Cost-effectiveness of Intensive Glycemic Control, Intensified Hypertension Control, and Serum Cholesterol Level Reduction for Type 2 Diabetes

The CDC Diabetes Cost-effectiveness Group

Context Several treatment interventions can reduce complications of type 2 diabetes, but their relative cost-effectiveness is not known.

Objective To estimate the incremental cost-effectiveness of intensive glycemic control (relative to conventional control), intensified hypertension control, and reduction in serum cholesterol level for patients with type 2 diabetes.

Design, Setting, and Patients Cost-effectiveness analysis of a hypothetical cohort of individuals living in the United States, aged 25 years or older, who were newly diagnosed as having type 2 diabetes. The results of the United Kingdom Prospective Diabetes Study (UKPDS) and other studies were used to create a model of disease progression and treatment patterns. Costs were based on those used in community practices in the United States.

Interventions Insulin or sulfonylurea therapy for intensive glycemic control; angiotensin-converting enzyme inhibitor or β-blocker for intensified hypertension control; and pravastatin for reduction of serum cholesterol level.

Main Outcome Measures Cost per quality-adjusted life-year (QALY) gained. Costs (in 1997 US dollars) and QALYs were discounted at a 3% annual rate.

Results The incremental cost-effectiveness ratio for intensive glycemic control is $41 384 per QALY; this ratio increased with age at diagnosis from $9614 per QALY for patients aged 25 to 34 years to $2.1 million for patients aged 85 to 94 years. For intensified hypertension control the cost-effectiveness ratio is –$1959 per QALY. The cost-effectiveness ratio for reduction in serum cholesterol level is $51 889 per QALY; this ratio varied by age at diagnosis and is lowest for patients diagnosed between the ages of 45 and 84 years.

Conclusions Intensified hypertension control reduces costs and improves health outcomes relative to moderate hypertension control. Intensive glycemic control and reduction in serum cholesterol level increase costs and improve health outcomes. The cost-effectiveness ratios for these 2 interventions are comparable with those of several other frequently adopted health care interventions.

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TYPE 2 DIABETES IS A MAJOR public health problem.[1-5] Although treatment for type 2 diabetes has traditionally focused on glycemic control for reducing microvascular complications, recent attention has also focused on reducing risks of macrovascular complications. Persons with type 2 diabetes have twice the risk for coronary heart disease (CHD) and stroke as persons without diabetes.[6-8] Available interventions to reduce CHD and stroke incidence in this population include aggressive blood pressure control and reduction in serum cholesterol level.

Evaluating whether interventions are cost-effective and yield acceptable benefits is important.[9] In this study, we evaluated whether the benefits (measured in quality-adjusted life-years [QALYs]) for type 2 diabetes of intensive glycemic control, intensified hypertension control, or reduction in serum cholesterol level justified the costs. We also evaluated the relative cost-effectiveness of each intervention and whether it varied with age.

A Markov model of type 2 diabetes disease progression was used to calculate incremental cost-effectiveness ratios for the interventions. Costs were measured from the perspective of the health care system, and outcomes were measured in QALYs.

METHODS

Our model builds on previous diabetes models,[10-13] but differs in several ways. We used a Markov model structure that placed greater emphasis on macrovascular complications, and introduced interdependencies among diabetes progression paths. Earlier models used data on patients with type 1 diabetes, while our model used data on key transition probabilities and intervention effects from patients with type

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2 diabetes in the United Kingdom Prospective Diabetes Study (UKPDS). (A technical report on the model is available from the authors.)

Model Structure

In the Markov framework, a series of patient cohorts newly diagnosed as having diabetes progressed through the model. Cohorts were defined by 10-year age groups (25 to 94 years), sex, race or ethnicity, hypertension status, hypercholesterolemia status, and current smoking status. Cohorts were followed-up along the disease paths until death or age 95 years. Overall, 55% of newly diagnosed patients were women and 8% were aged 25 to 34 years; 8%, 35 to 44 years; 26%, 45 to 54 years; 18%, 55 to 64 years; 23%, 65 to 74 years; 13%, 75 to 84 years; and 4%, 85 to 94 years.[14-16]

Patients progressed simultaneously through 5 different disease paths: nephropathy, neuropathy, retinopathy, CHD, and stroke (FIGURE 1). Transition probabilities depended on time since diagnosis of diabetes, time between onset and diagnosis of diabetes, age, sex, race or ethnicity, glycemic level, smoking, serum cholesterol level, and hypertension. Patients could die from lower extremity amputation, end-stage renal disease, CHD, stroke, or from other causes unrelated to diabetes.[12,17]

Progression Parameters, Costs of Complications, and Health Utilities

The initial distribution of patients at diagnosis (when the model begins) and transition probabilities between states were based on data from the UKPDS, previous disease progression models of type 2 diabetes[10-12] and CHD,[17-19] and other studies (see technical report).

Costs of diabetes complications were derived from the literature,[12,20-24] and are described in the technical report. Health utility values between 0 (deceased) and 1 (perfect health) were used to estimate QALYs for each disease state. Utility levels were 0.690 for blindness; 0.610, end-stage renal disease; 0.800, lower extremity amputation[25]; 0.500, stroke[26-27]; 0.880, cardiac arrest/myocardial infarction (MI)[28]; and 0.947, for angina.[29] Utility levels for all other health states were set to 1.

Interventions

Interventions affected transition probabilities, thereby changing the cumulative incidence of complications and costs. All patients were assumed to receive conventional treatment to control blood glucose levels. In the model, conventional treatment was based on resources and outcomes associated with the conventional blood glucose control arm of the UKPDS,[30] which produced an average glycosylated hemoglobin level of 7.9% over a median duration of 10 years.

Intensive Glycemic Control

In the UKPDS, conventional treatment primarily involved obtaining the best possible fasting plasma glucose concentration with diet alone; drug treatment was added if hyperglycemic symptoms or an excessive fasting plasma glucose concentration were present. Intensive glycemic control patients were randomly assigned to receive a sulfonylurea or insulin, with a goal of reducing their fasting plasma glucose concentration to less than 108 mg/dL (6 mmol/L). In our model, intensive glycemic control patients were initially treated with chlorpropamide, glipizide, and insulin, respectively, following trial proportions.

