Screening coronary artery disease with computed tomography angiogram should limit normal invasive coronary angiogram, regardless of pre-test probability.

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Short title: coronary artery disease screening with CTscan

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Abstract

Backgound

Performing functional testing (FT) or a computed tomography angiogram (CCTA) before invasive coronary angiogram (ICA) is recommended for coronary artery disease (CAD). We aimed to evaluate, in a real life setting, the rate of strictly normal invasive coronary angiogram (ICA) following a positive non-invasive test.

Methods

We included all patients who underwent an ICA with a prior positive FT or CCTA. Patients were categorized in 5 subgroups, according to pre-test probability (PTP) of having a coronary artery disease (CAD). Main results of ICA were defined as normal ICA, non-obstructive CAD (non-oCAD) and obstructive CAD (oCAD).

Results

For 4952 patients who underwent ICA following either a positive FT (3276, 66.2%) or CCTA (1676, 33.8%), the PTP was: (1) low [< 15%; n=968,19.5%], (2) lower intermediate [15 to 35%; n=1336,27.0%], (3) higher intermediate [35 to 50%; n=806,16.3%], (4) high [50% to 65%; n=806,17.7%], and (5) very high [> 65%; n=965, 19.5%]. ICA showed no CAD (819 patients, 16.5%), non-oCAD (1193 patients, 24.1%) or oCAD (2940 patients, 59.4%). Without considering the PTP values, CCTA compared to FT showed less frequently normal ICA (7% vs. 16.5%), and more frequently CAD (non-oCAD 27.9% vs. 22.2%; oCAD 65.1% vs. 56.4%)(all p<0.0001). When we considered the different PTP values, CCTA always showed lower rates of normal ICA than the FT. In low and lower intermediate-risk patients, CCTA detected more frequently oCAD compared to FT (p<0.001).

Conclusion

CCTA is a better alternative than FT to limit unnecessary ICA regardless of PTP value, without missing abnormal ICA.

Key words: invasive coronary angiogram, functional testing, computed tomography coronary angiogram, coronary artery disease.

Introduction

Detection of stable coronary artery disease (CAD) remains a major public health problem. Most guidelines recommend a stepwise approach for decision making in patients with suspected stable CAD. The process begins (Step 1) with a clinical assessment of the probability that CAD is present in a particular patient, i.e. determination of pre-test probability (PTP). This approach uses clinicians' PTP of CAD along with the results of diagnostic tests to generate individualized post-test CAD probabilities for a given patient. The PTP is influenced by the prevalence of the disease in the population studied, as well as clinical features (including the presence of cardiovascular risk factors). Major determinants of PTP are age, gender and the nature of symptoms (1). Step 1 is followed by non-invasive testing to establish the diagnosis of CAD (Step 2). Usually, based on available non-invasive test results, patients who may benefit from invasive coronary angiogram (ICA) are selected. Recent guidelines recommend that patients with presumed stable CAD and intermediate PTP should be screened with non-invasive functional testing before undergoing ICA (2,3). One of the guideline's objectives is to limit the number of unnecessary ICA, i.e. the number of patients who would undergo an ICA that would not lead to the diagnosis of CAD. Such strategy appears suboptimal as more than half of the patients undergo ICA without previous functional testing and more than one-third of ICA performed are normal (4). In the very recently published ESC 2019 guidelines for CAD, the PTP of CAD based on age, gender and nature of symptoms have undergone major revisions, notably as they introduced a new phrase "Clinical likelihood of CAD that utilizes also various risk factors of CAD as PTP modifiers" (5). This is precisely what we have done in the present study, i.e. PTP based on clinical likelihood.

Coronary computed tomography angiogram (CCTA) has emerged as a non-invasive anatomical imaging to detect CAD. Several studies have reported high levels of sensitivity and specificity of CCTA compared to the gold standard (5,7,6). The ability of CCTA to diagnose CAD in patients with suspected stable angina compared to stress-test has been demonstrated (8). Many studies have reported excellent operating

characteristics of CCTA for CAD diagnosis and a positive impact on referrals for ICA, although multicentre studies have yielded mixed results (9,10,11,12). However, in current guidelines, CCTA has been given limited place as an alternative to traditional functional testing, when ischemia inducing test is contraindicated or non-conclusive (1,2). To better estimate the diagnostic accuracy of CCTA as a first step-test to screen patients suspected to have a stable CAD in real-life practice, we performed a multicentre study comparing the prevalence rate of CAD on ICA in patients with either positive CCTA or positive functional tests, according to the pre-test probability value.

Methods

Patients

We retrospectively analyzed consecutive patients suspected of stable CAD, admitted for an ICA in three major interventional cardiology centres in Paris area, France between January 1st, 2014 and June 1st, 2018 (Ambroise Paré Clinic, Neuilly Sur Seine; Lagny Marne-la-Vallée Hospital, Lagny sur Marne; and Montsouris Mutualist Institute, Paris, FRANCE).

For the present analysis, patients should have had a positive functional testing or a positive CCTA indicating an ICA. Positive functional testing was defined by ischemia findings during stress or recovery, like patient chest pain, ECG modifications, left ventricle ejection fraction decrease, abnormal cinetic wall motion, and abnormal myocardial perfusion. CCTA findings were deemed positive if coronary artery stenosis ≥ 50% was reported, if the stenosis calcification was classified as severe, or if the coronary artery calcium score considering the Agatston method was too high (i.e. above 400) (13). Data were prospectively collected on patient's demographic characteristics, cardiovascular risk factors, history of chronic renal failure, stroke and peripheral vascular disease, symptoms and non-invasive tests motivating ICA. For all included patients, we calculated the PTP according to the Consortium Basic Score (14). Based on guidelines recommendations, patients were categorized in one of the 5 PTP following groups: (1) low risk [PTP <15%], (2) lower intermediate risk [PTP 15 to 35%], (3) higher intermediate risk [PTP 35 to 50%], (4) high-risk [PTP 50% to 65%] and (5) very high-risk [PTP > 65%]. Main results of ICA were defined as

follows: (1) obstructive CAD (oCAD, refers to diameter stenosis on ICA), as an estimated stenosis of 50% or more in any major epicardial vessels, including side branches of at least 2 mm in diameter; (2) non-obstructive CAD (non-oCAD), as an estimated stenosis below 50% in any major epicardial vessels, including side branches of at least 2mm in diameter; and (3) normal ICA (no CAD), as estimated stenosis of less than 20% in any vessel. Most guidelines use a threshold of 50% to define a significant coronary artery stenosis (15), and the tighter the stenosis found the higher is the risk of ischemia (16). All data were recorded prospectively before and just after ICA in the CardioReport™ software database (MediReport Ltd, Paris, France).

