Primary Prevention of Macroangiopathy in Patients With Short-Duration Type 2 Diabetes by Intensified Multifactorial Intervention

Seven-year follow-up of diabetes complications in Chinese

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OBJECTIVE—To explore whether intensified, multifactorial intervention could prevent macrovascular disease in patients with recently diagnosed type 2 diabetes.

RESEARCH DESIGN AND METHODS—A total of 150 type 2 diabetic patients, with disease duration of <1 year and without clinical arteriosclerotic disease or subclinical atherosclerotic signs confirmed by ultrasonographic scanning of three conducting arteries, were randomized into an intensive intervention group and a conventional intervention group. They then received intensive, multifactorial intervention or conventional intervention over 7 years of follow-up. The patients' common carotid intima-media thicknesses (CC-IMTs) were measured every year. The primary outcome was the time to the first occurrence of CC-IMTs ≥1.0 mm and/or development of atherosclerosis plaques in the carotid artery. The secondary outcome was clinical evidence of cardiovascular disease.

RESULTS—A total of 70 patients in the intensive group and 68 patients in the conventional group completed the 7-year follow-up. Subclinical macrovascular (primary) outcomes occurred in seven cases in the intensive group and 22 cases in the conventional group for a cumulative prevalence of 10.00 and 32.35%, respectively ($P < 0.05$). No significant differences between the two groups were observed regarding the secondary outcome.

CONCLUSIONS—Primary prevention of macrovascular diseases can be achieved through intensified, multifactorial intervention in patients with short-duration type 2 diabetes. Type 2 diabetic patients should undergo intensive multifactorial interventions with individual targets for the prevention of macrovascular diseases.

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The prevalence of diabetes, especially type 2 diabetes, is increasing markedly worldwide, including in China (1,2). The chronic complications of diabetes seriously affect quality of life and result in a significant decrease in life expectancy; they also impose a heavy economic burden. Therefore, the prevention and treatment of chronic diabetes complications have become a considerable medical problem attracting worldwide attention.

The macrovascular complications of diabetes, which can lead to cardiovascular diseases, are the major cause of death in patients with type 2 diabetes. A reduction in all-cause mortality among individuals with diabetes has occurred over time; however, the mortality rate from cardiovascular causes among individuals with diabetes remains approximately twofold higher than the rate in those without diabetes (3,4). In recent years, the results of several large-scale clinical trials have illustrated that interventions for the various atherosclerosis (AS) risk factors in patients with type 2 diabetes can reduce the risk of cardiovascular death by different degrees, although it remains controversial whether intensive glucose control can help prevent cardiovascular events. The Steno-2 study, which was conducted in patients with type 2 diabetes and microalbuminuria of any duration, demonstrated that target-driven, long-term, intensified interventions aimed at multiple risk factors can reduce the risk of cardiovascular and microvascular events by ~50% (5,6).

Thickening of the common carotid intima-media (CC-IMT) is considered a surrogate marker of early AS and vascular remodeling because it is correlated with all of the traditional vascular risk factors (7). Monitoring a combination of CC-IMT thickening and plaque formation could significantly improve the prediction of cardiovascular events (8). Moreover, these factors can be assessed quickly, noninvasively, and inexpensively with high-resolution ultrasound.

Thus, we designed a prospective study in which patients with short-duration type 2 diabetes without AS were assigned to receive a combined intervention targeting multiple risk factors of AS, and their CC-IMTs were measured to explore whether intensified, multifactorial intervention could prevent the occurrence of

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macrovascular disease over a 7-year period.

RESEARCH DESIGN AND METHODS—In brief, 150 patients with type 2 diabetes, diagnosed according to the World Health Organization criteria published in 1999, were recruited at the First Affiliated Hospital of Dalian Medical University. The enrollment took place from 1 April 2002 to 31 December 2002. The design of our parallel controlled study has previously been described (9).

The protocol for this study was in accordance with the Declaration of Helsinki and was approved by the ethics committee of the First Affiliated Hospital of Dalian Medical University. All of the patients provided written informed consent before enrollment and underwent a 7-year clinical follow-up.

