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How Do We Achieve Optimal Cardiovascular Risk Reduction?

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Summary: Optimizing coronary heart disease (CHD) risk reduction requires the application of clinical evidence to patient care, as well as the refinement of risk assessment. Clinical evidence indicates that most patients are not treated to optimal low-density lipoprotein (LDL) cholesterol goals. Despite the efficacy of statin therapy in reducing the incidence of CHD, many treated patients still experience CHD events. Targeting other lipid factors such as high-density lipoprotein cholesterol and triglycerides may augment the risk reduction achieved by lowering LDL cholesterol. Refined global risk assessment can lead to more accurate determinations of absolute risk and to the identification both of high-risk patients needing aggressive intervention and intermediate-risk patients who appear to be at low risk. Previous global risk assessment measures failed to identify a substantial proportion of primary prevention patients who would benefit from therapy. However, revised guidelines issued by the National Cholesterol Education Program introduce new criteria for more precise risk assessment and advocate use of the Framingham scoring system to calculate absolute risk. Although intensified treatment is recommended for high-risk patients, cost considerations may limit drug therapy for some lower-risk individuals.

Key words: low-density lipoprotein cholesterol, global risk assessment, statin therapy, coronary heart disease

Introduction

Two critical objectives in the ongoing efforts to achieve optimal reduction of cardiovascular risk are the appropriate application of clinical evidence to patient care and the refinement of risk assessment, particularly through improvement in global assessment of risk. In May 2001, the National Cholesterol Education Program (NCEP) issued its revised guidelines for the use of drug and nondrug therapy to reduce the risk for coronary heart disease (CHD).[1] The new guidelines will be reviewed later in this article. Compared with the NCEP recommendations issued in 1993, the 2001 document contains changes that have important implications for risk assessment and patient care. It is hoped that the new guidelines will result in significantly reduced rates of CHD. However, time will be needed for physicians to implement them and for outcomes to be documented.

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Application of Clinical Evidence

Several of the factors that must be considered in our attempts to optimize cardiovascular risk reduction arise from assessment of clinical evidence. One such factor, as emphasized by findings in the recently reported Lipid Treatment Assessment Project (L-TAP),[2] is that large proportions of dyslipidemic patients receiving lipid-lowering therapy have not achieved the 1993 NCEP goals for low-density lipoprotein (LDL)-cholesterol levels.[3] In L-TAP, participating physicians were in the top tertile of frequent prescribers, based on number of prescriptions for lipid-lowering medication. Patients who had been receiving the same lipid-lowering therapy for at least 3 months, were assessed for initial and follow-up LDL-cholesterol levels. Of the 4,888 evaluable patients, 4,137 were receiving a statin, gemfibrozil, a bile acid sequestrant, niacin, psyllium fiber, or combination therapy (statins plus niacin or bile acid sequestrants), and 751 were receiving nondrug lipid-lowering therapy. Figure 1 shows the proportions of patients achieving 1993 NCEP LDL-cholesterol goals by NCEP risk group. In total, goals were achieved by only 39% in the drug group and 34% in the nondrug group, with overall (drug plus nondrug group) success rates ranging from a high of 68% in the low-risk group to 37% in the high-risk group to 18% in those with coronary heart disease (CHD). Among those receiving lipid-lowering drugs, titration to higher dosages was seldom used, suggesting that treatment even by these apparently motivated physicians was not sufficiently aggressive.

