Cost-effectiveness of Screening for Coronary Artery Disease in Asymptomatic Patients with Type 2 Diabetes and Additional Atherogenic Risk Factors

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OBJECTIVE: Screening for coronary artery disease (CAD) in asymptomatic diabetic patients with two additional atherogenic risk factors has been recommended by the American College of Cardiology/American Diabetes Association, but its cost-effectiveness is yet to be determined. The present study aims to evaluate the cost-effectiveness of screening and determine acceptable strategies.

DESIGN: Cost-effectiveness analysis using a Markov model was performed from a societal perspective to measure the clinical benefit and economic consequences of CAD screening in asymptomatic men with diabetes and two additional atherogenic risk factors. We evaluated cohorts of patients stratified by different age groups, and 10 possible combination pairs of atherogenic risks. Incremental cost-effectiveness of no screening, exercise electrocardiography, exercise echocardiography, or exercise single-photon emission-tomography (SPECT) was calculated. Input data were obtained from the published literature. Outcomes were expressed as U.S. dollars per quality-adjusted life-year (QALY).

MEASUREMENTS AND MAIN RESULTS: Compared with no screening, incremental cost-effectiveness ratio of exercise electrocardiography was \$41,600/QALY in 60-year-old asymptomatic diabetic men with hypertension and smoking, but was weakly dominated by exercise echocardiography. Exercise echocardiography was most cost-effective, with an incremental cost-effectiveness ratio of \$40,800/QALY. Exercise SPECT was dominated by other strategies. Sensitivity analyses found that results varied depending on age, combination of additional atherogenic risk factors, and diagnostic test performance.

CONCLUSIONS: Incremental cost-effectiveness ratio of CAD screening in asymptomatic patients with diabetes and two or more additional atherogenic risk factors is shown to be acceptable from a societal perspective. Exercise echocardiography was the most cost-effective strategy, followed by exercise electrocardiography.

KEY WORDS: silent myocardial ischemia; ischemic heart disease; cost-effectiveness analysis; screening strategy; diabetes mellitus.

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Coronary artery disease (CAD) is the major cause of morbidity and mortality in patients with diabetes.^{1,2} More than half of all diabetic patients die from problems associated with coronary arteries.^{3,4} In diabetic patients, CAD is usually diagnosed at an advanced stage, with a correspondingly dismal prognosis.^{5,6} The delay in diagnosing CAD is due partly to the presence of silent myocardial ischemia, which is more frequently recognized angiographically in diabetic than nondiabetic patients. The reported prevalence of silent myocardial ischemia ranges from 10% to 60% in diabetic patients, possibly reflecting the differing numbers of atherogenic risk factors in differing studies.⁷⁻¹¹

The American College of Cardiology/American Diabetes Association recommends that cardiac testing be done irrespective of the presence of CAD symptoms in diabetic patients with two or more atherogenic risk factors, in view of the high prevalence of CAD.¹² Various screening methods are available including exercise electrocardiography, exercise echocardiography, and exercise single-photon emission-tomography (SPECT). From the point of view of health care policy, the value of a screening strategy is determined not only by diagnostic accuracy and risk but also by the cost associated with it. Sox et al. evaluated the cost-effectiveness of screening asymptomatic patients for CAD, and concluded that the effect of exercise testing was too small to justify screening in healthy persons.¹³ In high-risk patients with diabetes, however, the cost-effectiveness of screening strategies for CAD in patients has not yet been evaluated.

We have therefore performed a cost-effectiveness analysis of different screening strategies from the societal perspective, using a Markov model to examine the benefits and costs of screening for CAD in asymptomatic patients with diabetes and two additional atherogenic risk factors.

METHODS

We evaluated cohorts of patients stratified by age (50, 55, 60, 65, and 70 years of age), and 10 possible pairs of atherogenic risk factors (hypertension, smoking, low-density lipoprotein [LDL] level above 160 mg/dl, high-density lipoprotein [HDL] level below 35 mg/dl, and proteinuria) that are recommended by American College of Cardiology/American Diabetes Association.¹² The base-case cohort were asymptomatic men with type 2 diabetes mellitus and two additional atherogenic risk factors. Cohn has classified silent ischemia into 3 categories: 1) asymptomatic ischemia without a history of angina/myocardial infarction (MI); 2) asymptomatic ischemic episode with a history of angina; and 3) asymptomatic ischemia with a history of MI.¹⁴ We

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define silent myocardial ischemia as the first of these categories, because individuals suffering the second or third were taken already to be receiving specific medication or intervention, and not to benefit from screening. Because most of the available data relate to men of around 55 years of age with hypertension and smoking,¹ base-case analysis was conducted on this patient group. A Markov model was used to estimate the lifetime costs and the quality-adjusted life expectancy.¹⁵ We set the time horizon at 30 years because any effects of treatment should be apparent by 85 years of age.

