Journal of the American College of Cardiology
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Published by Elsevier Inc.

Vol. 46, No. 7, 2005
ISSN 0735-1097/05/$30.00
doi:10.1016/j.jacc.2005.07.006

VIEWPOINT

The Forgotten Majority

Unfinished Business in Cardiovascular Risk Reduction

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Despite meaningful progress in the identification of risk factors and the development of highly effective clinical tools, deaths from cardiovascular disease continue to increase worldwide. Sparked by an obesity epidemic, the metabolic syndrome and the rising incidence of type 2 diabetes have led to an upsurge of cardiovascular risk. Although pharmacologic treatments with the statin class of drugs have reduced cholesterol levels and lowered mortality rates, several large controlled clinical trials, including the Scandinavian Simvastatin Survival Study, the Cholesterol and Recurrent Events trial, the Air Force/Texas Coronary Atherosclerosis Prevention studies, and Long-term Intervention with Pravastatin in Ischemic Disease study, have indicated that cardiovascular events continue to occur in two thirds of all patients. Follow-up studies, such as the Heart Protection Study and the Pravastatin or Atorvastatin Evaluation and Infection Therapy/Thrombolysis In Myocardial Infarction-22 trials, reinforced these earlier results. Although therapy with gemfibrozil, a fibric acid derivative, showed reduced occurrence of cardiovascular events in the Helsinki Heart Study and the Veterans Affairs HDL Intervention Trial, results of other studies, e.g., the Bezafibrate Intervention Program and the Diabetes Atherosclerosis Intervention study, showed less encouraging results. Although lifestyle modifications, such as improved diet and increased exercise levels, benefit general health and the metabolic syndrome and insulin resistance in particular, most people continue to resist changes in their daily routines. Thus, physicians must continue to educate their patients regarding an optimal balance of drug therapy and personal behavior. (J Am Coll Cardiol 2005;46:1225–8) © 2005 by the American College of Cardiology Foundation

The early years of the new millennium have brought some satisfaction in the realm of cardiovascular risk. We have made substantial inroads against the ravages of cardiovascular disease, and we possess increasingly effective tools for controlling the factors that contribute to coronary heart disease, stroke, and hypertension. However, despite decreasing age-adjusted rates of cardiovascular mortality in the U.S. during recent years, the daunting residual burden of cardiovascular disease now reaches beyond our borders to grip the developing world. As the result of an aging population, the actual number of individuals who die from cardiovascular disease remained approximately constant at about three-quarters of a million per annum during the period of 1970 to 1998 (1,2). Unfortunately, cardiovascular deaths in women have declined less than those in men. Because elderly women will comprise an enlarging segment of our population, this growing burden of cardiovascular disease should sound an alarm.

Of particular concern, the increasing obesity in both developed and developing nations paves the way for an epidemic of diabetes and its attendant heightened risk of cardiovascular diseases. Unfortunately, minority populations in the U.S. will bear a great portion of this risk. In particular, African-American and Hispanic populations have increasing prevalence of the metabolic syndrome and type 2 diabetes mellitus. Worldwide, the predictions regarding the epidemic of cardiovascular diseases cause considerable concern. By the year 2020, cardiovascular disease will surpass infectious and communicable diseases as a reason for loss of productive life years worldwide (3).

Although we possess potent and effective new medications for controlling hypertension and hypercholesterolemia, even in the best of circumstances—the controlled clinical trial—most cardiovascular events still occur. The announcement of the results of the Scandinavian Simvastatin Survival Study (4S) heralded an era of evidence-based vindication of the cholesterol hypothesis of coronary heart disease (4). Following closely on the heels of 4S, the Cholesterol And Recurrent Events (CARE) study (5), the Air Force Coronary Atherosclerosis Prevention Study/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) (6), and the Long-term Intervention with Pravastatin in Ischemic Disease study (LIPID) study (7) all showed striking reductions in coronary heart disease events. In most studies, treatment with the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) reduced the incidence of strokes. When the studies were sufficiently powered, they documented statistically significant declines in overall rate of mortality, the "holy grail" of the lipid-lowering field. In many of this first

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Manuscript received February 4, 2005, accepted February 16, 2005.

JACC Vol. 46, No. 7, 2005
October 4, 2005:1225–8

Abbreviations and Acronyms

HDL = high-density lipoprotein
HMG-CoA = 3-hydroxy-3-methlyglutaryl coenzyme A
LDL = low-density lipoprotein

crop of statin "megatrials," subgroups such as patients with diabetes, women, and older patients benefited from therapy. These various studies encompassed a spectrum of patients that included those with low risk, average cholesterol levels, and no previous atherosclerotic event in addition to those who had already survived an acute myocardial infarction, had elevated levels of low-density lipoprotein (LDL) cholesterol, or had other markers of heightened risk.

