Cost-Effectiveness of Treating Hyperlipidemia in the Presence of Diabetes
Who Should Be Treated?

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Background—The objective of this study was to estimate the long-term costs and benefits of treating hyperlipidemia among diabetic patients with and without known cardiovascular disease after validating the Cardiovascular Life Expectancy Model.

Methods and Results—The model estimates were compared with the Scandinavian Simvastatin Survival Study (4S) and used to estimate the long-term costs and benefits of treatment with simvastatin. Simulations were performed for men and women, 40 to 70 years of age, having pretreatment LDL cholesterol values of 5.46, 4.34, and 3.85 mmol/L (211, 168, and 149 mg/dL). We forecasted the long-term risk of cardiovascular events, the need for medical and surgical interventions, and the associated costs in 1996 US dollars. The model validated well against the observed results of the of the 4S diabetic patients. In this validation, the model estimates fell within the 95% confidence interval of the observed results for 7 of the 8 available end points (coronary deaths, total deaths, and so forth). Treatment with simvastatin for patients with cardiovascular disease is cost-effective for men and women, with or without diabetes. Among diabetic individuals without cardiovascular disease, the benefits of primary prevention were also substantial and the cost-effectiveness ratios attractive across a wide range of assumptions ($\approx$$4000 to $40 000 per year of life saved). These conclusions were robust even among diabetics with lower baseline LDL values and smaller LDL reductions as observed in the Cholesterol and Recruitment Events (CARE) trial.

Conclusions—Among adults with hyperlipidemia, the presence of diabetes identifies men and women among whom lipid therapy is likely to be effective and cost-effective even in the absence of other risk factors or known cardiovascular disease. (***Circulation***. 2000;102:722-727.)

Key Words: prevention ■ cardiovascular diseases ■ diabetes mellitus

The effectiveness of HMG-CoA reductase inhibitors (statins) in both primary and secondary prevention has been consistently demonstrated. To date, successful clinical trials have included men and women with varying risks of future cardiovascular events caused by the presence of known cardiovascular disease or multiple risk factors.[1–4] The presence of diabetes is a particularly important risk factor for future cardiovascular events. Although randomized clinical trials among such individuals have not yet been completed, post hoc analyses in both primary and secondary prevention settings suggest that lipid therapy is particularly effective in reducing cardiovascular events among diabetic patients.[1,2,5] Most recently, a subanalysis of the Scandinavian Simvastatin Survival Study (4S)[6] demonstrated that diabetic patients with cardiovascular disease obtained a greater absolute benefit from simvastatin therapy compared with similarly enrolled nondiabetic patients. This result was consistent with previously published epidemiological data identifying diabetes as a significant independent risk factor of cardiac events among those with and those without known cardiovascular disease.[7,8]

We have estimated the effectiveness and cost-effectiveness of lipid therapy among patients with and those without diabetes in both primary and secondary prevention by using the Cardiovascular Life Expectancy Model.[9,10] This validated disease-simulation model has been previously shown to estimate the short-term benefits of risk factor modification across a wide range of primary and secondary prevention studies. Herein, we also demonstrated that the model appropriately forecasts the reduction in cardiovascular events observed in the 4S study among diabetic patients. We then demonstrated that the presence of diabetes identifies a subgroup of individuals among whom primary and secondary prevention is cost-effective.

Methods

The benefits and cost-effectiveness ratios associated with the treatment of hyperlipidemia were calculated by means of the Cardiovas-

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TABLE 1. Computer-Estimated Cardiovascular Events Versus Observed Results: 4S Diabetic Patients

Measure	Intervention Group	Events per 100		
		Computer Estimate	Observed Result	(95% CI)
CHD deaths	Simvastatin	14.1	11.4	(6.0, 19.1)
	Placebo	20.6	17.5	(10.6, 26.6)
Total deaths	Simvastatin	17.7	14.3	(8.2, 22.5)
	Placebo	25.0	24.7	(16.5, 34.5)
Nonfatal myocardial infarctions*	Simvastatin	39.9	17.1	(10.4, 25.7)
	Placebo	55.2	51.5	(41.1, 61.8)
Cerebrovascular events†	Simvastatin	6.2	4.8	(1.6, 10.8)
	Placebo	10.9	10.3	(5.1, 18.1)

*Defined as definite, probable, intervention-related, and silent myocardial infarction.

