Supplementary Online Content

Danad I, Raijmakers PG, Driessen RS, et al. Comparison of coronary CT angiography, SPECT, PET, and hybrid imaging for diagnosis of ischemic heart disease determined by fractional flow reserve. *JAMA Cardiol.* Published online August 16, 2017. doi:10.1001/jamacardio.2017.2471

This supplementary material has been provided by the authors to give readers additional information about their work.

eAppendix. Methods

Imaging protocols

Cardiac CT

Patients underwent coronary artery calcium (CAC) scoring and coronary angiography on a 256-slice CT scanner (Philips Brilliance iCT, Philips Healthcare, Best, the Netherlands) with a collimation 128 x 0.625 mm and a tube rotation time of 270 ms. A tube current between 200 and 360 mAs at 120 kV, adjusting primarily the mAs based on body habitus. Prospective ECG-gating (Step & Shoot Cardiac, Philips Healthcare, Best, The Netherlands) at 75% of the R-R interval was performed in order to minimize radiation burden. CAC scoring was obtained during a single breath hold and coronary calcification was defined as a plaque with an area of 1.03 mm^2 and a density ≥ 130 Hounsfield units. The CAC score was calculated according to the method described by Agatston (1). For visualization of the coronary artery lumen a bolus of 100 mL iobitidol (Xenetix 350) was injected intravenously (5,7 $mL \cdot s^{-1}$) followed immediately by a 50 mL saline chaser. The scan was triggered using an automatic bolus tracking technique, with a region of interest placed in the descending thoracic aorta and a threshold of 150 HU. Metoprolol 50 to 150 mg was administered orally for patients with a prescan HR ≥ 65 beats per minute (bpm) one hour before the start of the CT protocol. If necessary, 5 to 25 mg metoprolol was given intravenously during the scan to achieve a heart rate < 65 bpm. Each patient received 800 mcg of sublingual nitroglycerine immediately before CCTA.

$[^{15}O]H_2O$ Positron Emission Tomography

Patients were instructed to refrain from intake of products containing caffeine or xanthine 24 hours prior to the scan. Patients fasted for at least 4 hours before the imaging protocol. All patients were scanned on a hybrid PET/CT device (Philips Gemini TF 64, Philips Healthcare, Best, The Netherlands) using 370 MBq of $[^{15}O]H_2O$ as a perfusion tracer during resting conditions as well as vasodilator stress using intravenous infusion of adenosine (140 $\mu g \cdot kg^{-1} \cdot min^{-1}$). The cardiac $[^{15}O]H_2O$ PET protocol, image acquisition and quantification of myocardial blood flow (MBF) has been described in detail previously (2). We employed a quantitative approach to PET evaluation, without visual grading of the images. Prior studies support this approach, having demonstrated that quantitative PET MPI with $[^{15}O]H_2O$ outperforms visual PET diagnostically (3).

Single Photon Emission Computed Tomography / low dose CT

All patients underwent a 2-day stress-rest ^{99m}Tc-tetrofosmin protocol. A weight-adjusted dose of 370 to 550 MBq ^{99m}Tc-tetrofosmin was injected just after the PET stress image acquisition during continued infusion of adenosine (140 µg · kg^{-1} · min^{-1}). Adenosine infusion was terminated 3 minutes after the injection of ^{99m}Tc-tetrofosmin. After a delay of 60 min, ECG-gated stress SPECT images were acquired. Rest SPECT imaging was subsequently performed on the same day as ICA (Figure 1). Images were acquired on a dual-head hybrid SPECT/CT scanner (Symbia T2, Siemens Medical Solutions, Erlangen, Germany). Emission data was acquired with a parallel-hole, low energy, high-resolution collimator with a 20% symmetric window centred at 140 keV, whereby the two detector heads were positioned at a 90˚ angle. The camera heads performed a 180˚ rotation with in total 64 rotation steps of 40 seconds per rotational projection. ECG-gating was performed with an electrocardiogram R-wave detector with acquisition of 8 emission frames per cardiac cycle. Images were both reconstructed as static and gated perfusion images. The characteristics of the two-slice CT component, which is embedded in the Symbia system, were as follows: slice width 5.0 mm; pitch 1.5; 130 kV, 17 mA; rotation time 0.8 seconds. The SPECT acquisition was followed immediately by a low-dose CT scan during normal breathing and without ECG-gating to correct for attenuation using 130 keV, 20 mAs, and computed tomography dose index (CTDI) of 2.2, and dose length product (DLP) of 40. The CT images were reconstructed with a 128 x 128 matrix at a slice thickness of 5 mm.

