Cost-Effectiveness of Interventions to Prevent and Control Diabetes Mellitus: A Systematic Review

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OBJECTIVE — To synthesize the cost-effectiveness (CE) of interventions to prevent and control diabetes, its complications, and comorbidities.

RESEARCH DESIGN AND METHODS — We conducted a systematic review of literature on the CE of diabetes interventions recommended by the American Diabetes Association (ADA) and published between January 1985 and May 2008. We categorized the strength of evidence about the CE of an intervention as strong, supportive, or uncertain. CEs were classified as cost saving (more health benefit at a lower cost), very cost-effective (≤$25,000 per life year gained [LYG] or quality-adjusted life year [QALY]), cost-effective ($25,001 to $50,000 per LYG or QALY), marginally cost-effective ($50,001 to $100,000 per LYG or QALY), or not cost-effective (>$100,000 per LYG or QALY). The CE classification of an intervention was reported separately by country setting (U.S. or other developed countries) if CE varied by where the intervention was implemented. Costs were measured in 2007 U.S. dollars.

RESULTS — Fifty-six studies from 20 countries met the inclusion criteria. A large majority of the ADA recommended interventions are cost-effective. We found strong evidence to classify the following interventions as cost saving or very cost-effective: (I) Cost saving— *1*) ACE inhibitor (ACEI) therapy for intensive hypertension control compared with standard hypertension control; *2*) ACEI or angiotensin receptor blocker (ARB) therapy to prevent end-stage renal disease (ESRD) compared with no ACEI or ARB treatment; *3*) early irbesartan therapy (at the microalbuminuria stage) to prevent ESRD compared with later treatment (at the macroalbuminuria stage); *4*) comprehensive foot care to prevent ulcers compared with usual care; *5*) multi-component interventions for diabetic risk factor control and early detection of complications compared with conventional insulin therapy for persons with type 1 diabetes; and *6*) multi-component interventions for diabetic risk factor control and early detection of complications compared with standard glycemic control for persons with type 2 diabetes. (II) Very cost-effective— *1*) intensive lifestyle interventions to prevent type 2 diabetes among persons with impaired glucose tolerance compared with standard lifestyle recommendations; *2*) universal opportunistic screening for undiagnosed type 2 diabetes in African Americans between 45 and 54 years old; *3*) intensive glycemic control as implemented in the UK Prospective Diabetes Study in persons with newly diagnosed type 2 diabetes compared with conventional glycemic control; *4*) statin therapy for secondary prevention of cardiovascular disease compared with no statin therapy; *5*) counseling and treatment for smoking cessation compared with no counseling and treatment; *6*) annual screening for diabetic retinopathy and ensuing treatment in persons with type 1 diabetes compared with no screening; *7*) annual screening for diabetic retinopathy and ensuing treatment in persons with type 2 diabetes compared with no screening; and *8*) immediate vitrectomy to treat diabetic retinopathy compared with deferred vitrectomy.

CONCLUSIONS — Many interventions intended to prevent/control diabetes are cost saving or very cost-effective and supported by strong evidence. Policy makers should consider giving these interventions a higher priority.

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The cost of diabetes in the U.S. in 2007 was $174 billion (1). Many interventions can reduce the burden of this disease. However, health care resources are limited; thus, interventions for diabetes prevention/control should be prioritized. We wanted to compare the effectiveness and costs of various interventions to find those that were the most effective for the least expense. Cost-effective analysis is a useful tool for this purpose. Such analyses consist of compiling incremental cost-effectiveness ratios (ICERs), which are calculated as a ratio of the difference in costs to the difference in effectiveness between the intervention being evaluated and the comparison intervention.

With the same health outcome indicator, ICERs of interventions are comparable. Therefore, these ICERs can make it easier to decide how to allocate resources. Although many cost-effectiveness (CE) analyses of diabetes interventions have been published, their qualities and conclusions vary. A systematic review, which appraises individual studies and summarizes results, would aid policy makers and clinicians in prioritizing interventions to prevent or treat diabetes and its complications.

Few investigators have conducted systematic reviews of the CE of diabetes interventions (2–5). The systematic review presented here, following the Cochrane Collaboration's protocol (6), includes all English language studies available from 1985 to May 2008. The interventions included only those recommended by the 2008 American Diabetes Association (ADA) Standards of Medical Care in Diabetes (7).

RESEARCH DESIGN AND METHODS

Study selection and protocols for review

We searched the Medical Literature Analysis and Retrieval System Online (MEDLINE), Excerpta Medica (EMBASE), Cumulative Index to Nursing and Allied Health Literature (CINAHL), PsycINFO, Sociological Abstracts (Soc Abs), Web of

Science (WOS), and Cochrane databases to identify relevant studies. We created a search strategy involving medical subject headings. The key words—and what each indicated—were:

- Indicating diabetes: 26 key words indicating the disease of diabetes, such as "type 1 diabetes," "type 2 diabetes," "impaired glucose tolerance," and "insulin resistance";
- Indicating costs: ("cost or expenditure") OR ("costs and cost analysis") OR ("health care costs") OR ("cost of illness");
- Indicating effectiveness: ("benefit") OR ("life years") OR ("quality-adjusted life years") OR ("disability adjusted life years");
- Indicating CE analysis: [(key words for costs) AND (keywords for effectiveness)] OR ("cost-benefit analysis") OR ("cost-effectiveness analysis") OR ("cost-utility analysis") OR ("economic evaluation").

Database searches were based on matches in all four keyword categories. Reference lists of all the included articles were screened for additional citations, and *Diabetes Care* was reviewed manually, issue by issue, as the journal was expected to be highly relevant.

Criteria for inclusion in the review were *1*) original CE analysis; *2*) intervention directed toward patients with type 1, type 2, or gestational diabetes mellitus (GDM) and recommended in the 2008 ADA standards for medical care (7); *3*) outcomes were measured as life years gained (LYGs) or quality-adjusted life years gained (QALYs); and *4*) publication in the English language occurred between January 1985 and May 2008 (2). To ensure that only studies with acceptable quality were included, we limited the analysis to studies considered good or excellent according to a 13-item quality-assessment tool based on the *British Medical Journal* authors' guide for economic studies (8).

To make ICERs comparable across the studies, all costs are expressed as 2007 U.S. dollars with adjustment from other currencies, as needed, using the Federal Reserve Bank's annual foreign exchange rates (9) and from other cost years using the Consumer Price Index (10). If a study did not mention the year used in cost calculations, we assumed cost was as of one year before publication. ICERs were expressed as dollars per QALY or dollars per LYG and were rounded to the nearest hundred dollars per QALY or LYG.

Classification of cost-effectiveness of interventions

Interventions were classified based on the level of CE by convention as described in the literature (2,11,12)—cost saving (an intervention generates a better health outcome and costs less than the comparison intervention) or cost neutral (ICER = 0); very cost-effective ($0 < \text{ICER} \leq \$25{,}000$ per QALY or LYG); cost-effective ($\$25{,}000 < \text{ICER} \leq \$50{,}000$ per QALY or LYG); marginally cost-effective ($\$50{,}000 < \text{ICER} \leq \$100{,}000$ per QALY or LYG); or not cost-effective (>$100,000 per QALY or LYG)—and whether evidence for the intervention's CE was strong, supportive, or uncertain as described below.

There were two grades of evidence included in the "strong" group. Grade 1 was defined as *1*) CE of the intervention was evaluated by two or more studies; *2*) study quality was rated good or excellent; *3*) effectiveness of interventions based on well-conducted, randomized clinical trials with adequate power and generalizable results or meta-analysis or a validated simulation model; *4*) effectiveness of interventions rated as level A (clear evidence from well-conducted, generalizable, randomized controlled trials that were adequately powered; compelling nonexperimental evidence, i.e., the all or none rule developed by the Centre for Evidence-Based Medicine at the University of Oxford, U.K.) or level B (supportive evidence from well-conducted cohort studies or supportive evidence from a well-conducted case-control study) according to the 2008 ADA standards of medical care (7); and *5*) similar ICERs reported across the studies. Grade 2 was defined as the same as Grade 1 except that the CE was based on only one study and the study was rated as excellent.

We called the level of evidence "supportive" if only one study, rated lower than excellent, evaluated the CE of the intervention or if the effectiveness of the intervention was supported by either level C evidence (supportive evidence from poorly controlled or uncontrolled studies, or conflicting evidence with the weight of evidence supporting the recommendation) or expert consensus (level E) in ADA recommendations (7). The term "uncertain" was used to describe interventions with inconsistent evidence about CE across studies.

Reporting the results of the systematic review

We reported the study results in two ways: *1*) summarizing the key features and results for each included study; and *2*) synthesizing the CE of the interventions based on the classification criteria described above. For the summary, we grouped interventions based on their intended purposes: a) preventing type 2 diabetes among high-risk persons; b) screening for undiagnosed type 2 diabetes and GDM; c) management of diabetes and risk factors for complications; d) screening for and early treatment of complications; and e) treatment of complications and comorbidities. We considered cases where the same intervention was applied to different populations or was compared with different interventions as different specific interventions and reported the ICERs separately. This was because both incremental costs and effectiveness of an intervention, and thus the ICERs, varied if the population and/or comparison group differed. If the CE of an intervention was evaluated from different study perspectives, we report the ICERs separately. We presented the ICERs in subgroups if their ICERs differed substantially from base-case analysis, and original studies reported the ICERs this way. If the study reported the ICERs only for population subgroups, we provided a range and, when available, trend of the ICERs. Finally, if a study used both LYGs and QALYs as study outcome measures, we reported the ICER in both costs per LYG and QALY.

