

Sequential SPECT/CT imaging for detection of coronary artery disease in a large cohort: evaluation of the need for additional imaging and radiation exposure

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Background. Performing both single photon emission computerized tomography (SPECT) and coronary computed tomography angiography (CCTA) in patients suspected for coronary artery disease (CAD) leads to increased radiation exposure. We evaluated the need for additional imaging and following implications for radiation exposure of a sequential SPECT/computed tomography (CT) algorithm.

Methods and Results. 5018 consecutive patients without history of CAD were referred for stress-first SPECT and coronary artery calcium (CAC) scoring. If stress SPECT was abnormal, additional rest SPECT and, if feasible, CCTA were acquired. Stress SPECT was normal in 2617 patients (52%). CCTA was not performed in 1289 of the 2401 patients referred for additional imaging (54%), mainly because of severe CAC (47%) or fast/irregular heart rate (22%). 642 patients with abnormal SPECT underwent CCTA, which excluded significant CAD in 378 patients (59%). Mean radiation dose was 4.5 ± 0.3 mSv for stress-only imaging and 13.2 ± 3.3 mSv for additional imaging ($P < 0.001$).

Conclusions. Half of the patients do not require additional imaging in our sequential SPECT/CT algorithm, which is accompanied with low radiation exposure. CCTA cannot be performed in half of the patients who undergo additional imaging because of (relative) contra-indications. CCTA is able to correct for false-positive SPECT findings in our algorithm. (J Nucl Cardiol 2017;24:212–23.)

Key Words: Single photon emission computed tomography • coronary artery calcium score • coronary computed tomography angiography • sequential imaging • suspected coronary artery disease

Abbreviations

CAD Coronary artery disease
 CCTA Coronary computed tomography angiography
 CAC Coronary artery calcium
 SPECT Single photon emission computed tomography

CT Computed tomography
 MI Myocardial infarction
 LBBB Left bundle branch block
 BMI Body mass index
 CZT Cadmium zinc telluride

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BACKGROUND

Although coronary computed tomography angiography (CCTA) may be an excellent tool for ruling out relevant coronary artery disease (CAD),¹ it is not able to assess the hemodynamic relevance of luminal stenosis,^{2,3} and has limited diagnostic accuracy with higher coronary artery calcium (CAC) scores.⁴ Furthermore, CCTA requires specific patient characteristics such as normal renal function and low regular heart rhythm.⁵ Since the diagnostic and prognostic value of myocardial perfusion imaging with single photon emission computerized tomography (SPECT) has been well established, and is feasible in almost all patients, the combination of CCTA and SPECT has been suggested to result in a more definite diagnosis.⁶⁻⁸ However, performing both SPECT and CCTA in all patients suspected for CAD would lead to increased radiation exposure and costs, and therefore, various suggestions for a sequential SPECT/CT protocol have been made.⁹⁻¹² We incorporated a sequential diagnostic algorithm starting with stress SPECT and CAC scoring, if necessary followed by additional imaging with rest SPECT and CCTA. With the current study, we evaluated the need for additional imaging and following implications for total radiation exposure of this sequential SPECT/CT imaging algorithm in patients with a low to intermediate pre-test likelihood of CAD.

METHODS

Study Population

We performed a prospective observational single-center cohort study, in which consecutive patients with suspected CAD referred for non-invasive CAD detection with SPECT/computed tomography (CT) between January 2009 and June 2013 were included. Patients were referred from the cardiology outpatient clinics of our hospital, which is a large cardiovascular center with a local, regional, and supraregional catchment area. The pre-test likelihood of CAD was assigned according to the criteria of Diamond and Forrester,¹³ with a risk threshold of <13.4% for low risk, between 13.4% and 87.2% for intermediate risk, and >87.2% for high risk. Patients with known history of CAD were excluded, no other exclusion criteria were applied. Information regarding the presence of risk factors was collected by written questionnaires. All patients underwent a sequential 1-day 99mTc-tetrofosmin SPECT/CT protocol according to an individualized algorithm. All patients underwent initial stress SPECT combined with CAC scoring. Immediately after acquisition of stress SPECT and CAC scan, a cardiologist and nuclear physician together assessed the need for additional rest SPECT imaging and CCTA. In case of an abnormal stress perfusion, additional rest SPECT was performed, independent of CAC scoring result. The rest SPECT was combined with an additional CCTA if the

heart rate allowed optimal diagnostic CT acquisition, CAC score was not too high (generally <400 and the absence of large calcified segments) and contra-indications were absent (renal insufficiency, known hypersensitivity to iodine contrast media). The final diagnosis was considered normal (i.e., no or no significant CAD) if either SPECT perfusion was normal or if CCTA excluded obstructive CAD. All procedures were performed in accordance with the Declaration of Helsinki. The study was approved by the Committee on Research Ethics of our hospital, and written informed consent was obtained from all patients.

