Recent Advances of Intervention to Inhibit Progression of Carotid Intima-Media Thickness in Patients With Type 2 Diabetes Mellitus

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**Background and Purpose**—Type 2 diabetes is associated with a high cardiovascular morbidity and mortality. Recent advances of intervention studies in type 2 diabetes with use of carotid intima-media thickness (CIMT) measurement as a surrogate end point may allow for better understanding of the undetermined process of atherosclerosis, the effect of interventions, and the usefulness of CIMT to inhibit events of cardiovascular disease.

**Summary of Review**—Data were available from 11 studies (n=1578) in subjects with type 2 diabetes (including impaired glucose tolerance, n=132) that evaluated the effect of interventions on change in CIMT. The overall weighed rate of change in mean CIMT based on data among control groups (ie, type 2 diabetes without interventions) was 0.034 mm/y (95% CI, 0.029 to 0.039; median SD, 0.054), in which mean HbA1c was 7.86% (95% CI, 7.72 to 8.00; median SD, 1.5). A significant close correlation of HbA1c with rate of CIMT change was found (R²=0.35, P=0.01). Agents for lowering of blood glucose, platelet activation, or blood pressure significantly reduced the CIMT increase, independent of blood glucose control. This implies that other mechanisms of such agents to diminish CIMT increase should be explored.

**Conclusions**—CIMT measurement may contribute to elucidating the short- and/or long-term effect of interventions on the rate of change in CIMT in relation to the levels of various risk factors. Although the method needs further standardization, pharmacological interventions are likely to inhibit progression of CIMT, leading to a reduction of cardiovascular events. *(Stroke. 2006;37:2420-2427.)*

**Key Words:** atherosclerosis ■ carotid arteries ■ diabetes mellitus ■ glucose ■ intervention studies ■ intima-media thickness

Patients with type 2 diabetes mellitus are at 2- to 6-fold higher risk for cardiovascular disease than persons without diabetes.1,2 The clustering of traditional risk factors such as arterial hypertension and dyslipidemia cannot account for the excessive cardiovascular burden of patients with type 2 diabetes. Moreover, atherosclerosis is thought to begin in the prediabetic stage and to progress silently for decades before clinical events such as myocardial infarction or stroke occur.3 These facts call strongly for detecting early changes of atherosclerosis and starting intervention in type 2 diabetic subjects.

Carotid intima-media thickness (CIMT) is a well-described surrogate marker for cardiovascular risk. A thickened CIMT correlates with the presence of myocardial infarction and stroke by cross-sectional analysis.4-6 Several prospective studies have shown an association between increased CIMT and the incidence of cardiovascular disease in the general population with7,8 or without9-12 prior cardiovascular disease. CIMT is significantly higher in diabetic patients than in nondiabetic subjects,13-16 and an increased CIMT is associated with angiography-evaluated coronary artery disease17 and predicts future events of silent brain infarction17 and coronary heart disease18,19 in type 2 diabetic subjects.

CIMT measurements are currently used in clinical trials to evaluate the efficacy of interventions. In these trials, CIMT is used as an alternative end point (surrogate) for cardiovascular morbidity and mortality on the premise that changes in CIMT reflect changes in risk of cardiovascular disease. The advantage of using CIMT in a longitudinal trial as a surrogate end point to evaluate progression of atherosclerosis is the considerable reduction in sample size and in duration of follow-up, and it could contribute to investigating the cause-and-effect relationship in the process of atherosclerosis.

In the present report, risk factors contributing to CIMT in type 2 diabetic subjects are reviewed briefly as we discuss the importance and interpretation in recent advances of intervention studies with the use of CIMT measurements in patients with type 2 diabetes.

