



Intensified Multifactorial Intervention in Patients with Type 2 Diabetes Mellitus

Takayoshi Sasako¹, Toshimasa Yamauchi¹, Kohjiro Ueki^{2,3}

¹Department of Diabetes and Metabolic Diseases, Graduate School of Medicine, The University of Tokyo, Tokyo,

²Diabetes Research Center, Research Institute, National Center for Global Health and Medicine, Tokyo,

³Department of Molecular Diabetology, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

In the management of diabetes mellitus, one of the most important goals is to prevent its micro- and macrovascular complications, and to that end, multifactorial intervention is widely recommended. Intensified multifactorial intervention with pharmacotherapy for associated risk factors, alongside lifestyle modification, was first shown to be efficacious in patients with microalbuminuria (Steno-2 study), then in those with less advanced microvascular complications (the Anglo-Danish-Dutch Study of Intensive Treatment In People with Screen Detected Diabetes in Primary Care [ADDITION]-Europe and the Japan Diabetes Optimal Treatment study for 3 major risk factors of cardiovascular diseases [J-DOIT3]), and in those with advanced microvascular complications (the Nephropathy In Diabetes-Type 2 [NID-2] study and Diabetic Nephropathy Remission and Regression Team Trial in Japan [DNETT-Japan]). Thus far, multifactorial intervention led to a reduction in cardiovascular and renal events, albeit not necessarily significant. It should be noted that not only baseline characteristics but also the control status of the risk factors and event rates during intervention among the patients widely varied from one trial to the next. Further evidence is needed for the efficacy of multifactorial intervention in a longer duration and in younger or elderly patients. Moreover, now that new classes of antidiabetic drugs are available, it should be addressed whether strict and safe glycemic control, alongside control of other risk factors, could lead to further risk reductions in micro- and macrovascular complications, thereby decreasing all-cause mortality in patients with type 2 diabetes mellitus.


Keywords: Blood pressure; Diabetes complications; Diabetes mellitus, type 2; Glycemic control; Hypoglycemia; Lipids; Mortality; Vascular diseases

INTRODUCTION

Diabetes mellitus is a group of metabolic diseases characterized by chronic hyperglycemia due to insufficient insulin action, and it leads to abnormalities in almost the entire metabolic system [1,2]. One of the most important goals of diabetes management is to prevent the development or progression of diabetic complications [3], but it is well known that glycemic control alone is not sufficient, and indeed, multifactorial intervention is widely recommended in order to prevent not only macrovascular but also microvascular complications [3-7].

Results began to be reported from the late 1970s onwards

from clinical trials examining the efficacy of multifactorial intervention, which focused mainly on primary prevention of coronary heart disease through pharmacological or non-pharmacological approaches [8], but not in the field of diabetes. Notably, a meta-analysis of these trials found no significant effect on mortality, suggesting that the benefits of multifactorial intervention could be evident only in patients at high risk, such as those with hypertension [8]. To the best of our knowledge, the Risk Factor Intervention Study is the first trial to examine the effect of multifactorial intervention on diabetes, blood pressure, lipids, and smoking, in patients with treated hypertension and an additional risk factor including diabetes. It was

Corresponding author: Kohjiro Ueki  <https://orcid.org/0000-0003-1523-8102>
Diabetes Research Center, Research Institute, National Center for Global Health and Medicine, 1-21-2 Toyama Shinjuku-Ku, Tokyo 162-8655, Japan
E-mail: uekik@ri.ncgm.go.jp

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reported in 1994 that multifactorial intervention was associated with no reduction in mortality but with a reduction in the risk of stroke [9].

Two years before this report, the Steno-2 study was launched, the first trial to examine the effects of multifactorial intervention in patients with type 2 diabetes mellitus [10], with microalbuminuria defined as the key inclusion criterion [11,12]. This was a landmark study in the field of diabetes, despite involving only 160 participants.

Two other trials are of major interest, in that they were conducted to elucidate the role of multifactorial intervention in patients with type 2 diabetes mellitus [13,14]: the Anglo-Danish-Dutch Study of Intensive Treatment In People with Screen Detected Diabetes in Primary Care (ADDITION)-Europe [15], and the Japan Diabetes Optimal Treatment study for 3 major risk factors of cardiovascular diseases (J-DOIT3) [16], both of which recruited more than 2,000 patients with less advanced microangiopathies.

Moreover, results of two other trials were recently reported:

the Nephropathy In Diabetes-Type 2 (NID-2) study [17], and Diabetic Nephropathy Remission and Regression Team Trial in Japan (DNETT-Japan) [18], both recruiting a smaller number of patients with advanced microangiopathies.

Fig. 1 gives an overview of these five trials examining the efficacy of multifactorial intervention, polypharmacotherapy for multiple risk factors in combination with lifestyle modification, on ‘hard outcomes,’ i.e., cardiovascular and renal events, in patients with type 2 diabetes mellitus.