Another factor that should be considered when evaluating the body of available clinical evidence is that despite the remarkable efficacy of statin treatment in reducing cardiovascular risk, many individuals receiving such treatment neverthe-

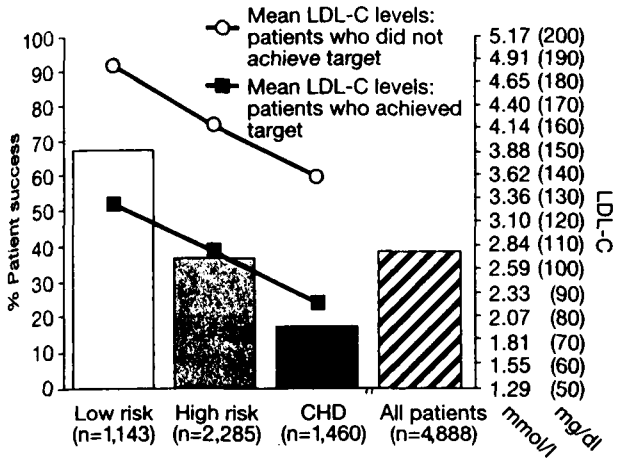

FIG. 1 Proportions of patients assessed in L-TAP study who achieved low-density lipoprotein (LDL) cholesterol goals according to risk group (shown by bars and left axis) and decrease in mean LDL-cholesterol levels in those achieving and not achieving goal levels (shown by lines and right axis). Target LDL-cholesterol levels are <160 mg/dl for the primary prevention low-risk group, <130 mg/dl for the primary prevention high-risk group, and < 100 mg/dl for the group with coronary heart disease (CHD). Reproduced with permission from *Arch Intern Med*, 2000,160;459–467. Copyrighted 2000, *American Medical Association*.

less proceed to a clinical coronary event. Assessment of the clinical effects of statins in primary and secondary prevention in five major study populations including both men and women has shown that treatment is associated with overall relative risk reductions of 22 to 37% for primary CHD endpoints.[4–8] One step toward optimizing prevention of the remaining 60 to 80% of events would be to ensure that recommended LDL-cholesterol goals are met; in addition, it may be that the strategy of reducing LDL cholesterol to even lower target levels, the subject of a number of ongoing clinical trials, will provide a greater relative risk reduction. Available data also suggest that lipoprotein targets other than LDL cholesterol should be taken into account in lipid-modifying therapy.

Data from recent trials of fibrates, for example, suggest that levels of high-density lipoprotein (HDL) cholesterol and triglycerides, the lipid factors affected by fibrate therapy, need to be considered in cardiovascular risk factor management. Watts and Dimmitt[9] recently compared outcomes in three clinical endpoint trials in patients with low HDL-cholesterol levels: the Veterans Administration HDL-Cholesterol Intervention Trial (VA-HIT) of gemfibrozil treatment (secondary prevention), the Bezafibrate Infarction Prevention (BIP) study of bezafibrate (secondary prevention), and the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) of lovastatin (primary prevention). The absolute reductions in cardiovascular risk observed in these trials were 4.4% with gemfibrozil treatment in VA-HIT, 1.4% with bezafibrate in BIP, and 4.1% with statin treatment in AFCAPS/TexCAPS, with relative risk reductions of 22, 9, and 37%, respectively; the relative risk reduction was not statistically significant in the BIP trial. These reductions in risk occurred in the context of changes in LDL cholesterol, HDL cholesterol, and triglycerides of −4, +6, and −31% in VA-HIT, −6, +18, and −21% in BIP, and −25, +6, and −15% in AFCAPS/TexCAPS. The risk reduction in patients in VA-HIT, who began treatment with mean LDL-cholesterol levels of 112 mg/dl, thus cannot be attributed to LDL-cholesterol reduction. In the BIP trial, the starting LDL-cholesterol level was nearly identical to that in AFCAPS/TexCAPS (151 and 150 mg/dl, respectively), and it is possible that failure of bezafibrate treatment to significantly reduce risk was related to the absence of effect on LDL-cholesterol levels in that population. It is worth noting, however, that a post hoc analysis showed a significant risk reduction in the subpopulation of BIP patients with elevated baseline triglyceride levels (≥ 200 mg/dl).[10] Therefore, such factors as low HDL-cholesterol levels and elevated triglycerides may represent important targets of treatment apart from LDL cholesterol.