In reporting the synthesized results, we applied the following rules: *1*) We used the median ICER to represent the CE of an intervention if the intervention was evaluated by more than one study. *2*) We reported the ICERs from the longer analytical time horizon if the intervention was evaluated from both short- and long-term perspectives. This was appropriate since many of the benefits of most diabetes prevention and control interventions would come from preventing diabetic complications, which occur later in life. *3*) We chose the health care system as our primary study perspective for the purpose of cross-study and cross-intervention comparisons. This study perspective included all the medical costs incurred no matter who paid. *4*) If the ICERs of an intervention differed substantially between the U.S. and other developed countries (mainly European countries, Australia, and Canada), we reported the

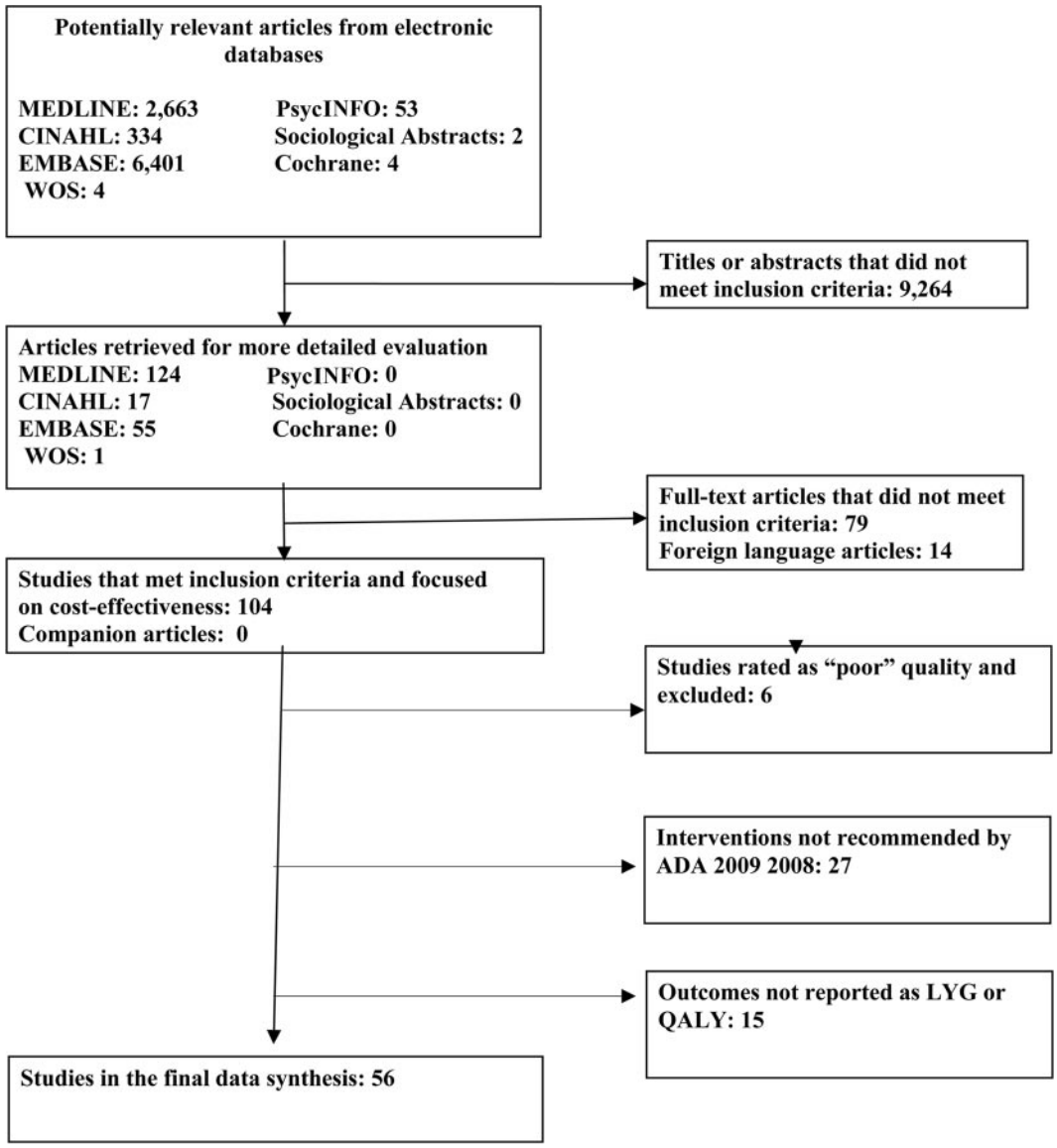

Figure 1—*Selection of cost-effectiveness studies for systematic review of interventions to prevent and control diabetes.*

summary results separately by labeling the ICER for the U.S. or for the other countries. 5) If the trial on which the CE of an intervention was based was conducted in a mixed population with type 1 or type 2 diabetes, we assumed the CE was the same for both types of diabetes.

RESULTS — The search yielded 9,461 abstracts. After reviewing the abstracts and subsequent reference tracking, we narrowed the focus to 197 possible original CE studies. Further review of the full text resulted in 56 CE studies that met our inclusion criteria. Figure 1 depicts the data abstraction process.

Table 1 shows the detailed description of the CE studies that we included according to intervention type (13–70). We first grouped similar interventions together, then arranged them chronologically and by the first author's last name. Some studies that evaluated multiple interventions appear in more than one category. The information used to describe each study included the intervention being evaluated; comparison intervention, population, and country setting; data sources for the effectiveness of the intervention; study methods; quality of the study; analytical time horizon; discount rate (a rate that is used to convert future costs and benefits into their present values); and ICER.

Thirty-nine of the 56 studies took a long-term analytical time horizon, such as 20–30 years or lifetime. Nearly all of the studies with the long-term horizon used simulation modeling. Only one study was conducted in a developing country (Thailand) (57). There were 48 excellent studies and 8 good studies. Only three studies took perspectives other than the health care system.

The interventions evaluated in these CE studies covered a wide range: lifestyle and medication therapy to prevent type 2 diabetes among high-risk individuals (eight studies); screening for undiagnosed type 2 diabetes or GDM (three studies); intensive glycemic control (12 studies); self-monitoring of blood glucose (one study); intensive hypertension control (four studies); statin therapy for cholesterol control (five studies); smoking cessation (one study); diabetic health education program (two studies); diabetes

Table 1—*Description of the cost-effectiveness studies for diabetes interventions

Source/study quality†/country	Study population	Intervention‡	Comparison	Effectiveness data	Methodology‖/analytical horizon/discount rate	Cost-effectiveness ratios (2007 U.S. $)
Preventing type 2 diabetes among high-risk individuals						
Segal et al. 1998 (59)§ Australia	Seriously obese or seriously obese with IGT	Intensive diet and education	Standard care	Literature review	25 years 5%	Cost saving
	Overweight or obese IGT or NGT and IGT	Group education in workplace on diet and physical activity for men	Standard care			Cost saving
	High-risk adults IGT or NGT and IGT	General practitioner advice on healthy lifestyle	Standard care			$1,000–$2,500/LYG
	Overweight adults in general population	Community-supported media campaign on obesity/sedentary lifestyle	No campaign			Cost saving
	Women with GDM history + NGT or IGT	Intensive diet and behavioral modification	Standard care			$1,300–$2,500/LYG
DPP 2003 (66) U.S.	IGT	Intensive lifestyle modification	Standard advice on lifestyle	DPP Multicenter RCT (n = 3,234)	3 years 0%	$32,900/QALY; if in 10-person group, $11,100/QALY
	IGT	Metformin	Standard advice on lifestyle			$134,000/QALY; if metformin cost reduced 50%, $76,500/QALY
	IGT	Intensive lifestyle modification‡‡	Standard advice on lifestyle			$69,400/QALY; if in 10-person group, $36,000/QALY
	IGT	Metformin‡‡	Standard advice on lifestyle			$133,400/QALY
Caro et al. 2004 (15) Canada	IGT	Intensive lifestyle modification	No intervention	DPP (n = 3,234), FDPS (n = 52)	10 years 5%	$700/LYG
	IGT	Metformin	No intervention			Cost saving in LYG and QALY
Palmer et al. 2004 (50) Australia, France, Germany, Switzerland, U.K.	IGT	Intensive lifestyle modification	Standard advice on lifestyle	DPP Multicenter RCT (n = 3,234)	Lifetime 5% except U.K.: cost 5%, effectiveness, 1.5%	Cost saving except U.K.; U.K.: $8,300/LYG
	IGT	Metformin	Standard advice on lifestyle			Cost saving, except UK; UK: $6,500/LYG
Eddy et al. 2005 (25) U.S.	IGT	Intensive lifestyle modification‡‡	No intervention	DPP Multicenter RCT (n = 3,234)	30 years 3%	$84,700/QALY; in 10-person group, $16,000/QALY
	IGT	Intensive lifestyle modification#	No intervention			$192,600/QALY; in 10-person group, $36,400/QALY
	IGT	Metformin‡‡	No intervention			$47,900/QALY
Herman et al. 2005 (34) U.S.	IGT	Intensive lifestyle modification	Standard advice on lifestyle	DPP Multicenter RCT (n = 3,234)	Lifetime 3%	$1,500/QALY; in 10-person group, cost saving
		Intensive lifestyle modification‡‡	Standard advice on lifestyle			$11,800/QALY
		Metformin	Standard advice on lifestyle			$42,000/QALY
		Generic Metformin‡‡	Standard advice on lifestyle			$2,400/QALY $40,200/QALY
Lindgren et al. 2007 (41) Sweden	IGT Age 60 years BMI >25 kg/m^2, FPG >6.1 mmol/l	Intensive lifestyle intervention (6 years)‡‡	General lifestyle advice	FDPS (n = 52)	Lifetime 3%	Cost saving not considering cost of extended life; $2,600/QALY including cost of extended life