The inclusion criteria were as follows: *1*) age 35–70 years; *2*) diabetes duration <1 year; *3*) no previous histories or present characteristics of cardiovascular diseases, cerebral vascular diseases, or peripheral artery disease as assessed by thorough examinations before enrollment; and *4*) IMT values in the conducting arteries (common carotid artery, femoral artery, and iliac artery) <1.0 mm and no AS plaques detected by ultrasonography (10).

Ultrasonographic scanning of the common carotid artery (between 5 cm upstream and 5 cm downstream of the carotid bulb), the femoral artery (within 10 cm upstream of the femoral artery bifurcation), and the iliac artery (within 10 cm downstream of the abdominal aorta bifurcation) was performed by designated physicians who were unaware of the clinical characteristics of the subjects.

The exclusion criteria included the following: *1*) type 1 diabetes or other special type of diabetes; *2*) acute diabetes complications within the previous 6 months, including diabetic ketoacidosis, hyperglycemic hyperosmolar status, lactic acidosis, and hypoglycemic coma; *3*) renal failure (serum creatinine >106 μmol/L) or hepatic dysfunction (serum alanine aminotransferase >80 units/L); *4*) diagnosis of coronary heart disease, cerebral vascular stroke, and/or peripheral artery disease; and *5*) a conducting artery IMT ≥1.0 mm or AS plaques detected by ultrasonography.

Sex, age, BMI, waist-to-hip ratio, systolic blood pressure (SBP), diastolic blood pressure (DBP), and resting 12-lead electrocardiogram were recorded upon enrollment in the clinical trial. Fasting serum total cholesterol, triglyceride, HDL cholesterol (HDL-C), LDL cholesterol (LDL-C), creatinine, and alanine aminotransferase levels, along with plasma glucose, were measured by routine laboratory techniques. HbA_{1c} was measured by high-performance liquid chromatography.

A total of 268 patients underwent screening, and 150 patients met the inclusion criteria. The 150 patients were randomized into an intensive, multifactorial intervention group or a conventional intervention group as shown in Fig. 1. The total duration of the follow-up was 7 years.

Intensive treatment protocol

Physical examination and plasma glucose (fasting plasma glucose [FPG] and 2-h plasma glucose [2hPG]) measurements were conducted monthly. HbA_{1c}, blood lipid, serum creatinine, and alanine aminotransferase levels were measured every 6 months. CC-IMTs and electrocardiograms were analyzed yearly. During the consultations, a healthy lifestyle (e.g., at least three 30-min sessions of light to moderate exercise per week) and diet (e.g., obtain 60–70% of daily caloric intake from carbohydrates from whole grains, fruits, and vegetables, together with monounsaturated fat) were recommended using one-to-one teaching or group counseling supplemented with audiovisual and printed materials monthly.

Hypoglycemic strategy

Overweight patients (BMI >24 kg/m^2) received metformin (starting at 0.25 g three times daily; maximum 0.5 g three times daily); nonoverweight patients received glipizide (starting at 2.5 mg three times daily; maximum 10 mg three times daily). At the next follow-up, if FPG was >7.0 mmol/L, 2hPG was >10.0 mmol/L, and/or HbA_{1c} was >7.0%, metformin was

