Diabetes and Coronary Risk Equivalency

What does it mean?

The National Cholesterol Education Program Adult Treatment Panel III (ATP III) listed diabetes as a coronary heart disease (CHD) risk equivalent for setting therapeutic goals for LDL cholesterol (1). A goal for LDL cholesterol of <100 mg/dl was recommended for patients with CHD and CHD risk equivalents. The latter included individuals with noncoronary forms of atherosclerotic cardiovascular disease (ASCVD), diabetes, and patients with a 10-year risk for major coronary events (myocardial infarction + coronary death) of >20%. For the majority of patients with diabetes, this LDL cholesterol goal would evoke the use of cholesterol-lowering drugs, particularly statins. Some investigators have questioned whether most or all patients with diabetes have a CHD risk equivalent and thus require cholesterol-lowering drugs (2). One approach to this issue is to examine epidemiological data relating to absolute risk for developing CHD in various populations of persons with diabetes.

In the present issue of *Diabetes Care*, Howard et al. (3) reported the incidence of CHD in the Strong Heart Study, a cohort study of cardiovascular disease (CVD) in 13 American-Indian tribes/communities conducted in three study centers in southwestern Oklahoma, central Arizona, and North and South Dakota. The population of the Strong Heart Study has a high prevalence of type 2 diabetes and CVD associated with diabetes. The findings of this study showed wide variation in rates of CHD in patients with diabetes, depending in part on coexisting risk factors. Most individuals had 10-year risk >20%, the threshold for ATP III's CHD risk equivalency, but only those with multiple risk factors had rates of CHD events equivalent to patients with established CHD. The authors conclude that it may be prudent to consider therapeutic goals for risk factors based on the entire risk factor profile, rather than just the presence of diabetes.

Other studies likewise have found considerable variability in risk for major coronary events when diabetes is present. Some reports (4–10) suggest that patients who have diabetes but not CHD do not carry as high a risk for major coronary events as do those with established CHD. Other studies (11–14) find that risk for CHD is similar in patients with diabetes and those with established CHD. The ATP III report (1) indicated that diabetes in general can be viewed as a high-risk state (CHD risk equivalent); this is generally true and adds simplicity to cholesterol management, just as it does for patients with established ASCVD. An alternate approach is to attempt to estimate 10-year risk for individuals with diabetes and to adjust LDL cholesterol goals accordingly. An example of individualized risk assessment is the U.K. Prospective Diabetes Study risk engine (15), which calculates risk for individuals with diabetes analogous to the risk algorithm of the Framingham Heart Study (8). Of interest, several reports suggest that Framingham scoring for patients with diabetes often underestimates absolute risk (16–18). If so, the choice of the risk assessment tool for estimating risk for CHD becomes an important issue when using an individualized approach.

Of course, there is variability in risk for major coronary events in patients with established CHD; therefore risk assessment could be carried out in individuals with CHD to tailor secondary prevention therapies. This approach however has been widely rejected by guideline panels for CHD prevention (1,19–21). For most cardiovascular guidelines, a diagnosis of ASCVD triggers a full therapeutic response for secondary prevention. The rationale is that the clinical simplicity of this approach will yield a net benefit that exceeds individual risk assessment based on problematic risk-assessment tools. This simplified strategy has been widely accepted by the cardiovascular community and appears to have improved implementation of secondary prevention therapies.

The National Cholesterol Education Program (1) proposed the same approach for patients with diabetes who as a group are known to be at high risk for ASCVD events. The concept is that most patients with diabetes in the U.S. are at least at high enough risk that a simple tactic for cholesterol-lowering therapy will be both efficacious and cost-effective. Even though an individualized risk assessment in patients with diabetes is reasonable in the hands of specialists, a broad application of risk assessment and adjustment of goals for LDL cholesterol on a patient-by-patient basis by most practitioners will be difficult to implement, just as it would be in management of patients with ASCVD. Moreover, beyond the simplicity of guidelines, several other reasons were given in the ATP III report for identifying patients with diabetes as having a CHD risk equivalent. These reasons can be summarized briefly.

