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Cost-effectiveness of Anatomic and Functional Test Strategies for Stable Chest Pain: Public Health Perspective from a Middle Income Country

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ABSTRACT

Objectives. To evaluate the relative cost-effectiveness of functional and anatomical strategies for diagnosing stable coronary artery disease (CAD), using exercise electrocardiogram (Ex-ECG), stress echocardiogram (ECHO), single-photon emission computed tomography (SPECT), coronary computed tomography angiography (CTA), or stress cardiac magnetic resonance (MRI).

Setting. Decision-analytic model, comparing strategies of sequential tests for evaluating patients with possible stable angina in low, intermediate and high pretest probability of CAD, from the perspective of a developing nation's public healthcare system.

Participants. Hypothetical cohort of patients with pretest probability of CAD between 20% and 70%.

Primary and secondary outcome measures. The primary outcome is cost per correct diagnosis of CAD. Proportion of false-positive or false-negative tests and number of unnecessary tests performed were also evaluated.

Results. Strategies using Ex-ECG as initial test were the least costly alternatives, but generated more frequent false-positive initial tests and false-negative final diagnosis. Strategies based on CTA or ECHO as initial test were the most attractive and resulted in similar cost-effectiveness ratios (I$ 286 and I$ 305 per correct diagnosis, respectively). A strategy based on C-MRI was highly effective for diagnosing stable CAD, but its high cost resulted in unfavorable ICERs in moderate- and high-risk scenarios. Noninvasive strategies based on SPECT have been dominated.

Conclusions. An anatomic diagnostic strategy based on CTA is a cost-effective option for CAD diagnosis. Functional strategies performed equally well when based on ECHO. C-MRI yielded acceptable ICER only at low pretest probability, and SPECT was not cost-effective in our analysis.

Strengths and limitations of this study:

- There is no evidence that diagnostic test selection impacts cardiovascular event rates in stable CAD, and economic results may help guide choice among tests.

- Our results show that incorporating coronary computed tomography into the Brazilian Public Health System would add a cost-effective option for CAD diagnosis.

- Among currently available technologies, the demonstration that stress echocardiography is more cost-effective than SPECT from this perspective may improve public resource allocation.

- Cost-effectiveness results are useful to establish the “standard” test for routine use, but flexibility in the choice among tests is still important, allowing physicians to select the best strategy for each particular case.

Key Words: cost-benefit analysis, coronary disease, diagnosis, cardiovascular imaging.

INTRODUCTION

Proper evaluation and diagnosis of coronary artery disease (CAD) is an essential part of public health strategies, given the importance of CAD in worldwide morbidity and mortality [1]. When a patient presents with chest pain symptoms, his or her probability of having CAD can vary from less than 10% to more than 90%, depending on clinical and epidemiological characteristics [2]. In the frequent cases with intermediate pre-test probability, additional diagnostic tests can aid in clinical decision-making and risk stratification.

Nowadays, several noninvasive tests for diagnosing coronary artery disease are widely available, and have varying accuracy and costs. In Brazil, the Unified National Health System (SUS) currently reimburses exercise electrocardiography (Ex-ECG), stress echocardiography (ECHO), and nuclear stress testing (SPECT), but not coronary computed tomographic angiography (CTA) or stress cardiac magnetic resonance (MRI) [3].

Recommendations for diagnostic test selection are not uniform in current practice guidelines [2 4 5], and in many, if not most occasions, the choice among these tests is determined primarily by individual physician preference and/or local availability. This may overlook several other important factors, from the efficacy of each test for a given pretest probability, to economic issues such as added cost per diagnosis, when an inexpensive test such as Ex-ECG is systematically replaced by a more expensive, albeit more accurate test such as SPECT.

Recently published data from a large randomized trial shows that anatomical testing using CTA results in similar long-term event rates as functional testing with Ex-ECG, SPECT or ECHO [6]. These results should increment the importance of economic data in the decision-making process for test selection.

We aimed to compare the cost-effectiveness, measured as cost per correct diagnosis, of various functional and anatomical testing strategies for patients with suspected CAD. This information can supplement efficacy data in decision-makers' choice of approved exams for health plans, and provide grounds for the development of nationwide protocols for the management of stable angina.

METHODS

Model

Decision-analytic model, comparing strategies for evaluating patients with possible stable angina, from the public health system's perspective; **Figure 1** schematically depicts the model structure. The model, developed in Treeage Pro 2013 (Williamstown, MA; TreeAge Software, Inc.), considered a hypothetical cohort of patients with pretest probability of CAD between 20% and 70%.

We defined eight functional strategies and three anatomical strategies, based on clinically realistic sequences of tests (**Table 1**); in each strategy, the patient undergoes an initial test, moving on to further testing in case of positive or indeterminate results. Negative results do not generate additional tests. Strategy 1, for example, begins with Ex-ECG as a first test. Patients with positive or indeterminate results perform the second test, ECHO; if the second test is positive or indeterminate, patients move on to invasive coronary angiography (CA) as a final test. In scenarios with high pretest probability, we also considered strategies that use CA as first test, reserving noninvasive test for equivocal CA results, such as coronary lesions of unknown hemodynamic significance.

Outcomes

The model ends with a test result (positive or negative), potentially true or false depending on the accuracy of the tests, resulting in final costs per correct diagnosis. There is also a small risk of death due to test-related adverse events **(Table 2)**.

Data sources

After systematic review of previous studies of accuracy, we used available data from published meta-analyses of test performance and risks to populate the model (**Table 2**).

Brazilian National Health System (Sistema Único de Saúde – SUS) 2013 reimbursement rates were the source of costs for diagnostic tests for currently reimbursed tests [3]; costs of CTA and MRI were estimated based on rates for currently reimbursed tests (chest computed tomography and rest cardiac magnetic resonance), inflated proportionally to cost differences among these tests in the private sector [7] (**Table 2**).

All costs were converted from Brazilian Real to International Dollars (I$), using the World Bank's latest available purchasing power parity conversion factor of 1.89 [8].

Assumptions

We assumed 100% sensitivity and specificity for coronary angiography, since it is the gold standard for diagnosing coronary artery disease. Another assumption was that for the last test in any strategy, whether it is CA (as in strategies 1-9) or a noninvasive test (as in strategies 10-11), the probability of indeterminate results is zero.

We assumed myocardial infarction (MI) as an example of serious investigation-related complication, and applied SUS data regarding average national costs for MI admissions in 2012, I$ 1,670 [3], as reference for cost of complications (including death).

Separate analyses were performed, with low (20%), medium (50%) and high (70%) pretest probabilities of CAD, corresponding to the range of pretest probability in which noninvasive tests are most useful, according to the American Heart Association's guidelines on stable angina [2].

Sensitivity Analysis

Aiming to test the robustness of the model and the weight of individual parameters on results, during sensitivity analysis, we varied test accuracies and rates of complications

and indeterminacy around their 95% confidence intervals. Alternative costs of tests ranged from half the original values to double those values.

In addition to one- and two-way sensitivity analyses, we performed probabilistic sensitivity analysis (PSA) with 10,000 samples, with simultaneous variation of model parameters around their confidence intervals. We used beta distributions for test accuracies and gamma distributions for costs.

Additionally, taking into account that in some situations CA may be considered an unacceptable first test due to patient or physician preferences, we considered an alternative scenario excluding strategies that begin with CA (strategies 10 and 11).

Willingness-to-pay

There is no broadly accepted willingness-to-pay (WTP) threshold for additional costs per correct diagnosis. For results per quality-adjusted life years, the World Health Organization (WHO) recommends a WTP threshold between 1 and 3 times a nation's gross domestic product (GDP) per capita for middle income countries [9]. For Brazil, these figures are I$ 11,700 to 35,200 per QALY.

Since per-diagnosis results could be considered to be of a lower magnitude than per-QALY results, we did not make any assumption regarding lower limit of WTP, but rather chose to describe the main findings.

RESULTS

Table 3 shows average costs, accuracy, and comparative cost-effectiveness results from testing a population with low (20%) to high (70%) pretest probability of CAD with each diagnostic strategy. In **Figure 2,** cost-effectiveness results for each pretest probability are illustrated, excluding dominated strategies.

Low pretest probability (20%)

With low probability of CAD, strategy 2 (Ex-ECG -> CTA -> CA) was the least costly strategy, with a mean cost per diagnosis of I$ 135, while retaining good overall performance (92.6% correct diagnosis, 5% invasive CA in patients without CAD). Upgrading to strategy 9 (CTA -> CA) increases effectiveness to 97.6% of correct diagnosis, with mean cost per diagnosis I$ 200 and incremental cost-effectiveness ratio (ICER) of I$ 1,420. Substituting strategy 9 with strategy 8 (C-MRI -> CA) modestly increases diagnostic accuracy to 97.9%, but raises mean cost per diagnosis to I$ 320, resulting in a much higher ICER of I$ 47,800.

