group did not reach statistical significance. Moreover, this study was prematurely interrupted because of increased mortality in the intensive treatment group; although the intensified therapy relatively rapidly improved blood glucose control within 1 year (median HbA1c, 8.1% to 6.4%), weight gain of >10 kg was observed in 27% of the participants, and of these, 16.2% of patients experienced severe hypoglycemia. Hypoglycemia stimulates the release of catecholamines, which have profound effects on the myocardium and blood vessels.[44] Catecholamines increase myocardial contractility, myocardial workload, and cardiac output. The lack of a significant reduction was observed for CVD events with intensive glycemic control in the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) and Veterans Affairs Diabetes Trial (VADT).[45,46] In a subanalysis of ACCORD, the risk of death with the intensive strategy linearly increased from approximately 6% to 9% HbA1c and seemed to be higher with the intensive than that with the standard strategy only when the mean HbA1c was >7%.[47] In a subanalysis of ADVANCE, severe hypoglycemia was associated with a significant increase in the adjusted risks of death from any cause [hazard ratio, 3.27 (2.39–4.65)] and cardiovascular events [3.79 (2.36–6.08)].[48] These findings suggest the necessity of various types of care depending on patients' characteristics such as age, duration of diabetes, glycemic control, and comorbidity based on a patient-centered approach.

In a meta-analysis of five randomized controlled trials [UKPDS, PROspective pioglitAzone Clinical Trial In macroVascular Events (PROactive), ACCORD, ADVANCE, and VADT] that included 33,040 patients, patients in the intensive glycemic control group had a significant reduction in nonfatal myocardial infarction and CHD events by 17% and 15%, respectively.[49] However, another meta-analysis of 14 clinical trials, including 28,614 patients, showed that intensive glycemic control did not reduce all-cause and cardiovascular mortality in patients with T2DM.[50] Thus, there is no certain conclusion on the effect of strict blood glucose control on macrovascular disease. Future studies are needed to assess these issues, particularly focusing on older age, weight gain, influence of hypoglycemia, and rapid improvement of glycemic control.

Metabolic memory and the legacy effect

Although long observation periods are needed to reveal the advantage of glycemic control, its benefits are sustained for a relatively long period. Intensive diabetes therapy during the Diabetes Control and Complications Trial (DCCT) (6.5 years) had long-term beneficial effects on the incidence of CVD and macrovascular complications and was associated with a decrease in the glomerular filtration rate in type 1 diabetes that persisted for up to 30 years.[51–53] Similarly, prolonged benefits of well-controlled blood glucose were observed in UKPDS in patients with T2DM.[54] These results illustrated that intensive glucose control should be initiated in the early phase of diabetes. The ACCORD Follow-on Study (ACCORDION) showed that intensive glycemic control had no beneficial effects on the incidence of death and nonfatal cardiovascular events. The increased risk of cardiovascular death reported during ACCORD remained significant during the long-term follow-up, although the magnitude of the risk was less.[55] No prolonged benefit of well-controlled blood glucose was observed in VADT,[56] whereas prolonged intensive treatment reduced the incidence of CVD in the ADVANCE posttrial observational study (ADVANCE-ON).[57] These

findings should be cautiously interpreted because the participants in ACCORD, ADVANCE, and VADT were at a high risk of developing CVD compared with those in DCCT and UKPDS.

Effect of Various Hypoglycemic Agents on CVD

Metformin
The UKPDS trial investigated 3,277 patients with newly diagnosed T2DM who were randomized to four different treatments [conventional treatment, insulin, sulfonylurea, or metformin (>120% ideal bodyweight)] and followed up for 5 years. Metformin significantly reduced the risk of myocardial infarction and death from any cause that persisted over time compared with the control group.[54] Based on this result, metformin was recommended as a first-line treatment option for T2DM in the consensus statement from the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD).[58] However, these guidelines should be interpreted cautiously because impaired insulin secretion had a greater impact compared with insulin resistance on the background of T2DM in a Japanese population.[59,60]

Alpha-glucosidase inhibitor
Treatment with the alpha-glucosidase inhibitor acarbose significantly reduced the progression of carotid intima–media thickness by 46%[61] and CVD by 49%.[62] Meta-analysis of Risk Improvement under Acarbose (MeRIA[7]), which evaluated the association between the control of postprandial hyperglycemia and the occurrence of cardiovascular events, showed a significant 64% decrease in the relative risk of myocardial infarction and a 35% decrease in the relative risk of any cardiovascular event.[63] Interestingly, the HbA1c difference between the treatment and placebo groups was only 0.57%, suggesting that clinicians need to pay close attention to the control of postprandial hyperglycemia.

