Intermittent Claudication: Cost-effectiveness of Revascularization versus Exercise Therapy[1]

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Abbreviations:
PTA = percutaneous transluminal angioplasty
QALY = quality-adjusted life year

PURPOSE: To compare the costs, effectiveness, and cost-effectiveness of alternative treatment strategies for intermittent claudication.

MATERIALS AND METHODS: By combining data from the literature and original patient data, a Markov decision model was developed to evaluate the societal cost-effectiveness. Patients presented with previously untreated intermittent claudication, and treatment options were exercise, percutaneous transluminal angioplasty (with stent placement, if necessary), and/or bypass surgery. Treatment strategies were defined as the initial therapy in combination with secondary treatment options should the initial therapy fail. The main outcome measures were quality-adjusted life days, expected lifetime costs (in 1995 U.S. dollars), and incremental cost-effectiveness ratios.

RESULTS: Compared with an exercise program, revascularization (either angioplasty or bypass surgery) improved effectiveness by 33–61 quality-adjusted life days among patients with no history of coronary artery disease. The incremental cost-effectiveness ratio was $38,000 per quality-adjusted life year gained when angioplasty was performed whenever feasible, as compared with exercise alone, and $311,000 with additional bypass surgery. The incremental cost-effectiveness ratios were sensitive to age, history of coronary artery disease, estimated health values for no or mild claudication versus severe claudication, and revascularization costs.

CONCLUSION: The results suggest that, on average, the expected gain in effectiveness achieved with bypass surgery for intermittent claudication is small compared with the costs. Angioplasty performed whenever feasible was more effective than was exercise alone, and the cost-effectiveness ratio was within the generally accepted range.

Treatment strategies for patients with intermittent claudication traditionally have been conservative (1,2). Few patients eventually develop limb-threatening symptoms, and the risks of perioperative mortality and morbidity—at least with surgical procedures—are considerable (3–5). Revascularization procedures are therefore generally postponed until initial conservative management fails. Many physicians consider exercise an inexpensive and effective method of improving the symptoms of claudication and recommend it as the initial treatment (6–9). However, individual responses to exercise vary considerably, and long-term compliance varies from 65% to 87% (10,11). Furthermore, because patients must invest time before reaping any health reward, exercise may not be as inexpensive as it seems when the societal perspective is considered: The cost of the time spent exercising must be taken into account.

With the development of percutaneous revascularization techniques, the interventional armamentarium for peripheral arterial disease has expanded considerably. Because the risks of periprocedural mortality and morbidity with percutaneous revascularization are low, some physicians advocate the use of such procedures at an early stage of treatment for intermittent claudication (12). Many patients with intermittent claudication eventually undergo revascularization, and earlier use of the currently available low-risk alternatives might prevent unnecessary suffering. On the other hand, both percutaneous and surgical

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procedures are expensive, and with a limited health care budget, one needs to consider whether the gain in quality-adjusted life expectancy justifies the costs.

The medical literature does not provide a direct answer as to what the optimal comprehensive treatment strategy is for patients with intermittent claudication. Research efforts have been directed mainly at comparing various initial revascularization procedures—for example, different types of material for aortic bifurcation grafts (13), primary versus secondary stent placement in iliac angioplasty (14), and bypass surgery versus angioplasty for femoropopliteal arterial disease (15,16). In two published clinical trials (17–19), revascularization was compared with exercise. Results of one of these studies (17) showed that the maximum walking distance was improved more with either bypass surgery or a combination of surgery and exercise than with exercise alone. In the other study (18,19), the investigators found that exercise improved the walking distance more than angioplasty. The numbers of patients in these two studies were small. Furthermore, treatment strategies in both studies were defined on the basis of the initial treatment only, and the economic consequences of the strategies were not taken into account.

The purpose of the present study was to evaluate the costs, effectiveness, and relative cost-effectiveness of various comprehensive treatment strategies for the treatment of intermittent claudication by assessing a combination of exercise, percutaneous transluminal angioplasty (PTA), and bypass surgery.

TABLE 1
Evaluated Treatment Strategies

Strategy No./Description	Initial Treatment	Secondary Treatment*
1/EX	Exercise	None
2/EX ± PTA	Exercise	PTA
3/EX ± PTA/BP	Exercise	PTA or BP
4/PTA/EX†	PTA or exercise	PTA
5/PTA/BP/EX‡	PTA, BP, or exercise	PTA or BP

Note.—BP = bypass surgery, EX = exercise strategy, EX ± PTA = strategy of exercise with or without PTA, EX ± PTA/BP = strategy of exercise with or without PTA or BP, PTA/EX = strategy of PTA or exercise, PTA/BP/EX = strategy of PTA, BP, or exercise. PTA refers to percutaneous transluminal angioplasty with stent placement, if necessary.

* With allowance for multiple secondary interventions, where necessary. The maximum number of possible revascularization procedures per limb was three and varied from two to four at sensitivity analysis.

† Only patients in whom PTA was not feasible entered the exercise program.

‡ For patients in whom PTA was not feasible, BP was considered. If neither PTA nor BP was feasible, the patient entered the exercise program.

MATERIALS AND METHODS

A decision model was developed to estimate, from the societal perspective (20), the quality-adjusted life expectancy, lifetime costs, and cost-effectiveness associated with five alternative treatment strategies for unilateral intermittent claudication. Therapeutic options included an exercise program, PTA, and/or bypass surgery. A treatment strategy was defined as the initial therapy combined with secondary treatment options should the initial treatment fail (Table 1). Treatment failure was defined as discontinuation of the exercise program in combination with severe claudication, graft failure or restenosis in combination with severe claudication, or progression to critical limb ischemia.

We assumed that all patients would undergo general examination and treatment for other atherosclerotic disease, and risk factor modification was not explicitly modeled. The treatment of critical limb ischemia—defined as pain at rest, ulcer, or gangrene—was the same for all strategies: In patients with suitable lesions, angioplasty was performed; in all other patients, bypass surgery was performed.

For analysis, data from the medical literature were combined with original patient data from three sources (3,14,21–52) (Appendix, Tables A1 and A2). Original patient data included those from a 5-year (1990–1995) consecutive series from *(a)* the vascular registry database at Brigham and Women's Hospital, Boston, Mass, which included 722 patients (ie, Boston database); *(b)* the database of the exercise program at the University Hospital Groningen, the Netherlands, which included 329 patients (ie, Groningen database); and *(c)* a Dutch trial on oral anticoagulants at the Dijkzigt Hospital, Rotterdam, the Netherlands, which included 547 patients (ie, Rotterdam database) (21). The protocols for these studies were approved by the appropriate institutional review boards, and informed consent was obtained from all patients. Baseline-case values and ranges for the key parameters of the model, technical details about the model structure, and data sources are presented in the Appendix. Pertinent assumptions are summarized in the following text.

