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Effect of intensive multifactorial treatment on the intima-media thickness of large arteries in patients with new-onset type 2 diabetes mellitus*

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Abstract: Objective: To quantify the changes in blood glucose, blood lipids, blood pressure, and the intima-media thickness (IMT) of large arteries in patients with new-onset type 2 diabetes mellitus who received either intensive multifactorial treatment or conventional treatment. Methods: Two-hundred and ten patients with new-onset type 2 diabetes mellitus were randomly assigned to two groups: an intensive treatment group (n=110) and a conventional treatment group (n=100). Fasting blood glucose (FBG), glycosylated hemoglobin A1c (HbA1c), blood pressure, blood lipids [total cholesterol (TC), triglyceride (TG), low-density lipoprotein C (LDL-C), and high-density lipoprotein C (HDL-C)], and IMTs of large arteries (carotid, iliac, and femoral arteries) were determined before and at one and two years after starting treatment. The patients in the conventional treatment group received routine diabetes management in our outpatient department. Targets were established for patients in the intensive treatment group. Their blood glucose, blood lipids, and blood pressure levels were regularly monitored and therapeutic regimens were adjusted for those whose measurements did not meet the target values until all the parameters met the established targets. Within-group and between-group differences were evaluated. Results: A significantly greater percentage of patients in the intensive treatment group had LDL-C levels that reached the target value one year after starting treatment than those in the conventional treatment group (52.04% vs. 33.33%, P<0.05). No significant differences were found between groups for FBG, HbA1c, blood pressure, TG, TC, or HDL-C. The percentages of patients with TG (51.02% vs. 34.48%), TC (52.04% vs. 33.33%), and LDL-C (61.22% vs. 43.67%) who met the respective target values in the intensive treatment group were all significantly higher than the corresponding percentages in the conventional treatment group two years after starting treatment (P<0.05). There were no significant differences in the percentages of patients with FBG, HbA1c, and blood pressure values meeting the respective targets between the groups at the two-year follow-up. One year after starting treatment, the LDL-C level, diastolic blood pressure (DBP), and the IMTs of the femoral and iliac arteries of the intensive treatment group were significantly lower compared to those of the conventional treatment group (P<0.05), although there was no significant difference in other metabolic parameters. Two years after starting treatment, the TC, LDL-C, blood pressure [systolic blood pressure (SBP) and DBP], and the IMTs of the carotid and femoral arteries of the intensive treatment group were significantly lower than those of the conventional treatment group (P<0.05). No significant differences in other metabolic parameters existed between the two groups two years after starting treatment. Conclusions: Early comprehensive and intensive treatment of type 2 diabetes mellitus can delay or even reverse the increase in IMT of large arteries. Lowering blood pressure and blood lipid regulation in patients with type 2 diabetes mellitus have great significance in decreasing the risk of diabetes-related macrovascular lesions.

Key words: Type 2 diabetes mellitus, Intensive treatment, Intima-media thickness (IMT), Large arteries
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1 Introduction

In 1999, the American Heart Association (AHA) recategorized diabetes mellitus as a cardiovascular (macrovascular) disease (Grundy *et al*., 1999). This reclassification caused a shift in the clinical research paradigm over the past decade and has been the impetus behind recent investigations into diabetes-related macrovascular lesions. A series of recent clinical trials, including the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, Veterans Affairs Diabetes Trial (VADT), and Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) did not support the notion that long-term intensive blood glucose control significantly reduces macrovascular events (Skyler *et al*., 2009). Contrary to these findings, several studies have reported a significant correlation between abnormal glucose metabolism and macrovascular events, including the 10-year follow-up study of the United Kingdom Prospective Diabetes Study (UKPDS), the nine-year follow-up of the Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) study, and a recent meta-analysis of several different trials (Gæde *et al*., 2008; Holman *et al*., 2008; Ray *et al*., 2009). These studies concluded that early intensive blood glucose control significantly reduced the risk of macrovascular events.