The point that risk reduction is not solely associated with LDL-cholesterol reduction is highlighted when CHD event rates in treatment trials are plotted against reduction in plasma cholesterol (as a surrogate for LDL-cholesterol reduction).[11] As shown in Figure 2, the outcomes of the statin trials, the Lipid Research Clinics (LRC) trial of cholestyramine, and the Program on the Surgical Control of Hyperlipidemias (POSCH) study of ileal bypass indicate a linear relation be-

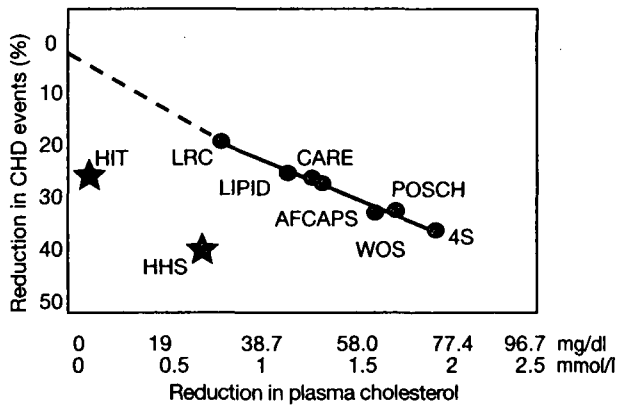

FIG. 2 Relation between reduction in plasma cholesterol level and reduction in coronary heart disease (CHD) events in the Lipid Research Clinics (LRC) trial of cholestyramine, the LIPID, CARE, AFCAPS/TexCAPS, WOSCOPS (WOS), and 4S trials of statin therapy, and the POSCH study of ileal bypass. These studies of treatments primarily intended to reduce low-density lipoprotein cholesterol indicate a linear relation between cholesterol reduction and event reduction. Results with fibrate therapy, which increases high-density lipoprotein cholesterol and reduces triglyceride levels, do not exhibit such a relation between cholesterol-lowering and risk reduction, as shown by plots for the HIT and HHS (Helsinki Heart Study) fibrate trials (indicated by stars). LIPID = Long-Term Intervention with Pravastatin in Ischaemic Disease, CARE = Cholesterol and Recurrent Events, AFCAPS = Air Force/Texas Coronary Atherosclerosis Prevention Study, WOS = West of Scotland Coronary Prevention Study, 4S = Scandinavian Simvastatin Survival Study, POSCH = Program on the Surgical Control of Hyperlipidemia, HIT = HDL Intervention Trial. Reproduced with permission from Ref. No. 11.

tween event reduction and cholesterol reduction; by contrast, the outcomes of two fibrate trials, the HDL Intervention Trial (HIT) and the Helsinki Heart Study (HHS), do not place them on this line, suggesting that mechanisms other than LDL-cholesterol reduction contribute to the observed reduction in CHD events in these two trials. Clinical trials employing specific HDL-cholesterol or triglyceride goals are needed to determine the clinical effects of attaining target levels of these lipid factors.

Ongoing or upcoming trials are designed to provide a better idea of whether additional reductions in LDL cholesterol—for example, to < 100 mg/dl in the secondary prevention setting—can improve reductions in CHD risk; these trials include the Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH), the Treating to New Targets (TNT) study, the Incremental Decrease in Endpoints through Aggressive Lipid Lowering (IDEAL) trial, and the Heart Protection Study (HPS). Other studies are emphasizing clinical research in at-risk populations, including the Atorvastatin Study for the Prevention of CHD Endpoint in Non-Insulin Dependent Diabetes Mellitus (ASPEN)/Collaborative Atorvastatin Diabetes Study (CARDS) in patients with diabetes, the Cerivastatin in Heart Outcomes in Renal Disease: Understanding Survival (CHORUS) trial in patients with renal disease, and the Pravastatin in the Elderly at Risk (PROSPER) trial. The effects of lipid modification with statin treatment in acute coronary syndromes have been reported in the recent Myocardial Ischemia with Aggressive Cholesterol Lowering (MIRACL) trial[12] and are being assessed in the Aggrastat to Zocor (A-2-Z) and the Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT) trials.

