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Diagnostic Performance of Noninvasive Myocardial Perfusion Imaging Using Single-Photon Emission Computed Tomography, Cardiac Magnetic Resonance, and Positron Emission Tomography Imaging for the Detection of Obstructive Coronary Artery Disease

A Meta-Analysis

Caroline Jaarsma, MD,*†‡ Tim Leiner, MD, PhD,†‡ Sebastiaan C. Bekkers, MD, PhD,*‡ Harry J. Crijns, MD, PhD,*‡ Joachim E. Wildberger, MD, PhD,†‡ Eike Nagel, MD, PhD,‖ Patricia J. Nelemans, MD, PhD,‡§ Simon Schalla, MD*‡

Maastricht, the Netherlands; and London, United Kingdom

Objectives This study aimed to determine the diagnostic accuracy of the 3 most commonly used noninvasive myocardial perfusion imaging modalities, single-photon emission computed tomography (SPECT), cardiac magnetic resonance (CMR), and positron emission tomography (PET) perfusion imaging for the diagnosis of obstructive coronary artery disease (CAD). Additionally, the effect of test and study characteristics was explored.

Background Accurate detection of obstructive CAD is important for effective therapy. Noninvasive myocardial perfusion imaging is increasingly being applied to gauge the severity of CAD.

Methods Studies published between 1990 and 2010 identified by PubMed search and citation tracking were examined. A study was included if a perfusion imaging modality was used as a diagnostic test for the detection of obstructive CAD and coronary angiography as the reference standard (≥50% diameter stenosis).

Results Of the 3,635 citations, 166 articles (n = 17,901) met the inclusion criteria: 114 SPECT, 37 CMR, and 15 PET articles. There were not enough publications on other perfusion techniques such as perfusion echocardiography and computed tomography to include these modalities into the study. The patient-based analysis per imaging modality demonstrated a pooled sensitivity of 88% (95% confidence interval [CI]: 88% to 89%), 89% (95% CI: 88% to 91%), and 84% (95% CI: 81% to 87%) for SPECT, CMR, and PET, respectively; with a pooled specificity of 61% (95% CI: 59% to 62%), 76% (95% CI: 73% to 78%), and 81% (95% CI: 74% to 87%). This resulted in a pooled diagnostic odds ratio (DOR) of 15.31 (95% CI: 12.66 to 18.52; I^2 63.6%), 26.42 (95% CI: 17.69 to 39.47; I^2 58.3%), and 36.47 (95% CI: 21.48 to 61.92; I^2 0%). Most of the evaluated test and study characteristics did not affect the ranking of diagnostic performances.

Conclusions SPECT, CMR, and PET all yielded a high sensitivity, while a broad range of specificity was observed. SPECT is widely available and most extensively validated; PET achieved the highest diagnostic performance; CMR may provide an alternative without ionizing radiation and a similar diagnostic accuracy as PET. We suggest that referring physicians consider these findings in the context of local expertise and infrastructure. (J Am Coll Cardiol 2012;59:1719–28) © 2012 by the American College of Cardiology Foundation

From the *Department of Cardiology, Maastricht University Medical Center, Maastricht, the Netherlands; †Department of Radiology, Maastricht University Medical Center, Maastricht, the Netherlands; ‡Cardiovascular Research Institute Maastricht, Maastricht University Medical Center, Maastricht, the Netherlands; §Department of Epidemiology, Maastricht University Medical Center, Maastricht, the Netherlands; and the ‖Division of Imaging Sciences, King's College London, London, United Kingdom. Dr. Nagel has received grant support from Bayer Schering Pharma and Philips Healthcare, unrelated to this study. All other authors have reported they have no relationships relevant to the contents of this paper to disclose.

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Abbreviations and Acronyms

CA = coronary angiography
CAD = coronary artery disease
CMR = cardiac magnetic resonance
CT = computed tomography
DE = delayed enhancement
DOR = diagnostic odds ratio
PET = positron emission tomography
RDOR = relative diagnostic odds ratio
SPECT = single-photon emission computed tomography
SROC = summary receiver-operating characteristic

Coronary artery disease (CAD) is still the leading cause of death in industrialized countries, and the prevalence is expected to increase worldwide (1–3). Ischemia is a strong predictor of adverse outcome such as future myocardial infarctions, and detection of ischemia is an important part of the diagnostic strategy in current guidelines (4–7). Moreover, a normal single-photon emission tomography (SPECT), cardiac magnetic resonance (CMR), or positron emission tomography (PET) perfusion scan indicates an excellent prognosis with a low rate of cardiac events (8–10). Noninvasive functional imaging modalities such as SPECT, CMR, and PET perfusion imaging are, therefore, increasingly being performed for the detection and risk stratification of obstructive CAD.

Previous meta-analyses have evaluated the individual diagnostic performance of perfusion imaging modalities for the detection of CAD as defined by invasive coronary angiography (CA) (11–14). However, the different perfusion techniques have not been compared directly. Thus, the current meta-analysis aimed to compare the diagnostic performance of the 3 most commonly used modalities for myocardial perfusion imaging (i.e., SPECT, CMR, and PET) and to provide an overview of test characteristics, benefits, and drawbacks of each technique. In addition, the effect of test and study characteristics on the diagnostic accuracy of perfusion imaging techniques was explored.

Methods

Data sources and study selection. We searched the PubMed database for English literature from January 1990 to February 2010 on the diagnostic accuracy of myocardial perfusion imaging for the detection of CAD. We used the following Medical Subject Headings and search terms: "single-photon emission computed tomography," "magnetic resonance imaging," "positron emission tomography," "contrast echocardiography," "perfusion echocardiography," "computed tomography," and "myocardial perfusion" in combination with the exploded term "coronary artery disease." The bibliographies of selected articles and relevant reviews were screened for potentially suitable references. A perfusion imaging modality was included in the meta-analysis if there were >10 studies reporting patient-based results of diagnostic accuracy. Therefore, myocardial perfusion echocardiography and computed tomography (CT) myocardial perfusion imaging were not included in the current meta-analysis.

We included a study if: 1) it assessed SPECT, CMR, or PET perfusion imaging as a diagnostic test to evaluate patients for the presence of CAD; 2) CAD was defined as at least ≥50% diameter stenosis on CA; and 3) it reported cases in absolute numbers of true positive, false positive, true negative, and false negative results, or if these data were derivable from the presented results. A study was eligible regardless of whether patients were referred for suspected or known CAD. Studies were excluded if they were conducted with: 1) phantom-only models; 2) animals; 3) normal healthy volunteers only without CA correlation; or 4) if they included <10 patients. Different articles by the same author or research group were included for analysis only when it was obvious that different patient samples were used.

