



Year: 2015

Detection of significant coronary artery disease by noninvasive anatomical and functional imaging

Neglia, Danilo ; Rovai, Daniele ; Caselli, Chiara ; Pietila, Mikko ; Teresinska, Anna ; Aguadé-Bruix, Santiago ; Pizzi, Maria Nazarena ; Todiere, Giancarlo ; Gimelli, Alessia ; Schroeder, Stephen ; Drosch, Tanja ; Poddighe, Rosa ; Casolo, Giancarlo ; Anagnostopoulos, Constantinos ; Pugliese, Francesca ; Rouzet, Francois ; Le Guludec, Dominique ; Cappelli, Francesco ; Valente, Serafina ; Gensini, Gian Franco ; Zawaideh, Camilla ; Capitano, Selene ; Sambuceti, Gianmario ; Marsico, Fabio ; Perrone Filardi, Pasquale ; Fernández-Golfín, Covadonga ; Rincón, Luis M ; Graner, Frank P ; de Graaf, Michiel A ; Fiechter, Michael ; Stehli, Julia ; Gaemperli, Oliver ; Reyes, Eliana ; Nkomo, Sandy ; Mäki, Maija ; Lorenzoni, Valentina ; Turchetti, Giuseppe ; Carpeggiani, Clara ; Marinelli, Martina ; Puzzuoli, Stefano ; Mangione, Maurizio ; Marcheschi, Paolo ; Mariani, Fabio ; Giannessi, Daniela ; Nekolla, Stephan ; Lombardi, Massimo ; Sicari, Rosa ; Scholte, Arthur J H A ; Zamorano, José L ; Kaufmann, Philipp A ; Underwood, S Richard ; Knuuti, Juhani

Abstract: **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; 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. **CLINICAL TRIAL REGISTRATION URL:** <http://www.clinicaltrials.gov>. Unique identifier: NCT00979199.

DOI: <https://doi.org/10.1161/CIRCIMAGING.114.002179>

Originally published at:

Neglia, Danilo; Rovai, Daniele; Caselli, Chiara; Pietila, Mikko; Teresinska, Anna; Aguadé-Bruix, Santiago; Pizzi, Maria Nazarena; Todiere, Giancarlo; Gimelli, Alessia; Schroeder, Stephen; Drosch, Tanja; Poddighe, Rosa; Casolo, Giancarlo; Anagnostopoulos, Constantinos; Pugliese, Francesca; Rouzet, Francois; Le Guludec, Dominique; Cappelli, Francesco; Valente, Serafina; Gensini, Gian Franco; Zawaideh, Camilla; Capitanio, Selene; Sambuceti, Gianmario; Marsico, Fabio; Perrone Filardi, Pasquale; Fernández-Golfín, Covadonga; Rincón, Luis M; Graner, Frank P; de Graaf, Michiel A; Fiechter, Michael; Stehli, Julia; Gaemperli, Oliver; Reyes, Eliana; Nkomo, Sandy; Mäki, Maija; Lorenzoni, Valentina; Turchetti, Giuseppe; Carpeggiani, Clara; Marinelli, Martina; Puzzuoli, Stefano; Mangione, Maurizio; Marcheschi, Paolo; Mariani, Fabio; Giannessi, Daniela; Nekolla, Stephan; Lombardi, Massimo; Sicari, Rosa; Scholte, Arthur J H A; Zamorano, José L; Kaufmann, Philipp A; Underwood, S Richard; Knuuti, Juhani (2015). Detection of significant coronary artery disease by noninvasive anatomical and functional imaging. *Circulation. Cardiovascular Imaging*, 8(3):e002179.

DOI: <https://doi.org/10.1161/CIRCIMAGING.114.002179>

Coronary Artery Disease

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

Danilo Neglia, MD, PhD; Daniele Rovai, MD; Chiara Caselli, PhD; Mikko Pietila, MD; Anna Teresinska, PhD; Santiago Aguadé-Bruix, MD; Maria Nazarena Pizzi, MD; Giancarlo Todiere, MD; Alessia Gimelli, MD; Stephen Schroeder, MD; Tanja Drosch, MD; Rosa Poddighe, MD, PhD; Giancarlo Casolo, MD, PhD; Constantinos Anagnostopoulos, MD; Francesca Pugliese, MD, PhD; Francois Rouzet, MD; Dominique Le Guludec, MD, PhD; Francesco Cappelli, MD, PhD; Serafina Valente, MD; Gian Franco Gensini, MD; Camilla Zawaidh, MD; Selene Capitano, MD; Gianmario Sambuceti, MD; Fabio Marsico, MD; Pasquale Perrone Filardi, MD; Covadonga Fernández-Golfín, MD; Luis M Rincón, MD; Frank P. Graner, MSc; Michiel A. de Graaf, MSc; Michael Fiechter, MD; Julia Stehli, MD; Oliver Gaemperli, MD; Eliana Reyes, MD, PhD; Sandy Nkomo, BSc; Maija Mäki, MD, PhD; Valentina Lorenzoni, MSc; Giuseppe Turchetti, PhD; Clara Carpeggiani, MD; Martina Marinelli, PhD; Stefano Puozuoli, BSc; Maurizio Mangione, PhD; Paolo Marcheschi, PhD; Fabio Mariani, MSc; Daniela Giannessi, MSc; Stephan Nekolla, PhD; Massimo Lombardi, MD; Rosa Sicari, MD; Arthur J.H.A. Scholte, MD, PhD; José L. Zamorano, MD; Philipp A. Kaufmann, MD; S. Richard Underwood, MD*; Juhani Knuuti, MD*; The EVINCI Study Investigators

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;

Received June 9, 2014; accepted January 8, 2015.

