Detection of Significant Coronary Artery Disease by Noninvasive Anatomical and Functional Imaging

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***Background*—**The choice of imaging techniques in patients with suspected coronary artery disease (CAD) varies between countries, regions, and hospitals. This prospective, multicenter, comparative effectiveness study was designed to assess the relative accuracy of commonly used imaging techniques for identifying patients with significant CAD.

***Methods and Results*—**A total of 475 patients with stable chest pain and intermediate likelihood of CAD underwent coronary computed tomographic angiography and stress myocardial perfusion imaging by single photon emission computed tomography or positron emission tomography, and ventricular wall motion imaging by stress echocardiography or cardiac magnetic resonance. If ≥1 test was abnormal, patients underwent invasive coronary angiography. Significant CAD was defined by invasive coronary angiography as >50% stenosis of the left main stem, >70% stenosis in a major coronary vessel, or 30% to 70% stenosis with fractional flow reserve ≤0.8. Significant CAD was present in 29% of patients. In a patient-based analysis, coronary computed tomographic angiography had the highest diagnostic accuracy, the area under the receiver operating characteristics curve being 0.91 (95% confidence interval, 0.88–0.94), sensitivity being 91%, and specificity being 92%. Myocardial perfusion imaging had good diagnostic accuracy (area under the curve, 0.74;

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confidence interval, 0.69–0.78), sensitivity 74%, and specificity 73%. Wall motion imaging had similar accuracy (area under the curve, 0.70; confidence interval, 0.65–0.75) but lower sensitivity (49%, $P<0.001$) and higher specificity (92%, $P<0.001$). The diagnostic accuracy of myocardial perfusion imaging and wall motion imaging were lower than that of coronary computed tomographic angiography ($P<0.001$).

Conclusions—In a multicenter European population of patients with stable chest pain and low prevalence of CAD, coronary computed tomographic angiography is more accurate than noninvasive functional testing for detecting significant CAD defined invasively.

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Key Words: coronary artery disease ■ coronary computed tomography angiography ■ echocardiography ■ magnetic resonance imaging ■ myocardial perfusion imaging ■ positron emission tomography ■ single photon computed emission tomography

According to international guidelines, patients with stable chest pain and an intermediate likelihood of underlying coronary artery disease (CAD) should undergo initial exercise ECG or stress coronary functional imaging.[1,2] The European guidelines favor imaging. Coronary computed tomography angiography (CCTA) is considered a reasonable alternative in low-likelihood patients. After diagnosis, failure of medical therapy to control symptoms or findings suggesting a high risk of coronary events justify invasive investigation as a prelude to possible intervention.[2,3] Initial diagnostic invasive coronary angiography (ICA) in patients with stable CAD is not recommended, although in current practice as many as 30% of patients undergo ICA with no symptoms (including no angina), 16% of patients undergo ICA without noninvasive testing, and an additional 15% undergo ICA even after normal noninvasive testing.[4] Possibly as a consequence, 62% of stable patients without known CAD who undergo elective coronary angiography in the United States and 42% of patients in Europe have no significant stenoses.[4,5] Conversely, noninvasive testing does not always guide clinical management because 27% of patients with high-risk imaging results do not undergo ICA.[6]

See Clinical Perspective
See Editorial by Douglas and Daubert

The choice of imaging technique varies between countries, regions, and hospitals, partly because of local expertise and customs and partly because guidelines do not specify a preferred technique. Among the noninvasive tests that are able to detect CAD, CCTA assesses coronary anatomy, whereas the others assess coronary function either from stress myocardial perfusion imaging (MPI) as single photon computed emission tomography (SPECT), positron emission tomography (PET), or cardiac magnetic resonance (CMR) or from stress myocardial wall motion imaging (WMI) as echocardiography or CMR. Previous studies have compared the diagnostic accuracy of some of these technologies,[7–10] but there is no large multicenter study comparing MPI, WMI, and CCTA. With this in mind, the Evaluation of Integrated Cardiac Imaging for the Detection and Characterization of Ischemic Heart Disease (EVINCI) study was designed to compare the diagnostic accuracy of noninvasive anatomic and functional imaging in identifying patients with significant CAD defined by ICA.

Methods

Study Design

Patients were enrolled prospectively from 14 European centers between March 23, 2009, and June15, 2012. Ethical approval was provided by each participating center, and all subjects gave written informed consent. The data were managed by the coordinating center and statistical analysis conducted by a dedicated partner. The study was funded under the 2009 FPVII project of the European Commission. Additional industry support consisted of unrestricted grants and equipment, but the companies had no role in study design, analysis, interpretation, or reporting. The study protocol is available at http://www.clinicaltrials.gov (NCT00979199).

