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GUIDELINES

Hybrid cardiac imaging: SPECT/CT and PET/CT. A joint position statement by the European Association of Nuclear Medicine (EANM), the European Society of Cardiac Radiology (ESCR) and the European Council of Nuclear Cardiology (ECNC)

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Abstract Improvements in software and hardware have enabled the integration of dual imaging modalities into hybrid systems, which allow combined acquisition of the different data sets. Integration of positron emission tomography (PET) and computed tomography (CT) scanners into PET/CT systems has shown improvement in the management of patients with cancer over stand-alone acquired CT and PET images. Hybrid cardiac imaging either with single photon emission computed tomography (SPECT) or PET combined with CT depicts cardiac and vascular anatomical abnormalities and their physiologic consequences in a single setting and appears to offer superior information compared with either stand-alone or side-by-side interpretation of the data sets in patients with known or suspected coronary artery disease (CAD). Hybrid systems are also advantageous for the patient because of the single short dual data acquisition. However, hybrid cardiac imaging has also generated controversy with regard to which patients should undergo such integrated examination for clinical effectiveness and minimization of costs and radiation dose, and if software-based fusion of images obtained separately would be a useful alternative. The European Association of Nuclear Medicine (EANM), the European Society of Cardiac Radiology (ESCR) and the European Council of

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Nuclear Cardiology (ECNC) in this paper want to present a position statement of the institutions on the current roles of SPECT/CT and PET/CT hybrid cardiac imaging in patients with known or suspected CAD.

Keywords Coronary angiography · Coronary artery disease · Hybrid cardiac imaging · PET/CT · SPECT/CT

Abbreviations

AC	Attenuation correction
CAC	Coronary artery calcium
CAD	Coronary artery disease
CCTA	Cardiac computed tomographic angiography
FFR	Fractional flow reserve
HR	Heart rate
ICA	Invasive coronary angiography
MACE	Major adverse cardiac event
MDCT	Multidetector computed tomography
MPI	Myocardial perfusion imaging
NPV	Negative predictive value
PET	Positron emission tomography
PPV	Positive predictive value
RCA	Right coronary artery
SPECT	Single photon emission computed tomography

Introduction

Multidetector computed tomography (MDCT) can now provide an angiographic visualization of the coronary arteries with reasonably high temporal and spatial resolution, offering an acceptable and attractive non-invasive alternative to invasive coronary angiography (ICA) [1]. On the other hand, it has been repeatedly demonstrated that myocardial perfusion imaging (MPI) with single photon emission computed tomography (SPECT) or positron emission tomography (PET) can reliably diagnose functionally significant coronary artery disease (CAD) and with great power predict short- and long-term prognosis [2–4].

Improvements in software [5] and hardware [6, 7] have enabled the integration of different imaging modalities into hybrid imaging. A recent survey regarding the use of hybrid imaging in Europe showed a wide heterogeneity in its current practice on the continent [8]. For the patient, the advantages of a single short non-invasive imaging procedure are obvious. A growing body of evidence is showing that combined use of cardiac computed tomographic angiography (CCTA) and MPI provides improved diagnostic accuracy for the non-invasive assessment of CAD [9–12]. However, hybrid cardiac imaging has also generated controversy with regard to which patients should undergo such integrated examination for clinical effectiveness and minimization of costs and radiation dose, and if software-based fusion of images obtained separately would be a useful alternative. The European Association of Nuclear Medicine (EANM), the European Society of Cardiac Radiology (ESCR) and the European Council of Nuclear Cardiology aim in this position statement to review the use of SPECT/CT and PET/CT hybrid cardiac imaging in patients with known or suspected CAD.

Stand-alone imaging

MPI

Prior to elective ICA, a test for ischaemia is strongly recommended by cardiological guidelines [2, 13, 14]; however, a recent retrospective analysis of 23,887 patients with stable CAD undergoing elective coronary angioplasty revealed that a stress testing prior to the procedure (either exercise treadmill, stress echocardiography or nuclear MPI) was performed in only 44% of patients [15]. MPI with SPECT is widely available and by far the best validated non-invasive method for this purpose [16]. MPI with SPECT is robust, not only in detecting haemodynamic obstructive CAD (with sensitivity and specificity >85%), but also in the quantification of the magnitude of jeopardized myocardium and assessing the extent of myocardial viability [16]. Ischaemic evaluation has shown superior prognostic value compared with visually analysed ICA, which adds no incremental prognostic value over the combination of gender, risk factors, exercise and SPECT MPI data [17, 18].

Although a normal or mildly abnormal SPECT MPI does not exclude the presence of subclinical non-obstructive CAD (rendering the patient prone to more aggressive cardiovascular risk modification), in a large cohort of patients it was associated with an annual major adverse cardiac event (MACE) rate of about 1%. This risk varies from a low of 0.3% for women to a high of nearly 2% for patients undergoing pharmacologic stress imaging [3, 19]. MPI is cost-effective as a gatekeeper to ICA in patients with stable chest pain [16, 20]. It has also been shown that patients with less reversible ischaemia on SPECT MPI have a survival advantage with medical therapy rather than revascularization, while those with more severe ischaemia are more likely to benefit from invasive procedures [21, 22]. In addition, in patients with apparently “false-positive” results in MPI, endothelial dysfunction can often be demonstrated, which is linked to adverse cardiovascular outcomes regardless of ICA visual anatomical findings [23]. The fourfold increase in cardiac risk associated with abnormal findings at SPECT MPI in patients with normal ICA further emphasizes the prognostic power of the technique [24].

However, SPECT MPI may fail to identify some of the lesions in multivessel CAD since the technique depicts only the territory supplied by the most severe stenosis. Balanced reduction of hyperaemic flow in patients with multivessel disease is probably rather rare but it may explain paradoxical underestimation of clinical risk in a normal or near-normal SPECT in high-risk cohorts.

PET MPI has higher spatial and temporal resolution than SPECT and inherently uses accurate depth-independent attenuation correction (AC), which allows quantification of basal and hyperaemic regional myocardial perfusion [25]. Quantification of regional perfusion appears to be useful in patients with diffuse CAD or balanced disease where the relative assessment of myocardial perfusion by SPECT may fail in uncovering true perfusion changes [26, 27]. PET is therefore supposed to have a higher accuracy than SPECT in the diagnosis of CAD, showing values of sensitivity and specificity ≥90% in two recent reviews [28, 29], although larger direct comparative studies between the two technologies are lacking. Several series with ^{82}Rb PET MPI reported an incremental contribution to prognostication by the addition of measurement of changes in the ejection fraction, improving the identification of multivessel CAD [30, 31]. It remains to be elucidated whether the improvement of accuracy of PET over gated SPECT will justify the higher costs. Clinical circumstances in which PET MPI may be particularly preferable to SPECT include obese patients with high soft tissue attenuation and patients with a higher pre-test likelihood of multivessel CAD [26].

MPI can reveal the existence and severity of perfusion abnormalities but without concerns about the responsible mechanism. Furthermore, MPI may be more difficult to interpret in patients with heart failure or cardiomyopathy, who usually have reduced and heterogeneous perfusion.

Cardiac CT imaging: coronary calcium assessment

Determination of coronary artery calcium (CAC) is supported by current guidelines, systematic reviews and large population studies reporting high MACE rates in patients with high CAC scores [32–34]. The risk of MACE increases with the extent of CAC, from an annual rate of 0.4% for patients with no CAC to an annual rate of ≥2% (similar to that of patients with established CAD) for patients with high CAC scores (≥400) [32]. However, this does not imply that a very high CAC confirms the presence of obstructive CAD or a very low or negative CAC completely excludes obstructive CAD (e.g. non-calcified plaques, typically present in younger patients or young smokers) [32]. Although increased calcium burden, atherosclerosis and obstructive CAD are correlated to each other, the relationship between calcified plaque burden and obstructive CAD is modest [35–37]. Information about CAC improves the pre-CCTA probability of obstructive CAD and can help in the interpretation of CCTA since the non-contrast scan used for CAC determination may demonstrate calcifications better than the contrast study used for CCTA.