From the Institute of Clinical Physiology, CNR, Pisa, Italy (D.N., D.R., C. Caselli, C. Carpeggiani, M. Marinelli, F. Mariani, D.G., R.S.); Cardiothoracic Department (D.N., G. Todiere), Imaging Department (A.G., M.L.) and Technology Department (S.P., M. Mangione, P.M.), Fondazione Toscana G. Monasterio, Pisa, Italy; Heart Center (M.P.) and Turku PET Center (M.Mäki, J.K.), University of Turku and Turku University Hospital, Turku, Finland; Department of Nuclear Medicine, Institute of Cardiology, Warsaw, Poland (A.T.); Department of Nuclear Medicine, University Hospital Val d'Hebron, Institut Catala de la Salut, Barcelona, Spain (S.A.-B., M.N.P.); Department of Cardiology, Alb-Fils-Kliniken, Göppingen, Germany (S.S., T.D.); Emergency Department, Cardiology, Ospedale della Versilia, Lido di Camaiore, Italy (R.P., G.C.); Center for Experimental Surgery, Clinical and Translational Research, Biomedical Research Foundation, Academy of Athens, Athens, Greece (C.A.); Centre for Advanced Cardiovascular Imaging, National Institute for Health Research Cardiovascular Biomedical Research Unit at Barts, William Harvey Research Institute, Barts and The London School of Medicine, Queen Mary University of London, London, United Kingdom (C.A., F.P.); Department of Nuclear Medicine, Bichat University Hospital, Département Hospitalo-Universitaire FIRE, Assistance Publique-Hôpitaux de Paris, University Paris Diderot, Paris, France (F.R., D.L.G.); Cardiothoracic and Vascular Department, Azienda Ospedaliera Universitaria Careggi (F.C., S.V., G.G.) and Don Carlo Gnocchi Foundation, IRCCS (G.F.G.), Florence, Italy; Department of Health Science and Internal Medicine, IRCCS Hospital San Martino, National Institute for Cancer Research and University of Genoa, Genoa, Italy (C.Z., S.C., G.S.); Department of Advanced Biomedical Sciences, Federico II University, Naples, Italy (F.Marsico, P.P.F.); Department of Cardiology, University Hospital Ramón y Cajal, Madrid, Spain (C.F.-G., L.M.R., J.L.Z.); Department of Nuclear Medicine, Klinikum Rechts der Isar der Technischen Universität München, München, Germany (F.P.G., S.N.); Department of Cardiology, Leiden University Medical Center, Leiden, The Netherlands (M.A.d.G., A.J.H.A.S.); Department of Nuclear Medicine, University Hospital Zurich, Zurich, Switzerland (M.F., J.S., O.G., P.A.K.); Biomedical Research Unit, Royal Brompton Hospital and National Heart and Lung Institute, Imperial College London, United Kingdom (E.R., S.N., S.R.U.); Institute of Management, Scuola Superiore Sant'Anna, Pisa, Italy (V.L., G.Turchetti).

*Drs Underwood and Knuuti are joint senior authors.

The Data Supplement is available at <http://circimaging.ahajournals.org/lookup/suppl/doi:10.1161/CIRCIMAGING.114.002179/-/DC1>.

Correspondence to Danilo Neglia, MD, PhD, Fondazione Toscana G. Monasterio & CNR Institute of Clinical Physiology, Via Moruzzi, 1, 56126 Pisa, Italy. E-mail dneglia@ifc.cnr.it

© 2015 American Heart Association, Inc.

Circ Cardiovasc Imaging is available at <http://circimaging.ahajournals.org>

DOI: 10.1161/CIRCIMAGING.114.002179

Downloaded from <http://circimaging.ahajournals.org/> at Universitaet Zuerich on February 23, 2016

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.

Clinical Trial Registration—URL: <http://www.clinicaltrials.gov>. Unique identifier: NCT00979199.

(*Circ Cardiovasc Imaging*. 2015;8:e002179. DOI: 10.1161/CIRCIMAGING.114.002179.)

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 June 15, 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.

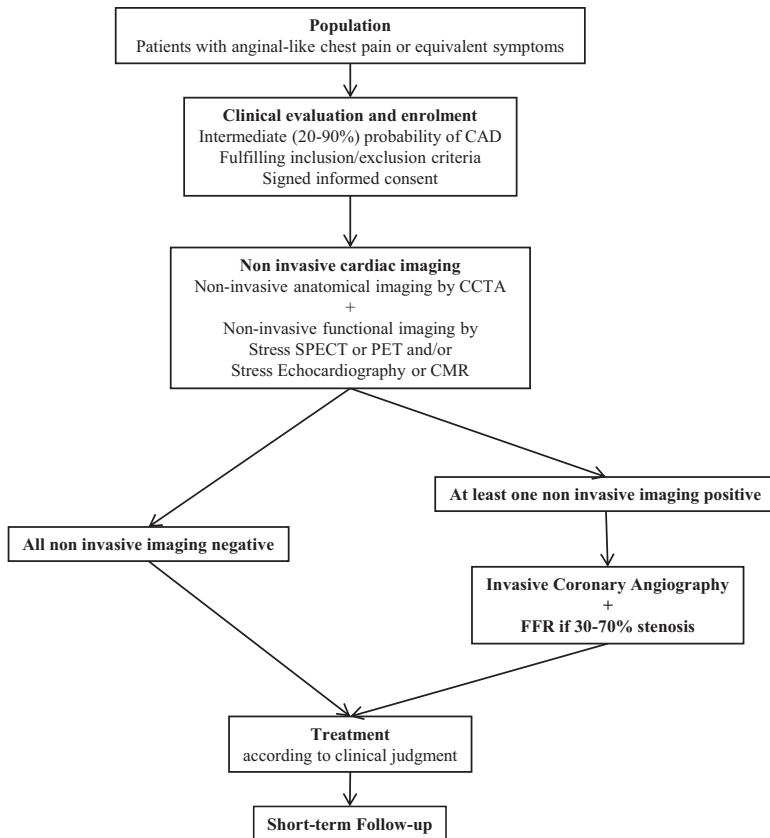


Figure 1. Study design. CAD indicates coronary artery disease; CCTA, coronary computed tomography angiography; CMR, cardiac magnetic resonance; FFR, fractional flow reserve; PET, positron emission tomography; SPECT, single photon computed emission tomography.