Myocardial Perfusion Imaging

Stress testing was routinely performed with pharmacological stress using adenosine (140 µg/min/kg for 6 min) in all patients, unless there was a contra-indication for pharmacological stress. Due to logistical reasons, this is common practice in our high-volume center. Patients were instructed to refrain from caffeine-containing beverages for at least 24 hours before the test. In case of a contra-indication for adenosine, patients underwent dobutamine (starting dose of 10 µg/kg per min, increased at 3-min intervals to a maximum of 50 µg/kg per min), regadenoson (fixed-dose of 400 µg bolus injection over 15 seconds), or bicycle testing. A weight-adjusted dose of 99mTc-tetrofosmin (standard 370 MBq, 500 MBq for patients >100 kg) was administered after 3 min (adenosine), after 35 seconds (regadenoson) or when the target heart rate of > 85% of predicted maximal was reached (dobutamine, bicycle test).¹⁴ Patients scheduled for rest imaging received a dose of 99mTc-Tetrofosmin (standard 740 MBq, but 1000 MBq for patients >100 kg). Both stress and rest SPECT images were acquired 45-60 min after tracer injection. Time delay between the stress and rest studies was >3 hours.¹⁵ All patients were imaged in the supine position with arms placed above the head.

From January 2009 until April 2010, patients (n = 977) were scanned on a conventional dual-detector gamma camera (Ventri-LightSpeed VCT XT, GE Healthcare), using a low-energy, high-resolution collimator, a 20% symmetrical window at 140 keV, a 64 × 64 matrix, and an elliptical orbit with step-and-shoot acquisition at 6° intervals over a 180° arc (45° right anterior oblique to 45° left posterior oblique) with 30 steps (30 views). Acquisition time was 12 min for the stress images and 15 min for the rest images as previously described.¹⁶

From May 2010 until June 2013, patients (n = 4057) were scanned with a cadmium zinc telluride (CZT)-based SPECT/CT camera (Discovery NM/CT 570c, GE Healthcare) with 19 stationary CZT detectors simultaneously imaging 19 cardiac views. Each detector comprised 32 × 32 pixelated (2.46 × 2.46 mm) CZT elements. Acquisition time was 5 min for the stress images and 4 min for the rest images. This was derived from the recommendations of the manufacturer, published experience and our own qualitative assessment in heart phantom studies, and our initial experience in patients.¹⁷ All SPECT studies were followed by an unenhanced low-dose CT scan during a breath-hold to provide the attenuation map for attenuation correction as previously described.¹⁸

Perfusion images were unblindedly and semiquantitatively interpreted using a 17-segment model.¹⁹ Segments were scored by consensus of two experienced nuclear cardiology observers using a 5-points scoring system (0 = normal, 1 = equivocal, 2 = moderate, 3 = severe reduction of radioisotope uptake, 4 = absence of detectable tracer uptake).²⁰ The combination of attenuation corrected and non-attenuation corrected images was reviewed and rest SPECT was acquired if there was uncertainty about normalcy of perfusion using both image sets. A stress study was interpreted as normal if the summed stress scores were ≤ 3 .²⁰ Additional rest SPECT was acquired if the stress images did not fulfill these criteria. Gated SPECT analysis was used as an aid to differentiate between artifacts and perfusion defects.

The perfusion images were reviewed again by a cardiologist and a nuclear physician after both stress and rest SPECT. An ischemic defect was defined as a summed difference score ≥ 2 .²⁰ Reversible defects not fulfilling these criteria were assessed as equivocal for ischemia. Perfusion defects which demonstrated no reversibility were defined as fixed defects. An abnormal SPECT was defined as either ischemia, equivocal for ischemia, or fixed defects. If, after reviewing both stress and rest SPECT, no reversible or fixed defects were observed, the SPECT was considered normal.

CAC Scoring and CCTA

All cardiac CT studies were performed by using the 64-section CT scanner of the integrated SPECT/CT scanner (LightSpeed VCT XT; GE Healthcare). All patients with heart rates greater than 70 beats per minute received oral beta-blocker therapy, with 50 or 100 mg of metoprolol tartrate (AstraZeneca, Zoetermeer, the Netherlands) before the CAC scan. A non-enhanced CT scan to calculate the total CAC score was acquired with ECG triggering at 75% of the R-R interval and the following scanning parameters: 40 or 48 sections and 2.5-mm section thickness; gantry rotation time, 330 ms; tube voltage, 120 kV; and a tube current ranging from 125 to 250 mA, depending on patient size. Post-processing was conducted at a dedicated workstation using Smartscore software (GE Healthcare). The CAC score was calculated using the standard Agatston criteria.²¹

Before acquiring CCTA images, patients with a heart rate exceeding the threshold of 65/min were administered beta-blocking medication (50-100 mg metoprolol, oral, or 5-10 mg metoprolol, intravenous). A scout view of the chest was first obtained, followed by prospectively (83%) or retrospectively (on indication) ECG-triggered CCTA according to the guidelines provided by the Society of Cardiovascular Computed Angiography.²² Coronary arteries were subdivided according to a 15-segment model as proposed by the American Heart Association.²³ Each segment was evaluated on at least two planes according to Society of Cardiovascular Computed Tomography guidelines,²⁴ and the degree of diameter stenosis was visually graded by consensus of the two readers as

obstructive CAD when narrowing of the coronary lumen was 50% or greater.