Cardiac CT imaging: coronary angiography

Two prospective multicentre single-vendor clinical trials of the diagnostic accuracy of 64-row MDCT CCTA have been recently published [38, 39]. In the ACCURACY trial [38], 230 patients underwent CCTA and ICA. On a patient-based model, the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were 95, 83, 64 and 99%, respectively, to detect ≥50% stenosis and 94, 83, 48 and 99%, respectively, to detect a ≥70% stenosis. Interestingly, no differences in sensitivity and specificity were noted for non-obese compared to obese subjects (a subset particularly problematic for SPECT MPI) or for patients with a heart rate (HR) >65 bpm compared with ≤65 bpm. However, CAC scores >400 reduced specificity significantly. In the CORE 64 trial [39] 291 patients with CAC scores ≤600 and body mass index ≤40 underwent CCTA and ICA. On a patient-based model, the sensitivity, specificity, PPV and NPV to detect ≥50% stenosis were 85, 90, 91 and 83%, respectively. The relatively high PPV and low NPV in this trial could possibly relate with the high prevalence of obstructive CAD (56% of patients) in the patients studied. However, another prospective, multicentre, multi-vendor study with 64-row MDCT CCTA involving 360 symptomatic patients with acute and stable anginal syndromes and an even higher prevalence of CAD (68%) reported values of sensitivity, specificity, PPV and NPV for detecting ≥50% stenoses, on a patient-based model, of 99, 64, 86 and 97%, respectively. In this trial, no patients or segments were excluded because of impaired image quality attributable to either coronary motion or calcifications, which may give good reason for the low specificity reported [40].

These and other single-centre studies, with the exception of the CORE 64 trial, have consistently shown that CCTA has a particularly high NPV and allows the identification of CAD at an early stage, before emergence of ischaemia. The various studies conducted so far also underscore that CCTA tends to overestimate the degree of stenosis, especially in the presence of dense calcified plaques (blooming artefact) resulting in lower PPV [1, 41, 42]. In addition, CCTA has reduced sensitivity in vessel sizes <1.5 mm (distal coronary segments and side branches) [29]. Furthermore, CCTA does not report on myocardial perfusion or metabolism. Besides, the ability of CCTA to determine plaque burden is currently hampered by insufficient reproducibility and an interobserver variability for determining plaque volumes of up to

37% [43, 44]. Motion artefacts, an overly low signal to noise ratio if the correct timing of the contrast bolus in the coronary arteries fails and limited spatial resolution of MDCT as compared to ICA account for most of the variability. Therefore, at least a ≥64-row MDCT is necessary. In addition, CCTA requires a regular heart rhythm and a relatively low HR, which reduces the number of patients amenable to the testing.

Percent narrowing or absolute stenosis lumen area on ICA correlates poorly with the degree of impaired coronary flow reserve [45]. Likewise, it has been demonstrated that only half of the lesions considered significant on CCTA are linked with abnormal perfusion [9, 28, 46, 47] and that the anatomical assessment of the haemodynamic significance of coronary stenoses determined by visual or quantitative CCTA does not correlate well with the functional assessment of intracoronary fractional flow reserve (FFR) [48]. These data indicate that coronary atherosclerosis with apparent luminal obstruction does not necessarily imply the presence of ischaemia. Although a normal CCTA practically excludes relevant haemodynamic CAD, the inverse is frequently not true. Many factors can influence the relation between anatomical findings and haemodynamic consequences, which cannot be fully clarified by anatomical evaluation alone [49]. This is particularly true in intermediate lesions, which warrant further perfusion imaging testing to identify those patients that may benefit from revascularization [50, 51].

At present, preliminary findings suggest that several coronary lesion characteristics by CCTA (stenosis severity and location, plaque composition and distribution, overall plaque burden and vascular remodelling) are useful for the prediction of MACE in a manner, which is incremental to clinical risk assessment, CAC and MPI. Inducible ischaemia appears to be more common in more advanced plaques (i.e. mixed or calcified plaques, in which constrictive remodelling results in flow limitations) than in non-calcified plaques, which would be more vulnerable to progression to acute coronary syndromes [52, 53]. Patients with no detectable plaque by CCTA appear to have an excellent prognosis with an annual event rate of 0.3% [54]. Further data from larger cohorts and multiple centres are needed to confirm these early findings and further delineate the additive value of CCTA in symptomatic individuals with suspected CAD.

Hybrid imaging

The purpose of hybrid imaging, i.e. SPECT or PET combined with CT, is to provide an accurate spatial alignment between two separate data sets into one fused image that provides information beyond that achievable with either stand-alone or side-by-side interpretation of the data sets, and beyond the information derived from AC. In hybrid imaging both data sets contribute equally to the image information, reducing the number of equivocal results [55].

Hybrid cardiac SPECT/CT [9] or PET/CT imaging [56] performed in one session has been proposed for dual system scanners equipped with MDCT. This integration of MPI/CCTA into one single hybrid system allows a patient-friendly image acquisition in only one visit to the imaging department and, additionally, needs less personnel compared with two stand-alone scanners, which may result in reduced healthcare costs. Furthermore, AC of the MPI data can also be performed with minimal effort by using the CAC scoring CT examination [57]. However, software coregistration is still required because the acquisition of emission and transmission data, albeit performed without moving the patient from the bed, is not simultaneous, and also because of mismatches in the respiratory phases between the two data sets [9].

Hybrid systems are now so well established in oncology that new PET scanners are only sold as PET/CT scanners. Nevertheless, in cardiac imaging the hybrid scanners are not used routinely because of the difficulty in predicting a priori which patients would benefit from the dual scanning. Furthermore, despite the fact that it has not been proved that >64-row MDCT would improve the diagnostic accuracy, most advanced scanners are preferred for CCTA, because they allow imaging of the entire heart region within a single heart beat. These high-end CT systems are currently not offered in hybrid configurations, and it is not likely that they will be in the near future due to the high cost involved and the limitation that long PET acquisitions pose to the CT workflow [58]. In addition, it has been suggested that only 15–30% of patients might require combined multimodality cardiac imaging and that these patients cannot be identified before one of the scans is performed [59]. Therefore, a sequential diagnostic approach is often applied in clinical practice, with additional scans (CCTA or MPI) performed only if the results of the initial modality are equivocal; however, when CCTA is performed first, about 50% of the patients will need perfusion imaging [27].

Hybrid MPI and CCTA with reliable image coregistration and fusion of three-dimensional information of myocardial territories onto their subtending coronary arteries can accurately allocate the culprit lesion in multivessel CAD, which is particularly important because the so-called standard distribution of myocardial perfusion territories does not correspond with the real world of coronary anatomy in more than half of the cases [60, 61]. Combining anatomical with perfusion data also helps to identify and correctly register possible subtle irregularities in myocardial perfusion. The reduced sensitivity of CCTA

in distal coronary segments and side branches can be offset by the MPI information. On the other hand, CCTA improves the detection of multivessel CAD, which as stated earlier is one of the main pitfalls of semiquantitative MPI. Finally, the assessment of regional myocardial perfusion and viability together with the coronary artery tree eliminates uncertainties in the relationship of perfusion defects, scar regions and diseased coronary arteries in watershed regions, which may be particularly helpful in patients with multiple perfusion abnormalities and multivessel CAD, including previous revascularization procedures.

