



Original Article

Cost-Effectiveness of Different Diagnostic Strategies in Suspected Stable Coronary Artery Disease in Portugal

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Abstract

Background: Cost-effectiveness is an increasingly important factor in the choice of a test or therapy.

Objective: To assess the cost-effectiveness of various methods routinely used for the diagnosis of stable coronary disease in Portugal.

Methods: Seven diagnostic strategies were assessed. The cost-effectiveness of each strategy was defined as the cost per correct diagnosis (inclusion or exclusion of obstructive coronary artery disease) in a symptomatic patient. The cost and effectiveness of each method were assessed using Bayesian inference and decision-making tree analyses, with the pretest likelihood of disease ranging from 10% to 90%.

Results: The cost-effectiveness of diagnostic strategies was strongly dependent on the pretest likelihood of disease. In patients with a pretest likelihood of disease of $\leq 50\%$, the diagnostic algorithms, which include cardiac computed tomography angiography, were the most cost-effective. In these patients, depending on the pretest likelihood of disease and the willingness to pay for an additional correct diagnosis, computed tomography angiography may be used as a frontline test or reserved for patients with positive/inconclusive ergometric test results or a calcium score of >0 . In patients with a pretest likelihood of disease of $\geq 60\%$, up-front invasive coronary angiography appears to be the most cost-effective strategy.

Conclusions: Diagnostic algorithms that include cardiac computed tomography angiography are the most cost-effective in symptomatic patients with suspected stable coronary artery disease and a pretest likelihood of disease of $\leq 50\%$. In high-risk patients (pretest likelihood of disease $\geq 60\%$), up-front invasive coronary angiography appears to be the most cost-effective strategy. In all pretest likelihoods of disease, strategies based on ischemia appear to be more expensive and less effective compared with those based on anatomical tests. (*Arq Bras Cardiol.* 2014; 102(4):391-402)

Keywords: Coronary disease / economics; Coronary disease / diagnosis; Cost-Benefit analysis.

Introduction

Clinical assessment of an individual with suspected stable coronary artery disease (CAD) is usually complemented by noninvasive tests such as the ergometric test (ET), myocardial perfusion scintigraphy (MPS), or stress echocardiography (StressEcho). Cardiac computed tomography angiography (CCTA) has broadened the options for the assessment of CAD patients and is a potentially beneficial alternative for individuals with an intermediate or a low pretest likelihood of disease (PLD)¹. However, the generalized adoption of new techniques that, although appealing, may entail additional costs and no added value, should be considered carefully

with regard to the increasing economic pressure to which healthcare systems are exposed. Therefore, it is important to determine the cost-effectiveness of diagnostic strategies routinely used for the diagnosis of stable CAD and identify patients for whom CCTA is a cost-effective alternative.

Methods

The cost-effectiveness of seven diagnostic strategies was assessed: (1) ET followed by MPS in positive or inconclusive cases, (2) ET followed by 64-detector CCTA in positive or inconclusive cases, (3) MPS (as first option), (4) StressEcho with dobutamine (as first option), (5) CCTA (as first option), (6) calcium scoring (CaSc) followed by CCTA (CACS-CCTA) when CaSc > 0 , and (7) invasive coronary angiography (CATH) as the first and only test. All considered strategies presuppose the end of the diagnostic procedures when a test is negative and a confirmation CATH when the last test of the noninvasive strategy is positive or inconclusive. In addition, an eighth alternative was assessed in individuals with a PLD of 10%, which involved not performing any complementary diagnostic tests and assuming the absence of obstructive CAD.

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A decision-making tree analysis was performed according to the method described by Patterson et al^{2,3} to assess the cost-effectiveness of each strategy according to PLD. In this method, hypothetical cohorts of patients with a certain PLD are subjected to each of the diagnostic strategies. Then, Bayesian inference is used to estimate the cost and effectiveness of each strategy according to the test characteristics. Sensitivity, specificity, and the rate of nondiagnostic tests were gathered from meta-analysis, clinical recommendations, and published series (Table 1). The rate of nondiagnostic ET and StressEcho tests was calculated as the mean percentage of patients who fail to reach the target heart rate. MPS was always considered to be diagnostic, and its accuracy was considered independent of the stress method used. In addition, CCTA tests were always considered diagnostic since the meta-analysis on its accuracy was performed on an intention-to-diagnose basis, assuming that all nondiagnostic tests would be false-positive, thereby decreasing the specificity of the test⁴. The sensitivity and specificity of CaSc > 0 for the diagnosis of obstructive CAD were obtained through combined analysis of the results of two international multicenter clinical trials^{5,6}. We assumed that CATH tests would always be diagnostic, with a sensitivity and specificity of 100%.

