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The Optimal Imaging Strategy for Patients With Stable Chest Pain

A Cost-Effectiveness Analysis

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Background: The optimal imaging strategy for patients with stable chest pain is uncertain.

Objective: To determine the cost-effectiveness of different imaging strategies for patients with stable chest pain.

Design: Microsimulation state-transition model.

Data Sources: Published literature.

Target Population: 60-year-old patients with a low to intermediate probability of coronary artery disease (CAD).

Time Horizon: Lifetime.

Perspective: The United States, the United Kingdom, and the Netherlands.

Intervention: Coronary computed tomography (CT) angiography, cardiac stress magnetic resonance imaging, stress single-photon emission CT, and stress echocardiography.

Outcome Measures: Lifetime costs, quality-adjusted life-years (QALYs), and incremental cost-effectiveness ratios.

Results of Base-Case Analysis: The strategy that maximized QALYs and was cost-effective in the United States and the Netherlands began with coronary CT angiography, continued with cardiac stress imaging if angiography found at least 50% stenosis in at least 1 coronary artery, and ended with catheter-based coronary angiography if stress imaging induced ischemia of any severity. For U.K. men, the preferred strategy was optimal medical therapy without catheter-based coronary angiography if coronary CT angiography found only moderate CAD or stress imaging induced only mild ischemia. In these strategies, stress echocardiography was consistently more effective and less expensive than other stress imaging tests. For U.K. women, the optimal strategy was stress echocardiography followed by catheter-based coronary angiography if echocardiography induced mild or moderate ischemia.

Results of Sensitivity Analysis: Results were sensitive to changes in the probability of CAD and assumptions about false-positive results.

Limitations: All cardiac stress imaging tests were assumed to be available. Exercise electrocardiography was included only in a sensitivity analysis. Differences in QALYs among strategies were small.

Conclusion: Coronary CT angiography is a cost-effective triage test for 60-year-old patients who have nonacute chest pain and a low to intermediate probability of CAD.

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For patients with nonacute chest pain and a low to intermediate pretest probability of coronary artery disease (CAD), evaluation with exercise electrocardiography is recommended by U.S. and European guidelines (1–3), whereas U.K. guidelines recommend against its use (4). In clinical practice, and contrary to the recommendations, most patients with chest pain in the United States are evaluated with cardiac stress imaging (5). However, the optimal diagnostic imaging strategy to select patients who may benefit from catheter-based coronary angiography is unknown (6).

Because coronary computed tomography (CT) angiography has high sensitivity (95% to 100%) (7–9), it identifies nearly all patients with CAD. However, its specificity is lower, which results in a relatively high number of false-positive results. Furthermore, the poor correlation between the anatomical and functional significance of stenosis (10, 11) makes it difficult to identify patients who would benefit from revascularization. Cardiac stress imaging with magnetic resonance imaging (MRI), single-photon emission CT, or echocardiography has lower sensitivity than coronary CT angiography, so these tests are less useful as first tests in a strategy that includes multiple ones (12–17). However, as follow-up studies, they may reveal false-positive results and identify stenosis with functional significance. Although previous studies have suggested that cardiac stress MRI may be superior to both stress single-photon emission CT and stress echocardiography in detecting functionally significant CAD (13–16), these 2 tests are done more often (5).

Our aim was to determine the optimal imaging strategy for patients with stable chest pain by analyzing the comparative effectiveness and costs of coronary CT angiography and cardiac stress imaging (cardiac stress MRI, stress single-photon emission CT, and stress echocardiography) from the perspective of the United States, the United Kingdom, and the Netherlands.

Methods

Decision Model

A microsimulation model was developed in DATA Pro 2009 Suite (TreeAge Software) to evaluate the comparative effectiveness and costs of coronary CT angiography and cardiac stress imaging. Diagnostic outcomes were modeled with a decision tree, and lifetime prognosis was modeled by using a state-transition model. Model parameters were based on evidence from the literature (Table 1 and Appendix Tables 1 to 4 [available at www.annals.org]). The model was analyzed from the perspective of the United Kingdom (health care perspective), the United States (societal perspective), and the Netherlands (societal perspective). Model details are provided in the Appendix (available at www.annals.org), and the most pertinent points are summarized in the following sections.

Target Population

Our target population consisted of 60-year-old patients with stable chest pain and a low to intermediate "preimaging" probability of CAD (defined as ≥50% stenosis) based on clinical characteristics and laboratory testing, regardless of whether they had undergone previous exercise electrocardiography. We considered patients without a history of CAD, percutaneous coronary intervention (PCI), or coronary artery bypass graft surgery (CABG). Our base case comprised patients who were eligible for cardiac imaging and had a 30% probability of CAD (1, 29).

Diagnostic Pathways

The following diagnostic strategies were modeled: no imaging, coronary CT angiography, cardiac stress imaging, coronary CT angiography with positive results followed by cardiac stress imaging, and direct catheter-based coronary angiography (Figure 1). All strategies were analyzed as both conservative and invasive diagnostic work-ups. In the invasive diagnostic work-up, patients with obstructive CAD on coronary CT angiography (≥50% stenosis in ≥1 vessel, regardless of severity) and patients with inducible ischemia on cardiac stress imaging (regardless of severity) were referred for catheter-based coronary angiography. In the conservative diagnostic work-up, patients with moderate CAD on coronary CT angiography or mild inducible ischemia on cardiac stress imaging received optimal medical treatment without referral to catheter-based coronary angiography. For cardiac stress imaging, we considered cardiac stress MRI, stress single-photon emission CT, and stress echocardiography. The cost-effectiveness of exercise electrocardiography, as well as cardiac stress imaging after a positive result on exercise electrocardiography, was considered in a sensitivity analysis.

Treatment and Prognosis

Disease severity was categorized into 8 subcategories (Appendix Table 3), which determined test results, costs, treatments, and prognosis. To keep the model tractable, we assumed that the initial optimal therapy if the true disease severity was known included risk factor management in patients with normal coronary arteries, mild CAD, and moderate CAD without ischemia; optimal medical treatment for patients with mild ischemia and moderate to severe CAD; PCI for patients with severe CAD and severe ischemia; and CABG for patients with 3-vessel or left main coronary stenosis. Consistent with clinical practice, PCI and CABG included optimal medical treatment, and optimal medical treatment included risk factor management. Figure 1 shows the treatment decisions based on test results. Appendix Table 4 provides details on medication use.

EDITORS' NOTES

Context

Many options exist for evaluating patients with stable angina.

Contribution

The investigators estimated the relative value of options that begin with cardiac imaging. They concluded that the preferred option in the United States and the Netherlands starts with computed tomography angiography of the coronary arteries, whereas the preferred option in the United Kingdom is the same for men but starts with stress echocardiography for women.

Caution

Exercise electrocardiography was included only in a sensitivity analysis.

Implication

Clinicians should consider computed tomography angiography of the coronary arteries as the initial imaging test for evaluating patients with stable angina.

The state-transition model for long-term prognosis included 3 health states: alive, post–myocardial infarction (MI), and dead (Figure 2). We modeled the risk for major adverse cardiac events (MACEs) (revascularization, nonfatal MI, and cardiac death), which depended on disease severity. The benefit of treatment was forgone by patients with CAD and false-negative test results. The reciprocal of the treatment hazard rate ratio was used to adjust the observed event rate for treated patients (those with true-positive results) to estimate the unknown event rate for untreated patients (those with CAD but false-negative results) (Appendix Table 3). To reflect clinical practice, we assumed that patients with false-negative results returned to their physicians with persistent symptoms, had additional testing, and began receiving appropriate treatment within the first year (except for patients with moderate CAD without ischemia, for whom we assumed that only 25% returned).

Costs and Quality of Life

Costs were based on evidence from the literature and expert opinion (Table 1 and Appendix Table 2). We used age- and sex-specific quality-of-life estimates for patients without obstructive CAD and those without inducible ischemia based on EQ-5D reference values for the general population (31). For patients with CAD who received treatment, we used published quality-of-life estimates based on the COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) (32) and SYNTAX (Synergy Between PCI

Table 1. Diagnostic Test Characteristics and Costs*

Variable	CCTA†		CMR	
	Mean Value	Source	Mean Value	Source
Test characteristics				
Sensitivity	0.98	References 7–9	0.89	Reference 14
Specificity	0.89	References 7–9	0.76	Reference 14
Radiation, *mSv*	5	–	–	–
Mortality, %	0.0006	Reference 19	0.01	–
Periprocedural MI, %	–	–	–	–
Disutility, *y*	0.0005	–	0.00075	–
Costs§				
United States, $	372	CPT 75574	621	CPT 75563 and 93015
United Kingdom, £	286	HRG RA14 and RA08Z	548	BSCI
The Netherlands, €	215	EMC fee	319	EMC fee

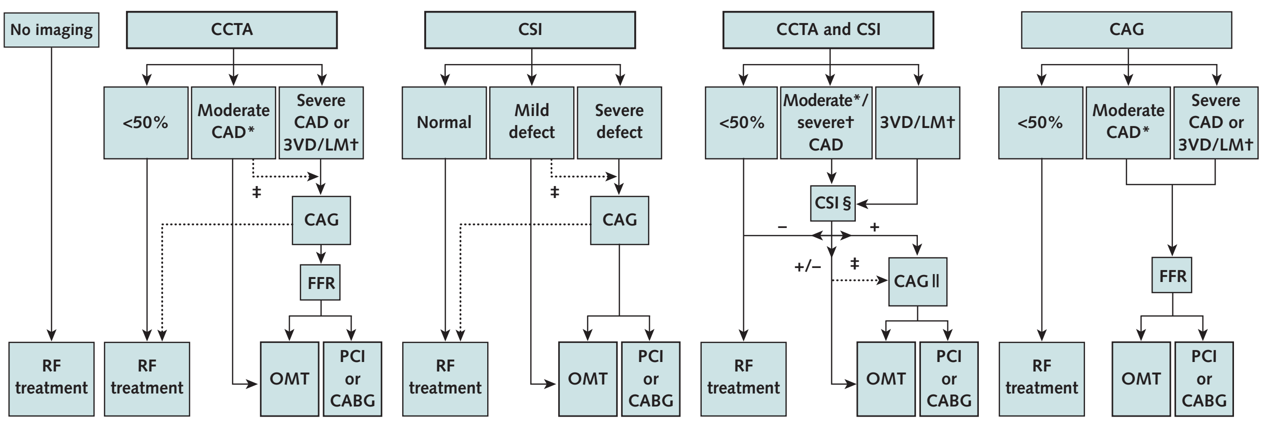
APC = Ambulatory Payment Classification; BSCI = British Society of Cardiovascular Imaging; CAG = catheter-based coronary angiography; CCTA = coronary computed tomography angiography; CMR = cardiac magnetic resonance imaging; CPT = Current Procedural Terminology; ECHO = stress echocardiography; EMC = Erasmus University Medical Center; HRG = National Health Service Health-Related Group; MI = myocardial infarction; SPECT = single-photon emission computed tomography.
* More details are provided in the **Appendix**.
† Incidental findings of indeterminate clinical importance that required follow-up testing were considered and occurred in 7% of all CCTAs, resulted in 9.4 mSv of extra radiation exposure, decreased quality of life by 0.001 y, and increased diagnostic costs by $559 (28) (corresponding to £359 for the United Kingdom and €434 for the Netherlands).
‡ Exercise or pharmacologic ECHO visualizing wall-motion abnormalities without use of contrast.
§ Converted to 2011 dollars (United States), pounds (United Kingdom), and euros (the Netherlands) using the country-specific consumer price indices (medical care component for the United States). All costs were modeled with a γ distribution using an SD of 20% of the mean. $1.00 was equivalent to £0.62 or €0.72. The CPT includes technical and professional cost components. The APC reflects the Medicare national average facility fee.

With Taxus and Cardiac Surgery) (33) studies (**Appendix Table 3**).