We incorporated intensive glycemic control by adjusting baseline hazard rates using the ratio of glycemic level under intensive control to glycemic level under conventional treatment raised to an exponent that varies across progression paths and stages. Using a similar equation, researchers have shown that hazard rates for type 1 diabetes depend on glycemic levels.[31] We assumed this functional form also worked for type 2 diabetes. Glycemic levels under conventional and intensive glycemic control and exponents were based on data from the UKPDS (TABLE 1).

The costs of glycemic control included 4 resource components: drug use based on the UKPDS and outpatient visits, self-testing, and case management that reflect clinical practice in the United States.[12,30-37] Total annual costs since diagnosis are shown in TABLE 2.

Intensified Hypertension Control

We compared the cost-effectiveness of intensified hypertension control (treatment with an angiotensin-converting enzyme inhibitor or a β-blocker) with a more moderate hypertension control (treatment with diet and drugs but without ACE inhibitors and β-blockers). In our model, intensified hypertension control affected the probability of stroke and reduced the transition probability for nephropathy and retinopathy (Table 2). The model only applied intensified hypertension control to persons who had hypertension (defined as systolic blood pressure of ≥160 mm Hg; diastolic blood pressure of ≥95 mm Hg; or by antihypertensive medication use).[14] Average blood pressure levels by age group for persons with diabetes were calculated using data from the third National Health and Nutrition Examination Survey (NHANES III).[38]

The efficacy of intensified hypertension control relative to moderate control came from the UKPDS.[39] Hypertensive patients with type 2 diabetes were randomized between intensified hypertension control and moderate hypertension control. Average systolic/diastolic blood pressure achieved was 144/82 mm Hg for persons receiving intensified control and 154/86 mm Hg for persons receiving moderate control. Angiotensin-converting enzyme inhibitors and β-blockers were equally effective in reducing the likelihood of stroke, so we present results for a single intensified hypertension intervention. Intensified hypertension control was assumed to reduce stroke risk by 44% relative to moderate hypertension control.[39]

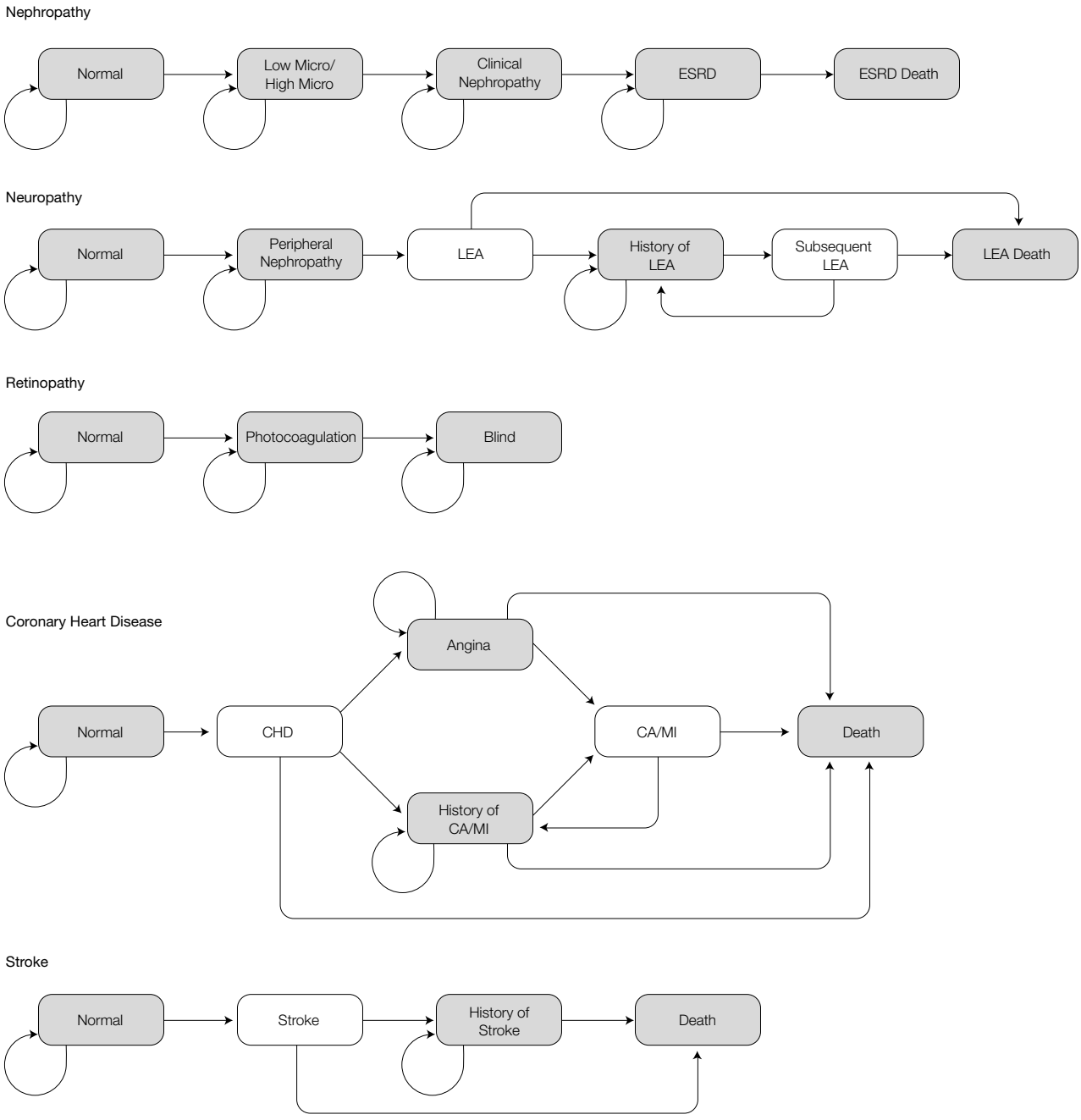
Because intensified hypertension control did not have a statistically significant effect on CHD, our base case analysis assumed that the intervention has no effect on the CHD transition probability. Our model assumed that all pa-

tients with a history of CHD or stroke received hypertension treatment, which is the accepted practice in the United States.