First, in ATP III, CHD risk equivalent defines the risk of developing a major coronary event (myocardial infarction + coronary death) over 10 years of >20%. The 20% risk was that of patients with stable angina who have not sustained a myocardial infarction (22,23). This risk is lower than for those who have a history of acute myocardial infarction, which is about 26% (24,25). Many subsequently assumed that the risk accompanying a history of myocardial infarction defined a CHD risk equivalent and not stable angina. This was not the position of ATP III (1), which identified the 20% level. Moreover, cost-effectiveness analysis showed that cholesterol-lowering drugs are highly cost-effective at the risk level of 20% (1). In fact, as the costs of cholesterol-lowering drugs decline, acceptable cost-effectiveness reaches down to 10% risk or even lower (1).

Beyond 10-year risk estimates, there were other reasons for applying the term of CHD risk equivalent to patients with diabetes. A common misconception is that this term came exclusively from the study of Haffner et al. (11), which reported that Finnish patients with type 2 diabetes have a risk for future major coronary events similar to that of patients with previous myocardial infarction. In ATP III, this was not the only rationale, although reference was made to this report (11) and others with similar findings

(12,13). But other reports showed that coronary mortality at time of acute myocardial infarction is essentially doubled in patients with diabetes compared with those without diabetes (26,27). Moreover, in survivors of myocardial infarction, follow-up mortality in patients with diabetes is essentially doubled compared with persons without diabetes (28–34). ATP III contends that this high risk following onset of CHD justifies more intensive primary prevention of ASCVD in individuals with diabetes even if their 10-year risk is in the range somewhat below 20%. Other reasons can be cited for elevating the risk category when diabetes is present. For instance, patients with diabetes live on a higher trajectory of long-term risk than those without the disorder (35–37). Several robust clinical trials, moreover, some of which were available at time of the ATP III report (1), have documented benefit of statin therapy in patients with diabetes (38–41). These trials have reassured many clinicians that more intensive cholesterol-lowering therapy is warranted when diabetes is present.

Recently, Alexander et al. (42) reported from the National Health and Nutrition Examination Survey (NHANES) III that persons with diabetes who have concomitant metabolic syndrome, as defined by ATP III, are the ones who are at highest risk. In fact, in patients without metabolic syndrome, diabetes conferred very little increased risk for major coronary events. In NHANES, ~86% of patients with type 2 diabetes over age 50 years had metabolic syndrome (43). The findings of Howard et al. (3) are consistent with the NHANES III findings; patients with multiple metabolic risk factors were those at highest risk. In other words, hyperglycemia in the absence of other risk factors did not impart much increased risk for CVD over the short term. This particularly is the case for plasma glucose elevations in the range of pre-diabetes independent of other risk factors (43,44). Of course, prediabetes carries a higher risk for type 2 diabetes, which in itself is accompanied by many complications other than CVD. Thus, for those who are uncomfortable with the generalized approach recommended by ATP III, an alternative strategy at least would be to count diabetes together with metabolic syndrome as a high-risk condition worthy of intensive cholesterol-lowering therapy. Whether type 2 diabetes without the metabolic syndrome in fact carries a higher long-term risk for CVD remains to be determined. By the same token, how to approach cholesterol-lowering therapy in patients with type 1 diabetes in its earlier stages is open to question (42). Most investigators do not favor use of cholesterol-lowering drugs in early years of type 1 diabetes, but as age advances, if LDL cholesterol levels rise or if metabolic syndrome becomes evident, cholesterol-lowering drugs become a reasonable option.

The recent update of ATP III (45) introduced the term high-risk to encompass ATP III's CHD and CHD risk equivalent category. This term may be less contentious and more generic. There appears to be increasing acceptance of the concept that most patients with diabetes are at high risk for ASCVD and that cholesterol-lowering therapy is an important component of risk reduction in this risk category. Acceptance of this term may dampen some of the dispute as to whether diabetes is a CHD risk equivalent.

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