Although it has been apparent for some time that coronary heart disease (CHD) is the major cause of morbidity and mortality in patients with type 2 diabetes, we do not seem to be gaining much ground in our efforts to understand either why this is the case or how best to prevent it. The dilemma was made explicit by the results of the United Kingdom Prospective Diabetes Study (UKPDS) showing that improvement in glycemic control was much more effective in reducing the microvascular complications of type 2 diabetes than it was in decreasing CHD. A subsequent analysis of the UKPDS data emphasized these differences in outcome by directly demonstrating that the impact of better glycemic control on incidence of CHD was strikingly attenuated as compared with the robust improvement in microvascular disease. The report by Wagenknecht and associates in this issue of Arteriosclerosis, Thrombosis, and Vascular Biology serves to both emphasize the magnitude of the problem as well as point out that the solution does not necessarily result from greatly increasing the number of CHD risk factors measured.

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The study by Wagenknecht and colleagues involved ultrasound evaluation of the progression over 5 years of carotid artery thickening in 1192 individuals, 336 of whom had type 2 diabetes at baseline, either undiagnosed (n=138) or diagnosed (228). Unfortunately, we are not told whether any of the participants developed clinical evidence of CHD during the 5-year period of observation. However, 40 deaths did occur, and the mortality rate was highest in the group with diagnosed diabetes at baseline (5.3%), as compared with 1.6%, 2.9%, and 1.6% in those with normal glucose tolerance (NGT), impaired glucose tolerance (IGT), or undiagnosed diabetes, respectively. Because important conclusions of this study are that carotid thickening: 1) did not increase at an increased rate in patients with IGT, and 2) increased at a greater rate in diagnosed than in undiagnosed diabetes, it might have been informative to know what the 5-year incidence of CHD was in the 4 experimental groups, as well as the medical conditions that accounted for the apparent differences in mortality rates.

Although the report by Wagenknecht et al provides powerful evidence of accentuated carotid artery intimal medial thickness (IMT) in patients with type 2 diabetes, some of their findings are not self-explanatory. For example, IMT at baseline appeared to be similar in subjects with NGT and undiagnosed type 2 diabetes in both the internal carotid artery (ICA) and the common carotid artery (CCA), and it is not immediately apparent that the IMT values in the CCA were substantively different in any of the 4 groups. In the same vein, IMT in patients with known diabetes was only increased in the ICA as compared with those with undiagnosed diabetes. However, when evaluated 5 years later, the progression of IMT in both the CCA and ICA in patients with either undiagnosed or diagnosed diabetes was 2 to 3 times greater than in those with either NGT or IGT. Viewed in a simple-minded manner, it is not immediately obvious why the baseline values could have been so relatively similar in view of these dramatic differences in rate of progression. Another simplistic observation relates to the apparent inability of antihyperglycemic treatment to prevent the progressive increase in IMT. In this context, it appears that IMT progression in patients with known diabetes progressed excessively despite the fact that ~75% of the population was treated with oral antihyperglycemic compounds, and ~25% were receiving insulin. Although the pharmacological approach was less intensive in those with previously undiagnosed diabetes, ~40 of these individuals had been placed on oral antihyperglycemic agents during the period of observation. Is the apparent lack of efficacy of antihyperglycemic agents due to the inability to achieve good glycemic control? Were there any differences the rate of IMT progression in the groups with previously undiagnosed diabetes as a function of whether or not they were receiving antihyperglycemic compounds? Did progression of IMT differ as a function of the kind of antihyperglycemic treatment? Perhaps the most surprising finding was the observation that IMT did not increase to a greater degree in patients with IGT as compared with those with NGT. Given the evidence of increased CHD risk in patients with IGT, the lack of progression of IMT is not self-evident.