†Nonfatal cerebrovascular events were estimated as transient ischemic attacks and nonfatal strokes.

cular Disease Life Expectancy Model.[9,10] The model estimates the reduction in cardiovascular events and the increased life expectancy or years of life saved (YOLS) after risk factor modification. The incremental cost-effectiveness ratios incorporate the direct costs of treatment and the cost savings of cardiovascular events averted. The economic perspective adopted in the present analysis is that of a third-party payer providing comprehensive coverage of all healthcare services.

Cardiovascular Disease Life Expectancy Model

The model has been previously described in detail.[9] It can be applied to groups of patients free of diagnosed cardiovascular disease (primary prevention) or those with prior coronary disease or stroke (secondary prevention). The yearly transition probabilities to fatal events such as coronary death, stroke death, and noncardiovascular death are estimated from multivariate risk equations developed from the 15% random sample of the Lipid Research Clinics (LRC) Program Prevalence and Follow-up Cohort.[11–15] The cardiovascular risk factors used by the model include age, sex, mean blood pressure, the natural logarithm of the LDL/HDL cholesterol ratio, the presence of cigarette smoking, diabetes, and diagnosed cardiovascular disease at baseline.

The model has been validated[9] on primary and secondary prevention lipid modification trials and hypertension trials. In the present study, the model was also validated on a published subgroup analysis performed on the diabetic patients of the 4S study[6] (Table 1).

For the purpose of the present analysis, a new stroke multivariate risk equation was used that excluded the presence of diabetes as an independent risk factor for stroke death. Although we believe the presence of diabetes is associated with an increased risk of stroke, we believed that this risk (odds ratio=7.1), as estimated from the LRC Program Prevalence and Follow-up Cohort, was inaccurate as the result of an over-fitted model.[9,16]

Estimating Benefits and Costs of Treatment

In the initial analyses, we compare treatment with simvastatin versus no treatment and calculate the benefits as YOLS by subtracting the life expectancy of untreated subjects from the life expectancy of treated subjects (YOLS=life expectancy with treatment minus life expectancy without treatment).

All healthcare cost estimates have been previously reported in detail.[10] Treatment costs included the costs of hospitalizations, physician fees, outpatient care, and emergency services where applicable. Hospital costs were estimated with the use of the Canadian Institute for Health Information (CIHI) methodology.[17] The average costs of physician services were based on reimbursement fee schedules from the provinces of Quebec and Ontario.[18–20] All costs were calculated on the basis of 1996 Canadian dollars and

converted to US dollars at the 1996 exchange rate (US $1=Canadian $1.364).[21] Outpatient care costs included costs of outpatient physicians visits, diagnostic tests, and drugs. For survivors of cardiovascular events, this included separate cost estimates for the first year after the event and the subsequent years. All drug costs were provided by IMS Canada.[22]

The average simvastatin dose was taken from the results of the 4S study: 61.6% patients were given 20 mg of simvastatin daily, 31.6% were given 40 mg daily, 0.1% were given 10 mg daily, and 6.7% discontinued the medication.[23] The annual costs of simvastatin were estimated at $667.

Costs of Diabetes

We estimated the annual outpatient costs of treating diabetes among patients. On the basis of a literature review,[24–27] we assumed that a diabetic patient with no prior cardiovascular disease would have 2 physician visits, with biochemical panels and glycosylated hemoglobin tests, per year. Each patient would also have an annual consultation with an ophthalmologist, a lipid profile, and a urinalysis. For those diabetic patients who subsequently developed cardiovascular disease, the marginal costs of managing diabetes included only the additional costs of the ophthalmologist visit, the glycosylated hemoglobin, and urinalysis.

