How Cost-Effective Is the Treatment of Dyslipidemia in Patients With Diabetes but Without Cardiovascular Disease?

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OBJECTIVE — Epidemiological studies have shown that the risk of myocardial infarction (MI) in diabetic patients without cardiovascular disease (CVD) is comparable to the risk of MI in patients with CVD. We used a validated Markov model to compare the long-term costs and benefits of treating dyslipidemia in diabetic patients without CVD versus treating CVD patients without diabetes in the U.S. The generalizability and robustness of these results were also compared across six other countries (Canada, France, Germany, Italy, Spain, and the U.K.).

RESEARCH DESIGN AND METHODS — With use of the Cardiovascular Disease Life Expectancy Model, cost effectiveness simulations of simvastatin treatment were performed for men and women who were 40–70 years of age and had dyslipidemia. We forecast the long-term risk reduction in CVD events after treatment. On the basis of the Scandinavian Simvastatin Survival Study results, we assumed a 35% reduction in LDL cholesterol and an 8% rise in HDL cholesterol.

RESULTS — In the U.S., treatment with simvastatin for CVD patients without diabetes was cost-effective, with estimates ranging from $8,799 to $21,628 per year of life saved (YOLS). Among diabetic individuals without CVD, lipid therapy also appeared to be cost-effective, with estimates ranging from $5,063 to $23,792 per YOLS. In the other countries studied, the cost effectiveness of treating diabetes in the absence of CVD was comparable to the cost effectiveness of treating CVD in the absence of diabetes.

CONCLUSIONS — Among diabetic men and women who do not have CVD, lipid therapy is likely to be as effective and cost-effective as treating nondiabetic individuals with CVD.

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C ardiovascular disease (CVD) is a major cause of mortality and morbidity in diabetic patients. Diabetes is reported to be associated with a two- to sevenfold increased risk of coronary and cerebrovascular events (1–5), and the prognosis of clinical CVD is worse in diabetic patients (6–8). Haffner et al. (5) have shown that the risk of myocardial infarction (MI) in diabetic patients without CVD is comparable to the risk of MI in patients with CVD. These observations suggest that strategies to reduce the risk of CVD and its complications may be particularly useful among diabetic patients. Modification of risk factors such as obesity and a sedentary lifestyle has been advocated for all patients with diabetes or impaired fasting glucose of 110–125 mg/dl (6.1–6.9 mmol/l). Recent guidelines have recognized the results of clinical trials demonstrating the value of aggressive management of blood pressure and blood lipids in addition to glucose. The American Diabetes Association recommends an LDL cholesterol goal of 100 mg/dl (2.60 mmol/l) for diabetic patients, which is consistent with the goal currently recommended by the National Cholesterol Education Program, Adult Treatment Panel II, for patients with CVD (9,10).

A post hoc analysis of diabetic subjects with coronary disease who received simvastatin in the Scandinavian Simvastatin Survival Study (4S) had LDL cholesterol levels 36% lower than placebo-treated subjects and a reduction in total mortality of 43% (95% CI 0.3–1.08) and a reduction of 55% (0.27–0.74) in major CVD events. Undiagnosed diabetic subjects with fasting glucose levels $\geq$126 mg/dl ($\geq$7.0 mmol/l) and those with impaired fasting glucose also benefited from simvastatin treatment (11). These results in diabetic subjects with CVD are supported by subgroup analysis of two other end point trials (the Cholesterol and Recurrent Events trial and the Long-Term Intervention with Pravastatin in Ischaemic Disease trial) that used pravastatin (12,13). These studies suggest that diabetic patients with coronary heart disease benefit from statin therapy by a reduction in the risk of coronary and other atherosclerotic events. Whether these results apply to diabetic patients without documented coronary heart disease is unknown.