The other strategies were either absolutely or relatively dominated. However, strategy 1 (Ex-ECG -> ECHO -> CA) had accuracy results that were practically identical to strategy 2 (92.4% correct diagnosis), with mean cost per diagnosis only marginally higher, I$ 150.

Moderate pretest probability (50%)

In moderate CAD probability scenario, strategy 2 (Ex-ECG -> CTA -> CA) remained the least costly strategy, at I$ 230 per correct diagnosis; however, in this scenario, this strategy resulted in a relatively low overall accuracy of 81%, with over 18% false negative final diagnoses. Strategy 4 (Ex-ECG -> CA) improves overall accuracy to 86%, with 14% false negative results, and costs I$ 240 per correct diagnosis. Resulting in an ICER versus strategy 2 of I$ 415.

In this range of pretest probability, the strategy based on CTA coronary angiography as initial test (strategy 9) yields significantly better outcomes, with 94% overall accuracy. Mean cost per diagnosis is I$ 285, resulting in an ICER versus strategy 4 of I$ 750 per correct diagnosis. Strategy 8, based on C-MRI, raises accuracy to 95%, while increasing mean cost per diagnosis to I$ 410. ICER for strategy 8 versus strategy 9 is I$ 17,800 per correct diagnosis.

Remaining strategies have been dominated by strategies 2, 4, 9 and 10. Once again, it should be noted that strategy 6 (Echo -> CA) yields accuracy results very close to the ones obtained with strategy 9 (93.6%), at a marginally higher mean cost per diagnosis of I$ 305.

High pretest probability (70%)

With a higher prevalence of CAD, strategies that involve two noninvasive tests before CA are dominated by strategy 4 (Ex-ECG -> CA), which results in 80% correct identification at I$ 280 per diagnosis. However, in this range of CAD risk, strategy 4 results in 20% false negative results, seriously hindering its usefulness in practice.

If strategies with false negative rates above 20% (1-4) are excluded from analysis, strategy 9 (CTA -> CA) emerges as an attractive option, with overall accuracy 92%, and mean cost per diagnosis of I$ 345. Strategy 6 (Echo -> CA) results in practically identical effectiveness (91%) at a somewhat higher cost per diagnosis of I$ 400.

A strategy based on invasive CA as first test (strategy 10) results in 98% accuracy, mean cost per diagnosis I$ 346, and ICER I$ 273 versus strategy 9.

Sensitivity Analysis

In one-way sensitivity analysis, the choice between CTA and ECHO-based strategies was sensitive to procedure costs and test sensitivity. For instance, in low-probability scenarios, CTA dominates ECHO if it costs less than I$ 129, has higher cost and

higher effectiveness with costs between I$ 129 and 182, and is extensively dominated by ECHO at higher costs. With high pretest probability, ECHO is the preferred noninvasive method if it costs up to I$ 56; and at its maximum price, ECHO is dominated by CTA.

Variation in cost and accuracy of other tests modified cost per diagnosis for each strategy, but did not alter base-case results to the extent of changing preferred strategies.

In probabilistic sensitivity analysis, there was significant overlap between CTA and ECHO in terms of cost-effectiveness, demonstrating a high level of uncertainty as to which of the two strategies would be preferred (**Figure 3**).

In the alternative scenario that excludes CA as an initial test, even in the high pretest probability group, strategy 8, based on C-MRI as first test, becomes the strategy with highest accuracy, with an ICER versus strategy 9 (CTA -> CA) slightly above $12,200 with 70% pretest probability.

Focusing on currently available imaging modalities, we performed two-way sensitivity analysis on the choice between ECHO-based and SPECT-based strategies, which showed ECHO-based strategies to be dominant across the defined spectrum of sensitivity analysis. SPECT-based strategies are preferred only if the cost of SPECT is no more than 10% higher than the cost of ECHO.

DISCUSSION

Significant interest has been placed on the choice between functional and anatomical strategies for CAD diagnosis. In the management of acute coronary syndrome, CTA outperformed functional testing in three clinical trials [10-12]. However, in stable CAD, randomized data on the clinical impact of selecting a functional or anatomical strategy have only recently been published.

In the PROMISE trial [6], an anatomic strategy based on CTA as initial test resulted in similar clinical outcomes over 2 years, when compared to functional testing. The CTA strategy, probably due to its high sensitivity, resulted in a lower rate of invasive CA with no evidence of CAD in the first 90 days. Coronary revascularization was more frequent with CTA, but long-term clinical significance of this finding is uncertain.

This similar performance of anatomical and functional strategies should prompt physicians and decision-makers to look beyond clinical outcomes in the selection of tests, taking into account information such as cost-effectiveness, resource use, and environmental impact. Recent studies suggest CTA may be a cost-effective option in developed countries [13-15].

In this study, we performed a cost-effectiveness analysis to assess currently available strategies for investigating chest pain in Brazil, and to compare them with new ones, that could become available upon inclusion of CTA and C-MRI among reimbursed tests.

Our study showed that, from the economic perspective, choice of functional test (Ex-ECG, ECHO, SPECT or C-MRI) influences whether a functional or anatomical strategy would be preferable.

The least costly diagnostic strategies are conservative ones, using Ex-ECG as a “gatekeeper”, and proceeding to a second round of noninvasive tests when results are positive. These low-cost strategies have the disadvantage of generating a larger

number of false-positive initial tests, thus subjecting patients without CAD to additional tests. Furthermore, their performance deteriorates as pretest probability rises, so that at 70% pretest probability their false-negative rate is above 20%. Therefore, such strategies may be an option for constrained budgets or lack of alternatives, but only when pretest probability is low or moderate (≤ 50%).

As pretest probability increased, costs per correct (positive or negative) diagnosis becomes higher for strategies based on sequential tests, since positive initial tests are more frequent, leading to further testing in more patients. This is particularly true for conservative strategies that require two noninvasive tests before proceeding to invasive CA. Strategies based on CTA and ECHO as initial test, result in almost superimposable cost-effectiveness results. These strategies would increase accuracy, at an ICER versus Ex-ECG-based strategies well below I$ 11,909 per correct diagnosis. This makes them attractive options across the entire spectrum of pretest probabilities.

Diagnostic strategies based on C-MRI showed to be highly effective, but their relatively high (estimated) cost resulted in unfavorable ICERs in moderate- and high-risk scenarios. If C-MRI costs could be reduced to figures lower than I$ 200 estimated, it could become cost-effective enough to recommend for widespread implementation in SUS. Nonetheless, it is important to emphasize that, for this cost, availability and acquisition values were not taken into account.

Noninvasive strategies based on SPECT generated consistently unfavorable results, due to the high cost of SPECT when compared to other noninvasive tests, and have been dominated in all scenarios. In addition, radiation-related risks were not included in our short-term model because potential effects of radiation exposure take more than a decade to manifest. Still, this could be an additional cause for concern regarding widespread use of tests such as SPECT and CTA.

Our study's main limitation is that, since public health system does not reimburse CTA and C-MRI, we had to estimate procedure costs from private practice. In case of incorporation of these tests into the public system, actual reimbursement values may vary, although we did not expect significant discrepancy based on previous cases. Still, our results were robust even when we halved or doubled the value of our initial cost estimate.

Current practice in Brazil usually prioritizes SPECT-based over ECHO-based strategies for diagnosing CAD. Based on the national database, in the year 2013, the Brazilian public health system reimbursed over 100,000 SPECT tests and less than 19,000 ECHO tests for outpatients [3]. Our results suggest that ECHO-based strategies should be more widely employed in SUS, especially considering their absence of radiation and low costs for implementation and maintenance.

Updating reimbursement values for ECHO may stimulate the availability of this test in the public health system, and seems justified, since our sensitivity analysis showed that ECHO would remain more cost-effective than SPECT even with costs up to 4 times higher than current rates.

CONCLUSIONS

For the diagnosis of stable CAD, strategies based on exercise ECG are the least expensive, but their lower effectiveness means they are best suited for constrained budgets, and only when pretest probability is low or moderate.

Regarding technologies that are currently available in SUS, stress echocardiography is more cost-effective than SPECT, and should generally be preferred if available.

