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CLINICAL TRIAL

Randomized trial of an intensified, multifactorial intervention in patients with advanced-stage diabetic kidney disease: Diabetic Nephropathy Remission and Regression Team Trial in Japan (DNETT-Japan)

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ABSTRACT

Aims/Introduction: We evaluated the efficacy of multifactorial intensive treatment (IT) on renal outcomes in patients with type 2 diabetes and advanced-stage diabetic kidney disease (DKD).

Materials and Methods: The Diabetic Nephropathy Remission and Regression Team Trial in Japan (DNETT-Japan) is a multicenter, open-label, randomized controlled trial with a 5-year follow-up period. We randomly assigned 164 patients with advanced-stage diabetic kidney disease (urinary albumin-to-creatinine ratio ≥300 mg/g creatinine, serum creatinine level 1.2–2.5 mg/dL in men and 1.0–2.5 mg/dL in women) to receive either IT or conventional treatment. The primary composite outcome was end-stage kidney failure, doubling of serum creatinine or death from any cause, which was assessed in the intention-to-treat population.

Results: The IT tended to reduce the risk of primary end-points as compared with conventional treatment, but the difference between treatment groups did not reach the statistically significant level (hazard ratio 0.69, 95% confidence interval 0.43–1.11; $P = 0.13$). Meanwhile, the decrease in serum low-density lipoprotein cholesterol level and the use of statin were significantly associated with the decrease in primary outcome (hazard ratio 1.14; 95% confidence interval 1.05–1.23, $P < 0.001$ and hazard ratio 0.53, 95% confidence interval 0.28–0.998, $P < 0.05$, respectively). The incidence of adverse events was not different between treatment groups.

†A complete list of steering committee and investigators in the DNETT-Japan is provided in the Appendix S1.

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Conclusions: The risk of kidney events tended to decrease by IT, although it was not statistically significant. Lipid control using statin was associated with a lower risk of adverse kidney events. Further follow-up study might show the effect of IT in patients with advanced diabetic kidney disease.

INTRODUCTION

Diabetic kidney disease (DKD) is the leading cause of end-stage renal failure in developed and developing countries[1,2]. DKD is also an important risk for cardiovascular disease[3,4]. Although the prognosis of DKD has been improving, effective intervention against the progression to end-stage renal disease (ESRD) is still required[5–7]. The Steno 2 study showed that multifactorial intervention can prevent the progression of DKD in patients with type 2 diabetes associated with microalbuminuria[8–10]. Recently, the Japan Diabetes Optimal Integrated Treatment study for three major risk factors of cardiovascular diseases (J-DOIT3) showed that multifactorial intervention prevents the onset and advancement of early-stage DKD in patients with Japanese type 2 diabetes as a secondary outcome[11]. The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study showed a significant effect of prior intensive treatment (IT) on estimated glomerular filtration rate (eGFR) down to a level of 45 mL/min/1.73 m^2 in patients with type 1 diabetes[12]. However, it has remained unclear that intensified multifactorial treatment can prevent the progression of advanced-stage DKD to ESRD. To clarify the efficacy of intensified multifactorial intervention on the progression of DKD in an advanced stage, we carried out a clinical study – the Diabetic Nephropathy Remission and Regression Team Trial in Japan (DNETT-Japan)[13]. DNETT-Japan is a multicenter, randomized, open-label, parallel-group trial to clarify whether intensive multifactorial intervention, including behavioral modifications and pharmacological intervention, can prevent the progression to ESRD in patients with type 2 diabetes with overt proteinuria. As described in the previous study, DNETT-Japan includes two protocols[13]. In the present study, we analyzed the results of protocol B, in which the patients with advanced-stage DKD are included.

METHODS

Trial design

The trial design was described previously[13]. Briefly, this study was a multicenter randomized, open, parallel trial carried out in Japan (Clinical Trials gov number, NCT00253786). The trial was approved by the institutional review board at each trial site, and carried out in accordance with the principles of the Declaration of Helsinki. All participants were informed fully by the investigators and gave written informed consent before trial entry. Members of the steering committee designed the trial, supervised its conduct and were responsible for reporting the results.