Global Risk Assessment

The primary goals of global risk assessment are to improve the calculation of absolute risk category, to identify high-risk patients for aggressive intervention, to identify intermediate-risk patients who appear to be at low risk, and to motivate patients to make changes in life habits. The 2001 NCEP guidelines address the question of global risk assessment by endorsing the risk scoring system developed from the Framingham Heart Study.[13] The Framingham system equates each risk factor with a percent probability of developing CHD over a 10-year period. Once each patient's risk factors have been identified, the physician can calculate a total score that represents the individual's absolute 10-year risk for developing CHD (i.e., > 20%, 10 to 20%, < 10%). The level of risk serves as the basis for determining an appropriate LDL cholesterol goal in primary prevention and the intensity of therapy needed to achieve that goal.

The need for refined risk assessment is pointed out by findings in the AFCAPS/TexCAPS study,[4] in which a 37% reduction in risk for initial CHD events was observed in a population in which only 17% of patients would have qualified for lipid-lowering treatment on the basis of the 1993 NCEP guidelines. Current European guidelines[14] incorporate separate global risk assessments for men and women in primary prevention, with high risk for an initial event defined as a 10-year risk of ≥ 20% based on these assessments; among high-risk individuals, drug therapy is recommended for those with LDL-cholesterol levels of ≥ 115 mg/dl. Under these guidelines, recommendation for drug intervention is generally associated with risk factors such as smoking, diabetes, or familial hypercholesterolemia. In AFCAPS/TexCAPS, an analysis that stratified the cohort according to risk subgroups based on the European guidelines showed that lovastatin treatment was associated with a 39% relative risk reduction in patients in whom treatment would not have been recommended on the basis of European guidelines (low, mild, or moderate risk) and a 34% relative risk reduction in those at high or very high risk.[15]

A risk algorithm for women, which was developed using data from the Framingham Heart Study,[13] is shown in Figure 3. As can be seen, the algorithm includes age, total cholesterol or LDL cholesterol, HDL cholesterol, blood pressure, cigarette smoking, and diabetes as risk factors but excludes potential risk factors such as obesity, physical inactivity, and family history of heart disease, as well as levels of triglycerides, apolipoproteins, lipoprotein (a), and homocysteine. In this algorithm, a score of 9 would be required for placement in the European high-risk category (a 10-year CHD event risk of ≥ 20%). Note that the algorithm places emphasis on HDL cholesterol for women, confirming the importance of below-average HDL cholesterol as an enrollment criterion for women (as well as men) in AFCAPS/TexCAPS.

Challenges for the Implementation of New Guidelines

As in 1993, the 2001 NCEP recommendations state that lowering LDL cholesterol is the primary goal of CHD risk reduction. However, the new guidelines introduce several features that refine the process of global risk assessment. In place of primary and secondary prevention, there are three risk categories: CHD or CHD risk equivalents (e.g., diabetes, other atherosclerotic disease), multiple (2+) major risk factors, or 0–1 major risk factor. For these categories, the LDL cholesterol–lowering goals are < 100 mg/dl, < 130 mg/dL, and < 160 mg/dl, respectively.

To determine the risk category and LDL cholesterol goal for patients without clinical evidence of CHD, physicians must conduct a global risk assessment based on the initial LDL cholesterol level and the presence of major risk factors (smoking; hypertension; HDL cholesterol < 40 mg/dl; family history of CHD; age of ≥ 45 years for men, ≥ 55 years for women). The major risk factors are used to determine 10-year absolute risk for CHD based on the Framingham risk scoring system.[13] For risk category 1, the level of risk is > 20% (CHD risk equivalent; long-term and short-term risk); for category 2, the risk is 10 to 20% (long-term and short-term risk) or, in some cases, < 10% (short-term risk); and for risk category 3, the level is < 10%. Within each risk category, some modification of LDL cholesterol goals is possible based on individual patient characteristics, including lifestyle and emerging risk factors and