Model Structure

Figure 1 is a schematic representation of the model. It is a Markov model (54) that simulates individual disease histories, from presentation to death, for all alternative treatment strategies and keeps track of the time spent in various health states and the accumulated costs. Health states were defined as all possible combinations of symptom severity in each limb: *(a)* asymptomatic or mild claudication; *(b)* severe claudication; *(c)* critical limb ischemia; *(d)* below-knee amputation, including transmetatarsal amputations; and *(e)* above-knee amputation. We did not define a separate health state for asymptomatic patients, because the available data did not allow us to distinguish them from patients with mild claudication.

Implicit in the definition of treatment failure is the assumption that no or mild claudication does not require treatment, other than general measures for atherosclerotic disease. A threshold maximum walking distance of 250 m—the upper tercile value at presentation in the patient cohort in the Groningen database—was used to distinguish severe claudication from no or mild claudication. In a sensitivity analysis, we used the lower tercile of this distribution, 175 m, as a threshold. Apart from symptom severity, additional details of disease history were modeled. These details included age, sex, duration of symptoms, history of angina pectoris or myocardial infarction, resting ankle-brachial index (lowest value of the two limbs), patient compliance with exercise, number of revascularization procedures performed, time since the last procedure, patency and predictors of failure, and effects on quality of life and costs.

At baseline-case analysis, we calculated the results for a 60-year-old man presenting with a 1-year history of severe unilateral claudication. We assumed that this patient had no history of coronary artery disease (ie, angina pectoris or myocardial

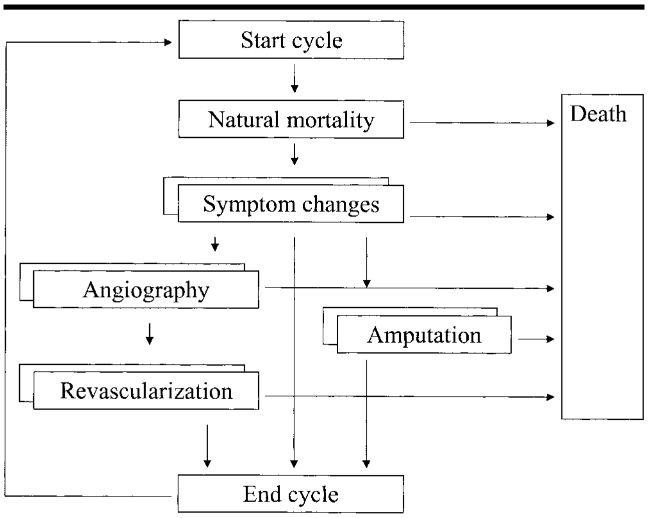

Figure 1. Schematic representation of the decision model structure. The model is a state transition Markov model that defines a number of health states and the possible transitions between those states. The structure and parameter values define how patients may move from one health state to another during one time cycle. Each box in this figure represents different possible events that may lead to such state transitions. For example, the *Symptom changes* box represents possible changes in symptom severity, with the actual probabilities of these changes depending on whether a patient participates in an exercise program and on graft patency. Where events are modeled separately for each limb, two boxes are shown. Patients participating in an exercise program move from the *Start cycle* box through the *Symptom changes* box to the *End cycle* box. These patients can only move to the *Angiography* box if invasive treatment (ie, PTA or bypass surgery) is performed because exercise failed to cause alleviation of claudication or if critical limb ischemia develops.

infarction) and that the initial ankle-brachial index (lowest value of two limbs) was 0.70. By using first-order Monte Carlo analysis, we simulated the disease history of this patient multiple times (n = 100,000) for each of the five strategies (54). In Monte Carlo analysis, a computer-generated random factor is used at each point in the model where chance plays a role. As a result, outcomes may differ from simulation to simulation, as in real life, where the outcomes of patients with the same characteristics may differ due to chance factors.

The average outcome per strategy was used for further calculations. Strategies were ordered according to increasing effectiveness (in quality-adjusted life years [QALYs]), and a dominated strategy was defined as a strategy with a lower effectiveness and higher cost than another strategy. Next, dominated strategies were eliminated and incremental cost-effectiveness ratios were calculated as the difference in mean lifetime costs divided by the difference in mean QALYs for each strategy compared with that for the next best strategy (55).

Exercise Program

We considered a 6-month exercise program developed at the Department of Internal Medicine of the University Hospital Groningen (41,51). In this program, patients are asked to walk a certain fixed distance each day. The exact distance varies from patient to patient (2–6 km) and depends on his or her performance at baseline. Patients are instructed to pause when symptoms of claudication occur. There are four control visits at the hospital during the first 6 months. After these 6 months, patients continue the exercises at home. We assumed that patients who discontinue the exercises do not re-enter the program.

Revascularization

Revascularization was assumed to be preceded by angiography. Findings at angiography, such as the level of disease and the feasibility of PTA, were incorporated as possible events in the decision model. We assumed that in a minority of patients (5%), the angiographic findings are such that no revascularization will be considered unless the patient develops critical limb ischemia. Of the remaining 95% of patients, those with suitable lesions will undergo PTA.

In the current study, a focal stenosis of 50%–99% above the knee joint was considered suitable for PTA. To make the problem tractable, we incorporated only the most commonly used procedures—specifically, PTA with selective stent placement and aortic bifurcation surgery for suprainguinal disease (14) and PTA and bypass surgery for infrainguinal disease. Thrombolysis was not considered a treatment option. The maximum number of possible revascularization procedures per limb was set at three. More than three interventions per limb were rarely encountered in the Boston database, and in a sensitivity analysis, we varied the number of interventions from two to four.

Quality of Life

QALYs were calculated as the sum of the time spent in each health state multiplied by a correction factor representing the quality of life in each of these health states. Correction factors generally are based on health value measures, which are instruments geared to measure quality of life on a 0–1 scale. Examples of such instruments include the standard gamble and the time trade-off (56). In the present study, we used time trade-off estimates. For the health states of no or mild claudication and severe claudication, responses on the EuroQol questionnaire were modified to estimate time trade-off values (43,49). We used the EuroQol questionnaire because it was the best for discriminating among patients with different symptom severities. Values obtained with other instruments were used in the sensitivity analyses.