Previously, the cost effectiveness of simvastatin treatment has been shown in the overall 4S population of patients with coronary disease as well as in the subgroup of subjects with diabetes by clinical history (14,15). In this analysis, we have estimated the long-term cost effectiveness of lipid therapy with simvastatin among diabetic patients without symptomatic CVD and compared the results to patients with CVD but without diabetes, using medication and health care service costs

Table 1—*Estimated YOLS after simvastatin therapy*

	YOLS after starting simvastatin			
	At age 40 years	At age 50 years	At age 60 years	At age 70 years
Men				
Diabetes*	5.36	4.13	2.56	0.81
CVD†	3.90	3.16	2.12	0.78
Women				
Diabetes*	2.83	2.36	1.59	0.54
CVD†	2.72	2.29	1.62	0.63

Baseline cardiovascular risk profile is based on the 4S results and includes the following: nonsmokers, total cholesterol 261 mg/dl (6.74 mmol/l), LDL cholesterol 188 mg/dl (4.87 mmol/l), HDL cholesterol 46 mg/dl (1.18 mmol/l), triglycerides 132 mg/dl (1.49 mmol/l), blood pressure 138.5/83.2 mmHg. Simvastatin therapy is assumed to decrease total cholesterol and LDL cholesterol by 25 and 35%, respectively, and increase HDL cholesterol by 8%. *Diabetes but no known CVD; †known CVD but no diabetes.

from the U.S. In the absence of clinical trial data demonstrating the benefit of lipid therapy among diabetic patients without CVD, we used a validated disease simulation model to compare the cost effectiveness of primary and secondary prevention across a wide range of patients (4,16). In addition to data from the U.S., we also integrated into the model direct health care costs from six other countries (Canada, France, Germany, Italy, Spain, and the U.K.) to ensure that the results were widely applicable.

RESEARCH DESIGN AND

METHODS — The costs and benefits associated with the treatment of dyslipidemia were estimated using the Cardiovascular Disease Life Expectancy Model (4,16). With use of cost data from the U.S. and six other countries, the incremental cost effectiveness ratios included the direct medical costs associated with treatment and the cost savings associated with a reduction in CVD events. The economic perspective adopted in the present analysis is that of a third-party payer providing comprehensive coverage of all health care services.

Cardiovascular Disease Life Expectancy Model

The Cardiovascular Disease Life Expectancy Model estimates the annual probability of fatal and nonfatal CVD events (4). This Markov model can be used in primary prevention among patients free of diagnosed CVD or in secondary prevention among patients with prior coronary disease or stroke. The annual probability of fatal and nonfatal CVD events over 12 years of follow-up is based on a multivariate logistic regression model using the 15% random

sample of the Lipid Research Clinic Follow-up cohort (17,18). Independent risk factors include age, sex, blood pressure, LDL cholesterol, HDL cholesterol, the presence of cigarette smoking, diabetes, and diagnosed CVD at baseline. The clinical criteria for coronary and cerebrovascular disease and the odds ratios for independent risk factors included in the final model have been reported elsewhere (4,19).

Briefly, a cohort of patients with or without CVD is entered into the model at a given age with specified levels of risk factors. Each year, subjects can die of coronary disease, cerebrovascular disease, or other causes. Survivors may have developed nonfatal coronary or cerebrovascular disease or remain disease free. Surviving subjects age 1 year and then reenter the model for the following year. This process continues until all subjects die. Mean life expectancy can be calculated by summing across the total person-years of life experienced by the cohort and dividing by the subjects at risk at entry into the model.

The model has been previously described in detail and shown to reasonably predict fatal events in nine clinical trials (4). These trials include treatments of dyslipidemia and hypertension. The model has also been validated on a published subgroup analysis of the diabetic subjects in the 4S (20).

Economic analysis

We compared costs and benefits of simvastatin (versus no treatment) among diabetic patients without CVD (primary prevention) versus patients with CVD but no known diabetes (secondary prevention). cost effectiveness ratios represent the cost per year of life saved (YOLS) associated

with simvastatin therapy where YOLS equals life expectancy with treatment minus life expectancy without treatment. Health care cost inputs into the model have previously been reported in detail and include the costs of hospitalizations, physician fees, outpatient care, emergency services, and drug prescriptions (16).

American health care costs were derived from published reports, including the following: hospital costs from the national Medicare Provider Analysis and Review data and the national sample of the Healthcare Cost and Utilization Project, laboratory tests and physician fees based on the Medicare Resource-Based Relative Value Scale, and annual medication costs from the 1998 Redbook (21–24).