Statistical analysis

Continuous variables are presented with the median and interquartile range (IQR); categorical variables are presented with counts and proportions. We compared baseline demographic characteristics, cardiovascular risk factors, history of chronic renal failure, stroke and peripheral vascular disease and results of ICA of patients who previously had either a positive functional testing or a positive CCTA. We compared the main results of ICA (normal ICA vs. oCAD) according to the PTP value of CAD. Categorical variables were compared using the chi-square test. P values of less than 0.05 were considered to indicate statistical significance. Statistical analyses were performed using R software version 3.2.4 (The R Foundation for Statistical Computing; Vienna, Austria).

No extramural funding was used to support this work. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents.

Results

From 7465 consecutive patients suspected of stable CAD who had an ICA in our institutions during the study period, we excluded 2513 patients who have had neither functional testing nor CCTA prior to ICA. Therefore, we analyzed data of 4952 patients who underwent ICA following either a positive functional testing (3276, 66.2%) or a positive CCTA (1676, 33.8%). Prior positive functional tests included single

photon emission computed tomography (SPECT) (1335 patients, 27%), exercise stress test (1179, 23.8%), stress echocardiography (603, 12.2%), and stress magnetic resonance imaging (MRI) (159, 3.2%). To estimate the pre-ICA probability of having a CAD, patients were categorized in the previously defined 5 PTP groups : (1) low risk [PTP < 15%; n=968,19.5%], (2) lower intermediate risk [PTP 15 to 35%; n=1336,27.0%], (3) higher intermediate risk [PTP 35 to 50%; n=806,16.3%], (4) high-risk [PTP 50% to 65%; n=806,17.7%], and (5) very high-risk [PTP > 65%; n=965, 19.5%].

Baseline characteristics of patients are presented in ***Table 1***. Compared to the functional test group, patients in the CCTA group were found to be older (66.6 vs. 65.8 years, p=0.01), less frequently male (69.7 % vs. 76.5%, p<0.0001), and had less frequently a diabetes (18.4% vs. 29.3%, p<0.0001) or a chronic kidney disease (0.1% vs. 1.5%, p<0.0001). The population of the CCTA group had a slightly lower median pre-test probability of CAD compared to the functional test group (25.4% vs 26.5%, p=0.03). Among the symptoms motivating the non-invasive tests for searching a CAD, patients in the CCTA group compared to the functional test group had more frequently atypical angina (22.3% vs. 17.2%, p<0.0001) and less frequently non-specific symptoms (46.4% vs. 51.5%, p =0.0006).

Main results of ICA showed, considering the entire population, a normal coronary angiogram (819 patients, 16.5%), non-oCAD (1193 patients, 24.1%) or oCAD (2940 patients, 59.4%) (***Table 2***). Our primary objective was to analyze the rates of normal ICA in the entire population according to the results of functional testing vs. CCTA, then according to the PTP values. When we analyzed patients without taking into account the PTP group, CCTA always showed significantly better results than functional tests, i.e. less frequently normal ICA (7% vs. 16.5%), and more frequently non-oCAD (27.9% vs. 22.2%) and oCAD (65.1% vs. 56.4%)(all p<0.0001)(***Table 2***, ***Figure 1***). When we considered the PTP values in the entire population, the rate of normal ICA ranged from 14.7% to 27.3% with lower rates in the groups with higher PTP values (***Table 2***). When we considered the different PTP values, CCTA always showed lower rates of normal ICA than the functional testing. Subjects with a very low risk of CAD (PTP < 15%) and a positive functional test prior to ICA had 4.7 times higher rate of normal ICA compared to those

with a positive CCTA (95% CI=3.2-7.0, p<0.001)(***Figure 2, suppl. Table 2***). Subjects with lower intermediate-risk (PTP 15-35%) or higher intermediate-risk (PTP 35-50%) who had a positive functional test had 4.0 and 2.4 times higher rate of normal ICA compared to subjects with a positive CCTA, respectively (95% CI=2.7-5.8 and 95% CI=1.5-3.9, respectively; p<0.01). Subjects at high-risk (PTP 50-65%) and very high-risk of CAD (PTP > 65%) who had a positive functional test prior to ICA had 1.9 and 2.3 times the rate of normal ICA compared to subjects with a positive CCTA, respectively (95% CI=1.2-2.9 and 95% CI=1.4-3.6, respectively; p<0.01). Because of the known lowest performance of exercise tests in the diabetic population, we did the same analyses after excluding exercise ECG which showed very similar results (***Supplementary Figures 1 and 2***). For the screening of oCAD, the ratio of positive functional testing/positive CCTA was significantly inferior to 1 only for the PTP groups <15% and 15-35% (p<0.001) (***Figure 2, suppl. Table 2)***. CCTA, compared to functional tests significantly better predicted the presence of CAD (non-oCAD and oCAD) on ICA in patients with very low and low PTP values (i.e. between 0% and 35%). For patients with higher PTP values (>35%), there was a trend for better prediction efficacy for CCTA versus functional tests although not reaching statistical significance (***Table 2***).

Discussion

This study shows that, in a real-life setting, patients suspected to have a stable CAD and a positive non-invasive test had lower rates of normal ICA in the CCTA group compared to the functional testing group, regardless of the PTP value. Having a positive CCTA prior to ICA led less frequently to a normal ICA compared to having positive functional testing (from 4.0 times less frequently when PTP<15% to 2.3 times when PTP>65%). The rate of obstructive CAD was significantly higher in patients who had a positive CCTA compared to those with positive functional testing only for low-risk and lower intermediate risk patients (PTP<35%).

