The early diagnosis and treatment of patients with stable chest pain and suspected coronary artery disease (CAD) can reduce adverse health events and prolong life (1). Although their diagnostic evaluation typically consists of electrocardiographic stress testing alone or in combination with conventional imaging studies, the evolution of coronary computed tomography angiography (CCTA) has expanded options for patient assessment and management.

Several studies have demonstrated that CCTA performed with 64-slice multidetector computed tomography can accurately characterize atherosclerotic lesions and distinguish patients with CAD from those with normal coronary vasculature (2–6). Research has also shown that its application in the emergency department might facilitate the triage of patients suspected of having acute coronary syndrome and reduce diagnostic time and resource use, compared with the current standard of care (7,8).

However, investigators have raised concerns about CCTA related to radiation exposure, its detection of incidental findings, and nondiagnostic exams.

The aim of this study was to project clinical outcomes, health care costs, and cost-effectiveness of coronary computed tomography angiography (CCTA), as compared with conventional diagnostic technologies, in the evaluation of patients with stable chest pain and suspected coronary artery disease (CAD).

With published data, we developed a computer simulation model to project clinical outcomes, health care costs, and cost-effectiveness of CCTA, compared with conventional testing modalities, in the diagnosis of CAD. Our target population included 55-year-old patients who present to their primary care physicians with stable chest pain.

All diagnostic strategies yielded similar health outcomes, but performing CCTA—with or without stress testing or performing stress single-photon emission computed tomography—marginally minimized adverse events and maximized longevity and quality-adjusted life-years (QALYs). Health outcomes associated with these strategies were comparable, with CCTA in men and women yielding the greatest QALYs but only by modest margins. Over-all differences were small, and performing the most effective test—compared with the least effective—decreased adverse event rates by 3% in men and women. Comparable increases in longevity and QALYs were 2 months and 0.1 QALYs in men and 1 month and 0.03 QALYs in women. CCTA raised overall costs, partly through the follow-up of incidental findings, and when performed with stress testing, its incremental cost-effectiveness ratio ranged from $26,200/QALY in men to $35,000/QALY in women. Health outcomes were marginally less favorable in women when radiation risks were considered.

CCTA is comparable to other diagnostic studies and might hold good clinical value, but large randomized controlled trials are needed to guide policy.
dental findings requiring follow-up, and its rate of non-diagnostic exams (9–12). In the evaluation of patients presenting to their primary care physicians with chest pain, no randomized controlled trial comparing CCTA with conventional diagnostic modalities has been performed, and the comparative effectiveness of computed tomography angiography (CTA) on patient outcomes and health care costs is unknown. In addition, Medicare has established a Category III Current Procedural Terminology code to track CCTA exams but, because it is an emerging technology, has not set a national payment rate, relegating reimbursement decisions to local carriers instead.

We aimed to address these concerns by constructing a model to project clinical outcomes, health care costs, and cost-effectiveness of CCTA, as compared with other diagnostic technologies, in the evaluation of patients with stable chest pain and suspected CAD. Our study joins a host of other studies that have been used to better understand the implications of emerging technologies and management approaches (13–16). We also build upon previous work investigating the cost-effectiveness of noninvasive imaging for the diagnosis of CAD (17).

Methods

Simulation model. We developed a Monte Carlo microsimulation model to assess CCTA in the evaluation of patients with stable chest pain, with conventional diagnostic modalities as comparators (18). Patient outcomes related to medical and surgical interventions for CAD, the incidence of nonfatal myocardial infarctions (MIs) and strokes, follow-up for incidental findings, all-cause mortality, health care costs, and cost-effectiveness were tracked. Quality-adjusted longevity was measured in quality-adjusted life-years (QALYs), and both QALYs and costs were converted to present a value with a 3% discount rate.

Population characteristics. Our patient population included men and women between the ages of 45 and 65 years who presented to their primary care physicians with a chest pain syndrome and were suspected of having CAD. Chest pain was considered to be nonanginal, atypical, or typical angina, as described by Diamond and Forrester (19). Clinically, we assumed that these patients had no prior history of CAD, MI, atrial fibrillation, diabetes mellitus, or left ventricular dysfunction. Our base case targets 55-year-old men and women with atypical chest pain, populations that correspond with CAD pre-test probabilities of 70% and 30%, respectively, on the basis of criteria described by Diamond and Forrester (19,20). The specific distribution of left main and 1-, 2-, and 3-vessel disease was 7%, 24%, 21%, and 18% for men, and 2%, 13%, 9%, and 6% for women, respectively. The distribution of normal and mildly stenosed arteries in this population was 13% and 16% in men and 47% and 23% in women, respectively (20). Although other characteristics, including smoking status and cholesterol level, augment the likelihood of CAD, the trio of age, sex, and chest pain quality has been demonstrated to be the most powerful predictor, and we limited our analysis to these factors (1).