Because previous results pertaining to prevention and treatment of diabetes-related macrovascular disease were contradictory, investigations elucidating the pathophysiological basis of diabetes-related macrovascular lesions and interventional strategies to address these pathways are needed to advance clinical practice. It has been established that the major pathological mechanism of cardiovascular disease (CVD) is atherosclerosis. Carotid intima-media thickness (IMT) is a noninvasive measure that enables clinicians to identify the early stages of atherosclerosis. Lorenz *et al.* (2006; 2007) have demonstrated that improvements in the utilization of carotid IMT technologies could improve the ability to predict the development of cardio-cerebrovascular complications. At present, control over blood glucose, blood lipids, and blood pressure in patients with diabetes mellitus in China is unsatisfactory. Only 7% of such patients have achieved the target values, which are blood glucose parameter glycosylated hemoglobin A1c (HbA1c)<7%, blood lipid parameter total cholesterol (TC)<200 mg/dl (5.18 mmol/L), and blood pressure<130/80 mmHg (Saydah *et al*., 2004). Therefore, disability and mortality rates attributed to the negative effects of diabetes remain unacceptably high.

Primary treatment for diabetes mellitus is directed at blood glucose control. Patients utilize dietary and pharmacological strategies to lower blood glucose levels to pre-identified target values with the intent of preventing or delaying the development and progression of the chronic complications of diabetes. However, as knowledge of diabetic pathology improves, additional risk factors such as blood pressure and blood lipid levels have been correlated to chronic diabetic complications. Therefore, treatment for the disease should be comprehensive and effective interventions should target all risk factors of future complications. These interventions include controlling blood glucose and blood pressure levels, regulating blood lipid levels, quitting smoking, losing weight, and changing behavioral habits towards a more active lifestyle. Although evidence-based medical studies have clearly demonstrated that reducing blood pressure and lowering cholesterol significantly improves the prognosis for patients with CVD and other high risk patients (Colhoun *et al*., 2004; Nissen *et al*., 2004), the effect of these interventions on the IMT of large arteries has not been evaluated. Therefore, the purpose of this study was to evaluate the effect of an intensive multifactorial treatment on the IMT of large arteries in patients with diabetes mellitus.

2 Subjects and methods

2.1 Subjects

Two hundred and ten patients with type 2 diabetes mellitus who visited our hospital from Dec. 2007 to Dec. 2008 were included in this study. Disease duration was less than one year for all subjects included in the analysis. Diet control and/or therapeutic regimens were followed for at least two weeks before entering the study and subjects ranged in age from 35 to 70 years. Body mass index (BMI) ranged from 19 to 35 kg/m^2. All patients signed an informed consent before participating in the study. Exclusion

criteria included diabetes mellitus other than type 2; disease duration of more than one year; pre-existing complications such as cardio-cerebrovascular disease, renovascular disease, or peripheral vascular disease that were diagnosed after the diabetes diagnosis; hepatic or renal dysfunction; progressive fatal illnesses; history of alcoholism or drug abuse; participation in another study within the previous four weeks; history of mental illness; and, inability to complete follow-up assessments. The diagnosis of type 2 diabetes mellitus was based on the 1999 World Health Organization (WHO) diagnostic criteria. Hypertension was based on the diagnostic criteria in the 1999 WHO/International Society of Hypertension (ISH) Hypertension Guidelines and hyperlipemia was based on the diagnostic criteria of the 2001 US National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) guidelines.

2.2 Methods and parameters

The 210 patients were randomly assigned to one of two groups: an intensive treatment group (n=110) and a conventional treatment group (n=100). Height and body weight were measured after fasting for more than 12 h. After resting for 10 min, blood pressure was measured while patients were in a seated position, using a desktop mercury sphygmomanometer. Blood pressure was measured twice on each patient and the average of the two values was recorded and used in the data analysis. Venous blood was drawn to measure blood glucose, HbA1c (turbidimetric testing using a kit from Bio-Rad Laboratories Inc., USA), TC, triglyceride (TG), high-density lipoprotein C (HDL-C), and low-density lipoprotein C (LDL-C) (Hitachi 7710 automated biochemistry analyzer, Japan). The IMTs of the carotid, femoral, and iliac arteries were measured with a B-scan ultrasound (GE Vivid7 Color Doppler Ultrasound Scanner, USA), and the measuring was conducted by the same physician with the same machine at each of the testing sessions. The IMT was defined as the vertical distance between the surface of intima and the outer surface of media on the posterior wall of the artery. The patients in the conventional treatment group received routine diabetes management in our outpatient department and no intensive control standard was established for these patients. Blood glucose, blood lipids, and blood pressure levels were monitored monthly for the patients in the intensive treatment group, and therapeutic regimens were adjusted for those whose measurements did not meet the target values until all the measurements were lowered to the established targets. The intensive treatment targets were: fasting blood glucose (FBG)≤7.0 mmol/L, HbA1c<7.0%; systolic blood pressure (SBP)≤130 mmHg, diastolic blood pressure (DBP)≤80 mmHg; TC<4.14 mmol/L (160 mg/dl), LDL-C≤2.59 mol/L (100 mg/dl), and TG<1.70 mmol/L (150 mg/dl). These parameters were measured one and two years after the initiation of the treatment.