Effective Radiation Dose

Radiation dose for SPECT was calculated as ^{99m}Tc -tetrofosmin activity times 7.9 mSv/GBq as suggested by the International Commission on Radiological Protection.²⁵ Effective radiation dose for CCTA was estimated as dose-length product times a conversion coefficient for the chest k (0.017 mSv/mGy/cm).²⁶

Follow-Up

Follow-up data were based on clinical visits, standardized telephone interviews, and by consulting the municipal population register. Events that were noted during follow-up were all-cause mortality and non-fatal myocardial infarction (MI). Non-fatal MI was defined based on the criteria of typical chest pain, elevated cardiac enzyme levels, and typical changes on the ECG as defined by Thygesen et al.²⁷

Statistical Analysis

Continuous variables are expressed as mean \pm SD or median [25th-75th percentile], and categorical variables are expressed as frequency (percentage). Differences between groups were assessed by unpaired Student t test, Mann-Whitney U test, and by Chi square test, where appropriate. We evaluated the differences in general characteristics of patients with normal or abnormal stress SPECT, of patients who underwent rest SPECT with or without additional CCTA and of patients with normal or abnormal final diagnosis. The patient's pre-test likelihood for CAD was determined with the standard Diamond criteria with the assumption that chest pain was atypical.¹³ Multivariate logistic regression was performed to investigate which general characteristics were independent predictors for an abnormal stress SPECT and abnormal final diagnosis after adjusting for other significant variables in univariate analysis. A value of $P < 0.05$ in univariate analysis was required for entry into the multivariate analysis. Significant variables analyzed are reported with their respective odds ratio and 95% confidence intervals. In the selected group of patients who underwent both SPECT and CCTA, sensitivity, specificity, negative predictive value, and positive predictive value of SPECT were calculated with CCTA as gold standard. The normalcy rate, the rate of normal perfusion scans in patients with $< 5\%$ likelihood of CAD, was reported as a surrogate for specificity to account for referral bias.²⁸ Differences in event-free survival over time were analyzed by the Kaplan-Meier method. Time 0 was defined as the date of SPECT imaging. Annualized event rate was calculated on the basis of events per patients-year. Two-sided p -values of less than 0.05 were considered statistically significant in all tests. All statistical analysis was performed with a commercially available software package (SPSS, version 20.0 for Windows).

RESULTS

Study Population

During a period of 4.5 years, a total of 5026 patients were included. Follow-up information was complete for 99.8% of the patients, only 8 patients were lost to follow-up. The remainder of 5018 patients are the subject of this report. The main indications for referral were atypical chest pain and dyspnoea. Pre-test likelihood was considered to be low in 9% of the patients and intermediate in 91% of the patients. The mean age was 61 ± 11 years, 57% of the patients were female, 14% were diabetic, and the mean body mass index (BMI) was 27.6 ± 4.8 . Stress testing was performed with adenosine in 4816 (96.0%), with dobutamine in 114 (2.3%), with regadenoson in 34 (0.7%), and with exercise testing in 54 (1.1%) of the patients.

Sequential SPECT/CT Algorithm

Figure 1 displays the individualized sequential SPECT/CT algorithm. All 5018 patients underwent stress SPECT. CAC score was obtained in 4897 patients (97.6%). A fast or irregular heart rate was the main reason for not acquiring CAC score. In 2617 patients (52% of the total population), the stress SPECT was normal, and these patients were discharged without additional rest SPECT or CCTA. Differences in the general characteristics between patients with normal and abnormal stress SPECT are demonstrated in Table 1. Independent predictors for abnormal stress SPECT were older age, male gender, diabetes mellitus, current smoking, left bundle branch block (LBBB), higher BMI, and higher CAC score (Fig. 2). In 2401 patients (48% of the total population), the stress SPECT was regarded abnormal, and these patients underwent additional rest SPECT and CCTA (if feasible). CCTA was not performed in 1289 patients (54%) because of high CAC scoring ($n = 591$, 46.7%), fast/irregular heart rate ($n = 281$, 21.8%), renal insufficiency ($n = 89$, 6.9%), small atypical perfusion defects suspected for artifact ($n = 251$, 19.5%), contrast allergy ($n = 9$, 0.7%), expected scatter from pacemaker lead ($n = 6$, 0.5%), anxiety/unable to hold breath ($n = 11$, 0.9%), or unclear reasons ($n = 51$, 3.9%). Table 2 demonstrates the differences in general characteristics between patients who underwent additional rest SPECT with or without CCTA.

Effective Radiation Dose

The mean radiation dose after completing the diagnostic algorithm was 8.6 ± 4.9 mSv for the entire cohort. The mean radiation dose was 4.5 ± 0.3 mSv in

patients who underwent stress-only imaging and 13.2 ± 3.3 mSv in patients who underwent additional imaging ($P < 0.001$).