Hoeger et al. 2007 (36) U.S.	U.S. population age 45–74 years, overweight and obese (BMI ≥ 25 kg/m^2) Groups	Screening for IGT and IFPG, DPP lifestyle intervention with IGT + IFPG	No screening and no lifestyle intervention	DPP (n = 3,234)	Lifetime 3%	$10,600/QALY; in group settings, cost saving
		Screening for IGT and IFPG, DPP lifestyle intervention with IFPG or IGT + IFPG	No screening and lifestyle intervention			$12,300/QALY; in group settings, $344/QALY
		Screening for IGT and IFPG, DPP lifestyle intervention with IGT + IFPG	Screening for IGT and IFPG, following DPP lifestyle intervention with IFPG, IGT, or IFPG + IGT			$13,100/QALY
		Screening and metformin treatment with IGT + IFPG	No screening and treatment			$26,600/QALY
		Screening and metformin treatment with IGT, IFPG, or IGT + IFPG	No screening and treatment			$26,000/QALY
Screening for undiagnosed type 2 diabetes and gestational diabetes						
Centers for Disease Control and Prevention 1998 (16) U.S.	U.S. population 25 years and older One-time	Opportunistic screening for undiagnosed type 2 diabetes starting at age 25 years, then treatment (universal screening)	No screening and treatment until clinical diagnosis of type 2 diabetes		Lifetime 3%	$374,900/LYG or $89,800/QALY; increasing with age (age ≥ 25 years) treatment (universal screening) $57,100/LYG or $21,400/QALY (age 25–34 years) $103,200/LYG or $29,700/QALY (age 35–44 years) 293,900/LYG or $70,100/QALY (age 45–54 years) $1 million/LYG or $185,000/QALY (age 55–64 years) $928,000/QALY (age ≥65)
	African Americans: age 25–34 years age 35–44 years age 45–54 years age 55–64 years age ≥65 years					$3,500/LYG or $1,300/QALY $10,200/LYG or $3,100/QALY $95,400/LYG or $19,600/QALY $764,100/LYG or $112,600/QALY $2 million/LYG or $500,000/QALY
Hoerger et al. 2004 (35) U.S.	Persons with hypertension	Targeted screening for undiagnosed diabetes among persons with hypertension	No screening or treatment until clinical diagnosis of type 2 diabetes		Lifetime 3%	$46,800–$130,500/QALY decreasing with age $70,500/QALY for age 45 years
	U.S. population	One-time opportunistic screening, then treatment (universal screening)	No screening or treatment until clinical diagnosis of type 2 diabetes			$72,200–$189,100/QALY decreasing with age $183,500/QALY for age 45 years
	U.S. population	One-time opportunistic screening, then treatment (universal screening)	Targeted screening, then treatment			$215,600–$699,800/QALY increasing with age
Nicolson et al. 2005 (44) U.S.	30-year-old pregnant women between 24–28 weeks' gestation	Sequential method (50-g GCT + 100-g GTT)‡‡	No screening 75-g GTT	A few unidentified RCTs	<1 year** 0%	Cost saving
		100-g GTT‡‡	No screening or 75-g GTT method			Cost saving
		100-g GTT‡‡	Sequential method			$35,200/QALY for maternal outcomes, $9,000/QALY for neonatal outcomes

Intensive glycemic control

DCCT 1996 (65) U.S.	Type 1 diabetes	Intensive glycemic control through insulin management, self-monitoring, and outpatient visits. The goal was to achieve A1C level as normal as possible (6%)	Conventional therapy (less intensive)	DCCT Multicenter RCT (n = 1,441)	Lifetime 3%	$47,600/life year gained, $50,800/QALY
Palmer et al. 2000 (46) Switzerland	Type 1 diabetes	Intensive insulin therapy	Conventional insulin therapy	Literature review	Lifetime 3%, 5%, 6% Reported results at 3% in the table	$46,600/LYG
Scuffham et al. 2003 (58) U.K.	Type 1 diabetes	Continous subcutaneous insulin intervention for persons using insulin pump	Multiple daily insulin injections	1 systematic review 1 meta-analysis	8 years 6%	$10,200/QALY
Roze et al. 2005 (56) U.K.	Type 1diabetes	Continuous subcutaneous insulin infusion	Multiple daily insulin injections	DCCT (n = 1,441) mainly meta-analysis	60 years 3%	$18,500/QALY
Eastman et al. 1997 (24) U.S.	Newly diagnosed type 2 diabetes	Intensive treatment targeting maintenance of A1C level at 7.2%	Standard antidiabetic treatment targeting A1C level at 10%	DCCT (n = 1,441)	Lifetime 3%	$17,400/QALY; sensitive to age at diabetes onset; CER <33,000 for age <50 years; $371,700/QALY for age 70–80 years
Gray et al. 2000 (30) U.K.	Type 2 diabetes	Intensive management with insulin or sulfonylurea aiming at FPG <6 mmol/l	Conventional management (mainly through diet) aiming at FPG <15 mmol/l	UKPDS Multicenter RCT (n = 5,120)	10 years** 6%	Cost saving in trial; $1,100/event-free year gained in clinic setting
Wake et al. 2000 (70) Japan	Type 2 diabetes	Intensive insulin therapy through multiple insulin injections A1C <7%	Conventional insulin injection therapy	Kumamoto study RCT (n = 110)	10 years** 3%	Cost saving
Clarke et al. 2001 (18) U.K.	Newly diagnosed type 2 diabetes Overweight	Intensive blood glucose control with metformin aiming at FPG <6 mmol/l	Conventional treatment primarily with diet	UKPDS (n = 5,120)	Median 10.7 years** 6%	Cost saving
Centers for Disease Control and Prevention 2002 (17) U.S.	Newly diagnosed type 2 diabetes	Intensive glycemic control with insulin or sulfonylurea aiming at FPG of 6 mmol/l	Conventional glucose control (mainly diet)	UKPDS (n = 5,120)	Lifetime 3%	$62,000/QALY; increasing rapidly with age at diagnosis: $14,400/QALY for age 25–34 years; $27,500–$56,000/QALY for age 35–54 years; > $100,000–$3.1 million for age 55–94 years Cost saving under UKPDS cost scenario (no case management cost, much less self-testing, slightly fewer physician visits) but using U.S. unit cost
Clarke et al. 2005 (19) U.K.	Newly diagnosed type 2 diabetes requiring insulin	Intensive glycemic control with insulin or sulfonylurea at FPG <6 mmol/l	Conventional glucose control therapy (mainly diet)	UKPDS (n = 5,120)	Lifetime 3.5%	$3,400/QALY
	Newly diagnosed type 2 diabetes Overweight	Intensive glycemic control with metformin	Conventional glucose control therapy (mainly diet)			Cost saving

Eddy et al. 2005 (25) U.S.	Newly diagnosed type 2 diabetes	Intensive DPP lifestyle with FPG >125 mmol/l Target: A1C level of 7% ‡‡	Dietary advice	DPP (n = 3,234)	30 years 3%	$33,100/QALY
Almbrand et al. 2000 (13) Sweden	Type 2 diabetes with acute MI	Insulin-glucose infusion for at least 24 h, then subcutaneous multidose insulin for ≥3 months	Standard antidiabetic therapy	DIGAMI study, RCT 1-year intervention, 4-year follow-up (n = 620)	5 years** 3%	$8,700/LYG, $12,400/QALY
Self-monitoring blood glucose						
Tunis 2008 (67) U.S.	Type 2 diabetes treated with oral agents in a large HMO	SMBG 1 time/day 40-year horizon public payer	No SMBG	Kaiser Permanente longitudinal study of cohort of "new antidiabetic drug users"	40 years 3%	$8,200/QALY; 52.6% probability less than $50,000/QALY
		SMBG 3 times/day 40-year horizon	No SMBG			$6,900/QALY; 60.7% probability less than $50,000/QALY
		SMBG 1 time/day 5-year horizon 10-year horizon	No SMBG			$24,200/QALY $9,700/QALY
		SMBG 3 times/day 5-year horizon 10-year horizon	No SMBG			$30,300/QALY $540/QALY
Intensive hypertension control						
UKPDS 1998 (68) U.K.	Type 2 diabetes Hypertension	Tight control of hypertension, BP <150/<80 mmHg, ACE inhibitor, β-blocker, and other agents	Less tight control of BP (mmHg), Initially <200/105, Later 180/105	UKPDS (n = 5,120)	Lifetime 6%	Cost saving in trial; $960/year free from occurrence of diabetes endpoint in clinic
Elliot et al. 2000 (26) U.S.	Type 2 diabetes Hypertension, initially free of CVD or ESRD	Reduction of BP to 130/85 mmHg Medications not mentioned	Reduction of BP to 140/90 mmHg	Meta-analysis of data from epidemiological studies and clinical trials	Lifetime 3%	
	Start of treatment					
	Age 50 years					$1,200/LYG
	Age 60 years					Cost saving
	Age 70 years					Cost saving
Centers for Disease Control and Prevention 2002 (17) U.S.	Type 2 diabetes Hypertension	Intensified hypertension control ACE inhibitor β-blocker Average BP 144/82 mmHg	Moderate hypertension control, Average BP 154/86 mmHg	UKPDS (n = 5,120)	Lifetime 3%	Cost saving
Clarke et al. 2005 (19) U.K.	Type 2 diabetes Hypertension	Tight BP control BP <150/85 mmHg, ACE inhibitor (captopril) or β-blocker (atenolol)	Less tight control of BP (mmHg), Initial <200/105, Later <180/105	UKPDS (n = 5,120)	Lifetime 3.5%	$200/QALY
Cholesterol control						
Herman et al. 1999 (33) U.S.	Type 2 diabetes Dyslipidemia, Previous MI or angina	Simvastatin	Placebo	4S study, Double-blind randomized, placebo-controlled, multicenter, multicountry trial (n = 4,444)	5 years** 3% for cost, 0% for benefit	Cost saving
Jonsson et al. 1999 (39) European countries	Type 2 diabetes Dyslipidemia, Previous MI or angina	Simvastatin	Placebo	4S study (n = 4,444)	Lifetime 3%	CS-$9,400/LYG in different countries, Median: $2,800/LYG