Based on the UKPDS hypertension study,[39] persons with type 2 diabetes and hypertension were assumed to have faster rates of progression to microalbuminuria, clinical nephropathy, and photocoagulation than their normotensive counterparts.

The costs of moderate and intensified hypertension control were estimated using UKPDS drug dosage data[40] and drug cost data from the 1997 *Red Book*[35] (Table 2). Treatment costs in-

Figure 1. States and Transition Probabilities: Microvascular and Macrovascular Complications



Arrows represent transitions between states; there is a transition probability associated with each transition. Micro indicates microalbuminaria; ESRD, end-stage renal disease; LEA, lower extremity amputation; CHD, coronary heart disease; and CA/MI, cardiac arrest/myocardial infarction.

cluded 2 physician visits and 3 chemistry panels annually.

Reduction in Serum Cholesterol Level

To determine the cost-effectiveness of reduction in serum cholesterol level, we compared pravastatin with no drug treatment for persons with a high serum cholesterol level but without a history of CHD (TABLE 3). In the model, the reduction intervention of serum cholesterol level lowered the probability of CHD and had no effect on the transition probabilities for other complications. The intervention was only applied to persons with a high serum cholesterol level, defined as a total serum cholesterol level of 200 mg/dL (5.18 mmol/L) or higher.[41] The NHANES III serum cholesterol level data for persons with diabetes was used in the Framingham calculations to determine CHD and stroke risks.[18]

Our estimates of risk reduction (31%) achieved for serum cholesterol level came from the West of Scotland Coronary Prevention Study,[42] a randomized controlled trial comparing pravastatin with placebo in individuals without a history of CHD. The risk reduction achieved by pravastatin was independent of diabetes.[43] The risk reduction was modeled as affecting the probability of developing CHD. After persons incurred CHD, the serum cholesterol level risk reduction for pravastatin came from a subgroup analysis of diabetic patients in the Cholesterol and Recurrent Events (CARE) trial,[44] in which pravastatin reduced CHD by 25%. We assumed that intervention patients would receive pravastatin for their remaining lifetime.

The cost of the first year of treatment with pravastatin ($1398) was based on a 40-mg daily dose and 4 physician visits with blood test samples, lipid profiles, and biochemical profiles. Subsequent yearly costs ($1288) included pravastatin and 2 physician visits with tests.

Cost-effectiveness

We report 3 cost components. Standard treatment cost is the cost of conventional glycemic control for all patients and moderate hypertension control for patients with hypertension. Complications cost is the cost of nephropathy, neuropathy, retinopathy, CHD, stroke, or death. Intervention cost is the incremental cost of the intervention, over and above standard treatment cost. The total cost is the sum of the 3 components.

We report 2 health outcomes: remaining life-years (the average undiscounted life expectancy for newly diagnosed patients) and the number of discounted QALYs.

The incremental cost-effectiveness ratio was calculated as the difference in total cost between the intervention and standard treatment divided by the difference in QALYs between the intervention and standard treatment. All measures were calculated per person. Costs (in 1997 US dollars) and QALYs were discounted at a 3% annual rate.[9]

One-Way Sensitivity Analyses

For intensive glycemic control, we dropped the base case analysis assumptions that patients became hypertensive once they reached microalbuminuria and that patients with hypertension progressed faster than nonhypertensive patients on the nephropathy and retinopathy disease paths. We assumed that intensive glycemic control reduced the probability of CHD by 16%, based on UKPDS reductions in MI that approached conventional levels of sig-

Table 1. Model Parameters and Costs for Intensive Glycemic Control*

Description of Parameter	Conventional	Intensive	Exponent
HbA_{1c} Level, %			
Initial level at onset[12]	6.8	6.8	NA
Annual rate of change before treatment[12]	0.2	0.2	NA
Years between onset and diagnosis (assumption)	10	10	NA
Treatment affect[30]	−2.0	−2.9	NA
Annual rate of change after treatment[30]	0.2	0.2	NA
Maximum level[12]			
Without treatment	12.0	12.0	NA
With treatment	11.0	9.0	NA
Hazard Rate			
Normal to microalbuminuria[30]	0.03253	0.02371	2.62
Microalbuminuria to clinical nephropathy[30]	0.07497	0.06561	1.08
Normal to peripheral neuropathy[30]	0.03600	0.02940	1.67
Normal to photocoagulation[30]	0.01100	0.00790	2.74
Cost of Treatment, in 1997 $			
Year			
0	372	1490	NA
1	413	1398	NA
2	447	1442	NA
3	490	1484	NA
4	538	1531	NA
5	594	1574	NA
6	642	1621	NA
7	679	1648	NA
8	717	1683	NA
9	741	1711	NA
10	771	1738	NA
11	839	1760	NA
12	860	1788	NA
13	870	1794	NA
14	870	1800	NA
≥15	870	1813	NA

*HbA_{1c} indicates glycosylated hemoglobin; NA, not applicable.

Table 2. Model Parameters and Costs for Hypertension Control

Description of Parameter	Moderate	Intensified
Risk Reduction		
Coronary heart disease	13%*	0%, 21%†
Stroke	17%*	44%‡
Hazard Rate		
Normal to microalbuminuria[39]	0.05584	0.03773
Microalbuminuria to clinical nephropathy[39]	0.15050	0.12810
Normal to photocoagulation[39]	0.01660	0.01020
Cost of Treatment, in 1997 $[35,40]		
Year		
0	241	599
1	277	630
2	287	656
3	292	664
4	301	667
5	304	675
6	349	689
7	349	685
≥8	404	703

*Relative to no treatment.[18,39]
†Base analysis; sensitivity analysis. Both are relative to moderate treatment.[39]
‡Relative to moderate treatment.[39]

Table 3. Model Parameters and Costs for Reduction in Serum Cholesterol Level

Description of Parameter	Pravastatin	No Treatment*
Risk Reduction		
Coronary heart disease	31%*; 25%†	0%
Cost of Treatment, in 1997 $		
Year		
0	1398	0
≥1	1288	0

*For patients without coronary heart disease.[42]
†For patients with coronary heart disease.[44]

nificance ($P=.05$).[30] Cost-effectiveness ratios are often sensitive to assumptions about costs. We reestimated the cost-effectiveness ratio under the assumption of no case management costs. The UKPDS did not report case management costs. We then applied a cost scenario that only included resources specifically identified in the UKPDS cost study.[45] We used US unit costs to convert resource use into total costs. The UKPDS cost scenario contained no case management costs, much less self-testing, and slightly fewer physician visits, yielding a conventional control cost of about $150 and an intensive control cost of about $900 less annually than the US cost scenario.