Diagnostic strategies. We considered 8 diagnostic strategies designed to capture a diverse range of management approaches but acknowledge that these strategies represent only a subset of diagnostic algorithms used in clinical practice. Two of the CCTA strategies incorporate stress testing, because this component allows physicians to identify patients more likely to benefit from revascularization. The management strategies are: 1) CCTA followed by stress electrocardiography (ECG); 2) stress ECG followed by CCTA; 3) CCTA alone; 4) stress ECG alone; 5) stress echocardiography alone; 6) stress single-photon emission computed tomography (SPECT) alone; 7) cardiac catheterization; and 8) no diagnostic testing. For the purpose of this analysis, CAD is defined as a ≥50% stenosis in the left main coronary artery or a ≥70% stenosis in any other coronary artery, and stress testing is performed with exercise rather than pharmacological agents.

In Strategy 1 (Fig. 1), CCTA is performed, and patients with evidence of severe CAD—defined as 3-vessel or left main CAD—are sent for diagnostic cardiac catheterization; true-positives are treated with aggressive medical therapy and revascularized with percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) surgery. Patients with evidence of 1- or 2-vessel CAD on CTA are evaluated with stress ECG, and those with markedly abnormal stress tests—defined as substantial ST-segment depression or hypotensive response during stage 1 of the Bruce protocol—are sent for angiography; true positives are treated with aggressive medical therapy and revascularized (21). Patients with more severe disease are more likely to have markedly abnormal results, and those with CTA evidence of 1- or 2-vessel CAD whose stress test results are positive but not markedly abnormal are initially managed with aggressive medical therapy alone (22). Patients with no evidence of significant CAD on CTA receive no additional therapies beyond baseline care. When the results of the CTA differ from those of the stress test (e.g., CTA demonstrates evidence of significant CAD, but exercise stress test is negative), only patients with a Bayesian post-test probability of disease exceeding 50% are treated. Note that a limitation of our approach is that it does not use the Duke treadmill score to help inform prognosis.
In Strategy 2 (Fig. 2), ECG stress testing is performed initially. Patients with markedly abnormal results are evaluated with invasive angiography, and true-positives are treated as in the preceding text. Patients whose stress ECGs are positive but not markedly abnormal are evaluated with CTA, and those with evidence of severe CAD are sent for diagnostic cardiac catheterization and managed as previously described. Patients with CTA-evidence of 1- or 2-vessel CAD are initially treated with CABG, while those with 3-vessel or left main coronary artery disease are referred for PCI/CABG. Patients with CTA-negative tests are treated with aggressive or baseline medications. Patients with ETT-negative tests are managed with baseline medications.
aggressively with medication alone, although patients with no
evidence of CAD are treated as described in the preceding text.

Strategy 3 is similar to Strategy 1, with the following
differences: patients with 1- or 2-vessel CAD on CTA are
not evaluated with stress ECG but rather initiated on
aggressive medical therapy alone. Strategy 4 (Fig. 3) is
similar to Strategy 2, except that patients whose stress
ECGs are positive but not markedly abnormal are not
evaluated with CTA but rather treated aggressively with
medication alone. Strategies 5 and 6 are similar to Strategy
4 but use stress echocardiography and SPECT, respectively.
Strategy 7 evaluates all patients with cardiac catheterization
and does not incorporate other diagnostic tests. Strategy 8 is
a natural history arm and provides a baseline for compari-
son; patients are not evaluated for CAD and receive no
therapies beyond their baseline.

Model pathways after diagnostic evaluation. After evalu-
ation, patients enter a natural history model and might expe-
rience nonfatal adverse events, medical and surgical interven-
tions, and death. They also accrue costs related to these events.
False negatives, along with patients who initially do not have
CAD but later develop the condition, are also tracked.

Diagnostic test characteristics. Test characteristics for
CCTA and stress ECG, echocardiography, and SPECT
were derived from meta-analyses and considered to be
conditionally independent (Table 1) (13,15,23). The meta-
analysis of CCTA included 5 studies of 64-slice devices, and
the authors pooled diagnostic accuracy estimates with a
random effects model. The prevalence of CAD across these
5 studies was 56%, and the highest reported rate of
nondiagnostic exams was 4% (2–6). Importantly, diagnostic
test characteristics in this study were similar to values
reported in another meta-analysis of 64-slice CT (24). In
our model, patients with nondiagnostic exams are evaluated
with stress ECG. The likelihoods of markedly abnormal
stress test results for patients with left main, 1-, 2-, and 3-vessel
disease and mildly stenosed and normal coronaries were 18%,
37%, 50%, 86%, 6%, and 6%, respectively (22). We also
performed a sensitivity analysis on CCTA anatomy misclassi-
fication with data from a recently published study (25).