The major goal of performing a non-invasive test before ICA is to avoid an unnecessary invasive test. Actual guidelines recommend functional testing in the first intention in patients with intermediate PTP (15-65%)(1,2). Because of its excellent negative predictive value,

CCTA appeared as a good alternative in patients with a lower intermediate-risk PTP (6,7). In a recent meta-analysis, Knuuti and al. reported that CCTA was superior to rule out the presence of a CAD when PTP value was intermediate (7). In this study, CCTA was superior to functional tests to avoid unnecessary ICA, regardless the PTP value, and this was mainly due to a lower rate of normal ICA (7.0% vs. 21.4%, respectively $p<0.001$). In a retrospective study evaluating symptomatic and asymptomatic patients without known CAD undergoing ICA, Patel *et al.* showed an overall rate of 39.2% of normal ICA (3). Non-obstructive coronary angiogram or normal ICA was present in 40.6% in our population (in 34.9% of positive CCTA group vs. 43.6% of positive functional testing group, $p <0.001$). The rate of non-obstructive CAD was not statistically different between these groups (CCTA 27.9% vs. functional testing 22.2%, $p=0.12$). In the Prospective Multicenter Imaging Study for Evaluation of Chest Pain (PROMISE) Study, evaluating the outcomes of anatomical study with CCTA vs. functional study for patients with symptoms suggestive of CAD, the rate of non-oCAD was 28% and 52% in the CCTA and functional testing group, respectively (18).

The recommended strategy for CAD screening is based on the determination of PTP before choosing further investigations. Despite technical improvements and the development of radial access, ICA remains an invasive method with a rate of complications estimated between 0.6% and 4.2% (19,20). However, retrospective data showed that 17.1% of low-risk patients and 15.9% of intermediate risk patients are directly referred to ICA without undergoing a non-invasive test (3). Up to 45% of patients are directly referred for percutaneous coronary intervention without prior functional testing (4). European guidelines recommend using the CAD consortium score while American guidelines recommend using the Diamond and Forrester score (1,2). The latter score seems to overestimate the risk of obstructive CAD while CAD consortium score seems to improve the PTP estimation (14). In the present study, 50.7% of patients in the very low-risk PTP group (58.9% in CCTA group vs. 45.6% in the functional testing group) had a non-oCAD or an oCAD. These data may question the relevance of these scores since guidelines consider that when PTP is under 15%, no further investigations are recommended. In the non-invasive strategy of CAD detection, using CCTA at step 1 appears an interesting option as it should permit to have two times less normal ICA without missing abnormal

ICA (including oCAD and non-oCAD)[***Figure 1***]. Interestingly, the latest ESC guidance continues to suggest CCTA should be for low-intermediate risk and functional testing for intermediate-higher risk (5). The current results clearly discounts such approach and reinforce the United Kingdom National Institute for Clinical Excellence guidance which does not recommend the assessment of pre-test probabilities but that CCTA should be the first line test of choice for patients with possible angina (21).

Data regarding whether CCTA leads more frequently to ICA are conflicting. Some studies showed that in patients with suspected stable CAD, compared to a SPECT or cardiac magnetic resonance, a positive anatomical test leads more frequently to ICA (8,18,22,23). Similar results were observed in patients presenting with a low risk of acute coronary syndrome (24). After a CCTA, the rate of revascularization was higher whereas the rate of myocardial infarction was lower as compared to functional testing (25). In the SCOT-HEART study, the prognosis of patients screened for stable angina was better after CCTA compared to functional testing without resulting in increasing referral for ICA or coronary revascularization (26). However, CCTA did show an early increase of coronary revascularisation, but beyond the first year there was significantly less revascularisation. This confirms that, by using at a first step CCTA the right patients were identified earlier with an increased number of revascularisation because more oCAD was found, as in the present study. This should prevent patients progressing to needing downstream revascularisation, and hence less late revascularisation. Recently, the Coronary Computed Tomographic Angiography for Selective Cardiac Catheterization (CONSERVE) trial showed that patients referred to ICA after a recommendation-based screening strategy compared to a systematic CCTA screening, had similar outcomes at one year, without increasing the number of ICA or revascularization (27). The authors suggested a revision of the current CAD management guidelines, consistently with the United Kingdom National Institute for Clinical Excellence guidelines (28).

Our study has several limitations. First, it was a retrospective study. So the comparison between anatomical and functional testing was not based on randomized inclusion. Second, as the study was not randomized, the proportions of each non-invasive functional testing were not equal. However, because the functional testing group were higher risk, it is even more surprising that CTCA managed to have lower rates of normal angiograms. Many exercise test and SPECT were realized in the CCTA and functional testing group whereas the number of stress tests (echocardiography and MRI) was low. This may have underestimated the interest of stress-testing, although it also reflects the small number of stress-MRI realized in a real-life setting. Patients in the functional testing group had slightly higher median PTP value and a more severe profile as they were more frequently male, suffered more frequently from diabetes, chronic kidney disease and had a higher BMI. In this study, we classified patients into 3 groups (oCAD, non-oCAD and normal ICA) instead of 2 groups (oCAD vs. non-oCAD). Previous studies showed that in multivariable analyses, an increased risk of major adverse cardiovascular events at 2 years was observed for both non-oCAD and oCAD when compared with patients with normal CCTA (14). Finally, exercise testing and as SPECT provide other functional information not given by CCTA such as exercise capacity, arrhythmias evaluation or blood pressure follow-up.

Conclusion

In a real-life condition, this study suggests that CCTA is a better alternative than functional testing to limit unnecessary ICA regardless of PTP value, as it should permit to have two times less normal ICA without missing abnormal ICA. This finding should weigh in the decision making to perform CCTA for screening patients suspected of stable CAD.

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Figure legends

Figure 1. Results of invasive coronary angiogram according to the positivity of previous non-invasive tests for coronary artery disease.

Figure 2. Normal coronary angiogram or obstructive coronary artery disease rate ratio in patients with prior positive functional testing or positive computed tomography angiogram, according to the pre-test probability of coronary artery disease.