Study Population and Investigation

Consecutive patients were considered for recruitment based on possible symptoms of stable CAD. Chest pain or discomfort was defined as typical angina if substernal, provoked by exertion or emotional stress and relieved by rest or nitrates, as atypical angina if satisfying 2 of the criteria, and as nonanginal if satisfying 1 or none.[11] Exertional dyspnea and fatigue suspected to be angina equivalents were classified as atypical angina. Patients with an interpretable resting ECG who were able to exercise underwent exercise electrocardiography (which was not mandatory). Patients with an intermediate probability of CAD (20%–90%) based on age, sex, symptoms, and exercise ECG when available were invited to participate.[11] Patients with acute coronary syndrome, known CAD, left ventricular ejection fraction <35%, more than moderate valve disease, and cardiomyopathy were excluded (see Methods in the Data Supplement for the full list of inclusion and exclusion criteria).

Patients underwent a study of coronary anatomy by CCTA and ≥1 functional imaging test (Figure 1). Functional imaging included MPI by either SPECT or PET and ventricular WMI by either stress echocardiography or CMR. In most of the patients, imaging tests were performed within 1 month of enrolment and in any case within 3 months. If ≥1 noninvasive anatomic or functional study was abnormal, patients underwent ICA. If both studies were normal, patients did not undergo additional investigations. Further clinical management was at the discretion of the local supervising clinician. Radiation exposure was estimated for CCTA, SPECT, PET, and ICA. Adverse events and revascularization procedures within 30 days of ICA were recorded.

Image Acquisition and Analysis

Standard acquisition and analysis protocols were agreed on for each technique covering patient preparation, cardiovascular stress, administration of radiopharmaceutical or contrast medium, image acquisition and quality control, image processing and interpretation. These procedures were based on available international guidelines.[12–15] Image analysis and reporting was performed independently at each recruiting center and at a core laboratory dedicated to each technique.

At local analysis, the observers were aware of the clinical data; ICA operators had full access to the clinical information and tests. Study quality was rated as suboptimal, good, or excellent.

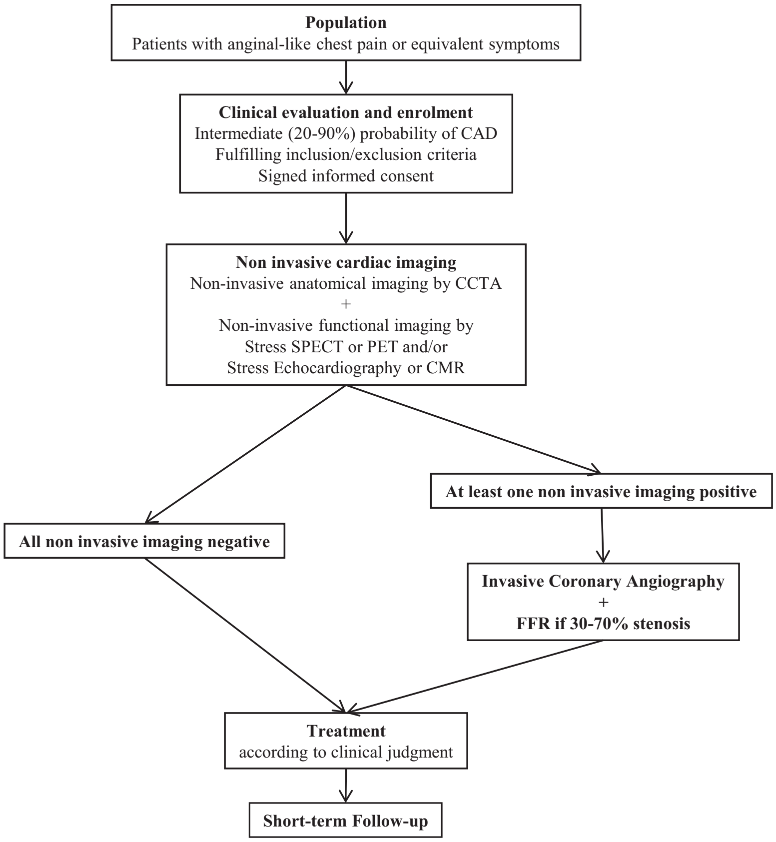

Figure 1. Study design. CAD indicates coronary artery disease; CCTA, coronary computed tomography angiography; CMR, cardiac magnetic resonance; FFR, fractional flow reserve; PET, positron emission tomography; SPECT, single photon computed emission tomography.