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 (\pm 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 100000 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. $P \leq 0.05$ 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

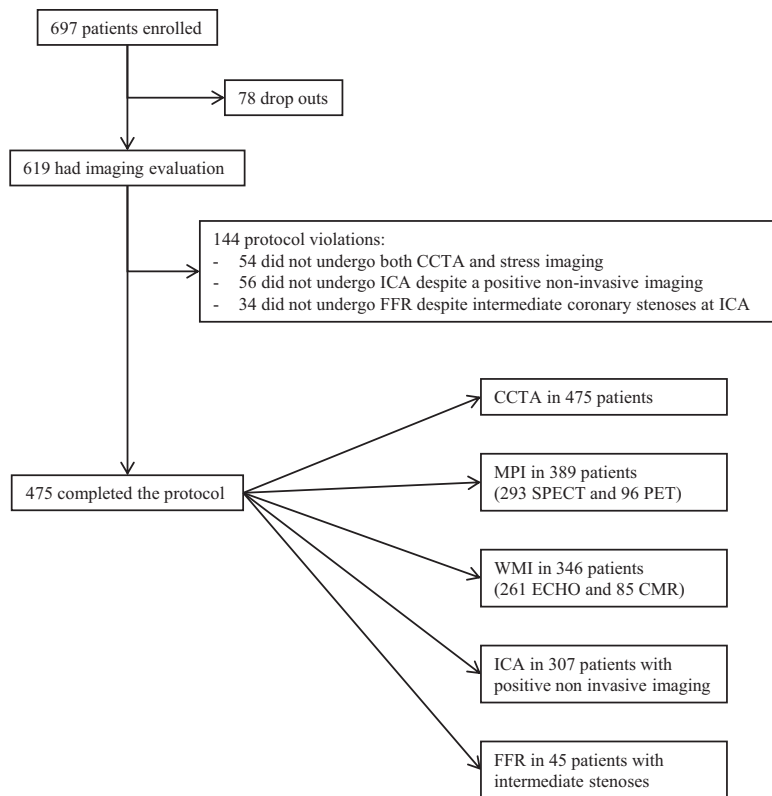


Figure 2. Enrolment and diagnostic procedures. CCTA indicates coronary computed tomography angiography; CMR, cardiac magnetic resonance; FFR, fractional flow reserve; ICA, invasive coronary angiography; MPI, myocardial perfusion imaging; PET, positron emission tomography; SPECT, single photon computed 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 model⁵ (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 $\geq 50\%$. 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.

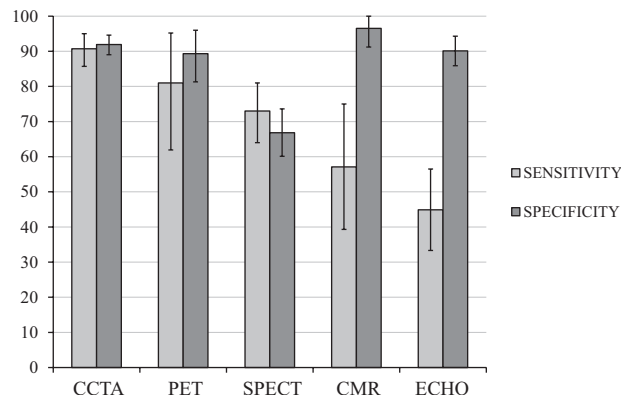
* $P < 0.001$ MPI or WMI vs CCTA.

† $P = 0.001$ 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

	Technique						
	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)
<i>P</i> 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)
<i>P</i> 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	<i>N</i>	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 $\geq 7\%$ 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.

Sources of Funding

This work was supported by a grant from the European Union FP7-CP-FP506 2007 (grant agreement no. 222915, EVINCI [Evaluation of Integrated Cardiac Imaging for the Detection and Characterization of Ischemic Heart Disease]). It was also supported in part by the Centre of Excellence in Molecular Imaging in Cardiovascular and Metabolic Research, the Academy of Finland, the Cardiovascular Biomedical Research Unit of the Royal Brompton & Harefield National Health Service Foundation Trust, the National Institute for Health Research Cardiovascular Biomedical Research Unit at St Bartholomew's Hospital, the Ministry of Science and Higher Education, Poland, and unrestricted grant and products from General Electric Healthcare. This work forms part of the research themes contributing to the translational research portfolio of the NIHR Cardiovascular Biomedical Research Unit at Barts, which is supported and funded by the National Institute for Health Research.

Disclosures

None.

References

1. American College of Cardiology Foundation Appropriate Use Criteria Task Force. CCF/AHA/ASE/ASNC/ HFSA/HRS/SCAI/SCCT/SCMR/ STS 2013 multimodality appropriate use criteria for the detection and risk assessment of stable ischemic heart disease: a report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, American Heart Association, American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Failure Society of America, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, Society for Cardiovascular Magnetic Resonance, and Society of Thoracic Surgeons. *J Am Coll Cardiol*. 2014; 63:380–406.
2. Task Force Members I. 2013 ESC guidelines on the management of stable coronary artery disease: The Task Force on the management of stable coronary artery disease of the European Society of Cardiology. *Eur Heart J*. 2013; 34:2949–3003.
3. ACCF/SCAI/AATS/AHA/ASE/ASNC/HFSA/HRS/SCCM/SCCT/SCMR/STS 2012 appropriate use criteria for diagnostic catheterization: a report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, Society for Cardiovascular Angiography and Interventions, American Association for Thoracic Surgery, American Heart Association, American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Failure Society of America, Heart Rhythm Society, Society of Critical Care Medicine, Society of Cardiovascular Computed Tomography, Society for Cardiovascular Magnetic Resonance, and Society of Thoracic Surgeons. *J Am Coll Cardiol*. 2012; 59:1995–2027.
4. Patel MR, Peterson ED, Dai D, Brennan JM, Redberg RF, Anderson HV, Brindis RG, Douglas PS. Low diagnostic yield of elective coronary angiography. *N Engl J Med*. 2010;362:886–895. doi: 10.1056/NEJMoa0907272.