Imaging Results

All 2617 patients who were discharged after stress SPECT and CAC scoring had normal myocardial perfusion. Among 2401 patients who underwent additional rest SPECT, myocardial perfusion was considered normal in 1175 patients (49%) after reviewing both stress and rest images. Finally, SPECT was considered normal in 3790 (76%) of the total population. In the remaining 1228 patients, SPECT was considered abnormal, of which 299 patients (24%) had equivocally reversible defects, 513 (42%) had findings clearly suggestive for ischemia and 416 (34%) showed fixed perfusion defects.

The median CAC scoring for the total population was 39 [25th-75th percentile, 0-282]. 1315 of the patients (27%) demonstrated a CAC score of zero, and 995 of the patients (20%) demonstrated a CAC score >400 . A total of 1112 patients underwent CCTA, of which 751 (68%) showed no obstructive CAD, 349 (31%) showed significant CAD, and 12 (1.0%) were assessed as non-evaluable due to limited image quality.

Of the 2617 patients with normal stress SPECT, the CAC score was 0 in 37%, 1-100 in 38%, 101-400 in 15%, and >400 in 11%. Of the 2401 patients who required additional imaging, the CAC score was 0 in 16%, 1-100 in 30%, 101-400 in 23%, and >400 in 31%. In the 1228 patients who had an abnormal SPECT, 13, 27, 24, and 36% had CAC scores of 0, 1-100, 101-400, and >400 , respectively.

Of the total of 1112 patients who underwent CCTA, in 470 (42%), SPECT perfusion was considered normal after viewing both stress and rest SPECT. CCTA excluded obstructive CAD in 373 (80%) of these 470 patients. In the remainder of the patients who underwent CCTA ($n = 642$, 58%), the perfusion was considered abnormal. Of these 642 patients, in 378 patients (60%), obstructive CAD was excluded with CCTA.

In the subpopulation of patients who underwent both CCTA and SPECT, the sensitivity of SPECT was 73% and the specificity was 50% (negative predictive value 79%, positive predictive value 41%). The normalcy rate of SPECT was 87%.

With the combination of SPECT and CCTA imaging, 4168 (83%) of the patients were concluded to have normal final diagnosis after completing the diagnostic algorithm. Differences in general characteristics between patients with normal and abnormal final diagnosis are demonstrated in Table 3. Independent predictors of final abnormal diagnoses were older age, male gender, diabetes mellitus, LBBB, higher BMI, and higher CAC scoring (Fig. 3).

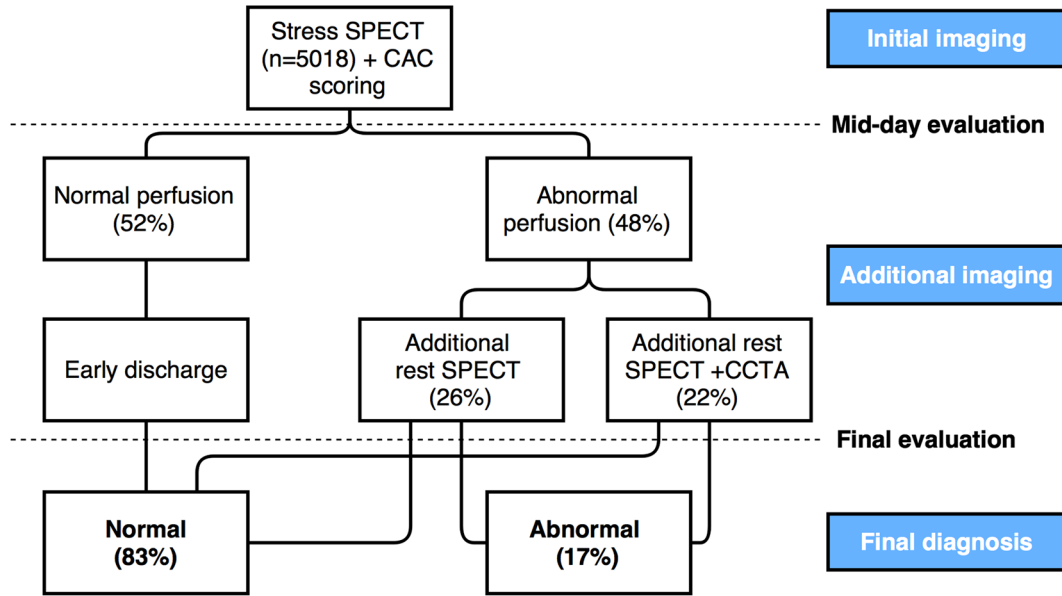


Figure 1. Flowchart of the individualized sequential SPECT/CT algorithm. CAC, coronary artery calcium; CCTA, coronary computed tomography angiography; normal final diagnosis, SPECT perfusion normal or CCTA without significant coronary artery disease.