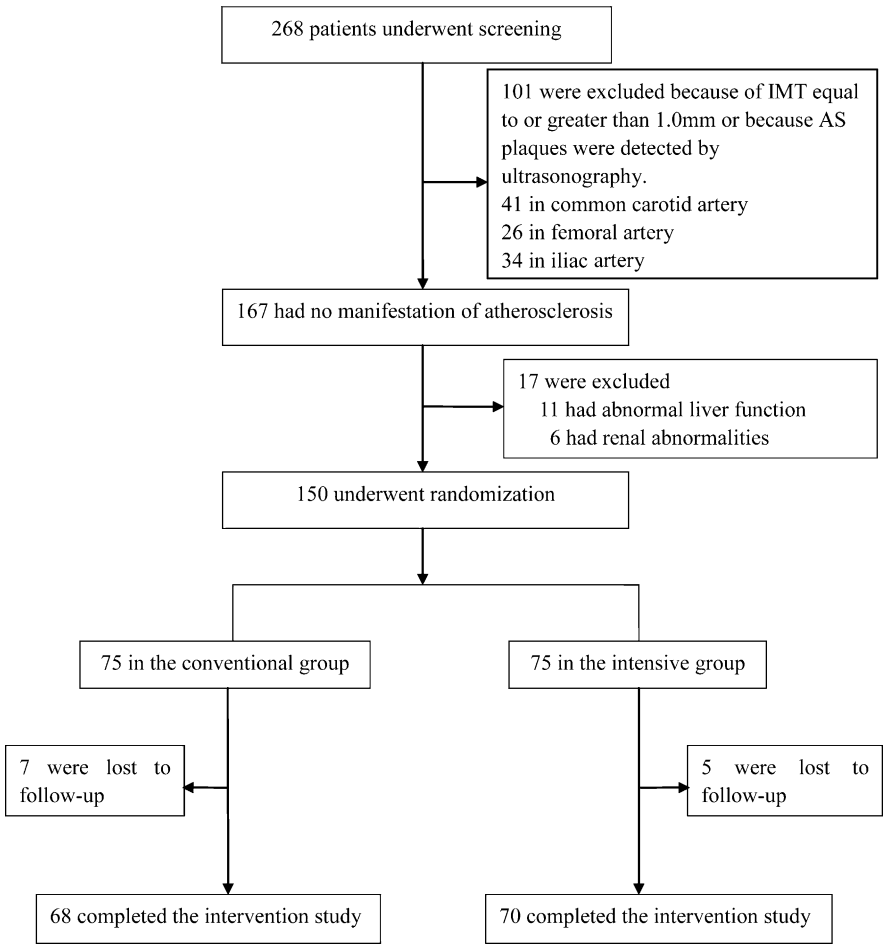

Figure 1—*Enrollment and outcomes.*

Table 1—*HbA_{1c}, FPG, SBP, DBP, LDL-C, HDL-C, triglyceride, and total cholesterol of the two groups at baseline and at every follow-up year*

	Baseline		Year 1		Year 2		Year 3	
	Conventional group	Intensive group	Conventional group	Intensive group	Conventional group	Intensive group	Conventional group	Intensive group
HbA_{1c} (%)	8.69 ± 1.74	8.86 ± 1.66	7.81 ± 0.65	5.44 ± 0.56*†	7.92 ± 0.81	5.66 ± 0.79*†	7.53 ± 1.61*	6.11 ± 0.97*†
FPG (mmol/L)	9.95 ± 0.74	9.98 ± 2.81	6.95 ± 1.03*	6.86 ± 1.43*	7.25 ± 2.03*	6.80 ± 3.88*†	8.22 ± 2.97	6.94 ± 4.56*†
SBP (mmHg)	128.80 ± 11.30	129.10 ± 15.20	123.45 ± 12.42	121.58 ± 14.21*	125.38 ± 12.77	120.67 ± 13.99*	127.35 ± 13.62	123.28 ± 13.18
DBP (mmHg)	76.90 ± 6.40	79.80 ± 11.80	78.91 ± 7.3	78.73 ± 9.74	79.43 ± 9.07	77.85 ± 9.05	80.30 ± 10.13	78.47 ± 9.53
LDL-C (mmol/L)	3.00 ± 0.52	2.99 ± 0.61	2.62 ± 0.61	2.56 ± 0.55	2.74 ± 0.56	2.57 ± 0.46	3.02 ± 0.63	2.59 ± 0.44
HDL-C (mmol/L)	1.01 ± 0.29	0.94 ± 0.72	1.14 ± 0.25	1.08 ± 0.33	1.04 ± 0.30	1.06 ± 0.48	1.19 ± 0.36	1.03 ± 0.39
TG (mmol/L)	2.28 ± 0.54	3.05 ± 1.46	1.62 ± 1.12*	1.55 ± 1.29*	1.61 ± 1.54*	1.54 ± 1.26*	1.75 ± 1.45*	1.85 ± 4.28
TC (mmol/L)	5.95 ± 1.15	5.92 ± 1.04	5.01 ± 1.15	4.42 ± 0.73*†	5.43 ± 1.09	4.49 ± 0.81*†	5.13 ± 0.98	4.49 ± 0.71*†
	Year 4		Year 5		Year 6		Year 7	
	Conventional group	Intensive group	Conventional group	Intensive group	Conventional group	Intensive group	Conventional group	Intensive group
HbA_{1c} (%)	6.43 ± 1.64*	5.96 ± 1.48*†	7.14 ± 1.06*	6.46 ± 1.15*	7.03 ± 1.72*	6.75 ± 1.08*	7.98 ± 1.95	7.13 ± 1.22*†
FPG (mmol/L)	7.64 ± 1.95	7.0 ± 1.76*	7.26 ± 0.64*	6.54 ± 1.81*	8.09 ± 1.79	7.35 ± 1.83*	8.33 ± 1.23	7.36 ± 1.37*†
SBP (mmHg)	128.16 ± 12.76	126.05 ± 11.66	121.40 ± 11.10*	120.50 ± 8.70*	128.57 ± 12.31	120.69 ± 9.09*†	127.78 ± 12.13	120.72 ± 9.61*†
DBP (mmHg)	79.48 ± 9.40	78.34 ± 7.44	73.90 ± 5.90	76.10 ± 7.10	78.08 ± 5.76	75.80 ± 5.72†	79.44 ± 8.47	76.20 ± 4.43
LDL-C (mmol/L)	3.04 ± 0.66	2.74 ± 0.43	2.42 ± 0.72	2.63 ± 0.63	3.10 ± 0.28	2.70 ± 0.55	3.03 ± 0.19	2.75 ± 0.43
HDL-C (mmol/L)	1.12 ± 0.59	1.05 ± 0.34	1.01 ± 0.14	0.99 ± 0.15	1.09 ± 0.28	1.11 ± 0.26	1.10 ± 0.37	1.02 ± 0.20
TG (mmol/L)	1.51 ± 0.78*	1.91 ± 1.62*	1.98 ± 0.73*	1.68 ± 1.05*	1.40 ± 0.55*	1.70 ± 1.36*	1.83 ± 1.06*	1.7 ± 1.23*
TC (mmol/L)	5.15 ± 1.12	4.61 ± 0.84*†	4.83 ± 0.56	4.50 ± 0.75*	5.19 ± 0.77	4.68 ± 0.93*†	5.10 ± 1.21	4.57 ± 0.84*†