5. Genders TS, Steyerberg EW, Alkadhi H, Leschka S, Desbiolles L, Nieman K, Galema TW, Meijboom WB, Mollet NR, de Feyter PJ, Cademartiri F, Maffei E, Dewey M, Zimmermann E, Laule M, Pugliese F, Barbagallo R, Sinitsyn V, Bogaert J, Goetschalckx K, Schoepf UJ, Rowe GW, Schuijf JD, Bax JJ, de Graaf FR, Knuuti J, Kajander S, van Mieghem CA, Meijis MF, Cramer MJ, Gopalan D, Feuchtner G, Friedrich G, Krestin GP, Hunink MG; CAD Consortium. A clinical prediction rule for the diagnosis of coronary artery disease: validation, updating, and extension. *Eur Heart J*. 2011;32:1316–1330. doi: 10.1093/eurheartj/ehr014.
6. Hachamovitch R, Nutter B, Hlatky MA, Shaw LJ, Ridner ML, Dorbala S, Beanlands RS, Chow BJ, Branscomb E, Chareonthaitawee P, Weigold WG, Voros S, Abbara S, Yasuda T, Jacobs JE, Lesser J, Berman DS, Thomson LE, Raman S, Heller GV, Schussheim A, Brunken R, Williams KA, Farkas S, Delbeke D, Schoepf UJ, Reichel N, Rabinowitz S, Sigman SR, Patterson R, Corn CR, White R, Kazerooni E, Corbett J, Bokhari S, Machac J, Guarnieri E, Borges-Neto S, Millstine JW, Caldwell J, Arrighi J, Hoffmann U, Budoff M, Lima J, Johnson JR, Johnson B, Gaber M, Williams JA, Foster C, Hainer J, Di Carli MF; SPARC Investigators. Patient management after noninvasive cardiac imaging results from SPARC (Study of myocardial perfusion and coronary anatomy imaging roles in coronary artery disease). *J Am Coll Cardiol*. 2012;59:462–474. doi: 10.1016/j.jacc.2011.09.066.
7. Marwick T, Willemart B, D'Hondt AM, Baudhuin T, Wijns W, Detry JM, Melin J. Selection of the optimal nonexercise stress for the evaluation of ischemic regional myocardial dysfunction and malperfusion. Comparison of dobutamine and adenosine using echocardiography and 99mTc-MIBI single photon emission computed tomography. *Circulation*. 1993;87:345–354.
8. Gaemperli O, Schepis T, Valenta I, Koepfli P, Husmann L, Scheffel H, Leschka S, Eberli FR, Luscher TF, Alkadhi H, Kaufmann PA. Functionally relevant coronary artery disease: comparison of 64-section CT angiography with myocardial perfusion SPECT. *Radiology*. 2008;248:414–423. doi: 10.1148/radiol.2482071307.
9. Kajander S, Joutsiniemi E, Saraste M, Pietilä M, Ukkonen H, Saraste A, Sipilä HT, Teräs M, Mäki M, Airaksinen J, Hartiala J, Knuuti J. Cardiac positron emission tomography/computed tomography imaging accurately detects anatomically and functionally significant coronary artery disease. *Circulation*. 2010;122:603–613. doi: 10.1161/CIRCULATIONAHA.109.915009.
10. Greenwood JP, Maredia N, Younger JF, Brown JM, Nixon J, Everett CC, Bijsterveld P, Ridgway JP, Radjenovic A, Dickinson CJ, Ball SG, Plein S. Cardiovascular magnetic resonance and single-photon emission computed tomography for diagnosis of coronary heart disease (CE-MARC): a prospective trial. *Lancet*. 2012;379:453–460. doi: 10.1016/S0140-6736(11)61335-4.
11. Diamond GA, Forrester JS. Analysis of probability as an aid in the clinical diagnosis of coronary-artery disease. *N Engl J Med*. 1979;300:1350–1358. doi: 10.1056/NEJM197906143002402.
12. Sicari R, Nihoyannopoulos P, Evangelista A, Kasprzak J, Lancellotti P, Poldermans D, Voigt JU, Zamorano JL; European Association of Echocardiography. Stress echocardiography expert consensus statement: European Association of Echocardiography (EAE) (a registered branch of the ESC). *Eur J Echocardiogr*. 2008;9:415–437. doi: 10.1093/ejehocard/jen175.
13. Hesse B, Tägil K, Cuocolo A, Anagnostopoulos C, Bardiés M, Bax J, Bengel F, Busemann Sokole E, Davies G, Dondi M, Edenbrandt L, Franken P, Kjaer A, Knuuti J, Lassmann M, Ljungberg M, Marcassa C, Marie PY, McKiddie F, O'Connor M, Prvulovich E, Underwood R, van Eck-Smit B; EANM/ESC Group. EANM/ESC procedural guidelines for myocardial perfusion imaging in nuclear cardiology. *Eur J Nucl Med Mol Imaging*. 2005;32:855–897. doi: 10.1007/s00259-005-1779-y.
14. Wahl A, Paetsch I, Gollersch A, Roethemeyer S, Foell D, Gebker R, Langreck H, Klein C, Fleck E, Nagel E. Safety and feasibility of high-dose dobutamine-atropine stress cardiovascular magnetic resonance for diagnosis of myocardial ischaemia: experience in 1000 consecutive cases. *Eur Heart J*. 2004;25:1230–1236. doi: 10.1016/j.ehj.2003.11.018.
15. Bluemke DA, Achenbach S, Budoff M, Gerber TC, Gersh B, Hillis LD, Hundley WG, Manning WJ, Printz BF, Stuber M, Woodard PK. Noninvasive coronary artery imaging: magnetic resonance angiography and multidetector computed tomography angiography: a scientific statement from the american heart association committee on cardiovascular imaging and intervention of the council on cardiovascular radiology and intervention, and the councils on clinical cardiology and cardiovascular disease in the young. *Circulation*. 2008;118:586–606. doi: 10.1161/CIRCULATIONAHA.108.189695.
16. Fawcett T. An introduction to ROC analysis. Pattern recognition letters. 2006;27:861–874.
17. Begg CB, Greenes RA. Assessment of diagnostic tests when disease verification is subject to selection bias. *Biometrics*. 1983;39:207–215.
18. Pepe MS. *The Statistical Evaluation of Medical Tests for Classification and Prediction*. New York, NY: Oxford University Press. 2004;168–173.
19. Gimelli A, Rossi G, Landi P, Marzullo P, Iervasi G, L'abbate A, Rovai D. Stress/rest myocardial perfusion abnormalities by gated SPECT: still the best predictor of cardiac events in stable ischemic heart disease. *J Nucl Med*. 2009;50:546–553. doi: 10.2967/jnumed.108.055954.
20. Sicari R. Risk stratification by stress echocardiography beyond wall motion analysis. *JACC Cardiovasc Imaging*. 2009;2:260–262. doi: 10.1016/j.jcmg.2008.12.007.
21. Skinner JS, Smeeth L, Kendall JM, Adams PC, Timmis A; Chest Pain Guideline Development Group. NICE guidance. Chest pain of recent onset: assessment and diagnosis of recent onset chest pain or discomfort of suspected cardiac origin. *Heart*. 2010;96:974–978. doi: 10.1136/hrt.2009.190066.
22. Chinnaiyan KM, Raff GL, Goraya T, Ananthasubramaniam K, Gallagher MJ, Abidov A, Boura JA, Share D, Peyser PA. Coronary computed tomography angiography after stress testing: results from a multicenter, state-wide registry, ACIC (Advanced Cardiovascular Imaging Consortium). *J Am Coll Cardiol*. 2012;59:688–695. doi: 10.1016/j.jacc.2011.10.886.
23. Miller JM, Rochitte CE, Dewey M, Arbab-Zadeh A, Niinuma H, Gottlieb I, Paul N, Clouse ME, Shapiro EP, Hoe J, Lardo AC, Bush DE, de Roos A, Cox C, Brinker J, Lima JA. Diagnostic performance of coronary angiography by 64-row CT. *N Engl J Med*. 2008;359:2324–2336. doi: 10.1056/NEJMoa0806576.
24. Arbab-Zadeh A, Miller JM, Rochitte CE, Dewey M, Niinuma H, Gottlieb I, Paul N, Clouse ME, Shapiro EP, Hoe J, Lardo AC, Bush DE, de Roos A, Cox C, Brinker J, Lima JA. Diagnostic accuracy of computed tomography coronary angiography according to pre-test probability of coronary artery disease and severity of coronary arterial calcification. The CORE-64 (Coronary Artery Evaluation Using 64-Row Multidetector Computed Tomography Angiography) International Multicenter Study. *J Am Coll Cardiol*. 2012;59:379–387. doi: 10.1016/j.jacc.2011.06.079.
25. Budoff MJ, Dowe D, Jollis JG, Gitter M, Sutherland J, Halamert E, Scherer M, Bellinger R, Martin A, Benton R, Delago A, Min JK. Diagnostic performance of 64-multidetector row coronary computed tomographic angiography for evaluation of coronary artery stenosis in individuals without known coronary artery disease: results from the prospective multicenter ACCURACY (Assessment by Coronary Computed Tomographic Angiography of Individuals Undergoing Invasive Coronary Angiography) trial. *J Am Coll Cardiol*. 2008;52:1724–1732. doi: 10.1016/j.jacc.2008.07.031.
26. Parker MW, Iskandar A, Limone B, Perugini A, Kim H, Jones C, Calamari B, Coleman CI, Heller GV. Diagnostic accuracy of cardiac positron emission tomography versus single photon emission computed tomography for coronary artery disease: a bivariate meta-analysis. *Circ Cardiovasc Imaging*. 2012;5:700–707. doi: 10.1161/CIRCIMAGING.112.978270.
27. Nandalur KR, Dwamena BA, Choudhri AF, Nandalur MR, Carlos RC. Diagnostic performance of stress cardiac magnetic resonance imaging in the detection of coronary artery disease: a meta-analysis. *J Am Coll Cardiol*. 2007;50:1343–1353. doi: 10.1016/j.jacc.2007.06.030.
28. Sicari R, Cortigiani L, Bigi R, Landi P, Raciti M, Picano E; Echo-Persantine International Cooperative (EPIC) Study Group; Echo-Dobutamine International Cooperative (EDIC) Study Group. Prognostic value of pharmacological stress echocardiography is affected by concomitant anti-ischemic therapy at the time of testing. *Circulation*. 2004;109:2428–2431. doi: 10.1161/01.CIR.0000127427.03361.5E.
29. Rigo F, Richieri M, Pasanisi E, Cutaia V, Zanella C, Della Valentina P, Di Pede F, Raviolo A, Picano E. Usefulness of coronary flow reserve over regional wall motion when added to dual-imaging dipyridamole echocardiography. *Am J Cardiol*. 2003;91:269–273.
30. Hamon M, Fau G, Née G, Ehtisham J, Morello R, Hamon M. Meta-analysis of the diagnostic performance of stress perfusion cardiovascular magnetic resonance for detection of coronary artery disease. *J Cardiovasc Magn Reson*. 2010;12:29. doi: 10.1186/1532-429X-12-29.
31. Fiechter M, Ghadri JR, Gebhard C, Fuchs TA, Pazhenkottil AP, Nkoulou RN, Herzog BA, Wyss CA, Gaemperli O, Kaufmann PA. Diagnostic value of 13N-ammonia myocardial perfusion PET: added value of myocardial flow reserve. *J Nucl Med*. 2012;53:1230–1234. doi: 10.2967/jnumed.111.101840.
32. Morton G, Chiribiri A, Ishida M, Hussain ST, Schuster A, Indermuehle A, Perera D, Knuuti J, Baker S, Hedström E, Schleyer P, O'Doherty M, Barrington S, Nagel E. Quantification of absolute myocardial perfusion in patients with coronary artery disease: comparison between cardiovascular magnetic resonance and positron emission tomography. *J Am Coll Cardiol*. 2012;60:1546–1555. doi: 10.1016/j.jacc.2012.05.052.