Patients

In a 2-month screening period, patients with type 2 diabetes who met the inclusion and exclusion criteria were enrolled in the trial (Table S1)[13]. Briefly, Japanese adults aged 20–75 years with type 2 diabetes, two consecutive urinary albumin-to-creatinine ratio (UACR) of ≥300 mg/g creatinine (first morning urine) and serum creatinine level of 1.2–2.5 mg/dL (men) or 1.0–2.5 mg/dL (women) were eligible for participation[13]. Exclusion criteria are described in Table S1.

Procedures

After the 2-month screening period, patients were randomly assigned by the block method in a 1:1 ratio to the two treatment groups: the multifactorial IT group and conventional treatment (CT) group (Table S2)[13]. The active treatment period was 5 years.

Patients of the IT group were treated and cared by a project team of a doctor, nurse, dietician and pharmacologist at each site, and managed to achieve the following predefined treatment goals[13] (Table S2): (i) hemoglobin A1c (HbA1c) <6.2%; (ii) systolic blood pressure <125 mmHg and diastolic blood pressure <75 mmHg by inhibitors of renin–angiotensin system: angiotensin-converting enzyme inhibitors (ACE-Is) or angiotensin receptor blockers (ARBs); (iii) total cholesterol <180 mg/dL, low-density lipoprotein (LDL) cholesterol <100 mg/dL and high-density lipoprotein cholesterol >40 mg/dL; and (iv) total intake of protein <0.8 g/kg/day, sodium intake <5 g/day and total daily energy intake <30 kcal/kg/day. Blood pressure was measured in the sitting position, and if the target blood pressure was not reached, both ACE-I and ARB were used concomitantly (long-acting calcium channel blockers were also added, if required). 3-Hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitors were added if the LDL cholesterol level was ≥100 mg/dL. Patients in the IT group who smoked were invited to smoking cessation courses. All patients in the IT group received a multivitamin supplement (Multivitamin; Takeda Pharmaceutical Company Limited, Tokyo, Japan) daily to avoid vitamin deficiency caused by protein restriction (Table S2).

All patients visited the outpatient of each site every 3 months. Blood pressure was measured, and blood and urine samples were collected at each visit. eGFR was calculated using the modified Modification of Diet in Renal Disease formula for Japanese participants[14]. Laboratory tests of HbA1c, serum creatinine level, LDL cholesterol level, urinary protein concentration, urinary albumin concentration and urinary creatinine concentration were carried out centrally at SRL (Hachioji, Japan). Other laboratory tests were carried out at each clinical site.

Trial outcomes

The outcomes were described previously and are shown in Table S3.[13] Briefly, the primary outcome is a composite of end-stage kidney failure (chronic dialysis or renal transplantation), doubling of serum creatinine or death. The secondary outcomes are eGFR, cardiovascular event, progression of retinopathy, UACR and urinary protein-to-creatinine ratio.

Trial safety monitoring

In the middle of the intervention period, we obtained the information regarding intervention-related serious adverse events from two major clinical trials; The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial[15] and The Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET)[16]. In the ACCORD trial, the intensive-therapy regimen (targeting a HbA1c level of <6.0%) was discontinued in February 2008 because of the increased incidence of death in the intensified therapy group than in the standard therapy group (targeting a HbA1c level from 7.0 to 7.9%). In the present trial, the adverse events related to hypoglycemia were assessed by the independent study monitoring committee in 2008; however, there was no evidence suggesting a hypoglycemia-related increase in adverse events in the IT group, and the continuation of the trial was approved by the independent study monitoring committee. In the ONTARGET, it was reported that the adverse events including renal dysfunction were increased by combination therapy with ACE-Is and ARBs, which raised concerns about the safety of combination therapy in the present trial. The continuation of this trial was approved by the independent study monitoring committee in 2008, because an increase of adverse effects related to the combination therapy was not found in the IT group.

Statistical analysis

The procedure of statistical analysis was described previously[13]. Briefly, we used the full analysis set (FAS) for the primary efficacy analysis set, and per-protocol set for the secondary efficacy analysis set, as described previously[13]. We used the Kaplan–Meier method to analyze the primary end-point and cardiovascular event. The Cox proportional hazards model was used to estimate the hazard ratios with 95% confidence intervals in the event rates. The covariates were sex, age, ACE-I treatment, baseline UACR and baseline serum creatinine level.