DATA 3.5.9 software (TreeAge Software, Inc., Williamstown, Mass) was used to calculate costs and outcomes. Costs were estimated from a societal perspective, and outcomes were measured in quality-adjusted life-years (QALYs). We then calculated the incremental cost-effectiveness for all competing strategies. The cost-effectiveness ratio for SPECT compared with echocardiography, for example, is the difference between costs of the two strategies divided by the difference between the QALYs produced by each. A strategy that was less effective and had a higher incremental cost-effectiveness ratio than another strategy was ruled out by weak dominance. A weakly dominated strategy was retained in the list and its cost-effectiveness ratio compared with the next strategy was put in parentheses in the tables, but the incremental cost-effectiveness ratios of the dominant strategy were recalculated using data other than the weakly dominated strategy. This method allowed us to examine whether extending therapy given a new indication is cost-effective. Components of effects or costs that did not differ among the alternative strategies (e.g., giving up smoking) were not evaluated in detail, because we employed incremental cost-effectiveness analysis.

Decision-analytic Model

We assumed that a diagnostic screening test was performed once only, at the first stage. Screening strategies included: 1) no screening; 2) exercise electrocardiography followed by coronary angiography (CAG) if positive; 3) exercise echocardiography followed by CAG if positive; and 4) exercise SPECT followed by CAG if positive. Patients with negative screening test results did not undergo CAG.

Our model was a revised version of the Coronary Heart Disease Policy Model proposed by Weinstein et al.¹⁶ We first simplified the model by incorporating cardiac arrest (CA) into death state, in view of the very low survival rates associated with CA. We then considered the states associated with coronary artery bypass grafting (CABG) and post-percutaneous transluminal coronary angioplasty (PTCA). Because of the nature of our study, we divided the angina state into silent ischemia and symptomatic ischemia. The original 12 CAD states were thereby modified and reduced to 7 CAD states: normal, silent ischemia, symptomatic ischemia, history of MI, post-PTCA, post-CABG, and death. An individual in the normal state at the time of the initial screening may remain in the normal state or move to the

CAD event state in the next year, with probabilities determined by demographic and epidemiological factors such as age, gender, and other atherogenic risk factors, including diabetes mellitus. These transition probabilities were calculated using Framingham data estimated from equations developed by Anderson et al.¹⁷ The method used to calculate the transition probabilities is described in detail in Appendices I to III (available online at www.jgim.org). Figure 1 shows a schematic representation of the decision tree.

If an individual in the normal state experiences a first CAD event, the event would be either myocardial ischemia (symptomatic or silent) or a non-fatal MI. Probabilities of myocardial ischemia or MI were assigned to these events.¹⁸ The probability that initial myocardial ischemia was asymptomatic was estimated from a review of the literature dealing with silent ischemia in patients with diabetes (Table 1).¹⁹ Those with myocardial ischemia then had the probability of falling in a particular disease category (1-, 2-, 3-vessel, or left-main trunk disease) in a certain age group assigned from the Coronary Artery Surgery Study (CASS) registry.²⁰

The following assumptions were made concerning medications/interventions in this model: 1) patients with negative screening test results received no specific therapy; 2) all patients received one 325 mg-tablet of aspirin per day (U.S. Preventive Service Task Force Recommendation); 3) patients received simvastatin (40 mg/day) irrespective of baseline LDL levels based on the latest studies or guidelines^{21,22}; 4) management after angiography was based on the anatomic pattern of vessel obstruction, and patients without vessel obstruction on angiography received no specific treatment; 5) patients with 1- or 2-vessel CAD on angiography underwent PTCA; 6) patients with 3-vessel or left-main trunk disease (LMD) on angiography underwent CABG; 7) patients who developed restenosis after PTCA underwent PTCA only one more time, so that PTCA was performed not more than twice—if they subsequently experienced restenosis, they underwent CABG; 8) patients with myocardial infarction developed relevant symptoms and received the appropriate treatment; 9) patients with silent myocardial ischemia did not receive specific anti-anginal therapy; and 10) PTCA reduced late MI in those with 1- or 2-vessel disease.

Baseline Prevalence of Coronary Artery Disease

We assumed that the prevalence of CAD in asymptomatic diabetic patients is determined by atherogenic risk factors age and gender to the same extent as in the general population; this was estimated from data provided by a review of the literature.¹⁹ The prevalence of CAD in each risk state was calculated from the prevalence of CAD in the general population and the odds ratio for associated atherogenic risk factors for CAD, stratified by age and gender (Appendix II, available online at www.jgim.org). The baseline prevalence of CAD in different age groups of diabetics was derived from the Third National Health and

FIGURE 1. A Markov model of screening strategies for CAD in diabetic patients with additional atherogenic risk factors. Patients with silent myocardial ischemia detected by initial screening and patients with symptomatic myocardial ischemia developing in the years following received PTCA or CABG according to the number or location of their diseased vessels. Patients with false negative results by screening tests and those with silent myocardial ischemia developing in the years following do not receive specific therapy. ECG, electrocardiography; UCG, echocardiography; SPECT, single-photon emission-tomography; LMT, left-main trunk disease; CAD, coronary artery disease; MI, myocardial infarction; PTCA, percutaneous transluminal coronary angioplasty; CABG, coronary artery bypass grafting.