For patients with critical limb ischemia or with amputations, we used time trade-off estimates from the medical literature and explored a wide range of alternative values at sensitivity analyses (42). With bilateral symptoms, we assumed that the most severe symptoms would determine the quality of life, ignoring the possible additional effects of milder contralateral symptoms on the quality of life. The average time trade-off among survivors of myocardial infarction was used as an approximation for the quality of life with a systemic complication (44), which was incorporated with the assumption of a multiplicative relationship.

Costs

Both medical and nonmedical costs were included. Medical costs included the costs of all diagnostic and therapeutic procedures, professional services, short- and long-term care after complications, follow-up visits, and rehabilitation and long-term care for patients with amputations. Estimates of the hospital costs for each revascularization procedure were obtained from the Boston database (46). Future medical costs for unrelated diseases were not considered, because none of the proposed treatment strategies offers any substantial survival advantage. If these medical costs had been included, all strategies would have been equally affected and the incremental cost-effectiveness ratio would not have changed.

Nonmedical costs included transportation costs and the opportunity costs of patient time invested in, for example, undergoing a procedure or exercising. At sensitivity analysis, the cost of patient time spent on exercise was set at zero with the assumption that patients enjoy this activity. Costs associated with productivity changes were considered to be negligible and not to differ across strategies. All costs were converted to 1995 U.S. dollars by using the medical care specific consumer price index of the Bureau of Labor Statistics (53). Both costs and QALYs were discounted at an annual rate of 3% (20). The discount rate was varied from 0% to 10% in the sensitivity analysis.

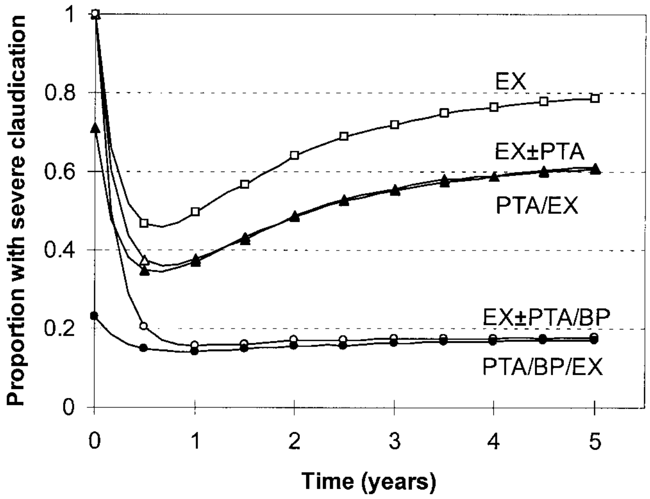

Figure 2. Graph illustrates proportions of patients with severe claudication during the first 5 years of follow-up, conditional on survival, at baseline-case analysis. The model predicts a lower probability of severe intermittent claudication for strategies that consist of more invasive treatment options. Initially, the difference between EX ± PTA/BP (○) and PTA/BP/EX (●) was large because invasive treatment was directly successful in many patients and walking exercises may take some time before leading to a health reward, but over time, the difference disappeared. □ = EX, △ = EX ± PTA, ▲ = PTA/EX. For an explanation of the strategies, see Table 1.

RESULTS

Baseline-Case Analysis

At baseline-case analysis, we calculated the outcomes for a 60-year-old man with no history of coronary artery disease. This model predicts a lower probability of severe claudication with increasingly intensive treatment efforts (Fig 2) and, correspondingly, a higher probability of having no or mild claudication (not shown). The difference in the predicted probability of severe claudication between the treatment strategies in which revascularization was considered a primary option and the corresponding strategies in which the same revascularization procedure(s) was considered a secondary option after a trial of exercise (ie, PTA/EX vs EX ± PTA and PTA/BP/EX vs EX ± PTA/BP) initially was large but quickly disappeared over time (Fig 2).

Invasive treatment of patients can be directly successful, whereas patients starting with walking exercises have to invest time before reaping any health reward. With the two strategies that include bypass surgery, the probability of severe claudication decreased sharply during the 1st year and increased only slightly during subsequent years. The two bypass surgery strategies were, however, associated with a substantially higher risk of periprocedural mortality (Fig 3) and morbidity (not shown) than were the other strategies. For the baseline case, the higher periprocedural mortality and morbidity did not substantially affect the unadjusted life expectancy: Without quality adjustment or discounting, estimates ranged from 10.37 years for PTA/BP/EX to 10.40 years for EX ± PTA. Estimates of QALYs varied more substantially, ranging from 6.05 for EX to 6.22 for EX ± PTA/BP (including discounting).

Generally, the expected lifetime costs also increased with increasing QALYs (Fig 4). EX ± PTA was inferior to PTA/EX by dominance, and PTA/BP/EX was inferior to EX ± PTA/BP by dominance. The differences between the dominant and dominated strategies, however, were minimal. The incremental cost-effectiveness ratios of the two remaining revascularization strategies were $38,000 per QALY gained for PTA/EX (compared with EX) and $311,000 per QALY gained for EX ± PTA/BP (compared with PTA/EX).

Sensitivity Analysis

For most parameters, we found that alternative assumptions either did not substantially affect the outcomes or affected all strategies similarly, without substantial effects on the incremental cost-effectiveness ratios. For example, varying the discount rate from 0% to 10% affected both the costs and the effects of all five strategies, but the incremental cost-effectiveness ratios hardly changed. Similarly, a higher or lower risk of mortality associated with peripheral arterial disease did not substantially affect the incremental results.

The results were, however, particularly sensitive to varying health values for severe claudication versus no or mild claudication (Table 2). The smaller the difference in health values between severe claudication and no or mild claudication was, the higher the incremental cost-effectiveness ratios were, whereas a larger difference between the health values resulted in lower incremental cost-effectiveness ratios. Also, the results of strategies that included bypass surgery were sensitive to the quality of life of a patient with systemic complications. For example, if the quality of life with systemic complications was lower, then the incremental cost-effectiveness ratio for EX ± PTA/BP increased. The effects of varying the health values for angina pectoris, above- or below-knee amputation, and critical ischemia were minimal.

