Long-term effects intensive medical therapy on the development and progression of subclinical atherosclerosis and the metabolic syndrome in Chinese patients with type 2 diabetes mellitus

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Abstract

Background: Few studies have investigated the progression of subclinical atherosclerosis and metabolic syndrome (MetS) in Chinese patients with type 2 diabetes mellitus (T2DM). This study was to compare the long-term effects of intensive medical therapy on the development and progression of subclinical atherosclerosis and MetS in Chinese T2DM patients with that of a conventional treatment regimen.

Methods: A total of 316 T2DM patients were randomized to receive conventional pharmacological treatment or intensive medical therapy, consisting of diet and exercise counseling, from 2002 to 2014 at our hospital in Changsha, China. Clinical indicators of subclinical atherosclerosis and MetS were evaluated over the 12-year follow-up period. A χ² analysis or t tests was used to compare the data between the 2 groups. Risk factors for subclinical atherosclerosis were identified using Cox proportional hazard models.

Results: The incidence of subclinical atherosclerosis increased in both groups over time, and did not differ significantly between the 2 groups at the end of the study. However, after 6 years of treatment, the risk of subclinical atherosclerosis was significantly lower in the intensive medical therapy group, based on intima-media thickness (IMT) measurements, compared with that in the conventional treatment (44.2% vs. 69.7%; P < 0.01). Age, creatinine, and IMT of the common iliac artery were significantly associated with subclinical atherosclerosis. Although the indicators of MetS did not differ significantly at the end of study, the success rate for the management of MetS in the intensive medical therapy group was significantly higher than that in the conventional treatment group in 2006, 2008, 2010, and 2012.

Conclusions: The incidence of atherosclerosis in the intensive medical therapy group was significantly lower than that in the conventional treatment group from 2006 to 2010 (P < 0.05), and the incidence of MetS in the intensive medical therapy group was significantly higher than that in the conventional treatment group from 2006 to 2012. Kaplan–Meier estimations showed that the risk of subclinical atherosclerosis in the intensive medical therapy group was significantly lower than that in the conventional treatment group (P < 0.001), whereas the risk of MetS was not significantly different between the treatment groups (P > 0.05).

Abbreviations: 2hPG = The 2-h postprandial plasma glucose level, ACR = albumin to creatinine ratio, ALT = Alanine aminotransaminase, BMI = body-mass index, BP = blood pressure, BUN = Blood urea nitrogen, CCA = common carotid artery, CI = confidence interval, CIA = common iliac artery, CR = urinary creatinine, DBP = diastolic BP, FA = femoral artery, FINS = Fasting plasma insulin, FPG = overnight fasting plasma glucose level, GFR = Glomerular filtration rate, HbA1c = glycated hemoglobin, HDL-C = high-density lipoprotein cholesterol, HOMA-IR = homeostasis model assessment of insulin resistance, HR = hazard ratio, IMT = intima-media thickness, LDL-C = low-density lipoprotein cholesterol, MetS = metabolic syndrome, SBP = systolic BP, T2DM = type 2 diabetes mellitus, TBil = total bilirubin, TC = Total cholesterol, TG = triglyceride, UAER = urinary albumin excretion rate, UAlb = urinary albumin, WC = waist circumference.

Keywords: metabolic syndrome, subclinical atherosclerosis, type 2 diabetes mellitus
1. Introduction

In recent decades, type 2 diabetes mellitus (T2DM) has become a major public health challenge in developed countries. According to the Diabetes Atlas (Sixth Edition) of the International Diabetes Federation, 387 million patients were treated for T2DM in 2014 worldwide, and the prevalence of T2DM is expected to rise to 592 million by 2035. The global burden of T2DM in 2013 was estimated to be approximately 548 billion USD. Atherosclerotic disease is a leading cause of morbidity and mortality. Previous studies have shown that T2DM is a major risk factor for atherosclerosis, and that T2DM accelerates the progression of atherosclerosis. The identification of atherosclerosis at subclinical stages would facilitate early intervention, leading to improved prognoses.