The Canadian costs have previously been described in detail and are based on data from provincial fee schedules, the Canadian Institute for Health Information, and IMS Canada (16). Public prices for simvastatin and hospital costs for the five European countries were based on independent local costing studies conducted in each country and were provided by Merck. Other treatment costs were derived using Canadian costs adjusted for differences in hospital costs between Canada and the five European countries.

The distribution of simvastatin dose was taken from the final dosages of subjects in the 4S: 61.6% were given 20 mg simvastatin daily, 31.6% were given 40 mg daily, 0.1% were given 10 mg daily, and 6.7% discontinued the medication. The lipid modification achieved with simvastatin included a 25 and 35% reduction in total cholesterol and LDL cholesterol, respectively, and an 8% increase in HDL cholesterol. For the purposes of this analysis, we assumed that all patients had lipid profiles similar to the mean values observed in the simvastatin group of the 4S, including total cholesterol levels of 261 mg/dl (6.74 mmol/l), LDL cholesterol of 188 mg/dl (4.87 mmol/l), HDL cholesterol of 46 mg/dl (1.18 mmol/l), and triglycerides of 132 mg/dl (1.49 mmol/l) (19,20). Blood pressure was assumed to be the mean of subjects in the study or 138.5/83.2 mmHg (19,20). For the purposes of these analyses, we assumed that all individuals were nonsmokers. Risk factor levels and the impact of treatment on lipid levels were assumed to be uniform across age-groups.

We also estimated the annual outpatient costs of treating diabetes. On the basis of a detailed literature review, we

Table 2—*Average hospitalization costs including inpatient physician fees (in 1998 U.S. dollars and local currencies)*

	U.S.	Canada		France		Germany		Italy		Spain		U.K.	
	(USD)	USD	CAD	USD	FRF	USD	DEM	USD	ITL	USD	ESP	USD	GBP
Surgical procedures													
Coronary artery bypass surgery	30,395	11,726	17,416	16,583	97,647	14,618	25,675	15,067	26,122,618	11,518	1,717,685	11,781	7,109
PTCA	13,040	5,153	7,654	5,805	34,181	5,588	9,815	6,922	12,000,000	4,231	630,931	3,925	2,368
Pacemaker insertion	13,695	8,142	12,093	11,902	70,082	11,503	20,204	11,516	19,964,787	8,423	1,256,063	9,368	5,652
Medical diagnoses													
Sudden death	754	373	554	545	3,209	527	925	527	914,104	386	57,510	429	259
Fatal MI	8,460	5,476	8,133	3,994	23,518	4,862	8,539	3,921	6,798,000	5,637	840,583	1,924	1,161
Nonfatal MI	7,642	5,020	7,456	5,224	30,760	4,862	8,539	4,701	8,149,362	5,897	879,343	2,259	1,363
Angina	3,081	2,186	3,247	2,494	14,687	2,692	4,729	2,434	4,220,000	2,265	337,703	1,256	758
Coronary insufficiency	6,337	2,842	4,221	4,166	24,530	4,138	7,269	2,566	4,448,394	1,977	294,822	2,060	1,243
Congestive heart failure	5,636	3,453	5,129	4,352	25,624	4,113	7,225	4,029	6,986,000	2,867	427,583	2,549	1,538
Arrhythmia	3,903	1,946	2,890	2,473	14,565	3,461	6,078	3,201	5,550,014	2,770	413,135	1,598	964
Stroke	6,607	5,606	8,327	4,482	26,390	5,235	9,195	4,385	7,603,000	1,139	169,925	4,233	2,554
Transient ischemic attack	3,643	2,233	3,317	2,630	17,360	4,513	7,926	2,747	4,763,000	2,215	330,330	3,200	1,931
Yearly costs of diabetes care	615	335	497	489	2,879	473	830	473	820,092	346	51,595	385	232
Yearly costs of simvastatin	1,027	613	910	622	3,664	882	1,549	737	1,277,007	367	54,688	598	361

Average hospitalization costs were adjusted by complications, comorbidities, and complexity. CAD, Canadian dollars; DEM, German marks; ESP, Spanish pesos; FRF, French francs; GBP, British pounds; ITL, Italian liras; PTCA, percutaneous transluminal coronary angioplasty; USD, U.S. dollars.