Nutrition Examination Survey (NHANES III).²³ We then calibrated the prevalence data to match the estimated number of patients with stable angina (16,500,000) according to the American College of Cardiology/American Heart Association, as NHANES data are self-reported and likely to be influenced by self-reporting bias.^{24,25} Relative risks were taken from the published literature, and were estimated by multivariate logistic regression using NHANES III data.^{26,27} Table 1 shows the baseline prevalence of CAD.

Number of Diseased Vessels

The extent of CAD is expressed by the number of diseased vessels (0 to 3), with a separate category for left-main trunk disease as revealed by CAG. Probability data for different numbers of diseased vessels and LMD stratified by age were derived from the CASS registry.²⁰

Characteristics of Screening Tests

The performances of screening tests were obtained from a meta-analysis of diagnostic tests, and are shown in Table 1. The sensitivity and specificity of exercise electrocardiography for detecting CAD were obtained from data pooled from 150 studies²⁸; sensitivity and specificity of exercise echocardiography and exercise SPECT came from another meta-analysis, based on a summary of receiver operating characteristics (ROC) curve analysis.²⁹

Complications of Intervention

We made the following assumptions concerning short-term sequels to intervention. CABG was associated with a 0.1% probability of death and a 0.06% of nonfatal MI, regardless of the extent of CAD.³⁰ PTCA was associated with mortality rates of 0.2% in 1-vessel disease and 0.9% in 2-vessel disease; the mortality rate of nonfatal MI was 3.5% in 1-vessel disease and 5.2% in 2-vessel disease.³¹ CABG was associated with a mortality rate of 3.2%, and the probability of nonfatal MI was 7.0%.³²⁻³⁴

Long-term Prognosis

We assumed that the prognosis of patients with asymptomatic ischemia is the same as for patients with symptomatic ischemia.^{16,35-38} We estimated the cycle-specific mortality in each health state based on a declining exponential approximation to life expectancy (DEALE; Appendix III, available online at www.jgim.org).³⁹⁻⁴¹ This method takes the mortality hazard as constant over a certain period of time (1 year in our analysis), and thus the survival probability declines exponentially over a certain period of time. Mortality rates were then determined according to patient characteristics (e.g., age, gender, extent of CAD, and treatment) using all-cause mortality from U.S. life tables, together with the standardized mortality ratio for patients with diabetes, the relative mortality ratio for the specific extent of disease from the CASS registry, and the mortality risk

Table 1. Baseline Values and Ranges in Sensitivity Analysis

Variables	Baseline Value	Lower Range	Upper Range	Reference
Prevalence of asymptomatic ischemia in base case (estimated)*	0.39	0.27	0.51	27, 38
Annual incidence of CAD in base case, per 1,000 (estimated)*	23.4	16.4	30.4	17
Proportion of silent ischemia in patients with myocardial ischemia [†]	0.4	0.38	0.62	19
Diagnostic performance of screening tests [‡]				
Exercise electrocardiography				
Sensitivity	0.68	0.23	1	28
Specificity	0.77	0.17	1	28
Exercise echocardiography				
Sensitivity	0.85	0.71	0.97	29
Specificity	0.77	0.37	0.96	29
Exercise SPECT				
Sensitivity	0.87	0.71	0.97	29
Specificity	0.64	0.27	1	29
Mortality risk reduction by CABG, % [‡]				
1- or 2-vessel disease	15	0	49	42
3-vessel disease	48	32	64	42
Left-main trunk disease	67	43	87	42
Risk reduction in late myocardial infarction with revascularization, %*				
PTCA	17	0	22	49
CABG	42	29	55	49
Risk reduction in the incidence of CAD by aspirin (primary prevention), %*	15	11	20	43
Risk reduction in late CAD events by aspirin (secondary prevention), %*	31	21	41	43
Risk reduction in all-cause mortality by aspirin (secondary prevention), %*	28	21	36	43
Risk reduction in the incidence of CAD by simvastatin (primary prevention), %*	25	18	33	21
Annual risk for revascularization by initial treatment and extent of disease* [§]				
Nonspecific therapy (1-vessel disease)	0.010	0.001	0.022	46, 50
Nonspecific therapy (2-vessel disease)	0.042	0.028	0.056	46, 50
Nonspecific therapy (3-vessel disease or left-main trunk disease)	0.075	0.061	0.089	46, 50
PTCA	0.036	0.026	0.046	29, 51
CABG	0.018	0.011	0.025	50, 51

* Ranges based on $\pm 30\%$ of base-case estimates. (Note: lower range of risk reduction in late myocardial infarction with PTCA was set to 0%.)

[†] Ranges based on reported proportions in the literature.

[‡] Ranges based on the actual range among original studies in a meta-analysis.

[§] The percentage of revascularizations that were CABG were as follows: 16% (1-vessel disease and initial nonspecific therapy); 58% (2-vessel disease and initial nonspecific therapy); 87% (3-vessel disease or left-main trunk disease and nonspecific therapy); 22% (initial PTCA); and 7% (initial CABG).