2.3 Statistical analysis

Quantitative data were expressed as mean± standard deviation (SD). A t-test was used when quantitative data showed a normal distribution, otherwise nonparametric methods were employed. The χ^2 test was used for qualitative data analysis. The trend of change of each parameter was assessed using within-group comparisons. Repeated-measures analysis of variances (ANOVA) was used for quantitative data and then paired comparison methods were employed for post-hoc testing when appropriate. Differences were considered significant at P<0.05.

3 Results

A total of 110 patients were included in the intensive treatment group. Ten patients withdrew from the study during the observation period for no specific reason; one patient was removed from the study because of abnormal hepatic function after taking atorvastatin. The patient's liver function returned to normal after discontinuation of antihyperlipidemic drugs. One patient was removed because of tumor development. The drop-out rate was 10.9% for the intensive treatment group. A total of 100 patients were included in the conventional treatment group. Twelve patients withdrew from the study during the observation period for no specific reason and one was removed because of a cerebrovascular accident, giving a drop-out rate of 13% in the conventional treatment group. The difference in the drop-out rates between the two groups was not statistically significant (P>0.05). After accounting for the patients who dropped out of the study, 98 patients in the intensive

treatment group and 87 patients in the conventional treatment group were assessed at the two-year follow-up. No hypoglycemic events occurred during the two-year follow-up period.

There were no significant differences in age, sex ratio, BMI, smoking history, concomitant hypertension rate, concomitant hyperlipemia rate, FBG, HbA1c, blood pressure (SBP and DBP), blood lipids (TG, TC, HDL-C, and LDL-C), or IMTs of carotid, femoral, and iliac arteries between the intensive and the conventional treatment groups at the baseline (P>0.05) (Table 1).

Table 1 Baseline comparisons between the two groups

Parameter	Intensive treatment group	Conventional treatment group
Patient number (male/female)	110 (59/51)	100 (57/43)
Median age (year)	55.5	55.0
BMI (kg/m^2)	24.42±2.80*	24.30±3.08
Hypertension history (%)	52.45	49.00
Hyperlipemia history (%)	40.00	38.38
Smoking history (%)	23.15	29.00
FBG (mmol/L)	7.30±2.27	7.67±3.03
HbA1c (%)	7.49±2.03	7.58±1.99
TG (mmol/L)	1.90±1.52	2.03±1.85
TC (mmol/L)	4.75±0.98	4.54±0.90
HDL-C (mmol/L)	1.16±0.34	1.14±0.34
LDL-C (mmol/L)	2.71±0.90	2.63±0.66
SBP (mmHg)	131.82±15.56	131.03±18.81
DBP (mmHg)	80.74±10.78	79.09±9.75
IMT of carotid artery (mm)	1.07±0.30	1.02±0.25
IMT of femoral artery (mm)	1.16±0.38	1.17±0.40
IMT of iliac artery (mm)	1.20±0.47	1.16±0.31

* Data are expressed as mean±SD. BMI: body mass index; FBG: fasting blood glucose; HbA1c: hemoglobin A1c; TG: triglycerides; TC: total cholesterol; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; SBP: systolic blood pressure; DBP: diastolic blood pressure; IMT: intima-media thickness

There were no significant differences between groups in the percentages of patients at the baseline who met the respective target values. A significantly greater percentage of patients in the intensive treatment group had LDL-C levels that reached the target value one year after starting treatment than those in the conventional treatment group (52.04% vs. 33.33%, P<0.05). No significant differences were found between groups for FBG, HbA1c, blood pressure, TG, and TC (Fig. 1a). The percentages of patients with TG (51.02% vs. 34.48%), TC (52.04% vs. 33.33%), and LDL-C (61.22% vs. 43.67%) who met the respective target values in the intensive treatment group were all significantly higher than the corresponding percentages in the conventional treatment group two years after starting treatment (P<0.05; Fig. 1b). There were no significant differences in the percentages of patients with FBG, HbA1c and blood pressure values meeting the respective targets between groups at the two-year follow-up (Fig. 1b).