STENO-2 STUDY

In the Steno-2 study, patients with microalbuminuria were registered and randomly assigned to either conventional therapy or intensive therapy aimed at stricter multifactorial treatment targets (e.g., glycosylated hemoglobin [HbA1c] <6.5%). The primary outcome for microangiopathies during 4 years of intervention was defined as progression to macroalbuminuria, and that for macroangiopathies during 8 years of intervention

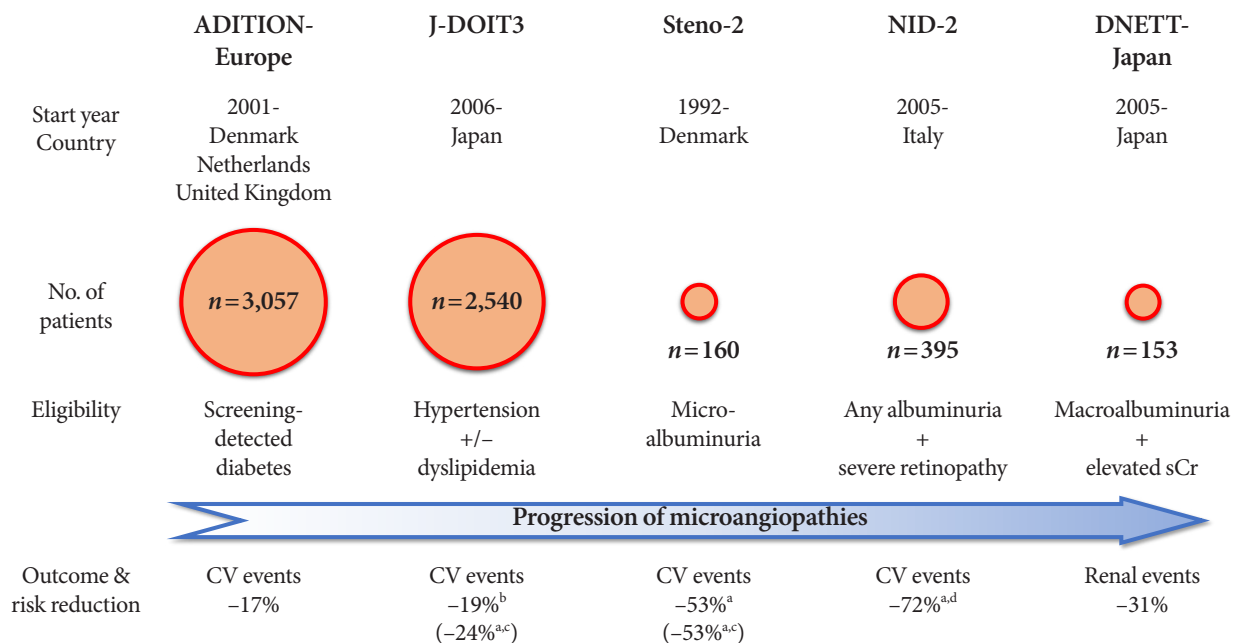


Fig. 1. Overview of clinical trials examining effects of multifactorial intervention on cardiovascular (CV) and renal events in patients with type 2 diabetes mellitus. Start year, the country in which the trial was undertaken, the number of patients with baseline characteristics available, eligibility, and the outcome with the risk reduction during intervention of the Anglo-Danish-Dutch Study of Intensive Treatment In People with Screen Detected Diabetes in Primary Care (ADDITION)-Europe [15], the Japan Diabetes Optimal Treatment study for 3 major risk factors of cardiovascular diseases (J-DOIT3) [16], the Steno-2 study [11,12], the Nephropathy In Diabetes-Type 2 (NID-2) study [17], and the Diabetic Nephropathy Remission and Regression Team Trial in Japan (DNETT-Japan) [18]. sCr, serum creatinine. ^aStatistically significant, ^bMarginally significant, ^cAfter adjustment for baseline characteristics, ^dAdditional secondary outcome.

was defined as a composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, amputation, and revascularization (Fig. 1) [11,12].

The baseline patient characteristics in the Steno-2 study are summarized in Table 1 [11,12]. In the microangiopathy study, during a mean follow-up of 3.8 years, intensive therapy was shown to be associated with a significant risk reduction in progression to macroalbuminuria (odds ratio, 0.27; 95% confidence interval [CI], 0.10 to 0.75) [11].

In the macroangiopathy study, during a mean follow-up of 7.8 years, and major risk factors were better with statistical significance in the intensive therapy group during the intervention period, such as HbA1c (7.9% in the intensive therapy group vs. 9.0% in the conventional therapy group, the same as below) (Table 1) [12].

Event rates in the Steno-2 study are summarized in Table 1. Intensive therapy was shown to be associated with a significant risk reduction in the primary outcome (hazard ratio [HR], 0.47; 95% CI, 0.24 to 0.73), even after adjustment for baseline risk factors (HR, 0.47; 95% CI, 0.22 to 0.74) (Fig. 1) [12], while it was later reported that this had not affected mortality at this point [19].