Comparison of cost-effectiveness

The cost-effectiveness of each strategy was defined as the cost per correct diagnosis (inclusion or exclusion of obstructive CAD) in a symptomatic patient. According to this definition, a lower cost value per correct diagnosis

translates into better cost-effectiveness. Comparison between the diagnostic strategies was made from the society's perspective (i.e., including all costs, regardless of the payer)¹⁴. To compare the incremental cost-effectiveness of each option with that of all the other alternatives, the diagnostic strategies were ranked in increasing order of cost and those outperformed by complete dominance (simultaneously more expensive and less effective) and incomplete dominance (less effective with a higher incremental cost-effectiveness ratio; ICER) were excluded. ICERs (added cost per additional correct diagnosis) were calculated for each strategy relative to the previous less expensive strategy.

Definition of cost

The cost of a diagnostic strategy includes direct and indirect costs. Direct cost was considered as the cost of the examinations performed for patients in each cohort, using the current *Tabela de Preços do Serviço Nacional de Saúde* (price list of the National Health Service), which was defined by the Ordinance 839-A/2009 of July 31, 2009, as a reference¹⁵. The price of cardiac CCTA was defined as the sum of the values of CCTA, intravenous contrast supplement, and post-processing (Table 2). In the CaSc-CCTA strategy, a cost of € 80.00 was assumed (identical to that of noncontrast chest CT)¹⁵ for patients who only underwent CaSc, while a cost of € 207.10 was assumed for those who also underwent CCTA.

Table 1 – Sensitivity, specificity, and rate of nondiagnostic tests for each method as assumed in the economic model

	ET (%)	MPS (%)	StressEcho (%)	CCTA (%)	CACS > 0 (%)
Sensitivity	68 ⁷	87 ^{8,9}	86 ¹⁰	98 ⁴	93 ^{5,6}
Specificity	77 ⁷	81 ¹¹	84 ¹⁰	85 ⁴	43 ^{5,6}
Rate of nondiagnostic tests	17 ¹²	0	18 ¹³	0 ⁴	0

ET: ergometric test; MPS: myocardial perfusion scintigraphy; StressEcho: stress echocardiogram with dobutamine; CCTA: computed tomography angiography of the coronary arteries; CaSc: calcium scoring

Table 2 – Price of tests included in the different diagnostic strategies (values for Portugal)

Code ¹⁵	Designation	Price (€)
40315	Stress test in ergometric bicycle or treadmill with continuous ECG monitoring and recording at each stage	36.80
58015	Myocardial perfusion scintigraphy under pharmacological stress	424.40
40660	Transthoracic echocardiography under pharmacological stress (includes the cost of the drug)	121.80
16350	CCTA	(129.40)
16325	CT, intravenous contrast supplement	(62.60)
16345	Post-processing	(15.10)
-	Total cardiac CCTA (three codes)	207.10
-	Calcium scoring	80.00
40820	Left catheterization with selective coronary angiography	585.50

ECG: electrocardiogram, CCTA: computed tomography angiography of the coronary arteries, CT: computed tomography.

The following indirect costs were included.

1. Cost associated with incidental findings during CaSc and cardiac CCTA. We assumed that 7% of these tests would exhibit incidental extracardiac findings of uncertain clinical significance, which would require direct investigation¹⁶, usually to assess lung nodules. We assumed that these cases would require noncontrast chest CT a few months later¹⁷ at an additional cost of € 80.00¹⁵.

2. Cost associated with complications caused by diagnostic CATH. We assumed that the rate of major iatrogenic adverse cardiovascular events (death, myocardial infarction, or stroke) was 0.05%¹⁸, while that of vascular access-related complications that required transfusion or surgery was 0.4% (for a rate of 80% for radial access use)¹⁹. With regard to major cardiovascular events, we considered acute myocardial infarction to be a typical complication^{3,20} and estimated its cost by adding the cost for a homogeneous diagnostic group (HDG) of patients with nonfatal myocardial infarction without major complications (€3,671.53)¹⁵ to the cost of 1 month of temporary incapacity to work, for a gross domestic product (GDP) *per capita* of €16,100, assuming that half of the population assessed for suspected CAD was active. The mean cost of an iatrogenic major cardiovascular event thus estimated was € 4,342. The mean cost of a vascular access complication requiring transfusion or surgery was estimated to be €1,500 (expert opinion).

3. Cost of false-negative tests. The potential cost of false-negative tests includes the cost of repeat tests for CAD diagnosis, other examinations for the differential diagnosis of chest pain, worse quality of life, and added risk for cardiovascular events due to the non-prescription of adequate medical therapy. These costs are particularly difficult to evaluate. Previous studies have used various methods to estimate that the cost of a false-negative test is 1.4–6.7 times higher than that of a false-positive test^{3,20,21}. Therefore, false-negative tests were allocated a cost that was three times higher than that of a false-positive test (€1.818 for each false-negative test). In the scenario where no further testing is performed assuming the absence of CAD (a hypothesis considered for patients with PLD of 10%), the costs of false-negatives were the only ones taken into account.

We did not include the cost of complications caused by noninvasive tests in the model because serious complications resulting from these tests are very rare and would only marginally increase costs. In addition, the cost associated with potential exposure to ionizing radiation was not included because this was a short-term cost-effectiveness model; furthermore, there is great uncertainty about the effects of radiation doses used in these tests²².