Grover et al. 2000 (31) Canada	Type 2 diabetes Dyslipidemia CVD history, Men and women 60 years old	Simvastatin	Placebo	4S study (n = 4,444) CARE (n = 4,159)	Lifetime 5%	$6,100–$12,300/LYG Increasing with pretreatment of LDL cholesterol level
	Type 2 diabetes Dyslipidemia, No CVD history	Simvastatin	Placebo			
	Men					
	Pretreatment LDL cholesterol level:					
	5.46 mmol/l (211 mg/dl)					$6,100–$15,000/LYG
	3.5 mmol/l (135 mg/dl)					$10,700–$23,000/LYG
	Women					
	Pretreatment LDL cholesterol level:					
	5.46 mmol/l					$15,300–$27,600/LYG
	3.5 mmol/l					$36,800–$61,300/LYG
Centers for Disease Control and Prevention 2002 (17) U.S.	Type 2 diabetes Dyslipidemia, No CVD history	Pravastatin	Placebo	West Scotland Coronary Prevention Study (n = 6,595 men)	Lifetime 3%	U-shape for age, $77,800/QALY
Raikou et al. 2007 (54) U.K. Ireland	Type 2 diabetes, No CVD history, No elevated LDL cholesterol level ≥1 CVD risk factor: retinopathy, microalbuminuria or macroalbuminuria, current smoking, or hypertension	Atorvastatin	Placebo	CARDS, Randomized, controlled, multicenter trial 94% white (n = 2,838)	Lifetime 3.5%	$2,800/LYG, $3,500/QALY Using UKPDS risk engine Low risk: $11,300/QALY; Medium risk: $4,700/QALY; High risk: $2,200/QALY
Smoking cessation						
Earnshaw et al. 2002 (23) United States	Newly diagnosed type 2 diabetes	Smoking cessation, Standard antidiabetic care	Standard antidiabetic care		Lifetime 3%	
	Smokers					
	Aged 25–84 years					<$25,000/QALY
	Aged 85–94 years					$89,800/QALY
Educational program						
Shearer et al. 2004 (61)§ Germany	Type 1 diabetes	Structured treatment and teaching program: educational course of training to self-manage diabetes and enjoy dietary freedom	Usual care (daily insulin injection)	Rosiglitazone trial CODE2 study of prevalence of complications, not an RCT	Lifetime 6%	Cost saving
Gozzoli et al. 2001 (29) Switzerland	Type 2	Standard antidiabetic care plus educational program, Self-monitoring, Recommendations on diet and exercise, Self-management of diabetes and complications, General health education	Standard antidiabetic care	Literature review (quality)	Lifetime 3%	$4,000/LYG

Diabetes disease management						
Mason et al. 2005 (43) England	Type 2 diabetes Hypertension	Policy to implement clinics led by specialist nurses to treat and control hypertension through consultation, medication review, condition assessment, and lifestyle advice	Usual care	SPLINT RCT (n = 1,407) UKPDS (n = 5,120)	Lifetime 5%	$4,800/QALY
	Diagnosed diabetes Dyslipidemia	Policy to implement clinics led by specialist nurses to treat and control hyperlipidemia by usual care	Usual care			$23,600/QALY
Gilmer et al. 2007 (27) San Diego County, California	Diabetes 48% Latinos	Culturally sensitive case management and self-management training program led by bilingual/bicultural medical assistant and registered dietitian stepped-care pharmacologic management of glucose and lipid levels and hypertension‡‡‡	Standard care	Project Dulce Observational cohort study with controls Average follow-up, 289 days (n = 3,893)	40 years 3%	$9,400/LYG or $12,000/QALY for uninsured; 100% probability to be less than $50,000 and $100,000/QALY, respectively $22,400/LYG or $29,100/QALY for patients in County Medical Services; 92% or 98% probability to be cost-effective if willingness to pay was $50,000 or $100,000/QALY, respectively $42,600/LYG or $53,120/QALY for patients in Medi-Cal; 57% or 81% probability to be cost-effective if willingness to pay was $50,000 and $100,000/QALY, respectively $68,400/LYG or $82,300/QALY for patients with commercial insurance; 31% and 62% probability to be cost-effective if willingness to pay was $50,000 and $100,000/QALY, respectively
Preventing diabetic complications						
Eye complications						
Javitt et al. 1994 (37)§ U.S.	Newly diagnosed type 2 diabetes	8 strategies for eye screening with dilation: Screening every 1, 2, 3, or 4 years and More frequent follow-up screening for diabetes patients with background retinopathy††	No screening	Cross-sectional and longitudinal studies	Lifetime 5%	All 8 strategies were cost saving

Javitt et al. 1996 (38) U.S.	Newly diagnosed type 1 and type 2 diabetes Type 1 diabetes Type 2 diabetes	Annual eye screening with dilation for all patients with diabetes but no retinopathy Examination every 6 months for those with retinopathy	Eye screening in 60% of diabetes patients	Cross-sectional and longitudinal studies	Lifetime 5%	$3,800/person-year of sight saved, $6,900/QALY $4,300/QALY $6,900/QALY
Palmer et al. 2000 (46) Switzerland	Type 1 diabetes	Annual eye screening and treatment, Conventional insulin therapy	Conventional insulin therapy	Literature review	Lifetime 3%	Cost saving
Vijan et al. 2000 (69) U.S.	Type 2	Eye screening for diabetes patients every 5 years Subsequent annual screening for those with background retinopathy	No screening	Epidemiological studies	Lifetime 3%	$23,500/QALY
		Eye screening for diabetes patients every 3 years Subsequent annual screening for those with background retinopathy	No screening			$27,000/QALY
		Eye screening for diabetes patients every 2 years Subsequent annual screening for those with background retinopathy	No screening			$30,700/QALY
		Eye screening annually for diabetes patients Subsequent annual screening for those with background retinopathy	No screening			$39,500/QALY
		Eye screening for diabetes patients every 3 years	5-year intervals			$32,800/QALY
		Eye screening for diabetes patients every 2 years	3-year intervals			$54,000/QALY
		Annual eye screening for diabetes patients	2-year intervals			$116,800/QALY
Maberley et al. 2003 (42) Western James Bay, Victoria, British Columbia, Canada	Type 1 diabetes and Type 2 diabetes	Screening using digital camera Immediate assessment of quality or electronically transferred to a remote reading center	Retina specialists visit Moose Factory every 6 months to examine people with diabetes, and patients in outlying communities are flown to Moose Factory, Canada		10 years 5%	Cost saving
Foot ulcers						
Tennval et al. 2001 (64) Sweden	Type 1 diabetes and Type 2 diabetes High risk: Previous foot ulcer Previous amputation Moderate risk: Neuropathy, PVD, and/or foot deformity	Optimal prevention of foot ulcer including foot inspection, appropriate footwear, treatment, and education	Usual care	Clinical and epidemiological data	5 years** 0%	 Cost saving Cost saving