The primary end point was a significant stenosis in ≥1 major coronary artery (left main, left anterior descending, left circumflex, and right) at ICA, defined as >50% reduction in lumen diameter in the left main stem or >70% elsewhere or between 30% and 70% with a fractional flow reserve (FFR) ≤0.80. The primary end point was set to negative in patients with all negative noninvasive tests, who did not undergo ICA.

CCTA was defined as abnormal if ≥1 major coronary artery had a diameter stenosis >50%. For MPI, perfusion in each of 17 segments was classified as normal, mild reduction, moderate reduction, severe reduction, or absent perfusion, and the segmental scores were summed for the stress and rest images. An inducible perfusion abnormality was defined as a summed segmental difference score between stress and rest images ≥2, either from a score ≥1 in ≥2 contiguous segments, or ≥2 in ≥1 segment. Scarring was defined similarly from the summed segmental rest score. For WMI, segmental myocardial wall motion was scored at rest and during stress as normal, hypokinetic, akinetic, or dyskinetic. Inducible ischemia was defined as an increase in segmental wall motion score ≥1 from rest to stress in ≥2 contiguous segments. Scarring was defined similarly from the resting wall motion score.

Core laboratory analysis was performed in the patients who completed the protocol and for whom noninvasive and invasive images were made available and were judged as interpretable. The observers were blinded to the clinical data and to any other test results. Image quality was rated using the same 3-point scale as the recruiting centers, and abnormality was defined in the same manner. Core laboratory images were compared with core laboratory quantitative ICA without FFR using >50% diameter stenosis as abnormal.

Definitions and Statistical Analysis

Sample size was calculated to detect at least a 7-point difference in diagnostic accuracy of the different imaging techniques, assuming true values for area under a single point receiver-operating-characteristic curves in the range 0.80 to 0.90 and correlations between curves 0.6. Foreseeing a 50% prevalence of disease, ≥300 patients were required to achieve 80% power with $P<0.05$ at a 2-sided test. To achieve these numbers, SPECT and PET were analyzed together as MPI and echocardiography and CMR together as WMI.

Continuous variables were expressed as mean (±SD) or median with 25th and 75th percentiles. Categorical variables were expressed as numbers and percentages. The diagnostic performance of noninvasive imaging to detect CAD was calculated by patient rather than by coronary artery. The accuracy of each technique was expressed as the area under a single point receiver-operating-characteristic curve using the trapezoidal rule,[16] which is equivalent to the average of the sensitivity and specificity. Sensitivity, specificity, positive, and negative predictive values were calculated with 95% confidence intervals obtained by a bootstrap method using 100 000 replicates. Sensitivity and specificity were compared using tests for 2 proportions. To account for possible selection bias caused by the referral criteria to ICA, bias corrected sensitivity and specificity were also estimated.[17,18] Based on the Bayes theorem, the method used provides estimates of sensitivity and specificity in the overall population adjusting for the empirical probability of verification by ICA. $P≤0.05$ was considered significant. Calculations were made using STATA v10 and pROC in R v2.15.2.

Results

A total of 697 patients were initially enrolled, 78 (11%) subsequently withdrew from the study and 144 (21%) were excluded for protocol violation (Figure 2). Of the excluded patients, 54 underwent ICA but did not undergo both anatomic and functional noninvasive imaging, 45 did not undergo ICA despite an abnormal functional test, 7 despite abnormal CCTA and 4 despite both abnormal tests. Finally, 34 patients were excluded because they did not undergo FFR measurement despite intermediate coronary stenoses by ICA. Thus, 475 patients (68%) completed the entire protocol and were included in the analysis. The estimated pretest probability of CAD was 65% (interquartile range, 33%–75%). The clinical