Sensitivity analysis

To assess the extent to which the results obtained depended on some of the variables under study, several sensitivity analyses were performed. Calculations were repeated using new assumptions such as decreasing the sensitivity and specificity values for cardiac CCTA to 96% and 81%, respectively (lower limits of 95% confidence intervals in the meta-analysis of 53 studies)⁴, decreasing the cost of MPS to €207.10 (equating the cost of MPS with that of CCTA), decreasing the rate of inconclusive StressEcho tests to 5%, and assuming zero cost for false-negative tests.

Results

Figure 1 shows the cost-effectiveness plans for the diagnostic strategies for each scenario of PLD. In general, costs increase and the percentage of correct diagnosis decreases with increasing PLD (due to the increase in the number of false-negative tests).

The composition of direct and indirect costs is shown in Table 3 (simulation of the expected results when a cohort of 100 patients with a PPT of 30% is assessed).

Table 4 summarizes the results of incremental cost-effectiveness of the diagnostic strategies applied to hypothetical cohorts of 100 patients with a PLD of 10%–90%. Diagnostic strategies were presented in increasing order of cost and respective ICER for each assessed PLD. In all scenarios of PLD, the diagnostic strategies for ET-MPS, MPS, and StressEcho are dominated by alternative strategies that are less expensive and more effective. According to the cost-effectiveness criterion, choosing the best diagnostic strategy depends on the percentage of false-negative tests that one is willing to accept and on the willingness to pay for an additional correct diagnosis (Figure 2). For example, for a limit of €5,000 per additional correct diagnosis, the preferred strategy would be CACS-CCTA for patients with a PLD of 10%, CCTA for those with a PLD of 20%–40%, and CATH for those with a PLD of ≥50%.

Results of sensitivity analysis

To assess the robustness of the results and the influence of several assumptions, we reformulated the model by altering some parameters such as diagnostic accuracy of CCTA, price of MPS, rate of inconclusive StressEcho tests, and cost of false-negative tests.

The decrease in sensitivity and specificity of CCTA to 96% and 81%, respectively, resulted in the increase in total cost and ICER of the strategies that include CCTA. Nevertheless, the ET-MPS, MPS, and StressEcho diagnostic strategies remained dominated, with the increasing order of cost-effectiveness shown in Table 4 being maintained for every assessed PLD.

When the cost of MPS is equated to the cost of CCTA (€ 207.10), the cost-effectiveness of the ET-MPS and MPS diagnostic strategies improves. However, these strategies remained dominated by other diagnostic methods (less expensive and more effective) for all assessed PLDs (Table 5).

The decrease in the rate of inconclusive StressEcho tests from 18% to 5% resulted in the improvement of its cost-effectiveness; however, this method remained dominated by other diagnostic strategies for all the assessed PLDs. When the StressEcho strategy was compared with the dominant noninvasive strategies (more cost-effective), at each level of PLD, the StressEcho strategy entailed an additional cost of €303 to €2,700 per 100 patients, along with an increase in false-negative tests from 1.1% to 5.7%.

In the model where the absence of indirect costs is assumed in patients with false-negative tests, the ET-CCTA strategy is the least expensive for all levels of PLD. However, this diagnostic procedure resulted in a significant number of false-negative tests, particularly for intermediate or high PLDs. The transition to more effective strategies becomes less expensive with the increasing prevalence of obstructive CAD (Table 6).