Previous studies have also shown that T2DM is a major risk factor for metabolic syndrome (MetS), which is characterized by insulin resistance, glucose intolerance, dyslipidemia, hypertension, and obesity. The National Health and Nutrition Examination Survey reported that the prevalence of MetS in the United States was approximately 34% between 1988 and 1994. The prevalence of MetS has been shown to increase with increasing age, and the interaction between the components of MetS has been shown to contribute to the development of atherosclerosis.

Various strategies are currently employed to treat T2DM, including lifestyle modifications and medical interventions. However, relatively few trials have investigated the effects of long-term pharmacological treatment for subclinical atherosclerosis and MetS in T2DM patients. In addition, relatively few studies of subclinical atherosclerosis and MetS have been reported for Asian populations, for whom diet and lifestyle risk factors can differ significantly from those of their Western counterparts.

We performed a randomized, controlled study comparing the efficacy of intensive medical therapy and that of conventional treatment regimens for slowing the development and progression of subclinical atherosclerosis and improving hyperglycemia, hypertension, dyslipidemia, and albuminuria in Chinese T2DM patients. Our findings provide valuable clinical evidence relevant to the development of more effective early intervention strategies for atherosclerosis and MetS-related complications in Chinese T2DM patients.

2. Participants and methods

2.1. Participants

We enrolled 316 patients who had received a diagnosis of T2DM at the Second Xiangya Hospital of Central South University (Changsha, China) between January 3 and October 31, 2002. The inclusion criteria were as follows: diagnosis of T2DM based on the World Health Organization (1999) diagnostic guidelines; 35 to 70 years of age; disease duration <1 year; and body mass index (BMI) of 19 to 35 kg/m². Patients meeting the following criteria were excluded from our study: diagnosis of type 1 diabetes mellitus; ≥2 episodes of diabetic ketoacidosis or other adverse stress responses within the first 6 months following T2DM diagnosis; a diagnosis of subclinical atherosclerosis at baseline based on a Doppler color ultrasound examination; serum creatinine >2.0 mg/dL; serum ALT >80 U/L; or acute diabetic complications, including heart disease, nephropathy, or peripheral vascular disease. Our study was approved by the institutional review board of our institution, and informed written consent was obtained from all of the patients before their participation in our study.

2.2. Data and sample collection

A standardized questionnaire was used to collect information on age, smoking (current, former, or never), alcohol consumption (yes, no, or former), and family history of MetS manifestations, as described previously. Blood samples were collected using EDTA as an anticoagulant. The blood samples were centrifuged, and the plasma was stored at −80°C.

2.3. Clinical variables

Height, weight, waist circumference (WC), hip circumference (HC), and blood pressure (BP) were recorded as described previously. Total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) were measured using a Hitachi 7170 Automated Clinical Analyzer (Tokyo, Japan) with proprietary reagents. The total bilirubin (TBil) and alanine aminotransferase (ALT) levels were measured using a Toshiba TBA200FR Automated Biochemical Analyzer (Tokyo, Japan). Blood urea nitrogen (BUN) was measured using a Hitachi 7180 Automated Clinical Analyzer using reagents from Roche Diagnostics (Indianapolis, IN). Urinary creatinine (CR) and 24-h urinary albumin (UA1b) were measured using a picric acid colorimetric method an immunoturbidimetric assay, respectively. The 2-hour postprandial plasma glucose level (2hPG) and overnight fasting plasma glucose level (FPG) were measured using the glucose oxidase method. Glycated hemoglobin (HbA1c) was measured using a Bio-Rad Variant II HPLC System (Hercules, CA) equipped with an ion exchange cartridge. Fasting plasma insulin (FINS) was measured using a chemiluminescent immunoassay (Siemens Healthcare, Erlangen, Germany). The insulin resistance index was evaluated based on the homeostasis model assessment of insulin resistance (HOMA-IR), as described previously, according to the following equation: [FPG (mmol/L)] × [FINS (µU/mL)]/22.5.