CT for MPI attenuation correction

Non-homogeneous photon attenuation in the thorax is one of the most important drawbacks of MPI, limiting the diagnostic accuracy, interpretive confidence, quantification and laboratory efficiency. On the one hand, attenuation artefacts may reduce MPI specificity, since non-uniform, regional perfusion distribution may be misinterpreted as a perfusion defect. On the other hand, attenuation artefacts may also reduce MPI sensitivity when images are improperly scaled to regions suppressed by attenuation, potentially masking true perfusion defects. To overcome this problem, MPI images are corrected by determination of photon attenuation from intervening tissue in the volume of interest. Unfortunately, cardiac imaging poses a particular difficulty for AC because of respiratory and cardiac motion [62, 63]. AC using the integration of CT components was a major step forward, improving the specificity of SPECT MPI to 80–90% [64]. Finally, AC images improve the confidence of the final interpretation by the physician, allowing emergency department use or making a stress-only approach more feasible.

Both PET/CT [65] and SPECT/CT [66] studies have shown that low-dose CT acquisitions are feasible for AC. However, a potential misalignment between emission and transmission data poses the risk of incomplete correction and thus artificial perfusion defects and requires careful quality control to avoid reconstruction artefacts. PET/CT [67, 68] and SPECT/CT [69, 70] studies have shown that the frequency of misalignment is quite high and the consequences clinically significant if not corrected. Recently, it has been shown that the effects of misalignment are less severe for SPECT/CT than for PET/CT, mainly because of reduced spatial resolution of SPECT [71]. The alignment of emission and transmission data is usually performed manually, a process that contributes to certain variability. However, automated methods for quality control are under investigation [72, 73]. It is relevant that even low-quality CT scans for AC can provide clinically useful extracardiac information that may result in legal liabilities if they are not taken into account [74].

Integration of CAC with MPI

The common trend toward the integration of low- and medium-quality CT devices into hybrid systems converts the less demanding imaging of CAC into a surrogate marker of atherosclerosis, as opposed to high-end systems suitable for the anatomical assessment of the coronary tree with CCTA. Simplistically, the addition of a CAC scan may be viewed as a “poor man’s” CCTA [75].

Detection of CAC has been shown to provide incremental value to MPI [76–78]. Specifically, when MPI is normal, the addition of a CAC score can improve the detection of CAD, particularly severe multivessel CAD. For patients with normal stress MPI, higher MACE rates are associated with higher CAC scores, especially in patients with known CAD or with greater comorbidity [75]. The documentation of CAC as a direct marker of atherosclerosis can be used to target patients requiring more intensive management of risk factors (such as secondary prevention goals in the presence of high levels of CAC).

Integration of MPI with CCTA

Sato el al. [12] recently reported superior performance of side-by-side interpretation of ^{201}Tl SPECT/64-row MDCT for detecting ≥50% stenosis on ICA than CCTA alone in patients with suspected CAD. Most of the patients had an intermediate pre-test likelihood of disease. Fourteen percent of the arteries were non-evaluable by CCTA (due to severe calcifications, motion artefacts and/or poor opacification) but were considered positive on the basis of an intention-to-diagnose analysis. Compared to CCTA alone, the combination of SPECT and CCTA resulted in a significant increase in specificity (from 80 to 92%) and PPV (from 69 to 85%) without any change in sensitivity (95%) and NPV (97%). This effect was preserved across all vascular territories and on a patient-based analysis.

The incremental prognostic value of CCTA over MPI has also been documented in a recent multicentre study of 541 patients at intermediate risk for CAD [54]. The annual event rate was 1.8% in patients with none or mild CAD by CCTA and 4.8% in patients with significant CAD by CCTA. Similarly, a normal MPI and abnormal MPI were associated with an event rate of 1.1 and 3.8%, respectively. After adjustment for clinical risk factors, obstructive plaque visualized by CCTA and abnormal MPI were independent predictors of late events, with significant incremental improved prediction of risk by the combination of the two modalities compared with either modality alone. An annual event rate of 1% was found in those with concordantly normal CCTA and MPI, and conversely those with concordantly abnormal CCTA and MPI had an event rate of 9%. Furthermore, the presence of non-calcified plaques

provided incremental prognostic information over baseline clinical variables, MPI and significant CAD on CCTA. Therefore, when used in combination with MPI, CCTA not only provides complementary information about the presence, extent and composition of atherosclerosis, but importantly also results in improved risk stratification compared with the use of MPI alone.

Other studies have underscored the incremental diagnostic accuracy of coregistration and fusion of stand-alone acquired MPI and CCTA over side-by-side interpretation (Table 1) [10, 11, 79]. These reports indicate that CCTA tends to overestimate coronary stenoses, and the combination with MPI allows identification of many false-positive CCTA findings. The specificity and PPV of stand-alone CCTA are particularly suboptimal in the presence of motion artefacts or severe coronary calcifications. Non-evaluable, severely calcified vessels especially benefit from further testing due to the relatively high likelihood of obstructive disease, whereas non-evaluable vessels with motion artefacts [particularly in the right coronary artery (RCA) territory] do not usually have haemodynamic significance [12]. Image fusion is of particular value in lesions of distal segments, diagonal braches, RCA and left circumflex artery [10, 11].

The feasibility and clinical robustness of integrated hybrid cardiac imaging was first documented by Namdar et al. in 2005 using a hybrid PET/4-row MDCT system [80]. Subsequent studies [9, 12, 47, 81] have shown that CCTA, despite an excellent NPV regarding exclusion of CAD, is not reliable for the exclusion of myocardial ischaemia. Conversely, a normal stress PET MPI is a poor discriminator of patients with subclinical or "not flow-limiting" CAD. Integration of both techniques thus has a complementary role in the evaluation of patients with suspected CAD (Table 2), with improved specificity and PPV and minor decrease in sensitivity and NPV as compared to CCTA alone. Kajander et al. [27] recently compared PET/CT (quantitative PET with ^{15}O-water) with ICA, including measurement of FFR when appropriate and feasible, in patients with stable chest pain with moderate pre-test likelihood of CAD. Interestingly, all patients entered ICA independently of the non-invasive imaging results, which provided unbiased data about the potential of hybrid imaging (Table 2) [27]. Although both stand-alone PET and CT provided excellent exclusion of CAD, false-positive findings were not uncommon. Hybrid imaging was significantly more accurate per patient than CTA or PET alone (98 vs 90 and 92%, respectively) and it was significantly better also in the vessel analysis (98 vs 91 and 92%, respectively).

The clinical results obtained so far support that the integrated use of SPECT or PET and CCTA by coregistration and fusion of either stand-alone or combined acquired images offers incremental diagnostic value beyond that of either device alone and that of side-by-side analysis in patients at intermediate risk for CAD. Integration of dual imaging appears to improve both the identification of the culprit vessel and the diagnostic confidence for categorizing intermediate lesions and equivocal perfusion defects, and provides added diagnostic information in almost one third of patients as compared to side-by-side analysis, thus optimizing management decisions.

Radiation exposure from hybrid imaging

The effective radiation dose for patients undergoing any of the aforementioned procedures (including ICA) lies between 1 and 20 mSv. Therefore, one of the obvious limitations of hybrid imaging is related to patient radiation dose. Indeed, active discussion is ongoing about the radiation risks of imaging even with regard to stand-alone CT [82, 83].