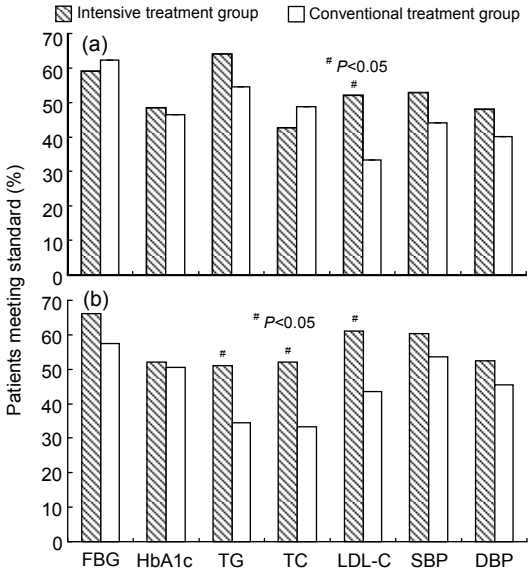

Fig. 1 Comparison of the percentages of patients with parameters meeting the respective target values at one (a) and two (b) years after starting treatment between the intensive and conventional treatment

The abbreviations are the same as those shown in Table 1

One year after starting treatment, the LDL-C level, DBP, and the IMTs of the femoral and iliac arteries of the intensive treatment group were significantly lower than those of the conventional treatment group (P<0.05), although there were no significant differences in other metabolic parameters (Table 2). Two years after starting treatment, the TC, LDL-C, blood pressure (SBP and DBP), and the IMTs of the carotid and femoral arteries of the intensive treatment group were significantly lower than those of the conventional treatment group (P<0.05). No significant differences in other metabolic parameters existed between the two groups two years after starting treatment (Table 2).

In the intensive treatment group, there was a significant decrease in the HbA1c, TC, LDL-C, blood pressure (SBP and DBP), and the IMT of the femoral artery (P<0.01) over the two years. This group also showed a significant increase in HDL-C over the same time period (P<0.01) (Table 3). In the conventional treatment group, there was a significant decrease in HbA1c and TC levels (P<0.01). This group also showed a significant increase in the IMTs of the carotid, femoral, and iliac arteries (P<0.05) and a significant decrease in HDL-C levels (P<0.05; Table 4).

Table 2 Comparison of metabolic parameters between the intensive and conventional treatment groups after one and two years treatment

Metabolic parameter	After one year		After two years	
	Intensive treatment group	Conventional treatment group	Intensive treatment group	Conventional treatment group
FBG (mmol/L)	7.29±2.17	6.89±2.09	6.85±1.47	7.55±2.75
HbA1c (%)	6.60±1.06	6.72±1.02	6.97±1.02	6.96±1.61
TG (mmol/L)	1.59±0.84	1.99±1.69	1.66±1.36	2.23±2.02
TC (mmol/L)	4.41±1.07	4.29±0.75	4.28±0.89**	4.61±0.87
HDL-C (mmol/L)	1.18±0.32	1.19±0.32	1.24±0.34	1.12±0.31
LDL-C (mmol/L)	2.47±0.88$^{\#\#}$	2.75±0.62	2.33±0.79**	2.67±0.71
SBP (mmHg)	129.67±20.13	131.26±20.46	122.80±15.20**	129.59±16.65
DBP (mmHg)	77.96±10.02$^{\#}$	81.07±11.06	75.42±9.35*	79.67±12.02
IMT of carotid artery (mm)	1.06±0.38	1.08±0.21	1.05±0.30**	1.20±0.22
IMT of femoral artery (mm)	1.04±0.43$^{\#}$	1.19±0.37	1.02±0.29**	1.21±0.36
IMT of iliac artery (mm)	1.12±0.32$^{\#}$	1.23±0.41	1.17±0.38	1.24±0.26

Data are expressed as mean±SD. Compared to the conventional treatment group one year after starting treatment: $^{\#}$ P<0.05, $^{\#\#}$ P<0.01. Compared to the conventional treatment group two years after starting treatment: * P<0.05, ** P<0.01. For the intensive treatment group n=98 and for the conventional treatment group n=87. The abbreviations are the same as those shown in Table 1