SPECT, single-photon emission-tomography; CAD, coronary artery disease; MI, myocardial infarction; PTCA, percutaneous transluminal coronary angioplasty; CABG, coronary artery bypass grafting.

reduction by medication or interventions.^{20,21,38,42–44} The standardized mortality ratio for patients with diabetes was the ratio of the all-cause mortality rate in persons with diabetes to the mortality rate of the general population. We used 1.5 as the standardized mortality ratio derived from the population-based Framingham Heart Study.⁴⁵

The mortality risk ratio for the extent of CAD and mortality risk reduction by CABG (the proportion of coronary artery disease-related mortality reduced by surgery) were derived so as to match the mean survival time at 10 years that was reported in a systematic review of 7 CABG trials.⁴² We assumed that the risk reduction by CABG persisted for 10 years, because the initial efficacy of therapeutic interventions usually has a near-linear decline. We also assumed that the efficacy of PTCA in patients with single- or double-vessel disease was the same as that of CABG.^{46,47} For the effect of medications, a 15% reduction for aspirin and 25% reduction for simvastatin in the relative risk for the incidence of major coronary events were applied to the incidence of

CAD in our model; these data were derived from studies conducted in primary prevention settings.^{21,44} In secondary prevention settings, a 31% reduction in the odds of nonfatal MI derived from pooled trials was applied to nonfatal MI and to death from chronic coronary disease.⁴³ Because the median follow-up time in the secondary prevention trials for high-risk patients was 3 years, the benefit of aspirin was taken to continue for 3 years.⁴⁸

We took the rates of nonfatal MI and revascularization to vary depending on the initial treatment, and assumed that the risks of subsequent nonfatal MI, PTCA, or CABG depend on the extent of the CAD and the type of initial treatment (Table 1).^{46,47,49–51}

Costs and Discounting

All cost estimates are shown in Table 2. For diabetes care, we used the costs of conventional diabetes control based on the U.S. scenario by the CDC (Centers for Disease

Table 2. Costs and Health Utility Estimates

Variables	Baseline Value	Lower Range	Upper Range	Reference
Costs (2003 \$)*				
Exercise electrocardiography	140	98	182	53
Exercise echocardiography	334	234	434	53
Exercise SPECT	730	511	949	53
Coronary angiography	6,035	4,225	7,846	53
PTCA	15,884	11,119	20,650	53
CABG	42,125	29,487	54,762	53
Annual cost				
Symptomatic myocardial ischemia	1,224	857	1,591	56
History of MI	1,431	1,002	1,860	56
Conventional diabetes care	1,113	779	1,447	52
Simvastatin	1,293	905	1,680	58
Aspirin	16	11	21	48
One-time cost				
Symptomatic myocardial ischemia	2,992	2,094	3,889	56
MI death	23,843	16,690	30,996	56
MI survival	21,161	14,813	27,509	56
Health utility [†]				
Symptomatic myocardial ischemia (SG) [‡]	0.947	0.663	1.0	61
History of MI (TTO) [‡]	0.880	0.616	1.0	62

* Ranges for cost estimates represent $\pm 30\%$ of baseline estimate.

[†] Ranges for health utility based on $\pm 30\%$ of base-case estimates.

[‡] SG, standard gamble; TTO, time tradeoff.

SPECT, single-photon emission-tomography; CAD, coronary artery disease; MI, myocardial infarction; PTCA, percutaneous transluminal coronary angioplasty; CABG, coronary artery bypass grafting.

Control) Diabetes Cost-effectiveness Group. This included drug costs based on the experience of the United Kingdom Prospective Diabetes Study (UKPDS) and costs of outpatient visits, self-testing, and care management based on U.S. clinical practice.⁵² We used the costs of diagnostic tests and interventions based on the other cost-effectiveness model of CAD, and verified the original citations. Exercise test costs were obtained from Medicare-allowed charges, including both technical and professional fees. Hospital costs for coronary angiography and revascularization were taken from Medicare administrative data, and professional costs associated with cardiac interventions came from the Medicare schedule.^{53–55} Annual costs of outpatient treatment for CAD were taken from the published literature that estimated the direct medical costs of CAD.^{56,57} The cost of aspirin was derived from the cost-effectiveness model for these drugs,⁴⁸ and the cost of simvastatin was calculated by using the average wholesale prices⁵⁸; we then adjusted for the adherence rate of the primary prevention trials.^{21,44,59} The costs of patient travel, waiting, and treatment time associated with office visits were also estimated using average hourly earnings of employed persons reporting earnings from the Current Population Survey in the United States.⁵⁵ We did not assign any CAD-specific costs for silent myocardial ischemia.

All costs were converted to 2003 U.S. dollars using the medical care component of the Consumer Price Index. All costs and years of life were discounted at 3% per year to

reflect time preference, because people are more likely to prefer having money and material goods sooner rather than later.⁶⁰

Health Utility

Health utility values, running between 1 for perfect health and 0 for death, were used to calculate QALYs for patients. The utilities for symptomatic myocardial ischemia and myocardial infarction were based on information from a literature search. Health utilities for an individual who experienced angina and MI are shown in Table 2. The health utility for symptomatic myocardial ischemia was a weighted average of the two most severe groups with angina, based on the data obtained from the literature.^{61,62} All other live statuses were set to 1 in health utility.