Data extraction. First, identifying information about the study such as first author, journal, and year of publication was extracted. Further extracted variables consisted of patient characteristics, technical information and absolute numbers of true negative, true positive, false negative, and false positive test results. If available, data were recorded on patient and coronary artery territory level (i.e., left anterior descending, left circumflex, and right coronary artery). Several studies used >1 cutoff value for CAD and, as a consequence, reported >1 pair of sensitivity and specificity. To improve the comparability of study results in the analysis of overall diagnostic performance, we selected a cutoff value of ≥50% whenever possible. However, if data were not reported for a cutoff value of ≥50%, we selected the cutoff value that was available (e.g., ≥70%). If a study presented multiple sensitivity and specificity estimates for the selected cutoff value due to different study protocols (e.g., exercise versus pharmacological stress), the data of the protocol with the highest estimates was extracted. In cases where >1 diagnostic technique was evaluated within a single publication (e.g., SPECT vs. CMR), each modality was considered separately. We also assessed the likelihood of verification bias, which occurs when patients with a positive result on the index test (i.e., the test under investigation) are referred to the reference standard more often than patients with a negative result. Four investigators (C.J., T.L., P.N., and S.S.) extracted data independently, and discrepancies were resolved by consensus.

Statistical analysis. On the basis of the results from the (derived) 2×2 contingency tables, pooled measures for diagnostic performance, such as sensitivity, specificity, diagnostic odds ratio (DOR), and area under the curve (AUC) with 95% confidence intervals (CIs) were calculated using random effects models. The pooled DOR for each imaging modality was used for the construction of summary receiver operating characteristic (SROC) curves. The SROC curves account for the so-called threshold effect in diagnostic studies arising when studies use different cutoff points or thresholds to define a positive or negative result. The DOR combines sensitivity and specificity into 1 measure for diagnostic performance. A DOR of 1 means that a test has no ability to discriminate. The higher the DOR, the better

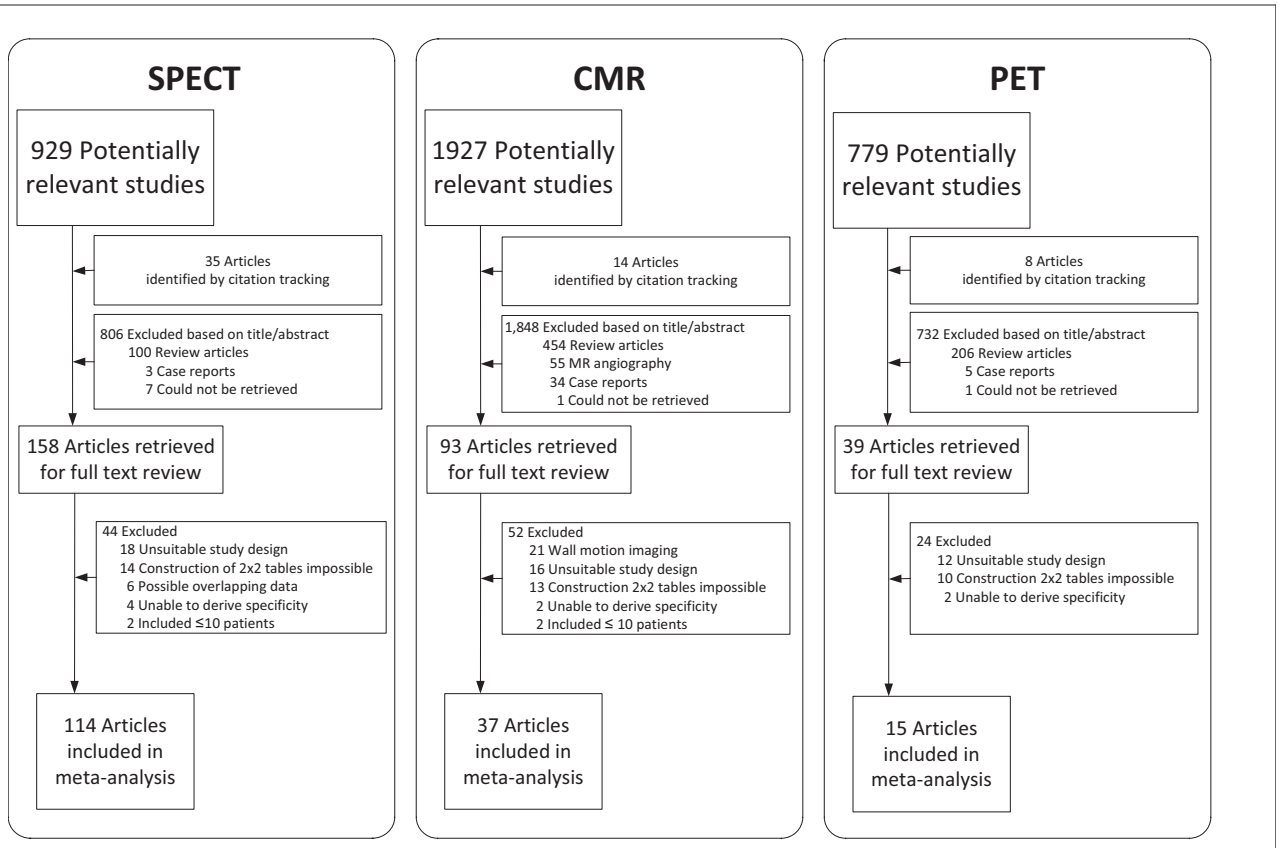

Figure 1 **Flow Diagram of Literature Search**

Of 3,635 potentially relevant citations, 166 articles met our inclusion criteria and were included in the meta-analysis.
CMR = cardiac magnetic resonance; PET = positron emission tomography; SPECT = single-photon emission computed tomography.

the ability of a test to discriminate between subjects with and without the disease of interest. Relative diagnostic odds ratios (RDOR) with 95% CI were calculated using meta-regression random effects models to evaluate significant differences in diagnostic performance between the 3 imaging modalities (15).