For all strategies, the expected lifetime

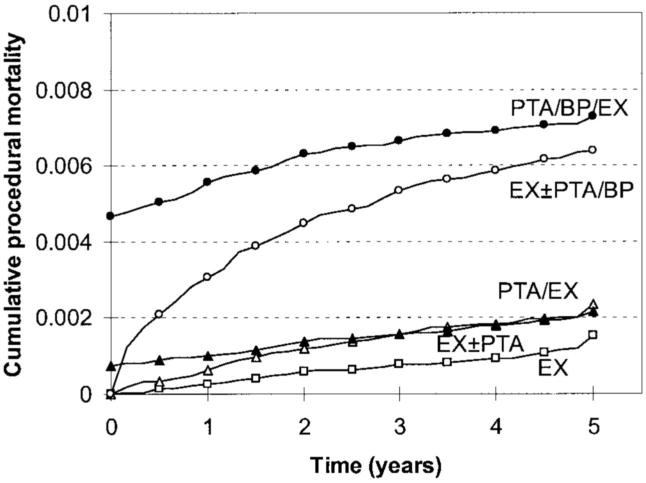

Figure 3. Graph illustrates cumulative procedural mortality rates (ie, mortality from angiography, amputation, bypass surgery, or percutaneous intervention) during the first 5 years of follow-up at baseline-case analysis, including mortality from initial invasive treatment (start of follow-up) for PTA/EX (▲) and PTA/BP/EX (●). The strategies that included bypass surgery had a higher risk of procedural mortality than did the other strategies. □ = EX, △ = EX ± PTA, ○ = EX ± PTA/BP. For an explanation of the strategies, see Table 1.

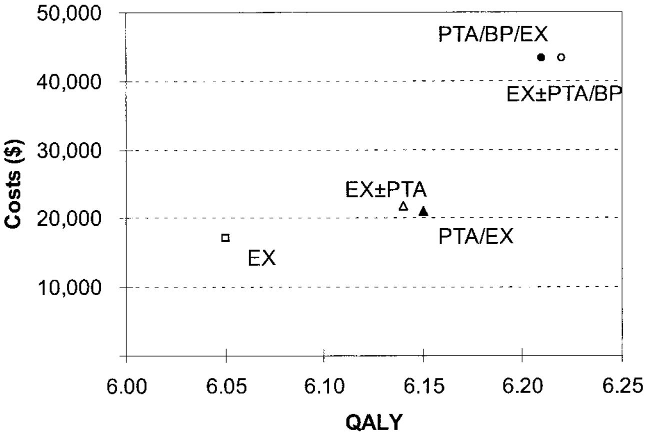

Figure 4. Graph illustrates expected lifetime costs versus QALYs at baseline-case analysis. With increasing QALYs, the lifetime costs also increased. EX ± PTA (△) and PTA/BP/EX (●) were inferior by dominance. □ = EX, ○ = EX ± PTA/BP, ▲ = PTA/EX.

costs were sensitive to the costs of revascularization procedures. Varying these costs between 50% and 150% of the original estimates resulted in incremental cost-effectiveness ratios ranging from $25,000 to $46,000 per QALY gained for PTA/EX and from $266,000 to $453,000 for EX ± PTA/BP. Assuming that the patient enjoyed walking—for which time costs for exercise were set to zero—led to a reduction in the total costs for strategies that started with exercise of approximately $3,500 and thus resulted in incremental cost-effectiveness ratios of $63,000 per QALY gained for PTA/EX and $230,000 per QALY gained for EX ± PTA/BP.

Assuming a small survival benefit to the patients who participated in the exercise program did not affect the results substantially. Using a threshold maximum walking distance of 175 m instead of 250 m to distinguish severe claudication from no or mild claudication increased the incremental cost-effectiveness ratios for PTA/EX ($53,000/QALY gained) and EX ± PTA/BP ($359,000/QALY gained). Assuming that the proportion of lesions suitable for PTA initially would be 50% higher than that during subsequent years decreased the incremental cost-effectiveness ratio for PTA/EX ($31,000/QALY gained) and increased the incremental cost-effectiveness ratio for EX ± PTA/BP ($1,504,000/QALY gained). Alternative assumptions concerning the effect of exercise or bifurcation grafts on the development of contralateral symptoms did not change the results substantially. For all five strategies, the outcomes with alternative assumptions regarding the maximum number of procedures per limb, which varied from two to four, were essentially the same.

For all patient characteristics except age and history of coronary artery disease, the effects on the incremental results were modest. Generally, the incremental cost-effectiveness ratios for the interventional strategies increased with increasing age or with a positive history of coronary artery disease. The latter characteristic was associated with a markedly shorter life expectancy with interventional strategies—especially those that included bypass surgery—owing to the increased procedural risk in patients with cardiac ischemia.

Table 2 summarizes the combined effects of those variables that had substantial effects on the incremental cost-effectiveness ratios for PTA/EX and EX ± PTA/BP at one-way sensitivity analyses: age, history of coronary artery disease, costs of revascularization, and health value difference between no or mild claudication and severe claudication. Each cell in Table 2 is based on simulations of 100,000 disease histories for each treatment strategy under the given parameter values. For example, with the assumption of a patient aged 40 years with a positive history of coronary artery disease, revascularization costs that are 50% lower than the baseline-case estimates, and a health value difference of 0.08 between no or mild claudication versus severe claudication, our analysis results indicate that the incremental cost-effectiveness ratio for PTA/EX was approximately $36,000 per QALY gained, whereas EX ± PTA/BP was dominated by the other two strategies.

The data in Table 2 suggest that EX ± PTA/BP is unattractive under most circumstances, especially for patients aged 80 years and those with a history of coronary artery disease, because it is dominated by EX or PTA/EX or because the incremental cost-effectiveness ratios are exceptionally high.

DISCUSSION

The development of percutaneous procedures for treatment of peripheral arterial disease during the past 2 decades has stirred up the debate about the optimal treatment strategy for patients with intermittent claudication (1,2,12,57–59). In this study, we addressed the question of whether the traditional conservative approach to treating claudication can still be justified in the present era of low-risk revascularization procedures. The results suggest that, from a societal perspective and with consideration of cost-effectiveness, a fairly conservative approach is warranted. The net effect on the quality-adjusted life expectancy with revascularization was relatively small, not only because of the modest difference in health values between patients with no or mild claudication and those with severe claudication, but also because the benefits of revascularization in terms of symptom severity were partly offset by the risks of procedural mortality and morbidity, especially for bypass surgery.