	Low risk: No specific risk factor					>$100,000/QALY
Ortegon et al. 2004§ (45) The Netherlands	Newly diagnosed type 2 diabetes Foot ulcer	Intensive glycemic control Optimal foot care	Standard care	UKPDS (n = 5,120) Literature review on trials and epidemiological studies	Lifetime 3%	$44,900/QALY Assuming 10% reduction of foot lesion, $308,300/QALY Assuming 90% reduction of foot lesion, $17,000/QALY
		Intensive glycemic control plus optimal foot care	Standard care			Assuming 10% reduction of foot lesion, $34,400/QALY Assuming 90% reduction of foot lesion, $11,010/QALY
End-stage renal disease						
Borch-Johnsen et al. 1993 (14)§ Germany	Type 1 diabetes	Annual screening for microalbuminuria at 5 years after diabetes onset, ACEI treatment	Treatment of macroalbuminuria	Danish cohort (n = 2,890)	30 years 6%	Cost saving
Kiberd et al. 1996 (40)§ Canada	Type 1 diabetes	Screening for microalbuminuria ACEI treatment	Treatment of hypertension and/or macroproteinuria	Clinical trial	Lifetime 5%	$58,400/QALY
Palmer et al. 2000 (46) Switzerland	Type 1 diabetes High total cholesterol level High systolic BP	Microalbuminuria monitoring, ACE treatment, Conventional insulin therapy	Conventional insulin therapy	Literature review	Lifetime 3%	Cost saving
Dong et al. 2004 (22) U.S.	Type 1 diabetes	ACEI treatment starting at 1 year after diagnosis	Annual screening for microalbuminuria ACE treatment	DCCT (n = 1,441)	Lifetime 3%	$38,000/QALY, Increased with lowering A1C level; at A1C level 9%, <25,000/QALY
Sakthong et al. 2001 (57)§ Thailand	Type 2 diabetes Microalbuminuria but normal BP	ACE inhibitors	Placebo	7-year RCT in Israel (n = 94)	25 years 8%	Cost saving
Souchet et al. 2003 (62) France	Type 2 diabetes Nephropathy	Losartan	Placebo	RENAAL study Multicenter international trial (n = 1,513)	4 years** Cost discounted at 8% Benefits not discounted	Cost saving
Szucs et al. 2004 (63)§ Switzerland	Type 2 diabetes Nephropathy	Losartan	Placebo	RENAAL study Multicenter international trial (n = 1,513)	3.5 years** 0%	Cost saving
Palmer et al. 2003 (47) Belgium, France	Type 2 diabetes Macroalbuminuria Hypertension	Irbesartan	Standard therapy for hypertension	IDNT study Multicenter, double-blind placebo controlled trial (n = 1,715)	Lifetime 3%	Cost saving
Palmer et al. 2004 (49) U.K.	Type 2 diabetes Hypertension Nephropathy	Irbesartan	Standard therapy for hypertension	IDNT study (n = 1,715)	10 years 6% for costs 1.5% for benefits	Cost saving
Palmer et al. 2005 (51) Spain	Type 2 diabetes Microalbuminuria Hypertension	Irbesartan	Standard therapy for hypertension, No ACEI, AIIRA, or β-blockers	IDNT study (n = 1,715) IRMA-2 trial Randomized controlled study (n = 582)	25 years 3%	Cost saving
Palmer et al. 2007 (52) Hungary	Type 2 diabetes Microalbuminuria	Adding irbesartan	Placebo + standard therapy for hypertension	IDNT study (n = 1,715) IRMA-2 trial (n = 582)	25 years 5%	Cost saving

Palmer et al. 2004 (48) U.S.	Type 2 diabetes Hypertension Microalbuminuria	Irbesartan at stage of microalbuminuria	Standard therapy for hypertension	IDNT study (n = 1,715)	25 years 3%	Cost saving
		Irbesartan at stage of macroalbuminuria	Standard therapy for hypertension			Cost saving
		Irbesartan at stage of microalbuminuria	Irbesartan at stage of macroalbuminuria			Cost saving
Palmer et al. 2007 (53) U.K.	Type 2 diabetes Hypertension	Irbesartan at stage of microalbuminuria	Standard therapy for hypertension	IDNT study (n = 1,715) IRMA-2 trial (n = 582)	25 years 3.5%	Cost saving
	Microalbuminuria	Irbesartan at stage of macroalbuminuria	Standard therapy for hypertension			Cost saving
		Irbesartan at stage of microalbuminuria	Irbesartan at stage of macroalbuminuria			Cost saving
Coyle et al. 2007 (21) Canada	Type 2 diabetes Hypertension Macronephropathy or Micronephropathy	Irbesartan added at stage of microalbuminuria	Conventional treatment for diabetes and hypertension, No ACEI or AIIRAs	IDNT study (n = 1.715) IRMA-2 trial (n = 582)	Lifetime 5%	Cost saving
		Irbesartan added at stage of overt nephropathy	Conventional treatment for diabetes and hypertension			Cost saving
		Irbesartan added at stage of microalbuminuria	Irbesartan added at stage of overt nephropathy			Cost saving
Golan et al. 1999 (28) U.S.	Newly diagnosed type 2 diabetes	Treat patients with new diagnosis with ACEI	Screening for macroalbuminuria and treatment with ACEI	U.S.-Canada Collaborative study for type 1 diabetes, RCT (n = 207) 2 RCT for type 2 diabetes in Israel (n = 94 and 156, respectively)	Lifetime 3%	Cost saving
		Screening for microalbuminuria and treatment with ACEI	Screening for macroalbuminuria and treatment with ACEI			Cost saving
		Treat patients with new diagnosis with ACEI	Screening for microalbuminuria and treatment with ACEI			$10,900/QALY
Clarke et al. 2000 (20) Canada	Type 1 diabetes	Province or territory paying for ACEI	Pay from out-of-pocket	Collaborative observational study using administrative data base (N=8.4 million)	21 years 5%	Cost saving Compliance rate and cost of ACEI affected ICER greatly
Rosen et al. 2005 (55) US	Medicare population Type 1 and type 2 diabetes	Medicare full-payment for ACEI Medicare paying for ACEI	Pay from out-of-pocket Current Medicare Modernization Act	HOPE Trial Multinational RCT	Lifetime 3%	Cost saving if ACEI use increased by at least 7.2% If use increased by 2.9%, <$20,000/QALY Cost saving if ACEI use increased by at least 6.2% If use increased by 2.2%, <$20,000/QALY

Comprehensive interventions						
Palmer et al. 2000 (46) Switzerland	Type 1 diabetes	C + ACEI therapy + eye screening and treatment (EYE)	Conventional glycemic control (C)	Literature review	Lifetime 3%	Cost saving
		Intensive insulin therapy (I) + ACEI therapy	I			$46,500/LYG
		I + EYE	I			$50,600/LYG
		I + ACEI therapy + EYE	I			$49,800/LYG
Gozzoli et al. 2001 (29) Switzerland	Type 2 diabetes	Added education program, nephropathy screening, and ACEI therapy to standard antidiabetic care	Standard antidiabetic care	Literature review	Lifetime 0%, 3%	Cost saving
		Added education program, nephropathy screening, ACEI therapy, and retinopathy screening and laser therapy to standard antidiabetic care	Standard antidiabetic care			Cost saving
		Multifactorial intervention included educational program, screening for nephropathy and retinopathy, control of CVD risk factors, early diagnosis and treatment of complications, and health education	Standard antidiabetic care			Cost saving
Treatment of diabetes-related complications						
Retinopathy						
Sharma et al. 2001 (60) U.S.	Diabetic retinopathy Health maintenance organization	Immediate vitrectomy for management of vitreous hemorrhage secondary to diabetic retinopathy	Deferral of vitrectomy	DRVS	Lifetime 6%	$2,900/QALY
Foot ulcer						
Habacher et al. 2007 (32) Austria	Newly diagnosed diabetic foot ulcer	Intensified treatment by international consensus on diabetic foot care	Standard treatment	Retrospective study of patient records on 119 consecutive ulcerations in 86 patients at tertiary outpatient clinic specializing in treatment of diabetic foot ulcers	15 years 0–8%	Cost saving

4S, Scandinavian Simvastatin Survival Study; **ACEI**, angiotensin converting enzyme inhibitors; **AHT**, arterial hypertension; **AIIRA**, angiotensin II receptor antagonists; **BP**, blood pressure; **C**, conventional glycemic control; **CAD**, coronary artery disease; **CARDS**, Collaborative Atorvastatin Diabetes Study; **CARE**, Cholesterol and Recurrent Events; **CDC**, Centers for Disease Control and Prevention; **CODE2** = the cost of diabetes type 2 in Europe; **CORE**, Center for Outcomes Research; **CVD**, cardiovascular disease; **DAIS**, Diabetes Atherosclerosis Intervention Study; **DCCT**, Diabetes Control and Complications Trial; **DIGAMI**, Diabetes Mellitus Insulin Glucose Infusion in Acute Myocardial Infarction; **DiGEM**, diabetes glycemic education and monitoring; **DPN**, diabetic peripheral neuropathy; **DPP**, diabetes prevention program; **DRVS**, Diabetic Retinopathy Vitrectomy Study; **DTTP**, diabetes treatment and teaching program; **EYE**, screening for retinopathy and ensuing treatment; **FDPS**, Finish Diabetes Prevention Study; **FPG**, fasting plasma glucose; **HMO**, Health Maintenance Organization; **HOPE**, Heart Outcome Prevention Evaluation; **I**, intensive glycemic control; **ICER**, incremental cost effectiveness ratio; **IDNT**, Irbesartan Type II Diabetic Nephropathy Trial; **IFPG**, impaired fasting plasma glucose; **IGT**, impaired glucose tolerance; **IMPACT**, Improving Mood-Promoting Access to Collaborative Treatment; **KORA**, Cooperative Research in the Region of Augsburg; **MI**, myocardial infarction; **NGT**, normal glucose tolerance; **NIDDM**, Non-Insulin Dependent Diabetes Mellitus; **OGTT**, oral glucose tolerance test; **PHN**, postherpetic neuralgia; **PROactive**, PROspective pioglitAzone Clinical Trial in macroVascular Events; **PROPHET**, Prospective Population Health Event Tabulation; **PVD**, peripheral vascular disease; **RCT**, randomized clinical trial; **RENAAL**, Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan; **ROSSO**, RetrOlective Study Self-Monitoring of Blood Glucose and Outcome; **RPG**, random plasma glucose; **SMBG**, self-monitoring blood glucose; **SPECT**, single proton emission computed tomography; **SPLINT**, specialist nurse-led intervention to treat and control hypertension and hyperlipidemia in diabetes; **QALY**, quality adjusted life year; **VA-HIT**, VA-HDL Intervention Trial. *The studies were ordered by grouping similar interventions together, then follow the year and alphabetical order of the first author's last name; the numbers in the parenthesis are the reference number. †The study was rated as "excellent" quality unless otherwise indicated. §The study was rated as "good" quality. ||The study is based on simulation modeling unless otherwise indicated. **Within trial or within epidemiological study. ‡The study was done from the perspective of the health system unless otherwise indicated. ‡‡The study was done from the societal perspective. #The study done from the perspective of the health plan. ††The study was done from the federal budget perspective. †††Third party payer perspective.