2.4. Diagnostic criteria

Proteinuria was defined as a UA1b concentration ≥30 mmol/L. Subclinical atherosclerosis was defined as IMT > 0.9 mm and/or detectable plaque in the lumen of the CCA, FA, or CIA without clinical manifestations. The diagnostic criteria for MetS were based on those published by the WHO in 1999, which require the presence of T2DM, impaired glucose tolerance, impaired fasting glucose, or insulin resistance and 2 of the following: a systolic blood pressure to diastolic blood pressure ratio (SBP/DBP) ≥140/90 mm Hg; dyslipidemia based on TG ≥1.7 mmol/L and HDL-C ≤0.9 mmol/L (men) or ≤0.9 mmol/L (women); central obesity based on BMI ≥30 kg/m² or a WC to HC ratio (WHR) ≥0.9 (men) or ≥0.85 (women); or microalbuminuria based on a UA1b excretion rate (UAE) ≥20 µg/min or a UA1b to CR ratio (ACR) ≥30 mg/g.

2.5. Treatment groups

Patients were randomly assigned to the intensive medical therapy group or the conventional treatment group. Patients in the intensive medical therapy group received diet and exercise...
counseling from a diabetes educator on a monthly basis. Their FPG, 2hPG, BP, body weight, heart rate, and pulse rate at the dorsal artery of the foot were measured monthly. When hyperglycemia occurred, obese and nonobese patients were first treated with metformin or glipizide, respectively, combined with additional glucose-lowering drugs in some cases. Insulin therapy was prescribed for cases in which metformin or glipizide was ineffective. When hypertension occurred, patients were first treated with captopril or valsartan combined with extended-release nifedipine or other antihypertensive drugs in some cases. When TC or TG levels exceeded the target concentrations, patients were treated with simvastatin or fenofibrate. When albuminuria occurred, patients were treated with captopril or valsartan. Patients also received dietary advice and exercise instructions to assist them in maintaining a near-normal bodyweight.

Patients in the conventional treatment group were treated in the outpatient clinic, and received conventional pharmacological therapy. They underwent a follow-up examination every 3 months from March 2002 to December 2014. Their FPG, 2hPG, BP, body weight, heart rate, and pulse rate at the dorsal artery of the foot were measured every 3 months, and their TC, TG, HDL-C, LDL-C, and HbA1c were measured every 6 months. Once yearly, their UAER, CR, FINS, height, WC, and HC were measured, and they underwent vascular ultrasound to assess the thickness of the intima-media (IMT) of the CCA, FA, and CIA. The IMT is used routinely in clinical practice to evaluate subclinical atherosclerosis. The target values for the clinical variables were as follows for both treatment groups: HbA1c <6.5%; SBP/DBP <130/80 mmHg; TG <<1.7 mmol/L; HDL-C >1.04 mmol/L (men) or >1.3 mmol/L (women); WHR <0.85 (men) or <0.8 (women); UAER <20 µg/min; and BMI <24 kg/m². All of the drugs required in both groups were purchased by the patients, and the costs were reimbursed through the national health insurance program.

2.6. Statistical analysis

The statistical analysis was performed using the SAS, version 9.3, software (SAS Institute, Cary, NC). Intergroup differences in the patient characteristics and clinical variables were evaluated using 2-tailed χ² tests for categorical variables and 2-tailed Student t test for continuous variables. A generalized linear mixed model was used to compare the intergroup differences in IMT values, which controlled for potential covariates, including sex, family history, BMI, BP, and FINS. Results with P < 0.05 were considered statistically significant. Univariate and multivariate regressions were performed using Cox proportional hazards models to identify factors associated with incident subclinical atherosclerosis. Significant risk factors (P < 0.2) identified in the univariate analysis were included in the multivariate analysis using the Cox proportional hazards model. The hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated, and P < 0.05 was considered to indicate a statistically significant association. Kaplan-Meier estimations of the risks of subclinical atherosclerosis and MetS were performed, and the significance of the difference in risk between the treatment groups was determined by the log-rank test.