For intensified hypertension control, we first applied control to patients who developed hypertension after diagnosis and who received the intervention only after developing hypertension. We dropped the assumption that patients with hypertension developed nephropathy and retinopathy faster than nonhypertensive patients. In the UKPDS, hypertension control reduced the incidence of MI by 21%, but the reduction was not statistically significant ($P=.13$).[39] In a sensitivity analysis, we assumed a 21% risk reduction for CHD. For reduction in serum cholesterol level, we assumed that the intervention required no additional office visits. For all interventions, we varied the discount rate from 0% to 5%.[9]

RESULTS

Intensive Glycemic Control

Intensive glycemic control applied to all persons in the United States newly diagnosed as having type 2 diabetes and led to an undiscounted 0.3173-year increase in life expectancy and a discounted 0.1915-year QALY increase (TABLE 4). Because patients lived longer, the standard treatment cost increased slightly; however, the complications cost dropped by about 12%. The intervention cost was $12213. Combining these costs, the incremental total cost was $7927. The cost-effectiveness ratio was $41384 per QALY. Cost-effectiveness ratios increased rapidly with age at diagnosis, starting at $9614 per QALY for patients aged 25 to 34 years and reaching $2.1 million for patients aged 85 to 94 years (TABLE 5).

Intensified Hypertension Control

Intensified hypertension control increased undiscounted life expectancy by 0.4744 years, and discounted QALYs increased by 0.3962, relative to moderate hypertension control (results were averaged for all patients newly diagnosed as having type 2 diabetes and hypertension). On average, intensified hypertension control reduced complications cost by $4836 during the patient's lifetime. Intervention cost was $3708, and standard treatment cost increased by $351 because life expectancy increased, thereby increasing the cost of conventional glycemic control. The incremental total cost was $776 lower. The cost-effectiveness ratio was negative (–$1959/QALY), indicating that the intervention saved costs relative to moderate hypertension control (ie, QALYs increased and total costs decreased). Age had relatively little effect on the cost-effectiveness ratio (Table 5).

Reduction in Serum Cholesterol Level

Primary reduction in serum cholesterol level using pravastatin increased undiscounted life expectancy by 0.6722 years and discounted QALYs increased by 0.3475. Standard treatment costs increased slightly because life expectancy increased. The increase in life expectancy also led to an increase in complications cost, as the cost of living longer with neuropathy, nephropathy, and retinopathy complications outweighed cost reductions from CHD and stroke. The incremental total cost was $18033 and the cost-effectiveness ratio was $51889 per QALY. Cost-effectiveness ratios for re-

duction in serum cholesterol level varied by age, with the lowest cost-effectiveness ratios for patients aged 45 to 84 years (Table 5).

Incidence of Complications

As shown in FIGURE 2, interventions directly affected cumulative incidence of complications by reducing the transition probabilities for complications. The direct effect of intensive glycemic control reduced the cumulative incidence of nephropathy, neuropathy, and retinopathy complications by 11% to 27%. Intensified hypertension control directly reduced the cumulative incidence of nephropathy, retinopathy, and stroke complications, whereas reduction in serum cholesterol level directly lowered the cumulative incidence of CHD complications.

Interventions also had indirect effects. For example, if reductions in directly affected complications caused patients to live longer, they had more time to develop other complications, causing the cumulative incidence of those complications to increase slightly. All 3 interventions led to increases in life expectancy so that there were small increases in the cumulative incidence of complications not listed above.

Sensitivity Analyses

For intensive glycemic control, dropping the assumptions about microal-

Table 4. Incremental Cost-effectiveness by Intervention

	Cost, $*				Remaining Life-Years (Not Discounted)	Quality-Adjusted Life-Years (QALYs)*	Incremental Cost-effectiveness Ratio (Total Cost/QALY), $
	Standard Treatment	Complications	Intervention	Total			
Intensive glycemic control†							
Conventional glycemic control (standard treatment)	10 741	37 602	0	48 343	17.2067	11.8791	
Intervention	10 785	33 271	12 213	56 270	17.5240	12.0707	
Incremental	44	−4330	12 213	7927	0.3173	0.1915	41 384
Intensive hypertension control‡							
Moderate hypertension control (standard treatment)	10 679	33 738	0	44 417	14.4380	10.3990	
Intervention	11 030	28 902	3708	43 641	14.9124	10.7952	
Incremental	351	−4836	3708	−776	0.4744	0.3962	−1959
Reduction in serum cholesterol level§							
Standard treatment	10 353	34 819	0	45 171	16.3187	11.4690	
Intervention	10 756	36 505	15 942	63 204	16.9909	11.8165	
Incremental	404	1687	15 942	18 033	0.6722	0.3475	51 889

*Discounted at 3% annual rate. Costs are for patient's lifetime and are reported in 1997 dollars.
†All patients who were newly diagnosed as having type 2 diabetes.
‡All patients who were newly diagnosed as having type 2 diabetes and hypertension.
§All patients who were newly diagnosed as having type 2 diabetes and above normal serum cholesterol level.