Data Analysis

All variables were entered into the model as distributions (**Appendix Tables 5** and **6**, available at www.annals.org). We used 2-level Monte Carlo microsimulation to calculate mean outcomes. Parameter values were randomly drawn from the distributions (10 000 samples) to perform probabilistic sensitivity analysis (second-order simulation). For each parameter value

Figure 1. Diagnostic strategies.



Diagnostic test results and treatment decisions based on them are shown. For simplicity, true disease severity (unknown to the physician) is not shown. 3VD = 3-vessel disease; CABG = coronary artery bypass graft surgery; CAD = coronary artery disease; CAG = catheter-based coronary angiography; CCTA = coronary computed tomography angiography; CSI = cardiac stress imaging; FFR = fractional flow reserve; LM = left main coronary stenosis; OMT = optimal medical treatment; PCI = percutaneous coronary intervention; RF = risk factor.
* Defined as 1- or 2-vessel disease (50% to 70%) or ≥70% stenosis in small vessels (no or mild inducible ischemia).
† Severe CAD was defined as 1- or 2-vessel disease with ≥70% stenosis (mild or severe inducible ischemia). 3VD/LM was defined as 3-vessel disease (≥50%) or left main coronary stenosis (≥50%) (severe inducible ischemia).
‡ The CCTA, CSI, and CCTA plus CSI strategies were analyzed according to conservative and invasive diagnostic work-ups. In the conservative strategy, patients with moderate CAD on CCTA or mild inducible ischemia on CSI (including those with false-positive results) were treated medically, without CAG. In the invasive strategy (*dashed lines*), patients with moderate CAD on CCTA or mild inducible ischemia were referred for CAG. Those with false-positive results on CCTA and CSI were thus identified as free of obstructive CAD or inducible ischemia, respectively.
§ Can show no inducible ischemia (−), suspected/mild inducible ischemia (+/−), or severe inducible ischemia (+). For patients with severe CAD and those with 3VD/LM, we assumed that 33% had mild ischemia and 67% had severe ischemia.
‖ FFR only if CSI was not done before CAG.

Table 1–Continued

SPECT		ECHO‡		CAG	
Mean Value	Source	Mean Value	Source	Mean Value	Source
0.88	Reference 14	0.79	Reference 17	1.00	–
0.61	Reference 14	0.87	Reference 17	1.00	–
9	Reference 18	–	–	7	Reference 18
0.01	–	0.01	–	0.11	Reference 20
–	–	–	–	0.05	Reference 21
0.00075	–	0.00075	–	0.005	–
549	CPT 78452 and 93015	264	CPT 93350 and 93015	2989	CPT 93454 and APC 80
343	HRG RA38Z-4	236	HRG EA45Z	1052	HRG EA36A
380	EMC fee	211	EMC fee	1513	EMC fee

set, 1000 random walks (representing individual patients) were simulated and outcomes were averaged across patients (first-order microsimulation). Using 1-way sensitivity analysis, we assessed the effect of varying key parameters.

Outcomes included lifetime costs, quality-adjusted life-years (QALYs), radiation exposure, and incremental cost-effectiveness ratios (ICERs). Parameter uncertainty is reflected in the 95% credible intervals (CrIs) of costs and QALYs (**Appendix**). We used country-specific recommendations for cost-effectiveness analysis (**Appendix Table 1**). Strategies were considered cost-effective when ICERs were less than \$50 000/QALY in the United States, less than £25 000/QALY in the United Kingdom, and less than €80 000/QALY in the Netherlands.

Role of the Funding Source

This study was supported by a Health Care Efficiency grant from the Erasmus University Medical Center. Additional funding came from the National Institute for Health Research Cardiovascular Biomedical Research Unit at Barts, Barts and The London Charity, and the National Institutes of Health. The funding sources had no involvement in the design or conduct of the study; the collection, management, analysis, or interpretation of the data; the preparation, review, or approval of the manuscript; or the decision to submit the manuscript for publication.

RESULTS

Base-Case Analysis

Radiation Exposure and Resource Use

Mean radiation exposure was low for strategies using stress echocardiography and cardiac stress MRI (6 to 9 mSv), intermediate for those using coronary CT angiography (11 to 14 mSv), and high for those using single-photon emission CT (15 to 18 mSv) (**Tables 2** and **3**).

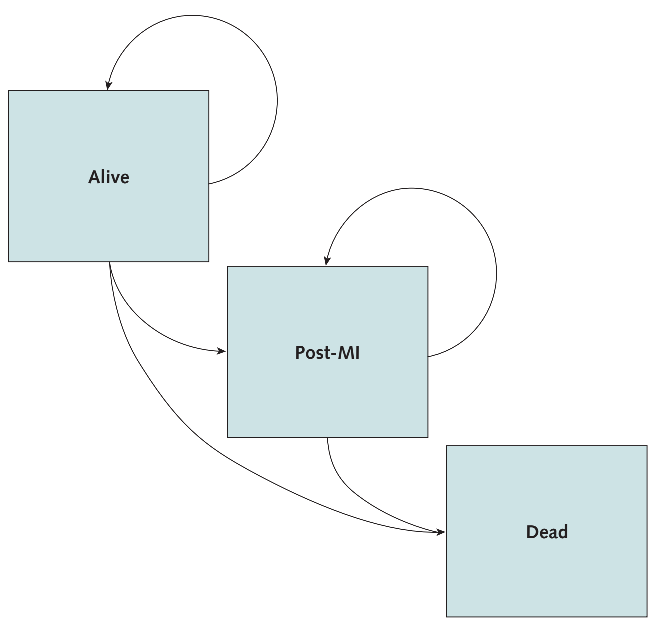
Optimal QALY Strategies

Estimated QALYs were similar across strategies (**Tables 2** and **3**). Using coronary CT angiography initially instead of cardiac stress imaging consistently increased effectiveness. Referral to catheter-based coronary angiography for all patients with abnormal test results (invasive diagnostic work-up) rather than referral only for those with severely abnormal test results (conservative diagnostic work-up) increased effectiveness.

Cost Implications and Cost-Effective Strategies

Strategies with multiple tests were less expensive and yielded more QALYs than single-test strategies. The strategy that maximized QALYs and was cost-effective in the United States and the Netherlands began with coronary CT angiography, continued with cardiac stress imaging if angiography found at least 50% stenosis in at least 1 coronary artery, and ended with

Figure 2. Long-term health states in the state-transition model for long-term prognosis.



The risk for a MACE depended on disease severity (see **Appendix Table 3**). Age- and sex-specific mortality (noncardiac) was modeled on the basis of country-specific vital statistics. To account for the higher risk for adverse events after MI, the rate of MACEs was increased with an HRR of 1.44 (95% CrI, 1.25 to 1.66) for patients in the post-MI health state (30). CrI = credible interval; HRR = hazard rate ratio; MACE = major adverse cardiac event; MI = myocardial infarction.

Table 2. Results of Base-Case Cost-Effectiveness Analysis: 60-Year-Old Men With a Pretest Probability of 30%*

Overall				United States (WTP Threshold of $50 000/QALY)			
Test	**Radiation Exposure, *mSv***	**Initial CAG, %**	**Initial PCI/CABG, %**	**Test**	**Cost, $**	**QALYs**	**ICER, *$/QALY***
No imaging	5	0	0/0	No imaging	6827	11.62	–
CCTA + ECHO-i	13	24	3/5	CCTA + ECHO-i	11 963	11.85	**22 000**
ECHO-i	8	33	3/5	ECHO-i	11 975	11.85	Dominated
CCTA + ECHO	11	6	3/3	CCTA + ECHO	12 144	11.85	Dominated
CCTA + CMR-i	13	28	3/5	CCTA + CMR-i	12 167	11.85	Dominated
CCTA + SPECT-i	16	29	3/5	CCTA + SPECT-i	12 170	11.85	Dominated
CCTA-i	13	37	4/6	CCTA-i	12 360	11.85	Dominated
CCTA + CMR	11	7	3/3	CCTA + CMR	12 445	11.85	Dominated
CCTA + SPECT	15	7	3/3	CCTA + SPECT	12 543	11.85	Dominated
CMR-i	8	43	4/5	CMR-i	12 606	11.85	Dominated
ECHO	6	6	3/3	ECHO	12 829	11.84	Dominated
SPECT-i	18	54	4/5	SPECT-i	12 848	11.85	Dominated
CCTA	11	12	4/6	CCTA	13 177	11.84	Dominated
CAG	12	100	4/6	CAG	13 823	11.84	Dominated
CMR	6	7	4/4	CMR	14 172	11.84	Dominated
SPECT	15	7	4/4	SPECT	15 312	11.83	Dominated

CABG = coronary artery bypass graft surgery; CAG = catheter-based coronary angiography; CCTA = coronary computed tomography angiography; CMR = cardiac magnetic resonance imaging; ECHO = stress echocardiography; i = invasive diagnostic work-up; ICER = incremental cost-effectiveness ratio; PCI = percutaneous coronary intervention; QALY = quality-adjusted life-year; SPECT = single-photon emission computed tomography; WTP = willingness-to-pay.
* ICERs were calculated vs. the next cheaper nondominated strategy. ICERs in boldface reflect the optimal strategy (under the WTP threshold).
† ICER exceeds that of another more costly and more effective strategy.

catheter-based coronary angiography if stress imaging induced ischemia of any severity. In contrast, for U.K. men, the preferred strategy was optimal medical therapy without catheter-based coronary angiography if coronary CT angiography found only moderate CAD or stress imaging induced only mild ischemia. In these strategies, stress echocardiography was consistently more effective and less expensive than other stress imaging tests. For U.K. women, the optimal strategy was stress echocardiography followed by catheter-based coronary angiography if echocardiography induced mild or moderate ischemia (Tables 2 and 3 and Figure 3).

Sensitivity Analysis

Pretest Probability

The model was reanalyzed at pretest probabilities (34) of 10%, 30%, 50%, 70%, and 90%. Coronary CT angiography plus stress echocardiography (invasive diagnostic work-up) was cost-effective when the pretest probability was 50% or less for U.S. men and 30% or less for U.S. women. For the United Kingdom, coronary

Table 3. Results of Base-Case Cost-Effectiveness Analysis: 60-Year-Old Women With a Pretest Probability of 30%*

Overall				United States (WTP Threshold of $50 000/QALY)			
Test	**Radiation Exposure, *mSv***	**Initial CAG, %**	**Initial PCI/CABG, %**	**Test**	**Cost, $**	**QALYs**	**ICER, *$/QALY***
No imaging	6	0	0/0	No imaging	7506	12.11	–
CCTA + ECHO-i	13	24	3/5	CCTA + ECHO-i	12 750	12.35	**21 000**
ECHO-i	8	33	3/5	ECHO-i	12 764	12.35	Dominated
CCTA + CMR-i	13	28	3/5	CCTA + CMR-i	12 951	12.35	Dominated
CCTA + SPECT-i	17	29	3/5	CCTA + SPECT-i	12 952	12.35	Dominated
CCTA + ECHO	12	6	3/3	CCTA + ECHO	13 000	12.35	Dominated
CCTA-i	14	37	4/6	CCTA-i	13 145	12.35	Dominated
CCTA + CMR	12	7	3/3	CCTA + CMR	13 315	12.35	Dominated
CMR-i	9	43	4/5	CMR-i	13 392	12.35	Dominated
CCTA + SPECT	15	7	3/3	CCTA + SPECT	13 421	12.35	Dominated
SPECT-i	18	54	4/5	SPECT-i	13 632	12.35	Dominated
ECHO	6	6	3/3	ECHO	13 771	12.34	Dominated
CCTA	12	12	4/6	CCTA	14 109	12.34	Dominated
CAG	12	100	4/6	CAG	14 619	12.34	Dominated
CMR	6	7	4/4	CMR	15 198	12.33	Dominated
SPECT	15	7	4/4	SPECT	16 448	12.33	Dominated

CABG = coronary artery bypass graft surgery; CAG = catheter-based coronary angiography; CCTA = coronary computed tomography angiography; CMR = cardiac magnetic resonance imaging; ECHO = stress echocardiography; i = invasive diagnostic work-up; ICER = incremental cost-effectiveness ratio; PCI = percutaneous coronary intervention; QALY = quality-adjusted life-year; SPECT = single-photon emission computed tomography; WTP = willingness-to-pay.
* ICERs were calculated vs. the next cheaper nondominated strategy. ICERs in boldface reflect the optimal strategy (under the WTP threshold).