The Heart Protection Study (HPS) reinforced and extended these results (8). Having enrolled some 20,000 patients, this study had sufficient power to examine the effects of treatment with the HMG-CoA reductase inhibitor simvastatin on a variety of cardiovascular outcomes in a broad range of individuals. Again, the statin treatment reduced cardiovascular events and strokes in all subgroups and strata of initial cholesterol levels studied. More recent studies comparing statin regimens indicate that "lower is better": In patients with acute coronary syndromes in the Pravastatin or Atorvastatin Evaluation and Infection Therapy/Thrombolysis In Myocardial Infarction-22 (PROVE-IT/TIMI-22) study, a median LDL cholesterol level of 62 mg/dl yielded better clinical outcomes versus patients treated less aggressively who achieved a median in-trial LDL cholesterol level of 95 mg/dl (9). In patients with stable coronary artery disease, more aggressive LDL lowering resulted in greater improvement in atheroma morphology, as assessed by intravascular ultrasonography (10).

Faced with the spectacular success of statin therapy, we can take heart at having begun to turn the tide in the worldwide battle against atherosclerotic disease. Yet, much remains to be done. In the best of circumstances, the decrease in cardiovascular mortality due to statin treatment still allows two thirds of cardiovascular events to occur (Fig. 1). Thus, although we justly take satisfaction in the benefits conferred by statin therapy, most events still happen.

Other modalities for treating dyslipidemia also have shown success in reducing cardiovascular events. For example, in certain populations, fibric acid derivatives such as gemfibrozil reduce coronary heart disease events and stroke. Although the fibrates, activators of the transcription factor peroxisome proliferation activating receptor-alpha, have reduced outcomes in some studies, such as the Helsinki Heart Study (11,12) and the Veterans Affairs HDL Intervention Trial (VA-HIT) (13,14), not all studies have shown such reductions. Thus, in the Bezafibrate Intervention Program (BIP), the fibrate did not reduce cardiovascular events (15,16). In the Diabetes Atherosclerosis Intervention Study (DAIS) trial, a secondary angiographic end point regarding progression of coronary artery disease achieved

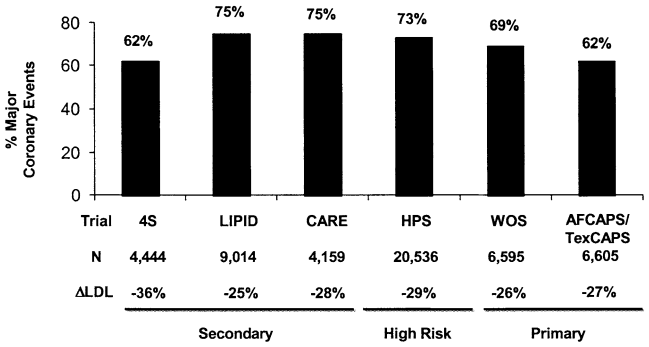

Figure 1. Percentage of patients experiencing major coronary events, according to several large outcomes studies. AFCAPS/TexCAPS = Air Force Coronary Atherosclerosis Prevention Study/Texas Coronary Atherosclerosis Prevention Study; CARE = Cholesterol And Recurrent Events trial; 4S = Scandinavian Simvastatin Survival Study; HPS = Heart Protection Study; LIPID = Long-term Intervention with Pravastatin in Ischemic Disease study; WOS = West of Scotland Coronary Prevention Study. Adapted from Kato H, et al. Am J Epidemiol 1973;97:372–85; HPS Collaborative Group. Lancet 2002;360:7–22; and LaRosa JC, et al. JAMA 1999;282:2340–6.

statistical significance (17,18). There was a nonstatistically significant reduction in morbid events in this trial, which by design lacked sufficient power to address events.

DO WE INTERVENE TOO LATE?

Given these therapies of proven effectiveness, how can we explain their inability to eradicate even a majority of cardiovascular events? Perhaps we initiate therapy too late. By the time patients have entered clinical trials, perhaps the "die has been cast," entraining an irreducible number of ineluctable subsequent events. Thus, even the most effective therapies might prove unable to eradicate events. However, the statin megatrials surely enrolled broad swaths of the population, including individuals in primary prevention with modest degrees of risk, and certainly without manifest atherosclerotic disease (e.g., AFCAPS/TexCAPS) (6).