Table 1. Baseline characteristics of patients suspected of coronary artery disease after a positive coronary computed tomography angiogram or a positive functional test for cardiac ischemia.

Variables	Total N = 4952 (100%)	CCTA N = 1676 (33.8%)	Functional test N = 3276 (66.2%)	p-value
Patient characteristics				
Age (years), mean (SD)	66.1 (10.3)	66.6 (10.0)	65.8 (10.4)	**0.01**
Male gender, n (%)	3674 (74.2%)	1168 (69.7%)	2506 (76.5%)	**< 0.001**
BMI kg/m^2, median, [IQR]	26.2 [24.0, 29.4]	26.1 [23.8, 29.4]	26.3 [24.1, 29.4]	**0.02**
Cardiovascular risk factors				
Diabetes mellitus, n (%)	1270 (25.6%)	309 (18.4%)	961 (29.3%)	**< 0.001**
Dyslipidemia, n (%)	2363 (47.7%)	791 (47.2%)	1572 (48.0%)	0.62
Hypertension, n (%)	2194 (44.3%)	759 (45.3%)	1435 (43.8%)	0.34
Current smoking, n (%)	2025 (40.9%)	698 (41.6%)	1327 (40.5%)	0.46
Chronic kidney disease, n (%)	50 (1.0%)	2 (0.1%)	48 (1.5%)	**< 0.001**
Peripheral vascular disease, n (%)	312 (6.3%)	91 (5.4%)	221 (6.7%)	0.08
Previous stroke, n (%)	111 (2.2%)	35 (2.1%)	76 (2.3%)	0.67

PTP, median [IQR]	26.2 [14.0, 46.2]	25.4 [13.5, 44.3]	26.5 [14.4, 47.1]	**0.03**
Symptoms				
Typical Angina	1549 (31.3%)	525 (31.3%)	1024(31.3)	0.99
Atypical angina	938 (18.9%)	374 (22.3%)	564 (17.2%)	**< 0.001**
Non-specific symptoms	2465 (49.8%)	777 (46.4%)	1688 (51.5%)	**< 0.001**
Prior positive function test for CAD				
SPECT		NA	1335 (40.7%)	-
Exercise stress test		NA	1179 (36.0%)	-
Stress echocardiography		NA	603 (18.4%)	-
Stress MRI		NA	159 (4.9%)	-

PTP, pre-test probability; BMI, body mass index; SD, standard deviation; IQR, interquartile range; SPECT, single photon emission computed tomography; MRI, magnetic resonance imaging; ICA, invasive coronary angiogram; CAD, coronary artery disease; CCTA, computed tomography angiogram; NA, not available

Table 2. Results of invasive coronary angiogram in patients with positive functional testing or positive coronary computed tomography angiogram, according to the pretest probability of coronary artery disease.

CCTA, computed tomography angiogram; PTP, pre-test probability

	Normal coronary angiogram				**Non-obstructive coronary artery disease**				**Obstructive coronary artery disease**			
	Total	CCTA	Functional testing	*P*	Total	CCTA	Functional testing	*P*	Total	CCTA	Functional testing	*P*
All PTP	16.5% (819)	7.0% (118)	16.5% (819)	***<0.001***	24.1% (1193)	467 (27.9%)	726 (22.2%)	***<0.001***	59.4% (2940)	65.1% (1091)	56.4% (1849)	***<0.001***
PTP 0-15%	27,3% (223)	7.0% (26)	33.1% (197)	***<0.001***	26.2% (254)	127 (34.1%)	127 (21.3%)	***<0.001***	22,5% (710)	58.9% (219)	45.6% (491)	***<0.001***
PTP 15-35%	26,3% (215)	5.6 % (28)	22.3 % (187)	***<0.001***	22.0% (294)	122 (24.5%)	172 (20.7%)	*0.097*	26,2% (827)	69.8 % (347)	57.2 % (480)	***<0.001***
PTP 35-50%	14,7% (120)	7.5 % (19)	18.3 % (101)	***<0.001***	23.6% (190)	68 (26.9%)	122 (22.1%)	*0.160*	15,7% (496)	65.6 % (166)	59.7 % (330)	*0.13*

PTP 50-65%	15,0% (123)	8.8 % (25)	16.6 % (98)	***0.003***	23.3% (204)	75 (26.3%)	129 (21.8%)	*0.165*	17,4% (549)	64.9 % (185)	61.6 % (364)	*0.38*
PTP 65-100%	16,7% (137)	7.4 % (20)	16.8 % (117)	***<0.00 1***	26.0% (251)	75 (27.9%)	176 (25.3%)	*0.458*	18,3% (577)	64.7 % (174)	57.9 % (403)	*0.06*

Supplementary Table 1: Baseline characteristics of patients suspected of coronary artery disease after a positive coronary computed tomography angiogram or a positive functional test for cardiac ischemia, according to each center.

	Center 1 (n=2184)	Center 2 (n=1466)	Center 3 (n=1302)	Total (n=4952)	p-value
Patient characteristics					
Age (years), mean (SD)	66.5 (10.1)	65.3 (10.0)	66.2 (10.7)	**66.1 (10.3)**	<0.001
Male gender, n (%)	1623 (74.3%)	1116 (76.1%)	935 (71.9%)	**3674 (74.2%)**	0.04
BMI kg/m², median, [IQR]	25.9 [23.8, 28.7]	27.1 [24.5, 30.8]	26.0 [23.7, 28.8]	**26.2 [24.0, 29.4]**	<0.001
Diabetes mellitus, n (%)	443 (20.3%)	479 (32.7%)	348 (26.7%)	**1270 (25.6%)**	<0.001
Dyslipidemia, n (%)	955 (43.7%)	748 (51.0%)	660 (50.7%)	**2363 (47.7%)**	<0.001
Hypertension, n (%)	965 (44.2%)	659 (45.0%)	570 (43.8%)	**2194 (44.3%)**	0.82
Current smoking, n (%)	879 (40.2%)	677 (46.2%)	469 (36.0%)	**2025 (40.9%)**	<0.001
CKD, n (%)	13 (0.6%)	28 (1.9%)	9 (0.7%)	**50 (1.0%)**	<0.001
Vascular disease, n (%)	112 (5.1%)	128 (8.7%)	72 (5.5%)	**312 (6.3%)**	<0.001
Previous stroke, n (%)	40 (1.8%)	50 (3.4%)	21 (1.6%)	**111 (2.2%)**	<0.001
PTP, median [IQR]	38.0 [18.5, 60.7]	38.9 [19.2, 61.2]	37.0 [18.5, 58.1]	**38.0 [18.9, 60.4]**	0.37
Positive pre-ICA tests					<0.001
SPECT	402 (18.4%)	693 (47.3%)	240 (18.4%)	**1335 (27.0%)**	
Exercise stress test	525 (24.0%)	210 (14.3%)	444 (34.1%)	**1179 (23.8%)**	
Stress echocardiography	269 (12.3%)	97 (6.6%)	237 (18.2%)	**603 (12.2%)**	