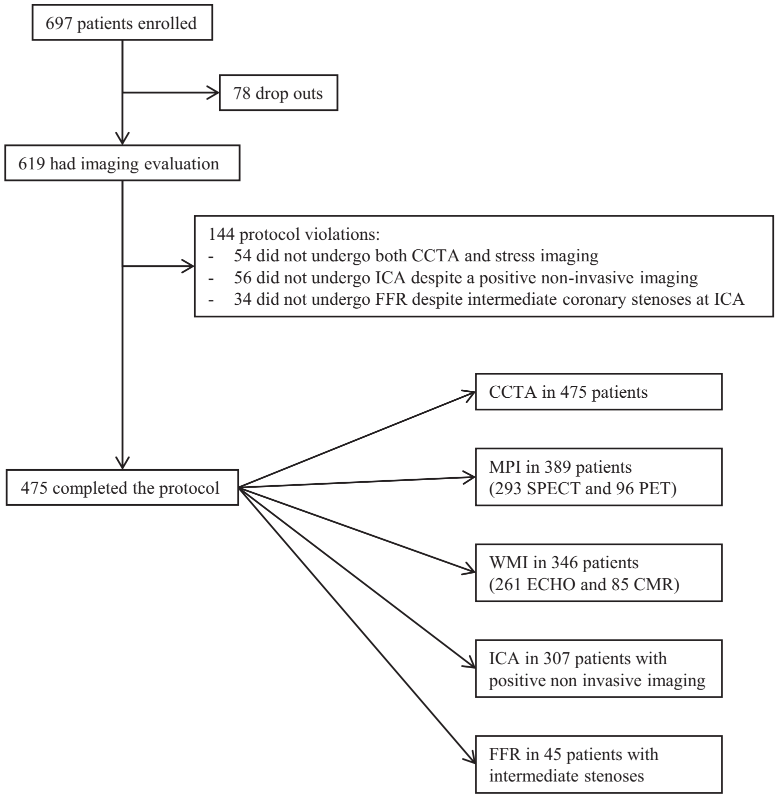

Figure 2. Enrolment and diagnostic procedures. CCTA indicates coronary computed tomography angiography; CMR, cardiac magnetic resonance; FFR, fractional flow reserve; ICA, invasive coronary angiography; MPI, myocardial perfusion imaging; PET, positron emission tomography; SPECT, single photon computed emission tomography; and WMI, wall motion imaging.

and angiographic characteristics of these patients are shown in Table 1.

Each of these patients underwent both a noninvasive study of coronary anatomy by CCTA and ≥1 noninvasive stress coronary functional test. A total of 389 patients underwent MPI (293 SPECT and 96 PET), 346 patients underwent WMI (261 echocardiography and 85 CMR), and 260 patients underwent both MPI and WMI. ICA was performed in 307 patients who had ≥1 abnormal noninvasive test. FFR was measured in 45 patients with 30% to 70% coronary stenoses. The primary end point of significant CAD was detected in 140 patients (29%). Within 30 days after ICA, 97 patients (20%), corresponding to 69% of patients with significant coronary stenoses, underwent myocardial revascularization by percutaneous coronary intervention (17% of patients) or coronary artery bypass grafting (3% of patients). Revascularization was performed in 54% of patients with positive CCTA, 37% of patients with positive MPI (33% SPECT and 60% PET), and 50% of patients with positive WMI (48% Echo and 56% MRI).

No serious adverse events were reported during noninvasive imaging, but 4 patients had severe chest pain during CCTA. One patient had a stroke during percutaneous coronary intervention. Mean radiation exposure was 11.2±8.1 mSv for CCTA, 10.0±2.7 mSv for SPECT, 1.7±1.5 mSv for PET, and 12.8±14.8 mSv for ICA, including revascularization when performed.

Accuracy of Noninvasive Imaging for Detecting CAD, Local Analysis

Table 2 shows the diagnostic accuracy of the imaging techniques using local analysis for the detection of significant CAD defined by ICA. CCTA was more accurate than MPI and WMI (P<0.001). The functional techniques had similar accuracy, although WMI had lower sensitivity with higher specificity (Figure 3). The relative accuracy of noninvasive imaging did not change substantially, selecting the patient with an intermediate probability of CAD calculated according to a more recent prediction model[5] (Table I in the Data Supplement). The relative accuracy was also unchanged, limiting the analysis to subgroups, such as male or female patients, patients >65 year, or patients with a pretest likelihood of ≥50%. In patients referring typical angina, the accuracy of CCTA and MPI was unchanged, whereas that of WMI increased being not significantly different from that of CCTA (Table II in the Data Supplement). Finally, the relative accuracy was unchanged considering as end point a merely angiographic variable: ie, a >50% coronary stenosis at ICA (Table III in the Data Supplement). Wall motion abnormalities were present at rest in 4% of echocardiographic and 8% of CMR studies. The relative accuracies of the techniques did not change significantly when restricting the analysis to patients with only stress-induced abnormalities (Table 3). After correction for verification bias, sensitivity of CCTA, MPI, and WMI was lower than that before correction, whereas specificity and comparative diagnostic performance were unchanged (Table 4).