TC, total cholesterol; TG, triglyceride. *$P < 0.05$, compared with baseline. †$P < 0.05$, compared with the conventional group.

prescribed to the nonoverweight patients and glipizide to the overweight patients. Acarbose was prescribed to only those patients with 2hPG still >10.0 mmol/L after any type of hypoglycemic administration. Insulin supplementation was recommended for patients whose HbA_{1c} remained >7.0% on maximal doses of oral agents or drug combinations and in patients who had intolerable adverse reactions to oral drugs. Premixed, combined human insulin (30% short-acting insulin and 70% neutral protamine Hagedorn insulin) was the first choice.

Antihypertensive strategy

Patients primarily received ACE inhibitor and/or calcium channel blockers; if unsuccessful, a diuretic and/or β-blocker was added as a supplemental therapy. The blood pressure target was 130/85 mmHg.

Lipid-lowering strategy

Statins or a Chinese herb complex called Xue-Zhi-Kang was recommended to patients with hypercholesterolemia and/or high levels of serum LDL-C, and fenofibrate was prescribed to patients with hypertriglyceridemia. Total cholesterol within 4.66 mmol/L, triglyceride within 1.7 mmol/L, and LDL-C within 2.6 mmol/L were considered controlled. Low-dose acetylsalicylic acid (100 mg/day) was also recommended to all of the patients who did not exhibit contraindications.

The dosages of the drugs were modulated every month based on the levels of FPG, HbA_{1c}, blood pressure, and blood lipid until target values were achieved. The patients were treated under the guidance of specialists, and all of the examinations and some of the drugs were freely provided.

Conventional treatment protocol

In the conventional group, loose outpatient management was performed without intensive intervention targets, and the drugs were not provided freely. These patients could go to any hospital at any frequency that they chose. The same research indices as those measured in the intensive group were measured each year free of charge in our center.

Primary and secondary outcomes

The primary outcome (subclinical AS) was the time to the first occurrence of CC-IMT ≥1.0 mm and/or development of AS plaques in the carotid artery. The secondary outcome (clinical AS) was clinical evidence of cardiovascular

diseases, such as asymptomatic myocardial ischemia (ST segment depression and/or T wave inversion on electrocardiogram), angina pectoris, myocardial infarction, transient ischemic attack, stroke, intermittent claudication, or critical limb ischemia.