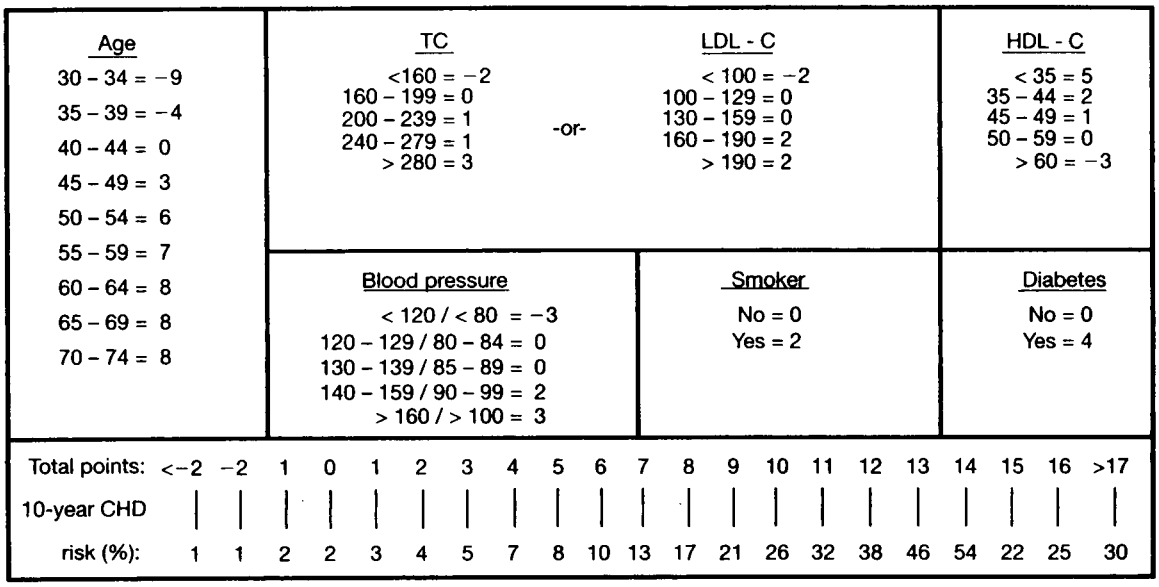

FIG. 3 The Framingham Heart Study cumulative point scale for estimating 10-year coronary heart disease (CHD) risk in women. TC = total cholesterol, LDL-C = low-density lipoprotein cholesterol, HDL-C = high-density lipoprotein cholesterol. Adapted with permission from Ref. No. 13.

the metabolic syndrome. In this way, triglyceride levels and nonlipid risk factors are taken into consideration, which helps identify intermediate-risk patients who may initially appear to be at low risk. Because the metabolic syndrome can increase CHD risk in any patient, it is a secondary target of therapy after LDL cholesterol lowering.

To reduce LDL cholesterol levels, therapeutic lifestyle changes (TLC) are recommended for every patient. Because the new guidelines stress the importance of intensified therapy in high-risk cases, some individuals may require drug therapy and TLC from the outset of treatment. In other patients, however, TLC should be tried for 3 months before drug therapy is considered. The LDL cholesterol cutpoints for initiating drug therapy are ≥100 mg/dl for risk category 1, ≥130 mg/dl for category 2, and ≥160 mg/dl for category 3. The NCEP notes that as drug prices decline, it may become cost effective to extend lipid-lowering therapy to more patients in the future.

While cost effectiveness is an important consideration in therapeutic decision making, deciding to initiate drug therapy based on economic factors alone would deny treatment to many patients whose risk for CHD could be substantially reduced, as indicated by the results of AFCAPS/TexCAPS.[4] Given the demands of current medical practice, it will be a challenge for physicians to implement the revised NCEP recommendations in a manner that benefits patients at intermediate levels of CHD risk.