Incorporation of coronary computed tomography into SUS would add a cost-effective option for CAD diagnosis. Stress cardiac magnetic resonance yielded acceptable ICER only at low pretest probability. Our results suggest that the immediate incorporation of coronary computed tomography into SUS is advisable if actual test costs can match our estimated cost of I$ 100 per test. Incorporation of stress cardiac MRI should be considered only if its costs can be reduced to values significantly lower than our estimate of I$ 200.

CONTRIBUTORSHIP STATEMENT

EGB and CAP designed the study, with input from LEPR and SFS. EGB and SFS collected the data. EGB analyzed the data with input from all authors. All authors contributed to the interpretation of the results and write up for publication.

COMPETING INTERESTS

None.

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DATA SHARING STATEMENT

No additional data are available.

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Figures and legends

Figure 1. Schematic representation of model structure.

Figure 2. Base-case cost-effectiveness results for predefined risk categories. Strategies 1-4 excluded from high-probability analysis (see text for details).

Ex-ECG = exercise electrocardiogram; ECHO = stress echocardiogram; SPECT = single-photon emission computed tomography; CTA = computed tomography coronary angiogram; MRI = cardiac magnetic resonance; CA = invasive coronary angiography

Figure 3. Scatterplot of incremental cost-effectiveness of strategy 9 (CTA-CA) versus strategy 6 (ECHO-CA).

ECHO = stress echocardiogram; CTA = computed tomography coronary angiogram; CA = invasive coronary angiography. Dotted line represents willingness-to-pay threshold; ellipse contains 95% of outputs.

Tables

Table 1. Test sequence in each modeled strategy.

* Strategies 10 and 11, in which invasive coronary angiography is the first test, are only considered in scenarios with high pretest probability.

SPECT = single-photon emission computed tomography; MRI = cardiac magnetic resonance.

Table 2. Characteristics of tests; range of values used in sensitivity analysis; and costs.

Ex-ECG = exercise electrocardiogram; ECHO = stress echocardiogram; SPECT = single-photon emission computed tomography; CTA = computed tomography coronary angiogram; MRI = cardiac magnetic resonance; CA = invasive coronary angiography

Table 3. Base-case results for different pretest probabilities. Dominated strategies not shown, except when significant uncertainty regarding dominance on sensitivity analysis.*ICER vs. strategy 1; †ICER vs. strategy 9; ‡ICER vs. strategy 2; §ICER vs. strategy 4

C-E = cost-effectiveness; ICER = incremental cost-effectiveness ratio; FN = false-negative; Ex-ECG = exercise electrocardiogram; ECHO = stress echocardiogram; CTA = computed tomography coronary angiogram; MRI = cardiac magnetic resonance; CA = invasive coronary angiography

Table 1. Test sequence in each modeled strategy.

	1st test	2nd test	3rd test
Strat. 1	exercise ECG	stress echocardiography	coronary angiography
Strat. 2	exercise ECG	coronary CT angiography	coronary angiography
Strat. 3	exercise ECG	SPECT	coronary angiography
Strat. 4	exercise ECG	coronary angiography	
Strat. 5	SPECT	coronary angiography	
Strat. 6	stress echocardiography	coronary angiography	
Strat. 7	stress echocardiography	coronary CT angiography	coronary angiography
Strat. 8	stress cardiac MRI	coronary angiography	
Strat. 9	coronary CT angiography	coronary angiography	
Strat. 10*	coronary angiography	stress echocardiography	
Strat. 11*	coronary angiography	SPECT	

Table 2. Characteristics of tests; range of values used in sensitivity analysis; and costs.

Test	Sensitivity (%) [range]	Specificity (%) [range]	Indeterm. (%)	Mortality (‰)	Cost (I$)	Sources
Ex-ECG	65 [42 – 92]	67 [43 – 83]	18	0.05	16	[3 16 17]
ECHO	85 [83 – 87]	77 [74 – 80]	15	0.05	87	[3 18 19]
SPECT	87 [84 – 88]	64 [60 – 76]	6.9	0.05	419	[3 18 19]
CTA	88 [83 – 92]	87 [80 – 92]	2	0.01	101	[3 20-22]
MRI	89 [88 – 94]	80 [75 – 87]	5	0.01	200	[3 19 23]
CA	100	100	10	0.2	325	Assumption, [3 4 24]

Table 3. Base-case results for different pretest probabilities.

Pretest Probability	Strategy	C-E (I$/diag)	ICER (I$/diag)	Accuracy (%)	FN (%)	Deaths (%)	Invasive CA (%)	Negative invasive CA (%)
LOW	2 (Ex-ECG -> CTA -> CA)	135	-	93	7.4	0.009	18	5
	1 (Ex-ECG -> ECHO -> CA)	153	-	92	7.6	0.012	25	12
	9 (CTA -> CA)	202	1,420*	98	2.4	0.007	29	12
	8 (C-MRI -> CA)	322	47,800†	98	2.1	0.008	37	19
MODERATE	2 (Ex-ECG -> CTA -> CA)	231	-	81	18.5	0.013	35	3
	4 (Ex-ECG -> CA)	240	415‡	86	14.3	0.017	58	23
	9 (CTA -> CA)	286	750§	94	5.9	0.011	51	7
	6 (ECHO -> CA)	305	-	94	6.4	0.017	61	17
	8 (C-MRI -> CA)	407	17,800†	95	5.2	0.012	57	12
HIGH	4 (Ex-ECG -> CA)	278	-	80	20.1	0.018	63	14
	9 (CTA -> CA)	345	790§	92	8.2	0.014	66	4
	6 (ECHO -> CA)	351	-	91	8.9	0.019	71	10
	10 (CA -> ECHO)	381	273†	98	1.7	0.02	100	30

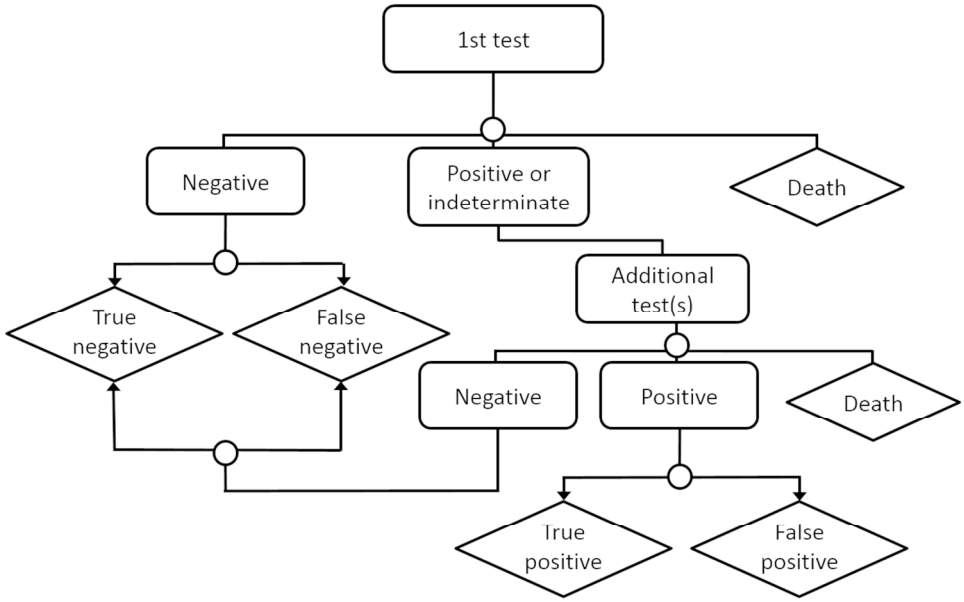

Figure 1. Schematic representation of model structure.