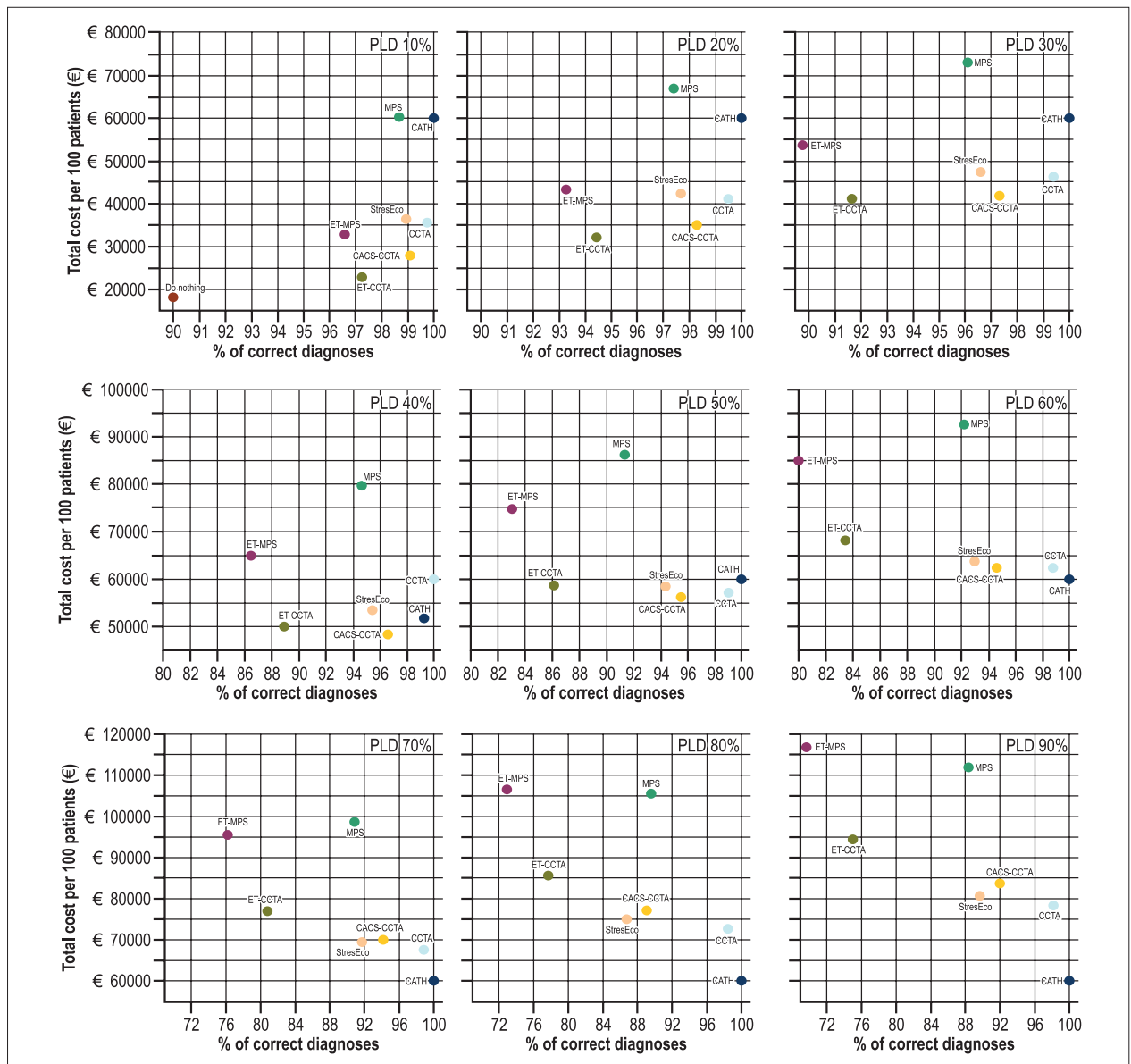


Figure 1 – Cost-effectiveness plans for the diagnostic strategies according to the pretest likelihood of disease.

Discussion

In recent years, the need to consider the cost of clinical decisions is becoming increasingly important. Cost-effectiveness analyses allow for more efficient use of health resources and rationalize the use of new technologies, often more expensive than their alternatives. To our knowledge, this is the first assessment of the cost-effectiveness of several strategies used for the diagnosis of stable CAD in Portugal. The results of this analysis indicate that, in this country, diagnostic algorithms that include cardiac CCTA are the most cost-effective methods in symptomatic patients with suspected obstructive CAD and a PLD of $\leq 50\%$. In high-risk patients (PLD $> 50\%$), immediate CATH appears to be the most cost-effective strategy. The model suggests that ischemia

imaging techniques (MPS and StressEcho) are more expensive and less effective compared with other diagnostic strategies for all assessed PLDs. With regard to patients with a PLD of $\leq 50\%$ and the conservative scenario wherein the willingness to pay for an additional correct diagnosis is €1,000, the results of incremental cost-effectiveness indicate that it is advantageous to perform an ergometric test before CCTA in patients with a lower PLD (10%), do a “rule-out” CaSc before CCTA in patients with a PLD of 20–30%, and perform up-front CCTA in patients with a PLD of 40–50%. In the more liberal scenario (willingness to pay €5,000 for an additional correct diagnosis), the preferred strategy would be SCa-CCTA for patients with a PLD of 10%, CCTA for patients with a PLD of 20–40%, and CATH for patients with a PLD of $\geq 50\%$.

Table 3 – Results of cost-effectiveness of the diagnostic strategies for 100 patients with a pretest likelihood of disease of 30%

	ET-MPS	ET-CCTA	MPS	StressEcho	CCTA	CACS-CCTA	CATH
After non-invasive testing							
True positive	19.2	21.6	26.1	21.2	29.4	27.4	-
False positive	4.8	3.8	13.3	9.2	10.5	6.0	-
True negative	65.2	66.2	56.7	48.2	59.5	64.0	-
False negative	10.8	8.4	3.9	3.4	0.6	2.6	-
Inconclusive	0	0	0	18	0	0	-
Invasive Angiographies	24	25.4	39.4	48.4	39.9	33.4	100
Normal invasive Angiographies	4.8 (20%)	3.8 (15%)	13.3 (34%)	21.8 (45%)	10.5 (26%)	6 (18%)	70 (70%)
Correct diagnoses (after CATH when applicable)	89.2	91.6	96.1	96.6	99.4	97.4	100
Costs							
Noninvasive tests	€ 23.752	€ 13.475	€ 42.440	€ 12.180	€ 20.710	€ 16.642	-
CATH	€ 14.033	€ 14.860	€ 23.069	€ 28.303	€ 23.362	€ 19.543	€ 58.550
CATH complications de CATH	€ 318	€ 337	€ 523	€ 643	€ 530	€ 443	€ 1.327
Incidental findings	-	€ 265	-	-	€ 560	€ 560	-
False-negative tests	€ 19.693	€ 15.287	€ 7.090	€ 6.261	€ 1.091	€ 4.785	-
Total cost	€ 57.796	€ 44.224	€ 73.122	€ 47.386	€ 46.252	€ 41.973	€ 59.877
Cost per correct diagnosis	€ 648	€ 483	€ 761	€ 491	€ 465	€ 431	€ 599

