The Scandinavian Simvastatin Survival Study (4S) Subgroup Analysis of Diabetic Subjects: Implications for the Prevention of Coronary Heart Disease

NIDDM is associated with a marked increase in coronary heart disease (CHD) (1). Reasons for the increased CHD risk in NIDDM are clearly multifactorial (2,3). In this commentary, I will focus on lipoproteins and their treatment in NIDDM.

Subjects with NIDDM have increased triglyceride levels and decreased HDL cholesterol levels relative to those in nondiabetic subjects (4). Increased triglyceride and decreased HDL cholesterol levels are also found before the onset of clinical diabetes (5), suggesting that these abnormalities are related to insulin resistance as well as to hyperglycemia. Although the absolute concentration of LDL cholesterol is similar in NIDDM and normoglycemic subjects (4), those with NIDDM have more small-dense LDL than nondiabetic subjects (6).

To summarize observational studies, while few data are available for HDL cholesterol, it may be a powerful predictor of CHD in NIDDM subjects (7). Both total cholesterol (8,9) and triglyceride (8,10) levels are significant predictors of CHD in NIDDM subjects. Total triglyceride may be a more powerful predictor of CHD than total cholesterol in NIDDM subjects (7,10); however, observational studies may not be reliable guides to clinical practice, since associations may not predict the effectiveness of interventions. In particular, triglyceride level is much more strongly associated with insulin resistance (11) than is total cholesterol, and in turn, insulin resistance is correlated with other risk factors such as PAI-1 (plasminogen activator inhibitor 1) and perhaps hypertension. Thus, it is possible that hypertriglyceridemia is a better predictor because it is a better *marker* of risk. Clinical trials are necessary to resolve this issue.

Improvement of glycemic control with insulin markedly reduces hypertriglyceridemia in NIDDM subjects (12), but it may have only modest effects on HDL and LDL levels. Improved glycemic control is the treatment of first choice for elevated triglyceride levels in diabetic subjects. In general, hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitors have been preferred to reduce LDL cholesterol levels and fibric acids to markedly reduce hypertriglyceridemia in diabetic subjects (13). Of particular note is that lovastatin at a dose of 40 mg reduced triglyceride levels by 30% (14) in NIDDM subjects with elevated triglyceride levels (~300 mg/dl at baseline), suggesting that HMG-CoA reductase inhibitors may be the drugs of first choice to treat combined hyperlipidemia (elevation of both VLDL and LDL) in subjects with moderate hypertriglyceridemia (after achievement of good glycemic control).

CLINICAL TRIALS — The Scandinavian Simvastatin Survival Study (4S) was a cholesterol-lowering trial of simvastatin in 4,444 subjects with clinical CHD followed for an average of 5.4 years (15). Subjects in this study had relatively high LDL cholesterol at baseline (~185 mg/dl); subjects with a triglyceride level >2.5 mmol/l (220 mg/dl) were excluded. In this issue, the investigators present the results of subgroup analyses in the 202 diabetic subjects who participated in the 4S (16). This is a landmark study for a number of different reasons. The investigators are the first to show that treatment of dyslipidemia in diabetic subjects significantly decreases the risk of CHD ($P = 0.002$). Particularly impressive is the magnitude of reduction in risk of CHD (55%) in diabetic subjects, which is actually greater than that in nondiabetic subjects (32%). Although the reduction in overall mortality was not quite statistically significant (43%) ($P = 0.087$), it too was greater than that in nondiabetic subjects (28%).

A second important implication of the 4S subgroup analyses is the 2.5-fold higher risk of CHD in diabetic subjects compared with nondiabetic subjects (who are already at high risk of CHD by virtue of having had a prior myocardial infarction). Diabetic subjects with a prior myocardial infarction thus fall into a group with very high risk for future disease. Simvastatin therapy in diabetic subjects reduced the risk of CHD to that in the nondiabetic group given placebo.

The third key observation is that in NIDDM subjects, simvastatin was effective in each of the lipid subgroups examined. Indeed, simvastatin appeared to be possibly more effective in subjects with initially low HDL cholesterol and/or high triglyceride levels. However, the latter statement is limited by the exclusion of subjects with very high triglycerides noted above. (On the other hand, most diabetic subjects in the U.S. have triglyceride levels that fall into the range studied in the 4S.) Thus, at least in diabetic subjects with CHD, aggressive LDL lowering appears to be very beneficial.