Effective patient radiation doses from different SPECT and PET examinations are shown in Table 3. As can be seen, the dose by routine stress-rest perfusion PET is lower than that given by SPECT [84]. For SPECT examinations, the use of ^{99m}Tc-labelled agents is associated with lower radiation dose than the use of ^{201}Tl. SPECT radiation dose can be markedly reduced with the combination of new iterative reconstruction methods and dedicated detectors and collimators optimized specifically for MPI [7, 85]. In addition, the omission of the rest study when the stress

Table 1 Diagnostic value of SPECT/CT or PET/CT software image fusion compared with side-by-side analysis

Technology	*N*	Benefit by hybrid imaging	Reference
SPECT/64-row MDCT and 3-D image fusion	38 patients with ≥1 SPECT defects	Among equivocal lesions, haemodynamic significance is confirmed in 35% and excluded in 25%	10
16- and 64-row MDCT and MPI (SPECT or ^{82}Rb PET)	50 patients suspected of CAD	Modification of the initial interpretation in 28% of the cases Trend to increase in 17% the sensitivity in patients with multivessel disease	11
Automated SPECT/64-row MDCT registration software	35 patients suspected of CAD	Improved diagnostic performance in the RCA and LCx, not in LAD	79

N number of patients, *RCA* right coronary artery, *LCx* left circumflex artery, *LAD* left anterior descending artery

Table 2 Diagnostic value of hybrid imaging with PET/CT or SPECT/CT

Hybrid system	*N*	Sens./ spec. (%)	PPV/NPV (%)	Gold standard	Reference
$^{13}NH_3$ PET/4-row MDCT	25	90/98	82/99	Identification of flow-limiting lesions requiring revascularization (according to ICA and PET)	80
^{82}Rb PET/64-row MDCT	33	96/100	100/91	Detection of >50% stenoses on ICA	81
SPECT/16-row MDCT	56	96/95	77/99	Detection of >50% stenoses on ICA	9
^{82}Rb PET/16- or 64-row MDCT	110			Presence of ischaemia on stress PET	47
				47% of significant stenoses on CCTA had normal PET; 50% of normal PET studies had some abnormality on CCTA	
$H_2{}^{15}O$ PET/64-row MDCT	107	95/100	100/98	Detection of ≥50% stenoses on ICA (and measurement of FFR when appropriate and feasible)	27

N number of patients, *Sens./spec.* sensitivity/specificity, *PPV/NPV* positive predictive value/negative predictive value, *FFR* fractional flow reserve

study is normal significantly reduces the radiation dose [86]. Recently, a statement document has been published considering the best practice methods to optimize the benefits of MPI by obtaining the highest quality diagnostic images while minimizing radiation exposure [87].

The effective patient radiation dose from cardiac CT varies widely depending on the protocol, instrumentation and patient size. Radiation dose is minimal (approximately 1 mSv) for a CAC scan, which can also be used to perform MPI AC [57]. The dose tends to be higher with lower slice thickness since the radiation dosage must be increased to obtain the same signal to noise ratio [82]. In a recent study of 1,965 CCTA examinations performed at 50 study sites in a cross-sectional, international, multicentre study, the estimated mean radiation dose was 12 mSv (interquartile range: 8–18 mSv) [88]. These results are in line with the radiation dose reported in previous studies of the accuracy of 64-slice CCTA [39]. Implementation of modern cardiac CT acquisition protocols such as prospective (step-and-shoot) ECG triggering [89, 90], ECG-controlled current modulation (reduction of the tube current by 80% during systole) [42] and body mass-adapted tube voltage (reduction of the tube voltage to 100 kV in patients <90 kg of weight) [91] allows reduction of the radiation dose from CCTA by 60–80%. With the latest technology on dual source CTs using prospectively triggered high-pitch spiral acquisition, it is also possible to acquire CCTAs with a dose below 1 mSV [92].

Recently, Javadi et al. [93] reported their initial experience with a prospective ECG-triggering CCTA protocol applied by use of hybrid PET/CT cardiac imaging with ^{82}Rb. The dose-length product-derived effective patient dose for CCTA was 5.5 mSv, with no difference in the number of evaluable coronary artery segments compared to conventional helical CCTA. This means that with the usually administered activity of ^{82}Rb (Table 1), the complete hybrid examination can be performed with a radiation dose of about 13–15 mSv. Likewise, Kajander et al. [94] reported a mean radiation dose of 9.5 mSv for a combined ^{15}O-water rest-stress PET perfusion/prospectively triggered CCTA protocol, with a mean effective dose of 7.6 mSv for the CT acquisition. The protocol could be applied to 87% of the patients with CT image quality comparable to conventional spiral acquisition. Husmann et al. [91] in a study with stress-only hybrid ^{99m}Tc-tetrofosmin SPECT/CT imaging have reported a total radiation dose of 5.4 mSv for a combined study using prospective ECG-triggering CT acquisition.

Table 3 Effective radiation dose for adult patients from radiopharmaceuticals used in nuclear cardiology

Radiopharmaceutical	Procedure	Effective dose (mSv/MBq)
^{99m}Tc-sestamibi	Rest (UAA: 300–1,200 MBq)	9.0E-03
	Stress (UAA: 300–1,200 MBq)	7.9E-03
^{99m}Tc-tetrofosmin	Rest (UAA: 300–1,200 MBq	7.6E-03
	Stress (UAA: 300–1,200 MBq)	7.0E-03
^{201}Tl-chloride	Stress/rest (UAA: 74–111 MBq)	2.1E-01
^{18}F-fluorodeoxyglucose	Rest (UAA: 200–350 MBq)	1.9E-02
^{13}N-ammonia	Rest or stress (UAA: 370–740 MBq)	2.0E-03
^{82}Rb-chloride	Rest or stress (UAA: 1,100–1,500 MBq)	3.4E-03
^{15}O-water	Rest or stress (UAA: 700–1,500 MBq)	9.3E-04

Adapted from [99]

UAA usually administered activity, adapted from [100]

Regarding the radiation exposure to the professional staff, PET studies, because of the emission of high-energy photons, are theoretically associated with higher radiation dose than SPECT studies. However, differences in radiotracer administration, scan acquisition and stress testing tend to lower the occupational exposure by PET compared to SPECT [95]. Occupational radiation exposure from MDCT will be minimal if the staff leaves the room during the procedures.

Clinical use of hybrid imaging (Fig. 1)

There is general agreement that clinical use of imaging should depend on the pre-test likelihood of CAD. Because software registration can reliably bring MPI and CCTA data acquired on different scanners into appropriate alignment, for most sites the practical current approach for overall clinical effectiveness and the minimization of the cost and radiation dose may be sequential scanning, facilitated by software tools for automatic image registration and fusion [79]. In the sites with appropriate infrastructure and tracer availability single session hybrid imaging is likely to be preferred since it gives obvious benefits for the patients. Based on the aforementioned published studies, for symptomatic patients without known CAD and low to moderate pre-test likelihood of disease (i.e. <50% likelihood), typically young and middle-aged patients, CCTA would probably be essential to (virtually) exclude CAD. When it is normal further diagnostic tests are avoided; however, abnormal or equivocal findings have to be confirmed or rejected by MPI or ICA. Thus, hybrid imaging leads to a more rapid diagnosis in these patients. This has been demonstrated by the higher normalcy rate reported by several of the studies mentioned above and could be applied for the proposed stepwise diagnostic approach, when initial tests yield equivocal results and further assessment to exclude CAD with final certainty is needed. So far many of these patients are referred for ICA, while hybrid imaging offers a substantially improved diagnostic confidence, resulting in a reduction of the number of patients today unnecessarily exposed to ICA.