TABLE 2
Results of Four-Way Sensitivity Analysis Based on Age, History of Coronary Artery Disease, Revascularization Costs, and Health Value Difference between No or Mild Claudication and Severe Claudication

	PTA/EX				EX ± PTA/BP†			
Variable*	0.04	0.08	0.12	0.16	0.04	0.08	0.12	0.16
No CAD history								
40 y								
50%	39,187‡	17,103	11,119	8,242	PTA/EX+	196,685	72,704	44,221
100%	49,295	21,514	12,445	9,225	PTA/EX+	239,872	89,216	54,264
150%	53,097	23,119	14,286	11,247	PTA/EX+	288,462	106,918	64,045
60 y								
50%	52,995	25,307	17,461	13,145	PTA/EX+	265,713	102,078	59,035
100%	76,141	36,360	24,386	18,358	PTA/EX+	359,948	140,054	80,997
150%	95,109	46,319	31,947	24,188	PTA/EX+	452,851	175,152	102,228
80 y								
50%	114,912	61,315	49,692	37,982	PTA/EX+	2,285,963	208,865	130,330
100%	181,209	96,690	80,732	61,707	PTA/EX+	3,594,454	327,320	204,245
150%	245,534	129,918	108,995	84,630	PTA/EX+	4,978,633	451,569	277,653
CAD history								
40 y								
50%	470,891	35,807	18,699	12,573	EX+	EX+	837,319	104,038
100%	578,047	43,955	23,173	15,582	EX+	EX+	1,036,061	128,732
150%	685,136	52,098	27,466	18,468	EX+	EX+	1,237,523	153,763
60 y								
50%	305,840	52,879	27,587	19,121	EX+	EX+	PTA/EX+	199,618
100%	434,018	75,040	37,736	26,155	EX+	EX+	PTA/EX+	276,732
150%	572,654	98,406	48,890	34,094	EX+	EX+	PTA/EX+	353,623
80 y								
50%	620,887	167,466	80,962	50,606	EX+	EX+	PTA/EX+	434,891
100%	1,005,651	271,245	127,903	79,947	EX+	EX+	PTA/EX+	685,366
150%	1,375,211	373,200	177,199	109,564	EX+	EX+	PTA/EX+	931,353

Note.—Data are incremental cost-effectiveness ratios (in 1995 U.S. dollars/QALY gained) of the given strategy compared with those of the next best strategy—that is, PTA/EX was compared with EX, and EX ± PTA/BP was compared with PTA/EX. The cost-effectiveness ratios are compared when the two treatment strategies have health value differences of 0.04, 0.08, 0.12, and 0.16. Health value difference refers to the difference between the health value for no or mild claudication and that for severe claudication. For baseline-case estimates, see Table A2 of the Appendix. CAD = coronary artery disease.

* Fifty percent, 100%, and 150% are revascularization costs, as percentages of the baseline-case estimated costs, at ages 40, 60, and 80 years.

† EX+ = EX and PTA/EX are superior to EX ± PTA/BP by full dominance. PTA/EX+ = PTA/EX is superior to EX ± PTA/BP by full dominance.

‡ For a 40-year-old man without a history of CAD, the costs of revascularization equaled 50% of the baseline-case estimates and a difference in health value of 0.04 between no or mild claudication and severe claudication; the incremental cost-effectiveness ratio was $39,187 per QALY relative to EX.

The expected lifetime costs of revascularization procedures, especially those strategies including bypass surgery, were substantially higher than those of exercise therapy alone. Furthermore, the results of strategies with a revascularization procedure as a possible initial step (ie, PTA/EX and PTA/BP/EX) were very similar to those of the corresponding strategies that considered the same procedure(s) as a secondary option after a trial of exercise (ie, EX ± PTA and EX ± PTA/BP, respectively).

The results of the sensitivity analysis emphasize that the expected gain in quality of life should be a crucial factor in the choice of treatment for intermittent claudication. We found that the cost-effectiveness ratios of the revascularization strategies depended to a large extent on the health values for no or mild claudication and severe claudication. The quality of life values for no or mild claudication and severe claudication in the current analysis were based on the results of a previous study (43), which were in close agreement with the values obtained in other studies (47,60).

The difference in the average observed EuroQol values (which were used in our analysis) for patients with no or mild claudication versus those with severe claudication was only modest (0.08) and led to high cost-effectiveness ratios for the revascularization strategies. With other quality-of-life instruments, differences between groups were even smaller and would have resulted in even higher cost-effectiveness ratios. The estimated health values were, however, average values, assuming that patients could be divided into fairly homogeneous groups on the basis of their walking distance. The effect of a change in walking distance from, for example, 300 to 150 m may for some patients have a far greater effect on their quality of life than the average effect on quality of life that we estimated. Thus, although our study results suggest that bypass surgery is not cost-effective, given the average observed difference in quality of life values between no or mild claudication and severe claudication, the sensitivity analysis results support the use of bypass surgery in exceptional cases where this difference is very large.

With constant improvements in percutaneous treatment techniques, more lesions will be suitable for PTA. Under these circumstances, our model predicted that the incremental cost-effectiveness ratio of the strategy with angioplasty as the only and the initial invasive treatment would decrease slightly and the incremental cost-effectiveness ratio of the strategy with bypass surgery would increase tremendously. We also assumed that invasive treatment was always preceded by angiography. Currently, angiography is often replaced by noninvasive imaging modalities such as magnetic resonance angiography and duplex ultrasonography. These modalities involve lower costs and risks than does angiography, but they can lead to false test results.

The cost-effectiveness ratio of more than $200,000 per QALY gained is outside the generally reported range of cost-effectiveness ratios (61); this observation implies that bypass surgery for intermittent claudication is an inefficient use of the limited resources in health care. Although practice patterns vary considerably, in many centers, bypass surgery is performed not only for limb-threatening symptoms but also for severe claudication. Our analysis results suggest that bypass surgery, even as only a secondary option, is very expensive relative to the achieved gain in effectiveness.

The incremental cost-effectiveness ratios for angioplasty were within the range of those reported for currently accepted technologies. For example, Wong et al (62) observed the cost of coronary artery bypass surgery for three-vessel disease in patients with severe angina to be $105,000 per QALY gained (adjusted to 1995 U.S. dollars). Compared with the cost-effectiveness ratios for coronary angioplasty for severe angina, $10,000–$18,000 per QALY gained (62), however, the cost-effectiveness ratios for peripheral angioplasty were somewhat unfavorable.

Our study was a synthesis of the existing knowledge of the risks, benefits, and costs of different therapeutic options for patients with peripheral arterial disease. The limitations of our study reflect shortcomings in the current knowledge and the necessity to make several simplifying modeling assumptions to keep the problem tractable. To test the robustness of our conclusions, we examined, where possible, the effect of choosing alternative assumptions about the outcomes of our study. For many assumptions, we observed that the alternatives either did not change the results substantially or changed the results for all strategies similarly; this finding indicates that the conclusions remained the same. However, a number of important points of discussion remain.