Recently, limited data on diabetic subjects with clinical CHD have been published from the Cholesterol and Recurrent Events (CARE) study (17). In this study, the average LDL cholesterol was 139 mg/dl and the upper limit of plasma triglyceride was 350 mg/dl. In 586 subjects with diabetes, 40 mg pravastatin was associated with a 25% decrease in CHD ($P = 0.05$), which was similar to the 23% decrease observed in nondiabetic subjects ($P < 0.001$). Further interpretation must await the publication of a full report of results in diabetic subjects. Overall mortality and lipid changes have not yet been reported in the diabetic subgroup. The percentage reduction in CHD in the CARE study (25%) was considerably less than that in the 4S study. The investigators hypothesized that the benefit is less in subjects with low LDL levels at baseline (<125 mg/dl) in the overall group, but this represents a post hoc analysis. The lesser effectiveness in reducing CHD in the CARE study could also have been due to less LDL lowering (28% [overall CARE group] vs. 35% [4S]). In spite of these uncertainties, the CARE study also supports the effec-

tiveness of LDL lowering in diabetic subjects with clinical CHD.

CAN THE 4S DATA BE APPLIED TO DIABETIC SUBJECTS WITHOUT CLINICAL CHD? — Although no study of LDL lowering by HMG-CoA reductase inhibitors in diabetic patients without clinical CHD currently exists, pravastatin therapy has shown significant reductions of CHD in nondiabetic subjects with hypercholesterolemia and without previous CHD in the West of Scotland Study (18).

In the Helsinki Heart Study, gemfibrozil was associated with a significant reduction in CHD events in nondiabetic subjects free of CHD at baseline, especially in those with elevated triglyceride levels and lower HDL cholesterol levels (19). There was no effect of gemfibrozil on overall mortality. A total of 135 subjects had diabetes at baseline (20). In these subjects, gemfibrozil reduced the risk of CHD by 60%, although this result was not statistically significant. Overall mortality was not reported separately for diabetic subjects. In the posttrial follow-up, there was a nonsignificant increase in noncardiovascular mortality in subjects who were randomized to gemfibrozil, such that at 8.5 years there was an excess overall mortality of 20% (21); this difference narrowed but did not disappear at 10 years (5 years after completion of the trial). The controversial effect of gemfibrozil on overall mortality is in sharp contrast to the overall mortality data on HMG-CoA reductase inhibitors, where there has clearly been a decrease (15,17,18), the most striking being in the 4S (15).

Since strong evidence suggests that aggressive lipid lowering might reduce the rate of CHD in diabetic subjects who have had a CHD event, one could make an argument that perhaps lipid therapy should be deferred until after diabetic subjects have had a CHD event. However, diabetic subjects who develop CHD have a worse prognosis than nondiabetic subjects who have had a clinical event (22). Moreover, if one includes the prehospital mortality (sudden death), the case fatality rate from onset of clinical symptoms through 1 year is 49% in diabetic men and 44% in diabetic women in a preliminary report from Finland (23). The latter study suggesting very high early mortality implies that all diabetic subjects should receive aggressive lipid lowering even if they have not experienced a CHD event.

The National Cholesterol Education Program (NCEP) Adult Treatment Panel II (24) suggests targets for LDL lowering that are geared to the degree of risk. For subjects with established CHD, the goal is to achieve an LDL cholesterol level <100 mg/dl, whereas for high-risk primary prevention, the goal is to achieve an LDL cholesterol level of ≤130 mg/dl and for low-risk primary prevention, the goal is 160 mg/dl. The presence of two or more "risk factors" defines high risk, and diabetes counts as a single risk factor in this algorithm. However, the NCEP panel report suggests that diabetic women may be at as high a risk for CHD as are diabetic men. The panel further suggested that diabetic subjects might be treated as though they had CHD (goal: LDL <100 mg/dl). I believe that the latter recommendation is strongly supported by the high case fatality rate in diabetic men and women (23) together with the efficacy of LDL lowering in the 4S diabetic subjects (16).

WHAT FURTHER CLINICAL TRIALS OF LIPID LOWERING IN NIDDM SUBJECTS SHOULD BE DONE? — On the basis of the 4S (16) and CARE (18), further placebo-controlled trials of lipid lowering by HMG-CoA reductase inhibitors in NIDDM subjects with clinical CHD should not be initiated. Although these conclusions are based on subgroup analyses of two major clinical trials, the observation that the benefits are at least as great in diabetic as in nondiabetic subjects makes further such studies unwarranted.