Stress MRI	59 (2.7%)	59 (4.0%)	41 (3.1%)	**159 (3.2%)**	
CCTA	929 (42.5%)	407 (27.8%)	340 (26.1%)	**1676 (33.8%)**	
Results of ICA					<0.001
Normal ICA	279 (12.8%)	303 (20.7%)	237 (18.2%)	**819 (16.5%)**	
Non-oCAD	510 (23.4%)	343 (23.4%)	340 (26.1%)	**1193 (24.1%)**	
oCAD	1395 (63.9%)	820 (55.9%)	725 (55.7%)	**2940 (59.4%)**	

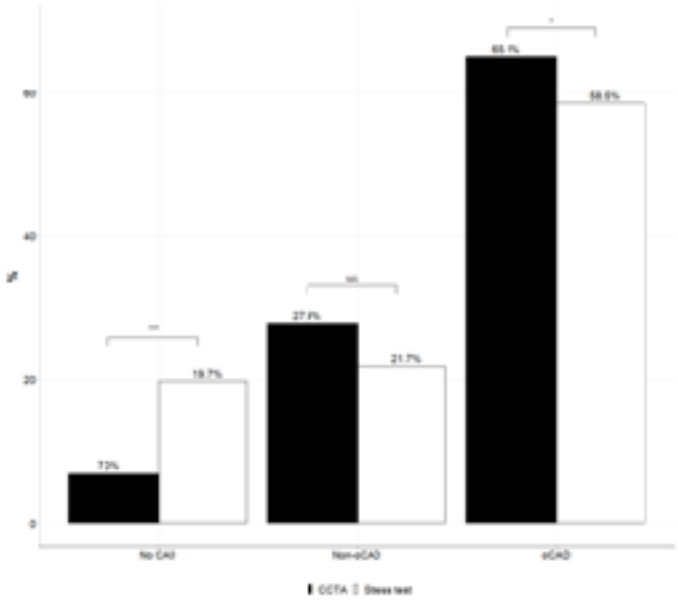
ICA, invasive coronary angiography; CAD, coronary artery disease; oCAD, obstructive coronary artery disease; CCTA, computed tomography angiogram; PTP, pre-test probability; GFR, glomerular filtration rate; BMI, body mass index; SD, standard deviation; IQR, interquartile range; SPECT, single photon emission computed tomography; MRI, magnetic resonance imaging; CKD, chronic kidney disease.

Supplementary Table 2. Rate ratio of positive functional testing/positive computed tomography angiogram in patients suspected of stable coronary artery disease, according to the pre-test probability of coronary artery disease and to the results of coronary angiogram.

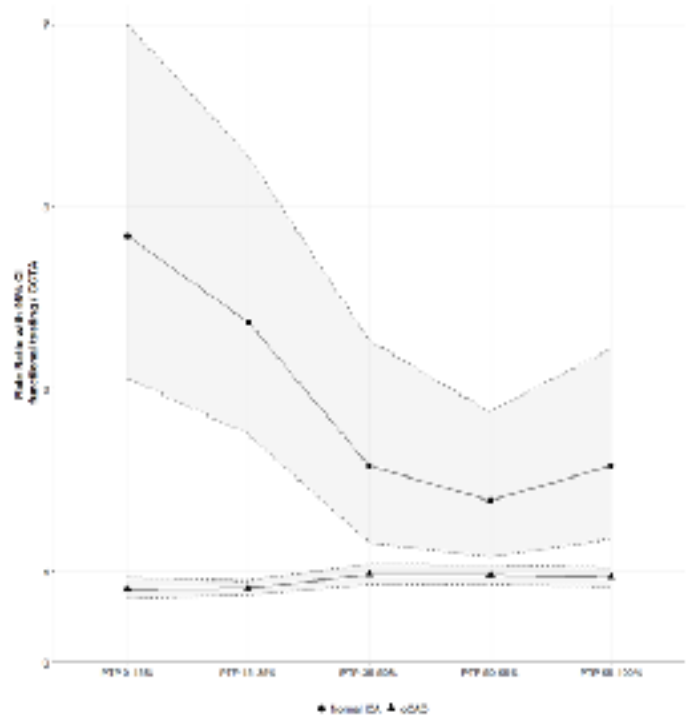
	Normal ICA			non-oCAD			oCAD		
PTP	**Rate Ratio**	**C.I.**	**p**	**Rate Ratio**	**C.I.**	**p**	**Rate Ratio**	**C.I.**	**p**
0-15%	4.729	3.209-6.970	***<0.001***	0.624	0.506-0.769	***<0.001***	0.775	0.686-0.876	***<0.001***
15-35 %	3.956	2.702-5.793	***<0.001***	0.835	0.681-1.024	*0.084*	0.819	0.755-0.890	***<0.001***
35-50 %	2.432	1.525-3.880	***<0.001***	0.821	0.635-1.061	*0.135*	0.909	0.813-1.018	*0.108*
50-65 %	1.890	1.247-2.865	***0.002***	0.829	0.648-1.062	*0.141*	0.949	0.853-1.055	*0.341*
65-100%	2.261	1.438-3.556	***<0.001***	0.907	0.720-1.142	*0.410*	0.895	0.803-0.998	*0.054*

ICA, normal coronary angiogram; non-oCAD, non-obstructive coronary artery disease; oCAD, obstructive coronary artery disease; PTP, pre-test probability.

