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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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. HbA1c 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. HbA1c, 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/m²) 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 HbA1c was >7.0%, metformin was...
Table 1—HbA1c, FPG, SBP, DBP, LDL-C, HDL-C, triglyceride, and total cholesterol of the two groups at baseline and at every follow-up year

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
<th>Year 4</th>
<th>Year 5</th>
<th>Year 6</th>
<th>Year 7</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Conventional group</td>
<td>Intensive group</td>
<td>Conventional group</td>
<td>Intensive group</td>
<td>Conventional group</td>
<td>Intensive group</td>
<td>Conventional group</td>
<td>Intensive group</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>8.69 ± 1.74</td>
<td>8.86 ± 1.66</td>
<td>7.81 ± 0.65</td>
<td>5.44 ± 0.56*</td>
<td>7.92 ± 0.81</td>
<td>5.66 ± 0.79*</td>
<td>7.53 ± 1.61*</td>
<td>6.11 ± 0.97†</td>
</tr>
<tr>
<td>FPG (mmol/L)</td>
<td>9.95 ± 0.74</td>
<td>9.98 ± 2.81</td>
<td>6.95 ± 1.03*</td>
<td>6.86 ± 1.43*</td>
<td>7.25 ± 2.03*</td>
<td>6.80 ± 3.88*</td>
<td>8.22 ± 2.97</td>
<td>6.94 ± 4.56†</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>128.80 ± 11.30</td>
<td>129.10 ± 15.20</td>
<td>123.45 ± 12.42</td>
<td>121.58 ± 14.21*</td>
<td>125.38 ± 12.77</td>
<td>120.67 ± 13.99*</td>
<td>127.35 ± 13.62</td>
<td>123.28 ± 13.18</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>76.90 ± 6.40</td>
<td>79.80 ± 11.80</td>
<td>78.91 ± 7.3</td>
<td>78.73 ± 9.74</td>
<td>79.43 ± 9.07</td>
<td>77.85 ± 9.05</td>
<td>80.30 ± 10.13</td>
<td>78.47 ± 9.53</td>
</tr>
<tr>
<td>LDL-C (mmol/L)</td>
<td>3.00 ± 0.52</td>
<td>2.99 ± 0.61</td>
<td>2.62 ± 0.61</td>
<td>2.56 ± 0.55</td>
<td>2.74 ± 0.56</td>
<td>2.57 ± 0.46</td>
<td>3.02 ± 0.63</td>
<td>2.59 ± 0.44</td>
</tr>
<tr>
<td>HDL-C (mmol/L)</td>
<td>1.01 ± 0.29</td>
<td>0.94 ± 0.72</td>
<td>1.14 ± 0.25</td>
<td>1.08 ± 0.33</td>
<td>1.04 ± 0.30</td>
<td>1.06 ± 0.48</td>
<td>1.19 ± 0.36</td>
<td>1.03 ± 0.39</td>
</tr>
<tr>
<td>TG (mmol/L)</td>
<td>2.28 ± 0.54</td>
<td>3.05 ± 1.46</td>
<td>1.62 ± 1.12*</td>
<td>1.55 ± 1.29*</td>
<td>1.61 ± 1.54*</td>
<td>1.54 ± 1.26*</td>
<td>1.75 ± 1.45*</td>
<td>1.85 ± 4.28</td>
</tr>
<tr>
<td>TC (mmol/L)</td>
<td>5.95 ± 1.15</td>
<td>5.92 ± 1.04</td>
<td>5.01 ± 1.15</td>
<td>4.42 ± 0.73†</td>
<td>5.43 ± 1.09</td>
<td>4.49 ± 0.81†</td>
<td>5.13 ± 0.98</td>
<td>4.49 ± 0.71†</td>
</tr>
</tbody>
</table>

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

Primary and secondary outcomes

The primary outcome (subclinical AS) was the time to the first occurrence of CCA/IMT ≥ 1.0 mm, and/or development of CAD. Patients in the control arm were followed with intensive management as in the intervention arm; however, the drugs were not prescribed based on the results of their evaluation, while the drugs were prescribed based on the results of their evaluation in the control arm. The dosage of the drugs was modified according to the level of control attained. The dosages of the drugs were modified to meet the goals set by the primary endpoint: HbA1c, blood pressure, and triglyceride levels.

In the intervention arm, the patients were treated under the guidance of specialists until all of the patients who did not exhibit contraindications were provided with the drugs. The patients were treated under the guidance of specialists until all of the patients who had mild contraindications were provided with the drugs. The patients were treated under the guidance of specialists until all of the patients who had moderate contraindications were provided with the drugs. The patients were treated under the guidance of specialists until all of the patients who had severe contraindications were provided with the drugs.

The secondary outcome (clinical AS) was the clinical evidence of cardiovascular events.
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 χ² 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, HbA1c, 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

<table>
<thead>
<tr>
<th></th>
<th>Baseline group</th>
<th>Conventional group</th>
<th>Intensive group</th>
<th>Follow-up events (n)</th>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
<th>Year 4</th>
<th>Year 5</th>
<th>Year 6</th>
<th>Year 7</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Follow-up events (n)</td>
<td>75</td>
<td>75</td>
<td>75</td>
<td>75</td>
<td>74</td>
<td>75</td>
<td>73</td>
<td>74</td>
<td>73</td>
<td>74</td>
</tr>
<tr>
<td></td>
<td>Thickened IMT/AS plaques (n)</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>5</td>
<td>2</td>
<td>7</td>
<td>2</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Subclinical macrovascular outcomes</td>
<td>0</td>
<td>0</td>
<td>2.67</td>
<td>1.33</td>
<td>6.76</td>
<td>3.67</td>
<td>9.59</td>
<td>2.70</td>
<td>4.58</td>
<td>2.70</td>
</tr>
<tr>
<td></td>
<td>Angina pectoris</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Myocardial infarction</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td></td>
<td>Silent myocardial ischemia</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<td>0</td>
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<tr>
<td></td>
<td>Transient ischemic attack</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<td>0</td>
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<tr>
<td></td>
<td>Intermittent claudication</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Sudden death</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Total clinical macrovascular end events (n)</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>4</td>
<td>1</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Final clinical macrovascular events</td>
<td>0</td>
<td>0</td>
<td>2.67</td>
<td>0</td>
<td>2.70</td>
<td>0</td>
<td>5.48</td>
<td>1.35</td>
<td>5.48</td>
<td>1.35</td>
</tr>
</tbody>
</table>

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, 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).

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 the benefits 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.

Ultrasoundography 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 IMT s and/or the occurrence of A Plaque s 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 HbA1c target of 7.0% was reached. However, during the 7-year follow-up, the mean HbA1c in the intensive group was actually ~6.5%; furthermore, no severe hypoglycemic events occurred, indicating that an HbA1c 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 HbA1c 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 HbA1c of 6.5% 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.

Acknowledgments—This research was supported by funds from the National Key Research Project for the Tenth Five-Year Plan (2001BA702B01), the National Key Research Project for the Eleventh Five-Year Plan (2006BA102B08), and the Key Research Project of Liaoning Province Bureau of Science and Technology (200222S003-6).

No potential conflicts of interest relevant to this article were reported.

Y.Y. and J.-J.Y. collected data and wrote the manuscript. J.-I.D. designed the research, directed the entire study, and revised the manuscript. R.B. collected data. L.-F.S. contributed to the ultrasonic 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.-I.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.

The authors thank Changchen Li for providing many constructive suggestions for the manuscript.

References