Table 2—Continued

United Kingdom (WTP Threshold of £25 000/QALY)				The Netherlands (WTP Threshold of €80 000/QALY)			
Test	**Cost, £**	**QALYs**	**ICER, £/QALY**	**Test**	**Cost, €**	**QALYs**	**ICER, €/QALY**
No imaging	1577	11.55	–	No imaging	5982	13.87	–
ECHO	2717	11.77	5000	CCTA + ECHO	7417	14.15	5000
CCTA + ECHO	2763	11.78	**7000**	CCTA + CMR	7491	14.14	Dominated
ECHO-i	2789	11.78	Extended dominance†	CCTA + ECHO-i	7518	14.15	**38 000**
CCTA + SPECT	2832	11.78	Dominated	ECHO-i	7542	14.15	Dominated
CCTA + ECHO-i	2853	11.78	32 000	CCTA + SPECT	7548	14.14	Dominated
CCTA	2859	11.77	Dominated	ECHO	7549	14.14	Dominated
CCTA + CMR	2893	11.78	Dominated	CCTA + CMR-i	7587	14.15	Dominated
CCTA + SPECT-i	2920	11.78	Dominated	CCTA + SPECT-i	7626	14.15	Dominated
CCTA + CMR-i	2986	11.78	Dominated	CCTA	7680	14.13	Dominated
CCTA-i	2988	11.78	Dominated	CCTA-i	7737	14.14	Dominated
SPECT	3085	11.76	Dominated	CMR-i	7783	14.14	Dominated
SPECT-i	3091	11.78	Dominated	CMR	7911	14.13	Dominated
CMR	3143	11.76	Dominated	SPECT-i	8004	14.14	Dominated
CMR-i	3186	11.78	Dominated	SPECT	8294	14.12	Dominated
CAG	3341	11.77	Dominated	CAG	8457	14.14	Dominated

CT angiography was cost-effective as a triage test before stress echocardiography when the probability was 30% or less for men and 10% for women. For the Netherlands, coronary CT angiography plus stress echocardiography (invasive diagnostic work-up) was cost-effective up to a pretest probability of 70% in both men and women. Above these thresholds, stress echocardiography alone (invasive or conservative diagnostic work-up) was cost-effective (**Appendix Table 7**, available at www.annals.org).

False-Negative Results

In the base-case analysis, we assumed that patients with false-negative test results returned to their physicians within 1 year. Changing this assumption to 3 years did not have a major effect on the results of our cost-effectiveness analysis. The strategies that involved only coronary CT angiography became more favorable, but the ICER for invasive coronary CT angiography was still above the willingness-to-pay threshold (**Appendix Figure 2**, available at www.annals.org).

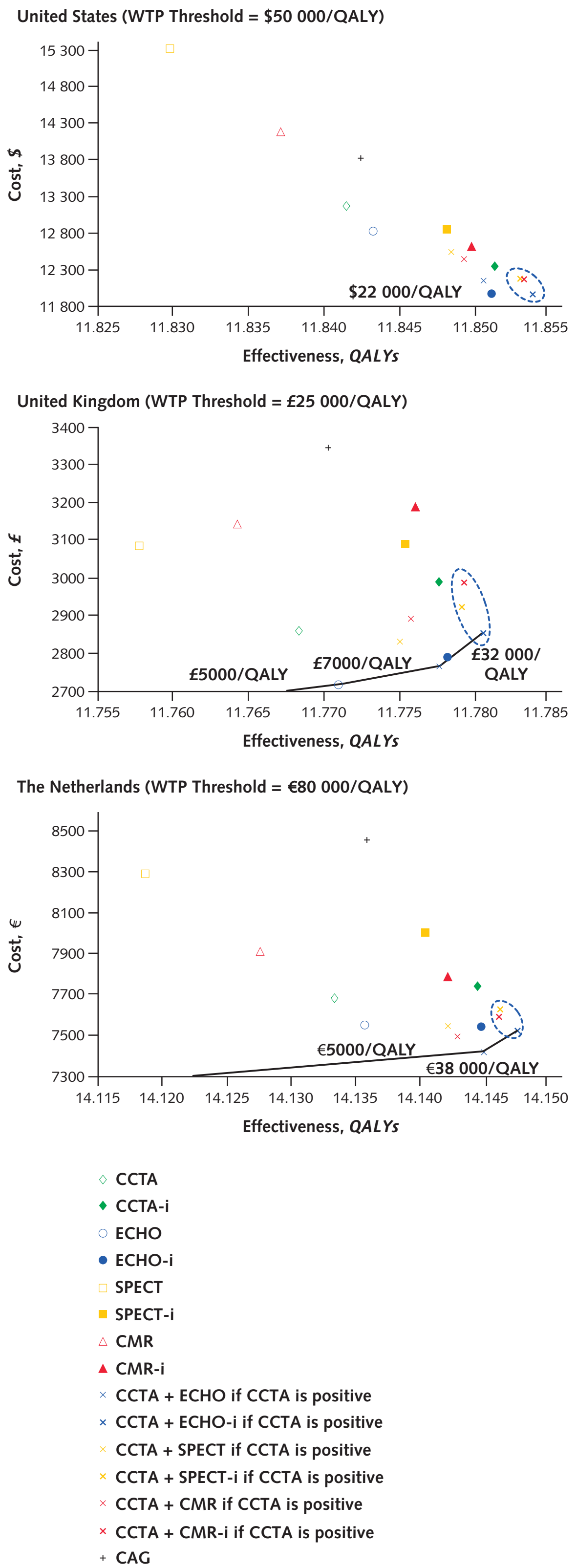
Invasive Versus Noninvasive Diagnostic Work-up

The invasive diagnostic work-up strategies identified all false-positive results as true-negative because all patients with a positive result were referred for catheter-based coronary angiography. However, in the strategies with a conservative diagnostic work-up, patients with false-positive results were not identified because only those with severely abnormal test results were referred for catheter-based coronary angiography. Instead, those with false-positive results received

Table 3—Continued

United Kingdom (WTP Threshold of £25 000/QALY)				The Netherlands (WTP Threshold of €80 000/QALY)			
Test	**Cost, £**	**QALYs**	**ICER, £/QALY**	**Test**	**Cost, €**	**QALYs**	**ICER, €/QALY**
No imaging	1687	11.85	–	No imaging	4997	14.85	–
ECHO	2844	12.08	5000	CCTA + ECHO	6453	15.15	5000
CCTA + ECHO	2881	12.08	7000	CCTA + CMR	6533	15.15	Dominated
ECHO-i	2900	12.06	**8000**	CCTA + ECHO-i	6535	15.16	**18 000**
CCTA + SPECT	2952	12.08	Dominated	ECHO-i	6559	15.15	Dominated
CCTA + ECHO-i	2964	12.09	53 000	CCTA + SPECT	6591	15.15	Dominated
CCTA	2984	12.07	Dominated	CCTA + CMR-i	6604	15.15	Dominated
CCTA + CMR	3012	12.08	Dominated	ECHO	6608	15.14	Dominated
CCTA + SPECT-i	3031	12.09	Dominated	CCTA + SPECT-i	6641	15.15	Dominated
CCTA + CMR-i	3096	12.09	Dominated	CCTA	6735	15.14	Dominated
CCTA-i	3098	12.08	Dominated	CCTA-i	6752	15.15	Dominated
SPECT-i	3200	12.08	Dominated	CMR-i	6799	15.15	Dominated
SPECT	3231	12.06	Dominated	CMR	6996	15.13	Dominated
CMR	3277	12.07	Dominated	SPECT-i	7018	15.15	Dominated
CMR-i	3295	12.08	Dominated	SPECT	7409	15.12	Dominated
CAG	3450	12.08	Dominated	CAG	7475	15.14	Dominated

Figure 3. Cost-effectiveness analysis for 60-year-old men with a 30% prevalence of obstructive CAD.



Note the different *x*- and *y*-axis scales among the graphs. Reported ICERs correspond to the strategies connected by a solid line. The CCTA plus cardiac stress imaging (invasive) strategies are enclosed by a dashed line. The "no imaging" strategy yielded 11.62, 11.55, and 13.87 QALYs at costs of $6827, £1577, and €598 for the United States, the United Kingdom, and the Netherlands, respectively. Results for women are provided in **Appendix Figure 1** (available at www.annals.org). CAD = coronary artery disease; CAG = catheter-based coronary angiography; CCTA = coronary computed tomography angiography; CMR = cardiac magnetic resonance imaging; ECHO = stress echocardiography; i = invasive diagnostic work-up; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; SPECT = single-photon emission computed tomography; WTP = willingness-to-pay.

lifelong optimal medical treatment, which increased costs and reduced quality of life. We reduced the quality-of-life estimates by 0.01 year for patients with false-positive results because they had to take unnecessary medication. Under the extreme assumption that patients with false-positive results were unharmed by taking unnecessary medication (no reduction in quality of life), coronary CT angiography plus stress echocardiography (conservative diagnostic work-up) became more favorable, with an ICER of $54 000/QALY for the United States, which is just above the willingness-to-pay threshold. We also performed an extreme sensitivity analysis in which all patients with false-positive results benefitted from optimal medical treatment. All invasive diagnostic work-up strategies were dominated by the conservative strategies, and coronary CT angiography plus stress echocardiography was cost-effective, with an ICER of $21 000/QALY for the United States.

Exercise Electrocardiography for Patients Who Had No Abnormalities on Resting Electrocardiography and Were Able to Exercise

Under the assumption that patients with equivocal results on exercise electrocardiography did not have additional imaging tests and that positive results were as informative as the presence of inducible ischemia on cardiac stress imaging, strategies with initial exercise electrocardiography followed by further imaging studies if results were positive were less expensive and at least as effective as initial imaging strategies. Exercise electrocardiography plus echocardiography (invasive diagnostic work-up) ($11 397; 11.86 QALYs) was cost-effective (**Appendix Table 8**, available at www.annals.org).

Probabilistic Sensitivity Analysis

Differences in QALYs among strategies were small, whereas differences in costs were more substantial. Uncertainty in outcomes is reflected in the CrIs and is summarized in **Appendix Tables 9** and **10** (available at www.annals.org).

DISCUSSION

Analysis of our decision model suggested that for patients with nonacute chest pain and a low to intermediate pretest probability of CAD (based on clinical presentation and risk factors [34] with or without exercise electrocardiography), coronary CT angiography as a triage test before cardiac stress imaging was cost-effective. Differences among the cardiac stress imaging tests were small, but stress echocardiographic strategies were consistently more effective and less expensive than the corresponding strategies with stress single-photon emission CT or cardiac stress MRI. For patients with an intermediate to high pretest probability, direct testing with echocardiography was cost-effective. The pretest probability thresholds for CAD below which coronary CT angiography plus stress echocardiography was cost-effective and above which stress echocardiography was cost-effective varied among countries. Compared with the conservative diagnostic work-up, the invasive work-up maximized QALYs and was cost-effective in the United States and the Netherlands.