3. Results

3.1. Patient characteristics

After screening a total of 489 patients with T2DM, 316 patients were enrolled in our study, with a baseline sample of 155 patients in the intensive medical therapy group and 161 patients in the conventional treatment group. One patient withdrew from the study owing to cerebral infarction, and another withdrew because of bladder cancer. A total of 70 patients were lost to follow-up, leaving a total of 246 patients (77.8%) who completed the study (Fig. 1). Although no significant differences were observed in patient characteristics at baseline, significantly greater percentages of smokers, alcohol users, and patients with a family history of MetS and higher levels of FPG, 2hPG, and LDL were observed in the conventional treatment group at the end of the study period, compared to those in the intensive medical therapy group in 2014 (Table 1).

3.2. Incidence of atherosclerosis

The incidence of atherosclerosis in the intensive medical therapy group was significantly lower than that in the conventional treatment group from 2006 to 2010 (Table 2). A Kaplan–Meier analysis showed that the risk of developing subclinical atherosclerosis in the conventional treatment group was significantly greater than that in the intensive medical therapy group (Fig. 2; P = 0.0093 by log-rank test).

3.3. Risk factors for atherosclerosis

To identify predictors of subclinical atherosclerosis in T2DM patients, we evaluated whether the various demographic and clinical variables were risk factors for the development of atherosclerotic plaque. We found that age, CR, and CIA-IMT were significantly associated with the incidence of subclinical atherosclerosis (Table 3). The incidence of atherosclerosis increased with increasing age at a rate of approximately 5% per year. The HR of CIA-IMT for the incidence of atherosclerosis was 5 times higher than that of the other risk factors identified (Tables 3 and 4).

3.4. Treatment effects on IMT

The IMTs of the CCA, FA, and CIA were significantly lower in the intensive medical therapy group in 2008 than that in the conventional treatment group (Table 5). However, the IMTs of

![Figure 1](image-url)
the intensive medical therapy and conventional treatment groups did not differ significantly at the end of the study period. The IMTs of all of the patients in both groups were >1 mm in 2014, indicating that all of the patients had subclinical atherosclerosis at the end of the study period.

3.5. Treatments effects on renal function and HOMA-IR

We also analyzed renal function and HOMA-IR as indicators of MetS. The HOMA-IR did not differ significantly between the intensive medical therapy and conventional treatment groups in 2003, 2008, and 2014 (Table 6). However, differences in renal function were observed. Albuminuria in 2003 was significantly higher than that of the intensive medical therapy group from 2006 to 2012 (Table 7). However, the Kaplan-Meier estimation did not show a significant difference in the risk of MetS between the study groups (Fig. 3; \( P=0.105 \) by log-rank test).

4. Discussion

We compared the effectiveness of intensive medical therapy for subclinical atherosclerosis and MetS in Chinese T2DM patients with that of conventional treatment. In the intensive medical therapy group, the Intima-media thickness (IMT) at the femoral artery, FH MetS, smoking status, and alcohol use were significantly lower than those in the conventional treatment group. The fasting plasma glucose, HbA1c, and TC were significantly lower in both groups over the 12-year follow-up period (Table 6).