The I^2 index was used to test for heterogeneity between study results. Significance of this index indicates that differences between study results cannot solely be attributed to sampling variation. Statistical heterogeneity was defined as an I^2 statistic value of >50% (16). Differences in study characteristics between modalities can be a cause of considerable heterogeneity (e.g., due to the use of different stressors or tracers) and can also affect the comparison of diagnostic performance between imaging modalities. Therefore, the distribution of study characteristics of SPECT, CMR, and PET studies were compared using the chi-square test to test for differences in variables with nominal values, and the *t* test for independent samples in case of continuous values (SPSS 17.0, SPSS Inc., Chicago, Illinois). Pooled estimates were calculated

Table 1 **Diagnostic Performance of SPECT, CMR, and PET Perfusion Imaging on Patient and Coronary Artery Territory Basis**

	No. of Studies	Sensitivity (95% CI)	Specificity (95% CI)	DOR (95% CI)	RDOR (95% CI)	p Value
Patient basis						
SPECT	105	88 (88–89)	61 (59–62)	15.31 (12.66–18.52)		—
CMR	27	89 (88–91)	76 (73–78)	26.42 (17.69–39.47)	1.67 (1.07–2.61)	<0.05
PET*	11	84 (81–87)	81 (74–87)	36.47 (21.48–61.92)	2.25 (1.05–4.84)	<0.05
Coronary territory basis						
SPECT	45	69 (68–70)	79 (78–80)	11.75 (9.26–14.91)		—
CMR	17	84 (81–86)	83 (81–86)	24.11 (15.68–37.07)	2.58 (1.53–4.35)	<0.001
PET†	7	77 (73–81)	88 (84–90)	24.74 (15.57–39.30)	2.30 (1.10–4.77)	<0.05

*Positron emission tomography (PET) studies compared to cardiac magnetic resonance (CMR) studies on a patient-based analysis: relative diagnostic odds ratio (RDOR) 1.44 (95% confidence interval [CI]: 0.62 to 3.34; p = 0.39). †PET studies compared to CMR studies on a coronary territory-based analysis: RDOR 0.95 (95% CI: 0.42 to 2.18; p = 0.91).
DOR = diagnostic odds ratio; SPECT = single-photon emission computed tomography.

for subgroups of studies that were defined according to specific study characteristics. The RDORs with 95% CI were calculated to quantify the differences in pooled odds ratios between subgroups. In addition to the comparison of subgroups within a single imaging modality, the pooled DORs of the subgroups were also compared between the different imaging modalities. Meta-DiSc 1.4 was used for data analysis (17). Publication bias was examined using funnel plots and Egger's test (18).

Results

A PubMed database search and additional citation tracking of review and original articles resulted in 3,635 potentially relevant citations (Fig. 1). A total of 166 articles (n = 17,901) met our inclusion criteria: 114 SPECT (n = 13,741), 37 CMR (n = 2,841), and 15 PET studies (n = 1,319). The study and population characteristics as well as a list of all studies included in the meta-analysis are presented in the Appendix (see Online Tables 1 through 6 and Online References).

Diagnostic performance of myocardial perfusion imaging. Pooled estimates of sensitivity, specificity, and DOR of the 3 perfusion imaging modalities on both patient and coronary artery territory levels are summarized in Table 1. The patient-based analyses show similar pooled sensitivities for the 3 modalities and differences in pooled specificities. Meta-regression resulted in significantly increased RDORs for CMR and PET studies when compared with SPECT studies. When comparing PET with CMR studies, the RDOR for PET was not significantly increased. The RDOR was 1.44 (95% CI: 0.62 to 3.34; p = 0.39) for patient-based analysis and 0.95 (95% CI: 0.42 to 2.18; p = 0.91), for coronary territory-based

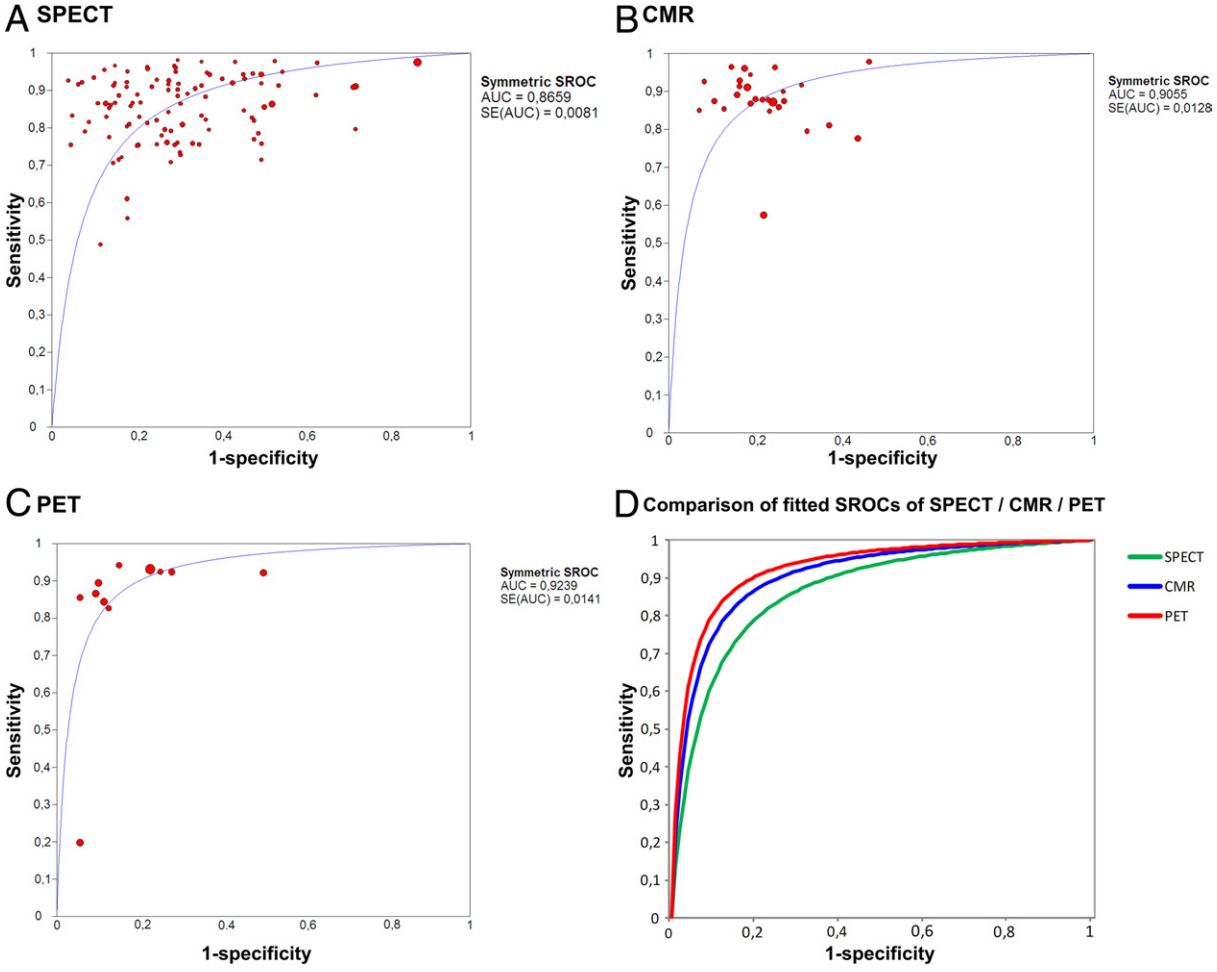

Figure 2 SPECT, CMR, and PET for Detecting CAD

Diagnostic performance of **(A)** single-photon emission computed tomography (SPECT); **(B)** cardiac magnetic resonance (CMR); and **(C)** positron emission tomography (PET) for the detection of coronary artery disease (CAD) on a patient-based level: graphic display of diagnostic accuracy with summary receiver-operating characteristics (SROC) curves. **(A, B, C)** Each **dot** represents a single study, with the size of the dot directly proportional to the sample size of the study. The area under the curve (AUC) reflects the overall diagnostic performance and is expressed as a value between 0 and 1, with higher values indicating better test performance. The AUC was 0.8659, 0.9055, and 0.9239 for SPECT, CMR, and PET, respectively. **(D)** Fitted SROC curves for direct comparison of the diagnostic performance of SPECT **(green line)**, CMR **(blue line)**, and PET **(red line)**.

analysis. The diagnostic performance of SPECT, CMR, and PET to detect CAD on a patient-based level is summarized in Figure 2.