**Risk Factors That Contribute to CIMT Increase in Patients With Type 2 Diabetes**

**From Cross-Sectional Studies**

The majority of cross-sectional studies in the nondiabetic population indicated that elevated levels of established cardiovascu-
lar risk factors, such as age, sex, total cholesterol, LDL cholesterol, systolic blood pressure, body mass index, and a decrease in HDL cholesterol, are associated with an increased CIMT in a graded manner (reviewed in reference 20). Similarly, in patients with type 2 diabetes, age, sex, total cholesterol, LDL cholesterol, systolic blood pressure, and a decrease in HDL cholesterol are associated with an increased CIMT. Duration of diabetes is indicated to increase CIMT. A slight increase of urinary albumin excretion is a significant determinant of CIMT independent of conventional risk factors in type 2 diabetic patients without cardiovascular disease. Platelet activation as measured by plasma concentrations of β-thromboglobulin and platelet factor 4 was increased in patients with increased CIMT. Heritability of CIMT was suggested in families with or without diabetes, and ethnicity appears to be associated with CIMT. Candidate genes in association with CIMT are still under investigation.

CIMT is increased even from the prediabetic stage, i.e., persons with impaired glucose tolerance (IGT) had elevated levels of CIMT compared with those of the same age with normal glucose tolerance. Studies in subjects at risk for the development of type 2 diabetes indicated that postprandial glucose levels were more strongly associated with CIMT than levels of fasting glucose and HbA1c, independent of age and sex. It is likely that postprandial glucose elevation is associated with a clustering of standard risk factors. Consequently, postprandial hypertriglyceridemia, which could be induced by postprandial hyperglycemia, was closely associated with increased CIMT despite normal levels of fasting triglycerides.

Several studies indicated that insulin resistance, which is directly associated with abdominal fat accumulation as assessed by anthropometric indicators such as waist circumference or waist-hip ratio, contributes to increased CIMT. The significant association of insulin resistance with CIMT was shown not only in the diabetic but also in the nondiabetic population. An underlying mechanism is that adipose tissue is an endocrine organ that produces many peptides, such as angiotensin, interleukin (IL)-6, tumor necrosis factor-α, plasminogen activator inhibitor-1, leptin, and adiponectin, which in turn affect vascular structure.

### From Longitudinal Studies

Although there have been many cross-sectional studies, only a few longitudinal studies have investigated the determinant of changes in CIMT in type 2 diabetic subjects. These included several intervention studies. Whereas most of the cross-sectional studies failed to demonstrate an association of blood glucose control with CIMT, longitudinal studies were able to find it significantly. Furthermore, the reduction of CIMT was correlated with reduction of postprandial glucose and insulin resistance as assessed by homeostasis model assessment–insulin resistance (HOMA-IR). Platelet activation, as assessed with the use of immunological markers such as CD63, correlated with 1-year progression of CIMT independent of putative cardiovascular risk factors.

### Intervention Studies to Inhibit CIMT Increase in Type 2 Diabetes

Intervention studies with CIMT measurement have been performed on the premise that CIMT reflects atherosclerosis and cardiovascular risk because numerous studies have shown graded relations between elevated levels of risk factors and increased CIMT, and increased CIMT has been related to atherosclerosis in the abdominal aorta, arteries in lower extremities, and coronary arteries (reviewed in references 20, 47, and 48). In the present article, we sought studies (1) of pharmacological interventions, (2) in type 2 diabetes, (3) in which annual changes of CIMT are described, (4) in type 2 diabetes, and (5) involving a significant determinant of CIMT independent of conventional risk factors.

Blood Glucose–Lowering Agents

Acarbose is an α-glucosidase inhibitor that specifically reduces postprandial glucose excursion by delaying the release of glucose from disaccharides and complex carbohydrates in the small intestine. Acarbose treatment was associated with significantly reduced progression of CIMT in subjects with IGT, namely, a prediabetic stage. The annual increase of CIMT was reduced by 50% in the acarbose group (0.007 mm/y) versus the placebo group (0.013 mm/y). Although no differences between the groups were seen at the end point with regard to fasting, 2-hour postchallenge glucose, HbA1c, and lipid profiles, implying that the study was inconclusive in terms of the cause-and-effect relationship, the study was important in suggesting an effect of acarbose to inhibit progression of early-stage atherosclerosis.