Table 1. General characteristics of patients with normal stress SPECT, compared to patients with abnormal stress SPECT

	Normal stress SPECT n = 2617	Abnormal stress SPECT n = 2401	P value
Age, years	60 ± 12	63 ± 11	<0.001
Males	851 (32.5)	1305 (54.4)	<0.001
Cardiac risk factors			
Diabetes mellitus	257 (9.8)	420 (17.5)	<0.001
Hypertension	1539 (58.8)	1521 (63.4)	0.001
Current smoking	386 (14.8)	406 (17.0)	0.034
Hyperlipidemia	1100 (42.0)	1058 (44.1)	0.139
Family history of CAD	1462 (56.0)	1255 (52.5)	0.015
LBBB	40 (1.5)	178 (7.5)	<0.001
Atrial fibrillation	56 (2.1)	81 (3.4)	0.007
BMI	27 ± 4	28 ± 5	< 0.001
Systolic blood pressure	138 ± 21	142 ± 21	<0.001
Diastolic blood pressure	84 ± 13	85 ± 13	0.218
Heart rate	72 ± 12	71 ± 12	0.374
Creatinine	76 ± 41	80 ± 37	<0.001
CAC score	8 [0-108]	130 [8-549]	<0.001

CAD, Coronary artery disease; LBBB, left bundle branch block; BMI, body mass index; CAC, coronary artery calcium; values are shown as number (percentage), mean ± SD, median [25th-75th percentile]

Follow-Up

Over a median follow-up duration of 965 days [25th-75th percentile, 600-1397], there were 205 events (166 all-cause deaths, 39 non-fatal MI). Annual event

rate of patients with normal myocardial perfusion after stress-only SPECT was slightly lower compared to those with normal myocardial perfusion after additional rest imaging (1.07% vs 1.60%, *P* = 0.04). For patients with

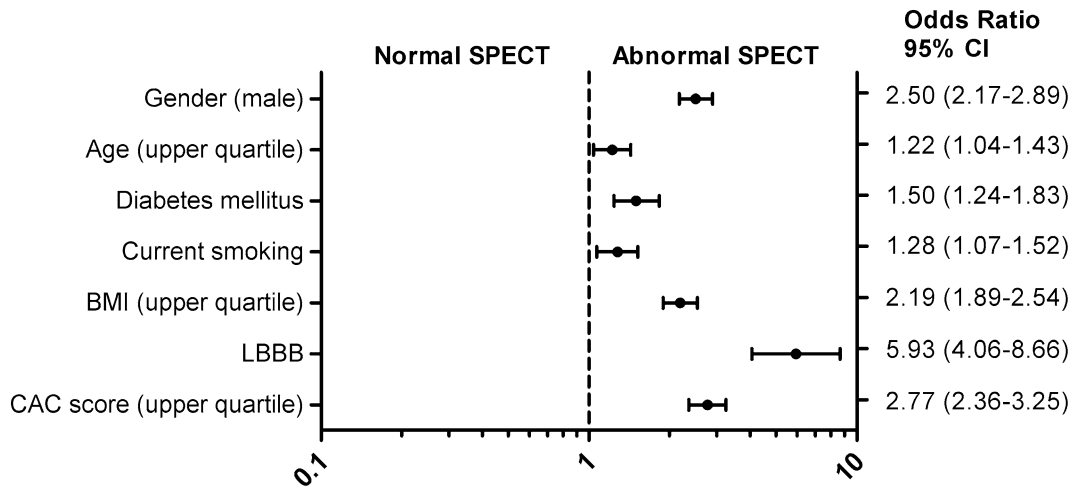


Figure 2. Significant independent predictors of initial stress SPECT result. Age (upper quartile 69); BMI, body mass index (upper quartile: 30); LBBB, left bundle branch block; CAC, coronary artery calcium (upper quartile: 282); CI confidence interval.

Table 2. General characteristics of 2401 patients undergoing additional rest SPECT with or without CCTA

	Additional rest SPECT without CCTA n = 1289	Additional rest SPECT with CCTA n = 1112	P value
Age, years	65 ± 11	60 ± 11	<0.001
Males	678 (52.6)	627 (56.4)	0.063
Cardiac risk factors			
Diabetes mellitus	294 (22.8)	126 (11.3)	<0.001
Hypertension	864 (67.1)	657 (59.1)	<0.001
Current smoking	185 (14.4)	221 (19.9)	0.001
Hyperlipidemia	582 (45.2)	476 (42.8)	0.235
Family history of CAD	643 (50.2)	612 (55.2)	0.016
LBBB	88 (6.9)	90 (8.2)	0.230
Atrial fibrillation	80 (6.2)	0	<0.001
BMI	29 ± 5	28 ± 5	0.004
Systolic blood pressure	143 ± 22	140 ± 20	0.001
Diastolic blood pressure	85 ± 13	84 ± 12	0.322
Heart rate	73 ± 13	70 ± 11	<0.001
Creatinine	84 ± 49	77 ± 16	<0.001
CAC score	260 [14-1119]	76 [5-258]	<0.001

CAD, Coronary artery disease; LBBB, left bundle branch block; BMI, body mass index; CAC, coronary artery calcium; CCTA, coronary computed tomography angiography; values are shown as number (percentage), mean ± SD, median [25th-75th percentile]

an abnormal SPECT but no obstructive CAD on CCTA, the annual event rate was 0.85% (9 deaths, 1 MI); for patients with normal SPECT but obstructive CAD, this was 1.64% (4 deaths, 1 MI) and for patients with both abnormal SPECT and obstructive CAD on CCTA this

was 2.15% (11 deaths, 6 MIs). Survival curves of these groups are demonstrated in Fig. 4. The annual event rate was significantly higher in patients with abnormal final diagnosis compared to those with normal final diagnosis (2.55% vs. 1.19%, $P < 0.001$).