Statistical analyses

SPSS 13.0 was used for the statistical analysis. Normally distributed data are presented as means ± SD. An independent *t* test was adopted for group comparisons, and a pair bond *t* test was adopted for intergroup comparisons. Numerical data are presented as absolute frequency or percentage, and the χ^2 test was used for comparison between groups. Statistical significance was accepted at $P < 0.05$.

RESULTS—A total of 268 patients who had type 2 diabetes for <1 year and no clinical AS underwent the screening, and 101 (37.69%) were found to have subclinical AS. One hundred and fifty patients who showed no signs of AS on ultrasound were randomly divided into an intensive group and a conventional group, with 75 cases in each group. Seventy patients in the intensive group and 68 patients in the conventional group finished the 7-year follow-up (6.67 and 9.33% lost to follow-up, respectively).

The biochemical characteristics of the patients at baseline have previously been described (9). The data at every follow-up year and at the end of the follow-up period (7 years) are shown in Table 1 and Supplementary Fig. 1. The two study groups were similar at baseline but differed significantly at the end of the intervention period, indicating that intensive therapy was superior to conventional therapy in controlling the level of FPG, SBP, HbA_{1c}, and fasting serum total cholesterol.

After 7 years of follow-up, among the 68 patients in the conventional group, IMTs ≥1.0 mm and/or AS plaques in the carotid artery were observed in 22 patients; 1 patient developed myocardial infarction, 4 patients suffered from angina pectoris, 1 patient developed silent myocardial ischemia (electrocardiogram showed that the ST segment was descended, and the T wave was low and calm in contrast to baseline), 2 patients had a transient ischemic attack, and 1 patient developed

Table 2—*Cumulative macrovascular end points at every follow-up year*

	Baseline		Year 1		Year 2		Year 3	
	Conventional group	Intensive group	Conventional group	Intensive group	Conventional group	Intensive group	Conventional group	Intensive group
Follow-up events (*n*)	75	75	75	75	74	75	73	74
Thickened IMT/AS plaques (*n*)	0	0	2	1	5	2	7	2
Subclinical macrovascular outcomes	0	0	2.67	1.33	6.76	2.67	9.59	2.70
Angina pectoris	0	0	2	0	2	0	3	0
Myocardial infarction	0	0	0	0	0	0	0	0
Silent myocardial ischemia	0	0	0	0	0	0	1	0
Transient ischemic attack	0	0	0	0	0	0	0	0
Intermittent claudication	0	0	0	0	0	0	0	0
Sudden death	0	0	0	0	0	0	0	1
Total clinical macrovascular end events (*n*)	0	0	2	0	2	0	4	1
Final clinical macrovascular events	0	0	2.67	0	2.70	0	5.48	1.35

	Year 4		Year 5		Year 6		Year 7	
	Conventional group	Intensive group	Conventional group	Intensive group	Conventional group	Intensive group	Conventional group	Intensive group
Follow-up events (*n*)	71	73	68	71	68	70	68	70
Thickened IMT/AS plaques (*n*)	9	2	9	4	13	5	22	7
Final subclinical macrovascular outcomes	12.68	2.74*	13.24	5.63	19.12	7.14*	32.35	10.00*
Angina pectoris	3	1	3	1	4	1	4	2
Myocardial infarction	0	0	1	0	1	0	1	1
Silent myocardial ischemia	1	0	1	0	1	1	1	1
Transient ischemic attack	0	0	0	0	1	0	2	0
Intermittent claudication	0	0	0	0	0	0	1	0
Sudden death	0	1	0	1	0	1	0	1
Total clinical macrovascular end events (*n*)	4	2	5	2	7	3	9	5
Final clinical macrovascular events	5.63	2.74	7.35	2.82	10.29	4.29	13.24	7.14

Data are percent unless otherwise indicated. *$P < 0.05$, compared with the conventional group.