assumed that a diabetic patient with no prior CVD would have two physician visits, two routine biochemical panels, and two HbA$_{1c}$ tests per year (25–27). Each patient would also have a lipid profile, a urinalysis, and an annual consultation with an ophthalmologist. For those patients who subsequently developed CVD, the marginal costs of managing diabetes included only the additional costs of the ophthalmologist visit, the HbA$_{1c}$ test, and the urinalysis. The annual costs of drug therapy for diabetes were based on the treatment identified in the 4S and health resource utilization data from an American health maintenance organization (1,28). We also estimated the costs of home glucose monitoring and assumed that each patient would have a half-hour consultation with a dietitian annually (28).

All costs data were expressed in 1998 local currencies and translated into U.S. dollars using 1998 annual exchange rates. Since the costs and health outcomes associated with disease prevention occurred at different times in the future, we discounted both by 3% annually. Sensitivity analyses were performed by varying patient age, sex, and health care costs across seven countries.

RESULTS — The benefits of primary prevention with simvastatin for diabetic individuals were estimated to range from 0.81 to 5.36 YOLSs (undiscounted) for men and from 0.54 to 2.83 for women (Table 1). Among men with CVD, secondary prevention was associated with an increased life expectancy ranging from 0.78 to 3.9 YOLSs. In the presence of CVD, the benefits for women were only
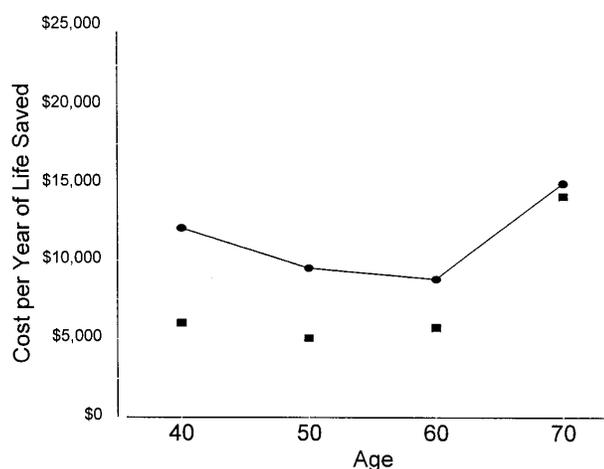

Figure 1—*The cost effectiveness (defined as cost per YOLS) of simvastatin therapy among U.S. diabetic men 40–70 years of age who do not have CVD (■) compared with nondiabetic men with CVD (●).*
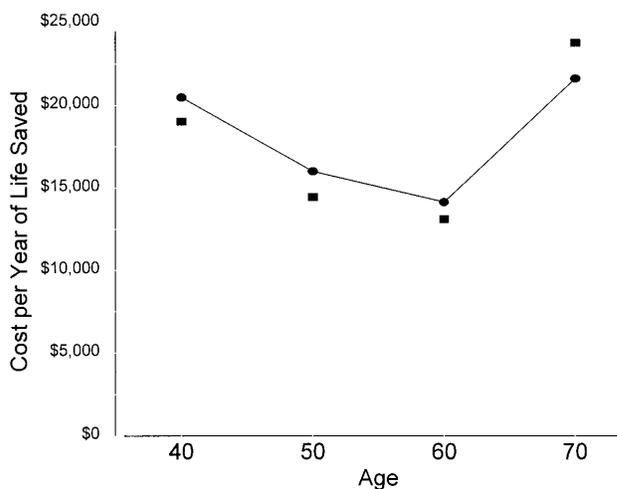
Figure 2—*The cost effectiveness (defined as cost per YOLS) of simvastatin therapy among U.S. diabetic women 40–70 years of age who do not have CVD (■) compared with nondiabetic women with CVD (●).*

slightly less than those for men ranging from 0.63 to 2.72 YOLSs. Accordingly, the estimated benefits of lipid therapy among diabetic patients without heart disease are comparable to those among heart disease patients without diabetes.