Incidental findings. We limit our analysis of incidental
developers to the identification of pulmonary nodules, a
well-described finding in the published data. By pooling
results from CCTA studies (26–30) and a logistic model
developed by Swensen et al. (31), we estimated the preva-
lence of pulmonary nodules and their likelihood of malig-
nancy (Table 2). We assumed that CTA would image 40%
of the lung space, reflecting the lung area typically visualized
in an exam (26). Management is in accordance with
Fleischner guidelines (Fig. 4), with a follow-up CT sched-
ule that is more aggressive for patients with large nodules or
a history of smoking.

Nodule growth was modeled with the monthly likelihood
of progression for benign and malignant lesions (32).
Patients with nodules that grow in size, along with patients
whose nodules are large at baseline, are evaluated for
evidence of malignancy with 18-fluorodeoxyglucose
positron emission tomography (32–34). Positive lung nod-
ules are excised with video-assisted thoracic surgery, and the
procedure is converted to a thoracotomy with lobectomy if
the nodule is found to be malignant (32).

Procedures and examinations. Stress testing, CT scans,
PCI, CABG, and pulmonary procedures were associated
with mortality risks, and repeat revascularization was also
modeled (Table 2) (35–40). Patients managed initially with
aggressive medical therapy alone or with bare-metal stent-
based PCI faced the highest rates of future revascularization events (21,41–43). These rates were lower for patients managed with drug-eluting stents and CABG (41,44). Partially guided by the Framingham risk model, we assumed that patients with CAD who are missed during their diagnostic exams face a 5% annual likelihood of receiving a correct diagnosis (45). Radiation risks associated with CCTA were not modeled explicitly, because we did not distinguish cancer deaths from non-cancer deaths. However, we evaluated these risks indirectly in a sensitivity analysis by setting the risk of mortality 20 years after a CCTA exam equal to the attributable cancer mortality risk associated with 8 to 10 mSv of CT radiation to the chest and abdomen (12,46). We assumed CCTA would be performed with electrocardiographically controlled tube current modulation, and although Einstein et al. (12) report only attributable cancer risk (as opposed to mortality), the majority of new cancers in our age group are lung cancers. We therefore multiply the risks they report—1 in 1,911 for men and 1 in 715 for women—by a factor of 1 minus the 5-year survival of patients diagnosed with lung cancer. These survival rates are 13.6% and 17.5%, as reported by the National Cancer Institute, and yield adjusted attributable cancer mortality risks of 1 in 2,212 and 1 in 867 in men and women, respectively (46). This risk was also applied to SPECT and cardiac catheterization, although the latter has a radiation dose of 6 to 9 mSv (47). We also attempted to evaluate the impact of nonfatal contrast-induced nephropathy but were unable to identify appropriate cost estimates for this condition in the published data.

### Nonfatal and fatal adverse events.

Patients diagnosed with CAD are treated according to Adult Treatment Panel (ATP) III guidelines and receive consultation for dietary and lifestyle modifications, aspirin, lipid-modifying therapy, antianginal therapy, and cardiac rehabilitation (48). We modeled overall survival and tracked the incidence of nonfatal MIs and strokes with adverse event and survival outcomes reported in the COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) trial and statin meta-analyses (Table 1) (21,49–51). These outcomes were used to develop calibration models for survival and adverse events. The calibration models yielded estimates for the annual relative risks of death for patients with treated 1-, 2-, and 3-vessel and left main disease—