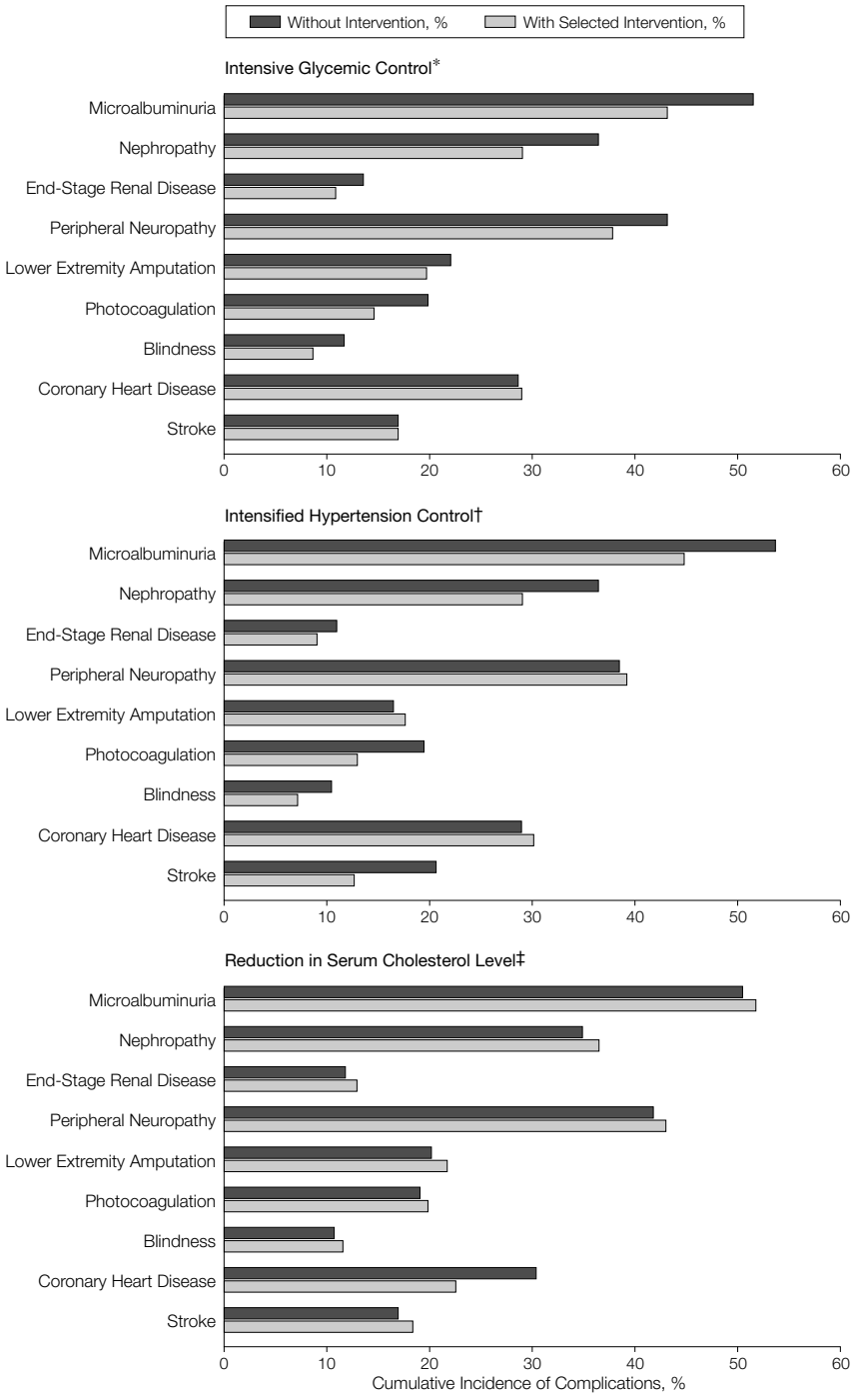
Table 5. Cost-effectiveness by Age Group*

	25-34 y	35-44 y	45-54 y	55-64 y	65-74 y	75-84 y	85-94 y
Intensive Glycemic Control†							
Change							
QALY	0.6482	0.4575	0.2527	0.1270	0.0507	0.0142	0.0017
Total cost, $	6232	8377	9372	9118	7821	5726	3668
Cost-effectiveness ratio (cost/QALY), $	9614	18 309	37 086	71 816	154 376	401 883	2.1 million
Intensified Hypertension Control‡							
Change							
QALY	0.6939	0.6154	0.5290	0.4350	0.3566	0.2282	0.0830
Total cost, $	−6609	−3328	−1341	−413	−167	−43	66
Cost-effectiveness ratio (cost/QALY), $	Cost saving	Cost saving	Cost saving	Cost saving	Cost saving	Cost saving	790
Reduction in Serum Cholesterol Level§							
Change							
QALY	0.2032	0.3443	0.4491	0.4351	0.3398	0.1675	0.0447
Total cost, $	28 805	27 361	23 604	18 852	13 752	8618	4928
Cost-effectiveness ratio (cost/QALY), $	141 728	79 473	52 554	43 331	40 471	51 459	110 124

*QALY indicates quality-adjusted life-year.
†All patients who were newly diagnosed as having type 2 diabetes.
‡All patients who were newly diagnosed as having type 2 diabetes and hypertension.
§All patients who were newly diagnosed as having type 2 diabetes and above normal serum cholesterol level.

buminuria and progression with hypertension led to moderate increases in the cost-effectiveness ratio (FIGURE 3). If intensive glycemic control reduced CHD risk, QALYs increased substantially (incremental QALYs = 0.3325) and the cost-effectiveness ratio decreased to less than $27 000 per QALY. Eliminating case management costs reduced intervention costs by $300 annually, causing the cost-effectiveness ratio to decrease to $22 299 per QALY. Under the UKPDS cost scenario, the intervention cost was only $3004, which was less than the reduction in complication costs; thus, the incremental total cost was $1309 lower, and the cost-effectiveness ratio was negative, indicating that the intervention saved costs. With a 0% discount rate, the cost-effectiveness ratio decreased. Conversely, with a 5% discount rate, the cost-effectiveness ratio increased.

Figure 2. Cumulative Incidence of Complications



Asterisk indicates patients newly diagnosed as having type 2 diabetes; dagger, patients newly diagnosed as having type 2 diabetes and hypertension; and double dagger, patients newly diagnosed as having type 2 diabetes and an above normal serum cholesterol level.

For intensified hypertension control, applying the intervention to persons who developed hypertension after being diagnosed as having diabetes resulted in an incremental cost-effectiveness ratio of $2091 per QALY (Figure 3). Dropping the assumption that patients with hypertension progressed faster on the nephropathy and retinopathy disease paths increased the cost-effectiveness ratio. If the intervention reduced the CHD transition probability by 21%, the incremental QALYs associated with the intervention increased from 0.3962 to 0.6020. The total cost of the intervention increased by about $1000 because patients lived longer and the incremental cost-effectiveness ratio became $287 per QALY. Changing the discount rate had little effect on the cost-effectiveness ratio.