Differences in the distribution of study characteristics potentially affecting the diagnostic performance of the imaging modalities are shown in Table 2. The I^2 index shows substantial heterogeneity for SPECT and CMR (I^2 63.6% and 58.3%, respectively). Subgroup analyses were performed to identify sources of variation between study results (Tables 3, 4, and 5) and to evaluate whether differences in distribution of study characteristics between modalities affect the comparison of the 3 modalities. The analyses revealed no significant effect of test and study characteristics on the diagnostic performance of the 3 modalities, except for a lower pooled DOR of SPECT studies using dipyridamole in comparison to adenosine. The CMR studies with dipyridamole also reported a lower diagnostic performance. The SPECT studies using attenuation correction demonstrated a lower sensitivity and higher specificity in comparison to studies without attenuation correction. Because of this decrease in sensitivity, pooled DORs for SPECT studies with and without attenuation correction were similar. Four CMR studies were performed with 3.0-T scanners and reported a higher diagnostic performance compared to studies using 1.5-T. For SPECT and PET studies, the pooled DOR for more recently published studies (2006 or later) was lower than for studies published before 2006. For SPECT and CMR studies, lower pooled DORs were observed for studies with a larger sample size (>70 patients) in comparison with studies with smaller sample size. For SPECT, studies with a higher prevalence of CAD and 3-vessel disease were associated with a lower diagnostic performance whereas CMR studies with a higher prevalence of CAD and 3-vessel disease showed a better performance than studies with a lower prevalence. Verification bias had no impact on the pooled DORs of the 3 modalities. The pooled sensitivity for studies with verification bias was higher and the pooled specificity lower in comparison to studies without verification bias.

The diagnostic accuracy of PET and CMR in comparison with SPECT remained unchanged within the majority of subgroup analyses. PET was consistently associated with a higher pooled DOR than CMR, whereas CMR demonstrated a higher pooled DOR than SPECT. In a few

Table 2 Distribution of Study Characteristics for SPECT, CMR, and PET Perfusion Imaging Studies*

	SPECT Studies (n = 105)		CMR Studies (n = 27)		PET Studies (n = 11)		SPECT Studies vs. CMR Studies	SPECT Studies vs. PET Studies	CMR Studies vs. PET Studies
Characteristic	Mean	n (%)	Mean	n (%)	Mean	n (%)	p Value	p Value	p Value
Year of publication†									
<2006	1997 ± 5	92 (88)	2006 ± 2	11 (41)	2001 ± 8	5 (45)	<0.001	0.16	<0.05
≥2006		13 (12)		16 (59)		6 (55)			
Mean age†									
<60, yrs	60 ± 5	50 (47)	62 ± 3	8 (30)	61 ± 4	3 (27)	0.12	0.52	0.72
≥60, yrs		48 (46)		19 (70)		6 (55)			
NS		7 (7)		—		2 (18)			
Study size†									
<70	129 ± 204	45 (43)	92 ± 84	15 (56)	69 ± 49	7 (64)	0.36	0.34	0.41
≥70		60 (57)		12 (44)		4 (36)			
Prevalence of CAD†									
<72%	70 ± 15	50 (48)	59 ± 17	18 (67)	81 ± 8	1 (9)	<0.05	<0.05	<0.001
≥72%		55 (52)		9 (33)		10 (91)			
Prevalence of 3-vessel disease†									
<18%	18 ± 10	37 (35)	14 ± 10	14 (52)	26 ± 12	1 (9)	0.11	0.06	<0.05
≥18%		41 (39)		5 (18)		5 (45)			
NS		27 (26)		8 (30)		5 (45)			
Cutoff value for CAD on invasive CA									
≥50%	—	88 (84)	—	12 (44)	—	9 (82)	<0.001	0.87	0.07
≥70%		17 (16)		15 (56)		2 (18)			
Patient selection									
Suspected CAD	—	56 (53)	—	18 (66)	—	4 (36)	0.19	0.34	0.08
Suspected or known CAD		46 (44)		8 (30)		7 (64)			
Other		3 (3)		1 (4)		—			
Verification bias									
No	—	44 (42)	—	21 (78)	—	6 (55)	<0.001	0.53	0.10
Likely/yes		61 (58)		4 (15)		5 (45)			
Possible		—		2 (7)		—			

*Studies were only included in multivariable meta-regression if data on patient-based level and the concerning study characteristic were available. †Cutoff values represent values less than and equal to or greater than median.

CA = coronary angiography; CAD = coronary artery disease; NS = not specified; other abbreviations as in Table 1.

Table 3 Subgroup Analyses for the Diagnostic Performance of SPECT on a Patient-Based Level*