ET: ergometric test, MPS: myocardial perfusion scintigraphy, CCTA: computed tomography angiography of the coronary arteries, StressEcho: stress echocardiography with dobutamine, CACS: calcium score, CATH: invasive coronary angiography

Ultimately, the selection of a diagnostic method on the basis of cost-effectiveness criteria depends on PLD and the willingness to pay for an additional correct diagnosis. Contrary to long-term cost-effectiveness studies, in this context, there is no commonly accepted cost-effectiveness limit [for example: € 30,000/quality-adjusted life-years (QALY)] to serve as a reference for the adoption or rejection of a diagnostic strategy. However, a recent study suggested that, for a CAD prevalence of $\geq 30\%$, values of incremental cost per correct diagnosis in the short-term model are similar to those of incremental cost per QALY estimated in long-term models²³. In a more conservative scenario, the willingness of the Portuguese society to pay for an additional correct diagnosis will be at least $\geq \text{€}1.010$, which corresponds to the sum of the direct costs of MPS followed by CATH, a diagnostic strategy that is well accepted and frequently used in Portugal.

Of the scenarios assessed in the sensitivity analysis, the one in which CCTA and MPS have the same price is particularly important because this is the case in some countries. Even in this scenario, MPS remains a dominated strategy (i.e., more expensive and less effective) because it is less accurate than CCTA, particularly in terms of sensitivity. The results would only be different in a scenario (not tested) where the price of scintigraphy was identical and where scintigraphy was more accurate.

In general, these results are in line with those obtained in other countries^{17,20,24-29} that consider cardiac CCTA as a cost-effective method for the diagnosis or exclusion of obstructive CAD in patients with an intermediate PLD. This is probably because of a favorable combination of cost (relatively affordable) and accuracy. Better diagnostic accuracy simultaneously increases the denominator of the cost-effectiveness equation (number of correct diagnoses) and decreases the numerator, with lower indirect costs from false-negative and false-positive tests.

The interpretation of these results and analysis of their potential implications should consider several factors. First, it should be noted that the cost-effectiveness of diagnostic strategies is critically dependent on the adequate selection of patients. The calculation of PLD is a key step in selecting a cost-effective diagnostic strategy. This assessment can be easily and quickly made using validated clinical scores that were recently calibrated in European contemporary populations³⁰. Second, the results of this analysis only apply to patients without known CAD. Therefore, these findings do not mean that functional tests are not useful or cost-effective in distinct contexts, namely in patients with established CAD. In the latter case, the performance of CCTA is suboptimal, and the key issues are the presence or absence of ischemia and the localization, extension, and severity of ischemia. Rather than seeing these results in terms of winners and losers, it is important to know the advantages and disadvantages of

Table 4 – Incremental cost-effectiveness of the diagnostic strategies applied to hypothetical cohorts of 100 patients with a PLD of 10%–60%. For a PLD of >=60%, all strategies are dominated by the CATH strategy.