Table 3. General characteristics of patients with normal final diagnosis, compared to patients with abnormal final diagnosis

	Normal final diagnosis N = 4168	Abnormal final diagnosis N = 850	P value
Age, years	60 ± 11	66 ± 10	<0.001
Males	1658 (39.8)	498 (58.6)	<0.001
Cardiac risk factors			
Diabetes mellitus	492 (11.8)	185 (21.8)	<0.001
Hypertension	2477 (59.4)	583 (68.6)	<0.001
Current smoking	643 (15.5)	149 (17.6)	0.129
Hyperlipidemia	1757 (42.2)	401 (47.2)	0.007
Family history of CAD	2270 (54.6)	447 (52.8)	0.322
LBBB	140 (3.4)	78 (9.3)	<0.001
Atrial fibrillation	98 (2.4)	39 (4.6)	<0.001
BMI	27 ± 5	29 ± 5	<0.001
Systolic blood pressure	138 ± 21	145 ± 22	<0.001
Diastolic blood pressure	84 ± 13	85 ± 13	0.204
Heart rate	71 ± 12	72 ± 13	0.035
Creatinine	77 ± 39	83 ± 39	<0.001
CAC score	20 [0-174]	406 [107-1117]	<0.001

CAD, Coronary artery disease; LBBB, left bundle branch block; BMI, body mass index; CAC, coronary artery calcium; normal final diagnosis, SPECT perfusion normal or CCTA without significant CAD; values are shown as number (percentage), mean ± SD, median [25th-75th percentile]

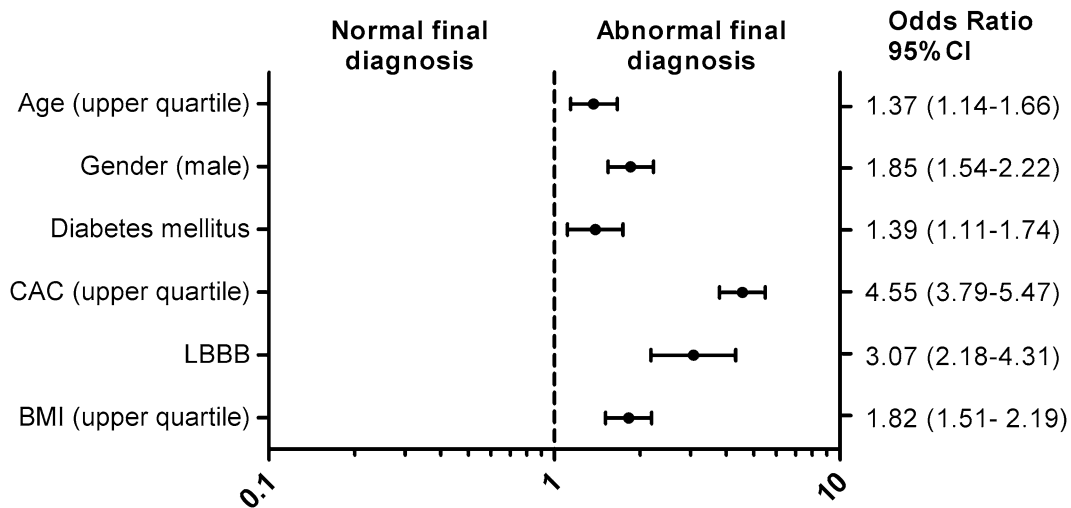


Figure 3. Significant independent predictors of final diagnosis. Age (upper quartile 69); BMI, body mass index (upper quartile: 30); LBBB, left bundle branch block; BMI, body mass index; CAC, coronary artery calcium (upper quartile: 282); normal final diagnosis, SPECT perfusion normal or CCTA without significant CAD.

DISCUSSION

This study evaluated the need for additional imaging and following implications for total radiation exposure of an individualized sequential SPECT/CT algorithm in a large, low- to intermediate-risk population suspected for CAD. After initial stress SPECT and CAC scoring,

additional rest SPECT imaging could be omitted in half of the patients, which is accompanied with a low radiation exposure. In patients who required additional imaging, CCTA could not be performed in nearly half of the patients because of (relative) contra-indications. CCTA was able to correct for false-positive SPECT findings in our algorithm.