The proportion of insulin-treated and non–insulin-treated patients were taken from the recent subanalysis of the 4S study.[6] The annual costs of insulin treatment, including syringes and alcohol preparation, were estimated at $417. The annual costs of oral hypoglycemics ranged from $74 for a sulfonylurea to $166 for metformin.

Diabetes management costs also included home monitoring costs of blood glucose. We estimated these costs by using data from a US health maintenance organization.[28] Home glucose monitoring varies substantially among patients, from $269 per year for insulin users to $80 and $36 for those taking oral hypoglycemics and on diet alone, respectively. We also assumed that each diabetic patient would have a half-hour consultation with a dietitian annually.

Finally, we calculated the incremental cost-effectiveness ratios of simvastatin among diabetic and nondiabetic patients by calculating the difference between lifetime medical costs of treated and untreated subjects divided by the difference in their forecasted life expectancies. Since the costs and the health outcomes occur at different times in the future, we discounted both by 5% annually.[29]

Lipid Modifications Achieved Through Use of Statins

The lipid modification achieved with simvastatin among all 4S participants[6] included a 25% and 35% reduction in total cholesterol and LDL cholesterol, respectively, and an 8% increase in HDL cholesterol. These values were used in simulations for both diabetic

TABLE 2. Benefits of Lipid Therapy Among Diabetic and Nondiabetic Patients With and Without Known Cardiovascular Disease

| | | | | Years of Life Saved | | | | | | | |
| | | | | Diabetics | | | | Nondiabetics | | | |
Disease Status	Sex	Baseline LDL in mmol/L (mg/dL)†	LDL/HDL* Ratio	40	50	60	70	40	50	60	70
Known CVD	Male	5.46 (211)	5	5.3	3.93	2.35	0.78	3.92	3.17	2.11	0.77
		4.34 (168)	3.9	5.03	3.85	2.38	0.81	3.26	2.68	1.82	0.68
		3.85 (149)	3.5	4.81	3.74	2.35	0.81	2.92	2.41	1.65	0.62
	Female	5.46 (211)	5	4.58	3.63	2.35	0.83	2.7	2.27	1.59	0.62
		4.34 (168)	3.9	3.97	3.21	2.13	0.77	2.12	1.79	1.27	0.5
		3.85 (149)	3.5	3.63	2.96	1.98	0.73	1.84	1.56	1.11	0.44
No CVD	Male	5.46 (211)	5	5.4	4.12	2.53	0.79	2.5	2.02	1.32	0.44
		4.34 (168)	3.9	4.84	3.8	2.38	0.74	1.84	1.51	1	0.34
		3.85 (149)	3.5	4.47	3.54	2.24	0.69	1.55	1.28	0.85	0.29
	Female	5.46 (211)	5	2.78	2.33	1.58	0.54	1.2	1.03	0.73	0.26
		4.34 (168)	3.9	2.14	1.79	1.21	0.42	0.85	0.73	0.51	0.19
		3.85 (149)	3.5	1.84	1.53	1.04	0.37	0.71	0.6	0.43	0.16

*HDL is assumed fixed at 1.1 mmol/L (42 mg/dL).
†LDL values of 5.46, 4.34, and 3.85 mmol/L correspond to values of 211, 168, and 149 mg/dL.

and nondiabetic men and women with and without preexisting cardiovascular disease. For simple comparisons, all patients were assumed to be nonsmokers with a blood pressure of 120/80 mm Hg.