Pretest likelihood	Diagnostic strategy	Total cost (€)	Number of correct diagnoses*	False-negative tests*	ICER**
10%	No test	18.180	90.0	10.0	-
	ET-CCTA	24.473	97.2	2.8	€ 874
	CACS-CCTA	27.975	99.1	0.9	€ 1.819
	ET-MPS	34.667	96.4	3.6	Dominated
	CCTA	35.585	99.8	0.2	€ 11.234
	StressEcho	36.338	98.9	1.1	Dominated
	CATH	59.877	100	0	€ 121.461
	MPS	60.252	98.7	1.3	Dominated
20%	ET-CCTA	34.349	94.4	5.6	-
	CACS-CCTA	34.974	98.2	1.8	€ 162
	CCTA	40.918	99.6	0.4	€ 4.388
	StressEcho	41.862	97.7	2.3	Dominated
	ET-MPS	46.232	92.8	7.2	Dominated
	CATH	59.877	100	0	€ 47.397
	MPS	66.687	97.4	2.6	Dominated
30%	CACS-CCTA	41.973	97.4	2.6	-
	ET-CCTA	44.224	91.6	8.4	Dominated
	CCTA	46.252	99.4	0.6	€ 2.106
	StressEcho	47.386	96.6	3.4	Dominated
	ET-MPS	57.796	89.2	10.8	Dominated
	CATH	59.877	100	0	€ 22.709
	MPS	73.122	96.1	3.9	Dominated
40%	CACS-CCTA	48.972	96.5	3.5	-
	CCTA	51.585	99.2	0.8	€ 964
	StressEcho	52.910	95.4	4.6	Dominated
	ET-CCTA	54.099	88.8	11.2	Dominated
	CATH	59.877	100	0	€ 10.365
	ET-MPS	69.361	85.6	14.4	Dominated
	MPS	79.557	94.8	5.2	Dominated
50%	CACS-CCTA	55.971	95.6	4.4	-
	CCTA	56.919	99.0	1.0	€ 280
	StressEcho	58.434	94.3	6.7	Dominated
	CATH	59.877	100	0	€ 2.959
	ET-CCTA	63.975	86.0	14.0	Dominated
	ET-MPS	80.925	82.0	18.0	Dominated
	MPS	85.992	93.5	6.5	Dominated
60%	CATH	59.877	100	0	-
	CCTA	62.252	98.8	1.9	Dominated
	CACS-CCTA	62.970	94.7	5.3	Dominated
	StressEcho	63.958	93.1	6.9	Dominated
	ET-CCTA	73.850	83.2	16.8	Dominated
	MPS	92.427	92.2	7.8	Dominated
	ET-MPS	92.490	78.3	21.7	Dominated

*At the end of the diagnostic strategy, i.e., including the results of CATH when the noninvasive tests are positive or inconclusive ** Incremental cost per additional correct diagnosis. ICER: incremental cost-effectiveness ratio (Δ cost/ Δ correct diagnosis), ET: ergometric test, CCTA: computed tomography angiography of the coronary arteries, CaSc: calcium scoring, MPS: myocardial perfusion scintigraphy, StressEcho: stress echocardiography