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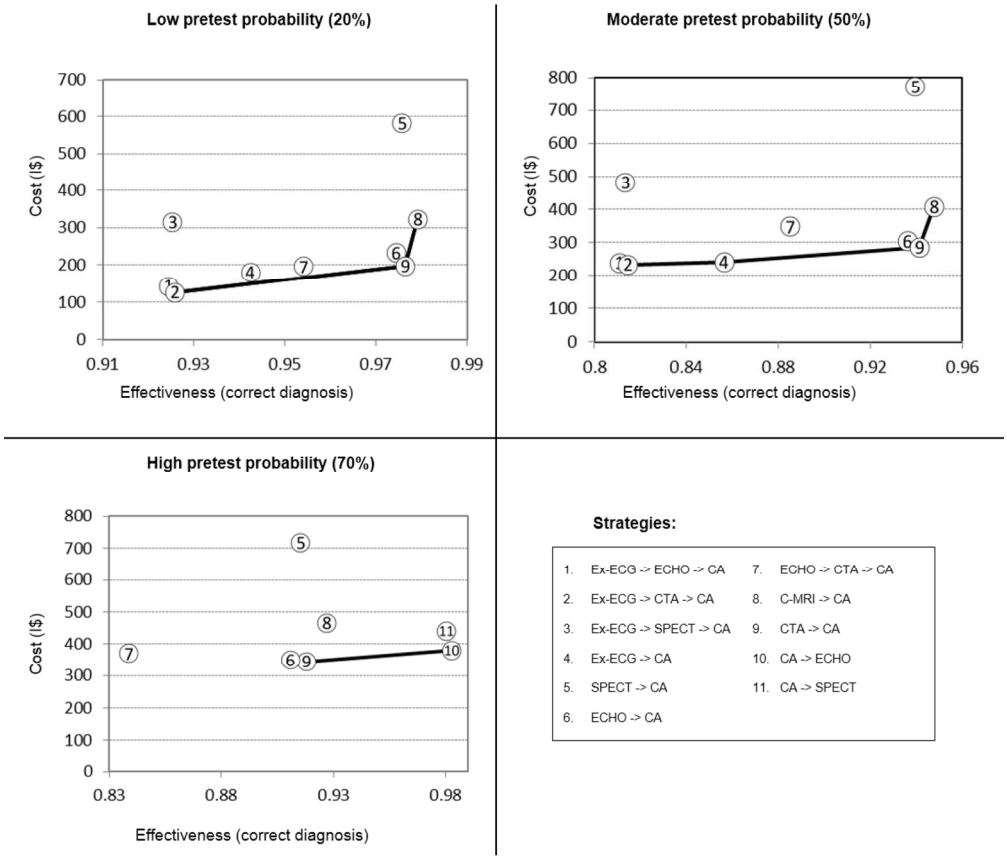

Figure 2. Base-case cost-effectiveness results for predefined risk categories. Strategies 1-4 excluded from high-probability analysis (see text for details).
Ex-ECG = exercise electrocardiogram; ECHO = stress echocardiogram; SPECT = single-photon emission computed tomography; CTA = computed tomography coronary angiogram; MRI = cardiac magnetic resonance; CA = invasive coronary angiography

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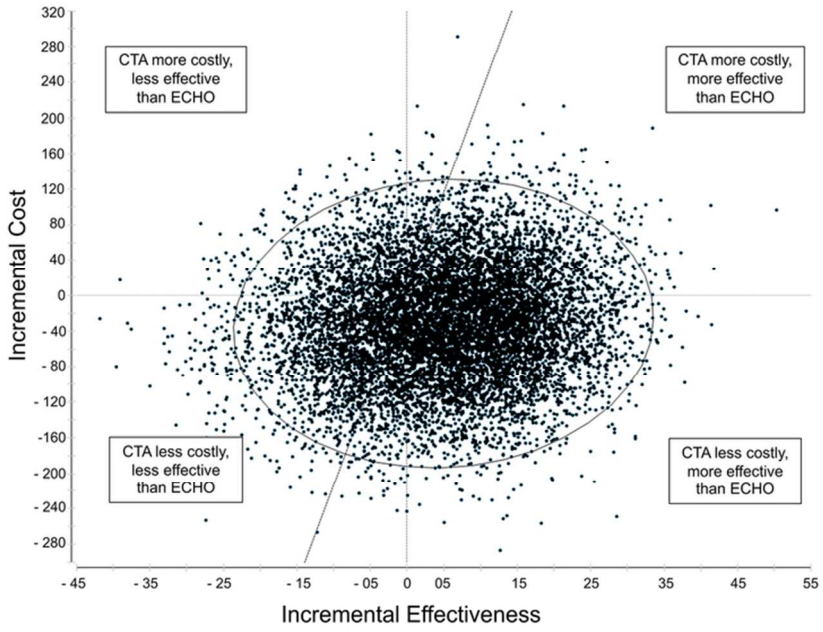

Figure 3. Scatterplot of incremental cost-effectiveness of strategy 9 (CTA-CA) versus strategy 6 (ECHO-CA).
ECHO = stress echocardiogram; CTA = computed tomography coronary angiogram; CA = invasive coronary angiography. Dotted line represents willingness-to-pay threshold; ellipse contains 95% of outputs.

75x56mm (300 x 300 DPI)

CHEERS Checklist
Items to include when reporting economic evaluations of health interventions

The **ISPOR CHEERS Task Force Report**, *Consolidated Health Economic Evaluation Reporting Standards (CHEERS)—Explanation and Elaboration: A Report of the ISPOR Health Economic Evaluations Publication Guidelines Good Reporting Practices Task Force*, provides examples and further discussion of the 24-item CHEERS Checklist and the CHEERS Statement. It may be accessed via the *Value in Health* or via the ISPOR Health Economic Evaluation Publication Guidelines – CHEERS: Good Reporting Practices webpage: http://www.ispor.org/TaskForces/EconomicPubGuidelines.asp

Section/item	Item No	Recommendation	Reported on page No/ line No
Title and abstract			
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	1 / 1
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	2 / 1
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions.	4
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	6
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	8
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	6
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	6
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	6
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	N/A
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	8
Measurement of effectiveness	11a	*Single study-based estimates:* Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	N/A

	11b	*Synthesis-based estimates:* Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	8
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	N/A
Estimating resources and costs	13a	*Single study-based economic evaluation:* Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	N/A
	13b	*Model-based economic evaluation:* Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	8
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	8 p.5 / fig.1
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	10
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	10
Results			
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	Table 2
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	Table 3
Characterising uncertainty	20a	*Single study-based economic evaluation:* Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact	N/A

		of methodological assumptions (such as discount rate, study perspective).	
	20b	*Model-based economic evaluation:* Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	pp. 15-16
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	pp. 15-16
Discussion			
Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	pp. 17-19
Other			
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	20
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	20

For consistency, the CHEERS Statement checklist format is based on the format of the CONSORT statement checklist

The **ISPOR CHEERS Task Force Report** provides examples and further discussion of the 24-item CHEERS Checklist and the CHEERS Statement. It may be accessed via the *Value in Health* link or via the ISPOR Health Economic Evaluation Publication Guidelines – CHEERS: Good Reporting Practices webpage: http://www.ispor.org/TaskForces/EconomicPubGuidelines.asp

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Cost-effectiveness of Anatomic and Functional Test Strategies for Stable Chest Pain: Public Health Perspective from a Middle Income Country

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ABSTRACT

Objectives. To evaluate the relative cost-effectiveness of functional and anatomical strategies for diagnosing stable coronary artery disease (CAD), using exercise electrocardiogram (Ex-ECG), stress echocardiogram (ECHO), single-photon emission computed tomography (SPECT), coronary computed tomography angiography (CTA), or stress cardiac magnetic resonance (MRI).

Setting. Decision-analytic model, comparing strategies of sequential tests for evaluating patients with possible stable angina in low, intermediate and high pretest probability of CAD, from the perspective of a developing nation's public healthcare system.

Participants. Hypothetical cohort of patients with pretest probability of CAD between 20% and 70%.

Primary and secondary outcome measures. The primary outcome is cost per correct diagnosis of CAD. Proportion of false-positive or false-negative tests and number of unnecessary tests performed were also evaluated.

Results. Strategies using Ex-ECG as initial test were the least costly alternatives, but generated more frequent false-positive initial tests and false-negative final diagnosis. Strategies based on CTA or ECHO as initial test were the most attractive and resulted in similar cost-effectiveness ratios (I$ 286 and I$ 305 per correct diagnosis, respectively). A strategy based on C-MRI was highly effective for diagnosing stable CAD, but its high cost resulted in unfavorable ICERs in moderate- and high-risk scenarios. Noninvasive strategies based on SPECT have been dominated.

Conclusions. An anatomic diagnostic strategy based on CTA is a cost-effective option for CAD diagnosis. Functional strategies performed equally well when based on ECHO. C-MRI yielded acceptable ICER only at low pretest probability, and SPECT was not cost-effective in our analysis.

Strengths and limitations of this study:

- There is no evidence that diagnostic test selection impacts cardiovascular event rates in stable CAD, and economic results may help guide choice among tests.

- Our results show that incorporating coronary computed tomography into the Brazilian Public Health System would add a cost-effective option for CAD diagnosis.

- Among currently available technologies, the demonstration that stress echocardiography is more cost-effective than SPECT from this perspective may improve public resource allocation.

- Cost-effectiveness results are useful to establish the “standard” test for routine use, but flexibility in the choice among tests is still important, allowing physicians to select the best strategy for each particular case.

Key Words: cost-benefit analysis, coronary disease, diagnosis, cardiovascular imaging.