The 4S participants had very elevated LDL levels at baseline (mean LDL=4.87 mmol/L or 188 mg/dL), which may not be representative of most diabetic patients. In a sensitivity analysis, we explored the cost-effectiveness of less intensive statin therapy among diabetic patients with less extreme lipid abnormalities. We therefore used the previous assumptions and data from the Cholesterol and Recruitment Events (CARE) trial[2] to estimate the cost-effectiveness of more modest lipid changes (total cholesterol −20%, LDL −28%, and HDL +5%) with the use of 40 mg/d pravastatin at a cost of $684.00 annually. These analyses focused on individuals with lower baseline lipid values, including a total cholesterol of 5.3 mmol/L (205 mg/dL), an LDL of 3.5 mmol/L (135 mg/dL), and HDL of 1.0 mmol/L (39 mg/dL). Although CARE was a secondary prevention study, we again estimated the impact of the observed lipid changes in primary prevention among individuals without known cardiovascular disease.

Results

The cardiovascular event rates predicted by the model (Table 1) were consistent with those observed among the 4S diabetic patient subgroup.[6] Among the diabetic patients, 11.4 coronary heart disease (CHD) deaths per 100 were observed (95% CI 6.0 to 19.1) in the simvastatin group and 17.5 events per 100 (95% CI 10.6 to 26.6) in the placebo group versus 14.1 and 20.6 per 100, respectively, forecasted by the model. Model estimates fell within the 95% confidence interval of the observed results for 7 of the 8 outcomes reported. Although the model tended to slightly overestimate outcomes, it should be noted that the 4S authors of the subgroup analysis reported that "the prognosis of diabetic CHD patients participating in the 4S was probably somewhat better than that of unselected diabetic CHD patients of the same age in the general population."[6]

The forecasted long-term benefits of treatment among patients with diagnosed cardiovascular disease are substantial (Table 2). Among diabetic men with cardiovascular disease,

the increased life expectancy ranges from 0.78 YOLS in 70-year-olds with a baseline LDL cholesterol of 5.46 mmol/L (211 mg/dL) to 5.30 YOLS for 40-year-olds, all other things being equal. Benefits among nondiabetic men with cardiovascular disease are less and range from 0.62 to 3.92 YOLS. Among women with cardiovascular disease, the benefits of lipid therapy are also substantially greater among those with diabetes. Benefits range from 0.44 to 2.70 YOLS among nondiabetics and from 0.73 to 4.58 YOLS among diabetic patients.

Among those without known cardiovascular disease, the estimated benefits of modifying lipids among diabetic men with a pretreatment LDL cholesterol level of 5.46 mmol/L (211 mg/dL) and an HDL cholesterol level of 1.10 mmol/L (42 mg/dL) range from 5.40 YOLS in 40-year-olds to 0.79 YOLS for 70-year-olds (Table 2). Among nondiabetic patients, these benefits are substantially less and range from 0.44 to 2.50 YOLS. For diabetic men with more modest lipid abnormalities such as a baseline LDL cholesterol value of 4.34 mmol/L (168 mg/dL), the benefits associated with simvastatin are slightly diminished but remain substantial. These estimates range from 0.74 to 4.84 YOLS. Diabetic men with even lower baseline LDL cholesterol values of 3.85 mmol/L (149 mg/dL) have forecasted benefits ranging from 0.69 to 4.47 YOLS. Again, nondiabetic men are estimated to gain substantially fewer benefits than diabetics having the same lipid profile.

For women free of cardiovascular disease, the benefits of lipid modification (Table 2) are less than those forecasted for similar men, reflecting the lower absolute cardiovascular risk in women. Among diabetic women with a pretreatment LDL cholesterol value of 5.46 mmol/L (211 mg/dL), the benefits range from 0.54 to 2.78 YOLS. In nondiabetic women with the same baseline lipids, the benefits of simvastatin are estimated to range from 0.26 to 1.20 YOLS. As in men, the

LDL-CHOLESTEROL = 5.46 mmol/L (211 mg/dl)

LDL-CHOLESTEROL = 4.34 mmol/L (168 mg/dl)