MPI might be a better first-line test compared with CCTA in patients with higher pre-test likelihood of disease (i.e. >50% likelihood), characteristically those with known CAD or older age, likely to have extensive CAC [96], and patients with known or suspected microvascular endothelial dysfunction, e.g. diabetics [12]. CCTA can be added in the presence of equivocal MPI findings suggestive of artefacts, microvascular disease or multivessel disease. Also in these patients hybrid imaging improves diagnostic accuracy, providing a complete evaluation of haemodynamic relevance of coronary stenoses and assessment of viability in territories subtended by occluded arteries. The accurate spatial association of coronary stenoses and perfusion defects allows evaluation of haemodynamic properties of even fairly small coronary branches allowing for timely and appropriate treatment.

For asymptomatic patients with moderate pre-test likelihood of disease, CAC imaging is recommended as a reasonable choice for refining the risk stratification [97].

Conclusions

Improvements in software and hardware have recently enabled the integration of different imaging modalities into hybrid imaging, producing important changes in the study of patients with known or suspected CAD. Rapid technological development makes it difficult to obtain evidence-based algorithms for the use of old and new imaging modalities before the technology tested becomes outdated. However, hybrid cardiac imaging combining SPECT or PET with MDCT data is an extremely promising non-invasive cardiac imaging tool, allowing detection and quantification of the burden of the extent of calcified and

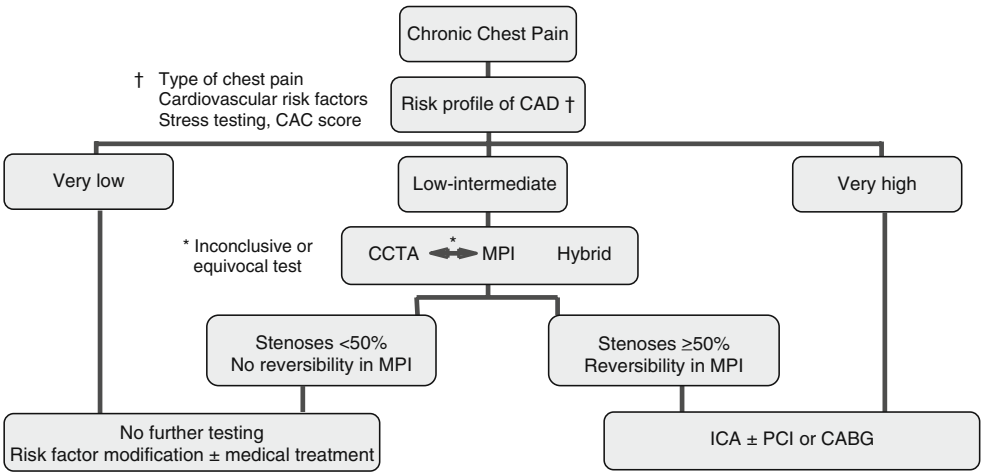

Fig. 1 Proposed clinical algorithm for the use of imaging techniques in patients with chronic chest pain. *CABG* coronary artery bypass grafting, *CAD* coronary artery disease, *CCTA* cardiac computed tomographic angiography, *ICA* invasive coronary angiography, *MPI* myocardial perfusion imaging (SPECT or PET), *PCI* percutaneous coronary intervention

non-calcified plaques (CAC and coronary angiography), quantification of vascular reactivity and endothelial dysfunction, identification of flow-limiting coronary stenoses and assessment of myocardial viability. Thus, hybrid imaging appears to offer superior diagnostic and prognostic information in patients with intermediate risk for CAD compared with either stand-alone or side-by-side interpretation of the data sets, and beyond the information derived from AC. Furthermore, integration of the detailed anatomical information from MDCT with the high sensitivity of MPI can be used to evaluate targeted molecular and cellular abnormalities; thus, in the future it may play an important role in molecular diagnostics and therapeutics. However, the clinical impact and incremental value of integrated imaging need to be evaluated and confirmed in larger cohorts and multicentre investigations. Moreover, increased imaging costs and radiation doses associated with hybrid imaging must be taken into consideration. It is anticipated that the ongoing prospective multicentre trials such as SPARC and EVINCI will bring important information about the prognostic value and post-test resource utilization of SPECT, PET and CCTA in current clinical practice [98].

Disclaimer This position statement summarizes the views of the Cardiovascular Committee of the EANM, the ESCR and the ECNC, for which the EANM, European Society of Radiology (ESR) and the European Society of Cardiology (ESC) cannot be held responsible.

References

1. Schroeder S, Achenbach S, Bengel F, Burgstahler C, Cademartiri F, de Feyter P, et al. Cardiac computed tomography: indications, applications, limitations, and training requirements: report of a Writing Group deployed by the Working Group Nuclear Cardiology and Cardiac CT of the European Society of Cardiology and the European Council of Nuclear Cardiology. Eur Heart J 2008;29:531–56.
2. Klocke FJ, Baird MG, Lorell BH, Bateman TM, Messer JV, Berman DS, et al. ACC/AHA/ASNC guidelines for the clinical use of cardiac radionuclide imaging—executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/ASNC Committee to Revise the 1995 Guidelines for the Clinical Use of Cardiac Radionuclide Imaging). J Am Coll Cardiol 2003;42:1318–33.
3. Shaw LJ, Iskandrian AE. Prognostic value of gated myocardial perfusion SPECT. J Nucl Cardiol 2004;11:171–85.
4. Marcassa C, Bax JJ, Bengel F, Hesse B, Petersen CL, Reyes E, et al. Clinical value, cost-effectiveness, and safety of myocardial perfusion scintigraphy: a position statement. Eur Heart J 2008;29:557–63.
5. Slomka PJ, Baum RP. Multimodality image registration with software: state-of-the-art. Eur J Nucl Med Mol Imaging 2009;36 Suppl 1:S44–55.
6. Schäfers KP, Stegger L. Combined imaging of molecular function and morphology with PET/CT and SPECT/CT: image fusion and motion correction. Basic Res Cardiol 2008;103:191–9.
7. Slomka PJ, Patton JA, Berman DS, Germano G. Advances in technical aspects of myocardial perfusion SPECT imaging. J Nucl Cardiol 2009;16:255–76.
8. Cuocolo A, Breatnach E. Multimodality imaging in Europe: a survey by the European Association of Nuclear Medicine (EANM) and the European Society of Radiology (ESR). Eur J Nucl Med Mol Imaging 2010;37:163–7.
9. Rispler S, Keidar Z, Ghersin E, Roguin A, Soil A, Dragu R, et al. Integrated single-photon emission computed tomography and computed tomography coronary angiography for the assessment of hemodynamically significant coronary artery lesions. J Am Coll Cardiol 2007;49:1059–67.
10. Gaemperli O, Schepis T, Valenta I, Husmann L, Scheffel H, Duerst V, et al. Cardiac image fusion from stand-alone SPECT and CT: clinical experience. J Nucl Med 2007;48:696–703.
11. Santana CA, Garcia EV, Faber TL, Sirineni GKR, Esteves FP, Sanyal R, et al. Diagnostic performance of fusion of myocardial perfusion imaging (MPI) and computed tomography coronary angiography. J Nucl Cardiol 2009;16:201–11.
12. Sato A, Nozato T, Hikita H, Miyazaki S, Takahashi Y, Kuwahara T, et al. Incremental value of combining 64-slice computed tomography angiography with stress nuclear myocardial perfusion imaging to improve noninvasive detection of coronary artery disease. J Nucl Cardiol 2010;17:19–26.
13. Smith Jr SC, Dove JT, Jacobs AK, Kennedy JW, Kereiakes D, Kern MJ, et al. ACC/AHA guidelines of percutaneous coronary interventions (revision of the 1993 PTCA guidelines)—executive summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (committee to revise the 1993 guidelines for percutaneous transluminal coronary angioplasty). J Am Coll Cardiol 2001;37:2215–39.
14. Fox K, Garcia MA, Ardissino D, Buszman P, Camici PG, Crea F, 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.
15. Lin GA, Dudley RA, Lucas FL, Malenka DJ, Vittinghoff E, Redberg RF. Frequency of stress testing to document ischemia prior to elective percutaneous coronary intervention. JAMA 2008;300:1765–73.
16. Underwood SR, Anagnostopoulos C, Cerqueira M, Ell PJ, Flint EJ, Harbinson M, et al. Myocardial perfusion scintigraphy: the evidence. Eur J Nucl Med Mol Imaging 2004;31:261–91.
17. Iskandrian AS, Chae SC, Heo J, Stanberry CD, Wasserleben V, Cave V. Independent and incremental prognostic value of exercise single-photon emission computed tomographic (SPECT) thallium imaging in coronary artery disease. J Am Coll Cardiol 1993;22:665–70.
18. Pancholy SB, Fattah AA, Kamal AM, Ghods M, Heo J, Iskandrian AS. Independent and incremental prognostic value of exercise thallium single-photon emission computed tomographic imaging in women. J Nucl Cardiol 1995;2(Pt 1):110–6.
19. 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.
20. Shaw LJ, Heller GV, Travin MI, Lauer M, Marwick T, Hachamovitch R, et al. Cost analysis of diagnostic testing for coronary artery disease in women with stable chest pain. Economics of Noninvasive Diagnosis (END) Study Group. J Nucl Cardiol 1999;6:559–69.
21. Boden WE, O'Rourke RA, Teo KK, Hartigan PM, Maron DJ, Kostuk WJ, et al. Optimal medical therapy with or without PCI for stable coronary disease. N Engl J Med 2007;356:1503–16.
22. Hachamovitch R, Hayes SW, Friedman JD, Cohen I, Berman DS. Comparison of the short-term survival benefit associated