Supplementary Figure 1. Results of invasive coronary angiogram according to the positivity of previous non-invasive tests for coronary artery disease, after excluding exercise ECG.



Supplementary Figure 2. Normal coronary angiogram or obstructive coronary artery disease rate ratio in patients with prior positive functional testing or positive computed tomography angiogram, according to the pre-test probability of coronary artery disease, after excluding exercise ECG.



Abbreviation list:

ICA: Invasive coronary angiography

CAD: coronary artery disease

CCTA: computed tomography angiogram

PTP: pre-test probability

CI: confidence interval

Table 1. Baseline characteristics of patients suspected of coronary artery disease after a positive coronary computed tomography angiogram (CCTA) or a positive functional test for cardiac ischemia.

Variables	Total N = 4952 (100%)	CCTA N = 1676 (33.8%)	Functional test N = 3276 (66.2%)	p-value
Patient characteristics				
Age (years), mean (SD)	66.1 (10.3)	66.6 (10.0)	65.8 (10.4)	**0.01**
Male gender, n (%)	3674 (74.2%)	1168 (69.7%)	2506 (76.5%)	**< 0.001**
BMI kg/m^2, median, [IQR]	26.2 [24.0, 29.4]	26.1 [23.8, 29.4]	26.3 [24.1, 29.4]	**0.02**
Cardiovascular risk factors				
Diabetes mellitus, n (%)	1270 (25.6%)	309 (18.4%)	961 (29.3%)	**< 0.001**
Dyslipidemia, n (%)	2363 (47.7%)	791 (47.2%)	1572 (48.0%)	0.62
Hypertension, n (%)	2194 (44.3%)	759 (45.3%)	1435 (43.8%)	0.34
Current smoking, n (%)	2025 (40.9%)	698 (41.6%)	1327 (40.5%)	0.46
Chronic kidney disease, n (%)	50 (1.0%)	2 (0.1%)	48 (1.5%)	**< 0.001**
Peripheral vascular disease, n (%)	312 (6.3%)	91 (5.4%)	221 (6.7%)	0.08
Previous stroke, n (%)	111 (2.2%)	35 (2.1%)	76 (2.3%)	0.67
PTP, median [IQR]	26.2 [14.0, 46.2]	25.4 [13.5, 44.3]	26.5 [14.4, 47.1]	**0.03**
Symptoms				
Typical Angina	1549 (31.3%)	525 (31.3%)	1024(31.3)	0.99
Atypical angina	938 (18.9%)	374 (22.3%)	564 (17.2%)	**< 0.001**
Non-specific symptoms	2465 (49.8%)	777 (46.4%)	1688 (51.5%)	**< 0.001**
Prior positive function test for CAD				
SPECT		NA	1335 (40.7%)	-
Exercise stress test		NA	1179 (36.0%)	-
Stress echocardiography		NA	603 (18.4%)	-
Stress MRI		NA	159 (4.9%)	-

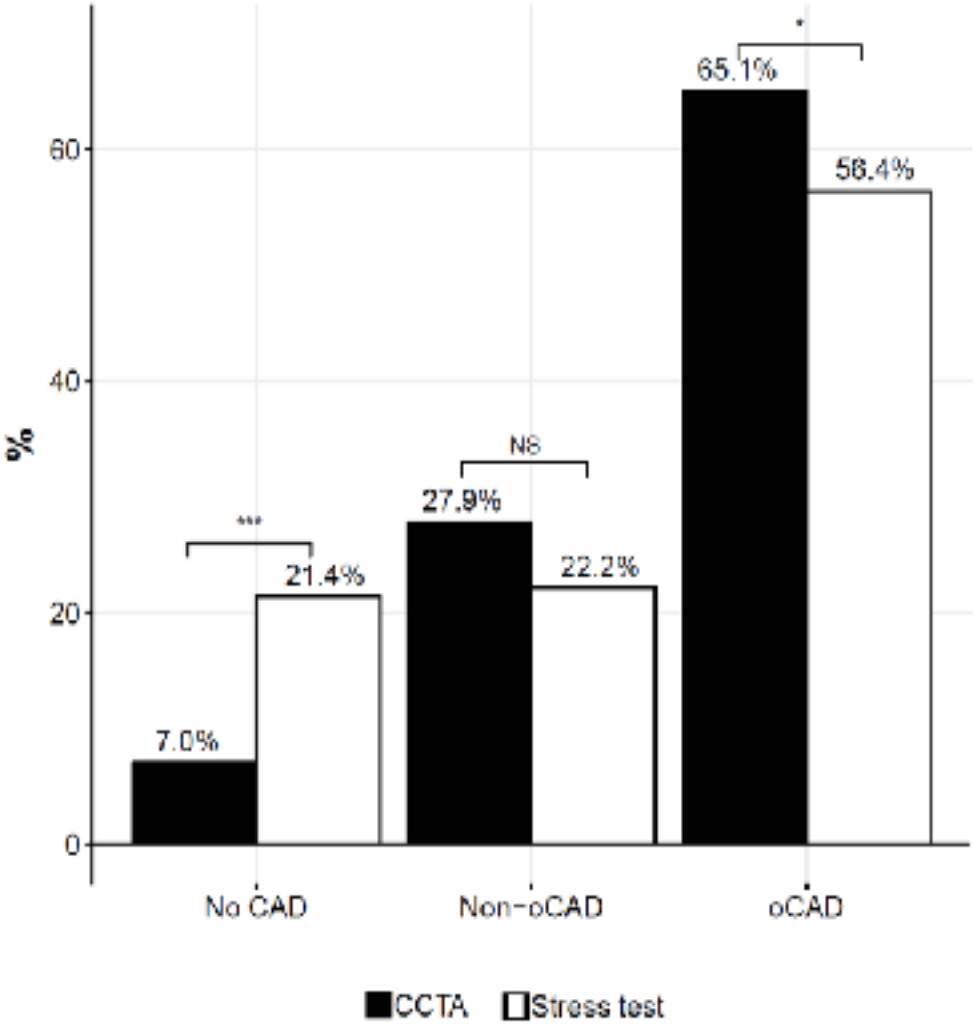
PTP, pre-test probability; BMI, body mass index; SD, standard deviation; IQR, interquartile range; SPECT, single photon emission computed tomography; MRI, magnetic resonance imaging; ICA, invasive coronary angiogram; CAD, coronary artery disease; CCTA, computed tomography angiogram; NA, not available.

