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Coronary computed tomography versus exercise testing in patients with stable chest pain: comparative effectiveness and costs ☆

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ABSTRACT

Background: To determine the comparative effectiveness and costs of a CT-strategy and a stress-electrocardiography-based strategy (standard-of-care; SOC-strategy) for diagnosing coronary artery disease (CAD).

Methods: A decision analysis was performed based on a well-documented prospective cohort of 471 outpatients with stable chest pain with follow-up combined with best-available evidence from the literature. Outcomes were correct classification of patients as CAD− (no obstructive CAD), CAD+ (obstructive CAD without revascularization) and indication for Revascularization (using a combination reference standard), diagnostic costs, lifetime health care costs, and quality-adjusted life years (QALY). Parameter uncertainty was analyzed using probabilistic sensitivity analysis.

Results: For men (and women), diagnostic cost savings were €245 (€252) for the CT-strategy as compared to the SOC-strategy. The CT-strategy classified 82% (88%) of simulated men (women) in the appropriate disease category, whereas 83% (85%) were correctly classified by the SOC-strategy. The long-term cost-effectiveness analysis showed that the SOC-strategy was dominated by the CT-strategy, which was less expensive (−€229 in men, −€444 in women) and more effective (+0.002 QALY in men, +0.005 in women). The CT-strategy was cost-saving (−€231) but also less effective compared to SOC (−0.003 QALY) in men with a pre-test probability of ≥70%. The CT-strategy was cost-effective in 100% of simulations, except for men with a pre-test probability ≥70% in which case it was 59%.

Conclusions: The results suggest that a CT-based strategy is less expensive and equally effective compared to SOC in all women and in men with a pre-test probability <70%.

1. Introduction

The current guideline still recommends stress electrocardiography(X-ECG) as first line diagnostic test for patients with stable chest pain [1]. However, the diagnostic accuracy of X-ECG is limited [2].

Coronary CT angiography(CCTA) is an alternative modality for diagnosing coronary artery disease(CAD). Its diagnostic accuracy compared to catheter-based coronary angiography(CAG) in highly selected patients has been studied extensively [3–7], demonstrating that CCTA is reliable in ruling out CAD (sensitivity 95–100%). Furthermore, previously published decision analyses indicate that CCTA as triage test in patients referred for CAG is cost-effective in patients with a low-intermediate probability of disease [8–10].

Recently, results from a Dutch outpatient chest pain clinic were published [11,12]. Patients with stable chest pain were evaluated by X-ECG, CT calcium scoring, and CCTA. Results suggested that CT calcium scoring, selectively followed by CCTA could replace X-ECG as first line diagnostic test. However, long-term effectiveness and costs of CCTA compared to standard-of-care (SOC) in outpatients presenting with chest pain remain unclear.

Ideally, a large randomized controlled trial (RCT) comparing a CT-based strategy to SOC should be performed to evaluate comparative effectiveness and costs. Exploration of diagnostic strategies and preliminary estimates of outcomes can help design such a trial and can justify the investment of research resources. Furthermore, trial results

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will only be available after several years and in the meantime diagnostic testing decisions have to be made. A decision-analytic approach summarizing the evidence can be helpful in such situations.

Aim of this study was to determine the comparative effectiveness and costs of a hypothetical CT-strategy compared with SOC using a decision-analytic approach combining data from a well-documented prospective patient cohort with the best-available evidence from the literature.

2. Materials and methods

2.1. Patient population

The model was based on a prospective clinical cohort [11] of 471 patients who presented with stable chest pain and no history of CAD. All patients were scheduled for X-ECG and CCTA (Table 1). During a mean follow-up (complete in 90%) of 2.6 years, 44 major adverse cardiovascular events (MACE: cardiac death, myocardial infarction, unstable angina requiring hospitalization, and revascularization) occurred in 30 patients [13] (Table A1). The study complied with the Declaration of Helsinki and the ethical committee at our institution approved the study. Informed consent was obtained from all patients.

Table 1
Baseline characteristics[a], diagnostic test results[a], cost estimates and radiation exposure.

Baseline characteristics	Value
Age, mean(SD)	56 (10)
Female: male	227:224 (0.48:0.52)
Risk profile	
Nicotine use	138 (0.29)
Hypertension	233 (0.49)
Diabetes	68 (0.14)
Dyslipidaemia	28 (0.59)
Family history of cardiovascular disease	214 (0.45)
Chest pain [36]	
Typical	146 (0.31)
Atypical	251 (0.53)
Non-anginal chest pain	74 (0.16)
Catheter-based coronary angiography	98 (0.21)
≥50% stenosis, any vessel	57/98 (0.58)
≥70% stenosis, any vessel	29/98 (0.30)
Percutaneous coronary intervention	46 (0.10)
Coronary bypass graft surgery	13 (0.03)
X-ECG Not performed	48/471 (0.10)
Normal	190/423 (0.45)
Non diagnostic	140/423 (0.33)
Abnormal	93/423 (0.22)
CCS Not performed	8/471 (0.02)
Mean CCS (median)	206 (15)
Range	0-4817
Interquartile range	0-145
CCTA Not performed	16/471 (0.03)
Non-diagnostic	3/471 (0.01)
No obstructive CAD	311/471 (0.66)
Obstructive CAD (≥50%)	141/471 (0.34)
Severe CAD (3VD, LM, prox. LAD)	48/141
CAG performed	121/471 (0.26)
≥50% stenosis, any vessel	71/121 (0.59)
≥70% stenosis, any vessel	34/121 (0.28)
Percutaneous coronary intervention	53/471 (0.11)
Coronary artery bypass graft surgery	18/471 (0.04)