with revascularization compared with medical therapy in patients with no prior coronary artery disease undergoing stress myocardial perfusion single photon emission computed tomography. Circulation 2003;107:2900–7.
23. von Mering GO, Arant CB, Wessel TR, McGorray SP, Bairey Merz CN, Sharaf BL, et al. Abnormal coronary vasomotion as a prognostic indicator of cardiovascular events in women: Results from the National Heart, Lung, and Blood Institute-Sponsored Women's Ischemia Syndrome Evaluation (WISE). Circulation 2004;109:722–5.
24. Adamu U, Knollmann D, Almutairi B, Alrawashdeh W, Deserno V, Vogt F, et al. Stress/rest myocardial perfusion scintigraphy in patients without significant coronary artery disease. J Nucl Cardiol 2010;17:38–44.
25. Knuuti J, Kajander S, Mäki M, Ukkonen H. Quantification of myocardial blood flow will reform the detection of CAD. J Nucl Cardiol 2009;16:497–506.
26. Le Guludec D, Lautamäki R, Knuuti J, Bax JJ, Bengel FM, European Council of Nuclear Cardiology. Present and future of clinical cardiovascular PET imaging in Europe—a position statement by the European Council of Nuclear Cardiology (ECNC). Eur J Nucl Med Mol Imaging 2008;35:1709–24.
27. Kajander SA, Joutsiniemi E, Saraste M, Pietilä M, Ukkonen H, Saraste A, et al. Cardiac positron emission tomography/computed tomography imaging accurately detects anatomically and functionally significant coronary artery disease. Circulation 2010 (Epub Jul 26).
28. Machac J. Cardiac positron emission tomography imaging. Semin Nucl Med 2005;35:17–36.
29. Di Carli MF, Hachamovitch R. New technology for noninvasive evaluation of coronary artery disease. Circulation 2007;115:1464–80.
30. Dorbala S, Vangala D, Sampson U, Limaye A, Kwong R, Di Carli MF. Value of vasodilator left ventricular ejection fraction reserve in evaluating the magnitude of myocardium at risk and the extent of angiographic coronary artery disease: an 82Rb PET/CT study. J Nucl Med 2007;48:349–58.
31. Lertsburapa K, Ahlberg AW, Bateman TM, Katten D, Volker L, Cullom SJ, et al. Independent and incremental prognostic value of left ventricular ejection fraction determined by stress gated rubidium 82 PET imaging in patients with known or suspected coronary artery disease. J Nucl Cardiol 2008;15:745–53.
32. Greenland P, Bonow RO, Brundage BH, Budoff MJ, Eisenberg MJ, Grundy SM, et al. ACCF/AHA 2007 clinical expert consensus document on coronary artery calcium scoring by computed tomography in global cardiovascular risk assessment and in evaluation of patients with chest pain: a report of the American College of Cardiology Foundation Clinical Expert Consensus Task Force (ACCF/AHA Writing Committee to Update the 2000 Expert Consensus Document on Electron Beam Computed Tomography) developed in collaboration with the Society of Atherosclerosis Imaging and Prevention and the Society of Cardiovascular Computed Tomography. J Am Coll Cardiol 2007;49:378–402.
33. Bellasi A, Lacey C, Taylor AJ, Raggi P, Wilson PW, Budoff MJ, et al. Comparison of prognostic usefulness of coronary artery calcium in men versus women (results from a meta- and pooled analysis estimating all-cause mortality and coronary heart disease death or myocardial infarction). Am J Cardiol 2007;100:409–14.
34. Detrano R, Guerci AD, Carr JJ, Bild DE, Burke G, Folsom AR, et al. Coronary calcium as a predictor of coronary events in four racial or ethnic groups. N Engl J Med 2008;358:1336–45.
35. Budoff MJ, Diamond GA, Raggi P, Arad Y, Guerci AD, Callister TQ, et al. Continuous probabilistic prediction of angiographically significant coronary artery disease using electron beam tomography. Circulation 2002;105:1791–6.
36. Rumberger JA, Schwartz RS, Simons DB, Sheedy 3rd PF, Edwards WD, Fitzpatrick LA. Relation of coronary calcium determined by electron beam computed tomography and lumen narrowing determined at autopsy. Am J Cardiol 1994;73:1169–73.
37. Rumberger JA, Simons DB, Fitzpatrick LA, Sheedy PF, Schwartz RS. Coronary artery calcium area by electron-beam computed tomography and coronary atherosclerotic plaque area. A histopathologic correlative study. Circulation 1995;92:2157–62.
38. Budoff MJ, Dowe D, Jollis JG, Gitter M, Sutherland J, Halamert E, et al. 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;52:1724–32.
39. Miller JM, Rochitte CE, Dewey M, Arbab-Zadeh A, Niinuma H, Gottlieb I, et al. Diagnostic performance of coronary angiography by 64-row CT. N Engl J Med 2008;359:2324–36.
40. Meijboom WB, Meijs MF, Schuijf JD, Cramer MJ, Mollet NR, van Mieghem CA, et al. Diagnostic accuracy of 64-slice computed tomography coronary angiography: a prospective, multicenter, multivendor study. J Am Coll Cardiol 2008;52:2135–44.
41. Cademartiri F, Schuijf JD, Mollet NR, Malagutti P, Runza G, Bax JJ, et al. Multislice CT coronary angiography: how to do it and what is the current clinical performance? Eur J Nucl Med Mol Imaging 2005;32:1337–47.
42. Hoffmann U, Ferencik M, Cury RC, Pena AJ. Coronary CT angiography. J Nucl Med 2006;47:797–806.
43. Leber AW, Becker A, Knez A, von Ziegler F, Sirol M, Nikolaou K, et al. Accuracy of 64-slice computed tomography to classify and quantify plaque volumes in the proximal coronary system: a comparative study using intravascular ultrasound. J Am Coll Cardiol 2006;47:672–7.
44. Ferencik M, Nieman K, Achenbach S. Noncalcified and calcified coronary plaque detection by contrast-enhanced multi-detector computed tomography: a study of interobserver agreement. J Am Coll Cardiol 2006;47:207–9.
45. Gould KL. Identifying and measuring severity of coronary artery stenosis. Quantitative coronary arteriography and positron emission tomography. Circulation 1988;78:237–45.
46. Hacker M, Jakobs T, Hack N, Nikolaou K, Becker C, von Ziegler F, et al. Sixty-four slice spiral CT angiography does not predict the functional relevance of coronary artery stenoses in patients with stable angina. Eur J Nucl Med Mol Imaging 2007;34:4–10.
47. Di Carli MF, Dorbala S, Curillova Z, Kwong RJ, Goldhaber SZ, Rybicki FJ, et al. Relationship between CT coronary angiography and stress perfusion imaging in patients with suspected ischemic heart disease assessed by integrated PET-CT imaging. J Nucl Cardiol 2007;14:799–809.
48. Meijboom WB, Van Mieghem CA, van Pelt N, Weustink A, Pugliese F, Mollet NR, et al. Comprehensive assessment of coronary artery stenoses: computed tomography coronary angiography versus conventional coronary angiography and correlation with fractional flow reserve in patients with stable angina. J Am Coll Cardiol 2008;52:636–43.
49. Schelbert HR. Anatomy and physiology of coronary blood flow. J Nucl Cardiol 2010;17:545–54.
50. Hachamovitch R, Hayes SW, Friedman JD, Cohen I, Berman DS. Comparison of the short-term survival benefit associated with revascularization compared with medical therapy in patients with no prior coronary artery disease undergoing stress myocar-