Accuracy of Noninvasive Imaging for Detecting CAD, Core Laboratory Analysis

The clinical characteristics of the patients included in the core laboratory analysis (350 for CCTA, 219 for SPECT, 59 for PET, 189 for echocardiography, and 82 for CMR) did not significantly differ from the whole population (Table IV in the

Table 1. Clinical and Angiographic Characteristics Shown as mean±SD, Median (Interquartile Range), or Number (%)

	Study Patients (n=475)
Demographics	
Age, y	60±9
Males	291 (61%)
Cardiovascular risk factors	
Family history of CAD	160 (34%)
Diabetes mellitus	115 (24%)
Hypertension	290 (61%)
Hypercholesterolemia	267 (56%)
Obesity	112 (24%)
Smoking within the last year	120 (25%)
Symptoms	
Typical angina	121 (25%)
Atypical angina	288 (61%)
Non-anginal chest pain	66 (14%)
ECG	
Normal	372 (78%)
Left bundle branch block	12 (3%)
Left ventricular hypertrophy	5 (1%)
Other abnormalities	86 (18%)
Left ventricular ejection fraction	
≥50%	451 (95%)
35–50%	24 (5%)
Exercise ECG	
Bicycle	267 (56%)
Treadmill	114 (24%)
Not done	94 (20%)
≥0.15 mV ST depression	71 (19%)
Probability of CAD	65% (33–75)
Coronary calcium score (Agatston)	
0	123 (26%)
1–99	107 (22%)
100–399	85 (18%)
≥400	83 (18%)
Not done	77 (16%)
Invasive coronary angiography	
Not done	168 (35%)
Normal vessels	112 (24%)
Nonobstructive disease	55 (12%)
Single vessel disease	99 (21%)
Double vessel disease	25 (5%)
Triple vessel disease	10 (2%)
Left main stem disease	6 (1%)
Revascularization within 30 days	
Percutaneous coronary intervention	85 (17%)
Coronary artery bypass graft surgery	13 (3%)

CAD indicates coronary artery disease.

Data Supplement). Stress response was considered submaximal in 41% of the echocardiographic studies and in 7% of the CMR studies. Anti-anginal treatment was not withdrawn in 23% of the echocardiographic studies. Image quality was judged as good or excellent in 40% of CCTA, 56% of SPECT, 49% of PET, 55% of echocardiographic, and in 84% of CMR studies.

The accuracy of each technique was substantially unchanged with local or core laboratory analysis, although the sensitivity of CCTA, SPECT, and echocardiography tended to be lower at core laboratory than at local analysis (Table 5). When only the patients in whom the image quality was rated good-to-excellent were included in the analysis, the relative accuracy of the different imaging modalities did not change, although the sensitivity of CCTA and SPECT were higher at 81% for both without loss of specificity (Table 5).

Discussion

In this prospective, pragmatic, multicenter comparative effectiveness study of patients with stable chest symptoms suggestive of CAD, the presence of significant stenoses at ICA was diagnosed more accurately by CCTA than by functional imaging. This study has several unique features: (1) CCTA and several different functional imaging techniques were compared prospectively using ICA as the diagnostic end-point; (2) patients had intermediate likelihood of CAD and were recruited from routine practice in 14 European centers with current techniques and equipment; and (3) images were analyzed both locally, according to common clinical practice, and in dedicated core laboratories to ensure uniformity of interpretation. For the above reasons, we think that our results closely reflect contemporary real-world practice in Europe.

The greater diagnostic accuracy of an anatomic test, CCTA, over functional imaging is most likely the result of the end point used, which was primarily anatomic. Ninety-one percent of patients with significant CAD had stenoses >70%, and only 9% had intermediate lesions with reduced FFR. This favored CCTA because 2 anatomic techniques are likely to agree more than when a functional technique is compared with an anatomic one. The findings might have differed if more patients with intermediate stenoses would have been submitted to FFR measurement or if a harder end point, such as clinical outcome or appropriateness of coronary revascularization, would have been used. Coronary function assessed as inducible perfusion abnormalities by SPECT or wall motion abnormalities by echocardiography is a stronger predictor of clinical outcome than coronary anatomy assessed by ICA.[19,20] For this reason, the most recent guidance regarding the assessment of stable CAD is that the presence of inducible ischemia should guide the need for revascularization, not just the degree of coronary stenosis.[2,3]

An important feature of this study is that the prevalence of CAD was 29%. CCTA has a high negative predictive value and would perform better at low prevalence of disease. The findings therefore support the role of CCTA in patients with lower pretest probability of CAD, in agreement with the recent ESC and NICE Guidelines.[2,21] Similar low prevalence has been reported in other studies.[5] In a large registry of symptomatic and asymptomatic patients who underwent ICA between 2004 and 2008, the prevalence of CAD was 38%, lower in

Table 2.Diagnostic Accuracy of Imaging Techniques for the Detection of Significant Coronary Stenoses at ICA Using Local Analysis