For reduction in serum cholesterol level, eliminating extra office visits for the intervention lowered the cost-effectiveness ratio to $47 716 per QALY. The cost-effectiveness ratio decreased with a 0% discount rate and increased with a 5% discount rate (Figure 3).

COMMENT

The US Panel on Cost-effectiveness in Health and Medicine[9] notes that no absolute standard exists for deciding whether an intervention's cost-effectiveness ratio is "cost-effective" or "not cost-effective." Instead, the panel recommended describing interventions as more or less cost-effective than other

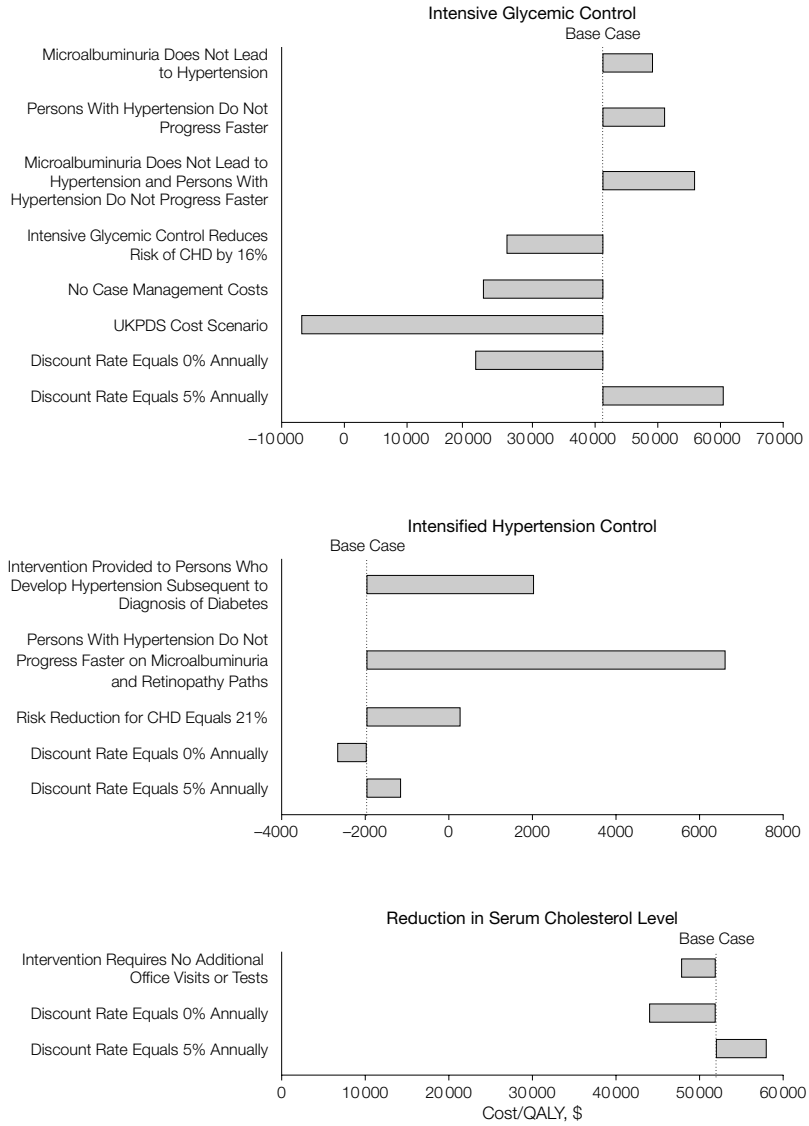
interventions. An exception occurs for interventions that reduce costs and improve health outcomes, thereby producing negative cost-effectiveness ratios. Such interventions save costs and should be adopted. Our results indicate that intensified hypertension control falls into the cost-saving category, relative to moderate hypertension control.

Both intensive glycemic control and reduction in serum cholesterol level improve health outcomes, but they also increase health costs. Based on panel recommendations, these interventions cannot be characterized as either cost-effective or not cost-effective. Still, the cost-effectiveness ratios of $40 881 per QALY for intensive glycemic control and $51 889 per QALY for reduction in serum cholesterol level are comparable with published cost-effectiveness ratios for commonly funded interventions, such as heart transplantation vs optimal conventional treatment among patients who need transplants ($46 000 per QALY), hypertension screening and therapy vs no screening among asymptomatic 20-year-old men ($40 000 per QALY), neonatal intensive care vs standard neonatal care among premature infants weighing 0.5 to 1 kg ($47 000 per QALY), and dual air bags vs driver-side air bag only ($69 000 per QALY).[46]

From a policy perspective, it is possible to compare the 3 interventions in Table 4. Intensive hypertension control is the most cost-effective, followed by reduction in serum cholesterol level and intensive glycemic control. Table 5 shows that the relative ranking varied somewhat with age, with intensive glycemic control performing better at younger than at older ages. It should be noted that the interventions affect different subgroups of the population of patients newly diagnosed as having type 2 diabetes (all patients receiving intensive glycemic control, those with hypertension receiving intensified hypertension control, and those with high serum cholesterol level seeking reduction). Each subsample has a different age and risk profile, affecting the potential gains from intervention.

The comparison of cost-effectiveness ratios across interventions in Tables 4 and 5 should not be interpreted as minimizing the need for glycemic control in patients with type 2 diabetes. Standard treatment for all interventions included conventional glycemic control that produced an average glycosylated hemoglobin level of 7.9%. The cost-effectiveness analysis for intensive glycemic control examined the incremental costs and outcomes associated with more intensive control than conventional control. In addition, sensitivity analyses indicate that if the incremental cost of the intensive glycemic control intervention can be reduced, the intervention will be more cost-effective. The sensitivity analysis also shows that the cost-effectiveness ratio will decrease if glycemic control reduces patients' risk for CHD. The UKPDS found a 16% risk reduction for intensive glycemic control that was almost statistically significant.[30]

Figure 3. Sensitivity Analyses



QALY indicates quality-adjusted life-year; CHD, coronary heart disease; and UKPDS, United Kingdom Prospective Diabetes Study.