ARE OUR INTERVENTIONS TOO SHORT?

Perhaps patients received statin treatment for too short a period in these clinical trials. Indeed, in lipid-lowering trials, the Kaplan-Meier plots show continued divergence of the survival or event-free survival curves for the duration and sometimes beyond the usual five-year span of these trials. Thus, if one were to enroll patients at an earlier stage of disease or at a younger age, perhaps a more complete benefit would accrue. However, long-term treatment in asymptomatic populations begs questions regarding the cost-benefit ratio. In this case, the cost would involve not only the financial considerations but also potential adverse effects. Although the statins indubitably, as a class, have an excellent record of safety and tolerability, broad or indiscriminate use in large populations might engender a small-but-potentially concerning number of adverse effects. Such unwanted effects of statins often occur in combination with other drugs. Adjustment of dosages of statins when com-

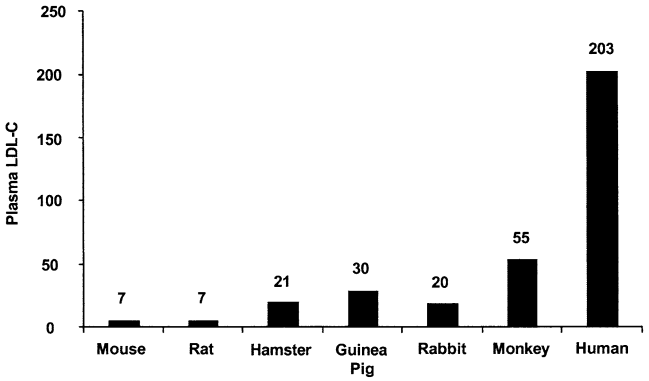

Figure 2. Cholesterol levels by species. Typical values of plasma low-density lipoprotein cholesterol (LDL-C) in several species, including human. Adapted from Dietschy JM, et al. J Lipid Res 1993;34:1637–59 and Ford ES, et al. Circulation 2003;107:2185–9.

bined with interacting agents, such as fibrates, could present a daunting challenge in large asymptomatic populations.

DO WE INTERVENE TOO LITTLE?

Another potential explanation for the residual burden of cardiovascular morbidity and mortality in the statin trials could relate to the degree of LDL-lowering achieved. We do not have clinical trial evidence that consistently and clearly indicates the "lower limit" of benefit achievable by LDL reduction. The recent HPS results suggest that even individuals with entry LDL levels less than average derive considerable benefit in association with lowered LDL levels because of statin therapy (8). The results of PROVE-IT in survivors of acute coronary syndromes also support the "lower is better" hypothesis (9). Thus, perhaps driving the LDL cholesterol levels to a range more suited for the human species, based on phylogenetic and comparative human studies, would make further inroads against the residual cardiovascular events. Indeed, in the animal kingdom, modern humans are "outliers" on the LDL scale. Our levels of LDL cholesterol exceed by far that of other species (Fig. 2). Certainly in adults, levels of LDL cholesterol well <100 mg/dl, the current target for highest risk patients according the Adult Treatment Panel III Guidelines of the National Cholesterol Education Program (19), seem free of adverse biological consequences. Comparative studies across human populations show that those with levels of LDL cholesterol that are well less than the average concentrations encountered in developed societies have low rates of cardiovascular disease and show no evidence of "cholesterol insufficiency" (Fig. 3). The "J-shaped curve phenomenon," which shows increased rates of mortality at low levels of cholesterol, may reflect disease-related decrements in cholesterol (e.g., because of cancer, liver disease, inanition) rather than an adverse effect of lower quantiles of cholesterol on rates of morbidity and mortality per se.

How can we approach the residual burden of cardiovascular mortality in the poststatin era? Certainly, increasing the dose of statins used could permit further reductions in LDL levels. However, statins have fairly "flat" dose-response curves. For a doubling in dose of a typical statin, LDL cholesterol declines approximately an additional 6% to 7%. Dose-ranging studies with statins generally have shown greater incidence of adverse effects, such as myopathy, at the higher doses. Therefore, increasing the doses of statins yields "diminishing returns" in terms of LDL lowering and risk-benefit ratio.

