<3.0 mmol/l. Only 49% of the study's diabetic subjects were free of overt CVD, and 19% had prior myocardial infarction.

The CARDS (Collaborative Atorvastatin Diabetes Study) (4) showed cardiovascular benefit of statin therapy for LDL >3.1 mmol/l or <3.1 mmol/l. Subjects were without CVD but had at least one of hypertension, retinopathy, proteinuria, or smoking.

I believe the more appropriate interpretation of these two studies is that cardiovascular benefits of the statin therapy on diabetic patients have been shown for LDL < or >3.1 mmol/l (or 3.0 mmol/l, depending on the study). However, the precise lower limit of LDL, where the cardiovascular benefits may or may not persist, has not been explored. Using a threshold of 3.0 mmol/l for LDL is not a replacement for using successively lower thresholds. Using an allegory may help. For example, one cannot claim that since antihypertensive therapy reduces cardiovascular events for patients with blood pressure of >160/100 mmHg, as well as <160/100 mmHg, antihypertensive medications should be used regardless of any baseline blood pressure. Our current ignorance of the lowest LDL threshold of statin's benefits should not be replaced by the statement that no lower limit to the benefit of LDL lowering exists. A recent study (5) not referenced in the position statement showed cardiovascular benefit of lowering LDL from 3.3 to 2.15 mmol/l, but again, it does not provide an answer as to whether unlimited lowering of LDL may cease to be useful (6).

Hence, I would recommend amending the statement, "For those over the age of 40 years, statin therapy to achieve an LDL reduction of 30–40%, regardless of baseline LDL levels, is recommended (A)." This can be replaced by "For those over the age of 40 years, without overt CVD or cardiovascular risk factors other than diabetes, statin therapy to lower LDL from >3.0 mmol/l to <3.0 mmol/l is advisable. The lowest baseline LDL where statin therapy might cease to be of benefit is currently unexplored and therefore unknown."

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Standards of Medical Care in Diabetes–2006

Response to Tseng

We appreciate Dr. Tseng's letter (1), as it identifies an error in our 2006 stated HDL cholesterol goals (2), when expressed in SI units, and allows us to comment further on our recommendation regarding the use of statins in those with type 2 diabetes.

Tseng is correct that the 2006 goals for HDL (2) should read 40 mg/dl (1.03 mmol/l) for men and 50 mg/dl (1.29 mmol/l) for women. We will make this change for the 2007 position statement.

Tseng also raises the issue that he does not feel that the evidence supplied supports our recommendation that "For those over the age of 40 years, statin therapy to achieve an LDL reduction of 30–40% regardless of baseline LDL is recommended." We are in disagreement on this point. While he is correct that in the Heart Protection Study (3), the cut point for LDL level was 3.0 mmol/l (116 mg/dl), they found that "lowering the LDL cholesterol from <3.0 mmol/l to <2.0 mmol/l (i.e., <116–<77 mg/dl) in people with diabetes reduces macrovascular disease" and concluded that "statin therapy should now be considered routinely for all diabetic patients at sufficiently high risk of such major vascular event, irrespective of their initial cholesterol concentrations." Similarly, while the cut point in the Coronary Artery Diabetes Study (4) was 3.1 mmol/l (120 mg/dl), the median LDL cholesterol on statin treatment was 2.0 mmol/l (77 mg/dl), and 25% had a concentration <1.7 mmol/l (66 mg/dl). The Coronary Artery Diabetes Study investigators also concluded that "no justification is available for having a particular threshold level of LDL cholesterol as the sole arbiter of which patients with type 2 diabetes should receive statins." Based on the above, we continue to feel our recommendation is appropriate and evidence based. Of note, we do review and revise the American Diabetes Association Clinical Practice Recommendations each year based on current evidence.

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Does the Metabolic Syndrome Exist

Response to Grundy

A key question in the debate concerning the metabolic syndrome (1,2) is whether the risk accompanying it is more than the sum of its parts. Grundy (1) asserts that "risk factors are multiplicative, i.e., risk for ASCVD [atherosclerotic cardiovascular disease] from risk factors rises geometrically, not linearly, as the number of risk factors increases. Therefore, total risk is more than a summation of the individual factors." The study by Yusuf et al. (3) is offered to support this statement, but this study is a standardized case-control study of 27,098 participants in 52 countries representing several major ethnic groups to assess the relation between BMI, waist and hip circumferences, and waist-to-hip ratio to myocardial infarction overall and for each group. The metabolic syndrome is not even mentioned in the article.

In the same issue of *Diabetes Care*, Sunderström et al. (4) published a study evaluating the risk factors for cardiovascular death in >2,000 individuals followed for 30 years after being studied at age 50. More than 1,000 of them were reexamined at age 70 and followed for 9 more years. Sunderström et al. showed that the "metabolic syndrome did not predict cardiovascular mortality independently of its individual components at any age" and concluded that "the metabolic syndrome might be viewed as a clinically handy summary measure of nontraditional risk factors rather than as a strong biological entity." Thus, this evidence suggests that the answer to the key question posed above is that the risk of the metabolic syndrome for cardiovascular events is no more than the sum of its parts. Whether the metabolic syndrome serves an important function to alert physicians and patients of the importance of addressing these risk factors is a separate issue.

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Does the Metabolic Syndrome Exist?

Response to Davidson

In response to Davidson (1), who questions whether the metabolic syndrome conveys more risk for cardiovascular disease (CVD) than that contained in its risk components, I suggest that this debate is partly confused by ambiguity over the issues of prediction versus causation. The argument based on prediction contends that among the diagnostic components of the syndrome (elevated blood pressure, low levels of HDL cholesterol, high triglycerides, elevated glucose, and abdominal obesity), most of the predictive power is contained in blood pressure and HDL cholesterol. Therefore, in epidemiological studies, the short-term risk for CVD for the syndrome as a whole, assessed by current diagnostic criteria, does not substantially exceed the risk contained in two of its risk factors. Consequently, from a predictive perspective, the metabolism syndrome is really nothing more than a higher blood pressure and a lower HDL. The argument from causation holds that these predictors of risk do not necessary reflect the true causes of the risk. Indeed, there are other types of data to indicate that several risk factors of the syndrome, such as elevations in VLDL, a prothromobotic state and a proinflammatory state also contribute to risk. It is possible to say that for causation, robust predictors are confounded by other risk factors, some of which are not routinely measured. In fact, there is still uncertainty as to whether a low HDL cholesterol is truly a direct cause of CVD or is only a marker for risk. Further, clinical trials indicate that reducing blood pressure does not fully reverse the risk predicted by a higher blood pressure; hence risk associated with a higher blood pressure must be confounded by other factors. The clinical implications of this distinction between prediction and causation are considerable. At present, it cannot be assumed that treatments directed toward the predictors will produce the expected reduction in risk; rather, it is important to identify the true causes of CVD associated with the metabolic syndrome so that they can be better targeted for therapy.

A second line of debate is whether the risk factors of the metabolic syndrome, or indeed for all CVD, are additive or synergistic in their effect on CVD risk. Synergism in effect is referred to as multiplicative risk. Several epidemiological studies and the risk algorithms developed from these studies support the synergism associated with multiple risk factors. If multiple risk factors are synergistic in their effects, as epidemiology indicates, then the risk associated with multiple risk factors is greater than what would be obtained by simple addition of their individual effects.

Finally, the metabolic syndrome is a progressive condition. It typically worsens with advancing age. Hence, risk is compounded by aging. This means that risk predicted at any one time underestimates the long-term risk associated with the syndrome.

These multiple lines of evidence support my contention that the CVD risk accompanying the metabolic syndrome