The primary limitation of our study was that differences among the various sources of evidence that we used may have biased the results. For example, we used two different data sets to model changes in the severity of claudication: one for patients participating in an exercise program and one for patients who underwent a revascularization. We adjusted the transition probabilities from both data sets for important potential confounders, including age, ankle-brachial index, presence of angina, and duration of the symptoms. Similarly, we corrected other parameter estimates for potential confounders, where possible. Thus, formal decision analysis offers opportunities to truly integrate information from different sources as an alternative to just comparing the outcomes of different studies. Nevertheless, in terms of preventing confounders, our analysis cannot replace a properly conducted randomized controlled trial. In our view, the current analysis is a prelude, rather than true alternative, to such a future trial, and the presented results may help focus the question-and-trial design.

Another limitation related to cost-effectiveness analysis involving decision models is the use of fixed values for the parameters in the model with the assumption that all of these values are precisely known. For example, in our model, we incorporated that 8.3% of patients undergoing aortic bifurcation bypass surgery would have systemic complications. This value was uncertain, however, and could have been 7% or 10%. Thus, there was uncertainty not only as to whether an event would occur, which was modeled with probabilities, but also surrounding the value of all the model parameters. We explored the effect of the uncertainty in the model parameters on the decision by performing sensitivity analysis, at which all estimates were varied across a plausible range of values. A sensitivity analysis varying up to four parameters simultaneously provided insight into the uncertainty surrounding the results.

Furthermore, we could have assessed the uncertainty in the model by performing a probabilistic sensitivity study with second-order Monte Carlo analysis (63,64). In a second-order Monte Carlo analysis, simulations are performed with a set of parameter estimates drawn from prespecified distributions, and this process is repeated multiple times, with a new set of parameter estimates drawn from the distributions each time. The results provide a distribution of the effectiveness and cost outcomes. Second-order Monte Carlo analysis, although useful at times, increases the complexity of the methods and results and does not provide more insight into which parameters are driving the decision. Moreover, the decision of which treatment strategy to use in clinical practice still would need to be made, and according to welfare economics, would still be best made on the basis of the incremental cost-effectiveness ratios calculated by using the means of the parameter estimates (65).

We recognize that our definitions of health states, especially those of no or mild claudication and severe claudication, are simplifications of more complex clinical realities. Most recommendations regarding revascularization procedures for intermittent claudication distinguish between disabling and nondisabling claudications, categories that take into account a patient’s lifestyle and occupation. Such subjective definitions, however, would make it difficult, if not impossible, to obtain the relevant data and to interpret the results. Thus, we used maximum walking distance to define no or mild claudication versus severe claudication. The threshold value that we used, 250 m, was necessarily an arbitrary one: This distance is in the upper tercile of the distribution of maximum walking distance at baseline for patients with intermittent claudication in the Groningen database. Some vascular surgeons would find 250 m too lenient a criterion and use lower thresholds to define severe claudication.

In a sensitivity analysis, we recalculated the transition probabilities in the model and the health values for no or mild claudication and severe claudication on the basis of a lower cutoff value (175 m, the lower tercile). The incremental cost-effectiveness ratios of the revascularization strategies increased with the lower threshold value, but the conclusions remained the same.

Another limitation of our analysis may be that we considered only one conservative treatment option. Exercise is generally regarded as the best conservative option. The exercise program that we considered in the current analysis is intermediate between more intensely supervised programs and a pure home-based exercise program. There are conflicting reports regarding the additional effect of supervision in exercise programs, and further research on a larger scale is required (66,67). There is little doubt, however, that the more intensely supervised programs are more expensive than is our program.

In addition to recommending exercise, many physicians would advise their patients to change their smoking habits. Cigarette smoking has been shown to increase the incidence of intermittent claudication (68), and smoking cessation may reduce the incidence of adverse events once intermittent claudication has developed (7,69). In many exercise programs, including ours, patients are motivated to stop smoking; thus, the effects of exercise and smoking cessation may overlap. We, therefore, chose not to include smoking cessation as a separate option. Of the drugs that have been marketed for intermittent claudication, pentoxifylline has probably been studied most widely; however, the results of a meta-analysis of 12 randomized trials could not provide conclusive evidence of this drug's effectiveness (7). Finally, we did not include platelet aggregation inhibitor therapy as a separate treatment option, but rather we considered this to be adjuvant therapy, the main benefit being the reduction of coronary and cerebrovascular events, which was not the focus of the current analysis.

Finally, we found that in the setting of coronary artery disease, revascularization for claudication is not cost-effective. We did not, however, model the option of coronary revascularization prior to peripheral revascularization, because this issue is different from that which we set out to address and was beyond the scope of this article. However, we did consider the presence of coronary artery disease and found that due to the increased procedural risk in patients with cardiac ischemia, the benefits of the interventional strategies—especially those that included bypass surgery—compared with those of the conservative strategies, were substantially reduced.

In conclusion, the results suggest that, on average, the small gain in effectiveness achieved with bypass surgery for intermittent claudication does not justify the additional costs. Angioplasty as an alternative to exercise, when feasible, was more effective than was exercise alone, and the cost-effectiveness ratio was within the generally accepted range.

APPENDIX

Model Structure

Transitions were modeled back and forth between no or mild claudication and severe claudication and between claudication and critical ischemia. We assumed that exercise does not reduce the risk of critical ischemia (50), that critical limb ischemia would not improve without revascularization, and that critical limb ischemia in a revascularized limb would develop only after loss of patency. Patients who developed critical limb ischemia were assumed to have undergone a revascularization procedure, unless the maximum number of procedures had been reached, in which case, amputation would follow. Amputation in patients with critical limb ischemia and progression from below-knee to above-knee amputation also were modeled.

Patency, symptom severity, and other details of the disease history were tracked for each limb separately. In comparing the results of limb- and patient-based reports of patency for bifurcation grafts, we found no evidence suggesting that patency in one limb depends on patency in the contralateral limb (26). Therefore, we assumed independent patency and failure in the two limbs. Patient characteristics, however, affected symptom severity in both limbs, and, thus, the events in the two limbs were related (39,41). Implantation of a bifurcation graft for unilateral symptoms was assumed not to affect the development of contralateral symptoms, and this assumption was examined in a sensitivity analysis. Exercise was assumed not to affect the development of contralateral symptoms, and at sensitivity analysis, we tested whether assuming a preventive effect of exercise (ranging from 0% to 100%) would substantially change the results.