Table 3 Comparison of metabolic parameters within the intensive treatment group

Metabolic parameter	Baseline	After one year	After two years	P value
FBG (mmol/L)	7.30±2.27	7.29±2.17	6.85±1.47	0.0763
HbA1c (%)	7.49±2.03$^{\#}$	6.60±1.06$^{\#}$	6.97±1.02$^{\#}$	<0.0001
TG (mmol/L)	1.90±1.52	1.59±0.84	1.66±1.36	0.5254
TC (mmol/L)	4.75±0.98$^{\#}$	4.41±1.07	4.28±0.89	<0.0001
HDL-C (mmol/L)	1.16±0.34	1.18±0.32	1.24±0.34$^{\#}$	0.0010
LDL-C (mmol/L)	2.71±0.90$^{\#}$	2.47±0.88	2.33±0.79	<0.0001
SBP (mmHg)	131.82±15.56	129.67±20.13	122.80±15.20$^{\#}$	<0.0001
DBP (mmHg)	80.74±10.78$^{\#}$	77.96±10.02$^{\#}$	75.42±9.35$^{\#}$	<0.0001
IMT of carotid artery (mm)	1.07±0.30	1.06±0.38	1.05±0.30	0.4536
IMT of femoral artery (mm)	1.16±0.38$^{\#}$	1.04±0.43	1.02±0.29	0.0007
IMT of iliac artery (mm)	1.20±0.47	1.12±0.32	1.17±0.38	0.1869

Data are expressed as mean±SD. $^{\#}$ The designated group showed significant differences from other groups through paired comparisons, P<0.05. The abbreviations are the same as those shown in Table 1

Table 4 Comparison of metabolic parameters within the conventional treatment group

Metabolic parameter	Baseline	After one year	After two years	P value
FBG (mmol/L)	7.67±3.03	6.89±2.09$^{\#}$	7.55±2.75	0.0510
HbA1c (%)	7.58±1.99$^{\#}$	6.72±1.02	6.96±1.61	<0.0001
TG (mmol/L)	2.03±1.85	1.99±1.69	2.23±2.02	0.2634
TC (mmol/L)	4.54±0.90	4.29±0.75$^{\#}$	4.61±0.87	0.0125
HDL-C (mmol/L)	1.14±0.34	1.19±0.32	1.12±0.31*	0.0383
LDL-C (mmol/L)	2.63±0.66	2.75±0.62	2.67±0.71	0.0699
SBP (mmHg)	131.03±18.81	131.26±20.46	129.59±16.65	0.5922
DBP (mmHg)	79.09±9.75	81.07±11.06	79.67±12.02	0.1205
IMT of carotid artery (mm)	1.02±0.25$^{\#}$	1.08±0.21	1.20±0.22	0.0024
IMT of femoral artery (mm)	1.17±0.40	1.19±0.37	1.21±0.36	0.0418
IMT of iliac artery (mm)	1.16±0.31	1.23±0.41	1.24±0.26	0.0026

Data are expressed as mean±SD. $^{\#}$ The designated group showed significant differences from other groups through paired comparisons, P<0.05. * No significant differences between the groups through paired comparisons with a conservative estimate. The abbreviations are the same as those shown in Table 1

4 Discussion

Diabetes-related macrovascular disease typically refers to coronary heart disease, cerebrovascular disease, and peripheral vascular disease caused by or concomitant with diabetes mellitus. These conditions are not unique to patients with diabetes, unlike diabetes-related microvascular diseases (including diabetic nephropathy and diabetic retinopathy), which are specific to patients with diabetes mellitus (Aronson, 2008; Orasanu and Plutzky, 2009). Because the macrovascular conditions are not solely associated with diabetes, the presence and relation of these conditions to the underlying diabetic pathology may be overlooked, which can negatively impact the long-term prognosis.