INTRODUCTION

Proper evaluation and diagnosis of coronary artery disease (CAD) is an essential part of public health strategies, given the importance of CAD in worldwide morbidity and mortality [1]. When a patient presents with chest pain symptoms, his or her probability of having CAD can vary from less than 10% to more than 90%, depending on clinical and epidemiological characteristics [2]. In the frequent cases with intermediate pre-test probability, additional diagnostic tests can aid in clinical decision-making and risk stratification.

Nowadays, several noninvasive tests for diagnosing coronary artery disease are widely available, and have varying accuracy and costs. In Brazil, the Unified National Health System (SUS) currently reimburses exercise electrocardiography (Ex-ECG), stress echocardiography (ECHO), and nuclear stress testing (SPECT), but not coronary computed tomographic angiography (CTA) or stress cardiac magnetic resonance (MRI) [3].

Recommendations for diagnostic test selection are not uniform in current practice guidelines [2 4 5], and in many, if not most occasions, the choice among these tests is determined primarily by individual physician preference and/or local availability. This may overlook several other important factors, from the efficacy of each test for a given pretest probability, to economic issues such as added cost per diagnosis, when an inexpensive test such as Ex-ECG is systematically replaced by a more expensive, albeit more accurate test such as SPECT.

Recently published data from a large randomized trial shows that anatomical testing using CTA results in similar long-term event rates as functional testing with Ex-ECG, SPECT or ECHO [6]. These results should increment the importance of economic data in the decision-making process for test selection.

We aimed to compare the cost-effectiveness, measured as cost per correct diagnosis, of various functional and anatomical testing strategies for patients with suspected CAD. This information can supplement efficacy data in decision-makers' choice of approved exams for health plans, and provide grounds for the development of nationwide protocols for the management of stable angina.

METHODS

Model

Decision-analytic model, comparing strategies for evaluating patients with possible stable angina, from the public health system's perspective; **Figure 1** schematically depicts the model structure; a more detailed, technical depiction of model structure is available online in **Supplemental Figure A**. The model, developed in Treeage Pro 2013 (Williamstown, MA; TreeAge Software, Inc.), considered a hypothetical cohort of patients with pretest probability of CAD between 20% and 70%.

We defined eight functional strategies and three anatomical strategies, based on clinically realistic sequences of tests (**Table 1**); in each strategy, the patient undergoes an initial test, moving on to further testing in case of positive or indeterminate results. Negative results do not generate additional tests. Strategy 1, for example, begins with Ex-ECG as a first test. Patients with positive or indeterminate results perform the second test, ECHO; if the second test is positive or indeterminate, patients move on to invasive coronary angiography (CA) as a final test. In scenarios with high pretest probability, we also considered strategies that use CA as first test, reserving noninvasive test for equivocal CA results, such as coronary lesions of unknown hemodynamic significance.

Outcomes

The model ends with a test result (positive or negative), potentially true or false depending on the accuracy of the tests, resulting in final costs per correct diagnosis. There is also a small risk of death due to test-related adverse events **(Table 2)**.

Data sources

After systematic review of previous studies of accuracy, we used available data from published meta-analyses of test performance and risks to populate the model (**Table 2**).

Brazilian National Health System (Sistema Único de Saúde – SUS) 2013 reimbursement rates were the source of costs for diagnostic tests for currently reimbursed tests [3]; costs of CTA and MRI were estimated based on rates for currently reimbursed tests (chest computed tomography and rest cardiac magnetic resonance), inflated proportionally to cost differences among these tests in the private sector [7] (**Table 2**).

All costs were converted from Brazilian Real to International Dollars (I$), using the World Bank's latest available purchasing power parity conversion factor of 1.89 [8].

Assumptions

We assumed 100% sensitivity and specificity for coronary angiography, since it is the gold standard for diagnosing coronary artery disease. Another assumption was that for the last test in any strategy, whether it is CA (as in strategies 1-9) or a noninvasive test (as in strategies 10-11), the probability of indeterminate results is zero.

We assumed myocardial infarction (MI) as an example of serious investigation-related complication, and applied SUS data regarding average national costs for MI admissions in 2012, I$ 1,670 [3], as reference for cost of complications (including death).

Separate analyses were performed, with low (20%), medium (50%) and high (70%) pretest probabilities of CAD, corresponding to the range of pretest probability in which noninvasive tests are most useful, according to the American Heart Association's guidelines on stable angina [2].

Sensitivity Analysis

Aiming to test the robustness of the model and the weight of individual parameters on results, during sensitivity analysis, we varied test accuracies and rates of complications and indeterminacy around their 95% confidence intervals. Alternative costs of tests ranged from half the original values to double those values.

In addition to one- and two-way sensitivity analyses, we performed probabilistic sensitivity analysis (PSA) with 10,000 samples, with simultaneous variation of model parameters around their confidence intervals. We used beta distributions for test accuracies and gamma distributions for costs.

Additionally, taking into account that in some situations CA may be considered an unacceptable first test due to patient or physician preferences, we considered an alternative scenario excluding strategies that begin with CA (strategies 10 and 11).

Willingness-to-pay

There is no broadly accepted willingness-to-pay (WTP) threshold for additional costs per correct diagnosis. For results per quality-adjusted life years, the World Health Organization (WHO) recommends a WTP threshold between 1 and 3 times a nation's gross domestic product (GDP) per capita for middle income countries [9]. For Brazil, these figures are I$ 11,700 to 35,200 per QALY.

Since per-diagnosis results could be considered to be of a lower magnitude than per-QALY results, we did not make any assumption regarding lower limit of WTP, but rather chose to describe the main findings.

RESULTS

Table 3 shows average costs, accuracy, and comparative cost-effectiveness results from testing a population with low (20%) to high (70%) pretest probability of CAD with each diagnostic strategy. In **Figure 2,** cost-effectiveness results for each pretest probability are illustrated, excluding dominated strategies.

Low pretest probability (20%)

With low probability of CAD, strategy 2 (Ex-ECG -> CTA -> CA) was the least costly strategy, with a mean cost per diagnosis of I$ 135, while retaining good overall performance (92.6% correct diagnosis, 5% invasive CA in patients without CAD). Upgrading to strategy 9 (CTA -> CA) increases effectiveness to 97.6% of correct diagnosis, with mean cost per diagnosis I$ 200 and incremental cost-effectiveness ratio (ICER) of I$ 1,420. Substituting strategy 9 with strategy 8 (C-MRI -> CA) modestly increases diagnostic accuracy to 97.9%, but raises mean cost per diagnosis to I$ 320, resulting in a much higher ICER of I$ 47,800.

The other strategies were either absolutely or relatively dominated. However, strategy 1 (Ex-ECG -> ECHO -> CA) had accuracy results that were practically identical to strategy 2 (92.4% correct diagnosis), with mean cost per diagnosis only marginally higher, I$ 150.

Moderate pretest probability (50%)

In moderate CAD probability scenario, strategy 2 (Ex-ECG -> CTA -> CA) remained the least costly strategy, at I$ 230 per correct diagnosis; however, in this scenario, this strategy resulted in a relatively low overall accuracy of 81%, with over 18% false negative final diagnoses. Strategy 4 (Ex-ECG -> CA) improves overall accuracy to 86%, with 14% false negative results, and costs I$ 240 per correct diagnosis. Resulting in an ICER versus strategy 2 of I$ 415.

In this range of pretest probability, the strategy based on CTA coronary angiography as initial test (strategy 9) yields significantly better outcomes, with 94% overall accuracy. Mean cost per diagnosis is I$ 285, resulting in an ICER versus strategy 4 of I$ 750 per correct diagnosis. Strategy 8, based on C-MRI, raises accuracy to 95%, while increasing mean cost per diagnosis to I$ 410. ICER for strategy 8 versus strategy 9 is I$ 17,800 per correct diagnosis.

Remaining strategies have been dominated by strategies 2, 4, 9 and 10. Once again, it should be noted that strategy 6 (Echo -> CA) yields accuracy results very close to the ones obtained with strategy 9 (93.6%), at a marginally higher mean cost per diagnosis of I$ 305.

High pretest probability (70%)

With a higher prevalence of CAD, strategies that involve two noninvasive tests before CA are dominated by strategy 4 (Ex-ECG -> CA), which results in 80% correct identification at I$ 280 per diagnosis. However, in this range of CAD risk, strategy 4 results in 20% false negative results, seriously hindering its usefulness in practice.

If strategies with false negative rates above 20% (1-4) are excluded from analysis, strategy 9 (CTA -> CA) emerges as an attractive option, with overall accuracy 92%, and mean cost per diagnosis of I$ 345. Strategy 6 (Echo -> CA) results in practically identical effectiveness (91%) at a somewhat higher cost per diagnosis of I$ 400.