The degree of clinical detail incorporated in our decision model exceeded the capacity of standard decision analysis software. Therefore, a C++ based programming language (Fast Decision Language; J. A. de Vries, Groningen, the Netherlands) was developed to construct the model. At the initial stage, for debugging purposes, a simpler version of the model was constructed in both Fast Decision Language and DATA (Decision Analysis by TreeAge; TreeAge Software, Williamstown, Mass) and the results were compared. Extensive sensitivity analyses were performed to check for inconsistencies in the model.

Exercise Program

Estimates of the transition probabilities between the health states associated with exercise were obtained from the Groningen database and adjusted for age, duration of symptoms, ankle-brachial index, presence of angina, and compliance (51). On the basis of 3-year follow-up at the University Hospital Groningen, we assumed that the rate of discontinuing the exercises was constant over time. Although no survival benefit following exercise programs for intermittent claudication has been demonstrated (52), in a sensitivity analysis, we tested whether a small survival benefit (ie, 20% reduction in mortality) among participants of the exercise program would substantially affect the results.

Revascularization

Patency estimates were obtained from three published meta-analyses (26,27,34) and adjusted for presenting symptoms (claudication vs critical limb ischemia) and, where applicable, lesion type (stenosis vs occlusion), level of distal anastomosis (above vs below the knee), and graft material (ie, autologous vein vs polytetrafluoroethylene). For iliac PTA, we used data from studies in which PTA was combined with stent placement, assuming that a stent would be placed if angioplasty alone yielded suboptimal results (14). We assumed that patients would not undergo multiple revascularization procedures at different arterial levels simultaneously, but the model does allow for new procedures in the same limb at a different (usually infrainguinal) arterial level during follow-up. In following up multiple procedures in one limb, we assumed that the procedure that was performed last would determine the overall probability of graft or PTA failure.

Transition probabilities between health states following revascularization were obtained from the Rotterdam database and adjusted for covariates and the effects of anticoagulant medication. In addition, we incorporated the effect of failure on changes in maximum walking distance by using a decrease in ankle-brachial index of more than 0.15 relative to the postrevascularization value as a patency criterion (39,40). Estimates of the rate of development of contralateral symptoms were obtained from the Boston database (36).

Costs

The main cost of the exercise program was the opportunity cost of the time invested by the patient (20). Questionnaire answers indicated that the participants at the University Hospital Groningen spent, on average, 6.4 hours per week exercising. Theoretically, the value of patient time depends on how much the patient enjoys or dislikes the activity (20,50). At baseline-case analysis, we used the 1995 U.S. average hourly wage rate of $11.35 (from Bureau of Labor Statistics [53]) as the value of patient time for all disease-related activities. For in-hospital vascular procedures, the value of patient time was estimated as the average length of stay (from the Boston database), in days, multiplied by 7.5 times the hourly wage rate. We also included transportation costs based on an average distance from the home address to the hospital of 49 km.

Estimates of the hospital costs for each of the revascularization procedures were obtained from the Boston database (46) and adjusted for age, sex, presenting symptoms, and history of coronary artery disease. More detailed information on the cost estimation can be found in the article by Jansen et al (46). The extra costs incurred from systemic complications or procedural mortality also were obtained from these data. We found that local complications had a minimal effect on the total hospital costs. We assumed that the extra long-term medical costs for patients with systemic complications would

TABLE A1
Rates and Probabilities

Variable	Baseline-Case Value*	Literature or Database Source
Mortality		
Mortality rate ratio for PAD	3.14 (2.74–3.54)	3,22–25
Revascularization procedures		
Aortic bifurcation grafts, high risk[†]	0.044 (0.032, 0.055)	26,28,37
Aortic bifurcation grafts, low risk	0.007 (0.005, 0.009)	26
Iliac PTA with selective stent placement, high risk[†]	0.013 (0, 0.037)	27
Iliac PTA with selective stent placement, low risk	0.001 (0, 0.029)	27
Femoropopliteal or infrapopliteal bypass, high risk[†]	0.047 (0.008, 0.127)	28
Femoropopliteal or infrapopliteal bypass, low risk	0.008 (0.001, 0.022)	28
Femoral or popliteal PTA, high risk[†]	0.025 (0, 0.264)	28
Femoral or popliteal PTA, low risk	0.002 (0, 0.021)	28
Diagnostic angiography	0.00033 (0.00029, 0.00162)	29,30
Amputation		
Age <75 y	0.098 (0.077, 0.119)	31
Age ≥75 y	0.147 (0.113, 0.181)	31
Systemic complications		
Revascularization procedures		
Aortic bifurcation grafts	0.083 (0.063, 0.102)	26
Iliac PTA with selective stent placement	0.013 (0, 0.035)	27
Femoropopliteal or infrapopliteal bypass	0.085 (0.027, 0.130)	28
Femoral or popliteal PTA	0.013 (0.002, 0.110)	28
Diagnostic angiography	0.017 (0.010, 0.025)	32
Amputation	0.380 (0.377, 0.383)	33
Two-year patency in patients with claudication or ischemia[‡]		
Aortic bifurcation grafts	0.95, 0.93	26
Iliac PTA with selective stent placement[§]		
Stenosis	0.84, 0.76	14,27
Occlusion	0.67, 0.60	14,27
Femoropopliteal or femoroinfrapopliteal bypass[‖]		
Autologous vein graft	0.89, 0.80	34,38
PTFE graft, above-knee anastomosis	0.86, 0.68	34,38
PTFE graft, below-knee anastomosis	0.80, 0.56	34,38
Femoral or popliteal PTA		
Stenosis	0.75, 0.56	34
Occlusion	0.46, 0.21	34
Arterial level: probability of suprainguinal disease		
First intervention[#]	0.56 (0.12, 0.85)	Boston database
Second or later intervention, previously suprainguinal disease	0.31 (0.13, 0.49)	Boston database
Second or later intervention, previously infrainguinal disease	0.17 (0.09, 0.25)	Boston database
Lesions (claudication or ischemia) suitable for PTA**		
Suprainguinal disease, first intervention	0.51 (0.43, 0.59), 0.27 (0.19, 0.35)	Boston database
Suprainguinal disease, second or later intervention	0.33 (0.03, 0.65), 0.19 (0, 0.38)	Boston database
Infrainguinal disease, first intervention	0.18 (0.11, 0.25), 0.07 (0.04, 0.10)	Boston database
Infrainguinal disease, second or later intervention	0.23 (0.07, 0.39), 0.06 (0, 0.12)	Boston database
Critical ischemia and amputation		
Annual rate of critical ischemia (natural history)		
Age <65 y[††]	0.017 (0, 0.039)	3,5,22,35
Age ≥65 y	0.036 (0, 0.075)	3,5,22,35
Five-week probability of critical ischemia following graft failure[‡‡]		
Pretreatment claudication	0.062 (0, 0.014)	39,40, Boston database
Pretreatment critical ischemia	0.242 (0.14, 0.36)	39,40, Boston database
Proportion of above-knee amputations among amputations for PAD	0.080 (0.030, 0.130)	Boston database
Annual rate of progression below- to above-knee amputation	0.015 (0, 0.070)	Boston database
Severe versus no or mild intermittent claudication[§§]		
Relative risk of severe claudication after stopping exercise	5.81 (1.8, 18.5)	39,40, Groningen database
Relative risk of severe claudication after graft failure	1.36 (0.96, 1.92)	39,40, Rotterdam database
Contralateral symptoms (mean annual rate)[‖‖]	0.149	36