The differences in quality-adjusted life expectancy among the strategies were marginal, which is explained in part by our assumption that patients with CAD who were missed (false-negative results) returned to their physician. Despite this, stress echocardiography was consistently more effective and less expensive than stress single-photon emission CT and cardiac stress MRI. We performed a sensitivity analysis assuming that false-negative results remained false-negative for 3 years instead of 1 year and found similar results. The cardiac stress MRI and stress single-photon emission CT strategies were most expensive, which is explained not only by their higher cost but also by their lower specificity, which results in more false-positive results. Patients with false-positive results either receive unnecessary medical treatment or have unnecessary catheter-based coronary angiography. In the conservative diagnostic work-up strategies, patients with mildly positive test results (including those with false-positive results) were not referred for catheter-based coronary angiography and subsequently received optimal medical treatment (unnecessary for those with false-positive results), which results in lifelong medication use and increases costs. In the United States, the invasive diagnostic work-up strategies were less expensive because they avoided the high cost of unnecessary medication. We performed an extreme sensitivity analysis that included a treatment benefit of optimal medical treatment for all patients with false-positive results, which increased the effectiveness (QALYs) of the conservative diagnostic work-up strategy beyond that of invasive strategies so that coronary CT angiography plus stress echocardiography (conservative diagnostic work-up) became cost-effective. This sensitivity analysis probably overestimated the benefit of optimal medical treatment because, in reality, only patients with false-positive results and an unhealthy cardiovascular risk profile would benefit substantially from optimal medical treatment. Thus, these results imply that if a patient without CAD has a risk factor profile that warrants medical treatment, performing invasive, catheter-based coronary angiography after a false-positive result will not change clinical management, whereas if a patient has a healthy risk factor profile, invasive, catheter-based coronary angiography after a false-positive result on a noninvasive test would change management by avoiding long-term medical treatment.

The U.S. guidelines (2) recommend functional noninvasive imaging in patients with chest pain who have greater than a 10% probability of CAD or contraindications for exercise electrocardiography, and the U.K. guidelines (4) recommend it in those with a 30% to 60% probability of CAD. This is consistent with our model, which suggested that invasive stress echocardiography (the United Kingdom) or coronary CT angiography plus stress echocardiography (the United States and the Netherlands) is cost-effective for patients with a 30% probability. In the United Kingdom, direct catheter-based coronary angiography is recommended if the probability is 61% to 90%, whereas in the United States it is recommended if the probability is greater than 90%. In contrast, our results suggest that stress echocardiography is optimal for such patients. Our model suggests that even if the pretest probability is as high as 90%, an initial noninvasive test is still worthwhile.

Although the diagnostic performance of coronary CT angiography, cardiac stress MRI, stress single-photon emission CT, stress echocardiography, and exercise electrocardiography has been studied extensively, literature on direct and long-term comparisons among these methods is scarce. Nevertheless, the incremental prognostic value of perfusion imaging is well-established, and complementary roles of coronary CT angiography and cardiac stress MRI in the diagnostic work-up for chest pain have been proposed (10). A cost analysis based on the European Cardiovascular Magnetic Resonance Registry showed that using cardiac stress MRI as a gatekeeper for catheter-based coronary angiography resulted in cost savings (35). A previously published cost-effectiveness analysis compared several coronary CT angiography–based strategies with stress single-photon emission CT and direct catheter-based coronary angiography and found that the coronary CT angiography–based strategies were optimal up to an 80% prevalence of obstructive CAD (36). However, other researchers found that Medicare costs for patients who had coronary CT angiography were higher than for those who had stress testing (37).

Some limitations of our decision model deserve attention. First, we analyzed several diagnostic strategies from the perspective of the United Kingdom, the United States, and the Netherlands. Health care costs can vary considerably among countries, which is why we used country-specific cost estimates. Although we recognize that diagnostic strategies and treatment decisions may also vary across countries (for example, because of differences in guidelines and local practices), these model characteristics were held constant to highlight the effect of country-specific costs on optimal evaluation strategies. Second, although our analysis takes into account the presence of inducible ischemia in patients with CAD, it does not differentiate between the presence of perfusion defects and wall-motion abnormalities, both of which are manifestations of inducible ischemia. Because stress echocardiography involves the visualization of wall-motion abnormalities and stress single-photon emission CT and cardiac stress MRI visualize perfusion defects, the implicit assumption is that a wall-motion abnormality is equivalent to a perfusion defect. This limitation may have an effect when stress echocardiography strategies are being compared with other strategies, with a bias against stress echocardiography. Of note, despite this bias, stress echocardiography strategies were cost-effective. Third, we assumed that patients with false-negative results were identified after the first year but that false-positive results remained false-positive, which biased against strategies with low specificity (Appendix). We also assumed that all patients with severe CAD (or moderate CAD with severe ischemia) had revascularization. For simplicity, we did not take into account exceptions to the rule. For example, in patients with diabetes, CABG may be preferred over PCI. Furthermore, we assumed that the relative benefit of treatment (adjusted hazard rate ratio) was the same for optimal medical treatment, PCI, and CABG. However, our simplifications with regard to treatment effects and quality of life affect all diagnostic strategies alike and are therefore unlikely to change the optimal decision.

The aim of our analysis was to determine the optimal imaging strategy for patients with chest pain with an intermediate probability of CAD based on clinical characteristics and laboratory testing, regardless of whether they had undergone exercise electrocardiography. Despite its poor diagnostic performance (38), evidence of cost-effective alternative strategies (39, 40), and evidence of an incremental prognostic benefit of imaging (41), U.S. guidelines (1, 2) recommend exercise electrocardiography for patients with a low to intermediate probability, and European guidelines (3) recommend it for those with a 10% to 90% probability. Therefore, in a sensitivity analysis that only applied to patients without resting electrocardiographic abnormalities who were able to exercise, we examined the cost-effectiveness of exercise electrocardiography. Most important, this analysis biased the analysis in favor of exercise electrocardiography by assuming that it detected all persons with inducible ischemia on imaging. Future research is necessary to investigate the relationship between the presence of abnormalities on exercise electrocardiography and the presence of inducible ischemia on imaging. Another limitation of our research is that we did not consider possible unavailability of tests or the presence of contraindications for coronary CT angiography or cardiac stress imaging (such as renal failure, contrast allergy, claustrophobia, or poor acoustic window). Our results apply to settings in which all of the tests considered are accessible, feasible, safe, and appropriate for patients.

In the current analysis, we considered coronary CT angiography and 3 different cardiac stress imaging tests for the diagnostic work-up of patients with chest pain. Other strategies, such as those involving stress positron emission CT and myocardial perfusion or fractional flow measurement by CT, may be of interest for future cost-effectiveness analyses.

In conclusion, for 60-year-old patients with a low to intermediate pretest probability of CAD, coronary CT angiography is a cost-effective triage test before any cardiac stress imaging test, and coronary CT angiography and cardiac stress imaging strategies were similar. Stress echocardiography is a good, widely available, and cost-effective cardiac stress imaging technology for the investigation of suspected CAD. However, the choice of cardiac stress imaging test may also be affected by patient factors (such as body habitus making echocardiography difficult or contraindications), local expertise, and local availability of imaging methods.

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Note: Dr. Hunink had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Reproducible Research Statement: *Study protocol, statistical code, and data set:* The authors have provided extensive detail about the structure of the model, the assumptions made, and the input data that will allow reproduction of the decision model in the Appendix. They are willing to share the decision model in the context of a collaborative project. Dr. Hunink may be contacted for this purpose (e-mail, m.hunink@erasmusmc.nl).

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Appendix: Model Details

A microsimulation model was developed in DATA Pro 2009 Suite (TreeAge Software). The model is available on request from the corresponding author. Further details on model parameters and assumptions are provided in the following sections.

Target Population

Our target population consisted of 60-year-old patients with stable chest pain with an intermediate "pre-imaging" probability of CAD (defined as ≥50% stenosis) based on clinical characteristics and laboratory testing, regardless of whether they had undergone previous exercise electrocardiography. We considered patients without a history of CAD, PCI, or CABG. Our base-case analysis comprised patients with a 30% probability of CAD, who are eligible for imaging (1, 29). Severity of disease (Appendix Table 3) in our target population was based on coronary CT angiography and catheter-based coronary angiography data from our hospital (54) and was slightly adjusted to ensure internal consistency of the model. For example, the actual observed percentage of patients with obstructive CAD on coronary CT angiography was 27%, which was rounded to 30% for simplicity. Because of the small numbers of patients with severe CAD and 3-vessel disease or left main coronary stenosis, we assumed both groups to be equal in size. For internal consistency, we assumed that the moderate CAD group was larger than the severe CAD group. Furthermore, limited data were available on ischemia detection, which is why for patients with severe CAD and those with 3VD/LM, we assumed that 33% had mild ischemia and 67% had severe ischemia.

Test Characteristics

Sensitivity and specificity estimates were derived from published meta-analyses (Table 1). Specificity applied to normal coronary arteries and mild CAD (<50% stenosis), which corresponds to the negativity criterion in the meta-analyses. We assumed that sensitivity applied equally to moderate CAD, severe CAD, and 3-vessel disease or left main coronary stenosis. We assumed conditional independence with regard to the sensitivity and specificity for coronary CT angiography and cardiac stress imaging. For coronary CT angiography and cardiac stress imaging, we assumed that false-positive results only showed mild CAD and mild inducible ischemia, respectively.

Relationship Perfusion Defect Versus Wall-Motion Abnormality

Although our analysis accounted for the presence of inducible ischemia in patients with CAD, it did not differentiate between the presence of perfusion defects and wall-motion abnormalities (both different manifestations of inducible ischemia). Because stress echocardiography involves the visualization of wall-motion abnormalities, whereas stress single-photon emission CT and stress cardiac MRI visualize perfusion defects, the implicit assumption was that a wall-motion abnormality is equivalent to a perfusion defect. This assumption may have resulted in a slight overestimation of the costs for the stress echocardiography strategies because one would find fewer wall-motion abnormalities than perfusion defects (given that it occurs later in the ischemic cascade), which would in turn lead to fewer coronary interventions. This limitation may have an impact when stress echocardiography strategies are compared with other strategies, with a bias against stress echocardiography. Despite this bias, stress echocardiography strategies are cost-effective. Furthermore, we assumed that a fractional flow measurement provided equivalent prognostic information as conferred by inducible ischemia demonstrated by a stress imaging test.

Treatment Strategies

Patients with false-positive test results were referred for catheter-based coronary angiography (invasive diagnostic work-up) and subsequently identified as negative. However, in the conservative diagnostic work-up, patients with false-positive results were not referred for catheter-based coronary angiography. We assumed such patients received optimal medical treatment for their remaining life span, and we modeled the effect on costs only and added a small disutility for taking unnecessary medication (no effect on the rate of MACEs).

Patients with moderate CAD without ischemia and a negative test result were labeled as false-negative in our model (because moderate CAD implies ≥50% stenosis and, thus, obstructive CAD), which implies that these patients did not receive appropriate treatment and were thus denied the benefit. However, in clinical practice, these patients are likely to be treated with medication. Using a tracker variable, we tracked this subgroup of patients and assumed that they received appropriate medical therapy. Similarly, patients with moderate CAD without ischemia and a positive test result were classified as true-positive and received optimal medical treatment according to our diagnostic pathways (Figure 1). However, optimal treatment for these patients was assumed to be risk factor management (because of the absence of inducible ischemia). Using a tracker variable, we tracked this subgroup of patients and labeled them as false-positive.

Medication use depends on the coronary CT angiography findings and the treatment assigned (Appendix Table 4). In the cardiac stress imaging strategies, the distinction between normal coronary arteries and mild CAD could not be made for patients without inducible ischemia and no further testing. For those patients, we assumed that baseline medication was maintained without optimal medical treatment.

The revascularizations that occurred during follow-up were assumed to be PCIs in 75% of the cases and CABG in 25%. This assumption was based on a cohort from the Erasmus University Medical Center (59), which was consistent with observations from the COURAGE (51) and SYNTAX (53) studies.