The Kaplan–Meier method was used to compute the cumulative event rate for each defined event for each treatment group. The overall mean values of risk factors and surrogate kidney outcomes (eGFR, UACR and urinary protein-to-creatinine ratio) during follow up were compared between treatment groups by using the linear mixed effects model including treatment groups, visit times and their interaction terms. For the adjusted analysis of surrogate kidney outcomes, baseline values of each outcome were also added to the relevant liner mixed model.

The frequency of the progression of diabetic retinopathy and all adverse events during the follow-up period were compared by using the χ^2-test. The associations of the risk factors at baseline or during follow up with the development of the primary outcome among the patients were estimated by using the Cox proportional hazards model with time-dependent covariates.

The mean, median and standard deviation for the clinical test values were calculated at each measurement point[13]. A two-sided value of $P < 0.05$ was considered to be statistically significant. The SAS statistical software program, version 9.3 (SAS Institute Inc., Cary, NC, USA) was used for the statistical analysis.

The sample size was determined based on the following considerations: (i) incidence of the primary composite outcome of 40% in the CT group and 25% in the IT group; (ii) two-sided type I error rate (α) of 0.05; (iii) power of 80%; and (iv) loss-to-follow-up of 20% in the study period. We calculated a sample size of 200 subjects for each study group, which would allow an 80% power to detect differences between groups with a significance level of <0.05.

RESULTS

From September 2005 through May 2009, a total of 438 patients were screened, of whom 274 were excluded because they did not meet inclusion and exclusion criteria; 164 underwent randomization at 65 sites in Japan and were randomly assigned to IT ($n = 80$) or CT ($n = 84$; Figure 1). The mean follow-up period was 168.4 weeks (standard deviation 88.4 weeks), the median follow-up period was 162.0 weeks (interquartile range 82.1–260.4 weeks). The baseline characteristics were similar in the two groups (Table 1).

Concomitant drug treatment during the follow-up period

Blood pressure-lowering agents were used for all patients in the IT group and 97.4% of the patients in the CT group ($P = 0.17$; Table S4). ARB was used for 98.6% of the patients in the IT group and 94.8% of the patients in the CT group ($P = 0.20$). The combination therapy of ACE-I and ARB was used for more patients in the IT group (53.4%) compared with the CT group (31.3%; $P = 0.006$).

The use of oral glucose-lowering agents was similar in the two groups, except for metformin. Metformin was used by more patients in the IT group (23.9%) compared with the CT group (7.8%; $P = 0.01$). The use of insulin was similar in the two groups. Glucagon-like peptide-1 receptor agonist was used for five patients in the CT groups.

Blood glucose

Key baseline characteristics were not different in the two groups (Table 1). At baseline, the mean HbA1c was 7.1% in both treatment groups (Table 1). The overall mean HbA1c was 6.8 % (95% confidence interval [CI] 6.63–7.09) in the IT group and 6.94% in the CT group (95% CI 6.72–7.16). There was no significant difference of HbA1c between the two groups throughout the observation period (Figure S1a).