disease management program (two studies); screening to prevent diabetic retinopathy (five studies); optimal foot care to prevent foot ulcer and amputation (two studies); ACE inhibitor (ACEI) or angiotensin receptor blocker (ARB) therapy to prevent diabetic end-stage renal diseases (ESRD) (15 studies); comprehensive interventions using a combination of several of the above secondary prevention interventions (two studies); and interventions treating diabetic retinopathy and foot ulcers (two studies).

The classification of the interventions based on their level of CE and strength of evidence is presented in Table 2. For each intervention, we also described the number of studies that evaluated the CE of this intervention, its comparison intervention, and the study population in which the intervention was implemented. We reported the median and range of the ICERs across the studies.

Twenty-six interventions were classified as supported by strong evidence concerning their CE (Table 2). Among these, six interventions were cost saving, eight were very cost-effective, six were cost-effective, two were marginally cost-effective, and four were not cost-effective. These interventions consisted of primary prevention, screening for undiagnosed type 2 diabetes, diabetic risk factor control, early prevention of diabetes complications, and treatment of diabetes complications.

The six cost-saving interventions with strong evidence were *1*) ACEI therapy for intensive hypertension control, as in the UK Prospective Diabetes Study (UKPDS), in persons with type 2 diabetes compared with standard hypertension control; *2*) ACEI or ARB therapy to prevent ESRD for type 2 diabetes compared with no ACEI or ARB therapy; *3*) early irbesartan therapy at the stage of microalbuminuria to prevent ESRD in people with type 2 diabetes compared with treatment at the stage of macroalbuminuria; *4*) comprehensive foot care to prevent ulcers in mixed population with either type 1 or type 2 diabetes compared with usual care; *5*) multi-component interventions for diabetic risk factor control and early detection of complications compared with conventional insulin therapy for persons with type 1 diabetes; and *6*) multi-component interventions for diabetic risk factor control and early detection of complications compared with standard glycemic control for persons with type 2 diabetes.

Of the eight very cost-effective interventions with strong evidence, six were for persons with type 2 diabetes, one for persons with type 1 diabetes, and one for a mixed population with type 1 or type 2 diabetes. Interventions for type 2 diabetes included: *1*) primary prevention through intensive lifestyle modification; *2*) universal opportunistic screening for undiagnosed type 2 diabetes in African Americans between 45 and 54 years old; *3*) intensive glycemic control as implemented in UKPDS; *4*) statin therapy for secondary prevention of cardiovascular disease; *5*) smoking cessation; and *6*) annual screening for diabetic retinopathy and early treatment of it. The intervention for type 1 diabetes was annual screening for diabetic retinopathy and treating the positive cases. The intervention for mixed population of type 1 and type 2 diabetes was immediate vitrectomy to treat diabetic retinopathy compared with deferral of vitrectomy.

The six cost-effective interventions with strong evidence were *1*) one-time opportunistic targeted screening for undiagnosed type 2 diabetes in hypertensive persons aged 45 years and older compared with no screening; *2*) intensive insulin treatment for persons with type 1 diabetes compared with conventional glycemic control; *3*) UKPDS-like intensive glycemic control applied to the U.S. health care system among adults younger than age 54 years with type 2 diabetes compared with conventional glycemic control; *4*) intensive glycemic control by a Diabetes Prevention Program (DPP) type of intensive lifestyle intervention in persons with newly diagnosed type 2 diabetes compared with conventional glycemic control; *5*) statin therapy for primary prevention of cardiovascular disease in persons with type 2 diabetes compared with no statin therapy; *6*) multi-component interventions including insulin therapy, ACEI therapy, and screening for retinopathy in persons with type 1 diabetes compared with intensive insulin therapy.

The two marginally cost-effective interventions with strong evidence were *1*) intensive glycemic control for all U.S. residents with type 2 diabetes diagnosed at age 25 years and older compared with usual care; and *2*) screening for diabetic retinopathy every two years compared with screening every three years in persons with type 2 diabetes.

The four interventions with strong evidence of not being cost-effective were *1*) one-time universal opportunistic screening for undiagnosed type 2 diabetes among those aged 45 years and older compared with no screening; *2*) universal screening for type 2 diabetes compared with targeted screening; *3*) intensive glycemic control in the U.S. setting for patients diagnosed with diabetes at older ages (55–94 years of age) compared with usual care; and *4*) annual screening for retinopathy compared with screening every two years. All these studies were for type 2 diabetes.

There were 18 specific interventions for which their CEs were based only on "supportive" evidence. Among them, 15 were each supported by one CE study, 13 were supported by level C or level E evidence, and five were supported by level A or B evidence as defined in the 2008 ADA standards of medical care in diabetes (7). For those interventions with level A or B evidence, the CE of each intervention was evaluated by one study with a quality of being "good."

In terms of the level of the CE, 10 of the 18 specific interventions based on "supportive" evidence were cost-saving, including *1*) screening using the sequential method (50-g glucose challenge test followed by 100-g glucose tolerance test [GTT]) for GDM in 30-year-old pregnant women between 24–28 weeks' gestation compared with no screening; *2*) screening for GDM using the 100-g GTT method compared with no screening; *3*) the sequential method compared with 75-g GTT screening for GDM; *4*) 100-g GTT compared with 75-g GTT screening for GDM; *5*) diabetes self-management education for persons with type 1 diabetes compared with no education; *6*) full-reimbursement policy for ACEI for patients with type 1 diabetes compared with patients paying out-of-pocket; *7*) full-reimbursement policy for ACEI for patients with type 2 diabetes compared with patients paying out-of-pocket; *8*) screening using a mobile camera at a remote area and processing data in a reading center compared with a retina specialist's visit in a mixed population of type 1 and type 2 diabetes; *9*) screening for diabetic nephropathy and ensuing ACEI or ARB therapy in persons with type 1 diabetes compared with no screening; and *10*) intensified foot ulcer treatment in a mixed population with type 1 or type 2 diabetes compared with standard treatment.

Seven of the 18 specific interventions were very cost-effective: *1*) primary prevention of type 2 diabetes in women with GDM history through intensive lifestyle

Table 2—*Summary of the cost-effectiveness studies by intervention**

Intervention	Comparison	Intervention population	Number of studies	Level of recommendation by ADA	Median of the cost-effectiveness ratios	Range of the cost-effectiveness ratios
			Strong evidence			
Cost saving						
ACEI therapy for intensive hypertension control	Standard hypertension control	Type 2	4	B	Cost saving	Cost saving-$1,200/LYG $230/QALY
Addition of ACEI or ARB therapy to prevent ESRD	No ACEI or ARB therapy	Type 2	7	A	Cost saving	Cost saving
Irbesartan therapy at the stage of microalbuminuria	Irbestartan therapy at the stage of macroalbuminuria	Type 2	3	A	Cost saving	Cost saving
Comprehensive foot care to prevent ulcer†	Usual care	Mixed population of type 1 and type 2	1	B	Cost saving	Cost saving
Multi-component interventions (conventional insulin control, ACEI treatment, eye screening, and treatment)	Conventional insulin control	Type 1	1	A: ACEI treatment B: eye screening and ensuing treatment	Cost saving	Cost saving
Multi-component interventions (standard antidiabetic care plus education, nephropathy screening, ACEI treatment, retinopathy screening)	Standard antidiabetic care	Type 2	1	B: education E: nephropathy screening B: ACEI therapy B: retinopathy screening	Cost saving	Cost saving
Very cost-effective						
Intensive lifestyle modification	Standard lifestyle recommendation or no intervention	IGT	8	B: medical nutritional therapy A: physical activity	$1,500/QALY	Cost saving-$84,700/QALY‡
Universal opportunistic screening for undiagnosed type 2 diabetes in African Americans between 45 and 54 years old	No screening	African Americans aged 45–54 years	1	B	$19,600/QALY	$19,600/QALY
Intensive glycemic control as in UKPDS setting	Conventional glycemic control	Type 2 newly diagnosed	6	A, B $3,400/QALY	Cost saving-$12,400/QALY	
Statin therapy	No statin therapy	Type 2, with hyperlipidemia, with CVD history	3	A	$2,800/LYG	Cost saving-$12,300/LYG
Smoking cessation	No smoking cessation	Type 2	1	A, B	<$25,000/QALY	<$25,000/QALY-$89,800/QALY (aged 85–94 years)
Annual screening for diabetic retinopathy	No screening	Type 1	2	B	$2,150/QALY	Cost saving-$4,300/QALY