Characteristic	Studies, n	Sensitivity % (95% CI)	Specificity % (95% CI)	DOR (95% CI)	RDOR (95% CI)	p Value
Stressor						
Adenosine	12	91 (89–93)	78 (73–82)	31.02 (14.86–64.77)	1.00	
Dipyridamole	15	85 (82–87)	72 (68–75)	11.36 (7.24–17.82)	0.40 (0.16–0.96)	0.04
Dobutamine	10	83 (80–86)	74 (67–79)	17.62 (9.34–33.27)	0.61 (0.21–1.81)	0.36
Treadmill exercise	22	90 (89–91)	59 (55–62)	15.51 (10.67–22.56)	0.70 (0.33–1.49)	0.34
Bicycle exercise	14	84 (82–86)	69 (64–74)	13.25 (8.36–21.01)	0.45 (0.18–1.15)	0.09
Tracer						
Tl-201	39	89 (87–90)	71 (68–73)	19.88 (14.38–27.48)	1.00	
99mTc MIBI	44	87 (85–88)	68 (65–71)	14.91 (11.20–19.87)	0.78 (0.50–1.20)	0.25
Rest Tl-201/stress 99mTc MIBI	7	88 (86–90)	54 (49–59)	11.11 (5.78–21.33)	0.60 (0.28–1.29)	0.18
99mTc tetrofosmin	7	79 (75–83)	72 (65–78)	10.26 (4.24–24.81)	0.49 (0.22–1.11)	0.09
Attenuation correction						
Noncorrected	100	89 (88–89)	60 (59–62)	15.39 (12.67–18.68)	1.00	
Corrected	5	80 (76–84)	78 (71–84)	13.18 (4.53–38.36)	0.75 (0.32–1.77)	0.51
Year of publication†						
<2006	92	89 (88–89)	61 (59–62)	16.23 (13.23–19.92)	1.00	
≥2006	13	86 (84–88)	62 (58–66)	10.55 (6.42–17.34)	0.64 (0.37–1.12)	0.12
Mean age†						
<60, yrs	50	86 (85–87)	72 (69–74)	15.42 (11.83–20.11)	1.00	
≥60, yrs	48	90 (89–91)	54 (52–56)	15.97 (11.91–21.41)	1.01 (0.68–1.50)	0.97
Study size†						
<70	45	86 (84–88)	75 (72–79)	17.64 (12.60–24.69)	1.00	
≥70	60	89 (88–89)	58 (56–59)	14.32 (11.40–17.98)	0.85 (0.55–1.29)	0.44
Prevalence of CAD†						
<72%	50	85 (84–86)	73 (71–76)	16.86 (12.62–22.54)	1.00	
≥72%	55	89 (89–90)	49 (47–51)	14.02 (10.91–18.02)	0.93 (0.62–1.39)	0.71
Prevalence of 3-vessel disease†						
<18%	37	86 (84–87)	75 (72–77)	19.05 (14.03–25.87)	1.00	
≥18%	41	91 (90–91)	47 (45–49)	14.96 (11.33–19.76)	0.87 (0.56–1.34)	0.52
Cutoff value for CAD on CA						
≥50%	88	87 (86–87)	69 (67–71)	16.04 (13.23–19.45)	1.00	
≥70%	17	93 (92–94)	43 (41–46)	11.81 (6.80–20.51)	0.70 (0.42–1.17)	0.17
Patient selection						
Suspected CAD	56	85 (84–86)	69 (67–71)	14.46 (11.15–18.75)	1.00	
Suspected or known CAD	45	91 (90–92)	51 (49–54)	16.25 (12.11–21.82)	1.19 (0.80–1.77)	0.39
Verification bias						
No	44	84 (83–86)	73 (70–75)	15.06 (11.45–19.82)	1.00	
Likely/yes	61	90 (89–90)	55 (53–57)	15.00 (11.69–19.25)	0.99 (0.66–1.49)	0.97

*Studies were only included in multivariable meta-regression if data on patient-based level and the concerning study characteristic were available. †Cutoff values represent values less than and equal to or greater than median.

99mTc-MIBI = technetium-99m 2-methoxy-isobutyl-isonitrile; Tl-201 = thallium-201; other abbreviations as in Tables 1 and 2.

subgroups, such as studies published in or after the year 2006, higher mean age, smaller sample size, and studies using a cutoff value of ≥70% stenosis, CMR was associated with a slightly higher pooled DOR than PET. The SPECT and CMR studies reported similar pooled DORs in studies with adenosine as stressor, lower mean age, and lower prevalence of CAD and 3-vessel disease.

Direct comparisons. Few studies directly compared the diagnostic accuracy of different imaging modalities within 1 study population. The study of Stewart et al. (Online Reference 95) reported an improvement of specificity to identify CAD for rubidium-82 PET in comparison with thallium-201 SPECT. Furthermore, Doyle et al. (Online Reference 19) and Sakuma et al. (Online Reference 83) investigated the diagnostic accuracy of SPECT and CMR on a patient-based level and found comparable diagnostic performance for both modalities. Finally, Ishida et al. (Online Reference 45), Sakuma et al. (Online Reference 83), and Thiele et al. (Online Reference 102) all reported a better diagnostic performance of CMR perfusion imaging on a coronary territory-based analysis in comparison with SPECT.

Publication bias. For SPECT and CMR studies, Egger's regression test showed significant funnel plot asymmetry (intercept 2.17 [95% CI: 1.59 to 2.77]; $p < 0.001$ for SPECT, intercept 1.58 [95% CI: 0.13 to 3.02]; $p = 0.03$ for CMR), indicating that publication bias was likely. There was no indication for funnel plot asymmetry in PET studies (intercept −0.01 [95% CI: −1.47 to 1.45]; $p = 0.99$).

Table 4 Subgroup Analyses for the Diagnostic Performance of CMR on a Patient-Based Level*

Characteristic	Studies, n	Sensitivity % (95% CI)	Specificity % (95% CI)	DOR (95% CI)	RDOR (95% CI)	p Value
Stressor						
Adenosine	21	90 (88–92)	79 (76–82)	29.70 (21.00–42.01)	1.00	
Dipyridamole	3	84 (76–90)	78 (71–83)	12.85 (2.65–62.30)	0.49 (0.17–1.40)	0.17
Dobutamine	1	87	76			
Nicorandil	1	94	94			
Field strength						
1.5-T	23	88 (87–90)	79 (76–81)	25.02 (17.13–36.56)	1.00	
3.0-T	4	94 (89–98)	82 (72–89)	51.71 (22.44–119.15)	1.71 (0.55–5.30)	0.34
Data assessment						
Qualitative	22	90 (88–91)	74 (71–77)	27.21 (17.97–41.22)	1.00	
Semiquantitative	5	87 (81–91)	80 (74–85)	24.62 (6.95–87.28)	0.96 (0.32–2.93)	0.94
Year of publication†						
<2006	11	88 (85–91)	80 (76–84)	25.04 (13.07–47.97)	1.00	
≥2006	16	90 (88–92)	73 (69–76)	27.75 (16.31–47.23)	0.89 (0.36–2.18)	0.78
Mean age†						
<60, yrs	8	85 (80–89)	76 (70–80)	13.44 (7.23–24.99)	1.00	
≥60, yrs	19	90 (89–92)	76 (72–79)	33.13 (20.97–52.34)	2.06 (0.84–5.03)	0.11
Study size†						
<70	15	90 (87–93)	81 (76–86)	29.70 (19.08–46.25)	1.00	
≥70	12	89 (87–91)	74 (70–77)	22.91 (12.24–42.87)	0.70 (0.30–1.59)	0.37
Prevalence of CAD†						
<72%	18	89 (86–91)	74 (70–77)	23.23 (13.10–41.17)	1.00	
≥72%	9	89 (87–91)	80 (75–85)	30.81 (21.58–43.98)	1.64 (0.71–3.78)	0.23
Prevalence of 3-vessel disease†						
<18%	14	88 (84–90)	72 (68–76)	20.79 (11.08–39.02)	1.00	
≥18%	5	90 (87–93)	83 (77–88)	37.57 (22.69–62.21)	1.90 (0.67–5.43)	0.21
Cutoff value for CAD on CA						
≥50%	12	88 (86–90)	79 (76–83)	24.38 (16.93–35.11)	1.00	
≥70%	15	90 (87–92)	78 (74–82)	32.90 (16.79–64.47)	1.20 (0.59–2.44)	0.59
Patient selection						
Suspected CAD	18	89 (86–91)	74 (71–77)	22.91 (13.49–38.92)	1.00	
Suspected or known CAD	8	90 (88–92)	80 (74–84)	34.83 (20.70–60.45)	1.50 (0.60–3.73)	0.37
Verification bias						
No	21	89 (87–91)	76 (73–79)	25.36 (15.81–40.70)	1.00	
Likely/yes	4	91 (85–95)	70 (61–78)	27.82 (10.70–72.33)	1.02 (0.29–3.67)	0.97

*Studies were only included in multivariable meta-regression if data on patient-based level and the concerning study characteristic were available. †Cutoff values represent values less than and equal to or greater than median.