Invasive Coronary Angiography and Fractional Flow Reserve

ICA imaging was performed in at least two orthogonal directions per evaluated coronary artery segment. Prior to contrast injection, 0.2 mL of nitroglycerin was administered intracoronary to induce epicardial coronary vasodilation. The coronary tree was divided into a 16-segment coronary artery model modified from the American Heart Association. All major coronary arteries were routinely interrogated by FFR except for occluded or subtotal lesions ≥ 90%. The operator refrained from FFR measurements in these tight lesions due to the potential risk of inflicting a coronary dissection by the pressure wire. The FFR was measured using a 0.014-inch sensor tipped guide wire (Volcano Corporation, Rancho Cordova, CA, USA), which was introduced through a 5- or 6-F guiding catheter, calibrated and advanced into the coronary artery. Furthermore, intracoronary (150 µg) or intravenous (140 µg · kg^{-1} · min^{-1}) adenosine infusion was used to induce maximal coronary hyperemia. The FFR was calculated as the ratio of the mean distal intracoronary pressure, measured by the pressure wire, to the mean arterial pressure (MAP) measured by the coronary catheter. The primary endpoint was defined as a FFR ≤ 0.80 in

at least one major coronary artery. In case of a missing FFR value, the endpoint was deemed positive in the presence of subtotal lesion ≥ 90%, and negative when diameter stenosis was ≤ 30% (obtained with QCA). All images and FFR signals were interpreted by two experienced interventional cardiologists (N.v.R. and P.K.) blinded to the noninvasive cardiac imaging results.

Outcome and safety

Follow-up data were collected at one year after the ICA from contact with the patients' physicians, medical record and telephone interviews using a standardized questionnaire. Outcome end points included a composite of major adverse cardiovascular events (MACEs: cardiovascular death, myocardial infarction, unplanned coronary revascularization and hospital admission for cardiovascular cause) within 12 months. Revascularization procedures related as a clinical consequence of the initial ICA were not considered as MACE. Complications directly related to study investigations resulting in prolonged hospital stay or specific treatment were prespecified as safety end points.

Power analysis

Assuming a sensitivity of PET of 90% and a non-inferiority margin of 10% a total number of 105 patients with hemodynamic significant stenosis yield 80% power to show non-inferiority of SPECT in case of the sensitivity of SPECT also being 90%. Power calculations are based on a one-sided non-inferiority test for correlated proportions and assuming a one-sided significance level of 5%. The total percentage of patients with discordant results is assumed to be 15% in this calculation. Similarly, 105 patients without hemodynamic significant stenosis are needed to test the same non-inferiority hypothesis for the specificity assuming specificity for PET of 90% (and a specificity of 90% for SPECT under the alternative hypothesis). Power for the test for sensitivity under these assumptions is still above 70% in case of sampling only 85 patients with hemodynamic significant CAD. The threshold of 10% was based on the meta-analysis of McArdle et al (4). Non-inferiority test of Tango (5) was used to separately test the primary hypotheses of non-inferiority of SPECT as compared to PET in terms of sensitivity and specificity (one sided $p < 0.025$ was considered significant to account for both testing sensitivity and specificity).

RESULTS

Fractional flow reserve measurements

FFR was not performed in 58 (9.4%) coronary arteries, which were either completely (n = 24) or sub-totally (n = 34) occluded. Of the subtotal occlusions, 4 were severe LM stenoses (≥ 90%) in which FFR wire passage was not attempted. These 58 sub-total lesions were deemed hemodynamically significant. In 3 (0.49%) vessels, FFR could not be performed due to severe coronary artery tortuosity that precluded the passage of the pressure wire. None of these vessels displayed a ≥ 30% stenosis and were therefore considered as being absent for hemodynamically significant CAD.