Our cost-effectiveness estimates for intensive glycemic control and reduction in serum cholesterol level vary widely across age groups. Intensive glycemic control is most cost-effective for younger patients. In part, this is driven by the model's assumption that the transition probabilities for nephropathy, neuropathy, and retinopathy are dependent on the duration of diabetes, not on patient age. Because younger patients are less likely to die from other causes, they have more time to progress to these complications. Given this assumption, intensive glycemic control has a greater potential to reduce complications in younger patients. For reduction in serum cholesterol level, the cost-effectiveness ratio initially decreases with age, as CHD risk increases.

Limitations

Chronic disease modeling usually requires extrapolating the results of an intervention on intermediate outcomes, which occur within the duration of a randomized controlled trial, to long-term or end-stage health outcomes that are most likely to occur after the trial has ended. Often, the intervention has a significant effect on intermediate outcomes, but the trial ends before significant effects on long-term outcomes can be observed. The UKPDS was an unusually long randomized controlled trial, with a median follow-up of 10 years, and intensive glycemic control that produced a 12% reduction ($P=.03$) in the aggregate end point of any diabetes-related event.[30] However, intensive glycemic control did not produce significant reductions in such long-term outcomes as all-cause mortality, MI, stroke, renal failure, and amputation. There were few cases of renal failure, blindness, or amputation under conventional glycemic control, virtually precluding a significant intervention effect on these outcomes. Intensive glycemic control did significantly reduce progression to microalbuminuria, photocoagulation, and neuropathy. When we incorporated into our model the effects of intensive glycemic control on these intermediate disease stages, the model indicated that such control would lead to long-term reductions in renal failure, blindness, and amputation.

Our results also rely on treatment compliance rates achieved during the UKPDS. If compliance rates are lower outside the trial setting, the interventions will have less impact on health outcomes, QALYs, and complications cost. However, lower compliance will also reduce intervention cost because noncompliant patients will be less likely to take prescribed drugs, visit physicians, and perform self-testing. The net impact on the cost-effectiveness ratio is uncertain.

Ideally, the model would combine resource use and health outcome data generated from the same study. Although we performed a sensitivity analysis that combined the UKPDS cost scenario with UKPDS outcome results for intensive glycemic control, treatment patterns may vary between the United States and the United Kingdom. Because the focus of our study was patients in the United States, our main analysis considered resource use associated with treatment patterns in the United States. This approach may have produced more conservative (higher) cost-effectiveness ratios than would be found if the higher resource use for intensive glycemic control produced larger reductions in diabetes complications than those observed in the UKPDS.

Our study considers costs from the perspective of a health care system. Because of data limitations, the model did not include nonmedical costs, such as lost productivity and the time provided by family and friends in caring for patients with diabetes. Thus, our model may underestimate the social costs of diabetes. In turn, this could affect the estimated cost-effectiveness ratios.

Implications

Using common metrics, economic evaluations can estimate the relative value of various interventions. The need for information usually dependent on long-term, expensive trials can partially be addressed by the modeling approach, which provides a feasible means to evaluate the cost-effectiveness of interventions for type 2 diabetes that produce benefits years or even decades after the interventions begin. The evaluation results provide information for policy makers as they decide whether to adopt the interventions.

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REFERENCES

1. Centers for Disease Control and Prevention. *National Diabetes Fact Sheet, 1997*. Atlanta, Ga: Centers for Disease Control and Prevention, Division of Diabetes Translation; 1997.
2. Harris MI, Flegal KM, Cowie CC, et al. Prevalence of diabetes, impaired fasting glucose, and impaired glucose tolerance in US adults: the Third National Health and Nutrition Examination Survey, 1988-1994. *Diabetes Care*. 1998;21:518-524.
3. Alberti KGM, DeFronzo RA, Zimmet P, eds. *International Textbook of Diabetes Mellitus*. New York, NY: John Wiley & Sons; 1995.

