Primary Prevention Lipid-Lowering Drug Therapy

To the Editor:

We appreciate the editorial comments provided by Drs Gotto and Kuller1 on our article published in the January 15, 2002, issue of Circulation,2 but we wish to respond to several issues raised.

The methodology used to project population size is standard for the Third National Health and Nutrition Examination Survey (NHANES III) and is described thoroughly in the publication by the National Center for Health Statistics, which we reference3 in our article. We did not feel it necessary to reiterate that method.

We assume that the phrase “significance of the data” is a controversial issue in some epidemiological analyses.4 Given the large sample size inherent to these types of studies, even small differences can be declared statistically significant with very low probability values. We therefore felt that a list of highly significant probability values would not add to the interpretation of results.

With regard to under-reporting of coronary heart disease, as Gotto and Kuller admit, the estimates in the survey reflect the misdiagnosis of coronary heart disease in women and elderly in actual practice. Because these same criteria will be used to determine eligibility for treatment in the clinician’s office, we maintain that the same level of misclassification will occur in the office as in the NHANES III survey. Thus, our estimates represent those who would be so classified (as primary) in actual practice. Admittedly, “other forms of cardiovascular disease (CVD),” such as peripheral artery disease and symptomatic carotid disease, would be detectable in clinical practice. These will not constitute a large percentage of the total misclassified.

Lastly, our estimates for primary prevention treatment-eligible patients under Adult Treatment Panel II correspond closely to those reported by Hoerger et al.5 That study reported 15.7 million patients under Adult Treatment Panel II correspond closely to those reported by Hoerger et al. That study reported 15.7 million patients aged ≥20 years as treatment eligible. Our study reported a similar number (15.1 million) for those aged 20 to 79 years.

We disagree with the conclusion that “more women than men aged 20 to 29 years are eligible for primary prevention.” In fact, the observed difference is actually very small (78 735) relative to the total eligible population in that age group (2.4 million).

We agree that global risk assessment is preferable to the narrow application of the Adult Treatment Panel III algorithm. However, it is unclear how the clinician will combine the algorithm’s quantitative output with the list of global risk factors (Table 2 of the editorial1) to decide treatment. That subjective judgment could not be reliably incorporated into our analyses. The fact remains that >70% of the eligible patients can be selected for treatment solely on the basis of having a low-density lipoprotein cholesterol level ≥160 mg/dL.

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Response

Fedder et al assume that physicians will diagnose coronary artery disease in a manner similar to that used in the Third National Health and Nutrition Examination Survey (NHANES III), and that eligibility for primary or secondary prevention can be based on a reported history of coronary heart disease (CHD).

There is a wide range of diagnostic technologies (eg, exercise testing, echocardiography, noninvasive and invasive measurements of coronary atherosclerosis) available to evaluate patients with possible CHD, including those who present with risk factors or with symptoms suggesting cardiovascular disease. Cardiovascular disease—the leading cause of death in men and women in the United States—is more prevalent among older than younger adults. With the use of these sophisticated tests, the prevalence of clinical CHD will likely increase, as will the number of patients eligible for secondary versus primary prevention.

Fedder and colleagues estimate the number of primary-prevention patients solely on the basis of low-density lipoprotein cholesterol (LDL-C) levels ≥160 mg/dL. The use of LDL-C levels to determine the need for primary prevention in the elderly may not be successful, especially for men. The Cardiovascular Health Study, which characterized the predictive role of traditional risk factors and subclinical atherosclerotic disease in adults aged ≥65 years, found that subclinical disease—but not plasma lipid levels—was associated with coronary disease. This suggests that the high incidence of a first major cardiovascular event among older adults is related to their LDL-C levels over a lifetime. Therefore, decisions regarding optimal lipid-modifying therapy in older individuals without a history of CHD require criteria other than an LDL-C level ≥160 mg/dL, or even ≥130 mg/dL, alone. These criteria include the presence of diabetes and hypertension, other lipoprotein parameters (eg, the distribution of LDL size, density of LDL particles, HDL-C levels), and perhaps most importantly, silent but extensive coronary atherosclerosis identified by the use of noninvasive imaging. With these criteria, a far larger number of older individuals without a history of CHD will likely require lipid-lowering therapy than at the present time.

Recent primary- and secondary-prevention trials have substantiated the benefits of lipid-lowering drug therapy in subgroups of older individuals,1-3 and a study now in progress is the first to evaluate clinical outcomes solely in the elderly.

The 2001 Adult Treatment Panel guidelines advocate global risk assessment based on more than lipid levels alone and go beyond the 5 major risk factors to include “emerging risk factors” (eg, subclinical atherosclerosis). To assess the effect of these guidelines as accurately as possible and to foster their use in clinical practice, our analyses must take global risk assessment into consideration.


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