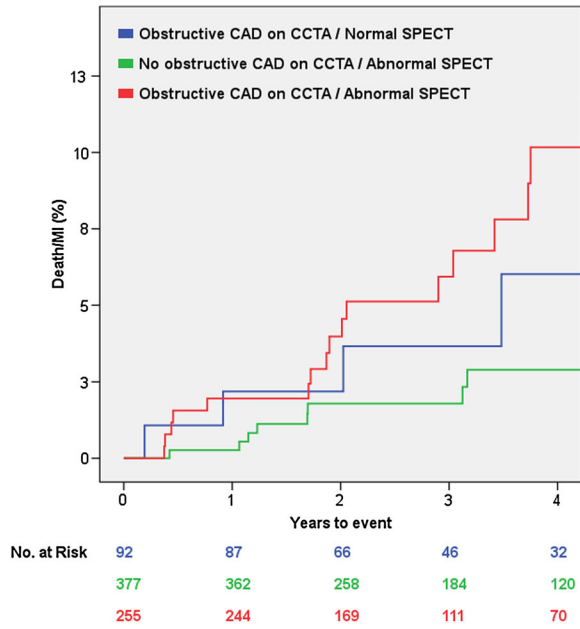


Figure 4. Event rates categorized by CCTA and SPECT results. CAD, coronary artery disease; CCTA, coronary computed tomography angiography; SPECT, single photon emission computerized tomography.

Non-invasive imaging using both functional (SPECT) and anatomical data (CT) has been suggested to be the optimal approach in the evaluation of patients with suspected CAD.⁶⁻⁸ Increasing concerns about both costs and radiation exposure gave rise to sequential use of these modalities. Protocols with either initial SPECT or initial CCTA have been proposed.^{9,10} CCTA might be appropriate as initial test in lower risk populations, due to its high negative predictive value. However, after initial CCTA, half of the patients still require SPECT imaging,¹⁰ and diagnostic quality of CCTA is reduced in a substantial number of patients due to extensive calcification, motion artifacts, or low image quality.^{6,8,29} SPECT is well established for the diagnostic and prognostic evaluation of patient suspected for CAD.³⁰ When SPECT is combined with CAC scoring, information about myocardial perfusion and the extent of CAD is acquired in a single setting. Therefore, we incorporated a sequential SPECT/CT algorithm starting with stress SPECT and CAC scoring, if necessary followed by additional imaging with rest SPECT and CCTA.

In general, there may be several advantages of simultaneous CAC scoring in combination with stress-only SPECT. First, knowledge of CAC score results in more interpretative certainty for SPECT imaging with better selection of patients who require additional rest SPECT.^{31,32} In the absence of any CAC, the prevalence of significant CAD is low, thereby subtle stress SPECT abnormalities are likely to be disregarded, whereas these

may warrant further imaging in patients with extensive coronary calcifications.^{18,33,34} The knowledge of CAC is likely to have contributed to our results that no additional rest SPECT was necessary in about half of the patients after stress SPECT. The patients with stress-only SPECT demonstrated an excellent prognosis during follow-up, which is in line with previous studies.³⁵⁻³⁹ Second, the CAC score assisted us to select patients suited to undergo additional CCTA, as we did not obtain additional CCTA in patients with very high CAC scores. By this means, the radiation dose from a CCTA with low expected diagnostic yield was prevented.⁴ Finally, information about the extent of subclinical CAD was available in patients with normal myocardial perfusion. It has been demonstrated that CAC scoring adds independent prognostic information in addition to SPECT.^{40,41} Therefore, a high CAC score in these patients could potentially influence treatment decisions with improved patient care through life style advise, intensification of medication use, and in case of persisting complaints an earlier invasive strategy.¹⁸

One of the most important findings in the current study was that CCTA was not performed in about half of the patients referred for additional imaging. In a small portion of the patients, this could be explained by inconsistent application of the clinical protocol leading to underuse of the CCTA in eligible patients (13% of the patients who underwent additional rest SPECT did not undergo CCTA because of atypical perfusion defect or unclear reasons). However, in the remaining 41% of the patients, CCTA indeed could not be performed. This percentage is higher than in previous observations, which demonstrated that up to 23% of the patients were unsuitable for CCTA because of calcifications or poor image quality.^{6,8,29} This difference is likely to be explained by both strict selection for CCTA and the different patient population which is considered for CCTA. In our study, only patients with abnormal stress SPECT were considered to undergo CCTA, and these patients probably have more (relative) contra-indications for CCTA. Of course, CCTA can be performed using less strict (relative) contra-indications, but this may be associated with more non-diagnostic scans.^{4,5,42} The main advantage of CCTA in our algorithm is correcting for false-positive SPECT, as previously suggested in the literature.⁴³ This can result in a reduction of unnecessary downstream invasive coronary angiography and thereby significant cost savings.⁴³

In patients who underwent both CCTA and SPECT imaging, specificity of SPECT was lower than expected according to current literature.⁴⁴ This may be caused by patient selection. Patients who were eligible for CCTA had a lower risk of CAD, as contra-indications for CCTA (high CAC score and renal insufficiency) are

well-known risk factors.^{45,46} The normalcy rate (as a surrogate for specificity to account for referral bias) was 87%, which is comparable with previous findings.²⁸ Sensitivity of SPECT was also lower than expected,⁴⁴ possibly due to exclusion of patients with normal stress SPECT, as these were not considered for CCTA in the current algorithm. Furthermore, CCTA is well known to overestimate the degree of coronary stenosis.⁴⁷