Long-Term Prognosis

Prognosis was modeled by using the rates of MACEs. For patients with 3-vessel disease or left main coronary stenosis, rates of MACEs were based on the CABG group of the SYNTAX trial (52, 53), which compared CABG with drug-eluting stenting for patients with 3-vessel disease or left main coronary stenosis (mean follow-up, 3 years). For patients with suspected or mild inducible ischemia and moderate to severe CAD (treated with optimal medical treatment) and patients with severe CAD and severe inducible ischemia (treated with PCI), prognosis was based on the optimal medical treatment and PCI groups of the COURAGE trial (51), respectively (mean follow-up, 4.6 years). To allow for a higher event rate in the first year after treatment initiation (for optimal medical treatment, PCI, and CABG), MACE rates were calculated separately for the first year versus all subsequent years. For patients without CAD or with mild CAD, prognosis was based on a recent meta-analysis of the prognostic value of coronary CT angiography (50). Coronary CT angiography findings probably altered medical management and, hence, prognosis in patients with mild CAD. For those with a negative finding who were "normal" on cardiac stress imaging and were not given optimal medical treatment, the favorable prognostic implications of having coronary CT angiography may have resulted in overestimation of survival in patients with mild CAD. The prognosis of patients with moderate CAD without inducible ischemia was assumed to be equal to the prognosis of those with mild CAD.

Harmful effects of radiation exposure were not modeled, but cumulative (lifetime) radiation exposure is reported in Tables 2 and 3.

Obtaining Rates of MACEs

For each disease category, we searched the literature for large studies that reported MACE rates for patients similar to those in our disease category. The original studies reported cumulative probabilities, which we converted to rates. The reported 1-year and long-term cumulative probabilities were used to calculate the rate for the first year and subsequent years separately. When the MACE outcome was not reported separately, it was calculated by adding the reported probability of revascularization and death (assuming that all patients with acute MI have revascularization). We calculated the rates of the composite outcome (listed in Appendix Table 3). To model costs and utilities separately for the components of the composite outcome, we also accounted for the rates of the MACE components (not listed in Appendix Table 3 but available on request). Because of competing risks, the sum of the rates of the components of the composite outcome usually exceeds the rate of the composite outcome. To correct for this, the rate of the component was divided by the sum of the rates of the components. The resulting proportion was multiplied by the rate of the composite outcome, which resulted in rates adjusted for competing hazards from the MACE components.

Natural History

Progression of disease was modeled through the MACE rates. The risk for death from noncardiac causes was based on the most recent age- and sex-specific mortality rates available for the United States (60), the United Kingdom (61), and the Netherlands (62). The proportion of background mortality that was considered noncardiac was based on Dutch life tables. The following codes from the International Classification of Diseases, 10th Revision, were considered as cardiac deaths: I-11, I-20 to I-25, I-42, I-44 to I-50, and R-96.

Patients with false-negative results were assumed to return to their physician within the first year and have additional testing. Additional testing consisted of cardiac stress imaging in the coronary CT angiography strategy and coronary CT angiography in the cardiac stress imaging strategy. Subsequent additional testing was based on the diagnostic strategies as described (invasive vs. conservative).

False-Negative and False-Positive Results

In our analysis, patients with false-positive test results had a substantial negative implication for a strategy because such results were assumed to remain false-positive. On the other hand, patients with false-negative results had fewer negative implications because we assumed that they were reevaluated within the first year. These assumptions created a bias against strategies with a low specificity. We performed a sensitivity analysis for U.S. men in which we assumed that those with false-positive results discontinued medical therapy after the first year (and that additional testing was not involved). We found that the expected QALYs for all strategies became similar (ranging from 11.995 to 12.008). This is explained by the minimal consequences of false-negative and false-positive results in this sensitivity analysis. The echocardiography (conservative) and coronary CT angiography (conservative) strategies were least expensive; all other strategies were dominated. The conservative coronary CT angiography strategy was cost-effective, with an ICER of $27 000/QALY.

Costs

Costs were based on evidence from the literature and expert opinion (Table 1 and Appendix Table 2) and were converted to 2011 dollars (United States), pounds (United Kingdom), and euros (the Netherlands) by using the country-specific consumer price indices (medical care component for the United States).

Quality of Life

We used age- and sex-specific quality-of-life estimates for patients without CAD and without inducible ischemia based on EQ-5D reference values for the general population (31). For patients with CAD who received treatment, we used published domain-specific Short-Form-36 and RAND-36 scores based on the optimal medical treatment group of the COURAGE trial (32) and the CABG group of the SYNTAX trial (33), respectively. The scores were converted to EQ-5D utilities by using a validated algorithm (63) and were subsequently used to calculate the quality-of-life decrement relative to the general population of the same age and sex. For the first year, quality of life for patients receiving optimal medical treatment, PCI, and CABG was based on the average utility decrement as observed in the trials. For subsequent years, the last observed utility in the trial was carried forward. Baseline utility measurements from the trials were used to model the quality of life for patients who forwent the benefit of treatment (false-negative results) (Appendix Table 3). The quality of life of patients with false-positive results was adjusted to reflect the small disutility of taking medication (64).

Other Assumptions

We assumed that all false-positive results on cardiac stress imaging were due to artifacts occurring in patients without obstructive CAD. However, abnormal cardiac stress imaging results in women without obstructive CAD on catheter-based coronary angiography may represent "real" ischemia (as opposed to artifacts) caused by small vessel disease and microvascular dysfunction.

We only report the cumulative radiation exposure and did not incorporate the potential harmful effects of radiation. Diagnostic strategies involving single-photon emission CT resulted in the highest mean exposure to radiation (Tables 2 and 3), which should be taken into account during interpretation of the results of our cost-effectiveness analysis.

Patients with false-positive results in conservative strategies were not referred for catheter-based coronary angiography and were assumed to receive optimal medical treatment for their remaining life expectancy. Using a disutility for taking medication, we adjusted the quality of life for patients with false-positive results. However, we did consider the potential benefit of optimal medical treatment in patients without obstructive CAD in sensitivity analysis.

Cardiac stress MRI has other advantages that were not modeled. In addition to visualizing myocardial perfusion, it can detect nonischemic causes of chest pain and myocardial viability, which may in turn guide decisions about revascularization. These advantages potentially improve the cost-effectiveness of cardiac stress MRI, particularly when the differential diagnosis includes nonischemic causes of chest pain.

Finally, the sensitivity and specificity estimates were derived from published studies probably conducted in experienced centers, which may not reflect the diagnostic performance when applied in other centers. Furthermore, the literature on diagnostic test performance may be subject to verification bias and publication bias.

Data Analysis

All variables were entered in the model as distributions (Appendix Table 5 and 6). Two-level Monte Carlo microsimulation was used to calculate mean outcomes. Parameter values were randomly drawn from the distributions (10 000 samples) to perform probabilistic sensitivity analysis (second-order simulation). For each parameter value set, 1000 random walks (representing identical individual patients) were simulated and outcomes were averaged across patients (first-order microsimulation). Using 1-way sensitivity analysis, we assessed the effect of varying key parameters across plausible values. Parameter uncertainty is reflected in the 95% CrIs of costs and QALYs (**Appendix Tables 9** and **10**). The ICER of strategy A versus strategy B was defined as the difference in costs divided by the difference in effectiveness (strategy A minus strategy B). An ICER below the willingness-to-pay threshold implies that strategy A is a cost-effective alternative to strategy B. Strategies were compared by calculating the ICER compared with the next costlier strategy, eliminating strategies that were dominated (more costly and less effective) and extended-dominated (when the ICER exceeded that of another more costly and more effective strategy). We used country-specific recommendations for cost-effectiveness analysis (**Appendix Table 1**). Strategies with ICERs of less than \$50 000/QALY, £25 000/QALY, and €80 000/QALY were considered cost-effective in the United States, the United Kingdom, and the Netherlands, respectively.

Extra Sensitivity Analysis (U.K. Perspective)

Changing the sensitivity and specificity for echocardiography to 0.70 and 0.80, respectively, resulted in coronary CT angiography plus invasive stress echocardiography (invasive) as the optimal strategy (**Appendix Figure 3**). If the cost of a cardiac stress MRI scan was decreased from £548 to £200, the total cost for the strategies that involved cardiac stress MRI decreased substantially, but the conclusion was the same (**Appendix Figure 4**).

Interpreting the Results: Invasive Versus Conservative Strategies

Increasing the pretest probability to 70% resulted in less favorable ICERs for the invasive strategies when compared with their corresponding conservative strategies. This may seem counterintuitive but can be explained by the number of patients with false-positive results, who had mildly abnormal cardiac stress imaging results but no obstructive CAD. The number of patients with false-positive results is highest when the pretest probability is low. The conservative diagnostic work-up implies further testing for patients with a severely abnormal cardiac stress imaging result and lifelong optimal medical treatment for patients with a mildly abnormal cardiac stress imaging result (which includes those with false-positive results), whereas the invasive diagnostic work-up results in referral to catheter-based coronary angiography for all patients with abnormal cardiac stress imaging results (regardless of whether the result was mildly or severely abnormal). The invasive diagnostic work-up therefore identifies patients with false-positive results as those without obstructive CAD and prevents unnecessary lifelong medical therapy in them. According to our results, when the pretest probability is 30%, the benefits and harms of catheter-based coronary angiography (after a positive result on stress echocardiography) outweigh the benefits and harms (primarily costs) of lifelong medical therapy for patients without obstructive CAD and false-positive results. In a population with a low pretest probability, most patients are free of obstructive CAD, so the invasive diagnostic strategy becomes more cost-effective by avoiding the lifelong costs and slightly reduced quality of life from medical therapy resulting from false-positive results on noninvasive tests. When the pretest probability is higher, the trade-off changes because a larger proportion of patients have obstructive CAD, resulting in more true-positive than false-positive results among those with mildly abnormal cardiac stress imaging results. Therefore, in the group of patients with mildly positive cardiac stress imaging results, direct medical therapy was more cost-effective than catheter-based coronary angiography. This trend was not observed in the analysis for the United States, which is explained by the higher cost of medical therapy compared with the United Kingdom and the Netherlands, making an invasive strategy worthwhile despite the higher pretest probability.

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Appendix Table 1. Parameter Estimates: General*

Variable	United States	United Kingdom	The Netherlands
CEA recommendations	References 22–24	Reference 25	References 26 and 27
Perspective	Societal	Health care	Societal
Costs	2011 dollars	2011 pounds	2011 euros
Discount rate for costs, %	3.0	3.5	4.0
Discount rate for effectiveness, %	3.0	3.5	1.5
WTP threshold	$50 000/QALY	£25 000/QALY	€80 000/QALY

CEA = cost-effectiveness analysis; QALY = quality-adjusted life-year; WTP = willingness-to-pay.
* Distributions are provided in **Appendix Tables 5** and **6**.

Appendix Table 2. Parameter Estimates: Cost*

Variable	United States		United Kingdom		The Netherlands	
	Cost, $	**Source**	**Cost, £**	**Source**	**Cost, €**	**Source**
FFR	715	Reference 42	460	Reference 42	555	Reference 42
Outpatient PCI†	6529	CPT 92980 and APC104	3676	HRG EA32Z	4168	DBC 140437, 140437-39, 140990, and 140990-1 (43)
CABG‡	38 217	AHRQ CCS44 (44)	7318	HRG EA14Z	11 887	DBC 140923 and 140923-4 (43)
Nonfatal MI§	10 208	DRG 280–282 (44)	1519 + PCI	HRG EB10Z	3983 + PCI	DBC 141527 and 141527-8 (43)
Annual medication‖						
Aspirin, 80 mg/d	24	RED BOOK¶	10	NHS (45)	63	CVZ (46)**
Simvastatin, 40 mg/d	100	Reference 47	14	NHS (45)	52	CVZ (46)**
Atenolol, 50 mg/d	315	RED BOOK¶	9	NHS (45)	82	CVZ (46)**
Isosorbide mononitrate, 60 mg/d	376	RED BOOK¶	126	NHS (45)	145	CVZ (46)**
Enalapril, 20 mg/d	587	RED BOOK¶	11	NHS (45)	34	CVZ (46)**

AHRQ = Agency for Healthcare Research and Quality; APC = Ambulatory Payment Classification; CABG = coronary artery bypass graft surgery; CCS = Clinical Classifications Software; CPT = Current Procedural Terminology; CVZ = Dutch Health Care Insurance Board; DBC = Dutch DRG; DRG = Diagnosis-Related Group; FFR = fractional flow reserve; HRG = NHS Health-Related Group; MI = myocardial infarction; NHS = National Health Service; PCI = percutaneous coronary intervention.