LDL-CHOLESTEROL = 3.85 mmol/L (149 mg/dl)
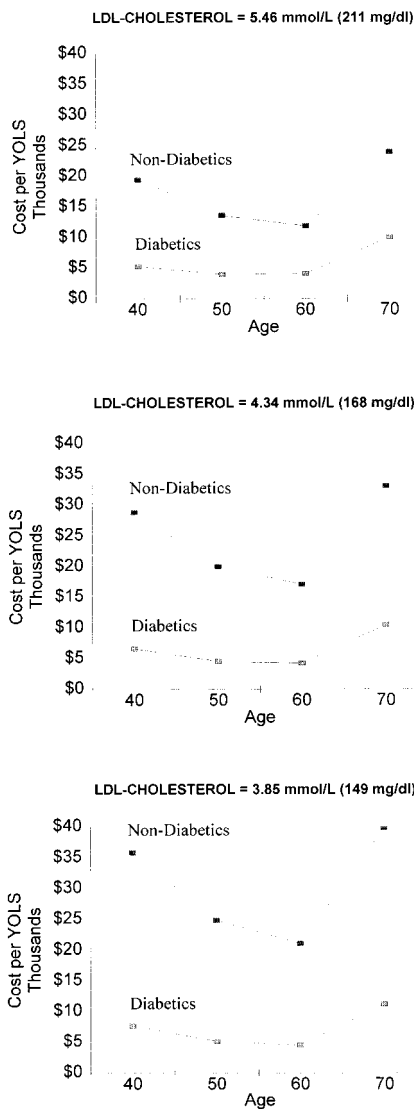
Figure 1. Cost-effectiveness of simvastatin among diabetic and nondiabetic men free of cardiovascular disease at various levels of baseline LDL cholesterol. Forecasted benefits are based on lipid changes observed in 4S study, including reduction in total and LDL cholesterol of 35% and 25%, respectively, and 8% increase in HDL cholesterol.
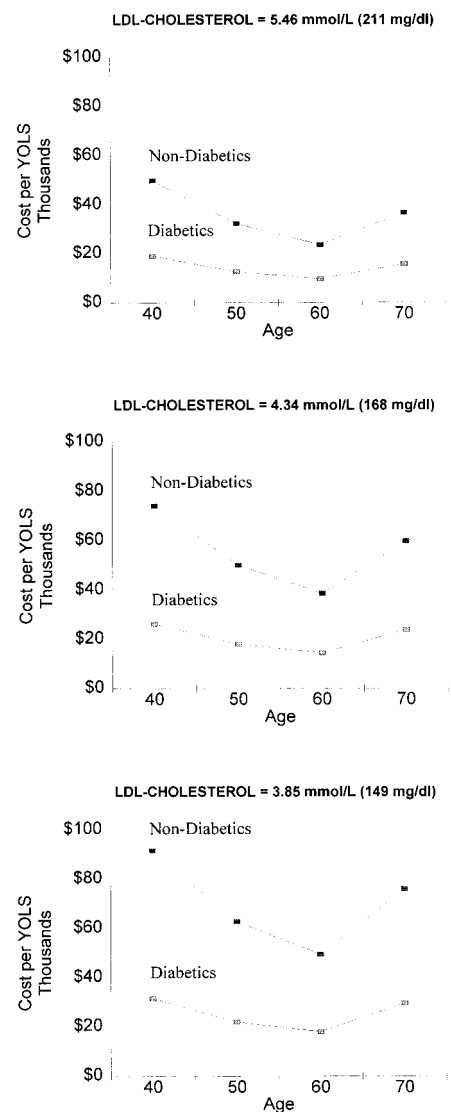
benefits of lipid modification decreased with decreasing pretreatment LDL cholesterol values.

The cost-effectiveness ratios among nondiabetic men with cardiovascular disease range from ≈$5000 per YOLS in 60-year-olds with a baseline cholesterol of 5.46 mmol/L (211 mg/dL) to $14 000 per YOLS in 40-year-olds with pretreatment LDL cholesterol of 3.85 mmol/L (149 mg/dL). Among similar diabetic men, cost-effectiveness ratios are lower and range from $4000 to $8000 per YOLS. Similar results are observed for women diagnosed with cardiovascular disease, indicating that the presence of diabetes identifies a subgroup among whom secondary prevention is particularly cost-effective.