It would still be acceptable to do studies of titration to various levels of LDL by HMG-CoA reductase inhibitors in diabetic subjects with CHD (e.g., LDL of 100 mg/dl vs. 60–80 mg/dl). Because the previous trials (16,17) have excluded diabetic subjects with marked hypertriglyceridemia (>350 mg/dl), this is an area where clinical trials with HMG-CoA reductase inhibitors or fibric acids might continue. Since definitive trials of fibric acids have not been carried out in diabetic subjects with preexisting CHD, one could possibly perform a placebo-controlled fibric acid trial in this patient subgroup. However, it is likely that HMG-CoA reductase–inhibitor therapy may become the standard of care in diabetic subjects with preexisting CHD, so fibric acid trials may need to be done either against HMG-CoA reductase–inhibitor therapy or with fibric acid as an additional agent.

Since few data are available on primary prevention of CHD in NIDDM subjects, this remains an appropriate area for clinical trials. Trials with HMG-CoA reductase inhibitors should be conducted comparing the conventional NCEP Adult Treatment Panel II recommendations (LDL <130 mg/dl) versus treatment to goals for CHD (LDL <100 mg/dl). A study addressing this question should perhaps have the highest priority at this time. These trials should try to enroll new NIDDM subjects, since NIDDM subjects with a long duration of diabetes could represent a selected group of survivors who may benefit less from lipid lowering.

SUMMARY: STRATEGIES FOR REDUCTION OF CHD — The subgroup analysis in diabetic subjects in the 4S is a landmark study (16) because it is the first to show that modification of lipoproteins will significantly reduce the incidence of recurrent myocardial infarction. On the basis of the 4S data (16), aggressive lowering of LDL cholesterol should be applied to diabetic as well as nondiabetic subjects with clinical CHD. Because the case fatality rate in diabetic subjects with a myocardial infarction is very high (22,23), aggressive lipid lowering should be extended to diabetic subjects who have yet to experience a clinical event. A reasonable goal suggested by the NCEP (24) is an LDL level <100 mg/dl. These recommendations should not be taken to exclude other modalities, such as improved glycemic control, which has been related to reduced microvascular events (8,25) and possibly reduced macrovascular events (25,26) in NIDDM subjects and has been associated with reductions in triglyceride levels (12). Primary prevention of NIDDM is also important because there is evidence of increased cardiovascular risk before the onset of NIDDM (5).

STEVEN M. HAFFNER, MD

From the Department of Medicine, University of Texas Health Science Center, San Antonio, Texas.

Address correspondence to Steven M. Haffner, MD, Department of Medicine, University of Texas Health Science Center, 7703 Floyd Curl Dr., San Antonio, TX 78284-7873.

References

1. Wingard DL, Barrett-Connor E: Heart disease and diabetes: In *Diabetes in America.* 2nd ed. Bethesda, MD, National Institutes of Health, National Institute of Diabetes and