Sensitivity Analysis

We performed one-way sensitivity analyses on all of the variables within clinically plausible ranges. The ranges used for this are shown in Table 1. Ninety-five percent confidence intervals (CI) were used as the range of the variables in the sensitivity analysis where applicable; otherwise a $\pm 30\%$ range was used. There were two exceptions: we used the range of sensitivities and specificities of diagnostic tests reported in the meta-analysis because the 95% CIs reported

in the meta-analysis were extremely narrow^{28,29}; and we allowed the lower range of risk reduction in late MI with PTCA to be 0%, because in diabetics with asymptomatic 1- or 2-vessel disease there is little evidence to support the effect of PTCA.

The results of one-way sensitivity analysis on diagnostic test performance could be misleading, because sensitivity and specificity are liable to move at the same time depending on the positivity threshold, that is, the sensitivity increases and the specificity falls when we take lenient positivity criteria (smaller ST depression as positive). We therefore conducted two-way sensitivity analysis on diagnostic test performance. We plotted 1 – specificity on the x-axis and sensitivity on the y-axis for comparison with the ROC curve. Straight lines indicate possible thresholds for allocating health care resources. For a particular cost-effectiveness threshold, points to the upper left of the lines indicate that these tests have a lower cost-effectiveness ratio relative to no screening than that depicted by the line. The asterisk indicates the combination of sensitivity and specificity for the base case. The point corresponding to sensitivity and 1 – specificity was expected to move around along the ROC curve through the asterisk, from the point (x = 0, y = 0) to the point (x = 1, y = 1) as the positivity criterion becomes lenient. For the usual diagnostic tests, the combination of sensitivity and specificity failed to take the point below the straight line that connects the point (x = 0, y = 0) and the point (x = 1, y = 1).

Analyses were also conducted for cohorts of different ages and/or different pairs of additional atherogenic risk factors. We also evaluated the effect of the discounting rate in the range recommended by the Panel on Cost-effectiveness in Health and Medicine (0% to 5%).⁶⁰

RESULTS

Baseline Analysis

Table 3 shows the quality-adjusted life expectancy, lifetime cost, and incremental cost-effectiveness ratio in asymptomatic 55- and 60-year-old diabetic men with hypertension and smoking. Compared to no screening strategy, the incremental cost-effectiveness ratio of exercise electrocardiography was \$93,500/QALY and that of exercise echocardiography was \$88,400/QALY in 55-year-old men. The incremental cost-effectiveness ratio of exercise electrocardiography was within the acceptable range (\$41,600/QALY), but was weakly dominated by that of exercise echocardiography (\$40,800/QALY) in 60-year-old men. The exercise SPECT strategy had higher cost and smaller benefit than exercise echocardiography, and was therefore dominated by other strategies.

Patients with Different Characteristics

The incremental cost-effectiveness varied depending on age and the pairing of additional atherogenic risk factors. The cost-effectiveness of exercise echocardiography relative to a no screening strategy was sensitive to the age of patients at screening. It fell from \$327,400/QALY to \$25,600/QALY as the age at the initial screening rose from 50 to 70 years (Fig. 2). Figure 3 shows incremental cost-effectiveness ratios for exercise echocardiography and exercise electrocardiography compared with no screening for two age groups (55 and 60 years of age), and the 10 possible pairs of additional atherogenic risk factors. The incremental cost-effectiveness ratio of exercise echocardiography

Table 3. Quality-adjusted Life Expectancy, Cost, and Cost-effectiveness Ratios for Asymptomatic 55- and 60-Year-old Diabetic Men with Hypertension and Smoking

Screening Strategy	Expected Value		Incremental Value		Incremental Cost-effectiveness Ratio*
	Cost	QALYs	Cost	QALYs	
	\$	Y	\$	y	\$/y
55-year-old					
No screening	135,447	11.754			
Exercise electrocardiography	142,179	11.826	(6,732)	(0.072)	(93,500)
Exercise echocardiography	143,847	11.849	8,400	0.095	88,400
Exercise SPECT	144,806	11.841			Dominated
60-year-old	Y	\$	y	\$/y	\$
No screening	123,301	9.911			
Exercise electrocardiography	129,617	10.063	(6,316)	(0.152)	(41,600)
Exercise echocardiography	131,180	10.104	7,879	0.193	40,800
Exercise SPECT	132,129	10.100			Dominated

* Incremental cost-effectiveness ratios for each strategy are calculated compared with the next strategy other than the weakly dominated/dominated strategy shown in the table, and are rounded to the nearest \$100. In this case, the incremental cost-effectiveness ratio of electrocardiography was weakly dominated by echocardiography, and thus was put in parentheses. Incremental cost-effectiveness ratio of echocardiography was calculated compared with no screening. (Note: cost-effectiveness ratios calculated directly by quality-adjusted life expectancies and costs from the table may differ due to rounding.)

SPECT, single-photon emission-tomography; QALY, quality-adjusted life-year.