### Table 1
Comparison of patient characteristics at baseline and study endpoint.

| Characteristic | 2002 | 2014 | 2002 | 2014 | P 2002 | P 2014 |
|---------------|------|------|------|------|-------|-------|
| Sample size (N) | 155 | 152 | 161 | 94 | 0.9881 | 0.529 |
| Men, n (%) | 82 (52.9) | 81 (53.3) | 86 (53.2) | 50 (53.2) | 1.000 | <0.0001 |
| Sample size (N) | 155 | 152 | 161 | 94 | 0.9881 | 0.529 |
| Age, y | 66.25±8.35 | 68.24±8.37 | 65.2±10.31 | 66.98±9.88 | 0.305 | 0.0065 |
| SBP, mmHg | 9.59 | 74.1 | 2.32 | 4.54 | 0.09 | 0.713 |
| DBP, mmHg | 9.56 | 74.1 | 2.32 | 4.54 | 0.09 | 0.713 |
| HOMA-IR | 9.59 | 74.1 | 2.32 | 4.54 | 0.09 | 0.713 |
| FINS, mIU/L | 9.59 | 74.1 | 2.32 | 4.54 | 0.09 | 0.713 |
| FPG, mmol/L | 9.59 | 74.1 | 2.32 | 4.54 | 0.09 | 0.713 |
| WC, cm | 9.59 | 74.1 | 2.32 | 4.54 | 0.09 | 0.713 |
| BMI, kg/m² | 9.59 | 74.1 | 2.32 | 4.54 | 0.09 | 0.713 |
| WC/HC | 9.59 | 74.1 | 2.32 | 4.54 | 0.09 | 0.713 |
| Weight, kg | 9.59 | 74.1 | 2.32 | 4.54 | 0.09 | 0.713 |
| Height, cm | 9.59 | 74.1 | 2.32 | 4.54 | 0.09 | 0.713 |
| FH MetS | 9.59 | 74.1 | 2.32 | 4.54 | 0.09 | 0.713 |
| Smoking status | 9.59 | 74.1 | 2.32 | 4.54 | 0.09 | 0.713 |
| Current | 9.59 | 74.1 | 2.32 | 4.54 | 0.09 | 0.713 |
| Former | 9.59 | 74.1 | 2.32 | 4.54 | 0.09 | 0.713 |
| Never | 9.59 | 74.1 | 2.32 | 4.54 | 0.09 | 0.713 |
| Albuminuria | 9.59 | 74.1 | 2.32 | 4.54 | 0.09 | 0.713 |
| Alcohol use | 9.59 | 74.1 | 2.32 | 4.54 | 0.09 | 0.713 |
| Yes | 9.59 | 74.1 | 2.32 | 4.54 | 0.09 | 0.713 |
| No | 9.59 | 74.1 | 2.32 | 4.54 | 0.09 | 0.713 |

2 hPG = 2-h postprandial glucose, ALT = Alanine transaminase, BMI = body mass index, BUN = blood urea nitrogen, CCA = common carotid artery, CIA = common iliac artery, CR = common renal artery, CRH = common renal artery, DBP = diastolic blood pressure, FA = femoral artery, FH = family history, FINS = fasting plasma insulin, TG = triglycerides, TC = total cholesterol, TG = triglycerides, HDL-C = high-density lipoprotein cholesterol, HOMA-IR = homeostasis model assessment of insulin resistance, IMT = intima-media thickness, LDL-C = low-density lipoprotein cholesterol, SBP = systolic blood pressure, TC = total cholesterol, UAID = urinary albumin, WC = waist circumference.

3.6. Treatment effectiveness for controlling MetS

We examined whether the target values for the HbA1c, BP, lipid profile, WHR, BMI, and microalbuminuria were achieved to assess the effectiveness of the treatments for controlling MetS. The success rate for the management of MetS in the conventional treatment group was significantly higher than that of the intensive medical therapy group from 2006 to 2012 (Table 7). However, the Kaplan-Meier estimation did not show a significant difference in the risk of MetS between the study groups (Fig. 3; \( P=0.105 \) by log-rank test).
therapy group, metformin or glipizide was the first choice for lowering blood glucose. Metformin is an oral biguanide drug, and glipizide is an oral, rapidly absorbed, short-acting sulfonylurea drug.[18,19] Captopril, an angiotensin-converting enzyme inhibitor, or valsartan, an angiotensin II receptor antagonist, was used to control hypertension and albuminuria, both of which have been used to treat hypertension and congestive heart failure.[18,19] Simvastatin or fenofibrate was used to treat dyslipidemia, as described previously.[20,21]

Atherosclerosis is a systemic disease affecting multiple layers of the arterial wall. We focused our investigation on subclinical atherosclerosis because it is a risk factor for cardiovascular events.[17,22] The presence of atherosclerotic plaque and IMT are both used as markers of subclinical atherosclerosis. We first compared the incidence of subclinical atherosclerosis between the

| Year | Received diagnosis | Intensive medical therapy (%) | Conventional treatment (%) | P |
|------|-------------------|------------------------------|---------------------------|---|
| 2002 | No                | 155 (100)                    | 161 (100)                 |   |
| 2004 | No                | 110 (70.1)                   | 92 (66.7)                 | 0.4271 |
| 2006 | No                | 92 (67.4)                    | 71 (49.3)                 | 0.0138 |
| 2008 | No                | 58 (55.8)                    | 40 (30.3)                 | <0.0001 |
| 2010 | No                | 55 (65.0)                    | 43 (36.1)                 | 0.0052 |
| 2012 | No                | 36 (46.8)                    | 32 (32.3)                 | 0.0511 |
| 2014 | No                | 12 (22.2)                    | 13 (18.8)                 | 0.6437 |

Table 2
Rates of developing subclinical atherosclerosis over the follow-up period.