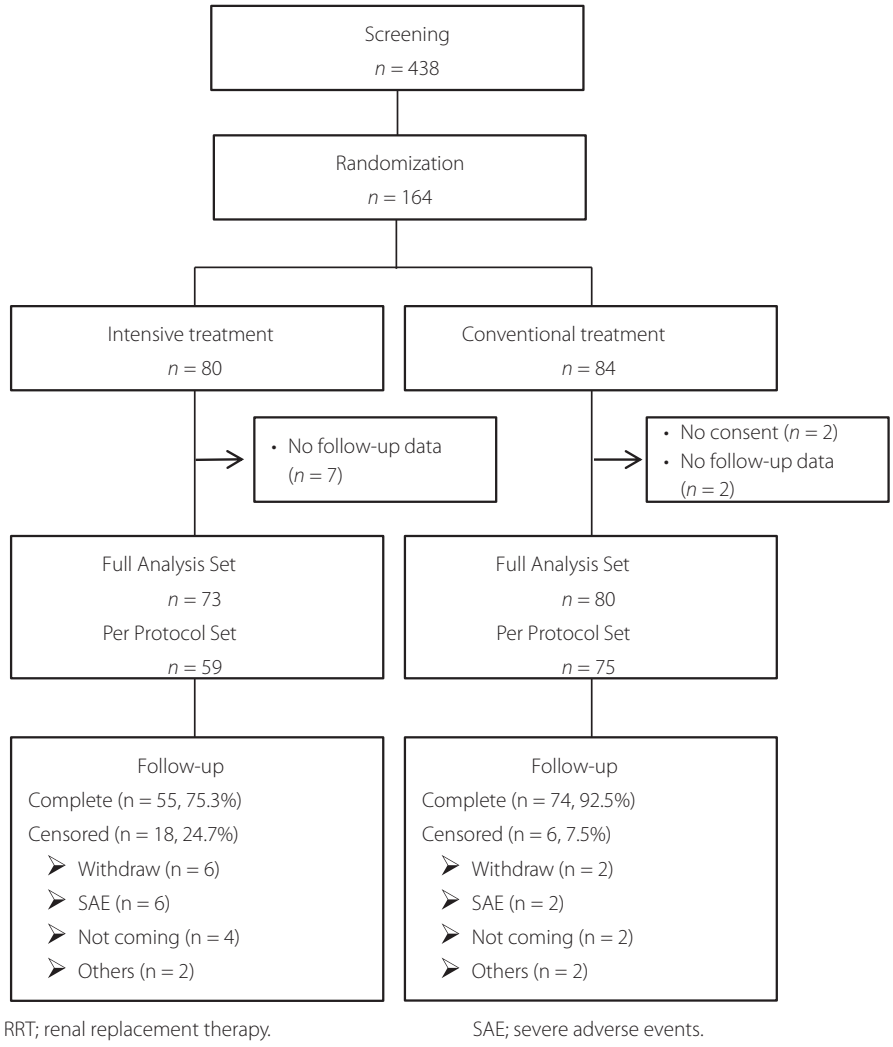

Figure 1 | Trial profile.

Blood pressure

The mean systolic and diastolic blood pressure was 138.5/76.9 mmHg in the IT group and 139.5/76.6 mmHg in the CT group at baseline. There was no significant difference in baseline blood pressure between the two groups. The overall mean systolic blood pressure was 132.2 mmHg (95% CI 129.5–134.9) in the IT group and 132.4 mmHg in the CT group (95% CI 129.9–135.0). The overall mean diastolic blood pressure was 72.2 mmHg (95% CI 70.2–14.2) in the IT group and 72.0 mmHg in the CT group (95% CI 72.2–73.9). There was no significant difference in blood pressure between the two groups through the observation period (Figure S1b).

Serum LDL cholesterol concentration

At baseline, the mean LDL cholesterol level was 118.0 mg/dL in the IT group and 118.9 mg/dL in the CT group. The serum LDL cholesterol level was not different at baseline between the two groups. The overall mean serum concentration of LDL cholesterol was 98.6 mg/dL (95% CI 92.2–105.1) in the IT group and 104.0 mg/dL in the CT group (95% CI 97.8–110.1). There was no significant difference of serum LDL cholesterol level between the two groups through the observation period, although the mean values of serum LDL cholesterol level were lower in the IT group (Figure S1c).

Waist circumference

The average waist circumference was 89.6 cm in the IT group and 91.0 cm in the CT group at baseline. There was no significant difference of waist circumference at baseline between the two groups. The overall mean waist circumference was 91.4 cm (95% CI 88.4–94.6) in the IT group and 92.3 cm (95% CI 89.5–95.1) in the CT group. There was no significant difference of waist circumference between two groups through the observation period (Figure S1d).