Intensive therapy was associated with a significant risk reduction in nephropathy (HR, 0.39; 95% CI, 0.17 to 0.87), retinopathy (HR, 0.42; 95% CI, 0.21 to 0.86), and autonomic neuropathy (HR, 0.37; 95% CI, 0.18 to 0.79). End-stage renal failure was reported only in the conventional therapy group (3.8%), while estimated glomerular filtration rate (eGFR) was lower by around 30 mL/min/1.73 m² in both groups compared to baseline (Table 1). Blindness was less frequent in the intensive therapy group (1.3% vs. 8.8%). Among major adverse events, severe hypoglycemia was shown to be also less frequent in the intensive therapy group (6.3% vs. 15.0%) [12].

In subsequent sub-analyses, intensive therapy was associated with a significant risk reduction in stroke [20]. The largest effect on the cardiovascular risk calculated on the basis of the UK Prospective Diabetes Study (UKPDS) [21] was accounted for by changes in lipids among those in major risk factors [20]. Besides, intensive therapy was shown to be more cost-effective than conventional therapy [22].

Moreover, the patients were followed up even after completion of intervention with death from any cause as the primary outcome. During a mean follow-up of 13.3 years, intensive therapy was shown to be associated with a significant risk reduction in mortality (HR, 0.54; 95% CI, 0.32 to 0.89). It was as-

sociated with a significant risk reduction in other events, and nearly half of deaths were shown to be due to cardiovascular disease in the conventional therapy group, which was significantly reduced in the intensive therapy group (Fig. 2) [19].

After a median follow-up of 21.2 years, intensive therapy was shown to be still associated with a significant risk reduction in mortality (HR, 0.55; 95% CI, 0.36 to 0.83), yielding an elongation of a median survival of at least 7.9 years, as well as a significant reduction in other events [23].

In sub-analyses, intensive therapy was associated with a significant reduction in stroke [24] and heart failure [25], as well as a significant reduction in the combined renal events including mortality, with the annual eGFR decline shown to be less rapid with intensive therapy (3.1 mL/min/1.73 m²/year vs. 4.0 mL/min/1.73 m²/year) [26]. Again, intensified multifactorial intervention was shown to be associated with no increase in total costs [27].

ADDITION-EUROPE

ADDITION-Europe examined the effects of multifactorial intervention on macrovascular complications and mortality in patients with screening-detected type 2 diabetes mellitus (Fig. 1) [15,28-31], who were randomly assigned to either routine care or intensive treatment following the Steno-2 study [12], with the primary outcome defined as a composite of cardiovascular mortality, nonfatal myocardial infarction, nonfatal stroke, revascularization, and amputation.

The baseline patient characteristics are summarized in Table 1 [15,32,33]. Major risk factors were slightly improved without statistical significance in the intensive treatment group during the intervention period, such as HbA1c (6.6% vs. 6.7%) (Table 1) [15], showing the feasibility of risk factor control in patients with screening-detected diabetes [34].

Event rates during the mean follow-up of 5.3 years are summarized in Table 1 [15]. Intensive treatment was shown to be associated with a non-significant risk reduction in the primary outcome (HR, 0.83; 95% CI, 0.65 to 1.05) (Fig. 1) and in mortality (HR, 0.91; 95% CI, 0.69 to 1.21), with no increase reported in adverse events including hypoglycemia [15].

In subsequent sub-analyses, intensive treatment was associated with a non-significant reduction not only in the first event but also in any events of the primary outcome [35]. It was associated with no reduction in nephropathy, retinopathy, or neuropathy, with the eGFR value shown to be rather elevated com-

Table 1. Details of the clinical trials to examine effects of intensified multifactorial treatment in patients with type 2 diabetes mellitus