Note.—PAD = peripheral arterial disease, PTFE = polytetrafluoroethylene.

* Presented data are probability values, unless stated otherwise. Numbers in parentheses are 95% CIs, except those for the mortality rate ratio for PAD, where numbers in parentheses are the range defined by the lowest and highest average from different subsets of studies (ie, population- vs hospital-based studies).

[†] High risk refers to patients aged 65 years with critical ischemia and/or patients with a history of coronary artery disease. The relative risk data for patients with high risk were obtained from Hunink et al and assumed to be the same for suprainguinal versus infrainguinal procedures.

[‡] The model incorporates time-dependent graft failure rates. The 2-year patency estimates are presented as examples. The first number is the patency in patients with claudication. The second number is the patency in patients with ischemia. The listed revascularization procedures together represent approximately 85% of all procedures performed for PAD at the Brigham and Women's Hospital during a recent 5-year period.

[§] Patency estimates for iliac PTA with selective stent placement have been shown to equal those for iliac PTA with primary stent placement.

[‖] The patency rates for femoroinfrapopliteal bypasses were assumed to be equal to those for femoropopliteal bypasses with a below-knee anastomosis.

[#] The model incorporates a logistic regression function, with age, sex, and presenting symptoms (claudication vs ischemia) as independent variables.

** Lesions were considered suitable for PTA if there was one focal stenosis of 50%–99% above the knee joint. The first set of numbers are values for patients with claudication. The second set of numbers are values for patients with ischemia.

[††] Relative risk data for patients aged 65 years or older obtained from Bloor.

[‡‡] Graft or PTA failure was defined as a decrease in ankle-brachial index of more than 0.15 compared with early postrevascularization values.

[§§] In addition to incorporating the presented relative risks, the model adjusts the probabilities of transition from no or mild claudication to severe claudication and vice versa for age, duration, ankle-brachial index, and presence of angina pectoris by using autoregressive logistic regression.

[‖‖] Includes both intermittent claudication and critical ischemia. In patients with previous unilateral ischemia, 67% of the contralateral symptoms are critical ischemia compared with 10% in patients with previous unilateral claudication.

TABLE A2
Health Values and Costs

Variable	Baseline-Case Value	Literature or Database Source
Health values		
Above-knee amputation[*]	0.20 (0.00–0.40)	42
Below-knee amputation[*]	0.61 (0.41–0.81)	42
Critical ischemia[*]	0.35 (0.15–0.55)	42
Severe claudication[†]	0.71 (0.67, 0.75)	43,49
No or mild claudication[†]	0.79 (0.75, 0.83)	43,49
Systemic complication[‡]	0.72 (0.60, 0.90)	44
Angina pectoris[§]	0.90 (0.60–1.00)	44
Costs[‖]		
Exercise		
Patient time (total costs per year)[#]	3,780 (800, 8,000)	53, Groningen database
Follow-up visit[**]	380	ACR
Diagnostic angiography	680	ACR
Amputation		
Above knee[††]	14,420	Medicare
Below knee[††]	7,790	Medicare
Long-term care of patients with above-knee amputation (per year)	31,920 (20,000, 40,000)	45
Revascularization procedures[‡‡]		
Aortic bifurcation bypass	23,490 (21,000, 26,000)	46
Iliac PTA with selective stenting[§§]	7,550 (5,000, 10,000)	14,46,47
Femoropopliteal or infrapopliteal bypass surgery	16,490 (14,000, 19,000)	46
Femoral or popliteal PTA	4,170 (1,200, 7,000)	46
Follow-up visit[**]	410	ACR
Systemic complications		
Short-term costs	9,770 (6,500, 13,000)	46
Annual long-term costs	10,780 (5,000, 15,000)	48
Mortality from revascularization procedures	11,620 (3,600, 20,000)	46

Note.—Numbers in parentheses are 95% CIs, unless otherwise noted. ACR = American College of Radiology.

[*] Time trade-off values. Numbers in parentheses are ranges. In the absence of sufficient information to construct 95% CIs, relatively large arbitrary ranges were chosen.

[†] Time trade-off values based on responses to the EuroQol questionnaire.

[‡] Average time trade-off values among survivors of myocardial infarction. This value was used as a proxy for the effect on quality of life of a systemic complication.

[§] Numbers in parentheses are ranges. In the absence of sufficient information to construct 95% CIs, relatively large arbitrary ranges were chosen.

[‖] All data cited in 1995 U.S. dollars.

[#] On average, 6.4 hours per week. The 1995 U.S. average hourly wage rate, $11.35 (from Bureau of Labor Statistics), was used as the value of patient time.

[**] Includes costs of office visit, noninvasive tests, patient time, and transportation.

[††] Average 1995 Medicare reimbursement for diagnostic related groups 113 and 114.

[‡‡] The model incorporates a linear regression function, with age, sex, history of coronary artery disease, and presenting symptoms (claudication vs ischemia) as independent variables. The presented estimates assume a 60-year-old male patient with intermittent claudication and without a history of coronary artery disease.

[§§] Assumes that in 43% of the cases, a stent was placed.

equal the yearly medical costs for survivors of myocardial infarction (48). Myocardial infarction is the most important major complication associated with invasive treatment of peripheral arterial disease (70). The long-term costs from systemic complications were varied over a wide range to explore the effects of major complications other than myocardial infarction.

All of the data used in the decision model are presented in Tables A1 and A2. The rates and probabilities are presented in Table A1, and the health values and costs are presented in Table A2.

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