Table 3
Univariate analysis of risk factors for subclinical atherosclerosis.

| Risk factor | HR (95% CI) | P |
|-------------|-------------|---|
| Therapy     |             |   |
| Intensive medical therapy | 1.0 | 0.0043 |
| Conventional treatment | 0.66 (0.50–0.88) |   |
| Sex         |             |   |
| Women       | 1.0         | 0.4120 |
| Men         | 1.13 (0.85–1.49) |   |
| Family history | Yes | 1.0 |
|             | No          | 1.11 (0.83–1.47) | 0.4867 |
| Smoking status | Current | 1.0 |
|             | Former      | 1.19 (0.80–1.77) | 0.3857 |
|             | Never       | 1.33 (0.98–1.82) | 0.0691 |
| Alcohol use |             |   |
| Yes         | 1.0         |   |
| No          | 1.00 (0.63–1.57) | 0.9835 |
| Former      | 1.39 (1.03–1.89) | 0.0330 |
| Age         |             | <0.0001 |
| Height      | 1.01 (0.99–1.02) | 0.4598 |
| Weight      | 1.00 (0.99–1.01) | 0.7806 |
| BMI         | 0.99 (0.97–1.01) | 0.4738 |
| Waist circumference | 1.01 (0.99–1.02) | 0.5416 |
| Hip circumference | 0.99 (0.97–1.01) | 0.3370 |
| Waist-hip ratio | 0.88 (0.86–54.93) | 0.0687 |
| Fasting plasma glucose | 0.97 (0.92–1.03) | 0.3015 |
| 2h postprandial plasma glucose | 1.01 (0.98–1.04) | 0.5333 |
| HbA1c       | 1.00 (0.96–1.04) | 0.8283 |
| Alamine transaminase | 1.00 (0.99–1.01) | 0.9509 |
| Total bilirubin | 0.99 (0.97–1.01) | 0.5137 |
| Blood urea nitrogen | 1.00 (1.00–1.01) | 0.7537 |
| Creatinine  | 1.01 (1.01–1.02) | 0.0006 |
| Triglyceride | 0.98 (0.91–1.05) | 0.5033 |
| Total cholesterol | 0.99 (0.87–1.12) | 0.8552 |
| High-density lipoprotein cholesterol | 0.85 (0.62–1.44) | 0.7907 |
| Low-density lipoprotein cholesterol | 1.04 (0.90–1.21) | 0.5983 |
| Microalbuminuria | 1.00 (1.00–1.01) | 0.0629 |
| CCA-IMT     | 6.19 (1.66–23.05) | 0.0066 |
| FA-IMT      | 1.29 (0.40–4.22) | 0.6722 |
| CIA-IMT     | 5.71 (1.57–20.77) | 0.0082 |
| Fasting plasma insulin | 0.99 (0.98–1.01) | 0.3246 |
| HOMA-IR     | 1.01 (1.00–1.02) | 0.0427 |
| Systolic blood pressure | 1.00 (0.99–1.01) | 0.9195 |

Table 4
Multivariate analysis of the risk of subclinical atherosclerosis.

| Risk factor | HR (95% CI) | P |
|-------------|-------------|---|
| Age         |             | <0.0001 |
| Urine creatinine | 1.01 (1.00–1.02) | 0.0197 |
| CIA-IMT     | 5.22 (1.20–22.65) | 0.0275 |
treatment group was higher than that in the intensive medical therapy group at the 6-year follow-up examination.