4. Rubin RJ, Altman WM, Mendelson DN. Health care expenses for people with diabetes mellitus, 1992. *J Clin Endocrinol Metab*. 1994;78:809A-809F.
5. American Diabetes Association. Economic consequences of diabetes mellitus in the US in 1997. *Diabetes Care*. 1998;21:296-309.
6. Wingard DL, Barrett-Connor E. Heart disease and diabetes. In: National Diabetes Data Group, eds. *Diabetes in America.* 2nd ed. Bethesda, Md: National Institute of Diabetes and Digestive and Kidney Diseases; 1995:429-448. NIH publication 95-1468.
7. Kuller LH. Stroke and diabetes. In: National Diabetes Data Group, eds. *Diabetes in America.* 2nd ed. Bethesda, Md: National Institute of Diabetes and Digestive and Kidney Diseases; 1995:449-456. NIH publication 95-1468.
8. Geiss LS, Herman WH, Smith PJ. Mortality in non-insulin-dependent diabetes. In: National Diabetes Data Group, eds. *Diabetes in America.* 2nd ed. Bethesda, Md: National Institute of Diabetes and Digestive and Kidney Diseases; 1995:233-257. NIH publication 95-1468.
9. Gold MR, Siegel JE, Russell LB, Weinstein MC, eds. *Cost-effectiveness in Health and Medicine*. Oxford, England: Oxford University Press; 1996.
10. Eastman RC, Javitt JC, Herman WH, et al. Model of complications of NIDDM, I: model construction and assumptions. *Diabetes Care*. 1997;20:725-734.
11. Eastman RC, Javitt JC, Herman WH, et al. Model of complications of NIDDM, II: analysis of the health benefits and cost-effectiveness of treating NIDDM with the goal of normoglycemia. *Diabetes Care*. 1997;20:735-744.
12. Dong F, Orians C, Manninen D. Economic evaluation of approaches to preventing diabetic end-stage renal disease. Seattle, Wash: Battelle/Centers for Public Health Research and Evaluation; 1997.
13. CDC Diabetes Cost-effectiveness Study Group. The cost-effectiveness of screening for type 2 diabetes. *JAMA*. 1998;280:1757-1763.
14. Cowie CC, Harris MI. Physical and metabolic characteristics of persons with diabetes. In: National Diabetes Data Group, eds. *Diabetes in America.* 2nd ed. Bethesda, Md: National Institute of Diabetes and Digestive and Kidney Diseases; 1995:117-164. NIH publication 95-1468.
15. US Census Bureau. National population estimates for the 1990s. Available at: http://eire.census.gov/popest/archives/national/nat_90s_detail/nat_90s_1.php. Accessibility verified April 18, 2002.
16. Centers for Disease Control and Prevention. *Diabetes Surveillance*. Atlanta, Ga: US Dept of Health and Human Services; 1997.
17. Weinstein MC, Coxson PG, Williams LW, Pass TM, Stason WB, Goldman L. Forecasting coronary heart disease incidence, mortality, and cost: the coronary heart disease policy model. *Am J Public Health*. 1987;77:1417-1426.
18. Anderson KM, Odell PM, Wilson PWF, Kannel WB. Cardiovascular disease risk profiles. *Am Heart J*. 1990;121:293-298.
19. Hunink MGM, Goldman L, Tosteson ANA, et al. The recent decline in mortality from coronary heart disease, 1980-1990. *JAMA*. 1997;277:535-542.
20. O'Brien JA, Shomphe LA, Kavanagh PL, Raggio G, Caro JJ. Direct medical costs of complications resulting from type 2 diabetes in the US. *Diabetes Care*. 1998;21:1122-1128.
21. Eckman MH, Greenfield C, Mackey WC, et al. Foot infections in diabetic patients. *JAMA*. 1995;273:712-720.
22. Russell MW, Huse DM, Drowns S, Hamel EC, Hartz SC. Direct medical costs of coronary artery disease in the United States. *Am J Cardiol*. 1998;81:1110-1115.
23. Taylor TN, Davis PH, Torner JC, Homes J, Meyer JW, Jacobson MF. Lifetime cost of stroke in the United States. *Stroke*. 1996;27:1459-1466.
24. Lubitz JD, Riley GF. Trends in Medicare payments in the last year of life. *N Engl J Med*. 1993;328:1092-1096.
25. Diabetes Control and Complications Trial Research Group. Lifetime benefits and costs of intensive therapy as practiced in the Diabetes Control and Complications Trial. *JAMA*. 1996;276:1409-1415.
26. Shin AY, Porter PJ, Wallace MC, Naglie G. Quality of life of stroke in younger individuals. *Stroke*. 1997;28:2395-2399.
27. Wolf PA, D'Agnostino RB, O'Neal A, et al. Secular trends in stroke incidence and mortality. *Stroke*. 1992;23:1551-1555.
28. Tsevat J, Goldman L, Soukup JR, et al. Stability of time-tradeoff utilities in survivors of myocardial infarction. *Med Decis Making*. 1993;13:161-165.
29. Nease RF, Kneeland T, O'Connor GT, et al. Variation in patient utilities for outcomes of the management of chronic stable angina. *JAMA*. 1995;273:1185-1190.
30. UK Prospective Diabetes Study Group. Intensive blood glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet*. 1998;352:837-853.
31. Diabetes Control and Complications Trial Research Group. The relationship of glycemic exposure (HbA1c) to the risk of development and progression of retinopathy in the Diabetes Control and Complications Trial. *Diabetes*. 1995;44:968-983.
32. UK Prospective Diabetes Study Group (UKPDS 16). Overview of 6 years' therapy of type II diabetes: a progressive disease. *Diabetes*. 1995;44:1249-1258.
33. UK Prospective Diabetes Study Group (UKPDS 24). A 6-year, randomized, controlled trial comparing sulfonylurea, insulin, and metformin therapy in patients with newly diagnosed type 2 diabetes that could not be controlled with diet therapy. *Ann Intern Med*. 1998;128:165-175.
34. Turner R, Holman R. The UK prospective diabetes study. Presented at: European Association for the Study of Diabetes Meeting; September 10, 1998; Barcelona, Spain. Available at: http://www.dtu.ox.ac.uk/index.html/maindoc=/ukpds/. Accessed November 22, 1999.
35. *Red Book.* Montvale, NJ: Medical Economics Co Inc; 1997.
36. Health Care Financing Administration. Durable medical equipment regional carrier instructions to implement balanced budget act of 1997 provision 4105, to provide expanded coverage of blood glucose monitors, and testing strips for all diabetics. Available at: http://www.hcfa.gov/pubforms/transmit/b981760.htm. Accessibility verified April 18, 2002.
37. Aubert RE, Herman WH, Waters J, et al. Nurse case management to improve glycemic control in diabetic patients in a health maintenance organization. *Ann Intern Med*. 1998;129:605-612.
38. US Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, National Center for Health Statistics. *Vital and Health Statistics, Plan and Operation of the Third National Health and Nutrition Examination Survey, 1988-1994.* Washington, DC: US Dept of Health and Human Services; 1994. DHHS publication 94-1308, series 1, No. 32 4-0485.
39. UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes (UKPDS 38). *BMJ*. 1998;317:703-713.
40. UK Prospective Diabetes Study Group. Efficacy of atenolol and captopril in reducing risk of macrovascular and microvascular complications in type 2 diabetes. *BMJ*. 1998;317:713-720.
41. National Cholesterol Education Program 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. *JAMA*. 1993;269:3015-3023.
42. Shepherd J, Cobbe SM, Ford I, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. *N Engl J Med*. 1995;333:1301-1307.
43. West of Scotland Coronary Prevention Study Group. Baseline risk factors and their association with outcome in the West of Scotland Coronary Prevention Study. *Am J Cardiol*. 1997;79:756-762.
44. Goldberg RB, Mellies MJ, Sacks FM, et al. Cardiovascular events and their reduction with pravastatin in diabetic and glucose-intolerant myocardial infarction survivors with average cholesterol levels. *Circulation*. 1998;98:2513-2514.
45. Gray A, Raikou M, McGuire A, et al. Cost effectiveness of an intensive blood glucose control policy in patients with type 2 diabetes: economic analysis alongside randomised controlled trial (UKPDS 41). *BMJ*. 2000;320:1373-1378.
46. Chapman RH, Stone PW, Sandberg EA, Bell C, Neumann PJ. A comprehensive league table of cost-utility ratios and a sub-table of "panel-worthy" studies. *Med Decis Making*. 2000;20:451-467.