<table>
<thead>
<tr>
<th>Variable Base Case Estimate</th>
<th>Range</th>
<th>Ref. #</th>
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</thead>
<tbody>
<tr>
<td><strong>Diagnostic test characteristics</strong></td>
<td></td>
<td></td>
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<tr>
<td>CCTA with 64-slice CT</td>
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<tr>
<td>Sensitivity for CAD (per patient)</td>
<td>0.98</td>
<td>0.95–0.99</td>
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<tr>
<td>Specificity for CAD (per patient)</td>
<td>0.92</td>
<td>0.90–0.98</td>
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<tr>
<td>Stress ECG</td>
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<tr>
<td>Sensitivity for 1- or 2-vessel CAD</td>
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<td>0.52</td>
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<tr>
<td>Sensitivity for 3-vessel or left main CAD</td>
<td>0.86</td>
<td>Not varied</td>
</tr>
<tr>
<td>Specificity for CAD</td>
<td>0.77</td>
<td>0.71</td>
</tr>
<tr>
<td>Stress echocardiography</td>
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<tr>
<td>Sensitivity for 1- or 2-vessel CAD</td>
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<td>0.85</td>
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<tr>
<td>Sensitivity for 3-vessel or left main CAD</td>
<td>0.94</td>
<td>0.92</td>
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<tr>
<td>Specificity for CAD</td>
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<td>0.77</td>
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<tr>
<td>Stress SPECT</td>
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<tr>
<td>Sensitivity for 1- or 2-vessel CAD</td>
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<td>0.87</td>
</tr>
<tr>
<td>Sensitivity for 3-vessel or left main CAD</td>
<td>0.98</td>
<td>0.92</td>
</tr>
<tr>
<td>Specificity for CAD</td>
<td>0.77</td>
<td>0.64</td>
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<td><strong>Coronary artery disease mortality risks</strong></td>
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<td></td>
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<tr>
<td>Risk ratios for treated CAD*</td>
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<td></td>
</tr>
<tr>
<td>1- and 2-vessel CAD</td>
<td>1.4</td>
<td>1.3–1.5</td>
</tr>
<tr>
<td>3-vessel CAD</td>
<td>2.2</td>
<td>2–2.4</td>
</tr>
<tr>
<td>Left main CAD</td>
<td>5.8</td>
<td>5.2–6.4</td>
</tr>
<tr>
<td>Risk ratios for untreated CAD†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonfatal MI</td>
<td>1.4</td>
<td>1.3–1.5</td>
</tr>
<tr>
<td>Nonfatal stroke</td>
<td>1.5</td>
<td>1.4–1.7</td>
</tr>
<tr>
<td>Death</td>
<td>1.3</td>
<td>1.2–1.4</td>
</tr>
<tr>
<td><strong>Nonfatal adverse events</strong></td>
<td></td>
<td></td>
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<tr>
<td>Annual risks in patients with treated CAD</td>
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<td></td>
</tr>
<tr>
<td>Nonfatal MI</td>
<td>0.028</td>
<td>0.01–0.05</td>
</tr>
<tr>
<td>Nonfatal stroke‡</td>
<td>0.0035</td>
<td>0.002–0.001</td>
</tr>
</tbody>
</table>

*Compared with no coronary artery disease (CAD); †compared with treated CAD; ‡nonfatal stroke rate estimated, because authors report combined rate of fatal and nonfatal strokes.

CCTA = coronary computed tomography angiography; CT = computed tomography; ECG = electrocardiography; MI = myocardial infarction; SPECT = single-photon emission computed tomography.
compared with patients without CAD—of 1.4, 1.4, 2.2, and 5.8, respectively. These risk ratios increased by a factor of 1.3 in patients with untreated CAD. The annual risks of nonfatal MI and stroke in patients with treated CAD were 0.028 and 0.0035, and these rates increased by a risk ratio of 1.4 and 1.5 in patients with untreated CAD, respectively (21,49,50,52). Finally, we assumed that lung nodules had no direct impact on survival, because no randomized controlled trials of lung cancer screening have demonstrated a survival benefit from their excision, although more recent trials are underway (11).

### Health-related quality of life and health care costs

Patient quality of life (QoL) was related to the existence and severity of angina and the incidence of nonfatal adverse events (Table 3). We assumed that the combination of aggressive medical therapy with PCI or CABG was more effective at relieving angina than aggressive medical therapy alone and that CABG was marginally more effective than PCI (1,53–55). The presence and severity of chronic stable angina have previously been used to estimate QoL in patients with CAD, and more severe angina is associated with poorer exercise and activity tolerance, a worse Canadian Cardiovascular Society angina class, and lower QoL (51,55–57). These relationships form the basis of estimating the utility or quality weight of health states in patients with CAD, and interventions that reduce angina improve QoL (56,57). Although this relationship is well-documented in the published data, we explored it further by performing a sensitivity analysis in which patients with treated CAD had a constant QoL that was unrelated to their angina symptoms.

We included the costs of all major tests, therapies, and events directly related to CAD over a lifetime horizon (Table 3). This included costs related to medications; diagnostic studies such as stress tests; PCI, CABG, and other procedures; and hospital stay and annual care costs for nonfatal MIs and strokes. As mentioned previously, we used a 3% discount rate to convert future costs to present value. Cost estimates were largely based on Current Procedural Terminology codes and national Medicare reimbursement but were also drawn from other studies (16,32,58–62). Note that the Medicare fee schedule is considered a reasonable proxy for economic costs (63). Because Medicare has not set a national payment amount for CCTA, we estimated its cost to be approximately $31 less than that of stress SPECT, on the basis of the cost difference reported in an earlier study (7). All costs were converted to 2005 U.S. dollars with the medical care component of the Consumer Price Index.