Table 2. Results of invasive coronary angiogram in patients with positive functional testing or positive coronary computed tomography angiogram (CCTA), according to the pretest probability (PTP) of coronary artery disease.

	Normal coronary angiogram				**Non-obstructive coronary artery disease**				**Obstructive coronary artery disease**			
	Total	CCTA	Functional testing	*P*	Total	CCTA	Functional testing	*P*	Total	CCTA	Functional testing	*P*
All PTP	16.5% (819)	7.0% (118)	16.5% (819)	***<0.001***	24.1% (1193)	467 (27.9%)	726 (22.2%)	***<0.001***	59.4% (2940)	65.1% (1091)	56.4% (1849)	***<0.001***
PTP 0-15 %	27,3% (223)	7.0% (26)	33.1% (197)	***<0.001***	26.2% (254)	127 (34.1%)	127 (21.3%)	***<0.001***	22,5% (710)	58.9% (219)	45.6% (491)	***<0.001***
PTP 15-35 %	26,3% (215)	5.6% (28)	22.3 % (187)	***<0.001***	22.0% (294)	122 (24.5%)	172 (20.7%)	*0.097*	26,2% (827)	69.8 % (347)	57.2 % (480)	***<0.001***

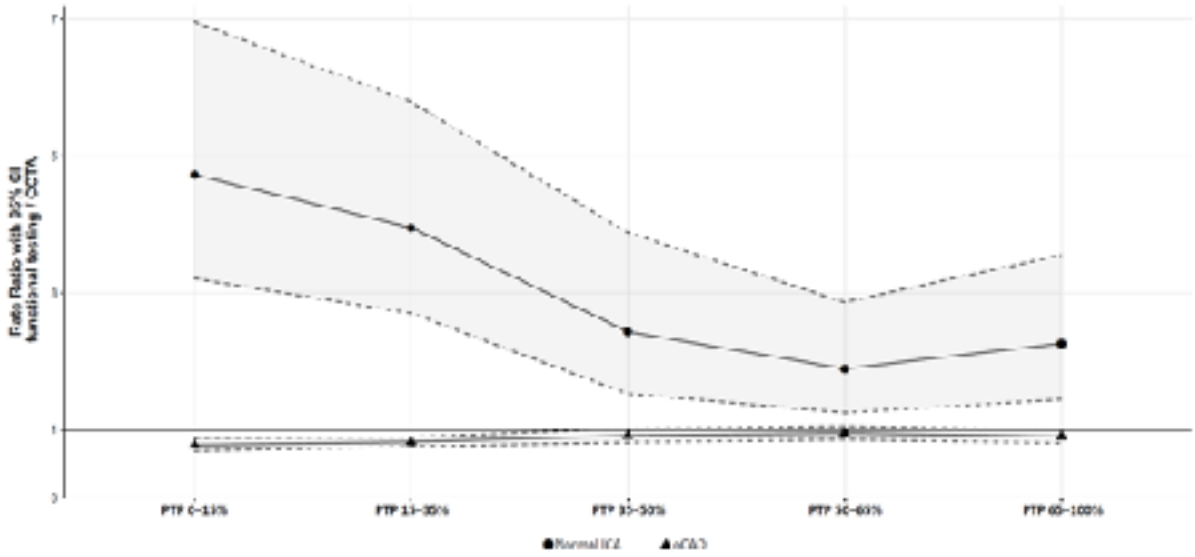
PTP 35-50 %	14,7 % (120)	7.5 % (19)	18.3 % (101)	***<0 . 001***	23.6% (190)	68 (26.9 %)	122 (22.1%)	*0.160*	15,7% (496)	65.6 % (166)	59.7 % (330)	*0.13*
PTP 50-65 %	15,0 % (123)	8.8 % (25)	16.6 % (98)	***0. 003***	23.3% (204)	75 (26.3 %)	129 (21.8%)	*0.165*	17,4% (549)	64.9 % (185)	61.6 % (364)	*0.38*
PTP 65-100%	16,7 % (137)	7.4 % (20)	16.8 % (117)	***<0 . 001***	26.0% (251)	75 (27.9 %)	176 (25.3%)	*0.458*	18,3% (577)	64.7 % (174)	57.9 % (403)	*0.06*

Figure 1. Results of invasive coronary angiogram according to the positivity of previous non-invasive tests for coronary artery disease.



CCTA, computed tomography angiogram; Stress test, functional test for cardiac ischemia; oCAD, obstructive coronary artery disease; *: p<0.01; ***: p<0.001

Figure 2. Normal coronary angiogram or obstructive coronary artery disease rate ratio in patients with prior positive functional testing or positive computed tomography angiogram, according to the pre-test probability of coronary artery disease.



PTP, pre-test probability; CCTA, computed tomography angiogram; Stress test, functional test for cardiac ischemia; oCAD, obstructive coronary artery disease; ICA, invasive coronary angiogram; CI, confidence interval.

Supplementary Table 1: Baseline characteristics of patients suspected of coronary artery disease after a positive coronary computed tomography angiogram or a positive functional test for cardiac ischemia, according to each center.