intermittent claudication. Thus, clinical macrovascular events occurred in nine cases. Five of the nine patients who developed clinical macrovascular events also had increased CC-IMTs and/or AS plaques in the common carotid arteries. However, among the 70 patients in the intensive group, IMTs ≥1.0 mm and/or AS plaques in the carotid arteries were observed in only 7 patients. One patient developed myocardial infarction in addition to increased CC-IMT, two patients suffered from angina pectoris, and one of these patients also had increased CC-IMT. One patient had silent myocardial ischemia, and one patient died suddenly. (No autopsy was performed; the cause of death was unknown and was considered relevant to diabetic macroangiopathy.) In total, final clinical macrovascular events occurred in five cases in the intensive group. Two of the five patients who developed clinical macrovascular events also had increased CC-IMTs and/or AS plaques in the common carotid arteries. The difference in the frequency of subclinical macrovascular outcomes between the two groups was significant ($P = 0.002$); however, no significant difference in the frequency of clinical macrovascular events was observed between the two groups ($P = 0.271$) (Table 2 and Fig. 2).

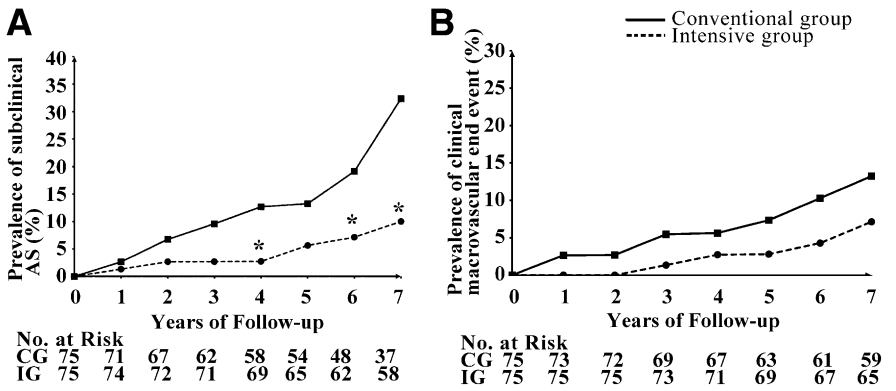

Figure 2—*Comparison of the prevalence of macrovascular end events in every follow-up year.* A: *Comparison of the prevalence of final subclinical macrovascular end points.* B: *Comparison of the prevalence of final clinical macrovascular events. CG, conventional group; IG, intensive group. *Compared with the conventional group,* $P < 0.05$.

CONCLUSIONS—Type 2 diabetes is usually accompanied by a number of cardiovascular risk factors, including hypertension, dyslipidemia, and platelet dysfunction. Trials of intensified interventions for single risk factors in patients with type 2 diabetes, including the UK Prospective Diabetes Study (UKPDS), Collaborative Atorvastatin Diabetes Study (CARDS), Microalbuminuria Cardiovascular Renal Outcomes–Heart Outcomes Prevention Evaluation (MICRO-HOPE) study, and Veterans Affairs Diabetes Trial (VADT), have demonstrated efficacy in reducing the development and progression of both micro- and macrovascular complications (11–14), although studies on intensive glucose control alone in patients with type 2 diabetes have reached conflicting conclusions regarding the incidence of major cardiovascular events or death (15–17). However, only a delayed effect in reducing the incidence of cardiovascular events was observed in UKPDS (18), suggesting that long-term observation might be necessary for the study of macroangiopathy in recent-onset type 2 diabetes and that cardiovascular events or death cannot be taken as indicators if the investigators want to draw conclusions about diabetes in the short term. In our study, we implemented a multifactorial intervention aimed at primary prevention for patients with type 2 diabetes without any manifestation of AS that used macrovascular end points, including subclinical AS lesions, as the evaluation index. We measured the preventive efficacy after 4–7 years of intervention, expanding upon the results of UKPDS and the STENO-2 trial and strengthening their conclusions. Our approach achieved the primary prevention of diabetic macrovascular complications, implying that intensive, multifactorial intervention should be administered to type 2 diabetic patients as soon as possible to provide the most benefits.