The clinical priority for patients diagnosed with diabetes mellitus is blood glucose control, which is typically monitored via HbA1c levels. The UKPDS revealed that a high blood glucose level was a risk factor for the development and progression of microvascular disease, and long-term lowering of blood glucose to near-normal levels achieved by intensive blood glucose control reduced the risk of microvascular disease (Turner *et al*., 1998). The UKPDS also found that a 1% reduction in HbA1c contributed to a 37% decrease in relative risk of microvascular complications (Stratton *et al*., 2000), highlighting the importance of this parameter in the long-term prognosis. Despite this, the UKPDS also indicated that tight control of blood glucose was not a sufficient measure to remarkably reduce the risk of macrovascular complications (Turner *et al*., 1998). In the absence of a clinical diagnosis of diabetes, factors like high blood pressure and lipid metabolism disorders increase the risk of macrovascular disease. Concomitant high blood glucose can synergistically amplify the effects of hypertension and hyperlipemia, which will lead to more extensive and serious macrovascular lesions with a younger age of onset (Kanter *et al.*, 2007). Because of this relationship, simply lowering blood glucose is effective in reducing the risk of microvascular disease, but has a limited effect on macrovascular disease.

An additional risk factor of macrovascular disease, high LDL-C levels, can also play an important role in the clinical management of diabetes. Lowering the LDL-C level to at most 2.59 mmol/L (100 mg/dl) is a common goal for patients with diabetes. A 1 mmol/l reduction in LDL-C level is associated with a 36% decrease in the risk of CVD. The 2001 US NCEP ATP III guidelines recommend that the LDL-C level should be lower than 1.8 mmol/L (70 mg/dl) for ultra-high-risk patients who have a medical history of coronary heart disease (CHD) or CHD risk equivalents (such as diabetes, carotid vascular disease, or peripheral vascular disease) (Grundy *et al*., 2004). Current intervention strategies targeting blood lipids may need to be improved because they cannot completely resolve atherogenic dyslipidemia. As such, these interventions only lower LDL-C to ideal levels, but increased levels of TG and/or decreased HDL-C still exist, leaving patients at a high residual risk (Fruchart *et al*., 2008). The percentage of patients with hypercholesterolemia in China is less than 30%. Lipid metabolism disorders in these patients are mainly mild to moderate, which is very common in patients with obesity, the metabolic syndrome, or diabetes mellitus. However, the number of such patients who engage in blood lipid regulation is far less than the number of the patients who participate in active blood pressure and blood glucose control. Hypertension is an independent risk factor for macrovascular and microvascular lesions in patients with type 2 diabetes mellitus. Therefore, with respect to associated vascular complications, lowering blood pressure is as important as lowering blood glucose level for patients with type II diabetes. In this population, an increase of 10 mmHg in SBP will lead to a 15% increase in related mortality, an 11% increase in the rate of myocardial infarction, a 19% increase in the risk of of stroke, and a 12% increase in congestive heart failure (Adler *et al.*, 2000; Sowers and Bakris, 2000). Increased IMT is a sign of early atherosclerosis and several studies have shown that IMT is independently associated with age, sex, blood pressure, LDL level, and TC level (Zanchetti *et al.*, 2001; Niiranen *et al*., 2007). Therefore, all of these metabolic parameters should be included in a comprehensive intervention to manage type II diabetes.

In the present study, the patients with new-onset type 2 diabetes mellitus were randomly assigned to either an intensive treatment or a conventional treatment group. There were no significant differences between groups in baseline general information and clinical parameters. After one or two years,

significant differences existed between the two groups in blood pressure and blood lipid levels but not in blood glucose levels. However, distinct changes had already occurred in the IMT of large arteries, which highlights the importance of blood pressure and blood lipid control to the reversion of macrovascular lesion in patients with type 2 diabetes mellitus. Another important finding was the decreasing trend of HbA1c, TC, LDL-C, blood pressure, and IMT of the femoral artery, and the increasing trend of HDL-C levels over time in patients in the intensive treatment group. These findings suggest that future treatment for diabetes should include a comprehensive treatment approach to manage signs associated with macrovascular disease. Tight regulation of blood glucose alone is not sufficient for delaying or reversing the increase in IMTs of large arteries. Aggressive management of blood pressure and blood lipids should be included in the comprehensive management to reduce the risk of diabetes-related macrovascular disease.

Two years after starting treatment, the percentages of patients with LDL-C, TG, and TC reaching the respective target levels in the intensive treatment group were all higher than the corresponding percentages in the control group. The intensive treatment group was not superior to the conventional treatment group with respect to the percentage of patients with target blood glucose levels and blood pressure. This potentially underscores the problem that patients in the conventional treatment group understood the need to regulate blood glucose and hypertension through prescribed antidiabetic and antihypertensive drugs, but were not as informed about the status or risk of their high blood lipids. Responsibility for the lack of education and informed decisions pertaining to the medical management of these patients also falls on the medical professionals in China. Improved patient and clinician education may increase the percentage of diabetic patients who actively manage blood lipids.