Technique	*N*	Accuracy, % (95% CI)	Sensitivity, % (95% CI)	Specificity, % (95% CI)	PPV, % (95% CI)	NPV, % (95% CI)
CCTA	475	91 (88–94)	91 (86–95)	92 (89–95)	83 (76–88)	96 (93–98)
MPI	389	74* (69–78)	74† (66–82)	73* (68–78)	56 (48–63)	86 (81–91)
SPECT	293	70 (64–75)	73 (64–81)	67 (60–74)	53 (45–62)	83 (76–88)
PET	96	85 (76–94)	81 (62–95)	89 (81–96)	68 (46–85)	94 (86–98)
WMI	346	70* (65–75)	49*‡ (38–59)	92‡ (88–95)	69 (57–80)	82 (77–86)
Echocardiography	261	68 (61–74)	45 (33–57)	90 (86-94)	62 (47–75)	82 (76–87)
CMR	85	77 (67–89)	57 (39–75)	97 (91–100)	89 (65–99)	82 (71–90)

CCTA indicates computed tomography coronary angiography; CI, confidence interval; CMR, cardiac magnetic resonance; ICA, invasive coronary angiography; MPI, myocardial perfusion imaging; NPV, negative predictive value; PET, positron emission tomography; PPV, positive predictive value; SPECT, single photon computed emission tomography; and WMI, wall motion imaging.

**P*<0.001 MPI or WMI vs CCTA.

†*P*=0.001 MPI vs CCTA.

‡*P*<0.001 MPI vs WMI.

patients who underwent CCTA alone.[4] Among patients who were undergoing CCTA within 3 months of stress testing in the ACIC consortium, the prevalence of patients with >50% stenosis was 19%.[22]

The reported accuracy of CCTA is variable, although generally lower than in this study.[23–25] In CORE-64, it was similar to this study (area under the curve 0.93 versus 0.91),

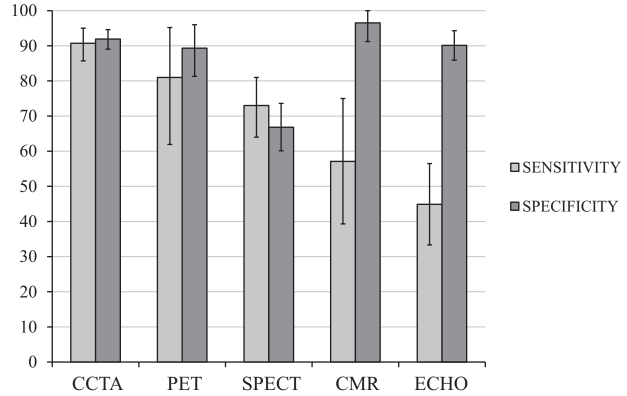

Figure 3. Sensitivity and specificity of noninvasive imaging techniques.

CCTA indicates coronary computed tomography angiography; CMR, cardiac magnetic resonance; ECHO, echocardiography; PET, positron emission tomography; and SPECT, single-photon computed emission tomography.

although the positive predictive value was higher (91% versus 83%) and negative predictive value lower (83% versus 91%).[23] These differences are likely to be the result of the higher prevalence of CAD (56%) in CORE-64 because with increasing prevalence, positive predictive value will increase, whereas negative predictive value will decrease. Other differences that explain the variation may be scanner technology, sample size, and the inclusion of patients with significant coronary calcification.

The accuracy of MPI in this study was comparable to that in others, even if at the lower end of the range.[26] Conversely, the accuracy of WMI was lower than previously reported for both echocardiography and CMR.[12,27] This could be the result of several factors. Sub-maximal stress was reported in 41% of echocardiographic examinations, and 23% of patients remained on medical therapy, both of which will have reduced sensitivity.[28] Additional information, such as Doppler coronary flow reserve by echocardiography, myocardial perfusion for CMR, and quantitative myocardial perfusion for PET, could have improved the performance of functional imaging.[29–33] Lack of clinical information in the core laboratories

Table 3.Diagnostic Accuracy of Imaging Techniques for the Detection of Significant Coronary Stenoses at ICA Using Local Analysis and Inducible Ischemia as the Only Positivity Criterion for Stress Imaging

Technique	*N*	Accuracy, % (95% CI)	Sensitivity, % (95% CI)	Specificity, % (95% CI)	PPV, % (95% CI)	NPV, % (95% CI)
CCTA	475	91 (88–94)	91 (86–95)	92 (89–95)	83 (76–88)	96 (93–98)
MPI	389	73* (68–78)	69* (61–78)	76* (71–81)	57 (48–65)	85 (79–89)
SPECT	293	70 (64–75)	68 (59–77)	71 (64–77)	55 (46–64)	81 (74–87)
PET	96	83 (73–92)	76 (57–91)	89 (81–96)	67 (45–84)	93 (85–98)
WMI	348	67* (62–72)	38*† (29–49)	95† (92–97)	75 (60–86)	80 (74–84)
Echocardiography	261	66 (60–72)	39 (28–51)	93 (90–96)	68 (51–81)	81 (75–86)
CMR	87	68 (60–77)	37 (20–53)	100	100 (62–100)	75 (64–84)