Thiazolidinediones
The PROactive study assessed pioglitazone for the secondary prevention of macrovascular events in patients with T2DM. Pioglitazone showed a nonsignificant 10% decrease in the relative risk of the primary composite endpoint (all-cause mortality; nonfatal myocardial infarction, including silent myocardial infarction; stroke; acute coronary syndrome; endovascular or surgical intervention in the coronary or leg arteries; and amputation above the ankle) and a significant 16% decrease in the relative risk of main secondary endpoints (death, myocardial infarction, and stroke) after a mean of 2.9 years.[64]

Thiazolidinediones were associated with increased body weight, heart failure, fracture, and malignancy.[65,66] Moreover, the relationship between rosiglitazone and CVD has gained interest worldwide. The US Food and Drug Administration stated that pioglitazone may pose an increased risk of bladder cancer[65,67]; hence, it is contraindicated for patients at risk of or with bladder cancer. Similar statements were made by the European Medicines Agency.[68] However, no association between the cumulative use of pioglitazone or rosiglitazone and the incidence of bladder cancer was observed in a large pooled multipopulation analysis.[69] Further studies are needed before drawing conclusions on this issue.

Glinides
The Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research trial investigated 9,306 persons with impaired glucose tolerance randomized to two different therapies (nateglinide or placebo) and followed up for 5.0 years. This trial showed no significant differences between the groups in the primary endpoints incidence of diabetes and cardiovascular outcomes (cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure).[70] However, the nateglinide group had an overall higher mean body weight throughout the study compared with the placebo group (mean difference, 0.35 kg). Thus, these findings suggest that the examination of treatment effects considering weight change in this type of study is necessary.

Dipeptidyl peptidase-4 inhibitors
Dipeptidyl peptidase-4 inhibitors (DPP-4Is) are key drugs for Asians, who are more likely to have impaired insulin secretion compared with Caucasians. The DPP-4I prescription rate has markedly increased in Japan in recent years.[71–74] A recent meta-analysis indicated that DPP-4Is exhibited better glucose-lowering efficacy in studies consisting of ≥50% Asians compared with those consisting of <50% Asians.[75] Sitagliptin attenuated the progression of carotid intima–media thickness in insulin-treated Japanese patients with T2DM.[76] In a number of randomized controlled trials that evaluated the effectiveness of DPP-4Is, no evidence showed that DPP-4Is prevent CVD.[77–79] The short observation period could have affected these results; hence, further studies are needed to conclude the effectiveness of DPP-4Is for CVD.

Sodium–glucose co-transporter 2 inhibitors
In the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME), empagliflozin added to the standard of care reduced the risk of three-point major adverse cardiovascular events (MACE) in patients with T2DM and established CVD as follows: composite of cardiovascular

death, nonfatal myocardial infarction, or nonfatal stroke by 14%, cardiovascular death by 38%, hospitalization for heart failure by 35%, and all-cause mortality by 32%.[80] The same results were observed in Asians.[81] However, these results should be interpreted cautiously because this study investigated empagliflozin for secondary prevention in those who were at a high risk of developing CAD. Indeed, the mean age, body mass index (BMI), and duration of diabetes were 63 years, ≥ 30 kg/m^2, and >10 years, respectively. Moreover, metabolic changes in addition to improvements in glycemic control by empagliflozin, such as weight loss, reduced BP, increased HDLC, and decreased uric acid, may affect CVD reduction. The Canagliflozin cardioVascular Assessment Study (CANVAS) showed that canagliflozin reduced cardiovascular events by 14% and decreased the rate of renal decline by 40%, but it also doubled the risk of lower-limb amputation.[82]

Glucagon-like peptide-1 receptor agonists

In the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial, the rate of the first four-point MACE (composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke) among patients with T2DM was lower with liraglutide than that with placebo.[83] Similar results were observed in the Semaglutide in Subjects with Type 2 Diabetes (SUSTAIN-6) study.[84] In contrast, no superior effect on CVD was observed in the Evaluation of Lixisenatide in Patients with T2DM and Acute Coronary Syndrome (ELIXA) study and Exenatide Study of Cardiovascular Event Lowering (EXSCEL).[85,86] The difference in the reduction of all-cause mortality was dependent on differences in the baseline cardiovascular risk among the sample population.

Severe Hypoglycemia, Comorbidities, and CVD

Prevention of severe hypoglycemia is an important issue in the treatment of diabetes. Severe hypoglycemia causes an approximately two-fold increase in the risk of CVD.[87] In this analysis, comorbid severe illness alone may not explain the association between hypoglycemia and CVD.[87] Thus, clinicians should avoid the risk of hypoglycemia in the treatment of diabetes. Future studies need to clarify the relationship between each class of drug use and CVD and mortality.

Weight Gain

Weight gain is a serious issue in the treatment of diabetes. Despite improved glycemic control, the weight gain in ACCORD and VADT was 3.5 kg and 8.2 kg, respectively,

compared with baseline BMI (28.0 kg/m^2 in ACCORD and 31.3 kg/m^2 in VADT).[43,46] Basically, the goal of diabetes treatment is the reduction of obesity through diet and exercise. These findings emphasize the necessity of achieving glycemic control while avoiding weight gain.