Diagnostic accuracy of CCTA, SPECT and PET imaging for diagnosis of ischemia-causing CAD as indicated by FFR - vessel specific analyses -

On a per-vessel level, PET demonstrated higher sensitivity ($p = 0.03$) than CCTA. Sensitivity of SPECT was significantly lower compared to CCTA and PET, respectively (for both $p < 0.0001$). Of note, NPV of SPECT was significantly lower than CCTA ($p = 0.05$) and PET ($p < 0.01$). Compared with CCTA, PPV was significantly higher for SPECT and PET protocols (both $p < 0.001$). Yet, specificity was higher for SPECT when compared to CCTA ($p < 0.001$), but no difference in specificity was found between PET and CCTA ($p = 0.74$). Overall, no difference in accuracy was seen between SPECT and PET MPI on a per-vessel level ($p=0.33$), yet diagnostic accuracy of SPECT was higher compared to CCTA ($p = 0.02$) for detection of lesion-specific ischemia. There were no clear patterns that could be identified to account for the false positive or false negative findings for each of the imaging modalities (e.g. age, gender, body weight, affected coronary artery, heart rate etc.). The assessment of functional extent of CAD as identified by 1, 2 or 3-vessel disease according to FFR ≤ 0.80 has been shown in eTable 3. The agreement between noninvasive cardiac imaging and FFR in assessing the functional extent of CAD as defined by 1, 2 or 3-vessel disease was 48%, 27%, and 36% for CCTA, SPECT, and PET, respectively.

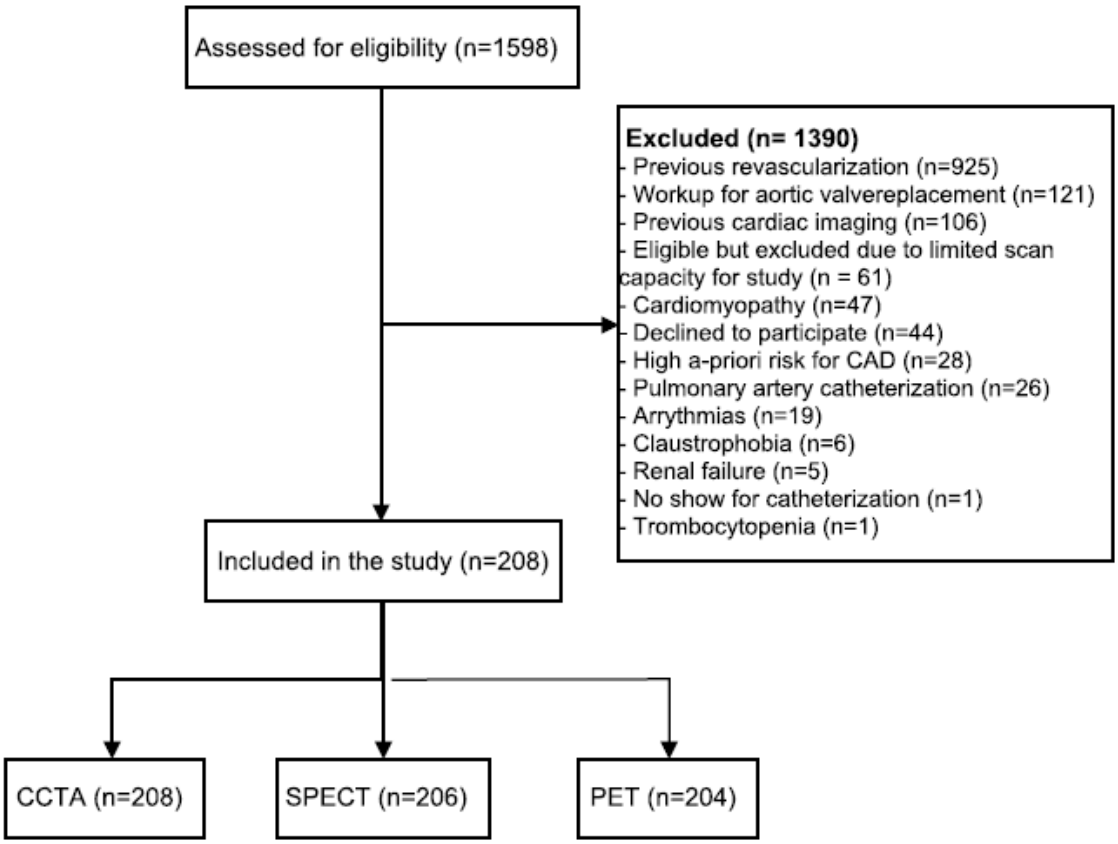
Diagnostic accuracy of hybrid cardiac imaging for diagnosis of ischemia-causing CAD as indicated by FFR - vessel specific analyses -

Similar results were observed for per-artery analyses **(**Table 2). Addition of SPECT or PET to CCTA improved specificity ($p = 0.02$ and $p < 0.001$, respectively). On the other hand, hybrid imaging comes at a cost of sensitivity. The sensitivity of CCTA was significantly lowered when

combined with SPECT ($p < 0.001$) or PET ($p = 0.006$) MPI. Compared to CCTA alone, hybrid imaging yielded a significantly lower NPV for both SPECT/CCTA ($p < 0.001$) and PET/CCTA ($p = 0.03$). Yet, hybrid imaging reduced the rate of false positive findings on CCTA as reflected by a significantly improved PPV for both SPECT/CCTA and PET/CCTA (both $p < 0.001$) when compared to CCTA alone.

