Cholesterol Screening
The Saga Continues

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Three years ago, the National Cholesterol Education Program (NCEP) provided recommendations for the detection, evaluation, and treatment of elevated blood cholesterol in adults. These recommendations were formulated by a panel of experts after more than a year of deliberation. They are based on the use of a screening test for total blood cholesterol to select individuals for further evaluation. Subjects selected on the basis of elevated total cholesterol levels and other risk factors are then advised to have a low density lipoprotein cholesterol (LDL) measurement. Those with elevated LDL levels are candidates for diet and drug therapy.

The panel hoped that a relatively inexpensive screening test for total cholesterol could be used to target those individuals who are in need of more complete lipoprotein evaluations. Inherent in this approach was the assumption that determination of total cholesterol level was a reliable surrogate for that of LDL level. The panel recognized that some individuals with isolated low high-density lipoprotein cholesterol (HDL) levels would not be identified. Low HDL was regarded as an additional risk factor, but not as a primary target of diet or drug intervention.

Inevitably, these guidelines have been questioned by those who feel they identify too many candidates for intervention as well as by those concerned by the inadequacy of total cholesterol level as a screening device. In an article appearing in this issue of Circulation Bush and Riedel, using data from consecutive measurements in a group of related population studies done in the 1970s (The Lipid Research Clinic [LRC] Prevalence Study), add their voices to the latter chorus.

As they point out, technical differences in the way the LRC Prevalence Study was conducted make it a less-than-perfect data source to use in testing the NCEP guidelines. However, it is close enough to provide a crude estimate of how these guidelines are likely to perform in detecting individuals at risk of coronary disease because of abnormal LDL or HDL levels. Not surprisingly, they perform less than perfectly.

In concert with NCEP recommendations, Bush and Riedel define those at risk as having either LDL levels greater than 160 mg/dl or HDL levels less than 35 mg/dl. Applying these criteria to the LRC population data and using the algorithms suggested in the NCEP report, they conclude that 21% of those with LDL levels over 160 mg/dl would be missed. Two-thirds of these are in the borderline-high range for total cholesterol (that is, total cholesterol levels ranging from 200 to 239 mg/dl). In addition, even if those with LDL levels less than 100 mg/dl are excluded (because of putative low risk), 47% of those with HDL levels less than 35 mg/dl would be missed. Overall, 41% of individuals considered to be at high risk by these LDL or HDL criteria would not be identified for follow-up.

The treatment of HDL in the NCEP guidelines has been questioned before. Those critical of the NCEP approach suggest that HDL should be included with total cholesterol as a screening parameter. They point out that low HDL is an important independent predictor of risk, that a small proportion (about 2–3% of adult men) with total cholesterol levels less than 200 mg/dl will have HDL levels below 35 mg/dl, and that 70% of those with total cholesterol levels less than 200 mg/dl and documented coronary disease have HDL levels less than 40 mg/dl. They also point out that the Helsinki Heart Study demonstrated the value of raising HDL levels in lowering heart attack risk.

Members of the panel have defended the NCEP approach, citing the relatively small risk imposed by low HDL levels when the total and LDL cholesterol levels are also low, the lack of clinical trial evidence addressing the benefit of isolated HDL level increases (without concomitant drops in LDL or triglyceride levels), and the expense of obtaining routine HDL screening determinations.

Bush and Riedel also point out a logical inconsistency in the NCEP recommendations. If only total cholesterol level is used in screening, HDL level could not be considered as one of the risk factors for selecting candidates for a more complete lipoprotein profile, because the HDL level would be unknown.
should be remembered, however, that the same list of risk factors is used to select those with borderline LDL levels who might be candidates for drug intervention. In weighing that decision, HDL levels are a useful and appropriate risk factor to consider.

Despite the findings by Bush and Riedel, however, the NCEP guidelines regarding HDL should not materially change until at least two questions are answered. First, which (if any) diet or drug interventions reliably raise HDL, particularly when triglyceride levels are below 250 mg/dl and LDL levels below 130 mg/dl? In other words, can any currently available lipid-altering regimen correct isolated low HDL levels? It should be noted that neither hygienic measures (including diet and exercise or weight loss) nor currently available lipid-altering drugs, including gemfibrozil and niacin, consistently increase HDL levels in cases where LDL and triglyceride levels are normal.

Second, we must determine whether correction of isolated low HDL levels provides coronary risk reduction. This is probably only answerable in a clinical trial, and such a trial should only be undertaken if a method for raising isolated low HDL levels can be identified. An alternative approach might be to lower current LDL therapeutic targets in those with HDL levels less than 35 mg/dl, but this too would probably require clinical trial evidence of benefit. In the meantime, HDL should remain, as is currently recommended, an important risk factor to consider in selecting candidates for LDL lowering but not an independent target for intervention.

The findings of this analysis regarding LDL are more disturbing. Twenty-one percent of those with LDL levels over 160 mg/dl would, by these estimates, be missed. There is little debate, even among critics of the NCEP approach, that such patients ought to be treated, although not all would require drug therapy.

Bush and Riedel suggest that all subjects with total cholesterol levels over 200 mg/dl have a complete lipoprotein profile done, including an LDL determination. This would double the number of individuals requiring a complete lipid profile. Like the addition of HDL to the screening package, such a change adds considerable cost. Bush and Riedel suggest that these conflicting considerations of cost versus potential benefit might be resolved by a cost-benefit analysis.

Where does this leave the NCEP guidelines? Should we abandon them as insufficient or inadequate? Most assuredly not. Detecting 80% of those with high LDL levels is better than detecting none. Future iterations of the NCEP report, however, should take into consideration the suggestion made by Bush and Riedel that all those with cholesterol levels over 200 mg/dl have an LDL determination done. With this change, the NCEP guidelines would be more likely to do what they are now purported to do, that is, provide a mechanism to detect and intervene with those individuals whose LDL levels place them at high risk of coronary disease.

Like Dock, who recently lamented the resistance of academic cardiologists to cholesterol-level intervention, I frequently encounter physicians who cling to the notion that the cholesterol issue is still a "controversy" and the NCEP guidelines too inclusive. Bush and Riedel's analysis will give them little comfort. Based on its results, the NCEP guidelines, if anything, are not inclusive enough. Future revisions of these guidelines are likely to widen, rather than constrict, their net.

References
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