The cost-effectiveness ratios associated with primary prevention among nondiabetic men with pretreatment LDL cholesterol of 5.46 mmol/L (211 mg/dL) (Figure 1) range

from ≈$12 000 per YOLS among 60-year-olds to $24 000 per YOLS among 70-year-olds. Among similar diabetic patients, the cost-effectiveness is substantially lower, ranging from $4000 to $10 000 per YOLS. The same is true for lower pretreatment lipid levels. Among women free of cardiovascular disease (Figure 2), cost-effectiveness ratios are higher than those obtained in men. However, once again, the presence of diabetes substantially increases the absolute risk of cardiovascular events and lowers the cost-effectiveness of treating even modest levels of hyperlipidemia.

Even among diabetic patients without known cardiovascular disease and with nearly "normal" lipid levels, (mean LDL of 3.5 mmol/L or 135 mg/dL), modest changes in blood lipids, as seen in the CARE study, still appear to be cost-effective (Figure 3). For diabetic men, the cost-effectiveness ratios range from $7000 to $15 000 per YOLS, whereas estimates for diabetic women range from $24 000 to $40 000 per YOLS. In the

LDL-CHOLESTEROL = 5.46 mmol/L (211 mg/dl)

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LDL-CHOLESTEROL = 3.85 mmol/L (149 mg/dl)

Figure 2. Cost-effectiveness of simvastatin among diabetic and nondiabetic women free of cardiovascular disease at various baseline lipid levels after reduction in total and LDL cholesterol of 35% and 25%, respectively, and 8% increase in HDL cholesterol.
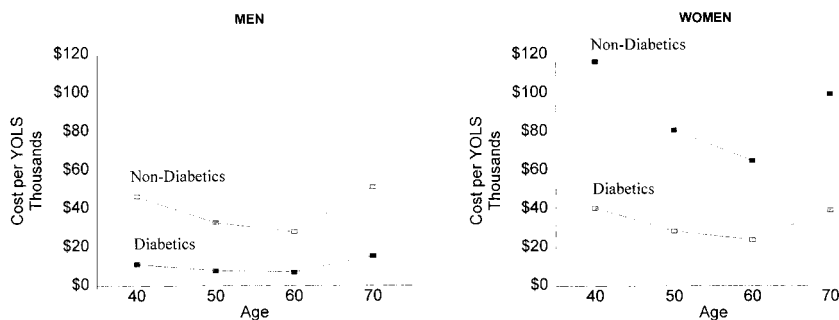
Figure 3. Cost-effectiveness of pravastatin among diabetic and nondiabetic men and women free of cardiovascular disease with baseline lipid values of 5.3 mmol/L (205 mg/dL), 3.5 mmol/L (135 mg/dL), and 1.0 mmol/L (39 mg/dL) for total, LDL, and HDL cholesterol, respectively. Forecasted benefits are based on lipid changes observed among CARE study subjects,[2] including reduction in total and LDL cholesterol of 20% and 28%, respectively, and 5% increase in HDL cholesterol.

absence of diabetes, cost-effectiveness ratios associated with primary prevention are substantially higher, ranging from $28 000 to $51 000 per YOLS for men and $65 000 to $116 000 per YOLS for women.

Discussion

These analyses demonstrate that the treatment of hyperlipidemia among a wide range of patients with diabetes is likely to be effective and cost-effective. These results underscore that diabetes is a strong risk factor for future cardiovascular events, independent of blood lipids or other risk factors.[7,9] Accordingly, even in primary prevention, individuals with lipid abnormalities and diabetes are at significantly increased cardiovascular risk despite the absence of other cardiovascular risk factors.