dial perfusion single photon emission computed tomography. Circulation 2003;107:2900–7.
51. Shaw LJ, Berman DS, Maron DJ, Mancini GB, Hayes SW, Hartigan PM, et al. Optimal medical therapy with or without percutaneous coronary intervention to reduce ischemic burden: results from the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial nuclear substudy. Circulation 2008;117:1283–91.
52. Narula J, Garg P, Achenbach S, Motoyama S, Virmani R, Strauss HW. Arithmetic of vulnerable plaques for noninvasive imaging. Nat Clin Pract Cardiovasc Med 2008;5:S2–S10.
53. Healy KO, Axsom K, Min JK. Prognosis and coronary computed tomographic angiography: current and emerging concepts. J Nucl Cardiol 2009;16:981–8.
54. van Werkhoven JM, Schuijf JD, Gaemperli O, Jukema JW, Boersma E, Wijns W, et al. Prognostic value of multislice computed tomography and gated single-photon emission computed tomography in patients with suspected coronary artery disease. J Am Coll Cardiol 2009;53:623–32.
55. Kaufmann PA. Cardiac hybrid imaging: state-of-the-art. Ann Nucl Med 2009;23:325–31.
56. Di Carli MF, Dorbala S, Hachamovitch R. Integrated cardiac PET-CT for the diagnosis and management of CAD. J Nucl Cardiol 2006;13:139–44.
57. Schepis T, Gaemperli O, Koepfli P, Rüegg C, Burger C, Leschka S, et al. Use of coronary calcium score scans from stand-alone multislice computed tomography for attenuation correction of myocardial perfusion SPECT. Eur J Nucl Med Mol Imaging 2007;34:11–9.
58. Giovanella L, Lucignani G. Hybrid versus fusion imaging: are we moving forward judiciously? Eur J Nucl Med Mol Imaging 2010;37:973–9.
59. Garcia EV, Gropler RJ. Ninth Nuclear Cardiology Invitational Conference, Annapolis, Maryland, 2008. J Nucl Cardiol 2008;15:e37–50.
60. Schindler TH, Magosaki N, Jeserich M, Oser U, Krause T, Fischer R, et al. Fusion imaging: combined visualization of 3D reconstructed coronary artery tree and 3D myocardial scintigraphic image in coronary artery disease. Int J Card Imaging 1999;15:357–68. discussion, 369–70.
61. Javadi MS, Lautamäki R, Merrill J, Voicu C, Epley W, McBride G, et al. Definition of vascular territories on myocardial perfusion images by integration with true coronary anatomy: a hybrid PET/CT analysis. J Nucl Med 2010;51:198–203.
62. O'Connor MK, Kemp BJ. Single-photon emission computed tomography/computed tomography: basic instrumentation and innovations. Semin Nucl Med 2006;36:258–66.
63. Madsen MT. Recent advances in SPECT imaging. J Nucl Med 2007;48:661–73.
64. Masood Y, Liu YH, Depuey G, Taillefer R, Araujo LI, Allen S, et al. Clinical validation of SPECT attenuation correction using x-ray computed tomography-derived attenuation maps: multicenter clinical trial with angiographic correlation. J Nucl Cardiol 2005;12:676–86.
65. Souvatzoglou M, Bengel F, Busch R, Kruschke C, Fernolendt H, Lee D, et al. Attenuation correction in cardiac PET/CT with three different CT protocols: a comparison with conventional PET. Eur J Nucl Med Mol Imaging 2007;34:1991–2000.
66. Preuss R, Weise R, Lindner O, Fricke E, Fricke H, Burchert W. Optimisation of protocol for low dose CT-derived attenuation correction in myocardial perfusion SPECT imaging. Eur J Nucl Med Mol Imaging 2008;35:1133–41.
67. Martinez-Möller A, Souvatzoglou M, Navab N, Schwaiger M, Nekolla SG. Artifacts from misaligned CT in cardiac perfusion PET/CT studies: frequency, effects, and potential solutions. J Nucl Med 2007;48:188–93.
68. Gould KL, Pan T, Loghin C, Johnson NP, Guha A, Sdringola S. Frequent diagnostic errors in cardiac PET/CT due to misregistration of CT attenuation and emission PET images: a definitive analysis of causes, consequences, and corrections. J Nucl Med 2007;48:1112–21.
69. Goetze S, Brown TL, Lavely WC, Zhang Z, Bengel FM. Attenuation correction in myocardial perfusion SPECT/CT: effects of misregistration and value of reregistration. J Nucl Med 2007;48:1090–5.
70. Kennedy JA, Israel O, Frenkel A. Directions and magnitudes of misregistration of CT attenuation-corrected myocardial perfusion studies: incidence, impact on image quality, and guidance for reregistration. J Nucl Med 2009;50:1471–8.
71. McQuaid SJ, Hutton BF. Sources of attenuation-correction artefacts in cardiac PET/CT and SPECT/CT. Eur J Nucl Med Mol Imaging 2008;35:1117–23.
72. Chen J, Caputlu-Wilson SF, Shi H, Galt JR, Faber TL, Garcia EV. Automated quality control of emission-transmission misalignment for attenuation correction in myocardial perfusion imaging with SPECT-CT systems. J Nucl Cardiol 2006;13:43–9.
73. Kovalski G, Israel O, Keidar Z, Frenkel A, Sachs J, Azhari H. Correction of heart motion due to respiration in clinical myocardial perfusion SPECT scans using respiratory gating. J Nucl Med 2007;48:630–6.
74. Goetze S, Pannu HK, Wahl RL. Clinically significant abnormal findings on the "nondiagnostic" CT portion of low-amperage-CT attenuation-corrected myocardial perfusion SPECT/CT studies. J Nucl Med 2006;47:1312–18.
75. Shaw LJ, Narula J. Risk assessment and predictive value of coronary artery disease testing. J Nucl Med 2009;50:1296–306.
76. Scholte AJ, Schuijf JD, Kharagjitsingh AV, Dibbets-Schneider P, Stokkel MP, Jukema JW, et al. Different manifestations of coronary artery disease by stress SPECT myocardial perfusion imaging, coronary calcium scoring, and multislice CT coronary angiography in asymptomatic patients with type 2 diabetes mellitus. J Nucl Cardiol 2008;15:503–9.
77. Haramati LB, Levsky JM, Jain VR, Altman EJ, Spindola-Franco H, Bobra S, et al. CT angiography for evaluation of coronary artery disease in inner-city outpatients: an initial prospective comparison with stress myocardial perfusion imaging. Int J Cardiovasc Imaging 2009;25:303–13.
78. Schenker MP, Dorbala S, Hong EC, Rybicki FJ, Hachamovitch R, Kwong RY, et al. Interrelation of coronary calcification, myocardial ischemia, and outcomes in patients with intermediate likelihood of coronary artery disease: a combined positron emission tomography/computed tomography study. Circulation 2008;117:1693–700.
79. Slomka PJ, Cheng VY, Dey D, Woo J, Ramesh A, Van Kriekinge S, et al. Quantitative analysis of myocardial perfusion SPECT anatomically guided by coregistered 64-slice coronary CT angiography. J Nucl Med 2009;50:1621–30.
80. Namdar M, Hany TF, Koepfli P, Siegrist PT, Burger C, Wyss CA, et al. Integrated PET/CT for the assessment of coronary artery disease: a feasibility study. J Nucl Med 2005;46:930–5.
81. Groves AM, Speechly-Dick ME, Kayani I, Pugliese F, Endozo R, McEwan J, et al. First experience of combined cardiac PET/64-detector CT angiography with invasive angiographic validation. Eur J Nucl Med Mol Imaging 2009;36:2027–33.
82. Einstein AJ, Henzlova MJ, Rajagopalan S. Estimating risk of cancer associated with radiation exposure from 64-slice computed tomography coronary angiography. JAMA 2007;298:317–23.
83. Gerber TC, Carr JJ, Arai AE, Dixon RL, Ferrari VA, Gomes AS, et al. Ionizing radiation in cardiac imaging: a science advisory from the American Heart Association Committee on Cardiac Imaging of the Council on Clinical Cardiology and Committee on Cardiovascular Imaging and Intervention of the Council on