Recent results from UKPDS suggested that the effects of blood pressure– and glucose-lowering interventions might be additive; there was a trend toward a greater benefit with a combination of intensive blood pressure– and glucose-lowering interventions. Because only a small subset of hypertensive subjects received both interventions, UKPDS had insufficient power to determine conclusively whether the effects of the treatments were additive in this group or in the broader population with type 2 diabetes (19). The new results of the Action in Diabetes and Vascular Disease (ADVANCE) trial demonstrated that a combined approach of routine blood pressure–lowering interventions and intensive glucose control resulted in substantial reductions in major renal events and all-cause deaths, supporting and strengthening the results of the UKPDS trial and providing further evidence for thebenefits of a multifactorial treatment approach in patients with type 2 diabetes (20). However, ADVANCE emphasized the control of only two risk factors for diabetic macroangiopathy. As demonstrated by the STENO-2 study, a target-driven, long-term, intensified intervention aimed at multiple risk factors in patients with type 2 diabetes and microalbuminuria can reduce the risk of cardiovascular and microvascular events by ~50%; furthermore, the benefits were maintained over the long term even after the randomized treatment period (5,6). However, the STENO-2 subjects were different from ours in that the statuses of their arterial intima were uncertain at baseline.

Ultrasonography to measure CC-IMT is a noninvasive test that can be used to determine the presence of coronary AS. IMT is an independent predictor of future cardiovascular events, and it is often used in research trials as a surrogate for the presence of cardiovascular disease (21–23). The 150 patients with a diabetes duration of <1 year included in our study had initial IMTs of <1.0 mm in the three conducting arteries (common carotid artery, femoral artery, and iliac artery) and no atherosclerotic plaques detected by ultrasonography in addition to an absence of clinical manifestations or history of macrovascular diseases; these patients were considered not to have AS. They then underwent intensified or conventional treatment. The reduced incidence of subclinical outcomes in the intensive group indicates that these interventions reduced the incidence of macroangiopathy, which suggests that this intensified, multifactorial intervention can produce

a marked effect on the primary prevention of macrovascular disease in patients with type 2 diabetes. No significant differences between the two groups were observed if only the secondary outcome was considered, irrespective of the primary outcome. Benefits emerged only after a relatively short period when IMTs and/or the occurrence of AS plaques were regarded as end points, implying that evidence of early-stage AS might be more important. These data also suggest that as a chronic progressive disease, subclinical AS might be considered an important index in the study of diabetic macroangiopathy.

In contrast to the uncertain follow-up frequency of those in the conventional group, the subjects in the intensive group were followed up every month. These monthly visits may themselves represent an intervention and may have partially contributed to the final outcomes.

In addition, incidence of macroangiopathy in our study decreased significantly when the HbA_{1c} target of 7.0% was reached. However, during the 7-year follow-up, the mean HbA_{1c} in the intensive group was actually ~6.5%; furthermore, no severe hypoglycemic events occurred, indicating that an HbA_{1c} of 6.5%, rather than 7%, might be desirable in patients with short-duration type 2 diabetes without macroangiopathy who are younger than 60 years old. The HbA_{1c} target in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial was <6.0%, and the all-cause mortality and cardiovascular fatality rates in the intensive blood glucose therapy group were both significantly higher than those in the control group (24). Therefore, it might be reasonable to consider an HbA_{1c} of 7.0% as the target for intensive blood glucose control in patients with relatively long durations of type 2 diabetes.

Because this study was performed in a small group of type 2 diabetic patients, there was insufficient information for a stratified analysis of the correlation between each hypoglycemic regimen and macrovascular end points. Additionally, the period of observation was only 7 years, and total clinical macrovascular events occurred in only 14 cases. We expect to observe the correlation between subclinical AS and clinical atherosclerotic disease, followed by increased clinical macrovascular events, as time progresses.

In conclusion, the primary prevention of macrovascular disease could be achieved through intensified, multifactorial intervention in patients with type 2 diabetes. Patients with short-duration type 2 diabetes should receive an intensive multifactorial intervention approach with individual targets for the prevention of macrovascular diseases.

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Y.Y. and J.-j.Y. collected data and wrote the manuscript. J.-l.D. designed the research, directed the entire study, and revised the manuscript. R.B. collected data. L.-p.S. contributed to the ultrasound examination of the three conducting arteries. G.-h.S. collected data from laboratory examinations. G.-r.S. contributed to the statistical analyses. S.-m.C., C.-h.S., Y.B., Q.X., and X.-y.Z. collected data. J.-l.D. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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