Digestive and Kidney Diseases. National Diabetes Data Group, 1995, p. 429–438
2. Pyörälä K, Laakso M, Uusitupa M: Diabetes and atherosclerosis: an epidemiologic view. *Diabetes Metab Rev* 3:463–524, 1987
3. Stern MP: Diabetes and cardiovascular disease: the "common soil" hypothesis. *Diabetes* 44:369–374, 1995
4. Assmann G, Schulte H: The Prospective Cardiovascular Munster (PROCAM) Study: prevalence of hyperlipidemia in persons with hypertension and/or diabetes mellitus and the relationship to coronary heart disease. *Am Heart J* 116:1713–1724, 1988
5. Haffner SM, Stern MP, Hazuda HP, Mitchell BD, Patterson JK: Cardiovascular risk factors in confirmed prediabetic individuals: does the clock for coronary heart disease start ticking before the onset of clinical diabetes? *JAMA* 263:2893–2898, 1990
6. Haffner SM, Mykkänen L, Stern MP, Paidi M, Howard BV: Greater effect of diabetes on LDL size in women than in men. *Diabetes Care* 17:1164–1171, 1994
7. Laakso M, Lehto S, Penttilä I, Pyörälä K: Lipids and lipoproteins predicting coronary heart disease mortality and morbidity in patients with non-insulin dependent diabetes. *Circulation* 88:1421–1430, 1993
8. West KM, Ahuja MMS, Bennett PH, Czyzyk A, De Acosta OM, Fuller JH, Grab B, Grabauskas V, Jarrett RJ, Kosaka K, Keen H, Krolewski AS, Miki E, Schliak V, Teuscher A, Watkins PJ, Stober JA: The role of circulating glucose and triglyceride concentrations and their interactions with other "risk factors" as determinants of arterial disease in nine diabetic population samples from the WHO Multinational Study. *Diabetes Care* 6:361–369, 1983
9. Stamler J, Vacaro O, Neaton JD, Wentworth D, the Multiple Risk Factor Intervention Trial Research Group: Diabetes, other risk factors and 12 year cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. *Diabetes Care* 16:434–444, 1993
10. Fontbonne A, Eschwege E, Cambien F, Richard JL, Ducimetière P, Thibult N, Warner JM, Claude JR, Rosselin GE: Hypertriglyceridemia as a risk factor of coronary heart disease mortality in subjects with impaired glucose tolerance on diabetes: results from the 11 year follow-up of the Paris Prospective Study. *Diabetologia* 32:300–304, 1989
11. Reaven GM: Banting Lecture 1988: role of insulin resistance in human disease. *Diabetes* 37:1596–1607, 1988
12. Taskinen MR, Packard CJ, Shepherd J: Effect of insulin therapy on metabolic fate of apolipoprotein B-containing lipoproteins in NIDDM. *Diabetes* 39:1017–1027, 1990
13. Garg A, Grundy SM: Management of dyslipidemia in NIDDM. *Diabetes Care* 13: 153–159, 1990
14. Garg A, Grundy SM: Lovastatin for lowering cholesterol levels in non-insulin dependent diabetes mellitus. *N Engl J Med* 318:81–86, 1988
15. The Scandinavian Simvastatin Survival Study Group: Randomized trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Study (4S). *Lancet* 344:1383–1389, 1994
16. Pyörälä K, Pedersen TR, Kjekshus J, Faergeman O, Olsson AG, Thorgeirsson G, the Scandinavian Simvastatin Survival Study (4S) Group: Cholesterol lowering with simvastatin improves prognosis of diabetic patients with coronary heart disease: a subgroup analysis of the Scandinavian Simvastatin Survival Study (4S). *Diabetes Care* 20:614–620, 1997
17. Sacks FM, Pfeffer MA, Moye LA, Rouleau JL, Rutherford JD, Cole TG, Brown L, Warnica JW, Arnold JMO, Wun CC, Davis BR, Braunwald E, 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* 335:1001–1009, 1996
18. Shepherd J, Cobbe SM, Ford I, Isles CG, Lorimer AR, Macfarlane PW, McKillop JH, Packard CJ, the West of Scotland Coronary Prevention Study Group: Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. *N Engl J Med* 333:1301–1307, 1995
19. Manninen V, Tenkanen L, Koskinen P, Huttunen JK, Manttari M, Heinanen OP, Frick MH: Joint effects of serum triglyceride and LDL cholesterol and HDL cholesterol concentrations on coronary heart disease risk in the Helsinki Heart Study: implications for treatment. *Circulation* 85:37–45, 1992
20. Koskinen P, Mänttäri M, Manninen V, Huttunen JK, Heinonen OP, Frick MH: Coronary heart disease incidence in NIDDM patients in the Helsinki Heart Study. *Diabetes Care* 15:820–825, 1992
21. Heinonen OP, Huttunen JK, Manninen V, Mänttari M, Koskinen P, Tenkanen L, Frick MH: The Helsinki Heart Study: coronary heart disease incidence during an extended follow-up. *J Intern Med* 235:41–49, 1994
22. Abbot RD, Donahue RP, Kannel WB, Wilson PW: The impact of diabetes on survival following myocardial infarction in men vs. women: the Framingham Study. *JAMA* 260:3456–3460, 1988
23. Miettinen H, Niemelä M, Lehto S, Haffner SM, Salomaa VV, Mähönen M, Tuomilehto J, the FINMONICA AMI Register Group: Short and long term case fatality of myocardial infarction in diabetic and non-diabetic patients (Abstract). *Diabetologia* 38 (Suppl. 1):A20, 1995
24. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol (Adult Treatment Panel II): Summary of the Second Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol (Adult Treatment Panel II): expert panel on detection, evaluation and treatment of high load cholesterol. *JAMA* 209:3015–3023, 1993
25. Klein R: Kelly West Lecture 1994: hyperglycemia and microvascular and macrovascular disease in diabetes. *Diabetes Care* 18:258–268, 1995
26. Kuusisto J, Mykkänen L, Pyörälä K, Laakso M: NIDDM and its metabolic control predict coronary heart disease in elderly subjects. *Diabetes* 43:960–967, 1994