Treatment with voglibose, an α-glucosidase inhibitor, reduced the progression of CIMT. Although postprandial glucose levels were not evaluated in the study, a significant linear relationship between annual changes of CIMT and mean HbA1c levels during the follow-up was seen. CIMT progressed by 0.0137 mm/y per 1% increase of HbA1c. Interestingly, treatment of voglibose reduced HbA1c levels by 0.6%, and it slowed CIMT progression by 0.08 mm/y compared with the control group, which is 10-fold the estimated value (0.0137 times 0.6 equal to 0.008 mm/y). It indicates that reduction of HbA1c can only partially explain the remarkable antiatherogenicity of voglibose; the reason was unknown.

Repaglinide, a rapid-onset/short-duration insulinitropic agent, significantly reduced the postprandial glucose peak (148 ± 28 mg/dL) compared with glyburide (180 ± 32 mg/dL; P = 0.01), a long-acting sulfonylurea, with a similar decrease of HbA1c (−0.9%), resulting in a significant reduction of CIMT (−0.029 versus −0.005 mm/y; P = 0.02). Repaglinide treatment also reduced IL-6 and C-reactive protein. The study clearly indicated that progression of carotid atherosclerosis can be prevented by the control of postprandial hyperglycemia in type 2 diabetes. Underlying mechanisms are considered as follows: Postprandial hyperglycemia causes an overproduction of superoxide, which activates many pathways involved in the pathogenesis of diabetic vascular complications such as polyol pathway flux, increased advanced glycation end product formation, protein kinase C,
nuclear factor-κB, and hexosamine, leading to DNA damage and endothelial dysfunction (reviewed in Reference 53).

Metformin in combination with glibenclamide, or glitza-
ide, was associated with significantly reduced progression of CIMT (0.003 and 0.032 mm/y, respectively) compared with glibenclamide alone (0.064 mm/y; \( P < 0.0001 \) and \( P = 0.005 \), respectively).\(^4\) Multiple regression analysis revealed that use of metformin or glitazide significantly and independently accounted for inhibition of the progression of CIMT, whereas the mechanism independent of the glycemic control remains undetermined in the study.

Pioglitazone was compared with glimepiride in terms of the inhibitory effect on CIMT.\(^40\) Despite similar improvements in HbA\(_1c\), CIMT regression was significantly greater in the pioglitazone group (−0.054 versus −0.011 mm/0.5 y; \( P < 0.005 \)). Reduction of CIMT correlated with improvement in insulin resistance \( (r = 0.29, P < 0.0005) \) and was independent of improvement in glycemic control. Another study was performed with the use of pioglitazone.\(^41\) Pioglitazone in combination with acarbose treatment, in addition to diet, sulfonylurea, or insulin injections, significantly reduced the progression of CIMT compared with the control group (−0.002 versus 0.043 mm/y; \( P < 0.0001 \)).\(^41\) The effect was again independent of HbA\(_1c\). Moreover, the intervention effect was seen similarly in subjects with diet, sulfonylurea, or insulin injections at baseline. In both studies, other confounding factors such as systemic blood pressure levels, lipid profiles, renin-angiotensin system (RAS) inhibition, statins, and antplatelet therapy were well controlled by equal distribution between the groups. The latter study had less magnitude of CIMT regression than the former despite the fact that the latter was in combination with acarbose, presumably because the baseline features of the patients in the latter had lower levels than in the former in terms of HbA\(_1c\), (6.6% versus 7.5%), blood pressure (128/70 versus 149/87 mm Hg), lipid profiles (LDL, 3.18 versus 3.51 mmol/L; HDL, 1.37 versus 1.19 mmol/L), and body mass index (25.9 versus 31.8). The magnitude of CIMT regression caused by pharmacological interventions could be influenced by the baseline levels of risk factors.

The 2 studies of pioglitazone indicate its antiatherogenic effect, which is independent of glycemic control. Both studies indicated slight but significant improvement of blood pressure levels, HDL cholesterol, insulin resistance index (HOMA-IR), and C-reactive protein levels. The former study showed a decrease of circulating concentrations of matrix metalloproteinase-9 and monocyte chemoattractant protein-1\(^{44}\) and the latter study showed a decrease of urinary albumin excretion rate in the pioglitazone group.\(^41\) All these variables are well-known athero-
genic factors. Pioglitazone, an agonist of peroxisome proliferator-activated receptor-γ, induces an improvement in various such risk factors that might reduce cardiovascular morbidity and mortality (reviewed in reference 55).