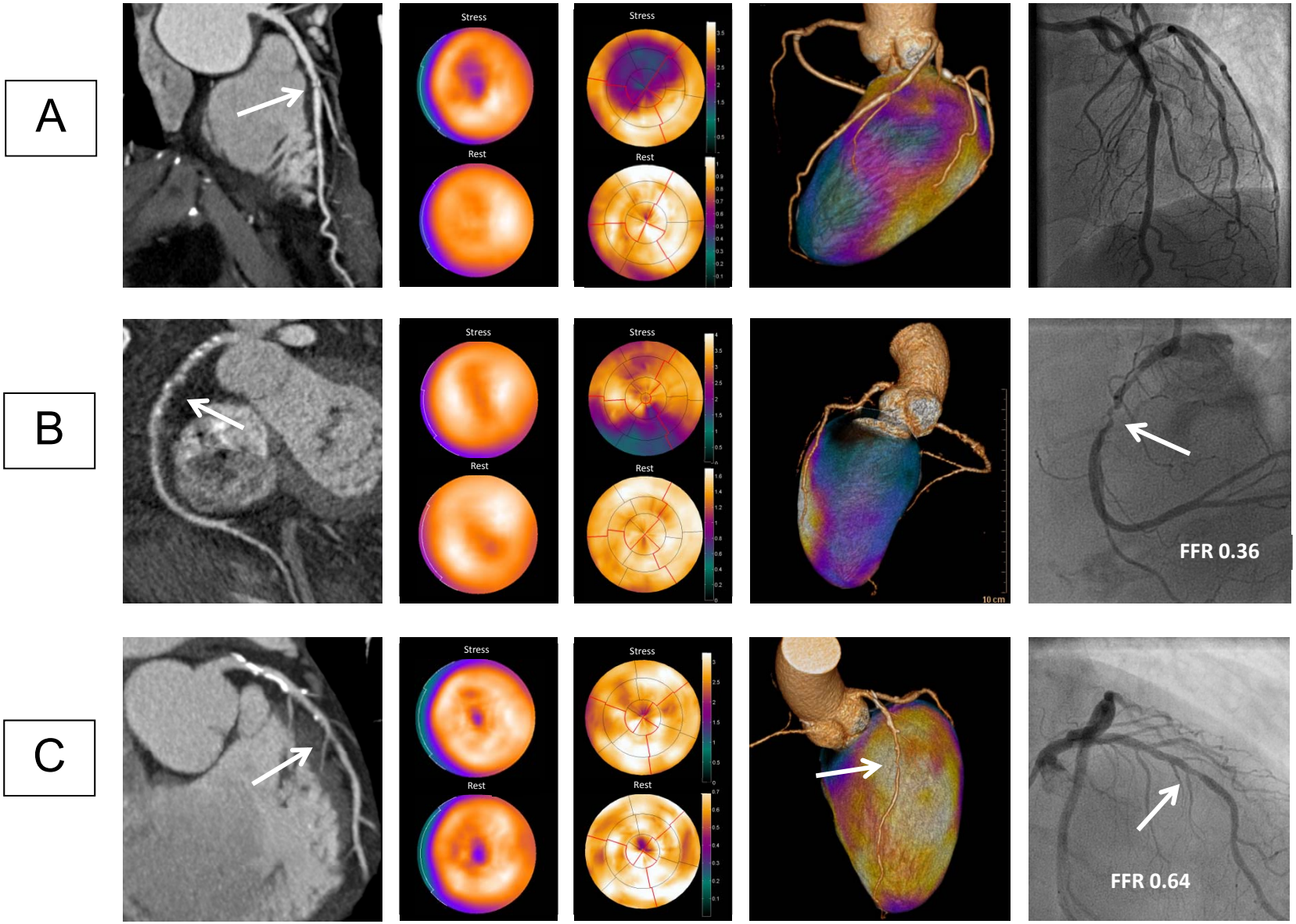
Outcome and safety

No study related complications occurred during the execution of the study protocol (including ICA). Out of 92 patients with obstructive CAD, 78 (85%) underwent an uncomplicated revascularization procedure (percutaneous coronary intervention in 46 and coronary artery bypass surgery in 32 patients). The remaining patients were treated with optimal medical therapy. During 12 months follow-up, one patient was admitted with an acute myocardial infarction and one patient underwent urgent percutaneous intervention due to refractory angina.