Table 1 | Baseline characteristics of randomized patients enrolled in the study

	Intensive (n = 73)	Conventional (n = 80)	P-value
Age (years)	56.8 (10.5)	57.6 (8.8)	0.62
Male sex (%)	58.9	55.0	0.63
Duration of diabetes† (years)	15.9 (9.6)	15.1 (8.0)	0.62
Systolic blood pressure (mmHg)	138.5 (19.7)	139.5 (17.6)	0.74
Diastolic blood pressure (mmHg)	76.9 (12.6)	76.6 (10.2)	0.88
Body mass index (kg/m^2)	25.5 (4.8)	26.5 (5.4)	0.25
Waist circumstance (cm)	89.6 (11.7)	91.0 (12.7)	0.49
Urinary chemistry			
Urinary protein-to-creatinine ratio (g/gCr)	2.0 (1.1–3.8)	2.3 (1.1–4.2)	0.58
Urinary albumin-to-creatinine ratio (mg/gCr)	1,450 (814–2,560)	1,725 (790–2,945)	0.51
Serum chemistry			
Urea nitrogen (mg/dL)	28.4 (9.3)	28.4 (9.8)	0.99
Creatinine (mg/dL)	1.6 (0.4)	1.6 (0.4)	0.92
Estimated glomerular filtration rate (mL/min/1.73 m^2)	40.1 (11.4)	39.5 (12.2)	0.76
Potassium (mEq/L)	4.6 (0.5)	4.6 (0.6)	0.54
Fasting blood glucose (mg/dL)	133.5 (43.7)	131.7 (47.3)	0.83
Hemoglobin A1c (%)	7.1 (1.4)	7.1 (1.1)	0.92
Total cholesterol (mg/dL)	205.4 (46.9)	207.6 (49)	0.78
HDL cholesterol	54.3 (17)	56 (22.2)	0.61
LDL cholesterol	118 (36.3)	118.9 (36.3)	0.88
Uric acid (mg/dL)	6.9 (1.6)	7 (1.2)	0.77
Total protein (mg/dL)	6.7 (0.6)	6.6 (0.9)	0.16
Albumin (mg/dL)		3.6 (0.6)	0.33
Total bilirubin (mg/dL)	0.5 (0.2)	0.5 (0.1)	0.75
Aspartate aminotransferase (IU/L)	20.7 (6.6)	21.5 (8.2)	0.51
Alanine aminotransferase (IU/L)	17.7 (7.9)	20.3 (11)	0.10
Gamma glutamyl transpeptidase (IU/L)	28.8 (27.2)	36.2 (35.9)	0.18
Lactate dehydrogenase (IU/L)	217.1 (48.7)	228.8 (63.5)	0.23
Hemoglobin (g/dL)	11.6 (1.6)	11.9 (2)	0.46
Other factors			
Smoking status (%)			
Never smoker	50.7	50.0	0.99
Ex-smoker	28.8	30.0	
Current smoker	20.6	20.0	
Alcohol intakes (%)	28.8	27.9	0.90
Diabetic retinopathy status (%)			
No	7.5	13.2	0.32
Simple	23.9	32.9	
Pre-proliferative	20.9	18.4	
Proliferative	47.8	35.5	
Electrocardiogram abnormalities (%)	15.3	11.3	0.46
Diet therapy (%)	97.3	97.5	0.93
Therapeutic exercise (%)	42.5	42.5	1.00

Values are shown as mean (standard deviation), median (interquartile range) or frequency. †Numbers of participants with available data of duration of diabetes were 70 participants for the intensive group and 71 participants for the conventional group.

Smoking status

Smoking status was not different between the two groups. The frequency of being a current smoker during the follow-up period was 20.6% in the IT group and 20.0% in CT group.

Primary outcome

IT tended to reduce the risk of primary end-points, consisting of end-stage kidney failure, doubling of serum creatinine level or death, as compared with CT, but the difference between the treatment groups did not reach the statistically significant level (hazard ratio [HR] 0.69, 95% CI 0.43–1.11, P = 0.13; Figure 2). For each component of the composite primary outcome, there was no significant difference between the IT group and the CT group in both the full analysis set and per-protocol set (Figure 3).

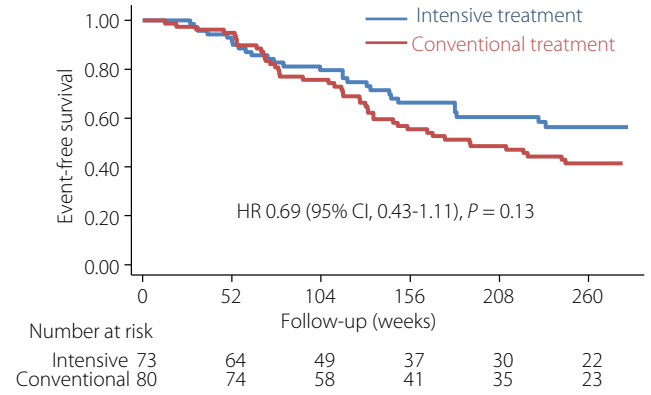

Figure 2 | Event-free survival of primary outcomes (dialysis, doubling of serum creatinine or death) in the randomized patients (full analysis set). The effects of treatment (hazard ratios with 95% confidence intervals, and *P*-values) were estimated by using a Cox proportional hazards model. CI, confidence interval; HR, hazard ratio.