### Pulmonary Nodule Characteristics and Risks Associated With Exams and Interventions

<table>
<thead>
<tr>
<th>Variable</th>
<th>Base Case Estimate</th>
<th>Range</th>
<th>Ref. #</th>
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</thead>
<tbody>
<tr>
<td><strong>Incidental findings</strong></td>
<td></td>
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</tr>
<tr>
<td>Prevalence of lung nodules</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Smokers</td>
<td>0.23</td>
<td>0–0.4</td>
<td>31</td>
</tr>
<tr>
<td>Nonsmokers*</td>
<td>0.003</td>
<td>Not varied</td>
<td>27</td>
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<tr>
<td>Lung field area visualized on CCTA</td>
<td>0.40</td>
<td>Not varied</td>
<td>26</td>
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<tr>
<td><strong>Lung nodule characteristics</strong></td>
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</tr>
<tr>
<td>Diameter of small nodules (&lt;8 mm)</td>
<td>—</td>
<td>2–8 mm</td>
<td>28</td>
</tr>
<tr>
<td>Diameter of large nodules (&gt;8 mm)</td>
<td>—</td>
<td>&gt;8 mm–2 cm</td>
<td>28</td>
</tr>
<tr>
<td>Portion of nodules that are small</td>
<td>0.6</td>
<td>Not varied</td>
<td>27,28</td>
</tr>
<tr>
<td>Probability of growth in first yr</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benign nodules</td>
<td>0.058</td>
<td>Not varied</td>
<td>32</td>
</tr>
<tr>
<td>Malignant nodules</td>
<td>0.96</td>
<td>Not varied</td>
<td>32,34</td>
</tr>
<tr>
<td><strong>Probability of growth in subsequent yrs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benign nodules</td>
<td>0.058</td>
<td>Not varied</td>
<td>32</td>
</tr>
<tr>
<td>Malignant nodules</td>
<td>1</td>
<td>Not varied</td>
<td>32,34</td>
</tr>
<tr>
<td><strong>FDG-PET test characteristics</strong></td>
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<tr>
<td>Sensitivity for malignant nodules</td>
<td>0.94</td>
<td>Not varied</td>
<td>33</td>
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<tr>
<td>Specificity for malignant nodules</td>
<td>0.83</td>
<td>Not varied</td>
<td>33</td>
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<tr>
<td><strong>Interventional mortality risks</strong></td>
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<tr>
<td>Stress testing</td>
<td>0.00005</td>
<td>Not varied</td>
<td>35</td>
</tr>
<tr>
<td>CCTA (and CT exams in general)†</td>
<td>0.000009</td>
<td>0.00008–0.0002</td>
<td>12,36</td>
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<tr>
<td>Invasive coronary angiography</td>
<td>0.001</td>
<td>Not varied</td>
<td>51</td>
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<tr>
<td>Percutaneous coronary intervention</td>
<td>0.011</td>
<td>Not varied</td>
<td>37</td>
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<tr>
<td>Coronary artery bypass graft surgery</td>
<td>0.0266</td>
<td>Not varied</td>
<td>38</td>
</tr>
<tr>
<td>Video-assisted thoracic surgery</td>
<td>0.005</td>
<td>Not varied</td>
<td>32</td>
</tr>
<tr>
<td>Lobectomy</td>
<td>0.0137</td>
<td>Not varied</td>
<td>39</td>
</tr>
</tbody>
</table>

*Estimated by generalizing Early Lung Cancer Action Project data and assuming overall nodule prevalence is a linear combination of nodules in smokers and nonsmokers; †varied to simulate attributable risk of cancer mortality from coronary computed tomography angiography (CCTA) radiation.

FDG-PET = 18-fluorodeoxyglucose positron emission tomography.
**Model analysis.** We ran 1,000,000 first-order Monte Carlo microsimulations for each patient population and performed 1-way sensitivity analyses on key parameters. The model was built with TreeAge Pro Suite 2007 (TreeAge Software, Inc., Williamstown, Massachusetts), and results were analyzed with Excel 2003 (Microsoft, Inc., Redmond, Washington) and Intercooled Stata 9.2 (StataCorp, College Station, Texas). We computed incremental cost-effectiveness ratios, comparing each diagnostic strategy with the next most costly alternative, eliminating: 1) strategies that cost more and were less effective; and 2) strategies whose incremental cost-effectiveness exceeded that of a more costly and beneficial strategy (18). Strategies were compared with each other, as opposed to each strategy being compared with the “no test” group, because doing so provides a more accurate assessment of incremental cost-effectiveness, as all viable diagnostic pathways are included.

**Results**

**Clinical outcomes.** In the base case analysis, which evaluated 55-year-old men and women with atypical angina, there was little difference in health outcomes across the diagnostic strategies. Performing CCTA alone or in combination with stress ECG (CTA–stress ECG strategy) or performing stress SPECT alone marginally minimized the lifetime prevalence of adverse events and maximized longevity and quality-adjusted life expectancy (QALE) (Table 4). Health outcomes associated with these strategies were comparable, with no strategy emerging as markedly superior to others. Cardiac catheterization also yielded similar health benefits to these 3 approaches, but its improved detection of CAD and reduction in post-test adverse events was counterbalanced by its higher mortality risk.