A strategy based on invasive CA as first test (strategy 10) results in 98% accuracy, mean cost per diagnosis I$ 346, and ICER I$ 273 versus strategy 9.

Sensitivity Analysis, Scenario Analysis and Radiation exposure

In one-way sensitivity analysis, the choice between CTA and ECHO-based strategies was sensitive to procedure costs and test sensitivity. For instance, in low-probability scenarios, CTA dominates ECHO if it costs less than I$ 129, has higher cost and

higher effectiveness with costs between I$ 129 and 182, and is extensively dominated by ECHO at higher costs. With high pretest probability, ECHO is the preferred noninvasive method if it costs up to I$ 56; and at its maximum price, ECHO is dominated by CTA.

Variation in cost and accuracy of other tests modified cost per diagnosis for each strategy, but did not alter base-case results to the extent of changing preferred strategies.

In probabilistic sensitivity analysis, there was significant overlap between CTA and ECHO in terms of cost-effectiveness, demonstrating a high level of uncertainty as to which of the two strategies would be preferred (**Figure 3**).

In the alternative scenario that excludes CA as an initial test, even in the high pretest probability group, strategy 8, based on C-MRI as first test, becomes the strategy with highest accuracy, with an ICER versus strategy 9 (CTA -> CA) slightly above $12,200 with 70% pretest probability.

Focusing on currently available imaging modalities, we performed two-way sensitivity analysis on the choice between ECHO-based and SPECT-based strategies, which showed ECHO-based strategies to be dominant across the defined spectrum of sensitivity analysis. SPECT-based strategies are preferred only if the cost of SPECT is no more than 10% higher than the cost of ECHO.

Average radiation dose per patient varied between 3.9 mSv for strategy 1 (Ex-ECG -> ECHO -> CA) and 16.4 mSv for strategy 5 (SPECT -> CA). For strategy 9, based on CTA, mean exposure was 15.1 mSv, and for strategy 8, based on C-MRI, it was 5.7 mSv (Supplementary Table A).

DISCUSSION

Significant interest has been placed on the choice between functional and anatomical strategies for CAD diagnosis. In the management of acute coronary syndrome, CTA outperformed functional testing in three clinical trials [10-12]. However, in stable CAD, randomized data on the clinical impact of selecting a functional or anatomical strategy have only recently been published.

In the PROMISE trial [6], an anatomic strategy based on CTA as initial test resulted in similar clinical outcomes over 2 years, when compared to functional testing. The CTA strategy, probably due to its high sensitivity, resulted in a lower rate of invasive CA with no evidence of CAD in the first 90 days. Coronary revascularization was more frequent with CTA, but long-term clinical significance of this finding is uncertain.

This similar performance of anatomical and functional strategies should prompt physicians and decision-makers to look beyond clinical outcomes in the selection of tests, taking into account information such as cost-effectiveness, resource use, and environmental impact. Recent studies suggest CTA may be a cost-effective option in developed countries [13-15].

In this study, we performed a cost-effectiveness analysis to assess currently available strategies for investigating chest pain in Brazil, and to compare them with new ones, that could become available upon inclusion of CTA and C-MRI among reimbursed tests.

Our study showed that, from the economic perspective, choice of functional test (Ex-ECG, ECHO, SPECT or C-MRI) influences whether a functional or anatomical strategy would be preferable.

The least costly diagnostic strategies are conservative ones, using Ex-ECG as a “gatekeeper”, and proceeding to a second round of noninvasive tests when results are positive. These low-cost strategies have the disadvantage of generating a larger

number of false-positive initial tests, thus subjecting patients without CAD to additional tests. Furthermore, their performance deteriorates as pretest probability rises, so that at 70% pretest probability their false-negative rate is above 20%. Therefore, such strategies may be an option for constrained budgets or lack of alternatives, but only when pretest probability is low or moderate (≤ 50%).

As pretest probability increased, costs per correct (positive or negative) diagnosis becomes higher for strategies based on sequential tests, since positive initial tests are more frequent, leading to further testing in more patients. This is particularly true for conservative strategies that require two noninvasive tests before proceeding to invasive CA. Strategies based on CTA and ECHO as initial test, result in almost superimposable cost-effectiveness results. These strategies would increase accuracy, at an ICER versus Ex-ECG-based strategies well below I$ 11,909 per correct diagnosis. This makes them attractive options across the entire spectrum of pretest probabilities.

Diagnostic strategies based on C-MRI showed to be highly effective, but their relatively high (estimated) cost resulted in unfavorable ICERs in moderate- and high-risk scenarios. If C-MRI costs could be reduced to figures lower than I$ 200 estimated, it could become cost-effective enough to recommend for widespread implementation in SUS. Nonetheless, it is important to emphasize that, for this cost, availability and acquisition values were not taken into account.

Noninvasive strategies based on SPECT generated consistently unfavorable results, due to the high cost of SPECT when compared to other noninvasive tests, and have been dominated in all scenarios. In addition, radiation-related risks were not included in our short-term model because potential effects of radiation exposure take more than a decade to manifest. Still, this could be an additional cause for concern regarding widespread use of tests such as SPECT and CTA.

Our study's main limitation is that, since public health system does not reimburse CTA and C-MRI, we had to estimate procedure costs from private practice. In case of incorporation of these tests into the public system, actual reimbursement values may vary, although we did not expect significant discrepancy based on previous cases. Still, our results were robust even when we halved or doubled the value of our initial cost estimate.

Current practice in Brazil usually prioritizes SPECT-based over ECHO-based strategies for diagnosing CAD. Based on the national database, in the year 2013, the Brazilian public health system reimbursed over 100,000 SPECT tests and less than 19,000 ECHO tests for outpatients [3]. Our results suggest that ECHO-based strategies should be more widely employed in SUS, especially considering their absence of radiation and low costs for implementation and maintenance.

Updating reimbursement values for ECHO may stimulate the availability of this test in the public health system, and seems justified, since our sensitivity analysis showed that ECHO would remain more cost-effective than SPECT even with costs up to 4 times higher than current rates.

CONCLUSIONS

For the diagnosis of stable CAD, strategies based on exercise ECG are the least expensive, but their lower effectiveness means they are best suited for constrained budgets, and only when pretest probability is low or moderate.

Regarding technologies that are currently available in SUS, stress echocardiography is more cost-effective than SPECT, and should generally be preferred if available.

Incorporation of coronary computed tomography into SUS would add a cost-effective option for CAD diagnosis. Stress cardiac magnetic resonance yielded acceptable ICER only at low pretest probability. Our results suggest that the immediate incorporation of coronary computed tomography into SUS is advisable if actual test costs can match our estimated cost of I$ 100 per test. Incorporation of stress cardiac MRI should be considered only if its costs can be reduced to values significantly lower than our estimate of I$ 200.

CONTRIBUTORSHIP STATEMENT

EGB and CAP designed the study, with input from LEPR and SFS. EGB and SFS collected the data. EGB analyzed the data with input from all authors. All authors contributed to the interpretation of the results and write up for publication.

COMPETING INTERESTS

None.

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DATA SHARING STATEMENT

No additional data are available.

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Figures and legends

Figure 1. Schematic representation of model structure.

Figure 2. Base-case cost-effectiveness results for predefined risk categories. Strategies 1-4 excluded from high-probability analysis (see text for details).

Ex-ECG = exercise electrocardiogram; ECHO = stress echocardiogram; SPECT = single-photon emission computed tomography; CTA = computed tomography coronary angiogram; MRI = cardiac magnetic resonance; CA = invasive coronary angiography

Figure 3. Scatterplot of incremental cost-effectiveness of strategy 9 (CTA-CA) versus strategy 6 (ECHO-CA).

ECHO = stress echocardiogram; CTA = computed tomography coronary angiogram; CA = invasive coronary angiography. Dotted line represents willingness-to-pay threshold; ellipse contains 95% of outputs.

Tables

Table 1. Test sequence in each modeled strategy.

* Strategies 10 and 11, in which invasive coronary angiography is the first test, are only considered in scenarios with high pretest probability.

SPECT = single-photon emission computed tomography; MRI = cardiac magnetic resonance.

Table 2. Characteristics of tests; range of values used in sensitivity analysis; and costs.

Ex-ECG = exercise electrocardiogram; ECHO = stress echocardiogram; SPECT = single-photon emission computed tomography; CTA = computed tomography coronary angiogram; MRI = cardiac magnetic resonance; CA = invasive coronary angiography

Table 3. Base-case results for different pretest probabilities. Dominated strategies not shown, except when significant uncertainty regarding dominance on sensitivity analysis.*ICER vs. strategy 1; †ICER vs. strategy 9; ‡ICER vs. strategy 2; §ICER vs. strategy 4. Avg = average.