	ADDITION-Europe [15,32,33]		J-DOIT3 [16,51]		Steno-2 [11,12]		NID-2 [17]		DNETT-Japan [18]	
	Control	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control	Intervention
Outcome & intervention										
Primary outcome	3-point MACE, revascularization, amputation		MI, stroke, revascularization, all-cause mortality		3-point MACE, revascularization, amputation		3-point MACE, revascularization, amputation		Doubling of sCr, ESRD, all-cause mortality	
Glycemic/BP/lipid control	Yes		Yes		Yes		Yes		Yes	
Smoking cessation	Yes		Yes		Yes		Yes		Yes	
Lifestyle modification	Yes		Yes		Yes		Yes		Yes	
Aspirin for primary prevention	Yes		No		Yes (after 1999)		Yes		No	
Others	-		Smoking cessation aid (if necessary)		Vitamin-mineral supplement		-		Vitamin supplement	
Baseline patient characteristics										
Mean age, yr	60.2	60.3	59.1	58.9	55.2	54.9	68.2	66.1	57.6	56.8
Female sex, %	42.7	41.5	37.8	38.2	30.0	21.3	55.9	50.2	45.0	41.1
Mean duration of diabetes, yr	- ^a	- ^a	8.47	8.58	Median 6.0	Median 5.5	Median 9	Median 9	15.1	15.9
History of CVD, % ^b	8.0	9.7	11.2	11.5	27.5	27.5	-	-	-	-
Mean HbA1c, %	7.0	7.0	7.98	8.01	8.8	8.4	7.3	7.5	7.1	7.1
Mean systolic BP, mm Hg	149.8	148.5	134.1	133.5	149	146	134.7	133.8	139.5	138.5
Mean diastolic BP, mm Hg	86.5	86.1	80.0	79.3	86	85	78.3	80.8	76.6	76.9
Mean LDL-C, mg/dL	135.3	131.5	125.6	125.5	131.5	127.6	73	69	118.9	118
Mean eGFR, mL/min/1.73 m ²	Median 77.8	Median 78.0	82.2	82.3	118	116	62.7	65.4	39.5	40.1
Median ACR, mg/g	8	8	10.8	11.1	69	78	57.3	120.5	1,725	1,450
Control status of risk factors during the intervention period										
Median duration, yr	Mean 5.3		8.5		Mean 7.8		3.40	3.84	3.11	
Mean HbA1c, %	6.7	6.6	7.20	6.79	9.0	7.9	7.4	6.9	6.94	6.86
Mean systolic BP, mm Hg	138.1	134.8	128.7	123.4	146	132	135.1	127.3	132.4	132.2
Mean diastolic BP, mm Hg	80.7	79.5	74.4	71.5	78	73	78.8	78.1	72.0	72.2
Mean LDL-C, mg/dL	88.9	81.2	103.7	85.5	119	81	122.3	100.5	104.0	98.6
Mean eGFR, mL/min/1.73 m ²	84.2	82.3	-	-	86	86	60.7	60.4	29.2	31.1
Event rates during the intervention period										
Primary outcome, %	8.5	7.2	10.5	8.6	43.8	23.8	26.6 ^c	11.6 ^c	-	-
Myocardial infarction, %	2.3	1.7	0.9 ^d	0.4 ^d	10.0 ^e	5.0 ^e	-	-	-	-
Stroke, %	1.4	1.3	2.9 ^d	1.2 ^d	13.8 ^e	3.8 ^e	-	-	-	-
Death, %	6.7	6.2	3.8	3.9	18.8	15.0	10.1	3.9	5.0	2.7
ESRD, %	-	-	0.4	0.0	3.8	0.0	2.7	3.4	-	-

Data in the control group or in the multifactorial intervention group are shown.

ADDITION-Europe, the Anglo-Danish-Dutch Study of Intensive Treatment In People with Screen Detected Diabetes in Primary Care; J-DOIT3, the Japan Diabetes Optimal Treatment study for 3 major risk factors of cardiovascular diseases; NID-2, the Nephropathy In Diabetes-Type 2; DNETT-Japan, the Diabetic Nephropathy Remission and Regression Team Trial in Japan; MACE, major adverse cardiovascular events; MI, myocardial infarction; sCr, serum creatinine; ESRD, end-stage renal disease; BP, blood pressure; CVD, cardiovascular disease; HbA1c, glycosylated hemoglobin; LDL-C, low-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate; ACR, urinary albumin-to-creatinine ratio.

^aScreening-detected diabetes was the key inclusion criterion, ^bSum of the number of participants with a history of myocardial infarction and that of those with a history of stroke in the ADDITION-Europe in this table; electrocardiographic evidence of ischemia in the Steno-2 study was excluded in this table; patients with a history of myocardial infarction or stroke were excluded in the NID-2 study; patients with a history of recent myocardial infarction or stroke were excluded in the DNETT-Japan, ^cPrimary outcome during the intervention period was an additional secondary outcome, ^dBreakdown of first events, ^eBreakdown of first events with fatal events excluded.