The direct health care costs associated with treating CVD complications are summarized in Table 2. These unit costs varied approximately threefold across the seven countries studied, with the U.S. at the high end. For instance, the average cost of coronary artery bypass surgery was $30,395 in the U.S. versus $11,726 (17,416 Canadian dollars) in Canada.

After both costs and benefits over the lifetime of treated individuals were discounted, the cost effectiveness of primary prevention among diabetic patients was compared with secondary prevention among CVD patients (Figs. 1 and 2). cost effectiveness ratios in men using U.S. costs ranged from $5,063 to $14,156 per YOLS in diabetic patients without CVD. In men with CVD but without diabetes, cost effectiveness ratios ranged from $8,799 to $14,996 per YOLS. Across all age and sex cohorts studied, the cost effectiveness of simvastatin in diabetic patients without CVD was similar to that in patients with CVD without diabetes.

Regardless of the health care costs involved in each country analyzed, primary prevention among diabetic patients was as cost-effective as secondary prevention among CVD patients (Table 3). For instance, among Canadian diabetic men who started therapy at 40 years of age, the cost effectiveness of simvastatin therapy was $3,869 (U.S. dollars) per YOLS versus $7,156 (U.S. dollars) for men with CVD. For 40-year-old diabetic women, the cost effectiveness of primary prevention ($10,932 [U.S. dollars] per YOLS) was similar to secondary prevention without diabetes ($11,189 [U.S. dollars]). These results were consistent among young and older patients in all seven countries studied.

Table 3—*Cost-effectiveness (cost/YOLS) of statin therapy among adults without CVD compared with nondiabetic adults with CVD*

		U.S.	Canada		France		Germany		Italy		Spain		U.K.	
	Diagnosis	(USD)	USD	CAD	USD	FRF	USD	DEM	USD	ITL	USD	ESP	USD	GBP
Age														
40 years														
Men	Diabetes	6,017	3,869	5,746	3,666	21,588	6,129	10,765	4,789	8,256,962	1,575	234,778	4,249	2,564
	CVD	12,111	7,156	10,629	7,233	42,589	10,790	18,952	8,850	15,258,378	3,815	568,516	7,467	4,505
Women	Diabetes	19,019	10,932	16,237	10,687	62,929	16,149	28,366	13,207	22,771,256	5,673	845,447	10,984	6,627
	CVD	20,494	11,189	16,618	10,967	64,578	16,568	29,101	13,526	23,320,388	5,833	869,261	11,259	6,793
50 years														
Men	Diabetes	5,063	3,213	4,773	3,001	17,670	5,174	9,087	3,997	6,890,998	1,211	180,409	3,586	2,164
	CVD	9,513	5,431	8,066	5,335	31,413	8,337	14,644	6,710	11,569,227	2,634	392,475	5,742	3,465
Women	Diabetes	14,481	7,880	11,703	7,367	43,381	11,810	20,744	9,438	16,272,491	3,587	534,634	7,961	4,803
	CVD	16,020	8,122	12,063	7,642	44,998	12,196	21,421	9,741	16,794,585	3,790	564,898	8,192	4,943
60 years														
Men	Diabetes	5,740	3,407	5,060	3,177	18,708	5,403	9,490	4,212	7,261,553	1,352	201,527	3,709	2,238
	CVD	8,799	4,679	6,950	4,398	25,894	7,271	12,771	5,733	9,884,296	2,013	299,988	4,943	2,983
Women	Diabetes	13,121	6,514	9,675	5,684	33,470	9,895	17,379	7,676	13,233,868	2,445	364,385	6,546	3,950
	CVD	14,164	6,424	9,541	5,617	33,076	9,788	17,192	7,568	13,047,885	2,487	370,654	6,419	3,873
70 years														
Men	Diabetes	14,156	8,139	12,089	8,126	47,845	12,067	21,196	9,958	17,169,140	4,490	669,169	8,190	4,942
	CVD	14,996	8,068	11,983	7,764	45,719	12,149	21,338	9,812	16,916,474	3,987	594,161	8,203	4,950
Women	Diabetes	23,792	11,953	17,753	10,736	63,218	17,837	31,330	14,100	24,310,398	5,148	767,234	11,766	7,099
	CVD	21,628	10,579	15,712	9,690	57,054	15,797	27,746	12,551	21,639,517	4,843	721,740	10,412	6,283

CAD, Canadian dollars; DEM, German marks; ESP, Spanish pesos; FRF, French francs; GBP, British pounds; ITL, Italian liras; USD, U.S. dollars.