* Distributions are provided in Appendix Tables 5 and 6. Costs were converted to 2011 dollars (United States), pounds (United Kingdom), and euros (the Netherlands) using the country-specific consumer price indices (medical care component for the United States). All costs were modeled with a γ distribution using an SD of 20% of the mean. $1.00 was equivalent to £0.62 or €0.72. The CPT includes technical and professional cost components. The APC reflects the Medicare national average facility fee.

† Mortality was 1.1% (48), radiation exposure was 15 mSv, and we used a disutility of 0.005 y (49).

‡ Mortality was 1.8% (48), and we used a disutility of 0.02 y (49).

§ We used a disutility of 0.04 y (49).

‖ For patients with false-positive test results, we assumed a disutility of 0.01 y for taking unnecessary medication.

¶ Midrange of the average wholesale price. RED BOOK accessed at http://micromedex.com/products/product-suites/clinical-knowledge/redbook on 9 January 2012.

** Total cost of the defined daily dosage.

Appendix Table 3. Target Population With Disease Severity Distribution, Annual Rates of MACEs, and HRRs*

Disease Severity	Mean Distribution, %†	Treatment in First Year			Treatment in Subsequent Years			No Treatment			Source	
		Annual Rate of MACEs	Utility		Annual Rate of MACEs	Utility		Annual Rate of MACEs	Utility		Annual Rate of MACEs	Utility
			Men	Women		Men	Women		Men	Women		
Normal coronary arteries	40	0.0008	0.851	0.824	0.0008	0.851	0.824	0.0008	0.851	0.824	Reference 50	Reference 31
Mild CAD‡	30	0.025	0.851	0.824	0.025	0.851	0.824	0.025	0.851	0.824	Reference 50	Reference 31
Moderate CAD§												
No inducible ischemia	12	0.025	0.851	0.824	0.025	0.851	0.824	0.025	0.851	0.824	Reference 50	Reference 31
Mild inducible ischemia	6	0.172	0.734	0.711	0.071	0.749	0.726	Rate × 1/HRR‖	0.699	0.677	COURAGE (51)	Reference 32
Severe CAD¶												
Mild inducible ischemia	2	0.172	0.734	0.711	0.071	0.749	0.726	Rate × 1/HRR‖	0.699	0.677	COURAGE (51)	Reference 32
Severe inducible ischemia	4	0.110	0.740	0.716	0.043	0.760	0.736	Rate × 1/HRR‖	0.699	0.677	COURAGE (51)	Reference 32
3VD/LM**												
Mild inducible ischemia	2	0.096	0.740	0.716	0.031	0.820	0.794	Rate × 1/HRR‖	0.659	0.638	SYNTAX (52, 53)	Reference 33
Severe inducible ischemia	4	0.096	0.740	0.716	0.031	0.820	0.794	Rate × 1/HRR‖	0.659	0.638	SYNTAX (52, 53)	Reference 33

3VD = 3-vessel disease; CAD = coronary artery disease; COURAGE = Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation; HRR = hazard rate ratio; LM = left main coronary stenosis; MACE = major adverse cardiac event; SYNTAX = Synergy Between PCI With Taxus and Cardiac Surgery.

* Quality-of-life estimates (utilities) are shown for men and women aged 60 y but were modeled using age-specific estimates to account for increasing age over time. More details are provided in the **Appendix**. MACEs include revascularization, nonfatal myocardial infarction, and cardiac death.

† Severity of disease was based on data on coronary computed tomography angiography and catheter-based coronary angiography from a cohort of 471 patients at our hospital (54).

‡ <50% obstruction.

§ 50% to 70% stenosis in proximal vessels or ≥70% stenosis in small vessels. We assumed that one third of patients with moderate CAD had mild inducible ischemia.

‖ Based on meta-analyses of optimal medical treatment (55–57), the HRR of treatment vs. no treatment on the outcome of MACE was estimated to be 0.70. Patients with false-negative test results forgo the benefit of treatment; therefore, their annual rate of MACEs was increased by the reciprocal of the HRR.

¶ ≥70% stenosis in 1 or 2 proximal vessels except in the left main coronary artery. We assumed that one third of patients with severe CAD had mild inducible ischemia and two thirds had severe inducible ischemia.

** ≥50% stenosis in 3 vessels (3VD) or in the left main coronary artery (LM). We assumed that one third of patients with 3VD/LM had mild inducible ischemia and two thirds had severe inducible ischemia.

Appendix Table 4. Annual Medication Use

Variable	Medication Use, %					Total Cost			Reference
	Platelet Inhibitor (Aspirin)	Statin (Simvastatin)	β-Blocker (Atenolol)	Nitrate (Isosorbide Mononitrate)	ACE Inhibitor (Enalapril)	United States, *2011 dollars*	United Kingdom, *2011 pounds*	The Netherlands, *2011 euros*	
Baseline	48	22	37	0	0	150	11	72	58
No CAD	12	17	17	1	7	118	4	34	54, 59
Mild CAD	32	31	16	5	11	172	16	61	54, 59
Moderate CAD*	73	72	40	11	27	415	37	142	54, 59
OMT†	95	92	86	61	62	979	113	288	51
PCI†	95	93	84	47	64	933	96	268	51
CABG†	83	86	77	8‡	53	688	42	189	52

ACE = angiotensin-converting enzyme; CABG = coronary artery bypass graft surgery; CAD = coronary artery disease; OMT = optimal medical treatment; PCI = percutaneous coronary intervention.
* Without inducible ischemia.
† At 3 y, except where noted.
‡ At 1 y (33).

Appendix Table 5. γ Distributions of Cost Parameters*

Parameter	United States, $	United Kingdom, £	The Netherlands, €
CABG	38 217 (24 698–54 446)	7318 (4726–10 442)	11 887 (7709–16 959)
CAG	2989 (1938–4266)	1052 (679–1505)	1513 (978–2154)
CCTA	372 (240–532)	286 (186–409)	215 (139–307)
ECHO	264 (170–377)	236 (153–337)	211 (137–301)
SPECT	549 (356–784)	343 (222–490)	380 (247–542)
CMR	621 (402–888)	548 (355–785)	319 (207–455)
MI	10 208 (6618–14 608)	5195 (3366–7414)	8151 (5291–11 632)
PCI	6529 (4218–9321)	3676 (2384–5248)	4168 (2686–5946)
FFR	715 (462–1019)	460 (298–658)	555 (359–793)
Travel costs	25 (16–36)	–	5 (3–7)
Incidental finding on CCTA	559 (361–798)	359 (233–512)	434 (281–620)

CABG = coronary artery bypass graft surgery; CAG = catheter-based coronary angiography; CCTA = coronary computed tomography angiography; CMR = cardiac magnetic resonance imaging; ECHO = stress echocardiography; FFR = fractional flow reserve; MI = myocardial infarction; PCI = percutaneous coronary intervention; SPECT = single-photon emission computed tomography.
* Values are means (95% credible intervals).

Appendix Table 6. Distributions of Model Parameters

Parameter (Distribution)	Mean Value (95% CrI)
Test characteristics	
Sensitivity	
CCTA (β)	0.98 (0.95–1.00)
ECHO (β)	0.79 (0.77–0.81)
SPECT (β)	0.88 (0.87–0.89)
CMR (β)	0.89 (0.87–0.91)
Specificity	
CCTA (β)	0.89 (0.83–0.94)
ECHO (β)	0.87 (0.85–0.90)
SPECT (β)	0.61 (0.59–0.63)
CMR (β)	0.76 (0.73–0.79)
Mortality probability	
CAG (β)	0.0011 (0.0009–0.0014)
CCTA (β)	0.00001 (0.00000–0.00002)
CSI (β)	0.0001 (0.00003–0.0002)
PCI (β)	0.011 (0.008–0.015)
CABG (β)	0.018 (0.014–0.022)
Morbidity probability	
MI during CAG (β)	0.0005 (0.0003–0.0007)
Incidental finding (β)	0.07 (0.06–0.09)
Radiation exposure, *mSv*	
CAG (γ)	7 (5–10)
CCTA (γ)	5 (3–7)
PCI (γ)	15 (10–21)
SPECT (γ)	9 (6–13)
Disutility, y	
Taking medication (triangular)	0.01 (0.00–0.01)
Uncertainty	
Medication costs (γ)	1.00 (0.65–1.43)
Disutility (γ)	1.00 (0.65–1.43)
Quality of life (γ)	1.00 (0.65–1.43)
Other events	
HRR after MI (log-normal)	1.44 (1.25–1.66)
HRR of treatment (log-normal)	0.70 (0.6–0.9)

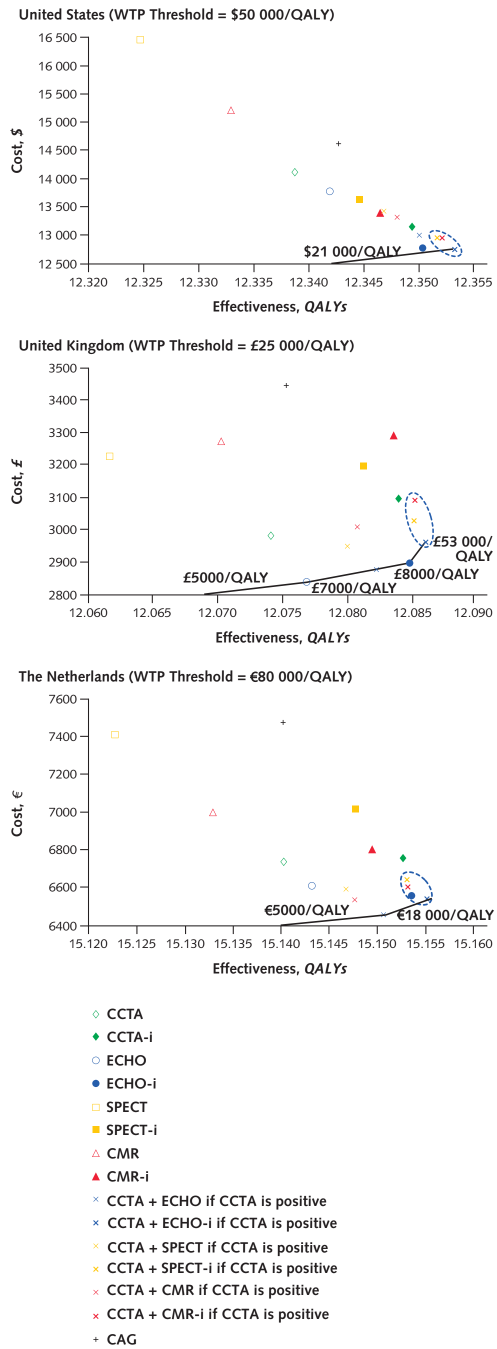
CABG = coronary artery bypass graft surgery; CAG = catheter-based coronary angiography; CCTA = coronary computed tomography angiography; CMR = cardiac magnetic resonance imaging; CrI = credible interval; CSI = cardiac stress imaging; ECHO = stress echocardiography; HRR = hazard rate ratio; MI = myocardial infarction; PCI = percutaneous coronary intervention; SPECT = single-photon emission computed tomography.