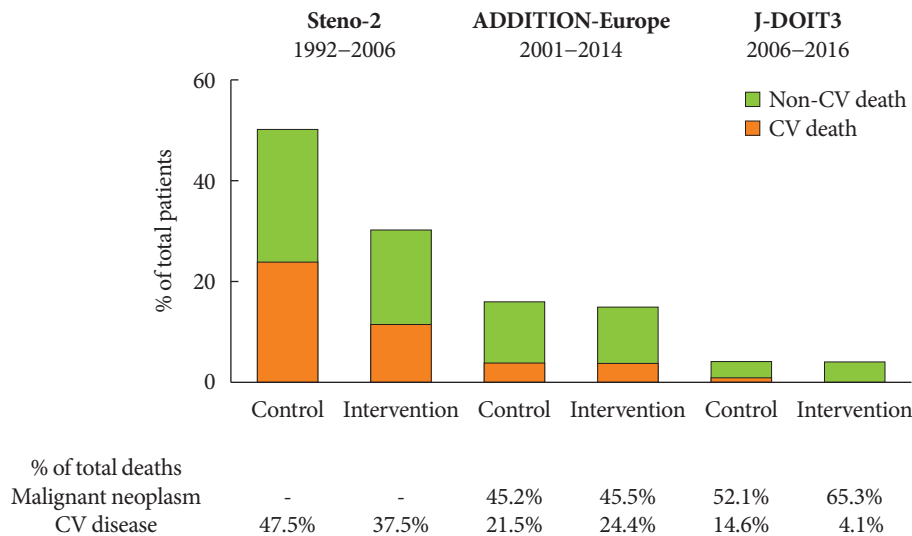


Fig. 2. Cause-specific deaths in clinical trials to examine effects of intensified multifactorial treatment in patients with type 2 diabetes mellitus. Cardiovascular (CV) and non-CV deaths (% of total patients) (upper panel), and deaths due to malignant neoplasm and CV disease (% of total deaths) (lower panel), in the Steno-2 study [19], the Anglo-Danish-Dutch Study of Intensive Treatment In People with Screen Detected Diabetes in Primary Care (ADDITION)-Europe [33], and the Japan Diabetes Optimal Treatment study for 3 major risk factors of cardiovascular diseases (J-DOIT3) [16]. Deaths due to malignant neoplasm were not available in the Steno-2 study. CV deaths in the J-DOIT3 consist of those due to myocardial infarction, stroke, heart failure, or sudden death.

pared to baseline in both groups compared to the baseline [32].

Intensive treatment was associated with an improvement in aortic stiffness [36], but not in peripheral neuropathy [37], cardiac autonomic neuropathy [38], peripheral arterial disease [37], or cognitive function [39]. It was not shown to be cost-effective [40], with only slight changes shown in psychological outcomes [41–43], although glycemic control was associated with diabetes-specific quality of life [44]. It was also reported that screening for diabetes per se was not associated with a reduction in mortality [45].

Moreover, the patients were followed up even after completion of intervention. During a mean follow-up of 9.61 years, intensive treatment was associated with a risk reduction, albeit non-significant, in the primary outcome (HR, 0.87; 95% CI, 0.73 to 1.04) and in morality (HR, 0.90; 95% CI, 0.76 to 1.07). Nearly half of deaths were due to malignant neoplasms in both groups (Fig. 2) [33]. A subsequent sub-analysis showed that intensive treatment did not affect psychological outcomes [46].

J-DOIT3

The J-DOIT3 examined the effects of multifactorial intervention on macrovascular complications and mortality in patients

with type 2 diabetes mellitus (Fig. 1) [16,47], as one of the programs comprising the strategic research, Japan Diabetes Outcome Intervention Trial, launched by the Ministry of Health, Labor and Welfare (MHLW) [48]. The J-DOIT3 was aimed at a 30% reduction in diabetic complications, whereas the J-DOIT1 was focused on conversion of impaired glucose tolerance to diabetes [49], and the J-DOIT2 was on dropout from diabetes treatment [50], respectively.

In the J-DOIT3 study, patients with type 2 diabetes mellitus with hypertension and/or dyslipidemia were registered and randomly assigned to either conventional therapy or intensive therapy for stricter multifactorial treatment targets (e.g., HbA1c <6.2%), with the primary outcome defined as a composite of myocardial infarction, stroke, revascularization, and all-cause mortality [16,47].

The baseline patient characteristics are summarized in Table 1 [16,51]. Major risk factors were significantly improved in the intensive therapy group during the intervention period, such as HbA1c (6.79% vs. 7.20%) (Table 1) [16,51].

Event rates during the median follow-up of 8.5 years are summarized in Table 1 [16]. Intensive therapy was shown to be associated with a non-significant risk reduction in the primary outcome (HR, 0.81; 95% CI, 0.63 to 1.04), which was statistical-

ly significant after adjustment for baseline risk factors (HR, 0.76; 95% CI, 0.59 to 0.99) (Fig. 1). It was associated with a significant risk reduction in cerebrovascular events in a *post hoc* breakdown (HR, 0.42; 95% CI, 0.24 to 0.74) [16], and also with a significant risk reduction in the secondary outcomes, i.e., nephropathy events (HR, 0.68; 95% CI, 0.56 to 0.82) [16,51], and retinopathy events (HR, 0.86; 95% CI, 0.74 to 1.00) [16], with end-stage renal failure reported only in the conventional therapy group (0.4%) and no blindness reported in either group [16].

Although the incidence of any hypoglycemia was higher in the intensive therapy group (41% vs. 22%), the incidence of severe hypoglycemia was quite low in both groups (0.6% and 0.3%) during the intervention period. More than half of deaths were due to malignant neoplasms in both groups (Fig. 2) [16].

In subsequent sub-analyses, glycemic control was associated with onset of nephropathy, and blood pressure control was associated with progression of eGFR decline, with the annual eGFR decline less than 2 mL/min/1.73 m²/year in both groups during the first 3 years [51]. Intensive therapy did not lead to an elevated risk in fractures [52].