CONCLUSIONS — The treatment of dyslipidemia among diabetic patients without CVD in the U.S. is estimated to be as cost-effective as treatment among CVD patients without diabetes. These results are consistent across Canada and the five European health systems evaluated in this study.

We have previously demonstrated that the Cardiovascular Disease Life Expectancy Model can reasonably predict the absolute risk reduction observed after lipid therapy among patients with both diabetes and CVD in such studies as the 4S (4,20). In the current model, the relative risk associated with diabetes for a future coronary death is only slightly less than that predicted after symptomatic CVD. Accordingly, the absolute risk for coronary death is approximately equal in the presence of either condition. This prediction is supported by a recent study by Haffner et al. (5) showing that the 7-year incidence of MI in nondiabetic subjects (45–64 years of age) with prior MI at baseline was shown to be similar to that for diabetic subjects without prior MI (18.8 vs. 20.2%, respectively). Furthermore, Miettinen et al. (8) showed that the 1-year case fatality rate for first MI (from the onset of symptoms, thus including prehospitalization mortality) in the FINMONICA population was 44% in diabetic men and 37% in diabetic women. These case fatality rates were significantly higher than rates in nondiabetic men and women (33 and 20%, respectively). Of the diabetic subjects who died, 63% of men and 28% of women died before hospitalization. These individuals, by definition, could not benefit from secondary prevention strategies, indicating that aggressive management of CVD risk factors in diabetic subjects should precede the onset of clinical CVD.

One must recognize the absence of clinical trial data confirming that treating dyslipidemia among diabetic patients without CVD significantly reduces primary CVD events and improves overall survival. Accordingly, the economic analyses presented here are based on a disease simulation model in which the relative risk reduction associated with treating dyslipidemia is consistent across a broad range of patients and that the absolute benefit associated with therapy is a function of this relative risk reduction and the absolute risk of disease. We also recognize that the lipid profiles of patients with diabetes versus CVD may be different outside of a clinical trial. Further analyses are therefore required on real population data.

On average in the U.S., Medicare beneficiaries with diabetes are ~50% more expensive than all Medicare beneficiaries (29). Direct medical expenditures attributable to diabetes in 1997 totaled $44.1 billion, and CVD represented the single most important diagnostic category, accounting for $7.6 billion (30). In the setting of managed care, health care expenditures for diabetic patients were 2.4 times those of matched nondiabetic subjects with CVD complications, accounting for >20% of excess health costs (31). Once CVD had developed, direct medical care costs among diabetic patients were also significantly higher than those for nondiabetic patients and approximated $3,000 more per person-year of observation (32).

The health care costs associated with diabetes have been evaluated in some countries and appear to be strongly associated with CVD. In Germany, the cost of prescription drugs was significantly increased among diabetic patients in comparison to that of nondiabetic patients. The relative costs were still 1.5 times higher after excluding medications specifically for diabetes and adjusting for age and sex differences. CVD drugs also represented the single most important drug class, accounting for 39% of pharmaceutical costs (33).

In the U.K., one study found a fourfold increased risk of cerebrovascular events among diabetic patients in comparison to nondiabetic people (34). Although the prevalence of known diabetes in this study population was <2%, these patients accounted for ~14% of the total cost of treating cerebrovascular disease and 17% of the total cost associated with treating coronary heart disease (34,35). In Spain, the total lifetime cost of treating type 1 diabetes has been estimated to average 12.7 million pesos ($85,000 [U.S. dollars]) (36). However, the annual cost associated with type 2 diabetes or CVD complications was not specified in this study.

Lipid therapy among diabetic patients with known CVD has been shown to be beneficial. We believe that the epidemiological data and the modeling results from this study strongly support the expectation that lipid therapy will reduce CVD complications among diabetic patients. Economic analyses surrounding these projections demonstrate that lipid therapy among diabetic patients is not only clinically justifiable, but also economically attractive compared with other currently accepted therapies (37).

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