Age, CR, and CIA-IMT were identified as significant risk factors for atherosclerosis in both groups, which is consistent with the findings of previous studies.\[25,26\] We also found that the IMT of the CCA, FA, and CIA of patients in the intensive medical therapy group were significantly lower after 6 years of treatment compared with those in the conventional treatment group. However, the IMTs did not differ significantly between the 2 groups at the end of the study period. These results showed that intensive medical therapy reduced the incidence of subclinical atherosclerosis from 2006 to 2010 only, but the Kaplan–Meier analysis of the data showed that intensive medical therapy significantly reduced the overall risk of subclinical atherosclerosis, compared with that in the conventional treatment group, suggesting that different treatment strategies might be needed to reduce atherosclerotic deposition in Chinese T2DM patients after 6 years of intensive medical therapy.

Our findings are also consistent with those of previous studies, which showed that the carotid artery IMT increased progressively in T2DM patients treated with metformin for 24 weeks,\[14\] and that it did not differ significantly between the patients treated with metformin for 18 months and those who received the placebo treatment.\[13\] The long-term effect of metformin treatment on the risk of cardiovascular disease remains largely unclear.\[20\] In addition, a previous study showed that, although treatment with valsartan for 24 months did not influence CCA-IMT, it did improve vascular wall function in patients with essential hypertension.\[14\]

The development of subclinical atherosclerosis has also been reported in patients who had been treated with simvastatin.\[23\] Fenofibrate has been shown to inhibit the progression of carotid IMT in people with essential hypertension and mild hyperlipidemia,\[26\] but did not significantly inhibit the progression of carotid IMT in T2DM patients.\[27\] A limited number of studies have investigated the role of glipizide and captopril in preventing subclinical atherosclerosis. In general, the use of these drugs alone is ineffective for preventing subclinical atherosclerosis. However, our results showed that the use of these drugs in combination reduced the risk of subclinical atherosclerosis in Chinese T2DM patients.

We also explored the effect of intensive medical therapy on indicators of MetS, and found that the HOMA-IR index, GFR, albuminuria, and CR decreased in both groups over the 12-year follow-up, suggesting that both therapies were effective for reducing markers of MetS in T2DM patients. The proportion of patients with albuminuria in the intensive medical therapy group was significantly lower in 2003 than that of the conventional treatment group. These results suggest that intensive medical therapy is more effective for maintaining renal function in

### Table 5
Comparison of atherosclerotic plaque deposition between the treatment groups based on intima media thickness.

| Year | Artery-IMT | Intensive medical therapy | Conventional treatment | P |
|------|------------|---------------------------|------------------------|---|
| 2002 | CCA-IMT    | 0.71±0.09                  | 0.69±0.17              | 0.195 |
|      |            | 0.72±0.07                  | 0.74±0.17              | 0.175 |
|      | FA-IMT     | 0.78±0.06                  | 0.79±0.18              | 0.511 |
| 2008 | CCA-IMT    | 0.69±0.19                  | 0.74±0.16              | 0.012 |
|      | FA-IMT     | 0.69±0.19                  | 0.76±0.16              | <0.0001 |
|      | OA-IMT     | 0.85±0.15                  | 0.95±0.21              | <0.0001 |
| 2014 | CCA-IMT    | 1.01±0.21                  | 1.00±0.19              | 0.657 |
|      | FA-IMT     | 1.02±0.23                  | 1.01±0.27              | 0.724 |
|      | OA-IMT     | 1.12±0.15                  | 1.23±0.24              | <0.0001 |

CCA=common carotid artery, FA=common iliac artery, FA=femoral artery, IMT=intima media thickness.