33. Kajander SA, Joutsiniemi E, Saraste M, Pietilä M, Ukkonen H, Saraste A, Sipilä HT, Teräs M, Mäki M, Airaksinen J, Hartiala J, Knuuti J. Clinical value of absolute quantification of myocardial perfusion with (15)O-water in coronary artery disease. *Circ Cardiovasc Imaging*. 2011;4:678–684. doi: 10.1161/CIRCIMAGING.110.960732.
34. Picano E, Vañó E, Rehani MM, Cuocolo A, Mont L, Bodi V, Bar O, Maccia C, Pierard L, Sicari R, Plein S, Mahrholdt H, Lancellotti P, Knuuti J, Heidbuchel H, Di Mario C, Badano LP. The appropriate and justified use of medical radiation in cardiovascular imaging: a position document of the ESC Associations of Cardiovascular Imaging, Percutaneous Cardiovascular Interventions and Electrophysiology. *Eur Heart J*. 2014;35:665–672. doi: 10.1093/eurheartj/ehz394.
35. De Bruyne B, Pijls NH, Kalesan B, Barbato E, Tonino PA, Piroth Z, Jagic N, Möbius-Winkler S, Möbius-Winkler S, Rioufol G, Witt N, Kala P, MacCarthy P, Engström T, Oldroyd KG, Mavromatis K, Manoharan G, Verlee P, Frobert O, Curzen N, Johnson JB, Jüni P, Fearon WF; FAME 2 Trial Investigators. Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. *N Engl J Med*. 2012;367:991–1001. doi: 10.1056/NEJMoa1205361.