Abbreviations as in Tables 1 and 2.

Discussion

The prevalence of CAD is rising worldwide, and noninvasive myocardial perfusion imaging is increasingly being performed to detect obstructive CAD, guide therapy, and provide prognostic information (1–3,19). The current meta-analysis revealed that the 3 most commonly used imaging techniques for myocardial perfusion, SPECT, CMR, and PET, can accurately detect obstructive CAD. Meta-regression demonstrated that CMR and PET have a significantly higher diagnostic accuracy than SPECT, on a patient and coronary territory basis. A higher but nonsignificant diagnostic performance was observed for PET in comparison with CMR on a patient-based analysis, and a similar diagnostic performance as CMR on coronary territory analysis. The diagnostic accuracy of PET and CMR in comparison with SPECT remained unchanged within most subgroup analyses. Clinical validation studies showed that advances in attenuation correction lead to an increase in specificity of SPECT with fewer false positive interpretations (20–22). Correspondingly, SPECT studies included in this meta-analysis using attenuation correction reported a higher overall specificity (Online References 6,23,26,28,37) However, because of a decrease in sensitivity, this did not result in an increase in overall diagnostic accuracy.

Although SPECT is the most widely used and validated perfusion imaging technique, the advantage of PET over SPECT could be explained by its higher spatial resolution, excellent attenuation correction, and the use of different tracers (13). Nevertheless, in spite of its high sensitivity and specificity, widespread use of PET is currently hampered by high costs and limited availability, although cost effectiveness has been suggested (23).

In comparison to nuclear techniques, CMR perfusion imaging does not suffer from attenuation artefacts, provides the

Table 5 Subgroup Analyses for the Diagnostic Performance of PET on a Patient-Based Level*

Characteristic	Studies, n	Sensitivity % (95% CI)	Specificity % (95% CI)	DOR (95% CI)	RDOR (95% CI)	p Value
Stressor						
Adenosine	2	90 (82–95)	88 (62–98)	43.34 (9.18–204.68)	1.00	
Dipyridamole	3	88 (80–93)	91 (72–99)	48.14 (12.76–181.59)	0.87 (0.01–101.91)	0.91
Dipyridamole/handgrip	3	91 (87–94)	83 (72–90)	46.88 (22.13–99.29)	1.08 (0.02–47.73)	0.94
Exercise	1	96	89			
Tracer						
Rubidium-82	10	84 (81–87)	81 (74–87)	36.56 (21.37–62.55)		
Copper-62	1	84	100			
Acquisition						
PET	8	82 (78–85)	86 (78–92)	44.31 (23.93–82.06)	1.00	
PET/CT	3	91 (85–95)	67 (49–81)	21.07 (7.49–59.26)	0.42 (0.09–1.97)	0.23
Data assessment						
Qualitative/ semiquantitative	9	90 (87–92)	81 (74–88)	41.08 (23.25–72.57)	1.00	
Quantitative	2	52 (42–62)	88 (62–98)	15.50 (2.06–116.43)	0.41 (0.06–2.99)	0.33
Year of publication†						
<2006	5	91 (87–94)	84 (74–91)	48.84 (24.30–98.17)	1.00	
≥2006	6	76 (70–81)	78 (66–87)	24.57 (10.91–55.33)	0.50 (0.14–1.77)	0.24
Mean age†						
<60 yrs	3	89 (82–95)	89 (73–97)	48.93 (15.86–150.93)	1.00	
≥60 yrs	6	76 (71–80)	81 (69–90)	24.84 (10.21–60.42)	0.51 (0.08–3.06)	0.39
Study size†						
<70	7	75 (70–80)	77 (65–87)	24.23 (10.68–54.96)	1.00	
≥70	4	90 (86–93)	84 (75–91)	48.90 (24.44–97.83)	2.03 (0.57–7.27)	0.23
Prevalence of CAD†						
<72%	1	93	50			
≥72%	10	83 (80–86)	86 (79–92)	44.18 (24.92–78.33)		
Prevalence of 3-vessel disease†						
<18%	1	85	91			
≥18%	5	92 (89–95)	81 (70–89)	47.16 (22.84–97.40)		
Cutoff value for CAD on CA						
≥50%	9	82 (79–86)	85 (78–91)	42.51 (23.25–77.73)	1.00	
≥70%	2	89 (82–94)	69 (51–83)	24.49 (4.84–124.01)	0.50 (0.11–2.29)	0.32
Patient selection						
Suspected CAD	4	91 (87–94)	77 (67–85)	34.41 (16.93–69.92)	1.00	
Suspected or known CAD	7	77 (72–82)	90 (79–97)	39.61 (16.31–96.18)	1.14 (0.29–4.57)	0.83
Verification bias						
No	6	80 (76–84)	85 (76–91)	39.76 (20.12–78.58)	1.00	
Likely/yes	5	90 (86–94)	77 (64–87)	31.96 (13.78–74.12)	0.80 (0.22–2.96)	0.70

*Studies were only included in multivariable meta-regression if data on patient-based level and the concerning study characteristic were available. †Cutoff values represent values less than and equal to or greater than median.

Abbreviations as in Tables 1 and 2.

highest spatial resolution, and is able to accurately detect even subendocardial perfusion deficits (24). However, only 3 tor 4 2-dimensional slices in short-axis view are usually imaged. Another benefit of CMR, similar to PET, is the ability to measure myocardial perfusion in absolute terms (25).

Currently, a multicomponent examination for CMR imaging is used in clinical practice, which combines imaging of myocardial perfusion and the presence and extent of infarct scar with delayed gadolinium-enhancement (DE) to detect CAD even more accurately (Online Reference 130). Four studies included in this meta-analysis reported absolute numbers on the diagnostic performance of CMR perfusion in combination with DE-CMR in patients without a known prior myocardial infarction (Online References 128–131). The reported sensitivities for this combined approach ranged from 84% to 92%, and the specificities from 57% to 88%. Combined approaches are also being implemented for PET (26) and SPECT (27) with integrated CT angiography to assess coronary anatomy.