FIGURE 2. Cost-effectiveness of screening strategies relative to no screening strategy as a function of age at screening. Triangles (Δ) represent exercise electrocardiography compared with no screening; plus signs (+) represent exercise echocardiography compared with no testing.

compared with no screening ranged from \$83,700/QALY (HTN [hypertension]/low HDL) to \$126,300/QALY (high LDL/proteinuria) in 55-year-old men, depending on the additional atherogenic risk factors. In 60-year-old men, our model was fairly insensitive to the difference between pairs of risk factors; the incremental cost-effectiveness ratio of exercise echocardiography compared to no screening ranged from \$38,600/QALY (HTN/low HDL) to \$50,500/QALY (high LDL/proteinuria), and from \$39,400/QALY to \$53,700/QALY (high LDL/proteinuria) for exercise electrocardiography compared to no screening.

Sensitivity Analysis

We performed sensitivity analyses on other variables in 60-year-old men, because the incremental cost-effectiveness ratio was within the acceptable range in this cohort. Our results were sensitive to sensitivity and specificity of diagnostic tests in one-way analysis, but were not sensitive to the discount rate, the cost of CABG, the mortality risk reduction by CABG or PTCA, the risk reduction of MI by CABG or PTCA, the cost of screening tests, the proportion of patients with silent myocardial ischemia, or the health utility of CAD.

Our results were also sensitive to diagnostic test performance in two-way sensitivity analysis (Fig. 4). For both exercise echocardiography and electrocardiography, the incremental cost-effectiveness ratio exceeded \$50,000/QALY if the sensitivity was very high, so that the specificity was very low. The incremental cost-effectiveness for echocardiography was always below \$60,000/QALY for any combination of sensitivity and specificity; in the case of electrocardiography, the incremental cost-effectiveness could exceed \$60,000/QALY, but this is very unlikely

FIGURE 3. Cost-effectiveness ratio for alternative patient cohorts. Squares ($\square$) represent SPECT compared with no screening; triangles (Δ) represent exercise electrocardiography compared with no screening; and plus signs (+) represent exercise echocardiography compared with no screening. SPECT, single-photon emission tomography; QALY, quality-adjusted life expectancy; LDL, low-density lipoprotein; HDL, high-density lipoprotein; HTN, hypertension.

because the cost-effectiveness threshold of \$60,000/QALY was close to the straight line connecting ($x = 0$, $y = 0$) to ($x = 1$, $y = 1$), below which no combination of sensitivity and specificity can fall.

DISCUSSION

No studies currently exist of the long-term costs and the effectiveness of CAD screening strategies in asymptomatic patients with diabetes. We have therefore developed a decision-analytic model to conduct cost-effectiveness analysis using published data to simulate patients in diverse situations. Our results suggest that screening of asymptomatic 60-year-old diabetic men with hypertension and smoking for CAD is cost-effective (relative to no screening). Exercise echocardiography dominated over electrocardiography and exercise SPECT. The initial screening cost advantage might be partially offset by the subsequent costs of medical care for patients with silent myocardial ischemia who eluded this screening test, although exercise electrocardiography is less expensive than exercise echocardiography. Its incremental cost-effectiveness ratio, however,

FIGURE 4. Two-way sensitivity analysis of the diagnostic performance of exercise electrocardiography and exercise echocardiography. Results of the two-way sensitivity analysis of the sensitivity and specificity of exercise electrocardiography and echocardiography, and the acceptable cost-effectiveness threshold for 60-year-old diabetic men with hypertension and smoking. We plotted $1 - \text{specificity}$ on the x-axis and sensitivity on the y-axis. Lines indicate four possible thresholds for allocating health care resources, and were confined to the actual data of sensitivity and specificity. For a particular cost-effectiveness threshold, points to the top left of the lines indicate that these tests, compared with no screening, have a lower cost-effectiveness ratio than that depicted by the line. The asterisks (*) indicate the pair of sensitivity and specificity for the base case; incremental cost-effectiveness of both tests was lower than \$50,000 compared with no screening. Plus signs (+) indicate other possible examples; incremental cost-effectiveness of both tests was between \$50,000 and \$60,000 compared with no screening.

was in the acceptable range in cases where exercise echocardiography would not be available for practical reasons. Exercise SPECT was less cost-effective than the other two screening strategies, and thus dominated the other strategies as its cost was disproportionately higher than

that for exercise echocardiography in spite of its favorable life-year saving effect.

Sox et al. suggested that the cost-effectiveness of exercise electrocardiography screening of CAD in 60-year-old men with one or more risk factors was \$20,504 per additional year of life, and concluded that it might be cost-effective in a high-risk population, though the decision is close.¹³ This conclusion would support our results, though we could not directly compare this with our results because that model did not consider utility, time preference, or the high mortality risk ratio for diabetics, and was not adjusted for the doubled consumer price index since then. The present results should also be interpreted in the context of other generally accepted screening strategies for various diseases. For example, screening mammography for women aged 50 years or older costs from \$3,400/QALY to \$84,830/QALY; annual screening for cervical cancer for women aged 21 years or older is \$50,000/QALY; and hypertension screening for asymptomatic 20-year-olds costs \$48,000/QALY for men and \$87,000/QALY for women.⁶³⁻⁶⁵ Thus, screening for CAD with exercise echocardiography in asymptomatic diabetic men with hypertension and smoking seems to be acceptable from a societal perspective.