Appendix Table 7. Sensitivity Analysis of Probability of CAD*

Variable	Probability of CAD									
	10%		30%		50%		70%		90%	
	Strategy	ICER, *cost per QALY*	Strategy	ICER, *cost per QALY*	Strategy	ICER, *cost per QALY*	Strategy	ICER, *cost per QALY*	Strategy	ICER, *cost per QALY*
United States (WTP threshold of $50 000/QALY)										
Men	CCTA + ECHO-i	$26 000	CCTA + ECHO-i	$22 000	ECHO-i	$21 000	ECHO-i	$21 000	ECHO-i	$21 000
	–	–	–	–	CCTA + ECHO-i	$46 000	–	–	CCTA + ECHO-i	$151 000
Women	CCTA + ECHO-i	$24 000	CCTA + ECHO-i	$21 000	ECHO-i	$21 000	ECHO-i	$20 000	ECHO-i	$20 000
	–	–	–	–	CCTA + ECHO-i	$91 000	CCTA + ECHO-i	$126 000	–	–
United Kingdom (WTP threshold of £25 000/QALY)										
Men	CCTA + ECHO	£9000	ECHO	£5000	ECHO	£4000	ECHO	£4000	ECHO	£4000
	CCTA + ECHO-i	£20 000	CCTA + ECHO	£7000	ECHO-i	£19 000	ECHO-i	£30 000	ECHO-i	£47 000
	–	–	CCTA + ECHO-i	£32 000	CCTA + ECHO-i	£51 000	CCTA + ECHO-i	£300 000	–	–
Women	CCTA + ECHO	£8000	ECHO	£5000	ECHO	£4000	ECHO	£4000	ECHO	£4000
	CCTA + ECHO-i	£12 000	CCTA + ECHO	£7000	ECHO-i	£15 000	ECHO-i	£23 000	ECHO-i	£30 000
	–	–	ECHO-i	£8000	CCTA + ECHO-i	£462 000	CCTA + ECHO-i	£394 000	CCTA + ECHO-i	£181 000
	–	–	CCTA + ECHO-i	£53 000	–	–	–	–	–	–
The Netherlands (WTP threshold of €80 000/QALY)										
Men	CCTA + ECHO	€5000	CCTA + ECHO	€5000	CCTA + ECHO	€5000	ECHO	€5000	ECHO	€5000
	CCTA + ECHO-i	€10 000	CCTA + ECHO-i	€38 000	ECHO-i	€31 000	ECHO-i	€29 000	ECHO-i	€43 000
	–	–	–	–	CCTA + ECHO-i	€35 000	CCTA + ECHO-i	€57 000	CCTA + ECHO-i	€3 181 000
Women	CCTA + ECHO-i	€4000	CCTA + ECHO	€5000	CCTA + ECHO	€5000	ECHO-i	€5000	ECHO	€5000
	–	–	CCTA + ECHO-i	€18 000	CCTA + ECHO-i	€28 000	CCTA + ECHO	€16 000	ECHO-i	€29 000
	–	–	–	–	–	–	ECHO-i	€22 000	CCTA + ECHO-i	€289 000
	–	–	–	–	–	–	CCTA + ECHO-i	€53 000	–	–

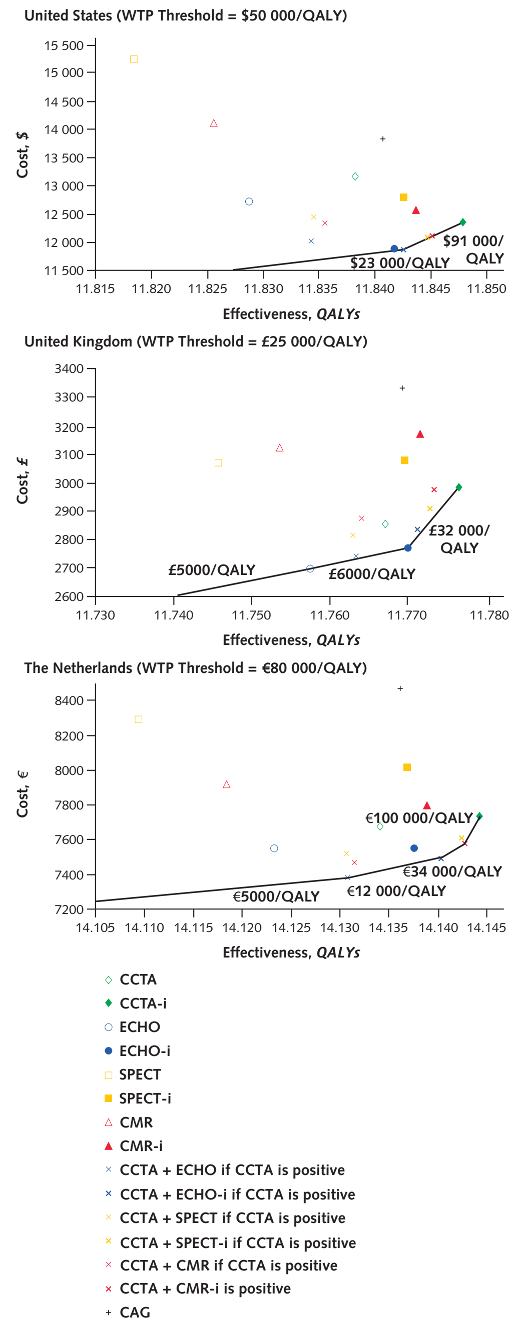
CAD = coronary artery disease; CCTA = coronary computed tomography angiography; ECHO = stress echocardiography; i = invasive diagnostic work-up; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; WTP = willingness-to-pay.
* Only nondominated strategies are listed. The first ICER listed for each subgroup is compared with the no-imaging strategy.

Appendix Figure 1. Cost-effectiveness analysis for 60-year-old women with a 30% prevalence of obstructive CAD.



Note the different *x*- and *y*-axis scales among the graphs. Reported ICERs correspond to the strategies connected by a solid line. The CCTA plus cardiac stress imaging (invasive) strategies are enclosed by a dashed line. The "no imaging" strategy yielded 12.11, 11.85, and 14.85 QALYs at costs of $7506, £1687, and €4997 for the United States, the United Kingdom, and the Netherlands, respectively. CAD = coronary artery disease; CAG = catheter-based coronary angiography; CCTA = coronary computed tomography angiography; CMR = cardiac magnetic resonance imaging; ECHO = stress echocardiography; i = invasive diagnostic work-up; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; SPECT = single-photon emission computed tomography; WTP = willingness-to-pay.

Appendix Figure 2. Sensitivity analysis of the consequences of a false-negative test result for 60-year-old men with a 30% prevalence of obstructive CAD.



Note the different *x*- and *y*-axis scales among the graphs. In the base-case analysis, we assumed that patients with false-negative results returned to their physicians within 1 y (see the Methods section). Results shown reflect the analysis in which we assumed this was 3 y. For the United States, the optimal strategy remained CCTA plus stress echocardiography (invasive); for the United Kingdom, the optimal strategy changed to invasive stress echocardiography. For the Netherlands, the optimal strategy changed to CCTA plus invasive cardiac stress MRI. CAD = coronary artery disease; CAG = catheter-based coronary angiography; CCTA = coronary computed tomography angiography; CMR = cardiac magnetic resonance imaging; ECHO = stress echocardiography; i = invasive diagnostic work-up; MRI = magnetic resonance imaging; QALY = quality-adjusted life-year; SPECT = single-photon emission computed tomography; WTP = willingness-to-pay.

Appendix Table 8. Sensitivity Analysis for U.S. Men of the Cost-Effectiveness of EE Alone and Followed by Cardiac Stress Imaging After a Positive Result*

Test	Radiation Exposure, *mSv*	Cost, *$*	QALYs	ICER, *$/QALY*†
No imaging	5	6833	11.62	–
EE + ECHO-i	6	11 397	11.86	**19 000**
EE + ECHO	5	11 434	11.85	Dominated
EE + CMR-i	6	11 553	11.86	Dominated
EE + SPECT-i	9	11 560	11.86	Dominated
EE + CMR	5	11 670	11.85	Dominated
EE-i	8	11 698	11.85	Dominated
EE + SPECT	8	11 766	11.85	Dominated
CCTA + ECHO-i	13	11 988	11.85	Dominated
ECHO-i	8	12 001	11.85	Dominated
CCTA + ECHO	11	12 170	11.85	Dominated
CCTA + CMR-i	13	12 190	11.85	Dominated
CCTA + SPECT-i	16	12 193	11.85	Dominated
EE	6	12 298	11.85	Dominated
CCTA-i	11	12 386	11.85	Dominated
CCTA + CMR	11	12 470	11.85	Dominated
CCTA + SPECT	15	12 568	11.85	Dominated
CMR-i	8	12 632	11.85	Dominated
ECHO	6	12 855	11.84	Dominated
SPECT-i	18	12 870	11.85	Dominated
CCTA	11	13 206	11.84	Dominated
CAG	12	13 854	11.84	Dominated
CMR	6	14 197	11.84	Dominated
SPECT	15	15 337	11.83	Dominated

CAG = catheter-based coronary angiography; CCTA = coronary computed tomography angiography; CMR = cardiac magnetic resonance imaging; ECHO = stress echocardiography; EE = exercise electrocardiography; i = invasive diagnostic work-up; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; SPECT = single-photon emission computed tomography.
* Analysis assumes sensitivity of 50%, specificity of 90%, and cost of $125 for EE. Cost estimates and QALYs for the listed strategies may differ slightly from the reported base-case estimates because of random variation in reanalysis of microsimulation model.
† ICERs were calculated vs. the next cheaper nondominated strategy. ICERs in boldface reflect the optimal strategy (under the willingness-to-pay threshold).

Appendix Table 9. Additional Results of Base-Case Cost-Effectiveness Analysis: 60-Year-Old Men With a Pretest Probability of 30%*

Test	United States		United Kingdom		The Netherlands	
	Mean Cost (95% CrI), *$*	QALYs (95% CrI)	Mean Cost (95% CrI), *£*	QALYs (95% CrI)	Mean Cost (95% CrI), *€*	QALYs (95% CrI)
No imaging	6827 (5587–8397)	11.621 (11.306–11.926)	1577 (1185–2034)	11.552 (11.278–11.821)	5982 (5233–6786)	13.867 (13.488–14.238)
CCTA	13 177 (10 120–16 667)	11.841 (11.528–12.150)	2859 (2312–3484)	11.768 (11.494–12.045)	7680 (6603–8853)	14.133 (13.753–14.514)
CCTA-i	12 360 (9748–15 366)	11.851 (11.536–12.159)	2988 (2457–3603)	11.778 (11.502–12.052)	7737 (6733–8838)	14.144 (13.763–14.522)
CMR	14 172 (10 881–17 881)	11.837 (11.523–12.145)	3143 (2563–3787)	11.764 (11.486–12.041)	7911 (6782–9145)	14.128 (13.745–14.509)
CMR-i	12 606 (9955–15 608)	11.850 (11.532–12.159)	3186 (2620–3822)	11.776 (11.501–12.054)	7783 (6774–8897)	14.142 (13.766–14.522)
SPECT	15 312 (11 668–19 462)	11.830 (11.512–12.140)	3085 (2492–3744)	11.758 (11.481–12.038)	8294 (7082–9640)	14.119 (13.737–14.493)
SPECT-i	12 848 (10 200–15 890)	11.848 (11.533–12.162)	3091 (2533–3726)	11.775 (11.498–12.056)	8004 (6965–9125)	14.140 (13.761–14.515)
ECHO	12 829 (9835–16 233)	11.843 (11.527–12.152)	2717 (2194–3319)	11.771 (11.496–12.046)	7549 (6491–8718)	14.136 (13.756–14.507)
ECHO-i	11 975 (9376–14 950)	11.851 (11.533–12.160)	2789 (2273–3381)	11.778 (11.505–12.050)	7542 (6549–8635)	14.145 (13.769–14.518)
CCTA + CMR	12 445 (9643–15 644)	11.849 (11.533–12.158)	2893 (2361–3493)	11.776 (11.499–12.051)	7491 (6470–8609)	14.143 (13.766–14.514)
CCTA + CMR-i	12 167 (9589–15 162)	11.853 (11.538–12.158)	2986 (2453–3591)	11.779 (11.501–12.054)	7587 (6591–8670)	14.146 (13.770–14.522)
CCTA + SPECT	12 543 (9712–15 765)	11.848 (11.533–12.156)	2832 (2305–3431)	11.775 (11.498–12.051)	7548 (6515–8688)	14.142 (13.764–14.515)
CCTA + SPECT-i	12 170 (9586–15 172)	11.853 (11.540–12.158)	2920 (2395–3527)	11.779 (11.499–12.057)	7626 (6624–8712)	14.146 (13.770–14.523)
CCTA + ECHO	12 144 (9403–15 287)	11.851 (11.534–12.158)	2763 (2247–3359)	11.778 (11.502–12.050)	7417 (6406–8528)	14.145 (13.772–14.515)
CCTA + ECHO-i	11 963 (9389–14 975)	11.854 (11.539–12.162)	2853 (2334–3449)	11.780 (11.504–12.053)	7518 (6524–8601)	14.148 (13.769–14.527)
CAG	13 823 (11 015–17 025)	11.842 (11.529–12.147)	3341 (2709–4053)	11.770 (11.492–12.045)	8457 (7336–9672)	14.136 (13.755–14.517)