Current research suggests that CT perfusion imaging has the potential to evaluate qualitative and quantitative myocardial blood flow (28), and stress myocardial perfusion echocardiography has also been performed for the detection of obstructive CAD, possibly with similar diagnostic accuracy as SPECT (29). An adenosine stress echocardiography study combining wall motion and myocardial contrast perfusion revealed a good diagnostic accuracy compared to CMR perfusion (30). We could not include the perfusion

imaging modalities echocardiography and CT in the current meta-analysis because of the very limited number of studies that met our inclusion criteria.

In contrast, stress echocardiography is widely performed to detect regional wall motion abnormalities in patients with obstructive CAD with a diagnostic accuracy comparable to that of SPECT, with a sensitivity of 40% to 100% and specificity of 62% to 100% (31). However, considering the objectives of this study and given the already large body of publications on myocardial perfusion imaging with SPECT, CMR, and PET, we performed a meta-analysis of perfusion imaging only and could not include imaging techniques beyond perfusion.

This is the first meta-analysis that directly compares the 3 most commonly used techniques for perfusion imaging, SPECT, CMR, and PET. The current study also provides a considerable update to previously conducted meta-analyses on individual modalities (11–14). However, we excluded several studies that were used in previous meta-analyses because: 1) we were not able to derive 2×2 contingency tables from the published data (2 CMR and 3 PET studies); 2) we could not distinguish the absolute numbers of patients from those in healthy controls (1 SPECT study); 3) the study design was not suitable (e.g., exclusively patients with left main/3-vessel disease or a multimodality approach was used to detect CAD) (1 SPECT and 2 PET studies); or 4) the study was not published in English (2 CMR studies). Overall, our results on sensitivity and specificity of the individual perfusion imaging modalities on patient-based and coronary territory-based analysis correspond well to preceding meta-analyses of individual modalities.

In the current meta-analysis, CA was used as the reference standard for the detection of obstructive CAD, as CA is traditionally considered the reference standard for the detection and assessment of severity of CAD. However, this invasive procedure is costly and not without risk. In addition, CA does not always provide sufficient information regarding the hemodynamic relevance of a stenosis, given that its presence does not necessarily result in a hemodynamic effect on perfusion. Therefore, regarding anatomical information from CA as the traditional reference standard could have potentially biased our results. Invasively measured fractional flow reserve detects the hemodynamic relevance of a stenosis more accurately than anatomic imaging by CA (32). However, invasive fractional flow reserve measurements were validated against PET and SPECT as the reference standard (32,33). Studies that compared CMR perfusion to fractional flow reserve also demonstrated an excellent sensitivity and specificity to detect functionally significant CAD (34) (Online References 121 and 134). An interesting topic for future studies on reference standards would be to assess the potential of noninvasive methods to quantitatively measure perfusion such as PET.

The therapeutic and prognostic implications of nonobstructive CAD are currently not fully understood. Although Virmani et al. (35) already suggested that acute coronary syndromes arise from (unstable) plaques and not necessarily from severely stenosed coronary arteries, and myocardial infarction can also occur in the absence of chronic coronary obstructions as, for example, embolic infarctions (36), the prognosis of patients with a negative SPECT, CMR, or PET test is good (8–10) even though the presence of plaques or minor coronary artery disease might not be known. The event rate for cardiac death or nonfatal myocardial infarction is as low as 1.1% per year in patients with a stenosis of <50% on invasive CA, whereas an increasing degree of stenosis is associated with an increasing risk for myocardial infarction (37–39).

Finally, as with any meta-analysis, limitations to the methods include heterogeneity between studies and presence of publication bias. Subgroup analyses demonstrated that most test and study characteristics did not significantly affect the diagnostic performance of the imaging modalities. However, the power to detect relevant differences between subgroups may have been limited by small numbers of studies in specific subgroups. The largest merit of the subgroup analyses was that differences in the distribution of test and study characteristics did not affect the comparison of the 3 modalities. Within most subgroup analyses, a relative superiority of PET and CMR over SPECT was observed. More extensive exploration of sources of heterogeneity with multivariable meta-regression analysis to enable simultaneous correction for >1 study characteristic was also not feasible because of the relatively small number of PET studies. By applying Egger's regression test, publication bias was suggested for SPECT and CMR. It is possible that small studies with low diagnostic performance remained unpublished (40,41).

Conclusions

Our meta-analysis revealed that SPECT, CMR, and PET all yielded a high sensitivity for the detection of obstructive CAD, with a wide range of specificity. Both CMR and PET showed a significantly higher diagnostic accuracy than SPECT. While PET demonstrated the highest diagnostic performance in a limited number of studies with small study populations and a high prevalence of CAD, SPECT imaging is widely available and most extensively evaluated. CMR perfusion imaging may provide an alternative without the use of ionizing radiation at a similar diagnostic accuracy as PET. We suggest that referring physicians consider these findings in the context of local expertise and infrastructure. Future technical developments are likely to improve diagnostic performance of all 3 modalities by combined imaging of prior myocardial infarction, coronary anatomy including plaque morphology, and myocardial perfusion.

Reprint requests and correspondence: Dr. Simon Schalla, Department of Cardiology, Maastricht University Medical Center, P. Debyelaan 25, P.O. Box 5800, 6202 AZ Maastricht, the Netherlands. E-mail: s.schalla@mumc.nl.

REFERENCES

1. Murray CJ, Lopez AD. Alternative projections of mortality and disability by cause 1990-2020: Global Burden of Disease Study. Lancet 1997;349:1498–504.