NID-2

In the NID-2 study, patients with type 2 diabetes mellitus with micro- or macroalbuminuria and severe retinopathy were registered and randomly assigned to either standard of care or multifactorial intensive therapy involving the same treatment targets (e.g., HbA1c <7%), with a history of myocardial infarction or stroke as one of the exclusion criteria. The primary outcome was defined as a composite of cardiovascular mortality, nonfatal myocardial infarction, nonfatal stroke, amputation, and revascularization [17,53].

The baseline patient characteristics are summarized in Table 1. Major risk factors were significantly improved in the multifactorial intensive therapy group during the intervention period, e.g., HbA1c (6.9% vs. 7.4%) (Table 1) [17].

Mortality rates during intervention for a median of 3.40 and 3.84 years in the standard of care group and the multifactorial intensive therapy group, respectively, are shown in Table 1. Multifactorial intensive therapy was shown to be associated with a significant risk reduction in the primary outcome during the intervention period (HR, 0.28; 95% CI, 0.13 to 0.63) (Fig. 1), although it was just an additional secondary outcome because the follow-up for the primary analysis was continued even after intervention was terminated until a sufficient num-

ber of events were reported [17].

eGFR was shown to be mildly declined in both groups (Table 1). Among adverse events, hyperkalemia and eGFR decline by 30% were shown to be more frequent, albeit non-significantly, in the multifactorial intensive therapy group (10% vs. 5% and 16% vs. 9%, respectively), possibly due to more frequent concurrent use of renin-angiotensin system blockers, while end-stage renal failure was reported in both groups (3.4% vs. 2.7%) [17].

After almost an additional decade of follow-up after the end of intervention, during the median follow-up of 13.0 years in total, multifactorial intensive therapy was shown to be associated with a significant risk reduction in the primary outcome (HR, 0.49; 95% CI, 0.35 to 0.69), and in mortality (HR, 0.58; 95% CI, 0.34 to 0.98), as well as in myocardial infarction and stroke [17].

Some other analyses were performed before the end of follow-up, and albuminuria and eGFR at baseline were shown to be associated with the risk of cardiovascular events [54], and HbA1c was also shown to be positively associated with the risk after adjustment for aspirin or statin use and other risk factors [55,56].

DNETT-JAPAN

In the DNETT-Japan, patients with type 2 diabetes mellitus with macroalbuminuria and elevated serum creatinine were registered and randomly assigned to either conventional treatment or multifactorial intensive treatment for stricter multifactorial treatment targets (e.g., HbA1c <6.2%), with a history of recent myocardial infarction or stroke as one of the exclusion criteria. The primary outcome was defined as a composite of end-stage renal failure, doubling of serum creatinine or death [18,57].

The baseline patient characteristics are summarized in Table 1. Major risk factors showed no significant between-group differences during the intervention period, e.g., HbA1c (6.86% vs. 6.94%) (Table 1) [18].

Mortality rates during the median follow-up of 3.11 years are shown in Table 1. Multifactorial intensive treatment was shown to be associated with a non-significant risk reduction in the primary outcome (HR, 0.69; 95% CI, 0.43 to 1.11) (Fig. 1). It was not associated with a reduction in cardiovascular events (HR, 0.56; 95% CI, 0.19 to 1.64), end-stage renal failure (HR, 0.77; 95% CI, 0.31 to 1.86), or mortality (HR, 0.54; 95% CI,

0.10 to 2.97) [18].

eGFR was shown to have declined by around 10 mL/min/1.73 m² in both groups (Table 1). Severe adverse events were not increased in the multifactorial intensive treatment group [18]. It was also shown that, low-density lipoprotein cholesterol (LDL-C) during the intervention was associated with the risk of the primary outcome after adjustment with baseline characteristics [18].

OTHER TRIALS

Intensive multifactorial therapy was shown to be feasible with less frequent hypoglycemia [58], with the improved risk factor profile shown to be sustained even after the end of intervention [59]. It suppressed progression of the intima-media thickness of the carotid artery in patients with short-duration type 2 diabetes mellitus [60-62], and those with type 2 diabetes mellitus and at least two insufficient risk factors [63]. It also delayed onset of microalbuminuria in patients with short-duration type 2 diabetes mellitus [64]. Moreover, intensive multifactorial therapy by structured care including administration of a renin-angiotensin system blocker showed no effect on renal outcomes in patients with elevated serum creatinine, but addressing multiple targets led to a risk reduction in the renal outcome [65]. Intensive multifactorial therapy for stricter targets in the elderly with a mean age over 70 years did not affect fatal or nonfatal events without inter-group difference in risk factors [66].

PERSPECTIVE

Overall, intensified multifactorial intervention is shown to be associated with risk reductions in micro- and macrovascular complications, which are shown to be significant in some trials and non-significant in others.