Although the CTA–stress ECG strategy marginally maximized QALE in men and women, it was closely followed by stress SPECT, CTA without stress testing, and catheterization. However, the difference in health outcomes across all of the test strategies was small, and performing the least effective test—compared with performing no exam—decreased the prevalence of nonfatal adverse events by 8% to 11% in men and 6% to 8% in women. The comparable increases in longevity and QALE were 7 months and 0.2 QALY in men and 2 months and 0.1 QALY in women. In contrast, performing the most effective test—compared with the performing the least effective test—decreased the prevalence of nonfatal adverse events by 3% in men and women. The comparable increases in longevity and QALE were 2 months and 0.1 QALY in men and 1 month and 0.03 QALY in women. The stress ECG-CTA strategy was particularly unfavorable, because it tended to decrease the overall sensitivity of diagnostic testing. Note that, although our estimation of differences in effectiveness between strategies is small, this finding is in agreement with the results of prior cost-effectiveness analyses of chest pain evaluation (13,51).

Pulmonary nodules were identified in 4% of patients whose initial diagnostic test was CCTA and in 2% of men and in 1% of women who were imaged only after receiving a positive stress ECG (stress ECG-CTA strategy). The detection rate for incidental findings was lower for women in the latter strategy, because their pre-test probability of CAD was lower and fewer of them were imaged. One in 6 patients with a lung nodule underwent a video-assisted surgical resection.
thoracic surgery procedure, on the basis of the model inputs and follow-up criteria that we adopted.

Costs. In men, resource use was greatest when cardiac catheterization was performed. The higher overall cost of this strategy was primarily due to higher initial costs and an elevated rate of detection and treatment for CAD, but treatment costs were partially offset by lower costs of care for nonfatal MIs and strokes.

In women, the most expensive diagnostic test was stress SPECT, followed closely by CTA-based strategies and cardiac catheterization. Despite the perfect sensitivity of catheterization, other strategies were more expensive, because the low prevalence of CAD in women increased the false positive rate, and treatment costs for false positives outweighed the cost of catheterization. Not testing patients at all was the cheapest strategy but was also associated with the greatest MI- and stroke-related costs. Follow-up for incidental findings was a small component of overall costs but translated into an average cost of $5,000/patient found with a lung nodule or approximately $60 to $200/patient evaluated with CTA. Table 5 decomposes average patient costs into its components.

Cost-effectiveness. Figures 5A and 5B summarize the results of the cost-effectiveness analysis. In women, the most efficient strategies (those that maximize health outcomes for a given level of spending) were stress ECG–CTA and CTA–stress ECG, whereas in men, the most efficient strategy was CTA–stress ECG. The incremental cost-
effectiveness ratio of the CTA–stress ECG algorithm was $26,200/QALY in men and $35,000/QALY in women.

**Sensitivity analysis.** We varied several key parameters to evaluate their impact on health outcomes and costs. When we considered 55-year-old patients with nonanginal chest pain, which corresponds to a CAD pre-test probability of 20% in men and 5% in women, the modest differences in health outcomes across all strategies shrank further, and stress SPECT maximized QALE in men and women. Incremental cost-effectiveness ratios also rose sharply: in men, the incremental cost-effectiveness ratio of stress SPECT was $89,800/QALY, whereas it increased to $206,300/QALY in women.

In populations with typical angina, 55-year-old women have a pre-test probability of 70%. The CTA–stress ECG strategy yielded the highest QALE, and its incremental cost-effectiveness ratio was $32,400/QALY. We did not consider men with typical angina, because their pre-test probabilities exceed 90%, and stress testing in this population generally targets risk stratification rather than diagnosis.

Although we assumed that patients found to have CAD on CTA would also have correct characterization of the severity of their disease, some degree of misclassification occurs in reality (e.g., patients with 3-vessel or left main disease might be found to have 1- or 2-vessel disease, and vice versa) (25). We simulated the effect of this misclassification by modeling a worst-case scenario for CCTA efficacy in which 25% of patients (on the basis of results of Miller et al. [25]) previously identified as having 3-vessel or left main disease were misclassified as having 1- or 2-vessel disease. These patients therefore receive medical management only and not CABG or PCI. We found that this modestly reduces the cost of CCTA, because fewer patients are treated with invasive therapies, and also modestly reduced longevity but did not significantly affect cost-effectiveness (Figs. 6A and 6B).

We performed a sensitivity analysis on the effect of interventions on angina by not allowing medical interventions, PCI, or CABG to affect QoL in patients with treated CAD. The CTA–stress ECG strategy continued to yield the highest QALE, but its cost-effectiveness fell to $23,700/QALY in men and $29,200/QALY in women.

