THE RISK OF DIABETES: CAN WE IMPACT CHD THROUGH THE ATP III CHOLESTEROL GUIDELINES?

Based on a presentation given by Steven M. Haffner, MD, MPH

ABSTRACT

Diabetes has been recognized among diabetologists as a risk factor for coronary heart disease (CHD) for several years, and is now identified as a CHD risk factor by the Third Adult Treatment Panel (ATP III) of the National Cholesterol Education Program (NCEP). The implementation of these new guidelines into the NCEP ATP III has enlightened the general population of this risk factor and will result in a significant increase in the number of Americans who qualify for aggressive lipid-modifying therapy. The relative risk of CHD is greater in diabetic women than in diabetic men, but the CHD risk in diabetic populations in general is equivalent to CHD risk in nondiabetic populations with a history of CHD. Studies have shown that glycemic control is not sufficient to reduce the risk of CHD in diabetic populations, but it is an important part of the risk reduction plan. Patients with the metabolic syndrome appear to have greater risk for CHD than nondiabetic persons, although the risks are not as high as in diabetic patients. This shows that having several moderate risk factors can be just as detrimental as having a few, severe risk factors. All of the data support aggressive lipid modifications in diabetic patients and clinical trials have shown that the statins, fibrates, and niacin are equally effective in diabetic and nondiabetic populations.

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On May 2001, the Third Adult Treatment Panel (ATP III) of the National Cholesterol Education Program (NCEP) published their revised guidelines on the detection, evaluation, and treatment of dyslipidemia in adults. Several significant changes were made since the previous set of guidelines, most notably (1) lower recommended levels of low-density lipoprotein cholesterol (LDL-C) in those at risk for coronary heart disease (CHD) and (2) the inclusion of diabetes as a risk factor for CHD.

The concept of diabetes as a risk factor for CHD has been recognized in the diabetic medical community for several years (eg, sixth report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure [JNC-VI]). With the NCEP ATP III (ie, outside diabetology circles), it can be considered a revolutionary concept because this recognition greatly affects the number of people needing lipid-lowering treatment. For example, the number of people qualifying for lifestyle changes is expected to be 65 million. The number of people who would qualify for both lifestyle changes and pharmacotherapy would be 36 million, which is almost 3 times the number currently prescribed a lipid-modifying drug.

The importance of the relationship between CHD and diabetes is best shown by the study based on data from 2 successive National Health and Nutrition Examination Survey (NHANES) populations. In this study, Gu et al reported a dramatic decline in coronary artery disease (CAD) mortality in nondiabetic patients over the course of 2 surveys (1971-1975 and 1982-1984).
A decline is seen for diabetic men, but the effect is less significant, whereas diabetic women appear to have an increased CAD mortality. These data suggest that we are not optimally managing diabetic patients and the extent of the management problem is a controversial issue. The major trials of cholesterol-modifying agents (ie, HMG-CoA reductase inhibitors [statins], fibrates, and niacin) show that these agents are as effective in diabetic as in nondiabetic populations, so the difference in CAD outcomes is not due to differences in response to pharmacotherapy.

In order to optimally manage CHD in diabetes patients, it is important to remember:

• The risk of vascular disease is similar in diabetic subjects without pre-existing vascular disease as in nondiabetic subjects with vascular disease.
• Glycemic control alone will not eliminate the excess risk of CHD in diabetic subjects; however, it is nonetheless an important part of lowering CHD risk.
• Lipid interventions to reduce CHD are equally effective in diabetic and nondiabetic subjects.

### Risk of Vascular Disease in Diabetic Patients

The relative risk of cardiovascular disease (CVD) is greater in diabetic women than diabetic men. This is true for CVD overall and its components (CHD, cardiac failure, intermittent claudication, and stroke), as shown in Figure 1. It is not yet understood why there is a gender difference, but it has been suggested that glycemia may have a more adverse effect on some risk factors in women than men, especially high-density lipoprotein cholesterol (HDL-C). Howard et al. showed in a study of 1846 American Indians that diabetic women were more adversely affected by certain CVD risk factors compared with diabetic men (ie, waist-to-hip ratio, HDL-C, apolipoprotein B, apolipoprotein A1, fibrinogen, and LDL size). They suggest “the apparent greater negative impact of diabetes on CVD risk factors in women may explain, in part, the greater risk for CVD in diabetic women.”

This theory bears out when analyzing the 7-year incidence of myocardial infarction (MI) in diabetic and nondiabetic populations. In a follow-up study of 1059 diabetic subjects and 1373 nondiabetic subjects, the 7-year incidence of MI for nondiabetic subjects with a history of MI was 18.8%, compared with 3.5% in nondiabetic subjects without a history of MI. In diabetic subjects with a history of MI, the incidence of MI was 45%, compared with 20% in diabetic subjects without prior MI. When hazard ratios were calculated, the risk of death from CHD for diabetic patients without prior MI was equivalent to that associated with nondiabetic patients with a history of MI. These data provide a rationale for the aggressive treatment of CVD risk factors in diabetic patients recommended by the NCEP ATP III. The current recommendation for LDL-C levels in patients with CHD is below 100 mg/dL. Given the data from this study, one can argue that diabetic patients with existing CHD should perhaps have even lower LDL-C levels, although this is not formally recommended.