Our model was sensitive to the age of patients and different pairs of additional atherogenic risk factors. Any screening strategy generally becomes more cost-effective by targeting groups of patients with a higher prevalence and lifetime incidence of CAD. In the present work, in a hypothetical cohort of 60-year-old diabetic men with proteinuria and high LDL, the incremental cost-effectiveness of exercise electrocardiography was \$53,400/QALY, but in 60-year-old diabetic men with HTN and smoking it falls to \$41,000/QALY.

Our model was also sensitive to diagnostic test performance. We explained the results of two-way sensitivity analysis in relation to the ROC curve; the sensitivity and specificity combination pair moves along the curve depending on the test threshold. By relaxing the threshold the point moves toward the right top; by tightening the threshold it moves to the bottom left. There are also other factors that could shift the ROC itself toward the point ($x = 0$, $y = 1$), such as younger age and high prevalence of disease, or away from this point.^{66,67} We should therefore interpret our results in the context of these factors. Our results suggest that the incremental cost-effectiveness ratio exceeds \$50,000/QALY if the sensitivity and specificity combination is close to the point ($x = 1$, $y = 1$). Our result was robust in terms of this point being so far from that of the base case, but we should realize the situations where the cost-effectiveness ratio is likely to fall into an unacceptable range; relaxing the positivity criteria (high-sensitivity test; e.g., use smaller ST depression as positive for exercise electrocardiography) makes the point shift to the top right; the ROC curve itself shifts toward the diagonal line if patients are older and/or at high risk. A test of high sensitivity is usually used for "screening," and a high-specificity test for "confirming" diagnoses.⁶⁶ From the standpoint of resource allocation, we

should therefore avoid a "screening" approach with very high sensitivity by tightening the positivity criteria (e.g., use larger ST depression as positive for exercise electrocardiography), especially when an older and/or lower risk population is being tested.

Assumptions were made in order to simplify the complex decision-making process of the real clinical setting and develop an understandable model. The present results must therefore be interpreted in light of the limitations of using heterogeneous data sources and these simplifying assumptions. For example, we did not incorporate the effects of intensive diabetes control, which should be encouraged when CAD is detected in asymptomatic patients with diabetes. In view of the increased morbidity and mortality from CAD in these patients, and the striking influence of diabetes mellitus observed in large-scale trials,^{68,69} the cost-effectiveness of CAD screening might be underestimated in our model.

Cost-effectiveness analyses of the present type assist not only in assessing the economic impact of a significant intervention, such as screening for CAD in patients with diabetes, but also in identifying areas of uncertainty to improve decision making. The present analysis has exposed uncertainty surrounding probability estimates. First, it was assumed that the prevalence of CAD in asymptomatic diabetic men and two other atherogenic risk factors was comparable to that in symptomatic diabetic men with the same atherogenic risk factors. The prevalence of CAD in asymptomatic patients with diabetes and the influence of atherogenic risk factors in these cases were not clear, and the reported prevalence of CAD in asymptomatic patients with diabetes ranged widely depending on the patients' characteristics.¹⁹ Recently, Bacci et al. studied the prevalence of myocardial ischemia using coronary angiography as a reference standard in asymptomatic type 2 diabetic patients having two or more additional atherogenic risk factors.⁷⁰ The prevalence data they found were not directly applicable to our analysis because they were not stratified by atherogenic risk factors, but our estimates were nevertheless broadly similar. Second, the effect of aspirin was assumed to continue for only 3 years, because of the lack of relevant data in secondary prevention of CAD. In cases of longer duration of the beneficial effect of aspirin, an initial screening strategy with exercise echocardiography might be more attractive. Third, we assumed that PTCA reduces MI in asymptomatic patients with 1- or 2-vessel disease, but there is little evidence to support this. We resolved this uncertainty by conducting strict sensitivity analysis assuming that the effect of PTCA was zero, and our model proved to be insensitive to this effect; this area of uncertainty, however, should be resolved for asymptomatic patients tests. Fourth, there were still few good data available on the degree of statins' risk reduction of CAD in those with diabetes in the primary care setting, especially for second-generation statins, such as atorvastatin. We therefore utilized currently available data, but the estimated cost-effectiveness of screening strategies might be less attractive if data on more

potent statins were available and incorporated into our model. Last, we did not specify race/ethnicity, because equations to estimate the incidence of CAD from the Framingham study did not allow us to incorporate the difference between racial and ethnic groups, and there were not sufficient race-specific data on differences in prevalence, therapy/intervention, or disease-specific mortality ratios.¹⁷

We also assumed that the prognosis of patients with asymptomatic ischemia was the same as for those with symptomatic ischemia. The prognostic importance of asymptomatic ischemia is still controversial despite a wealth of data on the subject, perhaps because the term loosely encompasses a wide range of findings from different investigative modalities (e.g., continuous electrocardiography monitoring).^{14,71} To find suitable estimates for our analysis, the prognosis of silent ischemia should be viewed from the standpoint of two groups of patients: those with and without a history of angina/MI, taking diagnostic modalities into account. Romeo et al. directly compared the prognoses between those without asymptomatic ischemia and those in whom it was detected by exercise tolerance testing, and found that the mortality risk ratios between the two groups were not different. Another way is to compare the mortality risk ratios of asymptomatic patients with that of the symptomatic.³⁵ The mortality risk ratios of hypercholesterolemic men with asymptomatic ischemia detected by exercise tolerance tests have been reported in two studies, and these ratios (5.2 and 5.9) are very similar to the mortality risk ratio of 5.9 estimated from the study on symptomatic patients and the U.S. life tables.^{16,36-38} Although these data support our assumption, we believe that further studies are needed to derive more accurate direct evidence by focusing more on the range of subjects and diagnostic modalities.