**Antiplatelet Agents**

As antiplatelet agents, aspirin, ticlopidine, and cilostazol were investigated in terms of the effect on CIMT.\(^{17,45}\) Although a significant correlation of HbA\(_1c\) with changes of CIMT was observed in these studies, administration of aspirin (81 mg/d), ticlopidine (200 mg/d), or cilostazol (100 to 200 mg/d) signifi-
cantly reduced the progression of CIMT by 0.032 mm/y, 0.041 mm/y, or 0.056 mm/y, respectively, independent of metabolic control. Whereas studies are scarce that demonstrated a direct relationship of CIMT changes with a hard end point, ie, onset of vascular diseases through pharmacological interven-
tions, intervention by cilostazol diminished progression of CIMT and onset of silent brain infarction by clearly demonstrating a significant correlation of CIMT changes and the number of infarctlike regions as detected by MRI.\(^{17}\)

**RAS Inhibitors**

Although angiotensin-converting enzyme inhibitors reduced the morbidity and mortality from myocardial infarction and stroke in patients including type 2 diabetes,\(^{46}\) and angiotensin II receptor blockers appear to have an anti-inflammatory effect by suppressing generation of reactive oxygen species in humans,\(^{57}\) few studies have investigated the effect of RAS inhibitors on CIMT in type 2 diabetes. A study showed that enalapril (10 mg/d), an angiotensin-converting enzyme inhibitor, reduced CIMT thickening by 0.01 mm/y.\(^{50}\) Half of the patients in this 2-year follow-up study had antihypertensive agents at baseline, and additional treatment with enalapril did not lower systemic blood pressure levels; therefore, the reduc-
tion of CIMT appeared independent of a blood pressure–lowering effect. The magnitude may be expected to increase in future studies because the study was performed under the condition that levels of HbA\(_1c\), blood pressure, and LDL chole-
terol were persistently high.

**Lipid-Lowering Agents**

Two studies thus far have investigated the effect of lipid-
lowering agents on changes in CIMT in type 2 diabetes, and both indicated no significant effect on CIMT; one was by bezafibrate,\(^{52}\) and the other was by cerivastatin.\(^{51}\) In both studies, type 2 diabetic patients without the intervention (control group) obtained regression of IMT. This finding was unfortunately inconsistent with the aforementioned studies. The former study investigated patients with extremely poor blood glucose control, which worsened during the study period. The poor control may have precluded a possible inhibitory effect of intervention on CIMT thickening. Nevertheless, the 2 studies were successful in demonstrating a significant reduction of cardiovascular events by the respective agent. The finding may point to speculation that a statin-induced (or fibrate-induced) cardiovascular event reduction is not related to CIMT regression but possibly is associated with plaque reduction, although this was not studied. From a pathophysiological point of view, the intimal and medial layers of the vessel wall in type 2 diabetes are changed by complex processes such as extra-
cellular matrix glycosylation and media calcification. The regression of CIMT is unlikely to occur without good or fair blood glucose control. On the other hand, lipid-
lowering agents may have a beneficial influence on plaque vulnerability. With the use of the integrated backscatter method, which enables quantification of the tissue charac-
teristics of the carotid plaque lesion, atorvastatin improved the fragility of the plaque without a significant reduction of CIMT.\(^{58}\) In addition, recent studies that evaluated plaque
volume with the use of intravascular ultrasound examinations of coronary arteries or noninvasive MRI indicated a beneficial effect of high-dose strong statin (atorvastatin) on plaque reduction. Because a number of studies in the nondiabetic population have indicated a beneficial effect of lipid lowering by statin on the rate of change in CIMT (reviewed in references 48 and 62), further studies in type 2 diabetes are required in terms of the lipid-lowering effect on CIMT and plaque.