This study demonstrates that early intensive intervention strategies of lowering blood glucose and blood pressure and regulating blood lipids can delay and even reverse the increase in the IMT of large arteries, which will contribute to a reduction in the risk of diabetes-related macrovascular complications and the mortality of CVD. One patient in the intensive treatment group showed abnormal liver function but recovered after discontinuation of antihyperlipidemic drugs. No hypoglycemic events occurred during the two-year follow-up period, which indicated that the established intensive control standard was safe and effective. In this study, the follow-up period was only two years and the sample size was relatively small. Future studies should evaluate similar treatment paradigms with a larger sample size and for a longer follow-up duration to observe the long term effects of intensive treatment on macrovascular lesions and endpoint events.

References

Adler, A.I., Stratton, I.M., Neil, H.A., Yudkin, J.S., Matthews, D.R., Cull, C.A., Wright, A.D., Turner, R.C., Holman, R.R., 2000. Association of systolic blood pressure with macrovascular and microvascular complications of type 2 diabetes (UKPDS 36): prospective observational study. *BMJ*, **321**(7258):412-419. [doi:10.1136/bmj.321.7258.412]

Aronson, D., 2008. Hyperglycemia and the Pathobiology of Diabetic Complications. *In*: Fisman, E.Z., Tenenbaum, A. (Eds.), Cardiovascular Diabetology: Clinical, Metabolic and Inflammatory Facets. Adv. Cardiol. Basel, Karger, vol.**45**, p.1-16. [doi:10.1159/000115118]

Colhoun, H.M., Betteridge, D.J., Durrington, P.N., Hitman, G.A., Neil, H.A., Livingstone, S.J., Thomason, M.J., Mackness, M.I., Charlton-Menys, V., Fuller, J.H., 2004. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. *Lancet*, **364**(9435):685-696. [doi:10.1016/S0140-6736(04)16895-5]

Fruchart, J.C., Sacks, F., Hermans, M.P., Assmann, G., Brown, W.V., Ceska, R., Chapman, M.J., Dodson, P.M., Fioretto, P., Ginsberg, H.N., *et al*., 2008. The residual risk reduction initiative: a call to action to reduce residual vascular risk in patients with dyslipidemia. *Am. J. Cardiol*., **102**(10 Suppl.):1K-34K. [doi:10.1016/j.amjcard.2008.10.002]

Gæde, P., Lund-Andersen, H., Parving, H.H., Pedersen, O., 2008. Effect of a multifactorial intervention on mortality in type 2 diabetes. *N. Engl. J. Med.*, **358**(6):580-591. [doi:10.1056/NEJMoa0706245]

Grundy, S.M., Benjamin, I.J., Burke, G.L., Chait, A., Eckel, R.H., Howard, B.V., Mitch, W., Smith, S.C.Jr., Sowers, J.R., 1999. Diabetes and cardiovascular disease: a statement for healthcare professionals from the American Heart Association. *Circulation*, **100**(10):1134-1146. [doi:10.1161/01.CIR.100.10.1134]

Grundy, S.M., Cleeman, J.I., Merz, C.N., Brewer, H.B.Jr., Clark, L.T., Hunninghake, D.B., Pasternak, R.C., Smith, S.C.Jr., Stone, N.J., 2004. Implications of recent clinical trials for the National Cholesterol Education Program

Adult Treatment Panel III guidelines. *J. Am. Coll. Cardiol.*, **44**(3):720-732. [doi:10.1016/j.jacc.2004.07.001]

Holman, R.R., Paul, S.K., Bethel, M.A., Matthews, D.R., Neil, H.A., 2008. 10-year follow-up of intensive glucose control in type 2 diabetes. *N. Engl. J. Med.*, **359**(15): 1577-1589. [doi:10.1056/NEJMoa0806470]

Kanter, J.E., Johansson, F., LeBoeuf, R.C., Bornfeldt, K.E., 2007. Do glucose and lipids exert independent effects on atherosclerotic lesion initiation or progression to advanced plaques? *Circul. Res.*, **100**(6):769-781. [doi:10.1161/01.RES.0000259589.34348.74]