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.

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

Danilo Neglia, Daniele Rovai, Chiara Caselli, Mikko Pietila, Anna Teresinska, Santiago Aguadé-Bruix, Maria Nazarena Pizzi, Giancarlo Todiere, Alessia Gimelli, Stephen Schroeder, Tanja Drosch, Rosa Poddighe, Giancarlo Casolo, Constantinos Anagnostopoulos, Francesca Pugliese, Francois Rouzet, Dominique Le Guludec, Francesco Cappelli, Serafina Valente, Gian Franco Gensini, Camilla Zawaideh, Selene Capitanio, Gianmario Sambuceti, Fabio Marsico, Pasquale Perrone Filardi, Covadonga Fernández-Golfín, Luis M Rincón, Frank P Graner, Michiel A. de Graaf, Michael Fiechter, Julia Stehli, Oliver Gaemperli, Eliana Reyes, Sandy Nkomo, Maija Mäki, Valentina Lorenzoni, Giuseppe Turchetti, Clara Carpeggiani, Martina Marinelli, Stefano Puzzuoli, Maurizio Mangione, Paolo Marcheschi, Fabio Mariani, Daniela Giannessi, Stephan Nekolla, Massimo Lombardi, Rosa Sicari, Arthur J.H.A. Scholte, José L. Zamorano, Philipp A. Kaufmann, S. Richard Underwood and Juhani Knuuti
The EVINCI Study Investigators

Circ Cardiovasc Imaging. 2015;8:

doi: 10.1161/CIRCIMAGING.114.002179

Circulation: Cardiovascular Imaging is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Copyright © 2015 American Heart Association, Inc. All rights reserved.

Print ISSN: 1941-9651. Online ISSN: 1942-0080

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://circimaging.ahajournals.org/content/8/3/e002179>

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Circulation: Cardiovascular Imaging* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the [Permissions and Rights Question and Answer](#) document.

Reprints: Information about reprints can be found online at:
<http://www.lww.com/reprints>

Subscriptions: Information about subscribing to *Circulation: Cardiovascular Imaging* is online at:
<http://circimaging.ahajournals.org/subscriptions/>

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Circulation: Cardiovascular Imaging* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the [Permissions and Rights Question and Answer](#) document.

Reprints: Information about reprints can be found online at:
<http://www.lww.com/reprints>

Subscriptions: Information about subscribing to *Circulation: Cardiovascular Imaging* is online at:
<http://circimaging.ahajournals.org/subscriptions/>

SUPPLEMENTAL MATERIAL

Supplement to: Neglia D, et al. Detection of Obstructive Coronary Artery Disease by Non-Invasive Anatomical and Functional Imaging

Supplemental Methods

Study inclusion and exclusion criteria	page 2
List of the Study Centres	page 4
Number of patients enrolled per center	page 5

Supplemental Tables

Supplemental Table 1	page 6
Supplemental Table 2	page 7
Supplemental Table 3	page 8
Supplemental Table 4	page 9
Supplemental Table 5	page 12

SUPPLEMENTAL METHODS

Study inclusion and exclusion criteria

Inclusion criteria

- Stable angina-like chest pain (typical, atypical or non-anginal)
- Dyspnea and fatigue on effort suspected as anginal equivalent

Exclusion criteria

- Age < 30 or > 75 years
- Low ($\leq 20\%$) or high ($\geq 90\%$) probability of coronary artery disease
- Pregnancy (suspected or ascertained)
- Acute coronary syndrome, defined by at least one of the following criteria:
 - Prolonged (> 20 minutes) chest pain
 - De novo or accelerated angina
 - Recent ST-T segment or T wave changes of ischemic nature
 - Elevated serum cardiac markers of necrosis
 - Hemodynamic or electrical instability
 - Acute myocardial infarction with or without ST segment elevation

- Known diagnosis of coronary artery disease, including
 - Previously known myocardial infarction
 - Previous percutaneous coronary interventions
 - Previous coronary artery bypass graft surgery
- Left ventricular dysfunction (ejection fraction < 35% by echocardiography or other method)
- Persistent/permanent atrial fibrillation or advanced atrioventricular block
- Asthma or chronic treatment with aminophilline
- Recent (< 6 months) cerebral ischemic attack
- Active cancer
- Severe hypertension
- Cardiomyopathy (e.g., dilated cardiomyopathy, hypertrophic cardiomyopathy, arrhythmogenic right ventricular dysplasia, amyloidosis)
- Inability to provide informed consent
- Congenital heart disease
- Known significant carotid stenosis or vascular aneurisms
- Significant (\geq moderate) valvular disease

List of the study centres (*Recruitment centers and Core Labs*):

- APHP, Groupe Hospitalier Bichat-Claude Bernard, Département Hospitalo-Universitaire FIRE and Université Paris Diderot, Paris, France
- Azienda Ospedaliero Universitaria Careggi, Firenze, Italy
- Centre for Advanced Cardiovascular Imaging, NIHR Cardiovascular Biomedical Research Unit at Barts, William Harvey Research Institute, Barts and The London School of Medicine, Queen Mary University of London, London, United Kingdom
- Fondazione Toscana G. Monasterio, Pisa, Italy
- Imperial College London, United Kingdom
- Institut Catala de la Salut, Barcelona, Spain
- Institute of Cardiology, Warsaw, Poland
- Institute of Clinical Physiology, National Research Council, Pisa, Italy
- Kliniken des Landkreises Göppingen, Göppingen, Germany
- Klinikum rechts der Isar der Technischen Universität München, München, Germany
- Leiden University Medical Center, Leiden, The Netherlands
- Ospedale della Versilia, Lido di Camaiore, Italy
- Università di Genova, Genoa, Italy
- Università di Napoli Federico II, Naples, Italy
- University Hospital Clinico San Carlos, Madrid, Spain
- University Hospital Zurich, Zurich, Switzerland