**Annual Increase of CIMT With and Without Interventions in Type 2 Diabetes**

The rate of change in CIMT differs considerably across studies. A substantial factor that influences the rate of change in CIMT may be blood glucose control. Each intervention group had obtained substantially improved glycemic control, whereas most studies showed statistical significance for the effect of intervention on CIMT after adjustment for glycemic control. At least when restricted to studies that showed a significant intervention effect on CIMT changes in type 2 diabetes, there was a strong close correlation of HbA1c during the study with CIMT changes ($R^2=0.38$, $P<0.01$; Figure 1). The result was similar when restricted further to data with follow-up of >1 year ($R^2=0.35$, $P=0.01$).

### Clinical Trials Evaluating the Effect of an Intervention on CIMT in Patients With Type 2 Diabetes

<table>
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<th>Follow-Up (y)</th>
<th>Intervention</th>
<th>No. of Subjects</th>
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<th>HbA1c (%)</th>
<th>Segment</th>
<th>Wall</th>
<th>Reading &amp; Edge</th>
<th>Detection</th>
<th>Age (y)</th>
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<td>CCA</td>
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<td>63</td>
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<td>Batch &amp;</td>
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<tr>
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</tr>
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</table>

*P<0.0001; †P<0.001; ‡P<0.01; §P<0.05 vs control; **change of IMT in half-year is given in stead of annual change.

The finding indicates that, in interventions to inhibit increase of CIMT in patients with type 2 diabetes, blood glucose control may play a principal role. In addition, mechanisms that are specific for each agent independent of blood glucose control contribute to the reduction of CIMT.

Methodological issues in CIMT measurements and/or differences in baseline clinical characteristics such as age, sex, duration, ethnicity, body mass index, HbA1c, blood pressure, LDL and HDL cholesterol, and smoking (as shown in the Table) could influence variations in the rate of changes in CIMT across studies. The underlying mechanisms for the variations are to some extent population differences, but a large effect is attributable to differences in ultrasound protocols, reading equipment (as shown in the Table), and potential bias attributable to drift over time in reading as a consequence of changes within readers from thick to thin or vice versa. Although this drift could affect progression rates, drift does not usually affect the observed differences between the treatment arms because drift occurs in both groups to the same extent. These issues have been discussed as well in regard to randomized controlled trials of various interventions not only in diabetics but also in nondiabetics and require further investigation.
What is an annual increase of CIMT in type 2 diabetes if there is no specific intervention? In control groups of 8 studies in which treatment for blood glucose control was unchanged during the study,\textsuperscript{17,41–43,45,50–52} it is evident that the rate of change in CIMT differed considerably across studies, depending at least in part on individual glycemic control. The overall weighted rate of change in mean CIMT based on data among control groups from the 8 studies was 0.034 mm/y (95% CI, 0.029 to 0.039), with a median SD of 0.054, in which mean HbA\textsubscript{1c} was 7.86% (95% CI, 7.72 to 8.00; median SD, 1.5; calculated by the formula shown below). Annual increase of CIMT is reported as 0.007 (Germany)\textsuperscript{63} and 0.008 (Japan)\textsuperscript{64} mm/y in healthy populations and as 0.015 mm/y (95% CI, 0.012 to 0.017) from intervention studies that studied patients at risk for cardiovascular disease without diabetes (diabetes <5%).\textsuperscript{47} The findings imply that traditional cardiovascular risk doubles the rate of change in CIMT, and type 2 diabetes further doubles the rate.

![Figure 1. Annual rate of CIMT change (mm/year) according to HbA\textsubscript{1c} levels (%). Linear regression line (solid) and 95% confidence bands of residual variation (dashed) are indicated. Each number indicates reference number. *The study period was half-year, so the data were doubled as annual rate, which were not included in the analysis.](image-url)
The pooled mean value was computed by the following equation:

$$
\text{pooled mean (Mp)} = \frac{n_1 \times \text{mean}_1 + n_2 \times \text{mean}_2 + \cdots + n_g \times \text{mean}_g}{n_1 + n_2 + \cdots + n_g}
$$

(1)

and the pooled variance value such as

$$
\text{pooled variance (Vp)} = \frac{(n_1 - 1) \times V_1 + (n_2 - 1) \times V_2 + \cdots + (n_g - 1) \times V_g}{n_1 + n_2 + \cdots + n_g - g}
$$

(2)

where g is the number of group, ni is the sample size, and Vi is the variance of the i group, respectively (i=1, 2, ..., g).