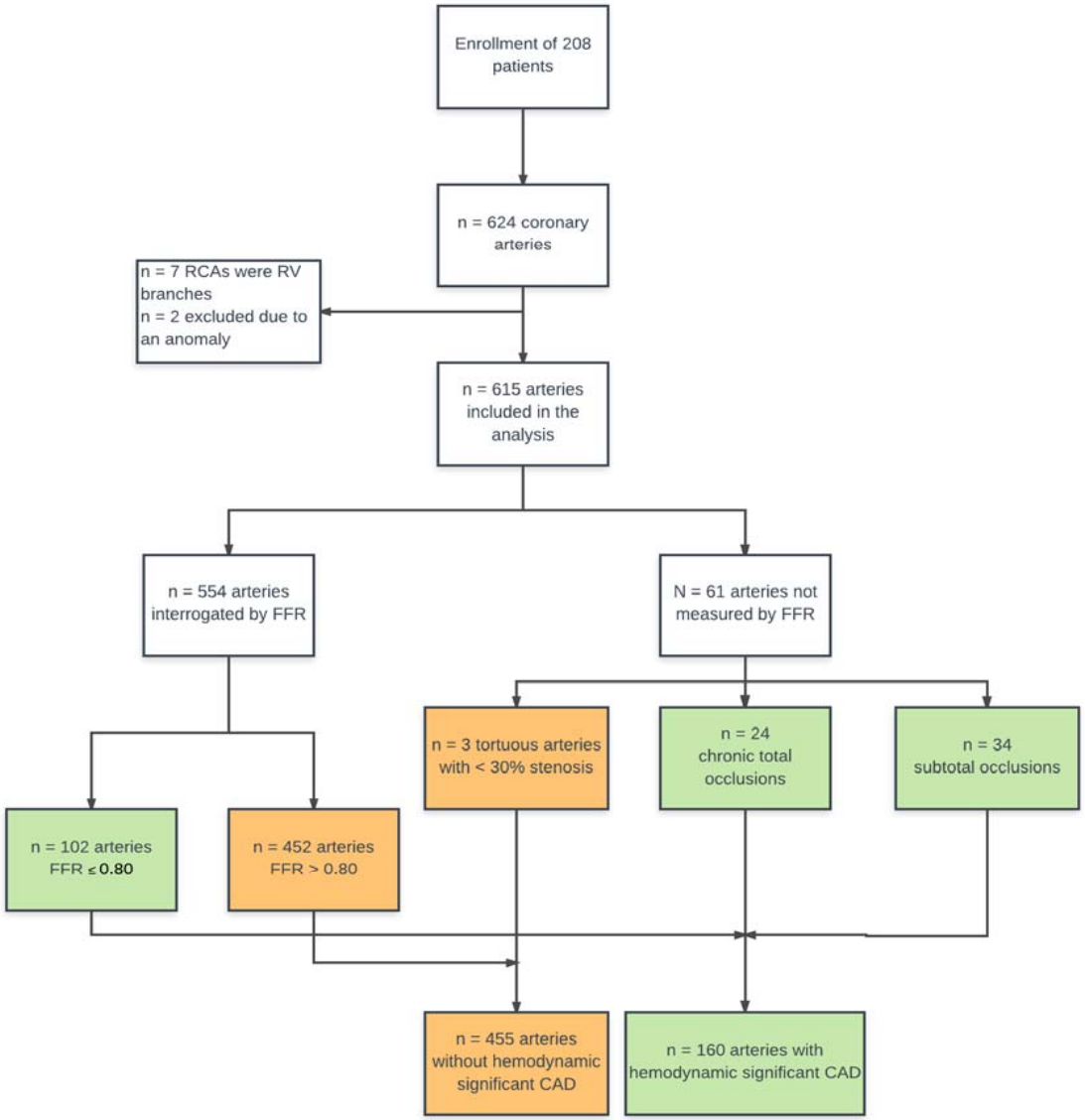
eFigure 1. Study Enrollment

CAD, coronary artery disease, CCTA, coronary computed tomography angiography; PET, positron emission tomography; SPECT, single-photon emission computed tomography.