A second series of unanswered questions raised by the findings of Wagenknecht and colleagues is the relationship between the CHD risk factors measured in this study and the changes in carotid IMT. It is difficult from the information given in their Table 1 to assess the statistical significance of any differences in CHD risk factors among the 4 experimental groups. However, given the variability in each of the measures listed, the mean values of the 4 groups do not seem all that different for many of the risk factors measured. Furthermore, the degree of IMT progression did not appear to

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change substantially when adjusted for differences in all of the CHD risk factors. The implication of this finding is not clear, but one gets the impression that the authors believe this is because diabetes, per se, and perhaps hyperglycemia, is the major change responsible for accelerated atherogenesis in these patients. However, if hyperglycemia was the major culprit, it is difficult to understand the apparent similarity between values for IMT in the subjects with NGT as compared with patients with undiagnosed diabetes. Alternatively, rather than concluding that the condition of diabetes and/or hyperglycemia is the major offender, it is possible that the metabolic changes in patients with type 2 diabetes that are most pro-atherogenic have not been measured. For example, evidence has been recently published showing that increased plasma concentration of asymmetric dimethylarginine (ADMA), an endogenous inhibitor of NO synthase, was an independent predictor of CHD in patients with renal disease. Given evidence that ADMA concentrations are increased in patients with type 2 diabetes, it could be argued that changes in ADMA, or some other measure of endothelial dysfunction, might represent the crucial link between type 2 diabetes and accelerated atherogenesis.

Finally, and this is written with great trepidation, it is possible that conventional statistical analyses of large observational studies may not be the most useful way to gain clinically relevant information concerning a situation as complex as the relationship between type 2 diabetes and macrovascular disease. For example, there is evidence that lowering plasma LDL cholesterol (LDL-C) concentrations decreases CHD in patients with type 2 diabetes. However, it does not seem likely that the analysis of the data collected by Wangenknecht and associates would have identified LDL-C as either playing a role in the accentuated progression of IMT in the 2 groups of diabetics, or suggesting that it would be a useful intervention to prevent CHD in these patients. In addition to the increased utility of intervention studies, based on a clear-cut hypothesis, useful information might be gained by analyzing observational data in a hypothesis-driven manner. For example, it is clear that enormous differences can exist in individuals with NGT regarding their degree of insulin resistance, plasma insulin concentrations, and prevalence of dyslipidemia. Given the 553 individuals with NGT in the study by Wangenknecht et al, would it have been useful to evaluate the progression of IMT by comparing the changes in IMT progression in the 100 most insulin-sensitive individuals with the 100 most insulin-resistant individuals? Similarly, in view of the recent demonstration that plasma insulin concentrations predict CHD in patients with diabetes, might we have learned something different if Wangenknecht and colleagues had stratified the newly diagnosed diabetics on the basis of their plasma insulin concentrations, and evaluated the ability of differences in this variable to predict progression of IMT? I don’t know the answers to any of these questions, but it seems possible that asking them might lead to some additional insight. At the least, it seems crucial to try to understand how on the one hand it is possible to demonstrate relatively robust relationships between CHD risk factors and CHD events in certain types of studies and not in others.

In conclusion, the results described by Wangenknecht et al have emphasized both the severity of the atherogenic process in patients with type 2 diabetes and our current lack of success in preventing it. It is difficult to take exception to their closing statement that “early diagnosis, treatment, and control of blood glucose may reduce this risk, as well as the intensified screening, prevention and management of CVD risk factors that accompany diabetes.” On the other hand, the evidence of rapid progression of IMT they documented in their study suggests that either we lack the ability to initiate the clinical interventions necessary to attenuate the atherogenic process in these patients, or the knowledge required to make these efforts effective is not available. There is little doubt that we can become more aggressive in therapeutic efforts based on current understanding, but to me, the major lesson learned from this study is how much more we need to know. In that latter context, I also believe that the more hypothesis-driven the study, and the more clearly defined the clinical phenotype; the more likely we are to gain new and useful information.

References
Type 2 Diabetes and Coronary Heart Disease: We Keep Learning How Little We Know
Gerald Reaven

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