We simulated the risk of radiation exposure by applying a CCTA mortality risk of 1 in 2,212 exams or 1 in 867 exams, our estimates for the 20-year attributable cancer mortality risks associated with 8 to 10 mSv of CT radiation to the chest and abdomen in 60-year-old men and women, respectively (12,46). This risk was also applied to SPECT and cardiac catheterization (47). The results in men were unchanged from the base case. In women, CCTA-based strategies continued to maximize QALE, but the incremental cost-effectiveness of CTA–stress ECG rose to $60,000/QALY.

### Table 4 Clinical Outcomes in 55-Year-Old Men and Women With Chest Pain

<table>
<thead>
<tr>
<th>Test Strategy</th>
<th>Nonfatal MI*</th>
<th>Nonfatal Stroke*</th>
<th>Life Expectancy, yrs</th>
<th>QALYs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men</td>
<td>Women</td>
<td>Men</td>
<td>Women</td>
</tr>
<tr>
<td>CTA–stress ECG</td>
<td>341</td>
<td>192</td>
<td>57</td>
<td>33</td>
</tr>
<tr>
<td>Stress ECG–CTA</td>
<td>350</td>
<td>198</td>
<td>59</td>
<td>34</td>
</tr>
<tr>
<td>CTA</td>
<td>341</td>
<td>192</td>
<td>57</td>
<td>33</td>
</tr>
<tr>
<td>Stress ECG</td>
<td>350</td>
<td>196</td>
<td>59</td>
<td>33</td>
</tr>
<tr>
<td>Stress echocardiography</td>
<td>347</td>
<td>195</td>
<td>59</td>
<td>33</td>
</tr>
<tr>
<td>Stress SPECT</td>
<td>343</td>
<td>193</td>
<td>57</td>
<td>33</td>
</tr>
<tr>
<td>Cardiac catheterization</td>
<td>339</td>
<td>192</td>
<td>57</td>
<td>33</td>
</tr>
<tr>
<td>No exam</td>
<td>380</td>
<td>211</td>
<td>66</td>
<td>37</td>
</tr>
</tbody>
</table>

*Lifetime prevalence/1,000 patients undergoing diagnostic testing; adverse events only tracked in patients with CAD.

Cath = invasive cardiac catheterization; QALY = quality-adjusted life-year; other abbreviations as in Table 1.

### Table 5 Health Care Costs in 55-Year-Old Men and Women With Chest Pain

<table>
<thead>
<tr>
<th>Test Strategy</th>
<th>Total Cost, $</th>
<th>Cardiac Care†</th>
<th>Nonfatal MIs, Strokes‡</th>
<th>Lung Nodules†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men</td>
<td>Women</td>
<td>Men</td>
<td>Women</td>
</tr>
<tr>
<td>CTA–stress ECG</td>
<td>35,500</td>
<td>18,210</td>
<td>18,750</td>
<td>8,980</td>
</tr>
<tr>
<td>Stress ECG–CTA</td>
<td>33,870</td>
<td>17,040</td>
<td>16,560</td>
<td>7,580</td>
</tr>
<tr>
<td>CTA</td>
<td>35,720</td>
<td>18,280</td>
<td>18,970</td>
<td>9,060</td>
</tr>
<tr>
<td>Stress ECG</td>
<td>33,970</td>
<td>17,880</td>
<td>16,770</td>
<td>8,520</td>
</tr>
<tr>
<td>Stress echocardiography</td>
<td>34,510</td>
<td>17,660</td>
<td>17,500</td>
<td>8,400</td>
</tr>
<tr>
<td>Stress SPECT</td>
<td>35,670</td>
<td>18,820</td>
<td>18,940</td>
<td>9,730</td>
</tr>
<tr>
<td>Cardiac catheterization</td>
<td>37,340</td>
<td>18,220</td>
<td>20,890</td>
<td>9,230</td>
</tr>
<tr>
<td>No exam</td>
<td>27,580</td>
<td>14,680</td>
<td>84,00</td>
<td>4,260</td>
</tr>
</tbody>
</table>

*Cost estimates are rounded; †includes diagnostic exams, procedures, medications, and cardiac rehabilitation; ‡adverse events only tracked in patients with CAD.

Cath = invasive cardiac catheterization; other abbreviations as in Table 1.
Eliminating the follow-up of incidental findings made no difference in QALE but did reduce the cost of CTA-based strategies. In men, the incremental cost-effectiveness ratio of CCTA–stress ECG fell to $27,100/QALY, and in women, its incremental cost-effectiveness ratio fell to $32,700/QALY. This particular sensitivity analysis provides some insight into the implications of limiting the CTA viewing window to cardiac tissue only, as some researchers advocate (9,11). We also varied the cost of CCTA and calculated the incremental cost-effectiveness of the CTA–stress ECG strategy (Fig. 7). This rose to as high as $34,100/QALY in men and $56,700/QALY in women, when CTA cost $1,200. Increasing the nondiagnostic test rate of CCTA to 10% made little qualitative difference in the results and only marginally raised cost-effectiveness ratios for CTA-based strategies.