CCTA indicates computed tomography coronary angiography; CI, confidence interval; CMR, cardiac magnetic resonance; ICA, invasive coronary angiography; MPI, myocardial perfusion imaging; NPV, negative predictive value; PET, positron emission tomography; PPV, positive predictive value; SPECT, single photon computed emission tomography; and WMI, wall motion imaging.

**P*<0.001 MPI or WMI vs CCTA.

†*P*<0.001 MPI vs WMI.

Table 4. Sensitivity and Specificity of Imaging Techniques for the Detection of Significant Coronary Stenoses at ICA Using Local Analysis, Without and With Correction for Verification Bias

	Techinique						
	CCTA (N=475)	MPI (N=389)	WMI (N=346)	SPECT (N=293)	PET (N=96)	ECHO (N=261)	CMR (N=85)
Sensitivity, % (95% CI)	91 (86–95)	74*† (66–82)	49‡ (38–59)	73 (64–81)	81 (62–95)	45 (33–57)	57 (39–75)
Sensitivity after correction for verification bias, % (95% CI)	82 (74–91)	59†‡ (50–69)	36‡ (27–45)	53 (43–63)	74 (53–95)	32 (22–43)	46 (27–64)
P value	0.008	0.001	0.011	<0.001	0.622	0.028	0.256
Specificity, % (95% CI)	92 (89–95)	73†‡ (68–78)	92 (88–95)	67 (60–74)	89 (81–96)	90 (86–94)	97 (91–100)
Specificity after correction for verification bias, % (95% CI)	92 (89–95)	70†‡ (63–76)	90 (86–94)	59 (50–68)	89 (82–96)	88 (84–94)	96 (90–100)
P value	0.920	0.232	0.524	0.023	0.891	0.572	1

CCTA indicates computed coronary tomography angiography; CI, confidence interval; CMR, cardiac magnetic resonance; ICA, invasive coronary angiography; MPI, myocardial perfusion imaging; PET, positron emission tomography; SPECT, single photon computed emission tomography; and WMI, wall motion imaging. *P* value from binomial probability test for comparison between corrected and uncorrected values.

*P=0.001 MPI vs CCTA.

†P<0.001 MPI vs WMI.

‡P<0.001 MPI or WMI vs CCTA.

could also explain the lower sensitivity in the core laboratories than in the centers, which was most evident for echocardiography, SPECT, and CCTA.

Current guidelines do not indicate which functional imaging technique should be favored, but it is recommended that the choice should consider local availability and expertise, the

Table 5. Diagnostic Accuracy of Imaging Techniques for the Detection of Significant Coronary Stenoses at ICA Using Core Laboratory Analysis

Technique	*N*	Accuracy, % (95% CI)	Sensitivity, % (95% CI)	Specificity, % (95% CI)	PPV, % (95% CI)	NPV, % (95% CI)
CCTA						
All images	350	82 (77–86)	71 (62–81)	92 (88–95)	77 (67–85)	89 (85–93)
Good or excellent quality	140	86 (77–94)	81 (65–96)	91 (86–96)	68 (49–83)	95 (90–98)
SPECT						
All images	219	74 (68–80)	58 (46–70)	90 (85–95)	73 (59–84)	82 (76–88)
Good or excellent quality	123	84 (76–90)	81 (69–93)	86 (79–94)	76 (60–87)	90 (81–95)
PET						
All images	59	81 (69–92)	80 (60–100)	82 (71–93)	60 (36–81)	92 (79–98)
Good or excellent quality	29	80 (58–96)	80 (40–100)	79 (63–96)	44 (14–79)	95 (75–100)
Echocardiography						
All images	189	60 (54–66)	24 (12–36)	95 (92–99)	63 (38–84)	78 (71–84)
Good or excellent quality	105	62 (54–71)	27 (12–46)	98 (94–100)	78 (40–97)	80 (71–88)
CMR						
All images	82	80 (67–87)	54 (35–73)	100	100 (68–100)	82 (71–91)
Good or excellent quality	69	75 (65–85)	50 (30–70)	100	100 (59–100)	83 (71–92)

CCTA indicates computed tomography coronary angiography; CI, confidence interval; CMR, cardiac magnetic resonance; ICA, invasive coronary angiography; MPI, myocardial perfusion imaging; NPV, negative predictive value; PET, positron emission tomography; PPV, positive predictive value; and SPECT, single photon computed emission tomography.

cost, and the risks of contrast agents and radiation exposure.[34] The health-economic analysis of the EVINCI study will be performed separately.