Secondary outcomes

Cardiovascular events were not changed between IT and CT (HR 0.56, 95% CI 0.19–1.64 $P = 0.29$). Progression of diabetic retinopathy was reached in four patients in the IT group (5.5%) and seven patients in the CT group (8.8%; $P = 0.43$). Overall geometric mean UACR was 986.7 mg/gCr in the IT group and 1,258.7 g/gCr in the CT group (Figure S2a). Overall geometric mean urinary protein excretion was 1.47 g/gCr in the IT group and 1.84 g/gCr in the CT group (Figure S2B). There was no significant difference of urinary albumin excretion and urinary protein excretion between the two groups. The overall mean eGFR was 31.1 mL/min/1.73 m^2 in the IT group and 29.2 mL/min/1.73 m^2 in the CT group, without significant difference (Figure S2c).

Relative risk of outcomes

The relationship between the risk factors at baseline or during the follow-up period and the development of primary composite outcome was analyzed using the Cox proportional hazards model (Table 2). Serum LDL cholesterol and use of statin were significantly related to the improvement of primary composite outcome. Combination therapy of ACE-I and ARB did not significantly contribute to the outcome. In the baseline risk factors, UACR (HR 3.00, 95% CI 1.91–4.72, $P < 0.0001$)) and eGFR (HR 1.49, 95% CI 1.13–1.96, $P = 0.0004$) were significantly related to the primary composite outcome (Table 2).

Adverse events

A total of 154 adverse events, including 39 severe adverse events, occurred in this trial (Table S5). The incidence of