CIMT as a Surrogate End Point Versus Event as a Hard End Point in Pharmacological Interventions: Is it Sufficient to Predict a Reduction of Cardiovascular Event in Type 2 Diabetes?

Thus far, only scarce information is available on the potential of regression (or dimensioned progression) of CIMT for reduction of cardiovascular events; only a cilostazol study has provided this information. In patients with type 2 diabetes, large-scale randomized controlled trials or meta-analyses have recently indicated a reduction of cardiovascular morbidity and mortality through interventions by pioglitazone, acarbose, metformin, statins, angiotensin II receptor blockers, and fibrates. Therefore, it is likely that these agents could inhibit progression of CIMT, thus leading to a reduction of cardiovascular events (Figure 2). Investigating changes of CIMT would contribute to the elucidation of unknown mechanisms of occurring myocardial infarction or stroke. One should acknowledge that CIMT is a measurement of a focal abnormality (not circumferential), of a layer combined with intimal and medial, and of chronically changed accumulation. Acute changes such as spastic vasoconstriction or plaque rapture cannot be reflected by CIMT measurement. In this regard, CIMT regression might not be a prerequisite for reducing the events in type 2 diabetes.

Apart from type 2 diabetes–related studies, whether CIMT is a valid surrogate for clinical end points has been discussed recently by proposing criteria to establish the surrogacy. Clinical and statistical criteria to meet establishment of the surrogacy have been investigated. We did not perform this investigation because the intervention agents were too various and the protocol remains complex; however, this logical, mathematical approach could provide extended analyses in the future.

Limitation of Interpretation

Interpretation across studies is limited and is subject to standardization of the methods of CIMT measurement and HbA1c. Normal values of CIMT and HbA1c were not provided in all publications. Furthermore, besides differences in clinical characteristics of subjects, the number of subjects (sample size) and follow-up period of the study may affect the rate of change in CIMT. It has not been completely elucidated whether CIMT progression is linear and is a function of basal CIMT. Therefore, whether a short-term effect of intervention on rate of CIMT change may last for years is questionable, and one should be cautious in calculating an annual increase by doubling half-year progression. Standardization of methods and longer follow-up periods would increase the overall precision of estimates. Alternatively, the present data may be viewed as the beginning of analysis, leading to elucidation of the short- and/or long-term effect of interventions in relation to the levels of risk factors on the rate of change in CIMT, as found in the Table and Figure 1.

Conclusion and Future Perspectives

In conclusion, the annual increase of CIMT was 0.034 mm/y (95% CI, 0.029 to 0.039) in subjects with type 2 diabetes without any specific interventions, as estimated from 8 studies with a mean HbA1c of 7.86%. The rate of CIMT change differs considerably across studies, which may be influenced by levels of blood glucose control and other various risk factors such as blood pressure, lipid profiles, platelet activity, ethnic difference, and insulin resistance. It is likely that intervention for these factors inhibits progression of CIMT, principally by improving blood glucose control and additionally by each agent-specific effect independent of blood glucose control, leading to a reduction of cardiovascular events. Standardization of CIMT measurement still remains an important issue. In subjects with type 2 diabetes, multifactorial interventions including several potent antiatherogenic agents, such as pioglitazone, α-glucosidase inhibitor, aspirin, statins, and RAS inhibitor, being used under the condition of good blood glucose control, would diminish IMT increase and reduce cardiovascular morbidity and mortality in the future. CIMT measurement could be a clue to explore the unknown mechanisms of development of atherosclerosis.

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Disclosures

None.
References


Recent Advances of Intervention to Inhibit Progression of Carotid Intima-Media Thickness in Patients With Type 2 Diabetes Mellitus
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