Conclusion

There is ample evidence that statin therapy can prevent the spectrum of cardiovascular events across a broad range of patient populations and baseline lipid levels by reducing LDL cholesterol and increasing HDL cholesterol. While LDL cholesterol is currently the most well established lipid risk factor, the contributions of other factors such as HDL cholesterol and triglycerides to CHD are gradually being elucidated. Future trials will seek to establish which lipid parameters have the greatest predictive value and to characterize more precisely the specific effects of lipid-lowering therapy on the acute coronary syndromes. In this way, we will be able to optimize the identification and treatment of those patients most likely to experience a cardiovascular event. For the present, a reasonable approach to optimal risk reduction is to broaden the pool of patients eligible for lipid-lowering therapy on the basis of the results of clinical trials conducted to date.

References

1. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *J Am Med Assoc* 2001;285:2486–2497
2. Pearson TA, Laurora I, Chu H, Kafonek S: The Lipid Treatment Assessment Project (L-TAP). A multicenter survey to evaluate the percentages of dyslipidemic patients receiving lipid-lowering therapy and achieving low-density lipoprotein cholesterol goals. *Arch Intern Med* 2000;160:459–467
3. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults: Summary of the Second Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II). *J Am Med Assoc* 1993;269: 3015–3023
4. Downs JR, Clearfield M, Weis S, Whitney E, Shapiro DR, Beere PA, Langendorfer A, Stein EA, Kruyer W, Gotto AM, for the AFCAPS/TexCAPS Research Group: Primary prevention of acute

coronary events with lovastatin in men and women with average cholesterol levels. Results of AFCAPS/TexCAPS. *J Am Med Assoc* 1998;279:1615–1622

5. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group: Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. *N Engl J Med* 1998;339: 1349–1357
6. Sacks FM, Pfeffer MA, Moyé LA, Rouleau JL, Rutherford JD, Cole TG, Brown L, Warnica W, Arnold JMO, Wun C-C, Davis BR, Braunwald E, for the Cholesterol and Recurrent Events Trial Investigators: The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. *N Engl J Med* 1996;335:1001–1009
7. Scandinavian Simvastatin Survival Study Group: Randomised trial of cholesterol lowering in 4,444 patients with coronary heart disease: The Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994;344:1383–1389
8. Shepherd J, Cobbe SM, Ford I, Isles CG, Lorimer AR, Macfarlane PW, McKillop JH, Packard CJ, for the West of Scotland Coronary Prevention Study Group: Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. *N Engl J Med* 1995; 333:1301–1307
9 Watts GF, Dimmitt SB: Fibrates, dyslipoproteinaemia and cardiovascular disease. *Curr Opin Lipidol* 1999;10:561–574
10. The BIP Study Group: Secondary prevention by raising HDL cholesterol and reducing triglycerides in patients with coronary artery disease. The Bezafibrate Infarction Prevention (BIP) study. *Circulation* 2000;102:21–27
11. Thompson GR, Barter PJ: Clinical lipidology at the end of the millennium. *Curr Opin Lipidol* 1999;10:521–526
12. Schwartz GG, Olsson AG, Ezekowitz MD, Ganz P, Oliver MF, Waters D, Zeiher A, Chaitman BR, Leslie S, Stern T: Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes. The MIRACL Study: A randomized controlled trial. *J Am Med Assoc* 2001;285:1711–1718
13. Wilson PWF, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB: Prediction of coronary heart disease using risk factor categories. *Circulation* 1998;97:1837–1847
14. Second Joint Task Force of European and Other Societies on Coronary Prevention: Prevention of coronary heart disease in clinical practice. Recommendations of the Second Joint Task Force of European and Other Societies on Coronary Prevention. *Eur Heart J* 1998;19:1434–1503
15. Gotto AM Jr, Whitney E, Stein EA, Shapiro DR, Clearfield M, Weis S, Jou JY, Langendörfer A, Beere PA, Watson DJ, Downs JR, de Cani JS: Application of the National Cholesterol Education Program and joint European treatment criteria and clinical benefit in the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS). *Eur Heart J* 2000;21:1627–1633