Annual screening for diabetic retinopathy	No screening	Type 2	3	B	$6,900/QALY	Cost saving-$39,500/QALY
Immediate vitrectomy to treat diabetic retinopathy	Deferral of vitrectomy	Mixed population of type 1 and type 2	1	Mentioned but not explicitly provided level, supported by trials	$2,900/QALY	$2,900/QALY
Cost-effective						
Targeted screening for undiagnosed type 2 diabetes	No screening	U.S. population with hypertension 45 years and older	1	B: in adults of any age who are overweight or obese and who have one or more additional risk factors for diabetes. In those without these risk factors, testing should begin at age 45	$49,200/QALY	$46,800–$70,500/QALY starting at different age
Intensive insulin treatment	Conventional glycemic control	Type 1	4	A, B	$28,900/QALY	$10,200–$50,800/QALY
Intensive glycemic control as in the U.S. setting	Conventional glycemic control	Type 2 newly diagnosed at 25–54 years old	1	A, B	$27,500/QALY	$14,400-$56,000/QALY
Intensive glycemic control through lifestyle modification	Conventional glycemic control	Type 2 newly diagnosed	1	A, B	$33,100/QALY	$33,100/QALY
Statin therapy	No statin therapy	Type 2, with hyperlipidemia, without CVD history	3	A: statin therapy for diabetic patients without CVD who are older than 40 years and have one or more other CVD risk factors	$38,200/LYG§	$6,100/LYG–$61,300/LYG $77,800/QALY
Multi-component interventions (intensive insulin control, ACEI treatment, eye screening and ensuing treatment)	Intensive insulin control	Type 1	1	A, B: intensive insulin control A: ACEI therapy B: eye screening	$49,800/LYG (non U.S.)	$46,500-$50,600/LYG
Marginally cost-effective						
Intensive glycemic control as in the U.S. setting	Conventional glycemic control	Type 2 newly diagnosed All age group diagnosed of diabetes at 25 years and older	1	A, B	$62,000/QALY	$14,400–$3 million/QALY
Eye screening every 2 years	Eye screening every 3 years	Type 2	1	B: annual eye screening recommended, less frequent exams (every 2–3 years) may be considered following one or more normal eye exams	$54,000/QALY	$54,000/QALY

Not cost-effective						
Universal opportunistic screening for undiagnosed type 2 diabetes	Targeted screening in persons with hypertension	U.S. population 45 years and older	1	B	>$100,000/QALY	$70,100-$928,000/QALY
Universal opportunistic screening for undiagnosed type 2 diabetes and ensuing treatment	No screening	U.S. population 45 years and older	2	B	>$100,000/QALY	$70,100-$1 million
Intensive glycemic control as in the U.S. setting	Conventional glycemic control	Type 2 Newly diagnosed at 55–94 years	1	A, B	>$100,000/QALY	>$100,000–$3 million/QALY
Eye screening every year	Eye screening every 2 years	Type 2	1	B	$116,800/QALY	$116,800/QALY
			Supportive evidence			
Cost saving						
Screening for GDM with sequential method‖	No screening	30-year-old pregnant women between 24–28 weeks' gestation	1	C	Cost saving	Cost saving
Screening for GDM with 100-g GTT	No screening	30-year-old pregnant women between 24–28 weeks' gestation	1	C	Cost saving	Cost saving
Screening for GDM with sequential method	75-g GTT	30-year-old pregnant women between 24–28 weeks' gestation	1	C	Cost saving	Cost saving
Screening for GDM with 100-g GTT	75-g GTT	30-year-old pregnant women between 24–28 weeks' gestation	1	C	Cost saving	Cost saving
Diabetes self-management education	No education	Type 1	1	B	Cost saving	Cost saving
Reimbursement for ACEI by public insurance	Paying out-of-pocket	Type 1	1	E	Cost saving	Cost saving
Reimbursement for ACEI by public insurance	Paying out-of-pocket	Type 2	1	E	Cost saving	Cost saving
Screening using mobile camera and electronically transmitted to a data reading center and read by trained personnel	Retina-specialists visit	Mixed population of type 1 and type 2 at a remote area	1	Recommended but not leveled, assume level E	Cost saving	Cost saving

Screening for diabetic nephropathy and ensuing ACEI or ARB therapy	Treat until macroalbuminuria	Type 1	3	E: screening A: ACEI treatment	Cost saving	Cost saving-$58,400/QALY
Intensified foot ulcer treatment	Standard treatment	A mixed population of type 1 and type 2	1	B	Cost saving	Cost saving
Very cost-effective						
Intensive diet and education	Standard antidiabetic care	Women with GDM history, currently IGT	1	A, B	$2,500/LYG	$2,500/LYG
Universal opportunistic screening for type 2 diabetes in younger and certain ethnic groups	No screening	African Americans, aged 25–44 years	1	B: if overweight or obese	$3,100/QALY	$1,300–$19,600/QALY
Screening for GDM 100-g GTT	Sequential method	30-year-old pregnant women between 24–28 weeks' gestation	1	E	$35,200/QALY for maternal outcomes, $9,000/QALY for neonatal outcomes	$9,000–$35,200/QALY
Diabetes self-management education	No education	Type 2	1	B	$4,000/LYG	$4,000/LYG
Disease management	No disease management program	Type 2 or mixed types	2	Mentioned but not provided level, assume level E	$23,350/QALY	$4,800–$68,400/QALY for groups with different insurance
SMBG 3 times/day¶	No SMBG	Type 2 treated with oral agents in a large HMO	1	E	$6,900/QALY	$540–$30,300/QALY for different time horizon
SMBG 1 time/day¶	No SMBG		1	E	$9,700/QALY	$8,200–$24,200/QALY for different time horizon
Cost-effective						
Metformin	Placebo	IGT	6	E	$26,600/QALY	Cost saving-$47,900/QALY‡
Marginally cost-effective						
NA						
Not cost-effective						
NA						
			Uncertain			
Optimal screening for type 2 diabetes starting age		U.S. population 45 years and older	2	B: recommend starting screening for type 2 diabetes at age 45 years if no other risk factors		

ACEI, angiotensin converting enzyme inhibitors; **ARB**, angiotensin receptor blocker; **CVD**, cardiovascular disease; **ESRD**, end stage renal disease; **GDM**, gestational diabetes; **GTT**, glucose tolerance test; **IGT**, impaired glucose tolerance; **LYG**, life year gained; **NA**, not available; **QALY**, quality adjusted life years; **SMBG**, self-monitoring blood glucose. **A**, as defined in Standards of Medical Care in Diabetes—2008: clear evidence from well-conducted, generalizable, randomized controlled trials that are adequately powered; compelling non-experimental evidence, i.e., "all or none" rule developed by the Centre for Evidence-Based Medicine at Oxford; supportive evidence from well-conducted randomized controlled trials that are adequately powered. **B**, as defined in Standards of Medical Care in Diabetes–2008: supportive evidence from well-conducted cohort studies; supportive evidence from a well-conducted case-control study. **C**, as defined in Standards of Medical Care in Diabetes–2008: supportive evidence from poorly controlled or uncontrolled studies; conflicting evidence with the weight of evidence supporting the recommendation. **E**, as defined in Standards of Medical Care in Diabetes–2008: expert consensus or clinical experience. *, the same interventions applied to different populations or compared with different comparison interventions were treated as different specific interventions. †, including foot exams, appropriate footwear, treatment, and education. ‡, the study for within trial and the results from health plan perspective are not used for determining the cost-effectiveness of the intervention. §, get this number by taking the median for women in one study (conservative, women > men) as the results for that study, then take the median of the three study. ‖, 50-g GTT + 100-g GTT. ¶, the evidence was very weak: there was an over 40% probability that the intervention would cost more than $50,000/QALY in a long-term.

intervention compared with usual care; 2) universal opportunistic screening for type 2 diabetes in African Americans aged 25–44 years compared with no screening; 3) 100-g GTT compared with the sequential screening method for detecting GDM in 30-year-old pregnant women between 24–28 weeks' gestation; 4) diabetes self-management education for persons with type 2 diabetes compared with no education; 5) disease management programs using specialist nurse–led clinics to treat and control hypertension or hyperlipidemia in patients with type 2 diabetes in a city in England or a culturally sensitive case–management training program to control diabetes and its risk factors in a Latino population with both type 1 and type 2 diabetes in a U.S. county compared with usual care only; 6) self-monitoring of blood glucose (SMBG) three times per day compared with no SMBG in type 2 noninsulin users; and 7) SMBG once per day compared with no SMBG in type 2 noninsulin users. One of the 18 specific interventions was cost-effective, i.e., the use of metformin to prevent type 2 diabetes in obese persons with impaired glucose tolerance compared with standard lifestyle intervention. No interventions in the "supportive" evidence category were "marginally cost-effective" or "not cost-effective."