Cardiovascular Radiology and Intervention. Circulation 2009;119:1056–65.
84. Thompson RC, Cullom SJ. Issues regarding radiation dosage of cardiac nuclear and radiography procedures. J Nucl Cardiol 2006;13:19–23.
85. Esteves FP, Raggi P, Folks RD, Keidar Z, Askew JW, Rispler S, et al. Novel solid-state-detector dedicated cardiac camera for fast myocardial perfusion imaging: multicenter comparison with standard dual detector cameras. J Nucl Cardiol 2009;16:927–34.
86. Pazhenkottil AP, Herzog BA, Husmann L, Buechel RR, Burger IA, Valenta I, et al. Non-invasive assessment of coronary artery disease with CT coronary angiography and SPECT: a novel dose-saving fast-track algorithm. Eur J Nucl Med Mol Imaging 2010;37:522–7.
87. Cerqueira MD, Allman KC, Ficaro EP, Hansen CL, Nichols KJ, Thompson RC, et al. Recommendations for reducing radiation exposure in myocardial perfusion imaging. J Nucl Cardiol 2010;17:709–18.
88. Hausleiter J, Meyer T, Hermann F, Hadamitzky M, Krebs M, Gerber TC, et al. Estimated radiation dose associated with cardiac CT angiography. JAMA 2009;301:500–7.
89. Husmann L, Valenta I, Gaemperli O, Adda O, Treyer V, Wyss CA, et al. Feasibility of low-dose coronary CT angiography: first experience with prospective ECG-gating. Eur Heart J 2008;29:191–7.
90. Lehmkuhl L, Gosch D, Nagel HD, Stumpp P, Kahn T, Gutberlet M. Quantification of radiation dose savings in cardiac computed tomography using prospectively triggered mode and ECG pulsing: a phantom study. Eur Radiol 2010;20:2116–25.
91. Husmann L, Herzog BA, Gaemperli O, Tatsugami F, Burkhard N, Valenta I, et al. Diagnostic accuracy of computed tomography coronary angiography and evaluation of stress-only single-photon emission computed tomography/computed tomography hybrid imaging: comparison of prospective electrocardiogram-triggering vs. retrospective gating. Eur Heart J 2009;30:600–7.
92. Achenbach S, Marwan M, Ropers D, Schepis T, Pflederer T, Anders K, et al. Coronary computed tomography angiography with a consistent dose below 1 mSv using prospectively electrocardiogram-triggered high-pitch spiral acquisition. Eur Heart J 2010;31:340–6.
93. Javadi M, Mahesh M, McBride G, Voicu C, Epley W, Merrill J, et al. Lowering radiation dose for integrated assessment of coronary morphology and physiology: first experience with step-and-shoot CT angiography in a rubidium 82 PET-CT protocol. J Nucl Cardiol 2008;15:783–90.
94. Kajander S, Ukkonen H, Sipilä H, Teräs M, Knuuti J. Low radiation dose imaging of myocardial perfusion and coronary angiography with a hybrid PET/CT scanner. Clin Physiol Funct Imaging 2009;29:81–8.
95. Schleipman AR, Castronovo Jr FP, Di Carli MF, Dorbala S. Occupational radiation dose associated with Rb-82 myocardial perfusion positron emission tomography imaging. J Nucl Cardiol 2006;13:378–84.
96. Berman DS, Hachamovitch R, Shaw LJ, Friedman JD, Hayes SW, Thomson LEJ, et al. Roles of nuclear cardiology, cardiac computed tomography, and cardiac magnetic resonance: assessment of patients with suspected coronary artery disease. J Nucl Med 2006;47:74–82.
97. Greenland P, Bonow RO, Brundage BH, Budoff MJ, Eisenberg MJ, Grundy SM, et al. ACCF/AHA 2007 clinical expert consensus document on coronary artery calcium scoring by computed tomography in global cardiovascular risk assessment and in evaluation of patients with chest pain: a report of the American College of Cardiology Foundation Clinical Expert Consensus Task Force (ACCF/AHA Writing Committee to Update the 2000 Expert Consensus Document on Electron Beam Computed Tomography). Circulation 2007;115:402–26.
98. Hachamovitch R, Johnson JR, Hlatky MA, Cantagallo L, Johnson BH, Coughlan M, et al. The study of myocardial perfusion and coronary anatomy imaging roles in CAD (SPARC): design, rationale, and baseline patient characteristics of a prospective, multicenter observational registry comparing PET, SPECT, and CTA for resource utilization and clinical outcomes. J Nucl Cardiol 2009;16:935–48.
99. International Commission on Radiological Protection (ICRP). Radiation dose to patients from radiopharmaceuticals. ICRP publication 80. Oxford: Pergamon; 1998.
100. Hesse B, Tägil K, Cuocolo A, Anagnostopoulos C, Bardiés M, Bax J, et al. EANM/ESC procedural guidelines for myocardial perfusion imaging in nuclear cardiology. Eur J Nucl Med Mol Imaging 2005;32:855–97.