**Discussion**

In our evaluation of diagnostic test strategies for patients with stable chest pain and suspected CAD, we found that there was little difference in health outcomes across all of the
strategies, although the use of CCTA—with or without subsequent stress testing and stress SPECT—was marginally associated with the greatest quality-adjusted longevity. We also found that CTA-based strategies raised overall health care costs, primarily by increasing the rate of CAD detection and treatment but also through the detection and follow-up of incidental findings. These higher costs were partially offset by lower costs of care for nonfatal MIs and strokes. Overall, the incremental cost-effectiveness ratio of performing CCTA in combination with stress ECG fell well within the range of what is generally considered to be cost-effective, although there were only modest differences in cost and health outcomes across all of the test strategies. As a reference, the threshold of $50,000/QALY is sometimes used as an estimate of what society might be willing to pay for health benefits. Overall, it is important to note that the finding of similarity in health outcomes across all of the diagnostic strategies offers support for the application of any
of the modalities to the diagnosis of CAD, including CCTA, but also highlights the relevance and importance of large randomized controlled trials to further illuminate decision-making and policy. Finally, it is notable that although our analytic approach to evaluating cost-effectiveness diverged from that taken by a prior study our overall conclusions about the cost-effectiveness of CCTA are similar (17).

Although the exam is now covered by all local Medicare carriers in the U.S., Medicare continues to consider it experimental on a national level, and many private insurers refuse to cover on the basis of concerns related to cost containment and clinical efficacy. Our sensitivity analyses suggested that neither incidental finding follow-up nor radiation risk significantly influenced outcomes, and these results along with our overall results on clinical effectiveness suggest that good value might be attained for the resources used. However, clinical outcomes data are needed to support our results.

**Study limitations.** First, our survival and adverse event rates were partially drawn from the COURAGE trial, which enrolled patients at higher risk than the population we are modeling (21). We used this study, however, because the COURAGE trial is one of the largest studies published to date that adopts contemporary care strategies. In future studies, additional refinement of mortality predictions with the Duke treadmill score should also be incorporated.

We also limited our accounting of adverse events to patients with significant CAD. In reality, however, many patients with nonobstructive CAD or angiographically normal coronary arteries might also benefit from risk-lowering cardiovascular therapies, and we did not incorporate this. A related limitation is that the parameters we derived from the COURAGE trial were not adjusted for age or sex but rather describe the cohort as a whole. Furthermore, the statin meta-analyses from which we draw morbidity and mortality risks included studies performed on populations with and without CAD.

Although we considered lung nodules, the exclusion of other incidental findings is an important limitation. Researchers have reported the incidental discovery of several types of findings, including lesions in the liver, breast, and chest wall (9,11,26,27,64). In the absence of guidelines constraining the tendency to follow-up these findings, they might increase the overall cost of performing CCTA. It is possible, however, that the identification of some of these findings will improve health outcomes, but supportive data are still forthcoming.

Regarding the diagnostic tests for CAD, we did not include a nondiagnostic exam rate for stress testing. This rate was not reported in the meta-analysis from which the sensitivity and specificity of stress echocardiography and stress SPECT were extracted or in the other major meta-analysis published on stress testing. Because a nondiagnostic rate for CCTA was included, this is a limitation of the study. We also did not incorporate the relationship between the likelihood of markedly abnormal stress test results and CCTA findings, because these data have not been pub-
lished. Furthermore, because we modeled CCTA as correctly classifying the severity of CAD when the test was appropriately positive, our base case overestimates the efficacy of this diagnostic modality. We were able to perform a sensitivity analysis to partially address this limitation, but more data on the specific distribution of coronary artery severity would further improve the analysis.

We evaluated—in terms of diagnostic strategies—8 algorithms, but other management approaches exist, and decision-making might vary by physician. Also, we did not evaluate the impact of managing patients with multivessel disease with PCI instead of CAGB or consider attributable radiation risks associated with more recent studies of prospective ECG gating for CCTA. Researchers have now demonstrated that CCTA can be performed at a radiation dose of 1 to 3 mSv (65,66).

**Conclusions**

Our study represents a preliminary exploration of CCTA in the evaluation of ambulatory patients with stable chest pain. Additional studies are warranted to further characterize the implications of incidental findings, radiation exposure, non-diagnostic examinations, and the identification of patients with nonobstructive atherosclerotic disease. Considering the results of our analysis and other evidence available in the published data, we believe that CCTA is comparable to other diagnostic studies and might hold good clinical value, but large randomized controlled trials are needed to guide policy.

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**REFERENCES**


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