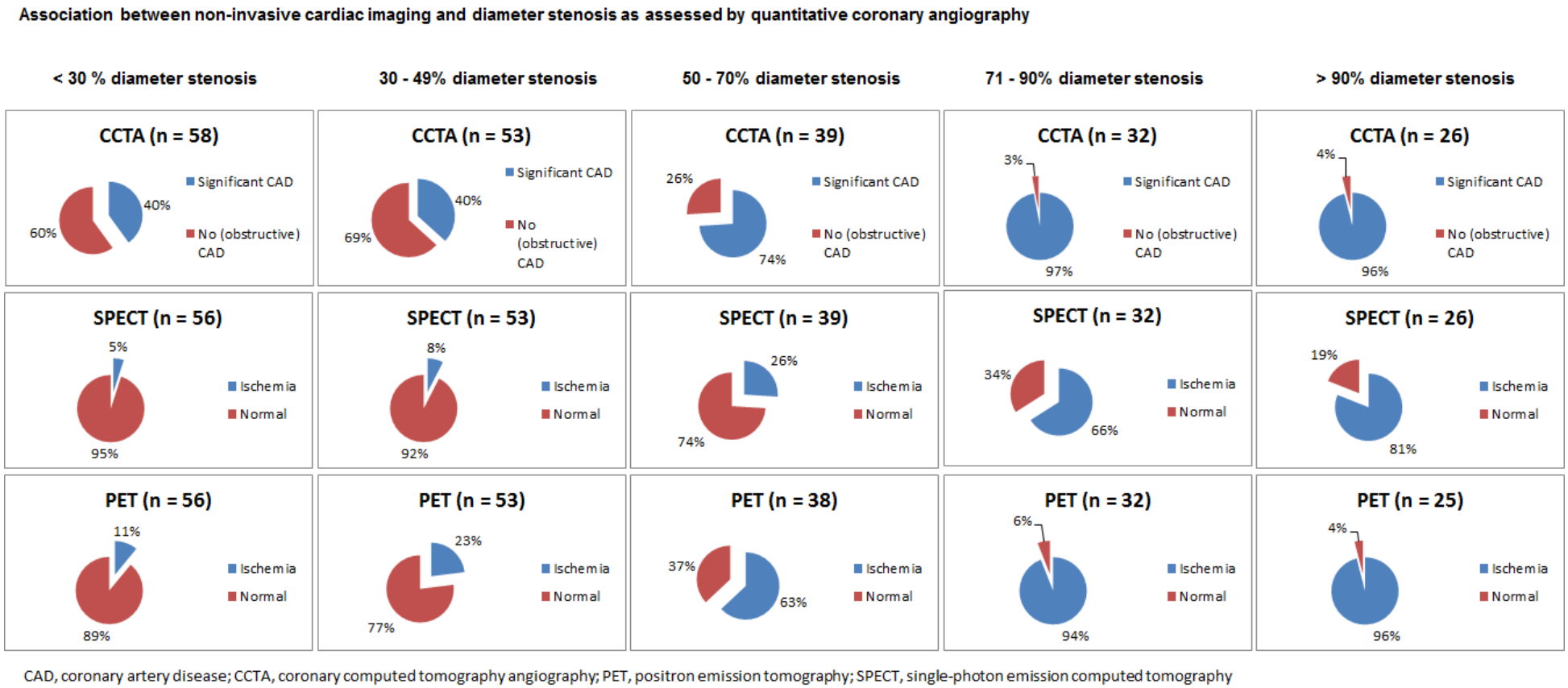


eFigure 2. Three Examples of CCTA, SPECT, PET, Hybrid PET/CCTA and Angiographic Findings

(A) CCTA shows a significant (≥ 50%) stenosis in the LAD artery (arrow shows stenosis), SPECT indicates reversible ischemia only in the anteroapical and apical segment. PET reveals ischemia in the whole anterior myocardial wall. Fused PET and CCTA images show severe ischemia in the area supplied by the LAD. ICA and FFR confirm the diagnosis of a hemodynamically severe LAD stenosis (FFR = 0.18). (B) CCTA shows a significantly mixed-plaque in the mid-RCA. SPECT reveals no abnormal perfusion, indicating non-ischemia causing CAD. Abnormal perfusion of the inferior wall was detected by PET suggesting myocardial ischemia. With a hybrid approach ischemia was seen in the vascular area subtended by the RCA. ICA and FFR confirmed the diagnosis of lesion-specific ischemia as reflected by a FFR of 0.36. (C) CCTA displayed a high-grade stenosis in the LAD, while both SPECT and PET did not show any perfusion defects during rest or vasodilator stress. Invasive coronary angiography subsequently demonstrated an intermediate lesion of the LAD. FFR was significantly reduced in the LAD (0.63). LAD, left anterior descending artery; RCA, right coronary artery. Other abbreviations as in Table 2.