	Center 1 (n=2184)	Center 2 (n=1466)	Center 3 (n=1302)	Total (n=4952)	p-value
Patient characteristics					
Age (years), mean (SD)	66.5 (10.1)	65.3 (10.0)	66.2 (10.7)	**66.1 (10.3)**	<0.001
Male gender, n (%)	1623 (74.3%)	1116 (76.1%)	935 (71.9%)	**3674 (74.2%)**	0.04
BMI kg/m², median, [IQR]	25.9 [23.8, 28.7]	27.1 [24.5, 30.8]	26.0 [23.7, 28.8]	**26.2 [24.0, 29.4]**	<0.001
Diabetes mellitus, n (%)	443 (20.3%)	479 (32.7%)	348 (26.7%)	**1270 (25.6%)**	<0.001
Dyslipidemia, n (%)	955 (43.7%)	748 (51.0%)	660 (50.7%)	**2363 (47.7%)**	<0.001
Hypertension, n (%)	965 (44.2%)	659 (45.0%)	570 (43.8%)	**2194 (44.3%)**	0.82
Current smoking, n (%)	879 (40.2%)	677 (46.2%)	469 (36.0%)	**2025 (40.9%)**	<0.001
CKD, n (%)	13 (0.6%)	28 (1.9%)	9 (0.7%)	**50 (1.0%)**	<0.001
Vascular disease, n (%)	112 (5.1%)	128 (8.7%)	72 (5.5%)	**312 (6.3%)**	<0.001
Previous stroke, n (%)	40 (1.8%)	50 (3.4%)	21 (1.6%)	**111 (2.2%)**	<0.001
PTP, median [IQR]	38.0 [18.5, 60.7]	38.9 [19.2, 61.2]	37.0 [18.5, 58.1]	**38.0 [18.9, 60.4]**	0.37
Positive pre-ICA tests					<0.001
SPECT	402 (18.4%)	693 (47.3%)	240 (18.4%)	**1335 (27.0%)**	
Exercise stress test	525 (24.0%)	210 (14.3%)	444 (34.1%)	**1179 (23.8%)**	
Stress echocardiography	269 (12.3%)	97 (6.6%)	237 (18.2%)	**603 (12.2%)**	
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Normal ICA	279 (12.8%)	303 (20.7%)	237 (18.2%)	**819 (16.5%)**	
Non-oCAD	510 (23.4%)	343 (23.4%)	340 (26.1%)	**1193 (24.1%)**	
oCAD	1395 (63.9%)	820 (55.9%)	725 (55.7%)	**2940 (59.4%)**	

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	Normal ICA			non-oCAD			oCAD		
PTP	**Rate Ratio**	**C.I.**	**p**	**Rate Ratio**	**C.I.**	**p**	**Rate Ratio**	**C.I.**	**p**
0-15%	4.729	3.209-6.970	***<0.01***	0.624	0.506-0.769	***<0.01***	0.775	0.686-0.876	***<0.001***
15-35 %	3.956	2.702-5.793	***<0.01***	0.835	0.681-1.024	*0.084*	0.819	0.755-0.890	***<0.001***
35-50 %	2.432	1.525-3.880	***<0.01***	0.821	0.635-1.061	*0.135*	0.909	0.813-1.018	*0.108*
50-65 %	1.890	1.247-2.865	***0.002***	0.829	0.648-1.062	*0.141*	0.949	0.853-1.055	*0.341*
65-100%	2.261	1.438-3.556	***<0.01***	0.907	0.720-1.142	*0.410*	0.895	0.803-0.998	*0.054*

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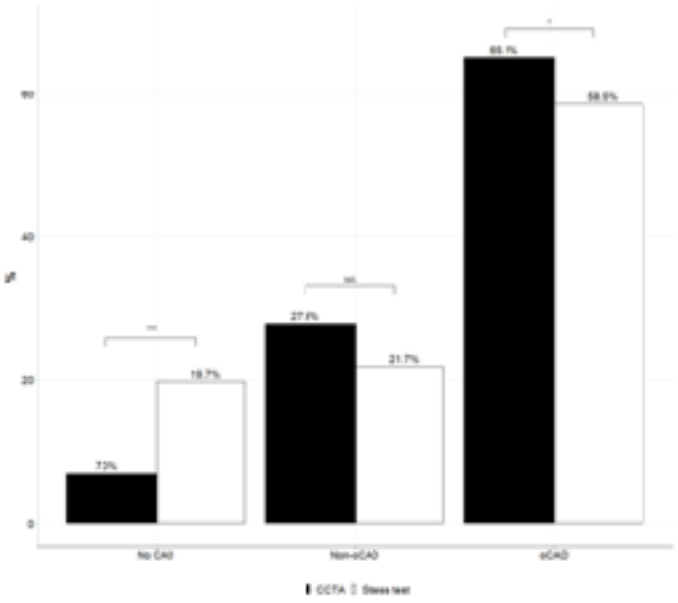
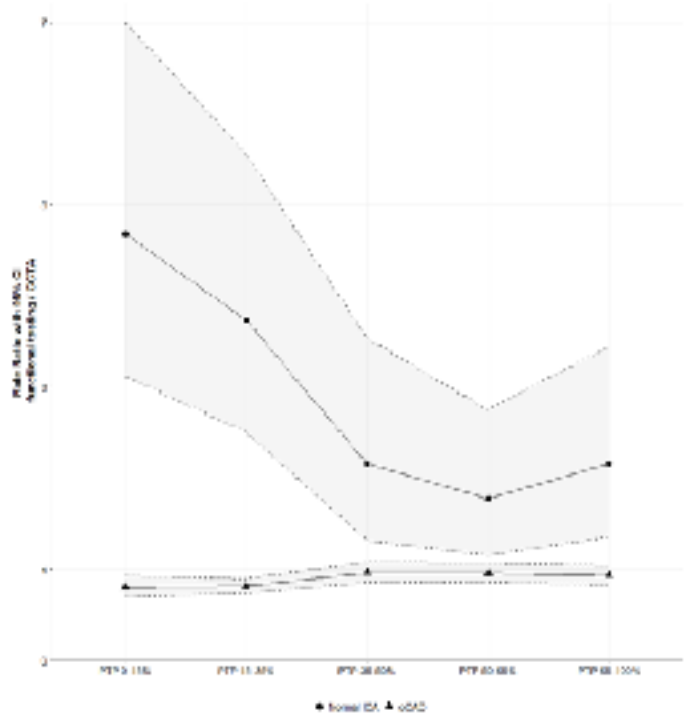


Supplementary Figure 2. Normal coronary angiogram or obstructive coronary artery disease rate ratio in patients with prior positive functional testing or positive computed tomography angiogram, according to the pre-test probability of coronary artery disease, after excluding exercise ECG.



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