Lorenz, M.W., von Kegler, S., Steinmetz, H., Markus, H.S., Sitzer, M., 2006. Carotid intima-media thickening indicates a higher vascular risk across a wide age range: prospective data from the Carotid Atherosclerosis Progression Study (CAPS). *Stroke*, **37**(1):87-92. [doi:10.1161/01.STR.0000196964.24024.ea]

Lorenz, M.W., Markus, H.S., Bots, M.L., Rosvall, M., Sitzer, M., 2007. Prediction of clinical cardiovascular events with carotid intima-media thickness: a systematic review and meta-analysis. *Circulation*, **115**(4):459-467. [doi:10.1161/CIRCULATIONAHA.106.628875]

Niiranen, T., Jula, A., Kantola, I., Moilanen, L., Kahonen, M., Kesaniemi, Y.A., Nieminen, M.S., Reunanen, A., 2007. Home-measured blood pressure is more strongly associated with atherosclerosis than clinic blood pressure: the Finn-HOME Study. *J. Hypert.*, **25**(6):1225-1231. [doi:10.1097/HJH.0b013e3280d94336]

Nissen, S.E., Tuzcu, E.M., Schoenhagen, P., Brown, B.G., Ganz, P., Vogel, R.A., Crowe, T., Howard, G., Cooper, C.J., Brodie, B., *et al*., 2004. Effect of intensive compared with moderate lipid-lowering therapy on progression of coronary atherosclerosis: a randomized controlled trial. *JAMA*, **291**(9):1071-1080. [doi:10.1001/jama.291.9.1071]

Orasanu, G., Plutzky, J., 2009. The pathologic continuum of diabetic vascular disease. *J. Am. Coll. Cardiol.*, **53**(5 Suppl.):S35-S42. [doi:10.1016/j.jacc.2008.09.055]

Ray, K.K., Seshasai, S.R., Wijesuriya, S., Sivakumaran, R., Nethercott, S., Preiss, D., Erqou, S., Sattar, N., 2009. Effect of intensive control of glucose on cardiovascular outcomes and death in patients with diabetes mellitus: a meta- analysis of randomised controlled trials. *Lancet*, **373**(9677):1765-1772. [doi:10.1016/S0140-6736(09)60697-8]

Saydah, S.H., Fradkin, J., Cowie, C.C., 2004. Poor control of risk factors for vascular disease among adults with previously diagnosed diabetes. *JAMA*, **291**(3):335-342. [doi:10.1001/jama.291.3.335]

Skyler, J.S., Bergenstal, R., Bonow, R.O., Buse, J., Deedwania, P., Gale, E.A.M., Howard, B.V., Kirkman, M.S., Kosiborod, M., Reaven, P., *et al*., 2009. Intensive glycemic control and the prevention of cardiovascular events: implications of the ACCORD, ADVANCE, and VA diabetes trials. *J. Am. Coll. Cardiol.*, **53**(3):298-304. [doi:10.1016/j.jacc.2008.10.008]

Sowers, J.R., Bakris, G.L., 2000. Antihypertensive therapy and the risk of type 2 diabetes mellitus. *N. Engl. J. Med.*, **342**(13):969-970. [doi:10.1056/NEJM200003303421310]

Stratton, I.M., Adler, A.I., Neil, H.A., Matthews, D.R., Manley, S.E., Cull, C.A., Hadden, D., Turner, R.C., Holman, R.R., 2000. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ*, **321**(7258): 405-412. [doi:10.1136/bmj.321.7258.405]

Turner, R.C., Holman, R.R., Cull, C.A., Stratton, I.M., Matthews, D.R., Frighi, V., Manley, S.E., Neil, A., McElroy, K., Wright, D., *et al*., 1998. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet*, **352**(9131):837-853. [doi:10.1016/S0140-6736(98)07019-6]

Zanchetti, A., Crepaldi, G., Bond, M.G., Gallus, G.V., Veglia, F., Ventura, A., Mancia, G., Baggio, G., Sampieri, L., Rubba, P., *et al*., 2001. Systolic and pulse blood pressures (but not diastolic blood pressure and serum cholesterol) are associated with alterations in carotid intima-media thickness in the moderately hypercholesterolaemic hypertensive patients of the Plaque Hypertension Lipid Lowering Italian Study. *J. Hypert.*, **19**(1):79-88. [doi:10.1097/00004872-200101000-00011]