In conclusion, screening of asymptomatic diabetic men age 60 years or older with two additional atherogenic high-risk factors for CAD should be cost-effective from the societal perspective. Exercise echocardiography offers the most rational use of health care resources, followed by exercise electrocardiography.

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APPENDIX I - Incidence of CAD

Transition probabilities associated with the incidence of CAD were calculated using the methods of the CDC Diabetes Cost-effectiveness Group.⁵² The probability of moving from the Normal state to CAD ($P(\text{CAD})$), adjusted for coronary risk factors, was derived from a Framingham Heart Study. The equations used to calculate $P(\text{CAD})$ are described in Anderson et al. in detail.¹⁷ The probability that initial CAD was MI ($P(\text{MI}|\text{CAD})$) was obtained from Hunink et al. (0.6171 for 35–44 year-old, 0.544 for 45–54, 0.4739 for 55–64, 0.4929 for 65–74, and 0.5101 for 75+).¹⁸

The probability that initial CAD was myocardial ischemia ($P(\text{Myocardial ischemia} | \text{CAD})$) was calculated by substituting the $P(\text{MI}|\text{CAD})$ ($1 - P(\text{MI}|\text{CAD})$), and the probability that initial myocardial ischemia was asymptomatic was assigned; then was multiplied by the probability that myocardial ischemia was in an certain disease category (1-vessel, 2-vessel, 3-vessel, or left main trunk disease) stratified by age groups based on data from the Coronary Artery Surgery Study (CASS) registry.²⁰

APPENDIX II - Prevalence of CAD

The prevalence of CAD (P_0) in a particular age group with a particular risk factor was calculated as follows:

$$P_0(\text{age, risk}) = P_{am} * RR_r$$

In this formula,

- age indicates the age group (55-64, 65-74, 75+)
- risk indicates the type of risk factor
- Pam indicates calibrated age-specific prevalence of CAD in the general male population. The original age- and sex-specific estimates of prevalence of CAD (P_{as}) were obtained from the Third National Health and Nutrition Examination Survey (NHANES III).²³ These self-reported data are liable to be influenced by self-reporting bias²⁴; therefore, to derive the prevalence of CAD (Pam), we calibrated P_{as} to match the estimated number of patients with stable angina (16,500,000) by the American College of Cardiology/American Heart Association,²⁵ using the following formula:

$$P_{am_{ij}} = P_{as_{ij}} * \frac{16,500,000}{\sum P_{as_{ij}} * Pop_{as_{ij}}}$$

In this equation, $P_{as_{ij}}$ denotes the age and sex specific prevalence of CAD from NHANES III ($i=25-34, 35-44, 45-54, 55-64, 65-74, \text{ or } 75+$; $j=\text{male or female}$), $Pop_{as_{ij}}$ denotes the corresponding age and sex specific population (U.S. census 2000), and $\sum P_{as_{ij}} * Pop_{as_{ij}}$ is the sum of the numbers of patients with stable angina in different age and sex groups estimated from NHANES III prevalence data.

RR_r denotes the ratio of the prevalence of CAD for those with a particular risk factor r to those without r . RR_r was estimated from the odds ratio (OR) using the following formula,²⁶ because we could only find ORs relevant to these risk factors:

Values of ORs for HTN (2.1), HDL<35mg/dl (2.1), Smoking (1.7), Proteinuria (1.7), LDL (1.0), and diabetes mellitus (1.4) were obtained from Alexander et al.²⁷

$$RR_r = \frac{OR}{(1 - P_{am}) + (P_{am} * OR)}$$

APPENDIX III – Mortality

We estimated the cycle specific mortality in each health state based on a falling exponential approximation to life expectancy (DEALE) method.³⁹⁻⁴¹ This method assumes that the mortality rate is constant (one year in our analysis), and thus the survival probability declines exponentially over a certain period of time. The patient specific probability of death in one year (P_3) is then given by:

$$P_3(\text{age, risk}) = 1 - \exp[-\mu_{am} * RR_r * (1 - RRR_t)]$$

In this equation,

- age indicates a patient's age
- risk indicates types of risk factors
- μ_{am} indicates the baseline age-specific mortality rate per year in males derived from U.S. life tables (2000).³⁸
- RR_r indicates the relative mortality ratio of a particular risk factor r compared with the baseline age-specific mortality rate. We used 1.5 as the standardized mortality ratio derived from the population-based Framingham Heart Study. The relative mortality ratio for patients with one-vessel (2.35), two-vessel (4.11), and three vessels/left-main coronary artery disease (6.61) were extracted from the CASS registry.²⁰
- RRR_t denotes the relative mortality risk reduction by a particular therapy or intervention t .