Intensive BP Control and CVD in Patients with T2DM

High BP has long been recognized as a major risk factor for CVD in patients with and without diabetes.[32,88] Recent results of the Framingham study showed that patients with diabetes with hypertension had an increased risk of CVD death compared with those with diabetes without hypertension.[89] In UKPDS, no legacy effect was observed with regard to intensive treatment of hypertension.[90] Thus, ensuring long-term achievement of BP control may be essential for the reduction of CVD in patients with T2DM.

Antihypertensive therapy has been shown to be an effective method for reducing the macrovascular complications in individuals with T2DM. However, the optimal target BP levels are still under debate. The ACCORD trial investigated 4,733 patients with T2DM who were randomized to two different systolic BP targets (120 mmHg and 140 mmHg) and followed up for 4.7 years. This trial showed no significant differences between the groups in the primary endpoints nonfatal myocardial infarction, nonfatal stroke, and cardiovascular mortality.[91] Results of a meta-analysis suggested that impaired fasting glucose, impaired glucose tolerance, or a systolic BP treatment goal of 130 to 135 mmHg was acceptable in patients with T2DM.[92] In addition, with more aggressive goals (<130 mmHg), target organ heterogeneity was observed in that the risk of stroke continued to decrease, but benefits with respect to the risk of other macrovascular events were not observed and the risk of serious adverse events increased. A recent meta-analysis of 49 clinical trials also showed that antihypertensive treatment reduced the risk of mortality and cardiovascular morbidity in patients with diabetes with a baseline systolic BP of ≥ 140 mmHg; for those a baseline systolic BP of <systolic blood pressure (SBP) 140 mmHg, further treatment was associated with a rather increased risk of cardiovascular death.[93]

A meta-analysis of 40 studies showed that BP lowering was associated with improved mortality and other clinical outcomes, with lower relative risks observed among those with a baseline systolic BP of ≥ 140 mmHg.[94] Angiotensin-converting enzyme inhibitors also reduced all-cause mortality, cardiovascular mortality, and major cardiovascular events in patients with diabetes, whereas angiotensin-receptor blockers had no benefits on these outcomes in patients with diabetes.[95] Nevertheless, al-

though achieving the target level of BP first is essential, and continuing the discussion of mortality and protection from organ damage among each class of drugs, including the drug effect, is necessary.

Lipid Control and CVD in Patients with T2DM

A number of studies showed that statin use reduces cardiovascular events in patients with T2DM. The Collaborative Atorvastatin Diabetes Study (CARDS) randomized 2,838 patients with T2DM aged 40–75 years with at least one other vascular risk factor to atorvastatin 10 mg or placebo groups. This study found a 40% reduction in the LDLC level, a 37% risk reduction in time to the first cardiovascular event, a 31% reduction in the risk of coronary revascularization, and a 48% reduction in the risk of stroke over 3.9 years with atorvastatin.[96]

Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese (MEGA) randomized 7,832 patients with hypercholesterolemia without a history of CHD or stroke to diet alone or diet plus low-dose pravastatin (10–20 mg/day) groups. Diet plus pravastatin reduced the mean LDLC by 18%, and this reduction was associated with a 33% lower incidence of CHD events compared with that in the diet group during the 5.3 years of follow-up.[97] In a subanalysis, these effects were confirmed in patients with diabetes and/or impaired fasting glucose.[98]

An LDLC reduction of 2.0–3.0 mmol/L (77–116 mg/dL) may be able to suppress vascular events by approximately 40%–50%. A meta-analysis investigating almost 170,000 people showed a significant reduction of 22% per 1.0 mmol/L (38.7 mg/dL) in the risk of LDLC.[99] A meta-analysis of 14 prospective studies that included 18,868 patients showed that independent of other conventional risk factors, statin therapy was associated with a 13% reduction in the risk of mortality.[100] However, these findings are about the absolute value of LDLC and do not mention the quality of LDLC. In patients with T2DM, hypertriglyceridemia and low HDLC are frequently observed rather than high total cholesterol and LDLC due to a decrease in insulin action. Indeed, hypertriglyceridemia is comparable to LDLC as a risk factor for CVD in East Asians, including Japanese.[25,101] Moreover, not LDLC but remnant, small dense LDL and glycated LDL are potent risk factors as atherogenic factors. In addition, the relationship between LDLC and other lipid variables, such as HDLC, is important. Thus, although we mainly focused on LDLC, clinicians must also pay attention to the control of the entire lipid profile.