In contemporary American society, seeking solutions with drug therapy seems to have more appeal than lifestyle modification. Physicians and other health care providers must redouble efforts to educate the public regarding the health benefits of a prudent diet and regular physical activity. Considerable barriers exist to lifestyle change, which we must address with education of both the public and physicians and with unrelenting efforts to improve implementation of sustainable lifestyle changes. These considerations apply particularly to the epidemic of obesity, attendant insulin resistance, and the cardiovascular toxicity of the metabolic syndrome. Our best current evidence suggests

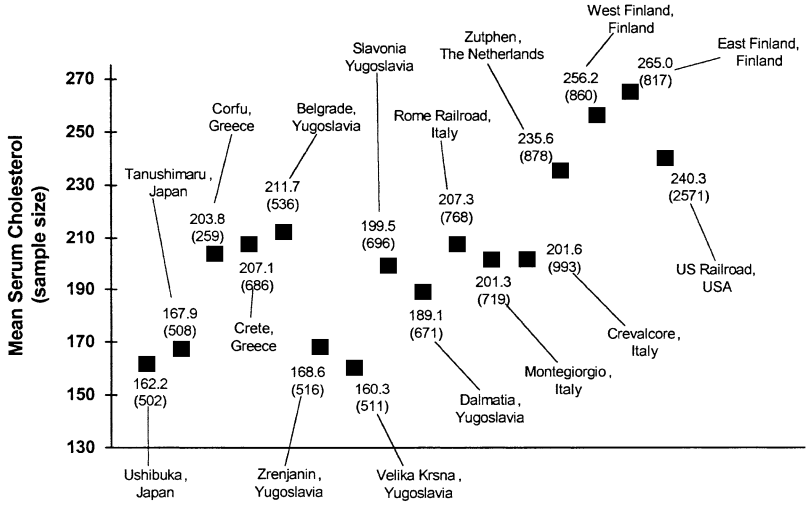

Figure 3. Mean baseline serum cholesterol in the Seven Countries Study. Adapted from Menotti A, et al. Eur J Epidemiol 1993;9:527–36.

JACC Vol. 46, No. 7, 2005
October 4, 2005:1225–8

Table 1. Some Emerging Targets for Cardiovascular Risk Reduction by Manipulation of Lipid Metabolism

Cholesteryl ester transfer protein (CETP)
Apolipoprotein AI Milano
Acyl coenzyme A-cholesterol acytransferase (ACAT)
Intestinal absorption of dietary and biliary cholesterol

that lifestyle modification, including changes in diet and physical activity, can significantly benefit individuals with, or at risk for, the metabolic syndrome.

New pharmacologic approaches on the horizon also may aid the effort to reduce further cardiovascular rates of morbidity and mortality in the poststatin age (Table 1). A number of strategies for increasing high-density lipoprotein (HDL) are under evaluation. Inhibitors of cholesteryl ester transferase can raise HDL (20). If the type of HDL particle that accumulates under conditions of cholesteryl ester transfer protein inhibition can affect reverse cholesterol transport and the other atheroprotective actions of HDL, this strategy might add to the cardiovascular benefit of statins. Strategies for increasing the major apoprotein of HDL, apolipoprotein A1, also might modulate atherosclerosis (10). Inhibitors of acyl cholesteryl ester transferase, an enzyme involved in packaging of lipids absorbed from the intestine and in storage of cholesterol in foam cells in the artery wall, also might favorably alter the biology of atherosclerotic plaques. Inhibitors of cholesterol absorption, minimally absorbed systemically themselves, can substantially decrease LDL cholesterol, add to the hypocholesterolemic effect of statins, and currently are under study for their cardiovascular benefits. This latter approach has particular appeal given the "diminishing returns" of increased statin dose discussed previously. Mice with targeted inactivation of the newly identified intestinal cholesterol transporter, the Niemann-Pick C-1Protein Like Protein-1 (i.e., NPC1L1, a putative target of the cholesterol absorption inhibitor ezetimibe) maintain a normal lipid profile by a compensatory increase in hepatic cholesterol synthesis (21). These findings underscore the rationale of combined inhibition of intestinal cholesterol absorption and inhibition of HMG-CoA reductase, the rate-limiting enzyme for sterol biosynthesis in the liver.

We have entered a "golden age" of preventive cardiovascular medicine. We possess not only potent tools for intervening mechanically on cardiovascular disease but also now effective medical therapy for preventing atherosclerotic events and the need for mechanical therapies. Despite this progress, we must not relax our guard. To address the majority of cardiovascular events that still occur despite our most powerful existing therapies, we must combine lifestyle change and evaluate new pharmacologic strategies that will move us toward the goal of eradicating cardiovascular disease in the future.

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