A large multicountry study supports the concept of increased risk for CHD in diabetic populations. The Organization to Assess Strategies for Ischemic Syndromes (OASIS) evaluated more than 8000 patients in their registry, of whom 21% (1718) had diabetes. The 2-year prognosis of the patients who were hospitalized with unstable angina or non-Q-wave MI was determined. Diabetic patients had significantly higher rates of coronary bypass surgery but...
similar rates of catheterization and angioplasty as their nondiabetic counterparts. The presence of diabetes was an independent predictor of mortality, CVD, new MI, stroke, and new congestive heart failure. Importantly, diabetic women had significantly higher risk than did diabetic men, and diabetic patients without prior CVD had the same event rates, including total mortality, as the nondiabetic patients with prior CVD.

The concept of equivalent risk for diabetic patients and prior CHD patients has been met with some skepticism. Evans et al, in combined cross-sectional and cohort studies of the population of Tayside, Scotland, from 1988 to 1995, showed that the risk may not be equivalent for all diabetic patients. The cross-sectional study included patients between the ages of 45 and 64 years with established diabetes or established history of MI. The study identified a cohort of patients with newly diagnosed diabetes (ie, the date of diagnosis was the index date for the study) and another cohort with a recent, first hospitalization for MI (ie, their date of hospitalization was the index date for the study). In the cohort study, patients with newly diagnosed diabetes had a much lower risk of cardiovascular outcomes compared with patients who were diagnosed with recent MI (ie, established CHD). The cross-sectional study of people with established type 2 diabetes versus those with established CHD did not show the differences in risk found in other studies.

Risk factors for diabetes affect the risk of diabetic microvascular complications as well. Data from the United Kingdom Prospective Diabetes Study (UKPDS) show that the incidence of MI and microvascular events increases with rising blood pressure, from 120 to 170 mm Hg (systolic); the pattern of increasing incidence for both complications is similar (Figure 2A). However, the incidence of MIs is higher than the incidence of microvascular events. In early stages of diabetes, microvascular disease dominates the pattern of complications. The American Diabetes Association (ADA) recommends maintenance of blood pressure below 130/80 mm Hg.

**Glycemic Control**

Similarly, the UKPDS data show that blood glucose levels (HbA1c) in the range of 5.5% to 11% are directly proportional to the increased incidence of MI and microvascular end points (Figure 2B). Of note, the risk of MI plateaus at 9.5%, so while glucose is related to MI incidence, the overall increase is modest relative to microvascular complications. As a result, glycemic control alone is not an effective way to reduce the risk of MI.

The reason for this may be found in a study we conducted several years ago, in which 614 Mexican Americans were assessed for diabetes or glycemia at...
baseline and again after 8 years of follow-up. Specific cardiovascular risk factors were noted as well, to determine if prediabetic individuals might have a pattern of cardiovascular risk factors (ie, before diabetes onset) that may explain the lack of association between glycemic severity or disease duration and macrovascular complications. The results showed that those who were not diabetic at baseline but developed diabetes by the 8-year follow-up had significantly higher levels of LDL-C, triglycerides (TG), fasting glucose and insulin, 2-hour glucose, body mass index, and blood pressure. By contrast, levels of HDL-C were lower compared with participants who remained nondiabetic. This pattern persisted even when those with impaired glucose tolerance at baseline were not considered. We hypothesized that hyperinsulinemia and insulin resistance preceded the onset of type 2 diabetes. The pattern of lipid and glucose changes is characteristic of the prediabetic state. In fact, longitudinal studies of diabetic patients show that TG levels increase when people become diabetic, but HDL-C levels remain the same.

A very recent study from the Nurses’ Health Study database (ie, more than 100 000 women) showed a substantially elevated risk of CVD in women before clinical diagnosis of diabetes, again suggesting that “aggressive management of cardiovascular risk factors is warranted in individuals at increased risk for diabetes.”

The UKPDS study ranked the specific CVD risk factors in diabetic patients in the following order of importance regarding treatment: LDL-C, HDL-C, HbA1c, systolic blood pressure, and smoking. For many years, the focus of treatment was on fibrates to affect HDL-C levels. However, despite the relatively “normal” levels of LDL-C in diabetic patients, the composition of LDL is altered and LDL-C is a very strong risk factor for CHD. This realization was critical in creating the ADA position paper in 2000.

LIPID INTERVENTIONS

A comparison of the results from the major primary and secondary prevention trials shows that statins are equally effective in diabetic and nondiabetic subjects in affecting lipid profiles and CHD risk reduction (Table 1). They are discussed elsewhere in this issue by Drs Leiter and Tuomilehto.