### Table 6
Comparison of renal function indexes and insulin resistance between the treatment groups.

| 2002 | 2008 | 2014* |
|------|------|-------|
| Blood urea nitrogen (mmol/L) | | |
| Intensive medical therapy | 5.38±1.43 | 5.49±1.45 | 5.54±1.45 | 5.62±1.40 |
| Conventional treatment | 7.42±9.47 | 7.71±9.89 | 5.9±1.58 | 5.96±1.62 |
| P | 0.3333 | 0.3258 | 0.0750 | 0.1625 |
| Urine creatinine (mmol/d) | | |
| Intensive medical therapy | 97.11±16.79 | 82.42±14.79 | 69.51±16.17 | 58.78±16.24 |
| Conventional treatment | 95.89±18.02 | 86.51±74.39 | 70.17±36.77 | 59.71±21.71 |
| P | 0.5343 | 0.5014 | 0.8955 | 0.7662 |
| GFR, mL/min/1.73 m2 | | |
| Intensive medical therapy | 127.94±36.13 | 95.73±31.57 | 64.99±35.11 | 35.49±35.07 |
| Conventional treatment | 123.26±38.88 | 105.46±157.86 | 71.57±41.04 | 38.17±42.88 |
| P | 0.2556 | 0.4517 | 0.2032 | 0.6754 |
| Microalbuminuria (n, %) | | |
| Intensive medical therapy | 133 (85.8) | 12 (7.7) | 10 (8.6) | 5 (9.3) |
| Conventional treatment | 138 (85.7) | 24 (17.4) | 20 (15.2) | 6 (6.7) |
| P | 1.000 | 0.0267 | 0.3287 | 1.000 |
| HOMA-IR | | |
| Intensive medical therapy | 6.2±2.73 | 4.35±2.8 | 3.23±4.14 | 4.09±6.06 |
| Conventional treatment | 5.6±5.15 | 5.31±5.03 | 4.29±5.02 | 4.24±4.08 |
| P | 0.1991 | 0.0369 | 0.0410 | 0.7954 |

GFR=glomerular filtration rate, HOMA-IR=homeostasis model assessment of insulin resistance.

1 2002, n = 156; 2014, n = 152.
2 2002, n = 161; 2014, n = 84.
the intensive medical therapy group did not differ significantly from that of conventional treatment group in the latter years of the follow-up period, and a Kaplan–Meier analysis did not show a significant difference in MetS risk between the treatment groups. Studies in both animals and humans have suggested that treatment with metformin, captopril, valsartan, simvastatin, or fenofibrate alone reduced the development of MetS, which is largely consistent with our findings. Because MetS increases the risk of cardiovascular disease, it seems unlikely that improvements in MetS indicators contributed to a lower risk of subclinical atherosclerosis in the intensive medical therapy group, compared with that in the conventional treatment group.

The average age of the intensive medical therapy and conventional treatment groups (66 and 65 years at baseline, respectively) may have confounded our results because the risks of MetS and subclinical atherosclerosis have both been shown to increase with increasing age, which might have contributed to the lack of a significant difference in incidence rates between the treatment groups in the latter years of the follow-up period. Although all patients were reimbursed for drug costs, the greater initial economic burden for the conventional treatment group may have contributed to a higher drop-out rate. The significantly greater percentages of smokers, alcohol users, and patients with a family history of MetS and higher levels of FPG, 2-hPG, and LDL in the conventional treatment group at the end of the study period, compared to those in the intensive medical therapy group in 2014, might have also influenced our results. However, these differences would seem more likely to contribute to a greater difference between the treatment groups, which was not the case for our analysis.

Although we are unaware of other investigations that have compared the effects of intensive medical therapy and conventional pharmacological treatment on both subclinical atherosclerosis and MetS in T2DM patients in China, the relatively small size of our study population warrants confirmation of our findings in a larger cohort of T2DM patients in China. Previous studies have investigated factors contributing to the development of subclinical atherosclerosis and MetS in Chinese Americans. However, diet and environmental factors for Chinese people in the United States differ from those of residents of mainland China. Furthermore, variation occurs between different methods of measuring atherosclerotic deposition. Therefore, the use of flow-mediated vasodilatation, arterial stiffness, or the ankle-brachial index for assessing atherosclerotic plaque deposition in future studies is also warranted.

In conclusion, we found that, although Chinese T2DM patients with subclinical atherosclerosis and MetS remained at a high risk for developing more severe atherosclerotic disease after 12 years of intensive medical therapy, the progression of subclinical atherosclerosis and MetS indicators were reduced in Chinese T2DM patients during the first 6 years of intensive medical therapy, compared with those of patients receiving conventional treatment. Our findings provide important clinical data for the improvement of strategies for the prevention and treatment of atherosclerosis and MetS in Chinese T2DM patients.

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