This study has several limitations. Sample size calculations assumed a 50% prevalence of obstructive CAD, true values for area under the curves in the range 0.80 to 0.90, and correlations between curves being 0.6 to detect a difference of ≥7% in the accuracy of CCTA and functional imaging. Some of the above assumptions were not met, and the difference in accuracy actually was higher (range 17–21%). The study power, recalculated according to the observed values, was >90% in pairwise comparisons of CCTA, MPI, and WMI, but was inadequate for comparing individual functional imaging modalities.

The enrolled patients were selected more often from stress imaging laboratories and cardiology divisions than from the emergency rooms; moreover, patients with >90% likelihood of CAD were excluded. Thus, the study cohort could not be representative of the higher risk patients referred for imaging testing.

To have had both a CCTA and a functional test is not common practice in most centers and could have favored protocol violations. However, of the 144 patients excluded from the analysis, 54 did not undergo any noninvasive test, 45 did not undergo ICA despite positive stress imaging test, 7 despite positive CCTA, and 4 despite both positive tests. Thus, it is unlikely that protocol violations could have modified the results in favor of CCTA. Similarly, 168 patients with normal CCTA and functional studies did not undergo ICA according to the protocol. To account for the potential of a selection bias consequent to the number of patient excluded, a sensitivity analysis was performed in the patients in whom imaging data were available, despite some protocol violation. No differences for any measurement of performance were observed in comparison with the primary analysis (Table V in the Data Supplement).

Setting the reference standard to negative in subjects with all negative noninvasive testing could have introduced a verification bias. After correction for verification bias, sensitivity of imaging modalities significantly decreased, whereas specificity and the relative performance were unchanged (Table 4).

To privilege local facilities and expertise, the decision regarding which patients underwent stress SPECT, PET, echocardiography, or CMR was not defined in the protocol but left to the enrolling centers. However, no significant difference in the prevalence of obstructive CAD was present in patients investigated by CCTA, MPI, and WMI.

Although acquisition and analysis protocols were agreed on for each technique before data acquisition, differences in imaging protocols between the different centers still persisted. This could have been one of the causes of the wide range in radiation exposure registered for some exams, such as CCTA.

For stress CMR, a significant number of laboratories now use contrast-enhanced MPI, deemed to provide superior accuracy as opposed to WMI. However, this standard was not so widely accepted when the EVINCI study was designed. Quantitative coronary angiography was not used at enrolling centers, but only at the ICA core laboratory. Although the core laboratory patients did not differ from the whole population, core laboratory analysis was not performed in each patient. Finally, a significant stenosis was defined as luminal narrowing >70%, and only stenoses between 30% and 70% were further investigated by FFR. After defining this study protocol, the FAME II study showed that only 72% of stenoses between 70% and 90% in women and 82% in men had abnormal FFR.[35] Almost half of the patients with intermediate stenoses did not undergo FFR and were thus excluded from the study, confirming that FFR did not still gain common clinical practice.

Conclusions

In a multicenter European population of patients with stable chest pain and low prevalence of disease, CCTA is the most accurate imaging technique for detecting significant CAD defined by ICA. Functional imaging based on myocardial perfusion is more sensitive but less specific than functional imaging based on ventricular wall motion.

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Disclosures

None.

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CLINICAL PERSPECTIVE

The choice of imaging techniques in patients with suspected coronary artery disease (CAD) varies between countries, regions, and hospitals. The Evaluation of Integrated Cardiac Imaging for the Detection and Characterization of Ischemic Heart Disease (EVINCI) Study was designed to compare the diagnostic accuracy of noninvasive anatomic and functional imaging in identifying patients with obstructive CAD, defined by invasive coronary angiography. The EVINCI population consisted of patients with stable chest pain or equivalent symptoms, currently referred for cardiac imaging. The prevalence of obstructive CAD at invasive coronary angiography was <30%. The results of the study show that coronary computed tomography angiography is the most accurate imaging technique to detect obstructive CAD in this population. Functional imaging based on myocardial perfusion is more sensitive but less specific than functional imaging based on ventricular wall motion. These findings support the role of coronary computed tomography angiography in patients with low-to-intermediate pretest probability of CAD in agreement with the recent ESC and NICE Guidelines.