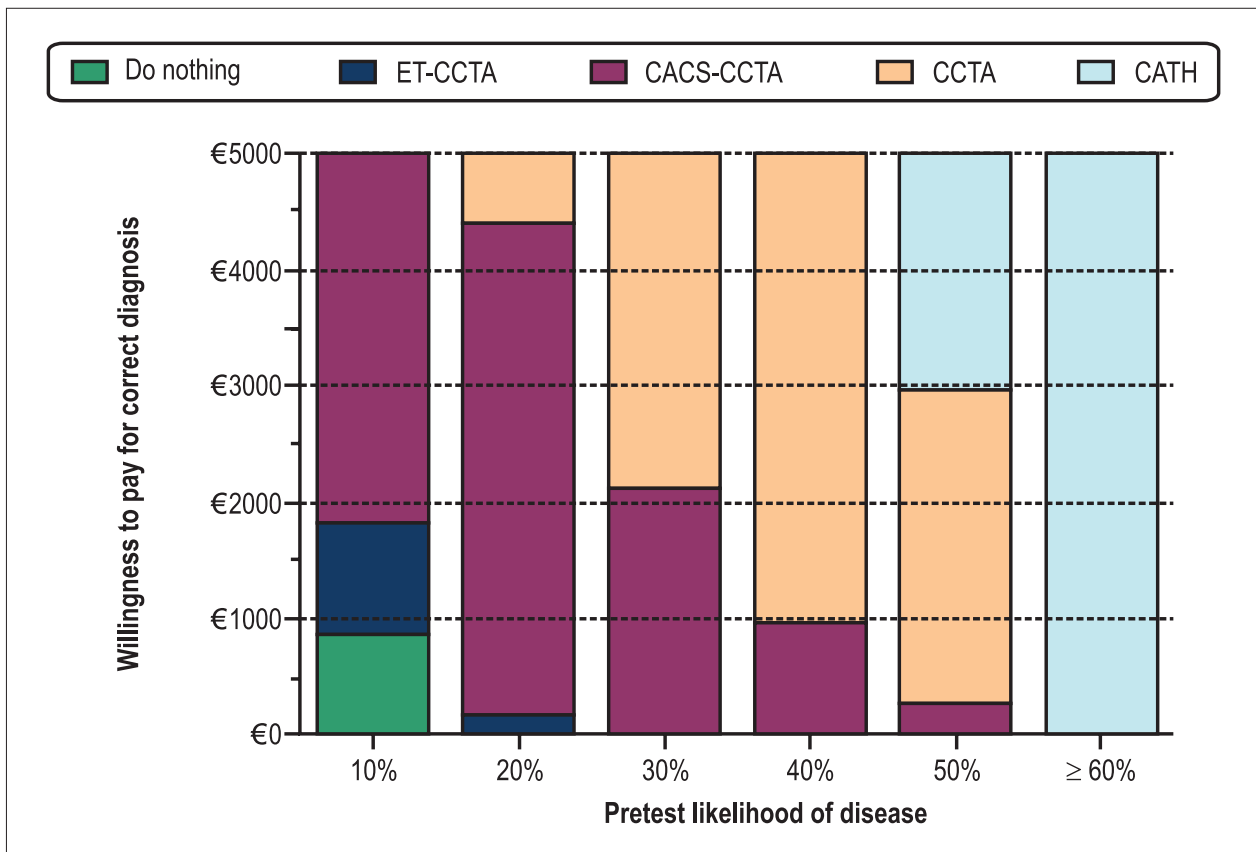


Figure 2 – Choice of the most cost-effective diagnostic strategy according to the PLD and willingness to pay for a correct diagnosis. Once the maximum value that society is willing to pay for an additional correct diagnosis is established, the strategy that represents the best use of these resources is the one that intercepts the line of the value that society is willing to pay. For example, for a willingness to pay €1,500 per additional correct diagnosis, the best method would be ET-CCTA when the pretest likelihood of disease is 10%, CACS-CCTA when the pretest likelihood is 20%–30%, CCTA when the pretest likelihood is 40%–50%, and CATH when the pretest likelihood is ≥60%.

the anatomical and functional methods in different contexts. Third, it should be acknowledged that the exclusive use of anatomical methods for the diagnosis of obstructive CAD carries some risks, namely the hazard of prompting unnecessary revascularizations. However, CATH, in the assessed strategies, had a diagnostic and not necessarily therapeutic objective (as in the COURAGE study)³¹, and although both coronary angiographies (invasive or CT) essentially provide anatomical information, there is a possibility of complementing this assessment with functional information provided by coronary fraction flow reserve (FFR) measurement, which is emerging as the gold-standard and has been demonstrated to be cost-effective³². It is probable that, in the near future, CCTA will allow the assessment of ischemia using perfusion techniques³³ or virtual CFR measurements^{34,35}; however, this is not yet an established procedure.

Limitations

This study has some limitations. First, it described a theoretical model, the results of which are dependent on factors such as sensitivity and specificity of various techniques that, in the real world, can be different from those reported in international studies of reference. With regard to CCTA, it should be noted that its specificity depends on PLD because of the varying prevalence

of coronary calcifications. The use of intermediate values may have led to the underestimation of the cost-effectiveness of CCTA in patients with a lower PLD and overestimation in patients with a higher PLD³⁶. Similarly, like in all analyses of this type, the results are only applicable to patients who are capable of undergoing any of the tests under study (i.e., able to exercise, without complete block of the left bundle branch, without severe renal impairment, and not allergic to iodinated contrast medium). We chose to exclude the costs and benefits related to periods after the diagnosis phase (such as costs of medication, revascularization, hospitalization, and possible gains in QALY) in the model because they entail greater complexity and uncertainty. However, there is evidence that the diagnosis of obstructive CAD (vs. false-negative tests) is associated with an increase of three QALYs over a period of 10 years³. Depending on the assumptions made, it is possible that long-term analysis produces results that are significantly different from those obtained in this analysis. In addition, to avoid a more complex analysis, not all possible diagnostic strategies were considered; we chose accessible and frequently utilized modalities and diagnostic procedures. Moreover, conclusive tests were classified as positive or negative, in a reductionist dichotomization which is inevitable in this type of analysis. Finally, cost-effectiveness should be one of the criteria considered in clinical decision-making. Other patient-related or context-

Table 5 – Incremental cost-effectiveness of diagnostic strategies in hypothetical cohorts of 100 patients with a PLD of 10%–60%, considering identical prices for MPS and CCTA of the coronary arteries. For a PLD of ≥60%, all strategies were dominated by CATH

Pretest likelihood	Diagnostic strategy	Total cost (€)	Number of correct diagnoses*	False-negative tests*	ICER**
10%	No test	18.180	90.0	10.0	-
	ET-CCTA	24.473	97.2	2.8	€874
	ET-MPS	26.013	96.4	3.6	Dominated
	CACS-CCTA	27.975	99.1	0.9	€1.819
	CCTA	35.585	99.8	0.2	€11.234
	StressEcho	36.338	98.9	1.1	Dominated
	MPS	38.522	98.7	1.3	Dominated
20%	CATH	59.877	100	0	€121.461
	ET-CCTA	34.349	94.4	5.6	-
	CACS-CCTA	34.974	98.2	1.8	€162
	TET-MPS	36.766	92.8	7.2	Dominated
	CCTA	40.918	99.6	0.4	€4.388
	StressEcho	41.862	97.7	2.3	Dominated
	MPS	44.957	97.4	2.6	Dominated
30%	CATH	59.877	100	0	€47.397
	CACS-CCTA	41.973	97.4	2.6	-
	ET-CCTA	44.224	91.6	8.4	Dominated
	CCTA	46.252	99.4	0.6	€2.106
	StressEcho	47.386	96.6	3.4	Dominated
	ET-MPS	47.519	89.2	10.8	Dominated
	MPS	51.392	96.1	3.9	Dominated
40%	CATH	59.877	100	0	€22.709
	CACS-CCTA	48.972	96.5	3.5	-
	CCTA	51.585	99.2	0.8	€964
	StressEcho	52.910	95.4	4.6	Dominated
	ET-CCTA	54.099	88.8	11.2	Dominated
	MPS	57.827	94.8	5.2	Dominated
	ET-MPS	58.272	85.6	14.4	Dominated
50%	CATH	59.877	100	0	€10.365
	CACS-CCTA	55.971	95.6	4.4	-
	CCTA	56.919	99.0	1.0	€280
	StressEcho	58.434	94.3	6.7	Dominated
	CATH	59.877	100	0	€2.959
	ET-CCTA	63.975	86.0	14.0	Dominated
	MPS	64.262	93.5	6.5	Dominated
60%	ET-MPS	69.025	82.0	18.0	Dominated
	CATH	59.877	100	0	-
	CCTA	62.252	98.8	1.9	Dominated
	CACS-CCTA	62.970	94.7	5.3	Dominated
	StressEcho	63.958	93.1	6.9	Dominated
	MPS	70.697	92.2	7.8	Dominated
	ET-CCTA	73.850	83.2	16.8	Dominated
ET-MPS	79.778	78.3	21.7	Dominated	