eFigure 3. Flow chart showing the number of arteries interrogated by fractional flow reserve. CAD, coronary artery disease; FFR, fractional flow reserve; RCA, right coronary artery; RV, right ventricle.



eFigure 4. Association Between Noninvasive Cardiac Imaging and Diameter Stenosis as Assessed by Quantitative Coronary Angiography

eTable 1. Detailed Inclusion and Exclusion Criteria

Inclusion criteria
1. First presentation to cardiologist with suspected CAD
2. No documented prior history of CAD
3. Intermediate pre-test likelihood for CAD as defined by Diamond and Forrester criteria
4. Presenting for a clinically referred ICA
5. Age above 40 years
6. Informed consent
Exclusion criteria
1. History of severe COPD or chronic asthma
2. Pregnancy
3. Renal failure (i.e. eGFR < 45 mL/min)
4. Use of sildenafil (Viagra) or dipyramidol (Persantin) that cannot be terminated
5. Contra-indications for β-blockers
6. Allergic reaction to iodized contrast
7. Concurrent or prior (within last 30 days) participation in other research studies using investigational drugs
8. Claustrophobia
9. Significant co-morbidities
10. Atrial fibrillation, second or third degree atrioventricular block
11. Tachycardia
12. (Acute) myocardial infarction
13. Percutaneous coronary intervention

14. Heart failure
15. LVEF estimated < 50%
16. Cardiomyopathies
17. Previous radiation exposure in the diagnostic work-up
18. Coronary artery bypass graft surgery (CABG)
19. Subjects intended for short-term medical treatment or an invasive coronary intervention

eTable 2. Patient Characteristics (n = 208) by ICA, FFR, CCTA, SPECT and PET

Angiographic Findings	**No. of lesions/total no. vessels (%)**
0 – 24% narrowing	265/615 (43%)
25 – 50% narrowing	189/615 (31%)
51 – 70% narrowing	72/615 (12%)
71 – 90% narrowing	50/615 (8%)
91 – 99% narrowing	15/615 (2%)
Total occlusion	24/615 (4%)
Fractional Flow Reserve Characteristics	**No. of patients (%)**
FFR > 0.80	116 (56%)
FFR ≤ 0.80 in 1 vessel	45 (21%)
FFR ≤ 0.80 in 2 vessels	25 (12%)
FFR ≤ 0.80 in 3 vessels	22 (11%)
Coronary Computed Tomography Angiography Findings	
No (obstructive) CAD	79 (38%)
≥ 50% stenosis in 1 vessel	64 (31%)
≥ 50% stenosis in 2 vessels	47 (23%)
≥ 50% stenosis in 3 vessels	18 (8%)
Number of segments with coronary plaques on CCTA	
No CAD	20 (10%)
1 segment	14 (7%)
2-5 segments	67 (32%)
6-10 segments	76 (36%)
>10 segments	31 (15%)
^{99m}Tc-tetrofosmin SPECT findings (n = 206)	
No ischemia	147 (71%)
Ischemia in 1 vascular territory	37 (18%)
Ischemia in 2 vascular territories	22 (11%)
Ischemic burden - ^{99m}Tc-tetrofosmin SPECT (n = 206)	
No to minimal (TPD < 5%)	145 (70%)

Mild (TPD 5 – 9%)	26 (13%)
Moderate to severe (TPD ≥ 10%)	35 (17%)
[^{15}O]H_2O PET Findings (n = 204)	
No ischemia	108 (53%)
Ischemia in 1 vascular territory	23 (11%)
Ischemia in 2 vascular territories	22 (11%)
Ischemia in 3 vascular territories	51 (25%)

CAD, coronary artery disease; CCTA, coronary computed tomography angiography; FFR, fractional flow reserve; ICA, invasive coronary angiography; PET, positron emission tomography; SPECT, single-photon emission computed tomography; TPD, total perfusion deficit.

eTable 3. Association Between Functional Extent of Coronary Artery Disease and Noninvasive Imaging