- University of Turku and Turku University Hospital, Turku, Finland

Number of patients enrolled (included in the analysis) per center

- University of Turku and Turku University Hospital, Turku, Finland: 96 (71) patients
- Institute of Cardiology, Warsaw, Poland: 44 (36) patients
- Institut Catala de la Salut, Barcelona, Spain: 50 (44) patients
- Fondazione Toscana G. Monasterio, Pisa, Italy: 118 (69) patients
- Kliniken des Landkreises Göppingen, Göppingen, Germany: 44 (35) patients
- Ospedale della Versilia, Lido di Camaiore, Italy: 35 (25) patients
- Centre for Advanced Cardiovascular Imaging, NIHR Cardiovascular Biomedical Research Unit at Barts, William Harvey Research Institute, Barts and The London School of Medicine, Queen Mary University of London, London, United Kingdom: 45 (27) patients
- APHP, Groupe Hospitalier Bichat-Claude Bernard, Département Hospitalo-Universitaire FIRE and Université Paris Diderot, Paris, France: 43 (28) patients
- Azienda Ospedaliero Universitaria Careggi, Firenze, Italy: 20 (17) patients
- Università di Genova, Genoa, Italy: 33 (18) patients
- Università di Napoli Federico II, Naples, Italy: 69 (21) patients
- University Hospital Clinico San Carlos, Madrid, Spain: 20 (17) patients
- Klinikum rechts der Isar der Technischen Universität München, München, Germany: 4 (0) patients
- University Hospital Zurich, Zurich, Switzerland: 76 (67) patients

SUPPLEMENTAL TABLES

Supplemental Table 1. Diagnostic accuracy of imaging techniques for the detection of significant coronary stenoses at ICA using local analysis and selecting the patients with an intermediate probability of CAD calculated according to a recently updated prediction model (Genders TS et al. Eur Heart J. 2011, Ref. 5)

Measure of Accuracy	Imaging Techniques						
	<i>CCTA</i> (<i>N</i> = 449)	<i>MPI</i> (<i>N</i> = 367)	<i>WMI</i> (<i>N</i> = 326)	<i>SPECT</i> (<i>N</i> = 282)	<i>PET</i> (<i>N</i> = 85)	<i>ECHO</i> (<i>N</i> = 247)	<i>CMR</i> (<i>N</i> = 79)
Positivity by test - no	150	155	66	131	24	48	18
Positivity by ICA - no	137	118	95	99	19	67	28
AUC (95% CI)	0.91 (0.88-0.94)	0.74** (0.69-0.79)	0.70** (0.65-0.75)	0.70 (0.65-0.76)	0.86 (0.76-0.94)	0.67 (0.61-0.74)	0.77 (0.67-0.86)
False positive - no	26	67	20	59	8	18	2
False negative - no	13	30	49	27	3	37	12
Sensitivity, % (95% CI)	91 (85-95)	75*# (67-82)	48** (39-59)	73 (64-81)	84 (68-1)	45 (33-57)	57 (39-75)
Specificity, % (95% CI)	92 (88-95)	73**# (67-78)	91 (87-95)	68 (61-74)	88 (80-95)	90 (86-94)	96 (90-100)
PPV, % (95% CI)	83 (76-88)	57 (49-65)	70 (57-80)	55 (46-64)	67 (45-84)	63 (47-76)	89 (65-99)
NPV, % (95% CI)	96 (93-98)	86 (80-90)	81 (76-86)	82 (75-88)	95 (86-99)	81 (75-87)	80 (68-89)

CCTA = computed coronary tomography angiography; CI = confidence interval; CMR = cardiac magnetic resonance; MPI = myocardial perfusion imaging; PET = positron emission tomography; SPECT = single photon computed emission tomography; WMI = wall motion imaging. **P<0.001, *P=0.001 MPI or WMI vs CCTA; #P<0.001 MPI vs WMI

Supplemental Table 2. Diagnostic accuracy of imaging techniques for the detection of significant coronary stenoses at ICA using local analysis and selecting the patients by gender, age, probability of CAD by D&F, or symptoms.

Subgroups	N	CAD prevalence, %	Imaging Techniques	AUC (95% CI)	Sensitivity, % (95% CI)	Specificity, % (95% CI)	PPV, % (95% CI)	NPV, % (95% CI)
Male gender	291	37	CCTA	0.92 (0.88-0.95)	92 (86-96)	92 (87-96)	87	95
			MPI	0.77 (0.71-0.82)	79 (70-86)	75 (67-81)	66	85
			WMI	0.69 (0.62-0.75)	49 (37-59)	89 (83-94)	73	74
Female gender	184	17	CCTA	0.90 (0.83-0.95)	87 (74-97)	92 (88-96)	69	97
			MPI	0.66 (0.56-0.76)	61 (43-79)	71 (63-79)	33	89
			WMI	0.71 (0.60-0.82)	48 (29-67)	95 (91-98)	59	92
> 65 years	159	37	CCTA	0.90 (0.85-0.95)	92 (83-98)	89 (83-95)	83	95
			MPI	0.74 (0.66-0.82)	72 (58-83)	77 (67-85)	66	81
			WMI	0.71 (0.63-0.79)	53 (38-67)	89 (81-96)	75	75
Probability of CAD >50%	324	34	CCTA	0.92 (0.89-0.95)	92 (86-96)	93 (89-96)	87	96
			MPI	0.73 (0.67-0.78)	75 (66-83)	71 (64-77)	59	84
			WMI	0.72 (0.66-0.78)	51 (39-62)	93 (89-97)	78	80
Typical angina	121	30	CCTA	0.90 (0.84-0.96)	89 (78-97)	92 (86-96)	82	95
			MPI	0.75 (0.66-0.84)	80 (67-93)	70 (57-81)	60	86
			WMI	0.82 (0.72-0.91)	70 (52-85)	93 (86-99)	79	90

Supplemental Table 3. Diagnostic accuracy of imaging techniques for the detection of coronary stenoses > 50% at ICA using local analysis