C-E = cost-effectiveness; ICER = incremental cost-effectiveness ratio; FN = false-negative; Ex-ECG = exercise electrocardiogram; ECHO = stress echocardiogram; CTA = computed tomography coronary angiogram; MRI = cardiac magnetic resonance; CA = invasive coronary angiography

Table 1. Test sequence in each modeled strategy.

	1st test	2nd test	3rd test
Strat. 1	exercise ECG	stress echocardiography	coronary angiography
Strat. 2	exercise ECG	coronary CT angiography	coronary angiography
Strat. 3	exercise ECG	SPECT	coronary angiography
Strat. 4	exercise ECG	coronary angiography	
Strat. 5	SPECT	coronary angiography	
Strat. 6	stress echocardiography	coronary angiography	
Strat. 7	stress echocardiography	coronary CT angiography	coronary angiography
Strat. 8	stress cardiac MRI	coronary angiography	
Strat. 9	coronary CT angiography	coronary angiography	
Strat. 10*	coronary angiography	stress echocardiography	
Strat. 11*	coronary angiography	SPECT	

Table 2. Characteristics of tests; range of values used in sensitivity analysis; and costs.

Test	Sensitivity (%) [range]	Specificity (%) [range]	Indeterm. (%)	Mortality (‰)	Cost (I$)	Sources
Ex-ECG	65 [42 – 92]	67 [43 – 83]	18	0.05	16	[3 16 17]
ECHO	85 [83 – 87]	77 [74 – 80]	15	0.05	87	[3 18 19]
SPECT	87 [84 – 88]	64 [60 – 76]	6.9	0.05	419	[3 18 19]
CTA	88 [83 – 92]	87 [80 – 92]	2	0.01	101	[3 20-22]
MRI	89 [88 – 94]	80 [75 – 87]	5	0.01	200	[3 19 23]
CA	100	100	10	0.2	325	Assumption, [3 4 24]

Table 3. Base-case results for different pretest probabilities.

Pretest Probability	Strategy	Avg cost per patient (I$)	C-E (I$/diag)	ICER (I$/diag)	Accuracy (%)	FN (%)	Deaths (%)	Invasive CA (%)	Negative invasive CA (%)
LOW	2 (Ex-ECG -> CTA -> CA)	125	135	-	93	7.4	0.009	18	5
	1 (Ex-ECG -> ECHO -> CA)	141	153	-	92	7.6	0.012	25	12
	9 (CTA -> CA)	197	202	1,420*	98	2.4	0.007	29	12
	8 (C-MRI -> CA)	315	322	47,800†	98	2.1	0.008	37	19
MODERATE	2 (Ex-ECG -> CTA -> CA)	188	231	-	81	18.5	0.013	35	3
	4 (Ex-ECG -> CA)	205	240	415‡	86	14.3	0.017	58	23
	9 (CTA -> CA)	269	286	750§	94	5.9	0.011	51	7
	6 (ECHO -> CA)	286	305	-	94	6.4	0.017	61	17
	8 (C-MRI -> CA)	385	407	17,800†	95	5.2	0.012	57	12
HIGH	4 (Ex-ECG -> CA)	222	278	-	80	20.1	0.018	63	14
	9 (CTA -> CA)	317	345	790§	92	8.2	0.014	66	4
	6 (ECHO -> CA)	320	351	-	91	8.9	0.019	71	10
	10 (CA -> ECHO)	373	381	273†	98	1.7	0.02	100	30

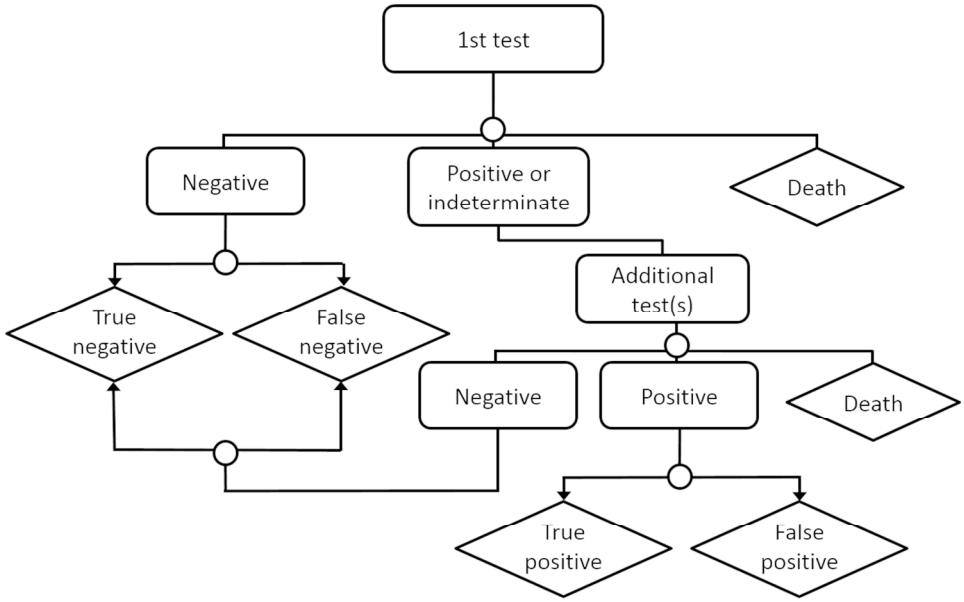

Figure 1. Schematic representation of model structure.

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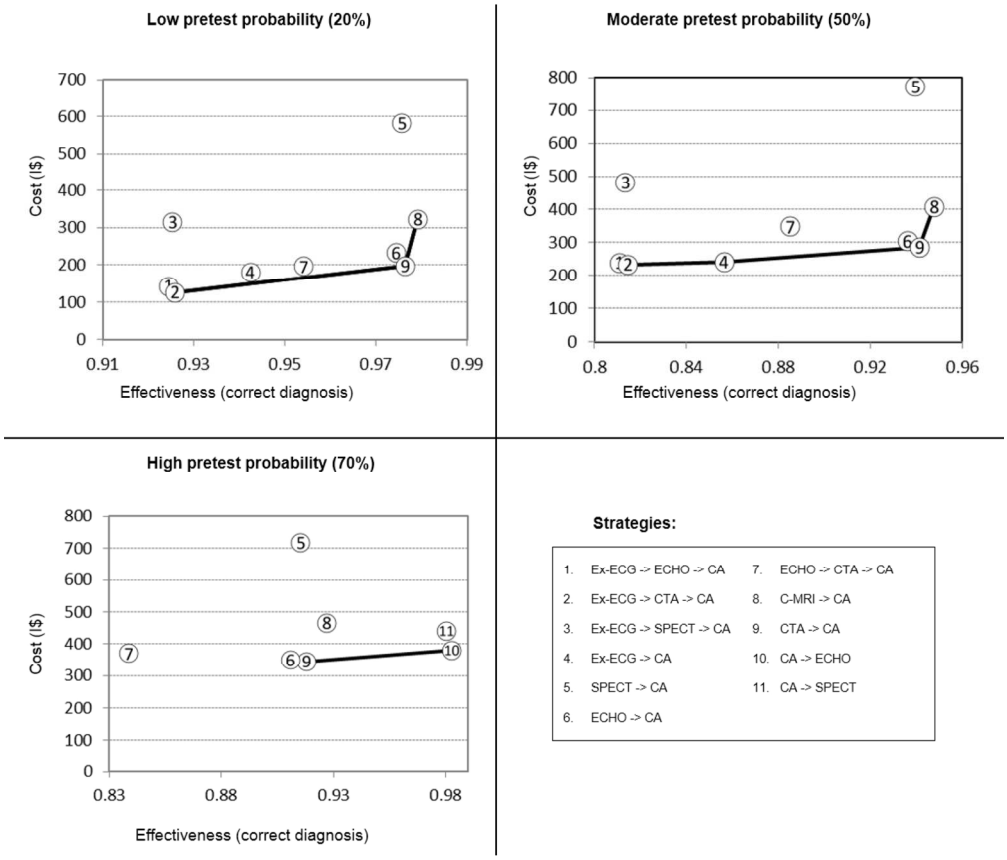

Figure 2. Base-case cost-effectiveness results for predefined risk categories. Strategies 1-4 excluded from high-probability analysis (see text for details).
Ex-ECG = exercise electrocardiogram; ECHO = stress echocardiogram; SPECT = single-photon emission computed tomography; CTA = computed tomography coronary angiogram; MRI = cardiac magnetic resonance; CA = invasive coronary angiography