### ADA GUIDELINES ON LIPID MANAGEMENT

Given the identification of diabetes as a CHD risk factor and the recommended target LDL-C of below 100 mg/dL in those with a CHD risk factor, the NCEP ATP III guidelines recommend the following treatment options, depending on LDL-C level:

- **LDL-C >130 mg/dL**: simultaneously initiate therapeutic lifestyle change (TLC) and LDL-lowering drugs, which are generally statins.
- **LDL-C 100-129 mg/dL**: intensify statin therapy and TLC; add drug to modify atherogenic dyslipidemia (fibrate or nicotinic acid).
- **If TG levels are ≥200 mg/dL after the LDL-C goal is met, non-HDL-C goal is <130 mg/dL.** [Non-HDL-C targets are calculated by adding 30 to the standard ATP III target LDL-C level.]

The primary targets may need to be revised based on recent results from the Heart Protection Study, in

### Table 1. CHD Prevention Trials With Statins in Diabetic Subjects: Subgroup Analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug (dose)</th>
<th>n</th>
<th>CHD Risk Reduction (Overall)</th>
<th>CHD Risk Reduction (Diabetes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Prevention</td>
<td>AFCAPS/TexCAPS</td>
<td>Lovastatin</td>
<td>155</td>
<td>-37%</td>
</tr>
<tr>
<td></td>
<td>HPS20</td>
<td>Simvastatin</td>
<td>3985</td>
<td>-24%</td>
</tr>
<tr>
<td>2 Prevention</td>
<td>CARE21</td>
<td>Pravastatin</td>
<td>586</td>
<td>-23%</td>
</tr>
<tr>
<td></td>
<td>4S49</td>
<td>Simvastatin</td>
<td>202</td>
<td>-32%</td>
</tr>
<tr>
<td></td>
<td>LIPID43</td>
<td>Pravastatin</td>
<td>782</td>
<td>-25%</td>
</tr>
<tr>
<td></td>
<td>4S Reanalysis</td>
<td>Simvastatin</td>
<td>483</td>
<td>-32%</td>
</tr>
<tr>
<td></td>
<td>HPS21</td>
<td>Simvastatin</td>
<td>1978</td>
<td>-24%</td>
</tr>
</tbody>
</table>

* Overall results for diabetic subgroup.

CHD = coronary heart disease; AFCAPS/TexCAPS = Air Force/Texas Coronary Atherosclerosis Prevention Study; HPS = Heart Protection Study; CARE = Cholesterol and Recurrent Events Trial; 4S = Scandinavian Simvastatin Survival Study; LIPID = Long-Term Intervention with Pravastatin in Ischaemic Disease; NS = Not significant.
which baseline LDL-C levels were not related to the response to lipid-modifying drugs. Therefore, patients with very low LDL-C levels at baseline can still benefit from LDL-C reduction.23,25

THE METABOLIC SYNDROME

The NCEP ATP III also defined the metabolic syndrome—a cluster of criteria that increase the risk of developing diabetes and therefore, CVD. As shown in Table 2, possessing 3 or more of the defined criteria qualifies a patient as having the metabolic syndrome.1 Note that many of the risk factors are set at lower cutoff points than the NCEP ATP III-recommended cutoff points. Therefore, having many risk factors can be as detrimental as having fewer, more severe risk factors.

Not surprisingly, CHD appears to be more prevalent in metabolic syndrome patients than in nondiabetic patients, but less prevalent than in diabetic patients.24 Thus, the metabolic syndrome might not be viewed as an equivalent to diabetes or CHD, but controlling the metabolic syndrome is a primary prevention of high-risk factors.

Approximately 85% of diabetic patients have the metabolic syndrome, and those patients also have twice the prevalence of CHD as diabetic patients without the metabolic syndrome. So, if cost is an issue in terms of aggressively treating dyslipidemia in diabetic patients, those with type 2 diabetes and the metabolic syndrome should receive higher priority for treatment than those without the metabolic syndrome.

CONCLUSION

Recent data now support aggressive treatment of LDL-C in diabetic patients, given that their risk of vascular disease is equivalent to the risk in nondiabetic patients with a history of vascular disease; the NCEP ATP III guidelines provide a useful framework on which to build a treatment strategy. Reducing or eliminating the epidemic of CVD among diabetic patients will require a variety of approaches, including glycemic control; prevention of type 2 diabetes; aggressive treatment of CVD risk factors; and innovative agents that lower blood sugar as well as affect cardiovascular risk factors and insulin resistance.

REFERENCES


PROCEEDINGS

Table 2. NCEP ATP III: The Metabolic Syndrome Diagnosis Is Established When ≥3 of These Risk Factors Are Present

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Defining Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal obesity</td>
<td></td>
</tr>
<tr>
<td>(Waist circumference)</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>&gt;40 in</td>
</tr>
<tr>
<td>W omen</td>
<td>&gt;35 in</td>
</tr>
<tr>
<td>TG</td>
<td>≥150 mg/dL</td>
</tr>
<tr>
<td>HDL-C</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>&lt;40 mg/dL</td>
</tr>
<tr>
<td>W omen</td>
<td>&lt;50 mg/dL</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>≥130/≥85 mm Hg</td>
</tr>
<tr>
<td>Fasting glucose</td>
<td>≥110 mg/dL</td>
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