Measure of Accuracy	Imaging Techniques						
	<i>CCTA</i> (<i>N</i> = 475)	<i>MPI</i> (<i>N</i> = 389)	<i>WMI</i> (<i>N</i> = 346)	<i>SPECT</i> (<i>N</i> = 293)	<i>PET</i> (<i>N</i> = 96)	<i>ECHO</i> (<i>N</i> = 261)	<i>CMR</i> (<i>N</i> = 85)
Positivity by test - no	154	162	68	137	25	50	18
Positivity by ICA - no	144	126	102	103	23	73	29
AUC (95% CI)	0.93 (0.90-0.95)	0.74** (0.70-0.79)	0.69** (0.64-0.75)	0.71 (0.65-0.76)	0.84 (0.75-0.93)	0.67 (0.61-0.73)	0.76 (0.66-0.85)
False positive - no	21	68	20	61	7	18	2
False negative - no	11	32	54	27	5	41	13
Sensitivity, % (95% CI)	92 (88-97)	75**# (67-82)	47** (37-57)	74 (65-82)	78 (61-96)	44 (33-55)	55 (38-72)
Specificity, % (95% CI)	94 (89-95)	74**# (68-78)	92 (88-95)	68 (61-74)	90 (84-96)	90 (86-94)	96 (91-100)
PPV, % (95% CI)	86 (80-91)	58 (50-66)	71 (58-81)	56 (47-64)	72 (51-88)	64 (49-77)	89 (65-99)
NPV, % (95% CI)	97 (94-98)	86 (81-90)	81 (75-85)	83 (76-88)	93 (84-98)	81 (75-86)	81 (69-89)

CCTA = computed coronary tomography angiography; CI = confidence interval; CMR = cardiac magnetic resonance; MPI = myocardial perfusion imaging; PET = positron emission tomography; SPECT = single photon computed emission tomography; WMI = wall motion imaging. **P<0.001 MPI or WMI vs CCTA; #P<0.001 MPI vs WMI

Supplemental Table 4. Baseline clinical and angiographic characteristics of patients included in the centers or core lab analyses

	Center patients (N=475)	Corelab patients (N=350)
Demographics		
Age—years	60±9	60±9
Male sex—no. (%)	291 (61)	209(60)
Cardiovascular risk factors		
Family history of premature CAD—no. (%)	160 (34)	115(33)
Diabetes mellitus—no. (%)	115 (24)	78(22)
Hypertension—no. (%)	290 (61)	208(59)
Hypercholesterolemia—no. (%)	267 (56)	194(55)
Obesity—no. (%)	112 (24)	277(79)
Smoking within the last year—no. (%)	120 (25)	88(25)
Symptoms		
Typical angina—no. (%)	121 (25)	87(25)
Atypical angina—no. (%)	288 (61)	213(61)
Non-anginal chest pain—no. (%)	66 (14)	50(14)
Electrocardiogram		

Normal —no. (%)	372(78)	268(80)
Left bundle branch block—no. (%)	12 (3)	4(1)
Left ventricular hypertrophy—no. (%)	5 (1)	4(1)
Other abnormalities—no. (%)	86 (18)	61(17)
Left ventricular ejection fraction 36-50%		
≥ 50%—no. (%)	451 (95)	334(95)
35-50%—no. (%)	24 (5)	16(5)
Exercise stress test		
Bicycle—no. (%)	267 (56)	204(58)
Treadmill—no. (%)	114 (24)	90(26)
Not done—no. (%)	94 (20)	56(16)
≥ 0.15 mV ST depression —no. (%)	71 (19)	57(19)
Probability of CAD by D & F [interquartile range]	65 [33-75]	65[38-78]
Total Coronary Calcium Score		
0—no. (%)	123 (26)	99(28)
1-99—no. (%)	107 (22)	85(24)
100-399—no. (%)	85 (18)	62(18)
≥ 400—no. (%)	83 (18)	67(19)

Not done—no. (%)	77(16)	37(11)
Invasive coronary angiography		
Not done—no. (%)	168 (35)	97(28)
Normal vessels—no. (%)	112 (24)	88(25)
Non-obstructive CAD—no. (%)	55 (12)	52(15)
One vessel disease—no. (%)	99 (21)	75(21)
Two vessel disease—no. (%)	25 (5)	22(6)
Three vessel disease—no. (%)	10 (2)	7(2)
Left main stem—no. (%)	6 (1)	4(1)

Supplemental Table 5. Diagnostic accuracy of imaging techniques for the detection of significant coronary stenoses at ICA using local analysis and including all the 511 patients of whom imaging data are available despite some protocol violations.

Measure of Accuracy	Imaging Techniques						
	<i>CCTA</i> (<i>N</i> = 511)	<i>MPI</i> (<i>N</i> = 428)	<i>WMI</i> (<i>N</i> = 388)	<i>SPECT</i> (<i>N</i> = 323)	<i>PET</i> (<i>N</i> = 105)	<i>ECHO</i> (<i>N</i> = 287)	<i>CMR</i> (<i>N</i> = 101)
Positivity by test - no	163	192	78	162	30	57	21
Positivity by ICA - no	147	130	109	109	21	77	32
AUC (95% CI)	0.92 (0.89-0.94)	0.72** (0.67-0.76)	0.70** (0.65-0.75)	0.68 (0.63-0.73)	0.83 (0.73-0.91)	0.67 (0.62-0.73)	0.76 (0.67-0.85)
False positive - no	29	94	25	81	13	22	3
False negative - no	13	32	56	28	4	42	14
Sensitivity, % (95% CI)	91 (86-95)	75*# (67-82)	49** (39-58)	74 (66-83)	81 (62-95)	45 (35-57)	56 (38-72)
Specificity, % (95% CI)	92 (89-95)	68**# (63-74)	91 (87-94)	62 (56-69)	85 (76-92)	90 (85-93)	96 (90-100)
PPV, % (95% CI)	82 (75-88)	51 (44-58)	68 (56-78)	50 (42-58)	57 (37-75)	61 (48-74)	86 (64-97)
NPV, % (95% CI)	96 (94-98)	86 (81-91)	82 (77-86)	83 (76-88)	95 (87-99)	82 (76-87)	83 (72-90)

CCTA = computed coronary tomography angiography; CI = confidence interval; CMR = cardiac magnetic resonance; MPI = myocardial perfusion imaging; PET = positron emission tomography; SPECT = single photon computed emission tomography; WMI = wall motion imaging. **P<0.001, *P=0.001 MPI or WMI vs CCTA; #P<0.001 MPI vs WMI