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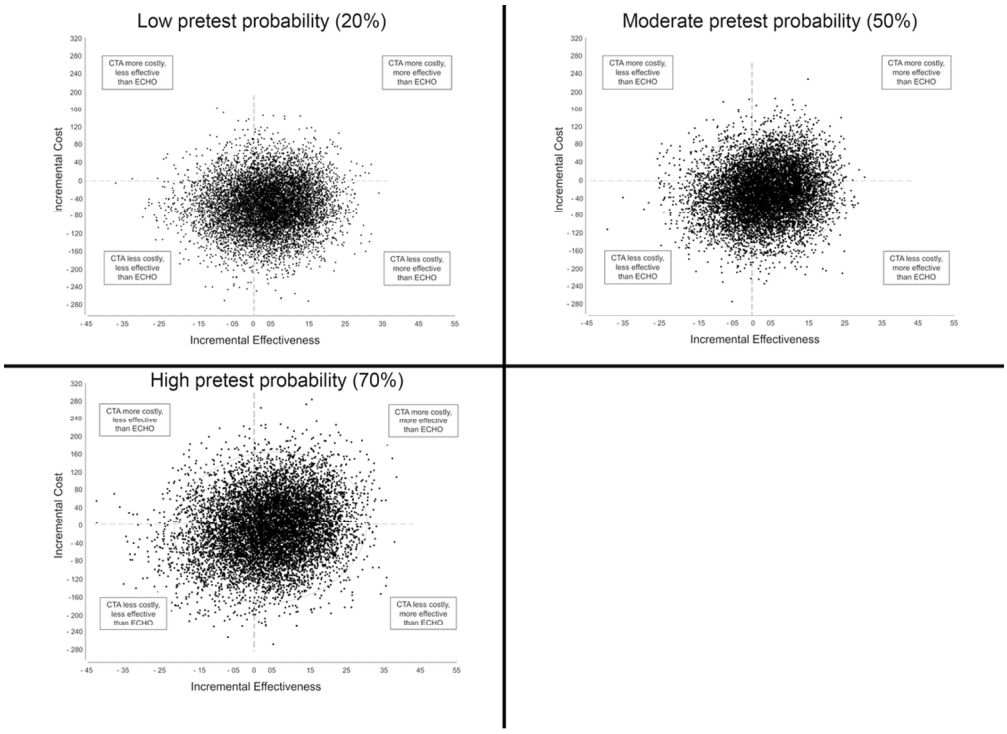

Figure 3. Scatterplot of incremental cost-effectiveness of strategy 9 (CTA-CA) versus strategy 6 (ECHO-CA).
ECHO = stress echocardiogram; CTA = computed tomography coronary angiogram; CA = invasive coronary angiography. Dotted line represents willingness-to-pay threshold; ellipse contains 95% of outputs.
Figure 3
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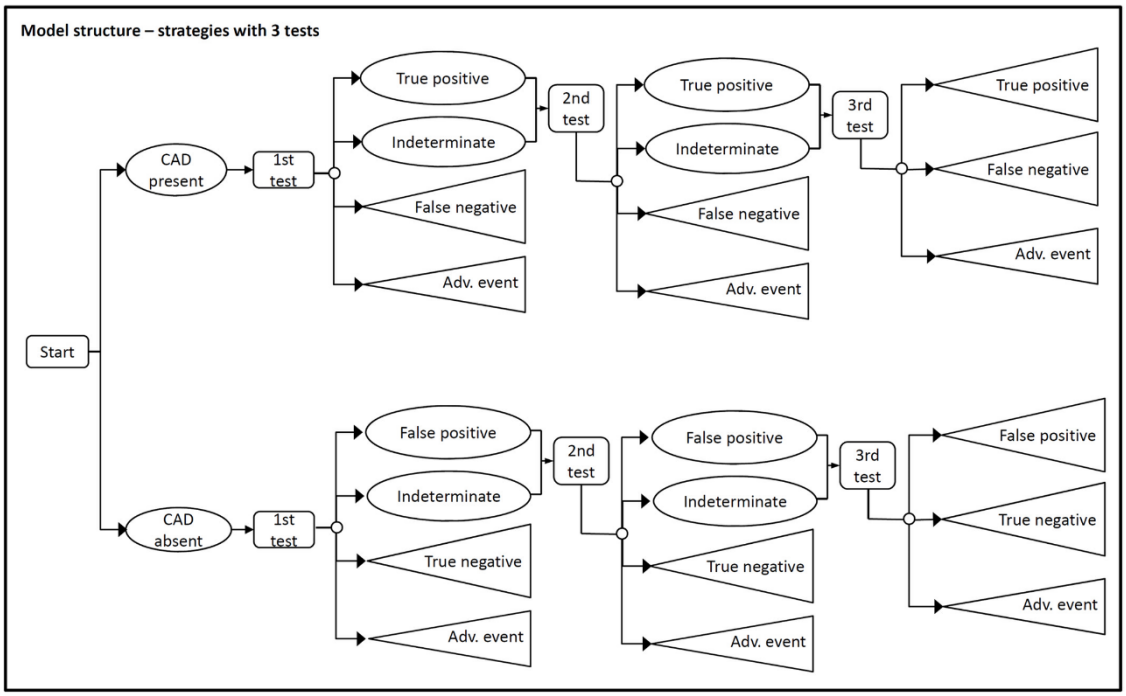
Supplementary Table A: Mean cumulative radiation dose per patient in each modelled strategy.

Strategy	Tests	Avg. dose (MSv)
1	Ex-ECG -> ECHO -> CA	3.9
2	Ex-ECG -> CTA -> CA	9.3
3	Ex-ECG -> SPECT -> CA	9.8
4	Ex-ECG -> CA	5.8
5	SPECT -> CA	16.4
6	ECHO -> CA	6.1
7	ECHO -> CTA -> CA	10.2
8	C-MRI -> CA	5.7
9	CTA -> CA	15.1
10	CA -> ECHO	10
11	CA -> SPECT	11

Ex-ECG = exercise electrocardiogram; ECHO = stress echocardiogram; SPECT = single-photon emission computed tomography; CTA = computed tomography coronary angiogram; C-MRI = cardiac magnetic resonance; CA = invasive coronary angiography

Supplementary Figure A: Detailed depiction of model structure



CAD = Coronary artery disease.

CHEERS Checklist
Items to include when reporting economic evaluations of health interventions

The **ISPOR CHEERS Task Force Report**, *Consolidated Health Economic Evaluation Reporting Standards (CHEERS)—Explanation and Elaboration: A Report of the ISPOR Health Economic Evaluations Publication Guidelines Good Reporting Practices Task Force*, provides examples and further discussion of the 24-item CHEERS Checklist and the CHEERS Statement. It may be accessed via the *Value in Health* or via the ISPOR Health Economic Evaluation Publication Guidelines – CHEERS: Good Reporting Practices webpage: http://www.ispor.org/TaskForces/EconomicPubGuidelines.asp

Section/item	Item No	Recommendation	Reported on page No/ line No
Title and abstract			
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	1 / 1
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	2 / 1
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions.	4
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	6
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	8
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	6
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	6
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	6
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	N/A
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	8
Measurement of effectiveness	11a	*Single study-based estimates:* Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	N/A

	11b	*Synthesis-based estimates:* Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	8
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	N/A
Estimating resources and costs	13a	*Single study-based economic evaluation:* Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	N/A
	13b	*Model-based economic evaluation:* Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	8
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	8 p.5 / fig.1
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	10
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	10
Results			
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	Table 2
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	Table 3
Characterising uncertainty	20a	*Single study-based economic evaluation:* Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact	N/A

		of methodological assumptions (such as discount rate, study perspective).	
	20b	*Model-based economic evaluation:* Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	pp. 15-16
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	pp. 15-16
Discussion			
Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	pp. 17-19
Other			
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	20
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	20

For consistency, the CHEERS Statement checklist format is based on the format of the CONSORT statement checklist

The **ISPOR CHEERS Task Force Report** provides examples and further discussion of the 24-item CHEERS Checklist and the CHEERS Statement. It may be accessed via the *Value in Health* link or via the ISPOR Health Economic Evaluation Publication Guidelines – CHEERS: Good Reporting Practices webpage: http://www.ispor.org/TaskForces/EconomicPubGuidelines.asp

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Husereau D, Drummond M, Petrou S, et al. Consolidated health economic evaluation reporting standards (CHEERS)—Explanation and elaboration: A report of the ISPOR health economic evaluations publication guidelines good reporting practices task force. Value Health 2013;16:231-50.