* At the end of the diagnostic strategy, i.e., including the results of CATH when the noninvasive tests are positive or inconclusive. ** Incremental cost per additional correct diagnosis. ICER: incremental cost-effectiveness ratio (Δ cost/ Δ correct diagnosis), ET: ergometric test, CCTA: computed tomography angiography of the coronary arteries, CaSc: calcium scoring, MPS: myocardial perfusion scintigraphy, StressEcho: stress echocardiography

Table 6 – Incremental cost-effectiveness of diagnostic strategies in hypothetical cohorts of 100 patients with a PLD of 10%–90%. considering zero cost for false-negative tests. The dominated strategies are not shown

Pretest likelihood	Diagnostic strategy	Total cost (€)	Number of correct diagnoses*	False-negative tests*	ICER** (€)
10%	ET-CCTA	19.378	97.2	2.8	-
	CACS-CCTA	26.379	99.1	0.9	3.637
	CCTA	35.221	99.8	0.2	13.052
	CATH	59.877	100	0	123.279
20%	ET-CCTA	24.157	94.4	5.6	-
	CACS-CCTA	31.783	98.2	1.8	1.980
	CCTA	40.191	99.6	0.4	6.206
	CATH	59.877	100	0	49.215
30%	ET-CCTA	28.937	91.6	8.4	-
	CACS-CCTA	37.187	97.4	2.6	1.428
	CCTA	45.161	99.4	0.6	3.924
	CATH	€59.877	100	0	24.527
40%	ET-CCTA	33.717	88.8	11.2	-
	CACS-CCTA	42.591	96.5	3.5	1.152
	CCTA	50.131	99.2	0.8	2.782
	CATH	59.877	100	0	12.183
50%	ET-CCTA	38.496	86.0	14.0	-
	CACS-CCTA	47.995	95.6	4.4	987
	CCTA	55.101	99.0	1.0	2.098
	CATH	59.877	100	0	4.777
60%	ET-CCTA	37.581	83.4	16.6	-
	StressEcho	51.435	93.1	6.9	822
	CACS-CCTA	53.399	94.7	5.3	1.210
	CATH	59.877	100	0	1.231
70%	ET-CCTA	48.059	80.4	19.6	-
	StressEcho	54.872	92.0	8.0	588
	CATH	59.877	100	0	623
80%	ET-CCTA	52.836	77.6	22.4	-
	CATH	59.877	100	0	314
90%	ET-CCTA	57.615	74.8	25.2	-
	CATH	59.877	100	0	90

* At the end of the diagnostic strategy. i.e., including the results of CATH when the noninvasive tests are positive or inconclusive. ** Incremental cost per additional correct diagnosis. ICER: incremental cost-effectiveness ratio (Δ cost/ Δ correct diagnosis). ET: ergometric test. CCTA: computed tomography angiography of the coronary arteries. CaSc: calcium scoring. MPS: myocardial perfusion scintigraphy. StressEcho: stress echocardiogram with dobutamine

related factors (availability, experience, etc.) should be considered during the selection of a complementary diagnosis method.

Conclusions

The diagnostic algorithms that include cardiac CCTA are the most cost-effective in symptomatic patients with suspected stable coronary disease and a PLD of $\leq 50\%$. In these patients,

depending on the PLD and the willingness to pay per correct diagnosis, CCTA may be used as a first-line test or reserved for patients with positive/inconclusive ergometric test results or CaSc > 0 . In high-risk patients (PLD $\geq 60\%$), immediate CATH appears to be the most cost-effective strategy. For all PLDs, strategies based on ischemia tests appear to be more expensive and less effective compared with strategies based on anatomical tests.

Author contributions

Conception and design of the research; Writing of the manuscript; Analysis and interpretation of the data and Critical revision of the manuscript for intellectual content: Gonçalves PA, Cardim N, Marques H, Ferreira AM. Acquisition of data and Statistical analysis: Ferreira AM.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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