	Number of hemodynamic significant diseased vessels by FFR ≤ 0.80			
	1	2	3	Total
Number of diseased vessels by CCTA				
0	5	1	2	8
1	21	6	3	30
2	13	12	8	33
3	2	5	8	15
Total	41	24	21	86
Number of ischemic vascular territories by SPECT				
0	20	10	5	35
1	16	6	7	29
2	4	7	9	20
3	0	1	0	1
Total	40	24	21	85
Number of ischemic vascular territories by PET				
0	9	2	0	11
1	10	4	3	17
2	9	4	2	15
3	11	13	16	40
Total	39	23	21	83

CCTA, coronary computed tomography angiography; FFR, fractional flow reserve; PET, positron emission tomography. SPECT, single-photon emission computed tomography.

eTable 4. Cardiovascular Risk Factors, Type of Chest Pain and CCTA (A), SPECT (B), and PET (C) as Predictors of Myocardial Ischemia as Indicated by FFR

A	Characteristics	β-coefficient	OR (95% CI)	P-value
	Male gender	1.855	6.390 (2.799 – 14.586)	< 0.0001
	Age (yrs)	0.028	1.029 (0.985 – 1.074)	0.206
	BMI (kg/m^2)	0.010	1.010 (0.904 – 1.128)	0.865
	Diabetes Mellitus Type II (yes vs. no)	0.230	1.259 (0.416 – 3.807)	0.683
	Hypertension (yes vs. no)	-0.110	0.895 (0.416 – 1.928)	0.778
	Hypercholesterolemia (yes vs. no)	0.893	2.441 (1.127 – 5.290)	0.0237
	Smoking history (yes vs. no)	0.225	1.253 (0.603 – 2.602)	0.546
	Family history of CAD (yes vs. no)	0.257	1.293 (0.623 – 2.684)	0.491
	Type of chest pain			
	Typical vs. aspecific	0.717	2.047 (0.801 – 5.230)	0.134
	Atypical vs. aspecific	0.486	1.626 (0.644 – 4.107)	0.304
	Stenosis ≥ 50% on CCTA	2.612	13.629 (5.746 – 32.328)	< 0.0001

B	Characteristics	β-coefficient	OR (95% CI)	P-value
	Male gender	1.715	5.557 (2.408 – 12.828)	0.0001
	Age (yrs)	0.001	1.001 (0.957 – 1.046)	0.977
	BMI (kg/m^2)	0.025	1.025 (0.921 – 1.141)	0.651
	Diabetes Mellitus Type II (yes vs. no)	0.209	1.232 (0.429 – 3.536)	0.698
	Hypertension (yes vs. no)	-0.077	0.926 (0.421 – 2.034)	0.848
	Hypercholesterolemia (yes vs. no)	0.761	2.140 (0.984 – 4.650)	0.055
	Smoking history (yes vs. no)	-0.142	0.867 (0.414 – 1.817)	0.706
	Family history of CAD (yes vs. no)	0.245	1.277 (0.614- 2.660)	0.513
	Type of chest pain			
	Typical vs. aspecific	-0.017	0.983 (0.382 – 2.531)	0.972
	Atypical vs. aspecific	0.130	1.139 (0.459 – 2.826)	0.779
	Ischemia on SPECT	2.838	17.022 (6.522 – 44.323)	< 0.0001

C	Characteristics	β-coefficient	OR (95% CI)	P-value
	Male gender	0.701	2.016 (0.765 – 5.309)	0.156
	Age (yrs)	0.001	1.001 (0.953 – 1.051)	0.975
	BMI (kg/m^2)	-0.018	0.982 (0.868 – 1.110)	0.769
	Diabetes Mellitus Type II (yes vs. no)	0.718	2.050 (0.602 – 6.973)	0.251
	Hypertension (yes vs. no)	0.000	1.000 (0.421 – 2.376)	0.999
	Hypercholesterolemia (yes vs. no)	0.342	1.408 (0.595 – 3.332)	0.437
	Smoking history (yes vs. no)	0.005	1.005 (0.443 – 2.278)	0.991
	Family history of CAD (yes vs. no)	-0.016	0.984 (0.441 – 2.192)	0.968
	Type of chest pain			
	Typical vs. aspecific	-0.205	0.815 (0.283 – 2.345)	0.704
	Atypical vs. aspecific	0.168	0.846 (0.296 – 2.414)	0.754
	Ischemia on PET	3.281	26.591 (10.859 – 65.114)	< 0.0001

BMI, body mass index; CAD, coronary artery disease, CCTA, coronary computed tomography angiography; CI, confidence interval; FFR, fractional flow reserve; OR, odds ratio; PET, positron emission tomography; SPECT, single-photon emission computed tomography.

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