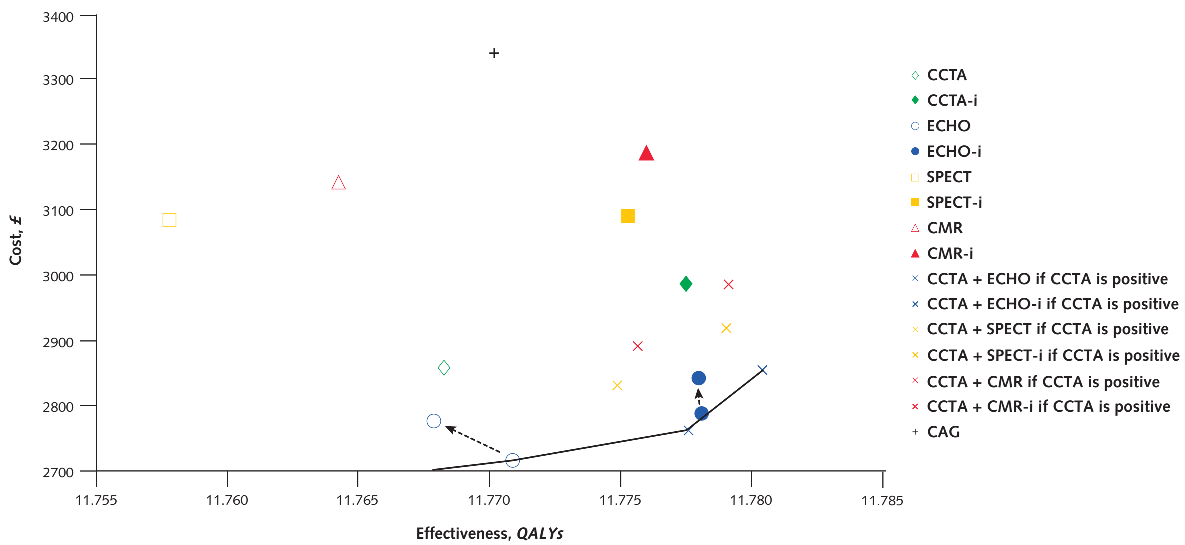
CAG = catheter-based coronary angiography; CCTA = coronary computed tomography angiography; CMR = cardiac magnetic resonance imaging; CrI = credible interval; ECHO = stress echocardiography; i = invasive diagnostic work-up; QALY = quality-adjusted life-year; SPECT = single-photon emission computed tomography.
* 95% CrIs are based on 10 000 samples from the parameter distributions (1000 trials per sample).

Appendix Table 10. Additional Results of Base-Case Cost-Effectiveness Analysis: 60-Year-Old Women With a Pretest Probability of 30%*

Test	United States		United Kingdom		The Netherlands	
	Mean Cost (95% CrI), $	QALYs (95% CrI)	Mean Cost (95% CrI), £	QALYs (95% CrI)	Mean Cost (95% CrI), €	QALYs (95% CrI)
No imaging	7506 (6135–9202)	12.108 (11.808–12.401)	1687 (1276–2164)	11.848 (11.577–12.113)	4997 (4319–5773)	14.850 (14.467–15.214)
CCTA	14 109 (10 834–17 850)	12.339 (12.042–12.636)	2984 (2416–3633)	12.074 (11.810–12.331)	6735 (5675–7930)	15.140 (14.765–15.508)
CCTA-i	13 145 (10 357–16 392)	12.349 (12.053–12.654)	3098 (2550–3726)	12.084 (11.820–12.345)	6752 (5770–7856)	15.153 (14.779–15.522)
CMR	15 198 (11 626–19 285)	12.333 (12.038–12.630)	3277 (2675–3955)	12.070 (11.808–12.327)	6996 (5867–8241)	15.133 (14.763–15.500)
CMR-i	13 392 (10 604–16 622)	12.346 (12.047–12.644)	3295 (2717–3944)	12.084 (11.821–12.344)	6799 (5810–7898)	15.149 (14.775–15.518)
SPECT	16 448 (12 521–20 924)	12.325 (12.025–12.626)	3231 (2612–3925)	12.062 (11.796–12.315)	7409 (6195–8778)	15.123 (14.749–15.491)
SPECT-i	13 632 (10 845–16 904)	12.345 (12.043–12.646)	3200 (2633–3851)	12.081 (11.811–12.338)	7018 (6015–8132)	15.148 (14.774–15.521)
ECHO	13 771 (10 534–17 473)	12.342 (12.047–12.639)	2844 (2294–3468)	12.077 (11.814–12.335)	6608 (5559–7781)	15.143 (14.769–15.513)
ECHO-i	12 764 (10 021–15 981)	12.350 (12.052–12.648)	2900 (2363–3518)	12.085 (11.822–12.346)	6559 (5585–7651)	15.154 (14.785–15.522)
CCTA + CMR	13 315 (10 311–16 733)	12.348 (12.049–12.646)	3012 (2465–3647)	12.081 (11.817–12.338)	6533 (5530–7645)	15.148 (14.774–15.514)
CCTA + CMR-i	12 951 (10 194–16 149)	12.352 (12.050–12.650)	3096 (2552–3725)	12.085 (11.820–12.345)	6604 (5632–7691)	15.153 (14.789–15.523)
CCTA + SPECT	13 421 (10 366–16 895)	12.347 (12.048–12.645)	2952 (2410–3576)	12.080 (11.818–12.337)	6591 (5581–7708)	15.147 (14.771–15.517)
CCTA + SPECT-i	12 952 (10 181–16 169)	12.352 (12.051–12.652)	3031 (2494–3652)	12.085 (11.817–12.343)	6641 (5665–7729)	15.153 (14.785–15.524)
CCTA + ECHO	13 000 (10 056–16 349)	12.350 (12.052–12.648)	2881 (2345–3489)	12.082 (11.819–12.340)	6453 (5460–7563)	15.151 (14.777–15.519)
CCTA + ECHO-i	12 750 (10 005–15 939)	12.353 (12.054–12.650)	2964 (2428–3583)	12.086 (11.817–12.345)	6535 (5574–7618)	15.155 (14.784–15.523)
CAG	14 619 (11 675–17 997)	12.343 (12.041–12.639)	3450 (2819–4171)	12.075 (11.810–12.338)	7475 (6370–8716)	15.140 (14.768–15.502)

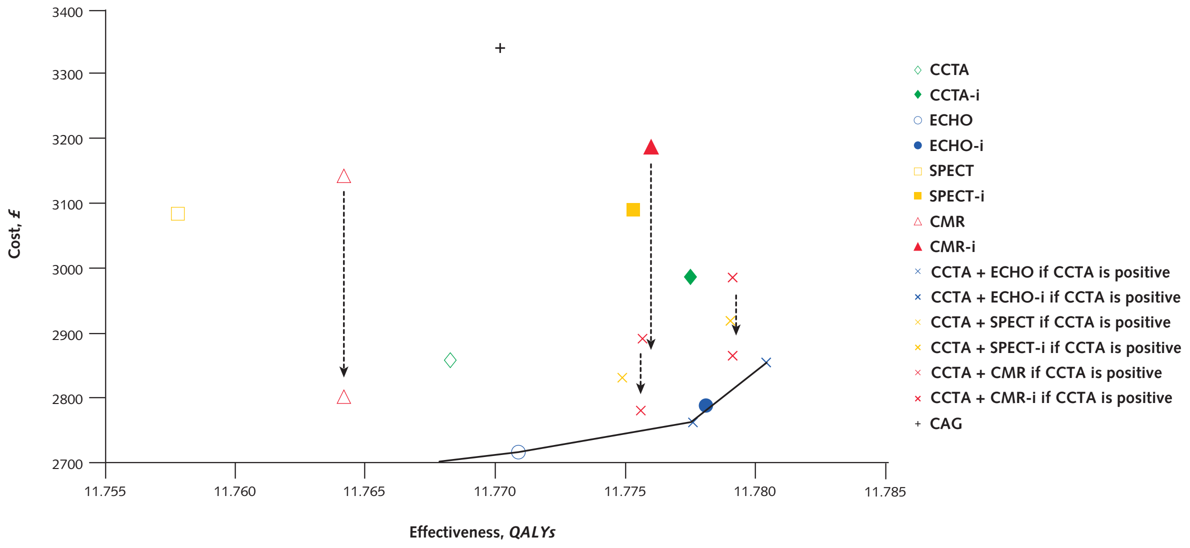
CAG = catheter-based coronary angiography; CCTA = coronary computed tomography angiography; CMR = cardiac magnetic resonance imaging; CrI = credible interval; ECHO = stress echocardiography; i = invasive diagnostic work-up; QALY = quality-adjusted life-year; SPECT = single-photon emission computed tomography.
* 95% CrIs are based on 10 000 samples from the parameter distributions (1000 trials per sample).

Appendix Figure 3. Sensitivity analysis varying the diagnostic performance of stress echocardiography.



Results are for men from the U.K. perspective at a WTP threshold of £25 000/QALY. The sensitivity of stress echocardiography decreased from 0.79 to 0.70, and the specificity decreased from 0.87 to 0.80. The dashed arrows originate at cost and effectiveness estimates for the base-case sensitivity and specificity of stress echocardiography and point toward the revised cost and effectiveness estimates for stress echocardiography when the diagnostic performance worsened. The cost and effectiveness of CCTA plus stress echocardiography did not change. CAG = catheter-based coronary angiography; CCTA = coronary computed tomography angiography; CMR = cardiac magnetic resonance imaging; ECHO = stress echocardiography; i = invasive diagnostic work-up; QALY = quality-adjusted life-year; SPECT = single-photon emission computed tomography; WTP = willingness-to-pay.

Appendix Figure 4. Sensitivity analysis varying the diagnostic costs for cardiac stress MRI.



Results are for men from the U.K. perspective at a WTP threshold of £25 000/QALY. The cost of cardiac stress MRI decreased from £548 to £200. Dashed arrows originate at the result for the base-case estimate of the cost of cardiac stress MRI and point toward the results if cardiac stress MRI were less expensive, thereby decreasing the cost of each cardiac stress MRI strategy (less so for the CCTA plus CMR strategies). CAG = catheter-based coronary angiography; CCTA = coronary computed tomography angiography; CMR = cardiac magnetic resonance imaging; ECHO = stress echocardiography; i = invasive diagnostic work-up; MRI = magnetic resonance imaging; QALY = quality-adjusted life-year; SPECT = single-photon emission computed tomography; WTP = willingness-to-pay.