2. Lloyd-Jones D, Adams RJ, Brown TM, et al. Heart disease and stroke statistics—2010 update: a report from the American Heart Association. Circulation 2010;121:e46–215.
3. World Health Organization. World Health Statistics 2008. Geneva, Switzerland: World Health Organization, 2008.
4. Hachamovitch R, Berman DS, Shaw LJ, et al. Incremental prognostic value of myocardial perfusion single-photon emission computed tomography for the prediction of cardiac death: differential stratification for risk of cardiac death and myocardial infarction. Circulation 1998;97:535–43.
5. Jahnke C, Nagel E, Gebker R, et al. Prognostic value of cardiac magnetic resonance stress tests: adenosine stress perfusion and dobutamine stress wall motion imaging. Circulation 2007;115:1769–76.
6. Wijns W, Kolh P, Danchin N, et al. Guidelines on myocardial revascularization: the Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J 2010;31:2501–55.
7. Smith SC Jr., Feldman TE, Hirshfeld JW Jr., et al. ACC/AHA/SCAI 2005 guideline update for percutaneous coronary intervention: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/SCAI Writing Committee to Update the 2001 Guidelines for Percutaneous Coronary Intervention). J Am Coll Cardiol 2006;47:e1–121.
8. Yoshinaga K, Chow BJ, Williams K, et al. What is the prognostic value of myocardial perfusion imaging using rubidium-82 positron emission tomography? J Am Coll Cardiol 2006;48:1029–39.
9. Metz LD, Beattie M, Hom R, Redberg RF, Grady D, Fleischmann KE. The prognostic value of normal exercise myocardial perfusion imaging and exercise echocardiography: a meta-analysis. J Am Coll Cardiol 2007;49:227–37.
10. Lerakis S, McLean DS, Anadiotis AV, et al. Prognostic value of adenosine stress cardiovascular magnetic resonance in patients with low-risk chest pain. J Cardiovasc Magn Reson 2009;11:37.
11. Fleischmann KE, Hunink MG, Kuntz KM, Douglas PS. Exercise echocardiography or exercise SPECT imaging? A meta-analysis of diagnostic test performance. JAMA 1998;280:913–20.
12. 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;50:1343–53.
13. Nandalur KR, Dwamena BA, Choudhri AF, Nandalur SR, Reddy P, Carlos RC. Diagnostic performance of positron emission tomography in the detection of coronary artery disease: a meta-analysis. Acad Radiol 2008;15:444–51.
14. Hamon M, Fau G, Nee G, Ehtisham J, Morello R. 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.
15. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177–88.
16. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327:557–60.
17. Zamora J, Abraira V, Muriel A, Khan K, Coomarasamy A. Meta-DiSc: a software for meta-analysis of test accuracy data. BMC Med Res Methodol 2006;6:31.
18. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629–34.
19. Mendis S, Thygesen K, Kuulasmaa K, et al. World Health Organization definition of myocardial infarction: 2008-2009 revision. Int J Epidemiol 2011;40:139–46.
20. Prvulovich EM, Lonn AH, Bomanji JB, Jarritt PH, Ell PJ. Effect of attenuation correction on myocardial thallium-201 distribution in patients with a low likelihood of coronary artery disease. Eur J Nucl Med 1997;24:266–75.
21. Kluge R, Sattler B, Seese A, Knapp WH. Attenuation correction by simultaneous emission-transmission myocardial single-photon emission tomography using a technetium-99m-labelled radiotracer: impact on diagnostic accuracy. Eur J Nucl Med 1997;24:1107–14.
22. Chouraqui P, Livschitz S, Sharir T, et al. Evaluation of an attenuation correction method for thallium-201 myocardial perfusion tomographic imaging of patients with low likelihood of coronary artery disease. J Nucl Cardiol 1998;5:369–77.
23. Patterson RE, Eisner RL, Horowitz SF. Comparison of cost-effectiveness and utility of exercise ECG, single-photon emission computed tomography, positron emission tomography, and coronary angiography for diagnosis of coronary artery disease. Circulation 1995;91:54–65.
24. Wagner A, Mahrholdt H, Holly TA, et al. Contrast-enhanced MRI and routine single-photon emission computed tomography (SPECT) perfusion imaging for detection of subendocardial myocardial infarcts: an imaging study. Lancet 2003;361:374–9.
25. Jerosch-Herold M, Muehling O, Wilke N. MRI of myocardial perfusion. Semin Ultrasound CT MR 2006;27:2–10.
26. Namdar M, Hany TF, Koepfli P, et al. Integrated PET/CT for the assessment of coronary artery disease: a feasibility study. J Nucl Med 2005;46:930–5.
27. Thilo C, Schoepf UJ, Gordon L, Chiaramida S, Serguson J, Costello P. Integrated assessment of coronary anatomy and myocardial perfusion using a retractable SPECT camera combined with 64-slice CT: initial experience. Eur Radiol 2009;19:845–56.
28. Bastarrika G, Ramos-Duran L, Rosenblum MA, Kang DK, Rowe GW, Schoepf UJ. Adenosine-stress dynamic myocardial CT perfusion imaging: initial clinical experience. Invest Radiol 2010;45:306–13.
29. Sicari R, Nihoyannopoulos P, Evangelista A, et al. Stress echocardiography expert consensus statement—executive summary: European Association of Echocardiography (EAE) (a registered branch of the ESC). Eur Heart J 2009;30:278–89.
30. Arnold JR, Karamitsos TD, Pegg TJ, et al. Adenosine stress myocardial contrast echocardiography for the detection of coronary artery disease: a comparison with coronary angiography and cardiac magnetic resonance. J Am Coll Cardiol Img 2010;3:934–43.
31. Fox K, Garcia MA, Ardissino D, et al. Guidelines on the management of stable angina pectoris: executive summary: the Task Force on the Management of Stable Angina Pectoris of the European Society of Cardiology. Eur Heart J 2006;27:1341–81.
32. Pijls NH, De Bruyne B, Peels K, et al. Measurement of fractional flow reserve to assess the functional severity of coronary-artery stenoses. N Engl J Med 1996;334:1703–8.
33. De Bruyne B, Baudhuin T, Melin JA, et al. Coronary flow reserve calculated from pressure measurements in humans. Validation with positron emission tomography. Circulation 1994;89:1013–22.
34. Watkins S, McGeoch R, Lyne J, et al. Validation of magnetic resonance myocardial perfusion imaging with fractional flow reserve for the detection of significant coronary heart disease. Circulation 2009;120:2207–13.
35. Virmani R, Burke AP, Farb A, Kolodgie FD. Pathology of the vulnerable plaque. J Am Coll Cardiol 2006;47:C13–8.
36. Larsen AI, Galbraith PD, Ghali WA, Norris CM, Graham MM, Knudtson ML. Characteristics and outcomes of patients with acute myocardial infarction and angiographically normal coronary arteries. Am J Cardiol 2005;95:261–3.
37. Kemp HG, Kronmal RA, Vlietstra RE, Frye RL. Seven-year survival of patients with normal or near normal coronary arteriograms: a CASS registry study. J Am Coll Cardiol 1986;7:479–83.
38. Bruschke AV, Kramer JR Jr., Bal ET, Haque IU, Detrano RC, Goormastic M. The dynamics of progression of coronary atherosclerosis studied in 168 medically treated patients who underwent coronary arteriography three times. Am Heart J 1989;117:296–305.
39. Waters D, Lesperance J, Francetich M, et al. A controlled clinical trial to assess the effect of a calcium channel blocker on the progression of coronary atherosclerosis. Circulation 1990;82:1940–53.
40. Dickersin K, Min YI. Publication bias: the problem that won't go away. Ann N Y Acad Sci 1993;703:135–46, discussion 146–8.
41. Easterbrook PJ, Berlin JA, Gopalan R, Matthews DR. Publication bias in clinical research. Lancet 1991;337:867–72.

Key Words: cardiovascular magnetic resonance imaging ■ meta-analysis ■ perfusion ■ positron emission tomography ■ single-photon emission computed tomography.

APPENDIX

For Supplementary Tables 1 through 6 and References, please see the online version of this article.