As summarized in Table 1, the background patient characteristics are shown to vary among the trials, with HbA1c and eGFR, for instance, shown to be higher in the Steno-2 study than in the other four trials (Table 1). Thus, the study results might not apply to patients with microalbuminuria, but with better glycemic control and without glomerular hyperfiltration, in a 'straight forward' manner, although they could possibly be 'extrapolated' to these patients as well.

Although risk factor targets were not fully achieved in the Steno-2 study, as was pointed out previously [67], those are

shown to have been generally well controlled in the trials launched after 2000, with the mean HbA1c shown to be less than 7% in the intervention groups in all trials, as well as in the control groups in the ADDITION-Europe and the DNETT-Japan. The mean systolic blood pressure was less than 130 mm Hg even in the conventional therapy group in the J-DOIT3, and the mean LDL-C was less than 100 mg/dL even in the routine care group in the ADDITION-Europe (Table 1). This could be due to recent advances in diabetes care resulting in low event rates during intervention [68]. The incidence of the primary outcome in the ADDITION-Europe was lower than expected on the basis of the preceding UKPDS, which was initiated in the late 1970s [69]. The incidences of myocardial infarction and stroke in the J-DOIT3 were almost half or less of those observed in the Japan Diabetes Complications Study [70], a preceding clinical trial initiated in the mid 1990s [16]. The mortality rate in the J-DOIT3 is also deemed to be much lower than those in recent surveys in the general population [71].

Still there remain several issues to be addressed, and first, the long-term effects of multifactorial intervention on vascular complications and mortality should be further evaluated [68,72], given that the potential benefits of intensive multifactorial therapy may become more evident during a long-term follow-up, as in the UKPDS, the Steno-2 study, and the 10-year follow-up of the Veterans Affairs Diabetes Trial (VADT) [19,73,74], while any observed benefits could be seen to fade, as in the 15-year follow-up of the VADT [75].

Given the mean patient age of around 60 years in these trials, it is also important to examine the effects of intensive multifactorial intervention in younger patients [71], as well as in elderly patients, as they were not included in many of the clinical trials conducted to date, with some exceptions [66], possibly due to low event rates in younger patients and susceptibility to adverse events in elderly patients. Retrospective real-world data may complement prospective clinical trials and provide us with insight into the effects of intensified multifactorial intervention in these patients, although it should also be noted that adverse events are carefully monitored in clinical trials but are not necessarily analyzed in retrospective cohort studies [76,77]. Especially in elderly patients with diabetes, the treatment would be better to be individualized rather than uniformly intensified on the basis of their prognosis and preferences [78].

Moreover, intensive multifactorial intervention using the so-called new classes of antidiabetic drugs, e.g., dipeptidyl pepti-

dase 4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists, and sodium-glucose cotransporter 2 (SGLT2) inhibitors, may contribute to better and safer glycemic control [68]. In the J-DOIT3, in which intervention was continued until as recently as March, 2016, DPP-4 inhibitors were administered in over half of its participants at the end of intervention, but the use of GLP-1 receptor agonists or SGLT2 inhibitors remained still less common [16], while the latter two drugs are expected to show beneficial effects on cardiovascular and renal events [79,80].

Furthermore, while the mortality rate was lower in the J-DOIT3 study than in the others [16,71], it is deemed important to assess the effects of intensive therapy on all-cause mortality. In the Steno-2 study, almost half of deaths were due to cardiovascular disease in the conventional therapy group, but in the ADDITION-Europe, nearly half of deaths were due to malignant neoplasm and less than a quarter of them were due to cardiovascular disease in both groups. Again, in the J-DOIT3 study, over half of deaths in both groups were due to malignant neoplasm, whereas 15% of deaths in the conventional therapy group and only 4% of deaths in the intensive therapy group were due to cardiovascular disease, although direct comparisons are difficult between these three trials, due to differences in baseline characteristics, e.g., age, race, sex, and duration of diabetes, and course of treatment (Table 1, Fig. 2). Cardiovascular deaths have also been relatively decreased in the general population with diabetes, accounting for over one-third, around a quarter, and just 15% of all deaths in the United States [81], the United Kingdom [82], and Japan [83], respectively. Indeed, deaths from malignant neoplasm are almost equivalent to those from cardiovascular deaths in the United Kingdom [82], and over twice as frequent as those from cardiovascular deaths in Japan [83]. Thus, it is increasingly important to focus on how best to achieve further risk reductions not only in micro- and macrovascular complications but also in diseases whose risks are increased by diabetes, such as malignant neoplasm, frailty and dementia, thereby decreasing all-cause mortality in patients with type 2 diabetes mellitus.

Lastly, it is essential to clarify the contribution of each risk factor targeted in multifactorial intervention to events and to what extent it should be controlled. Classically, it was assumed based on epidemiological findings that the contribution of risk factors to events, especially macroangiopathies, vary from one risk factor to the next, e.g., lipids largely affect coronary heart disease, blood pressure affects stroke, and hyperglycemia af-

fects amputation [10,84].