Although the treatment of hyperlipidemia among diabetic patients has not been conclusively evaluated in a prespecified randomized clinical trial, there are a number of lipid intervention trials that have included diabetic patients. The subanalysis of the 4S study provides the foundations for the analyses presented herein.[6] In this study, major coronary events were significantly reduced among diabetic patients after lipid therapy. Although the risk reduction associated with lipid therapy was similar for diabetic and nondiabetic patients, the absolute event rate was substantially higher among diabetic patients. These results were consistent with the events predicted by the Cardiovascular Life Expectancy Model,[9] supporting the conclusion that the benefits of lipid therapy are relatively similar among diabetic and nondiabetic patients but absolutely greater in the former group because of their increased risk of future events.

These analyses strongly support the intensive management of lipid abnormalities among diabetics. Although the secondary prevention of cardiovascular disease has previously been reported to be both effective and cost-effective[1,2,9,10,30,31] in general, among diabetic patients it would appear to be particularly cost-effective.

The situation in primary prevention is more complex. Previous analyses have suggested that primary prevention should be targeted only to those individuals at increased risk due to the presence of severe lipid abnormalities and/or additional cardiovascular risk factors.[4,9,31,32] On the other hand, isolated lipid abnormalities among individuals without other risk factors is associated with only a modestly increased risk of disease, and the long-term costs of therapy may not necessarily result in substantial clinical gain, given the large numbers that must be treated to prevent 1 event. Therefore,

although clinical trials have demonstrated that the treatment of lipid abnormalities in primary prevention patients may be associated with clinical benefit, the cost-effectiveness of these treatments remains controversial. What about primary prevention among diabetic patients with lipid abnormalities?

A post hoc analysis of the Helsinki Heart Study has confirmed that diabetic patients in both arms of the study were at increased risk of cardiovascular events.[5] After treatment with gemfibrozil, CHD incidence among the treated diabetic men was 3.4% compared with 10.5% in the placebo group. However, this reduction was not statistically significant in large part because of the small numbers of diabetic patients.

The AFCAPS/TexCAPS study (Air Force/Texas Coronary Atherosclerosis Prevention Study) also demonstrated that coronary events could be prevented with lovastatin in a primary prevention setting among individuals with only modestly elevated LDL cholesterol levels and depressed HDL cholesterol,[33] a common profile among diabetics. Once again, the number of diabetics enrolled in the study was small. Nonetheless, diabetic patients demonstrated a higher incidence of coronary event rates and a reduction in risk associated with statin therapy that although nonsignificant was consistent with the significant reductions observed in the larger nondiabetic population.

Clinical decisions based on model simulations must remain speculative in the absence of clinical trial data.[9,10,32] However, the model validation presented herein reinforces the results of our analyses. Even without other cardiovascular disease risk factors, diabetic patients with lipid abnormalities are at extremely increased risk of cardiovascular events. Accordingly, if the relative risk reduction associated with therapy is similar to that observed among diabetics in secondary prevention studies such as 4S[6] or CARE[2] or primary prevention studies in general, then one can conclude that intensive lipid therapy will be clinically and economically worthwhile. On the other hand, we note that many previous lipid guidelines such as the 1993 National Cholesterol Education Program identify diabetes as one of many risk factors such as mild hypertension, male sex, cigarette smoking, and so forth.[34] However, more recently published data have demonstrated that the presence of diabetes is associated with a risk of cardiovascular death comparable to that seen among individuals who already have diagnosed cardiovascular disease.[35] Moreover, another recent study suggests that hyperlipidemia may be relatively undertreated among diabetics.[36] Future guidelines will undoubtedly consider this new information.

These analyses suggest that lipid abnormalities among diabetic patients should be treated with the same intensive intervention that is currently recommended for patients with cardiovascular disease. This is consistent with the LDL goal of <100 mg/dL (2.59 mmol/L) recently recommended by the American Diabetes Association.[37] Clinical trials should also be considered to determine if treating "normal" lipid levels among diabetics would be beneficial. Even in the absence of diagnosed cardiovascular disease or other risk factors, the forecasted long-term benefits of treating hyperlipidemia appear substantial and the cost-effectiveness ratios represent good value. As lipid therapy becomes less expensive, this value should increase accordingly.

Acknowledgments

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