Current evidence is uncertain on how the CE of screening for undiagnosed type 2 diabetes would change with the age of those screened. Two studies evaluated the CE of screening for undiagnosed type 2 diabetes; one study reported that cost-effectiveness ratios (CERs) increased with initial screening age (16) while the other reported that they decreased with screening age (35).

CONCLUSIONS — Our systematic review showed that, with few exceptions, ADA-recommended interventions for preventing or treating diabetes and its complications were cost saving, very cost-effective, or cost-effective (i.e., with an ICER of less than $50,000 per QALY or LYG), although the strength of evidence varied. Generally, interventions that cost less than $50,000 per QALY are considered an efficient use of resources and worth recommending (11). Interventions with strong evidence for being cost saving, very cost-effective, or cost-effective should be considered for implementation. Interventions with supportive evidence for being cost saving, very cost-effective, or cost-effective should be adopted if extra resources are available or if similar interventions with strong evidence are unavailable or infeasible in a specific setting.

The one intervention recommended by the ADA that was shown as not CE was screening for type 2 diabetes of all U.S. residents aged 45 years and older. When considering allocating resources efficiently, universal screening for undiagnosed diabetes should be undertaken with great caution. The high CE ratio for universal screening for undiagnosed type 2 diabetes was primarily attributable to the small gain in health benefit. For example, screening everyone aged 45 years and older gained only 0.003 QALY per eligible person compared with no screening. However the additional costs associated with screening and early treatments were relatively large ($564 per person). Although detecting and treating diabetes earlier can prevent future diabetes-related complications and their associated medical costs, such savings are relatively small ($57 per person). Combining the health benefit and costs would yield an ICER of more than $1 million per QALY (35). An alternative to broad screening is to focus on screening persons with additional risk factors, such as hypertension. Such targeted screening is shown to be cost-effective when compared with no screening or universal screening.

Intensive glycemic control for all U.S. residents with type 2 diabetes diagnosed at age 25 years and older is marginally CE. However the cost-effectiveness of this intervention varies by age at the time of the diabetes diagnosis. The intervention is cost-effective in persons diagnosed at 25–54 years of age. However, intensive glycemic control for those diagnosed with diabetes at 55 years of age and older is not cost-effective. In fact, this result is consistent with the ADA's recommendation of less stringent A1C goals for patients with limited life expectancies.

The ADA recommended annual eye screening for diabetic retinopathy. This recommended intervention is very cost-effective compared with no screening in persons with type 2 diabetes. If considering the efficient allocation of resources, however, screening every other year might be a better alternative. Screening annually leads to a small health benefit but results in a moderate additional cost. For example, Vijan et al. (69) showed that, compared with a 2-year screening, annual screening among persons at moderate risk (65 years old with A1C level 9%) resulted in an increase of 2–3 days of sight at a cost of $540–690 per person. However the ADA also stated in its recommendation that "less frequent exams (every 2–3 years) may be considered following one or more normal eye exams."

For the interventions with uncertain CE (including optimal age of starting screening for type 2 diabetes), following the current treatment guidelines may be the best option until more evidence on their CE is available.

The CEs of 43 ADA-recommended interventions were evaluated. Of these, 25 were in the "strong" evidence category. This number would probably have been larger if we had used less stringent criteria to define evidence as being strong. For example, evidence on the CE of using metformin to prevent type 2 diabetes among high-risk individuals was considered "supportive" in our current classification even though the efficacy of the intervention was shown by well-conducted multi-center large clinical trials in different country settings (71,72), and its CE was evaluated by "excellent" CE studies (25,34). This intervention was considered to have supportive evidence because it ranked lower in the ADA recommendations (7).

Among all the interventions considered, evidence for the CE of primary prevention through intensive lifestyle modification was the strongest regarding the quantity and quality of the CE studies and efficacy data. Several well-conducted clinical trials have shown the efficacy of intensive lifestyle modification in preventing diabetes in different country settings, such as the U.S. DPP (71), Finnish Diabetes Prevention Study (73), China Da Qing Diabetes Prevention Study (74), and Indian DPP (72). Eight cost-effectiveness studies (seven of them rated as excellent quality) have been conducted by different groups in different countries based on data from these well-conducted clinical trials (15,25,34,36,41,50,59,66). The results from these studies consistently showed that intensive lifestyle modification in persons with impaired glucose tolerance was cost saving or very cost-effective in the long run (15,25,34,36,41,50,59). Even in a short-term and one-on-one consulting setting, the intervention remained cost-effective (66). The intervention would be more cost-effective than existing studies show if the cost of the lifestyle intervention could be reduced. This might be achieved by changing the setting in which the inter-

vention is provided. Only one study found a DPP-like intervention to be marginally cost-effective (25). Even in this study, however, the intervention would have been very cost-effective (23) if done in the type of group environment that is most likely in a real-world setting. A group-based, DPP-style lifestyle intervention partnership with the YMCA costs $275 to $325 per participant in the first year compared with $1,400 in the one-on-one setting of the DPP trial (75). Preventing diabetes, in particular by lifestyle modification, is not only effective but also a very efficient use of health care resources.

The CE of an intervention can vary by country setting. For example, intensive glycemic control (with a goal A1C level of 7%) in type 2 diabetic patients diagnosed at 25 years of age and older was marginally cost-effective in the U.S. but very cost-effective in other developed countries. Although the efficacy data of all studies of intensive glycemic control in type 2 diabetic patients were based on the same UKPDS data, the cost data were based on how residents of the different countries used health services and the cost of those services. The incremental cost of intensive glycemic control was much higher in the U.S. than in the U.K. because of different practice patterns. Patients outside the U.S. did not receive diabetes disease management services and had less frequent self-testing and physician office visits than their U.S. counterparts at the time these studies were conducted. If using the health services as described in the UKPDS setting but with the U.S. cost of these services, the CE of the intensive glycemic control in the U.S. would resemble that of other developed countries.

Future economic evaluation of diabetes interventions should consider the following. First, more studies are needed to evaluate the CE of interventions that fell in the "supportive" evidence category. For studies with weaker efficacy data, further efficacy studies are needed. Second, there are also 38 interventions recommended by the ADA but they have not been evaluated for their CE or the studies did not meet the inclusion criteria for our review (list is available upon request from the authors). The CE of these interventions should be assessed. Third, more CE studies are needed that address interventions in real-world settings. For example, few studies considered attrition rate, noncompliance, and dropout rates in evaluating CE. Fourth, more studies are needed to evaluate the CE of public policy changes. Only two studies evaluated public insurance reimbursement of ACEI therapy and both found this intervention to be cost saving. Finally, the CE of multiple interventions needs to be evaluated. In most real-world settings, patients receive multiple interventions simultaneously. Nearly all previous studies only evaluated the CE of a single intervention.

This review's conclusions should be used with caution. First, our conclusions are based on available information up to May 2008. More studies have been published since then. In addition, data on both the effectiveness and cost of an intervention could have changed since the time the original study was conducted. Using the newly available data could change our current conclusion. For example, in our review, we concluded that the CE of optimal age to start screening for type 2 diabetes was uncertain. A recently published CE study on age at initiation of screening for type 2 diabetes, released after our analysis was complete, might change that conclusion (76). Another example is the large decrease in costs for metformin, statins, and ACEIs. Studies that evaluate CE using current costs might look more favorably on interventions that include statins and ACEIs than those reported here. Reevaluating the costs and benefits of these interventions, using current-day costs, is beyond the scope of this study. Second, when using the results and conclusions of our review, readers need to be certain that terms are understood correctly. For example, "intensive insulin treatment" in our review meant "multiple insulin injection" or "insulin infusion." Developments in medical technology might make continuous glucose monitoring systems, which record blood glucose levels throughout the day and night, more common. Drugs such as TZD Byetta and Gliptin, not available at the time covered by this review, are increasingly used to achieve intensive glycemic control. The CE of treatment with these and other new devices and drugs are unknown. New CE analyses are needed for these new interventions. Third, not everyone will necessarily agree with our classification criteria. Different classification criteria might have changed some conclusions. Fourth, most of the CE studies are based on simulation modeling. Although good-quality simulation modeling can provide information at a much lower cost than clinical trials, models are based on assumptions and represent a simplification of—and therefore might depart from—reality. Fifth, these CE studies use different methods, which could account for some differences in CERs. If the results from different models were consistent, we would have more confidence in the conclusion on the CE of the intervention. Sixth, we used the same threshold for the classification of the CE of interventions regardless of whether the ICERs were expressed as dollars per LYG or dollars per QALY, although they are different measures. The studies that reported costs per LYG did not incorporate the impact of the intervention on quality of life into the analysis. If they did, the cost per QALY could be higher, lower, or the same depending on the relative magnitude of the health benefit of the intervention on quality of life. Seventh, the interpretation of the CE of an intervention must include consideration of variables such as study population, comparison interventions, and country setting. Lastly, our recommendations are based on the CE of the interventions and not their efficacy; therefore, these recommendations are not necessarily the same as the ADA recommendations.

The importance of CE in decision making should not be overstated. CE is only one aspect to consider. CE analysis does not address the distribution of costs and the benefits of an intervention, societal or personal willingness to pay, social and legal aspects, or ethical issues associated with each intervention. All these aspects are important in formulating public policy. The good news is that our study shows that a majority of the recommended diabetes interventions provide both health benefits and good use of health care resources.

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