Although the Steno-2 study suggested the importance of lipid control over glycemic control [20], recently, growing attention has been focused on the impact of glycemic control on cardiovascular events. A meta-analysis of classical five trials showed that intensive glycemic control was associated with a significant reduction in nonfatal myocardial infarction and coronary heart disease, but not in stroke and mortality [85]. More patients receiving intensive glycemic control were shown to experience hypoglycemia in these trials [85], thus raising their risk of cardiovascular events and mortality [86]. An analysis of these five and more than 10 additional trials showed that differential glycemic exposure (% HbA1c \times years) was negatively correlated with reductions in cardiovascular risk [87], suggesting that it could be effective to maintain good glycemic control for a longer duration to prevent cardiovascular events. Similarly, an analysis of more recent 15 trials treating patients with type 2 diabetes mellitus with DPP-4 inhibitors, GLP-1 receptor agonists, and SGLT2 inhibitors, all of which are considered to be associated with a low risk of hypoglycemia, showed that differential glycemic control was significantly correlated with a risk reduction in cardiovascular events and nonfatal stroke, irrespective of the class of drugs, but not in nonfatal myocardial infarction [88]. The 8-year data of the NID-2 study stated above also seem to suggest the importance of glycemic control in the prevention of cardiovascular events [55,56].

Further analyses are expected to clarify how intensive glycemic control without involving an increase in hypoglycemia, which might have been difficult to achieve and analyze, in combination with multifactorial intervention for other risk factors, could contribute to reductions in risk of cardiovascular events and mortality. The treatment target for HbA1c as well as those for other risk factors should be also explored, as they could differ depending on the event of interest.

CONCLUSIONS

Intensified multifactorial intervention for major risk factors, e.g., HbA1c, blood pressure, and lipids, is expected to reduce the risk of not only macroangiopathies but also microangiopathies in patients with type 2 diabetes mellitus. Multifactorial intervention needs to be examined for its effects over a longer duration and in younger or elderly patients, and new classes of antidiabetic drugs are expected to augment the treatment ben-

efits. Given the recent relative decrease in cardiovascular deaths, it remains to be addressed whether intensified multifactorial intervention could reduce the risk of all-cause mortality over the long-term. Moreover, multifactorial intervention should be further optimized by clarifying how the risk of individual events may be affected by control of HbA1c and other individual risk factors.

CONFLICTS OF INTEREST

Takayoshi Sasako reports personal fees from AstraZeneca, Daiichi Sankyo, Eli Lilly Japan, Kissei, Kowa, Mitsubishi Tanabe, MSD, Nippon Boehringer Ingelheim, Novartis Pharma, Novo Nordisk, Ono, Sanofi, Sumitomo Pharma, Takeda, and Teijin Pharma. Toshimasa Yamauchi reports personal fees from Abbott Japan, Astellas, AstraZeneca, Bayer Yakuhin, Covidien Japan, Daiichi Sankyo, DOJINDO LABORATORIES, Eli Lilly Japan, FUJIFILM Toyama Chemical, Kissei, Kowa, Kyorin Pharma, Kyowa Kirin, Mitsubishi Tanabe, MSD, Musashino Co. Ltd., Nippon Becton Dickinson, Nippon Boehringer Ingelheim, Novartis, Novo Nordisk, Ono, Roche DC Japan, Sanofi, Sanwa Kagaku Kenkyusho, Sumitomo Pharma, Taisho Pharma, Takeda, Teijin Pharma, Terumo, and Viatrix Japan; grants and endowments from Aero Switch Therapeutics Inc., Astellas, AstraZeneca, Daiichi Sankyo, EA Pharma, Kowa, Kyowa Kirin, Minophagen Pharmaceutical, Mitsubishi Corporation Life Sciences, Mitsubishi Tanabe, MSD, Nippon Boehringer Ingelheim, Nipro, Novartis, Novo Nordisk, Ono, Sanofi, Sanwa Kagaku Kenkyusho, SHIONOGI, Sumitomo Pharma, Takeda, Taisho Pharma, TOSOH, and Asahi Mutual Life Insurance. Kohjiro Ueki reports personal fees from AstraZeneca, Bayer Yakuhin, Daiichi Sankyo, Eli Lilly Japan, Kowa, Mitsubishi Tanabe, Nippon Boehringer Ingelheim, Novo Nordisk, Ono, Sumitomo Pharma, and Taisho Pharmaceutical; grants and endowments from Nippon Boehringer Ingelheim, Kyowa Kirin, Mitsubishi Tanabe, Novo Nordisk, Ono, Sanofi, Sumitomo Pharma, and Takeda; consulting fees from Abbott Japan, AstraZeneca, Bayer Yakuhin, Kyowa Kirin, Mitsubishi Tanabe, Sumitomo Pharma, and Terumo.

ORCID

Takayoshi Sasako <https://orcid.org/0000-0002-7644-309X>
Kohjiro Ueki <https://orcid.org/0000-0003-1523-8102>

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