With regard to the effects of long-term fenofibrate therapy on cardiovascular events in 9,795 people with

T2DM (the FIELD study), although fenofibrate did not significantly reduce the primary outcome consisting of incident CHD, cardiovascular mortality, or total mortality in patients with T2DM treated for 5 years, it reduced CHD.[102] In a subanalysis of the benefit from long-term fenofibrate in patients with T2DM and various eGFR categories in comparison with placebo, risks of side effects of fenofibrate were not increased in any eGFR category.[103] In the ACCORD Lipid study, a benefit was shown in a prespecified subanalysis of participants with both higher triglycerides (≥204 mg/dL) and low HDLC (≤34 mg/dL) at baseline.[104] Although statins are recommended as first-line therapy for CVD prevention, these findings suggested the effectiveness of fibrate treatment, particularly in East Asians because hypertriglyceridemia is a risk factor of CVD in this population.[25,105]

Aspirin for Primary Prevention of CVD in Patients with T2DM

The Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes (JPAD) study examined the efficacy of low-dose aspirin for the primary prevention of cardiovascular events in a randomized 163-center, open-label trial conducted in 2,539 Japanese patients with T2DM but without a history of CVD. The patients were assigned to either aspirin (81–100 mg daily) or no aspirin groups and were followed up for a mean of 4.4 years. This trial revealed no significant differences between the groups in the primary endpoints fatal or nonfatal ischemic heart disease, fatal or nonfatal stroke, and peripheral arterial disease [hazard ratio, 0.80 (0.58–1.10)].[106] In subgroup analyses, however, among participants aged >65 years, the incidence of the primary endpoint was lower with aspirin [hazard ratio, 0.68 (0.46–0.99)]. Based on these studies, a position statement of the ADA, American Heart Association, and American College of Cardiology Foundation noted that aspirin should not be recommended for CVD prevention in adults with diabetes at a low risk of CVD (men <50 years and women <60 years without major additional CVD risk factors; 10-year CVD risk of <5%) because the potential adverse effects of bleeding offset the potential benefits.[107,108]

In the Principal Results of the Diabetic Atherosclerosis Prevention by Cilostazol (DAPC) Study, the investigators compared the efficacy of cilostazol (100–200 mg/day) and aspirin (81–100 mg/day) on carotid atherosclerosis in a randomized, open, blinded endpoint study conducted in four East Asian countries on participants with T2DM. The patients were assigned to either the phosphodiesterase inhibitor cilostazol or no aspirin group and were followed for 2.0 years. Compared with aspirin, cilostazol potently inhibited the progression of carotid intima–media thickness.[109]

Effect of Control of Multiple Risk Factors for CAD in Patients with T2DM

The Steno-2 study investigated 160 patients with T2DM randomized to two different therapies (intensive therapy and usual treatment) and followed up for approximately 8 years. Intensive multifactorial treatment (including glycemic control) reduced CVD by 53%.[110] Moreover, intensive intervention showed beneficial effects with respect to vascular complications over a period of time.[111] The Japan Diabetes Optimal Integrated Treatment Study for 3 Major Risk Factors of Cardiovascular Diseases (J-DOIT3) trial investigated 2,540 patients with T2DM aged 45 to 69 years who were randomized to two different therapies (intensive therapy and usual treatment) and followed up for approximately 8.5 years.[112] Although the reduction in the primary outcome was nonsignificant, adjustment for variables, such as smoking, showed that a significantly reduced risk of these outcomes was found among the intensive therapy group.[112]

Prediction of CVD in Japanese Patients with T2DM

Epidemiology shows the mean or trends of a specific group. By integrating the risk factor for each complication of CVD, future complications in each patient with T2DM can be possibly predicted. The risk engine (Japan Diabetes Complications Study/the Japanese Elderly Diabetes Intervention Trial risk engine) made from data of the JDCS and The Japanese Elderly Intervention Trial (J-EDIT) accurately predicted macro- and microvascular complications and would provide helpful information in risk classification in Japanese.[113]

Future Perspectives

Although a number of clinical studies of diabetes and CVD are being conducted worldwide, clinical studies involve a large cost, enormous effort, and cooperation of participants. To resolve such issues, using new and alternative research sources, such as big data, is essential. Big data has the following characteristics that can complement the abovementioned issues: use of available existing datasets, low cost, available data accumulated over a long period, and expectation of an increasing number of events with time. In the future, comprehensive big medical databases covering lifestyle habits and genetic information will make it possible to achieve more precise treatment of patients with T2DM.

Conclusion

Considering that East Asian patients with T2DM, including Japanese, have different features compared with western patients, applying the same guidelines for the treatment of these two groups is difficult. Clinical studies demonstrated that intensive glucose control should be initiated in the early phase of diabetes for macrovascular disease accompanied by lipid and BP control. In the future, in addition to standardized therapies, comprehensive medical big databases covering lifestyle habits and genetic information will make it possible to achieve precision in the treatment of patients with T2DM.

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