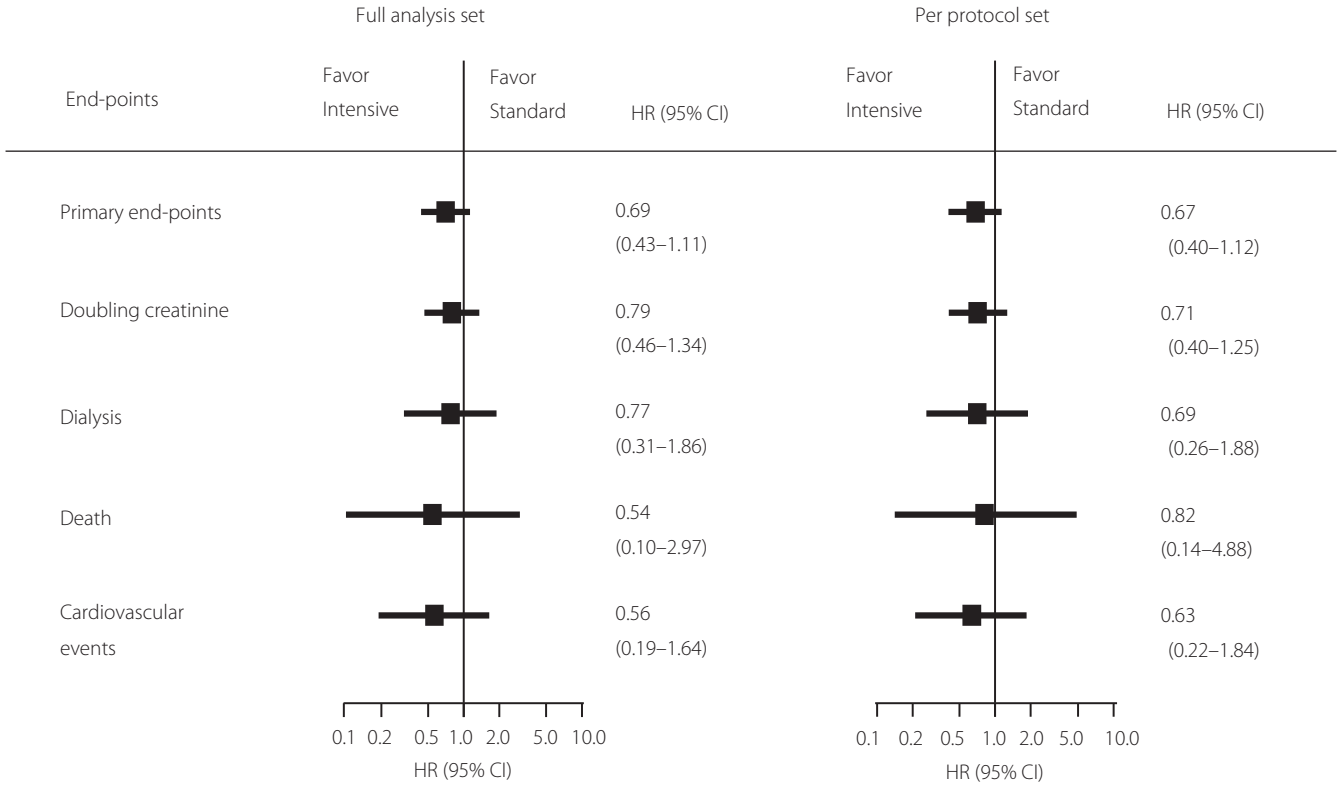

Figure 3 | Effects of trial treatment on each outcome in the randomized patients. The effects of treatment (hazard ratios with 95% confidence intervals and *P* -values) were estimated by using a Cox proportional hazards model. CI, confidence interval; HR, hazard ratio.

Table 2 | Relationship between the risk factors at baseline or during follow up and the development of the primary end-point among the patients (full analysis set)

Variables	Unit	HR (95% CI)	*P*
Risk factors during follow up			
Systolic blood pressure (mmHg)	per 10 mmHg increment	1.07 (0.93–1.23)	0.35
Serum LDL cholesterol (mg/dL)	per 10 mg/dL increment	1.14 (1.05–1.23)	0.001
Serum HDL cholesterol (mg/dL)	per 10 mg/dL decrement	0.93 (0.81–1.08)	0.37
HbA1c (%)	per 1% increment	0.96 (0.78–1.2)	0.74
Combination of ACE-I + ARB	vs no combination of ACE-I + ARB	0.79 (0.46–1.36)	0.4
Statin use	vs no statin use	0.53 (0.28–0.998)	0.049
Risk factors at baseline			
Age (years)	per 5 years older	0.99 (0.85–1.16)	0.93
Men	vs women	1.92 (0.99–3.7)	0.05
eGFR (mL/min/1.73 m^2)	per 10 mL/min/1.73 m^2 decrement	1.49 (1.13–1.96)	0.0004
Log transformed UACR (log[mg/gCr])	per 1 log(mg/gCr) increment	3.00 (1.91–4.72)	<0.0001
Hemoglobin (g/dL)	per 1 g/dL increment	1.02 (0.86–1.21)	0.84
Electrogram abnormalities	vs no	0.92 (0.41–2.07)	0.85
Diet therapy	vs no	1.05 (0.12–9.02)	0.97
Therapeutic exercise	vs no	1.29 (0.74–2.22)	0.37
Current smoker	vs no	0.89 (0.43–1.83)	0.75
Alcohol intakes	vs no	0.78 (0.4–1.52)	0.47

The model included the risk factors during follow up (systolic blood pressure, serum high-density lipoprotein [HDL] cholesterol, serum low-density lipoprotein [LDL] cholesterol, hemoglobin A1c [HbA1c], statin use and combined use of angiotensin-converting enzyme inhibitor [ACE-I] and angiotensin-receptor blocker [ARB]) and the other risk factors at baseline. eGFR, estimated glomerular filtration rate; UACR, urinary albumin-to-creatinine ratio.

adverse events was not significantly different between the two groups (32 in the IT group and 35 in the CT group, $P = 0.95$). There was also no significant difference in severe adverse events, life-threatening adverse events, adverse events requiring hospital admission and adverse events with physical disability between the two groups (16 in the IT group and 23 in the CT group, $P = 0.31$). As for the event of death, one deceased patient in the IT group was not reported as an adverse event, because detailed information of death was not obtained.

DISCUSSION

In the current study, IT tended to reduce the risk of the primary end-points compared with CT, but the difference between the treatment groups did not reach the statistically significant level.

It is clear that blood glucose lowering prevents new onset or progression of early-stage DKD[17–22]. Recent meta-analysis has suggested that intensive glucose control decreases the risk for surrogate renal outcomes; microalbuminuria and macroalbuminuria. However, it has remained unclear whether intensive glycemic control decreases the risk for renal outcomes, including doubling of the serum creatinine concentration, ESRD or death[23]. In DNETT-Japan, Cox regression analyses did not show the superiority of strict blood glucose control. It might be possible that this trial could not show the efficacy of blood glucose control, because the HbA1c level was controlled <7.0% in both groups and there was little difference.