	Cost estimates (euros)	Radiation exposure (mSv)
Exercise tolerance test (Expert opinion)	106	–
Coronary calcium score [8]	64	0.8
CT coronary angiography [8]	206	4.7
Single photon emission CT (Expert opinion)	545	12
Cathether-based coronary angiography [8]	1394	7.0
Percutaneous coronary intervention [37]	5000	15
Coronary bypass graft surgery [37]	14,000	–

Results are shown as numbers (proportion of total) unless stated otherwise. X-ECG, exercise electrocardiography; CCTA, coronary computed tomography angiography; CAG, catheter-based coronary angiography.
[a] Modified with permission from Nieman et al. [11].

2.2. Decision model

We developed a decision model (in DATA Pro 2009 Suite, TreeAge Software Inc, Williamstown, MA, USA) to evaluate the comparative effectiveness and costs of a hypothetical CT-based strategy compared to an X-ECG-based strategy (reflecting standard-of-care; SOC-strategy). Short-term diagnostic outcomes were modeled with a decision tree (Figs. 1, 2). Long-term prognosis (lifetime) was modeled using a Markov-Model (Figure A1). Model parameters were based on the clinical cohort with follow-up combined with best-available evidence from the literature (Table A2, A3). See supplementary material for a detailed model description.

Model probabilities for diagnostic test results were based on the clinical cohort and conditional on the "underlying truth", sex, and the pre-test probability. To model the "underlying truth", a disease category was assigned to all patients in the cohort: No obstructive CAD (CAD−), Obstructive CAD (CAD+) or Revascularization (Revasc) (Fig. 3), which represents the true disease status at baseline. This was based on CAG(if performed), the treatment initiated and CCTA otherwise and included 6-month follow-up information. For example, if a patient was initially treated with medication only, but electively revascularized within 6 months, the patient was labelled as Revascularization. The modified reference standard was used in all analyses.

The diagnostic model classifies patients in one of the disease categories. Classification is correct if the classified category matches the underlying truth, and incorrect when the classified category does not match the underlying truth. Underlined categories refer to the underlying 'true' disease category, whereas *italic* categories refer to the disease category as classified by the diagnostic work-up. Individuals classified as *CAD−* by the diagnostic strategy, who are CAD+ or Revascularization according to their underlying truth are "under-classified". Patients classified as *CAD+* who are Revascularization according to the underlying truth are "under-classified". Individuals classified as *CAD+*, who are CAD− according to the underlying truth, are "over-classified". The next paragraph explains how patients are classified by the diagnostic work-up.

2.3. Short-term decision tree

The SOC-strategy consists of initial evaluation with X-ECG according to the guideline [1] (Fig. 1). Non-diagnostic X-ECGs are common (~25% [14])– which warrants further testing with pharmacological stress myocardial perfusion imaging (MPI) using single photon emission CT (SPECT). Patients unable to exercise are evaluated by MPI. We assume that a CAG classifies patients in the correct category.

The CT-strategy starts with a coronary artery calcification (CAC) scan in every patient and a CCTA in patients with a CAC > 0 and < 400 (Fig. 2). Patients with CAC = 0 and a pre-test probability < 70% do not undergo CCTA, because obstructive CAD is unlikely to be present [15]. This cutoff was chosen to capture the high-risk patients with typical presentation [16], which is consistent with clinical practice at our institution. Thus, a patient with zero calcium and a pre-test probability ≥70% will undergo CCTA (Fig. 2). Based on evidence that revascularization does not always improve survival beyond optimal medical treatment in patients with moderate disease [17], the CT-strategy consists of medical treatment for patients with moderate disease on CCTA and referral to CAG only if the CCTA shows severe CAD (left main-, three vessel-, or proximal left anterior descending artery disease).

2.4. Long-term Markov model

We used a Cox proportional hazards model to estimate the sex-specific rates of MACE for CAD−, CAD+, and Revascularization patients in the clinical cohort. Prognosis after the diagnostic work-up in the model depended on the correct vs incorrect classification. Correctly classified individuals in the model were assigned the adjusted event rate as observed in the cohort. Under-classified (and under-treated) individuals experienced a higher event rate because of the forgone benefit of treatment (hazard rate ratio (HRR) based on the combined effectiveness of statins [18] and aspirin [19]). Over-classification only occurs when a CAD− patient is classified as *CAD+* and we assumed that medical treatment does not alter the event rate in these patients. See supplementary material for more details.

To mimic clinical follow-up of patients with chest pain, we assumed that every under-classified patient will be diagnosed with the correct disease category within the first year. We assumed that those patients remain symptomatic prior to the correct diagnosis because they are under-treated for a short period. As in clinical practice, patients with persistent angina are re-evaluated by the cardiologist. This implies that our model assumes that the benefit in terms of better outcomes of a diagnostic strategy can only be obtained in the first year after the initial assessment. In contrast, individuals who are over-classified are assumed not to reclassify to the CAD− category, but to remain in *CAD+*. The negative implications of overestimating the severity of disease in a CAD− patient consists of extra costs for medication and a (slightly) lower quality-of-life.

We modeled the risk of dying from non-cardiac causes based on age- and sex-specific mortality rates from the Dutch Central Bureau for Statistics [20].