Antihypertensive treatment is another substantial strategy for the therapy of DKD[24,25]. Several guidelines recommend maintaining blood pressure <130/80 mmHg in patients with DKD[26,27]. In the present trial, the average level of systolic/diastolic blood pressure during the trial period was 132/72 mmHg in both groups, and there was no difference between the two groups. Although blood pressure was considerably well managed, it seems to be difficult to achieve the treatment goal in the IT group. In particular, in the first year, the average level of blood pressure was elevated in the IT group, because some patients resistant to antihypertensive drugs were included.

There have been several randomized controlled trials that showed the strong effect of ARBs and ACE-Is on DKD[28–30]. In the current trial, 100% of the patients in the IT group and 97.4% in the CT group were taking renin–angiotensin system inhibitors. Dual blockade of the renin–angiotensin system did not significantly contribute to the outcome, whereas the incidence of adverse events was not increased by the dual blockade. A previous meta-analysis showed that reduction of proteinuria by ACE-Is and ARB was similar, but their combination was more effective than either drug alone[31]. However, in the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET), no renal benefit was shown by combination treatment, and the risk of hyperkalemia and acute kidney injury was increased[16]. In addition, in The Veterans Affairs Nephropathy in Diabetes (VA NEPHRON-D) study, combination treatment of ACE-I and ARB was

associated with an increased risk of adverse events in patients with DKD[32]. Combination therapy with ACEIs and ARB seems not to be beneficial for patients with advanced-stage DKD compared with monotherapy in the current trial.

Interestingly, a decrease in serum LDL cholesterol level and use of statin are significantly related to the decrease in primary composite outcome. Statin treatment reduces the risk for cardiovascular diseases in patients with chronic kidney disease, including DKD[33]. In contrast, it is still controversial whether lipid-lowering therapy using statins is beneficial for the development of DKD or not. Several studies and systematic reviews showed that statin reduces proteinuria in patients with DKD, although it is uncertain whether statin prevents ESRD[34–36]. Statin treatment is recommended for patients with DKD in the Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guideline[37]. It has been suggested that pleiotropic effects of statin might be beneficial for DKD in animal experiments[38]. It has remained unclear whether LDL cholesterol lowering per se was effective for the prevention of the primary end-point, because we cannot statistically analyze the effects of LDL cholesterol lowering independent from the effect of statin in the present study. The results from the current trial suggest that LDL cholesterol lowering by statin was effective on the primary composite outcome in patients with advanced-stage DKD. Recent clinical trials showed the protective effect of sodium–glucose cotransporter 2 inhibitors and glucagon-like peptide-1 receptor agonists on DKD[39,40]. Sodium–glucose cotransporter 2 inhibitor and glucagon-like peptide-1 receptor agonist are new options to improve the prognosis of DKD.

The limitations of this trial are as follows. The number of patients enrolled in the analysis was small and the statistical power was not sufficient. The rate of continuation of this trial was lower in the IT group. In addition, the majority of the patients in the IT group were not able to achieve the predefined treatment goals, and therefore, there was little difference between two groups. One of the explanations might be that the patients in both groups were treated by the same doctors, who are diabetologists or nephrologists at each site. The factor that contributed to the tendency of decrease in renal events by IT was unclear. The lower level of serum LDL cholesterol might have contributed.

In conclusion, there was an overall trend toward a lower risk of the development of kidney events in the IT group than in the CT group in the present trial, but the benefit of IT could not be confirmed statistically. Lipid control by statin was associated with a lower risk of kidney events in addition to strict control of blood glucose and blood pressure. Further follow-up study is required to clarify the efficacy of multifactorial intensified intervention on delaying progression of DKD to ESRD.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1 | Mean hemoglobin A1c, blood pressure, serum low-density lipoprotein cholesterol and waist circumference during the follow-up period among the randomized patients.

Figure S2 | Mean urinary protein-to-creatinine ratio, urinary albumin-to-creatinine ratio and estimated glomerular filtration rate during the follow-up period.

Table S1 | Eligibility criteria.

Table S2 | Treatment goals and interventions for conventional and intensive treatment groups.

Table S3 | Primary and secondary end-points.

Table S4 | Concomitant treatments during the follow-up period.

Table S5 | Number and frequency of adverse event for each treatment group.

Appendix S1 | List of clinical sites and participating investigators. List of committee members.