With our sequential SPECT/CT algorithm, 83% of the patients had normal final diagnosis (i.e., no or non-significant CAD). This high rate of normal findings in our study is explained by the fact that patients with known CAD were excluded and that our algorithm was not performed in patients with a high pre-test likelihood of CAD. Furthermore, CCTA increased the percentage of patients with a normal final diagnosis in case of an abnormal SPECT. The frequency of normal SPECT findings in our study is comparable to other studies.^{47,48}

In our study, several predictors for normal initial stress SPECT were identified. Younger age, female gender, no current smoking, and lower CAC score are indicators for low risk, with a subsequent lower prevalence of an abnormal stress SPECT, which is in line with previous studies.^{37,38} As a lower CAC score is associated with a higher frequency of normal SPECT, it is not surprising that patients with lower CAC scores less frequently required additional imaging.^{40,49,50} The absence of LBBB is an independent predictor for normal initial stress SPECT. This is likely due to anteroseptal and septal perfusion defects associated with LBBB.^{51,52} Patients with lower BMI more often demonstrated normal stress SPECT perfusion, likely because of the lower risk of soft tissue attenuation artifacts. These predictors for normal initial stress SPECT could be taken into account when planning patients for the SPECT/CT algorithm, optimizing capacity utilization.

The mean radiation dose for the total population after completing our diagnostic algorithm is lower compared to the radiation dose after the traditional stress-rest SPECT protocol.⁵³ Half of the patients did not require additional imaging after stress SPECT and CAC scoring and thereby had a low mean radiation dose of 4.5 mSv. Thus, the current algorithm easily complies with the recommendations of the American Society of Nuclear Cardiology to decrease patient radiation exposure to <9 mSv in 50% of patients by 2014.⁵⁴

Although our current algorithm proves feasible in daily practice, with very low event rates in patients with normal final diagnosis, alternative algorithms could be considered. A protocol starting with CAC scoring, without additional imaging in case of a CAC score of zero, could be very efficient.⁵⁵ However, whether it is safe to omit further imaging in patients with a CAC score of zero

remains a subject of debate, due to conflicting data with regard to the negative predictive value of CAC zero.^{56,57} If the CAC score is low and CCTA is feasible, additional imaging should be performed with CCTA. Otherwise, an additional functional test should be performed. Another option could be modification of our protocol, by implementing a second evaluation after rest SPECT to assess if additional CCTA is necessary. Thereby, CCTA could be prevented in patients with a normal SPECT after stress and rest imaging. Finally, a protocol starting with CCTA could be incorporated, although it is well known that half of the patients still require SPECT imaging after initial CCTA.¹⁰ Irrespective of which specific algorithm used, when implementing SPECT/CT imaging in a clinic, it is advised to opt for an individualized sequential algorithm to lower radiation dose and costs. Local expertise and logistics should be taken into consideration when choosing such an algorithm.

Although our study reflects true daily practice and included consecutive patients, we have to acknowledge several limitations. The observational design remains a major limitation of the current study, as end-points were not pre-specified, and no head-to-head comparison to other diagnostic algorithms was performed. Also, this is a single-center study in patients with suspected CAD and a low- to intermediate pre-test likelihood undergoing predominantly pharmacological stress. Therefore, extrapolation of the present results is difficult to populations with different pre-test likelihood or patients undergoing traditional exercise testing. Although CAC scoring was not included in the diagnostic algorithm to decide whether or not additional rest SPECT was performed, the SPECT observers were not blinded for the CAC score. Thus, it cannot be excluded that the need for additional rest SPECT is biased by the CAC score, as subtle stress SPECT abnormalities are possibly disregarded if the CAC score was 0. Furthermore, our current results are based on SPECT scanning predominantly performed on state-of-the-art imaging equipment (CZT-based SPECT/CT camera). The result can be different if other SPECT/CT cameras are used. CCTA was not performed in about half of the patients referred for additional imaging, which was partially caused by a strict selection for the eligibility for CCTA. Possibly, results of the current algorithm would be different if patients underwent CCTA with less strict selection. Although downstream invasive coronary angiography was performed for clinical reasons in selected patients during follow-up, this was not included in the current report, as this was not part of our research question. Finally, we did not include revascularizations as an outcome for the current study, as these outcomes can be driven by imaging results.

CONCLUSIONS

Half of the patients do not require additional imaging in our sequential SPECT/CT algorithm, which is accompanied with low radiation exposure. CCTA cannot be performed in half of the patients who undergo additional imaging because of (relative) contra-indications. CCTA is able to correct for false-positive SPECT findings in our algorithm.

NEW KNOWLEDGE GAINED

Sequential SPECT/CT imaging is feasible in clinical daily practice, without need for additional imaging after stress SPECT and CAC scoring in half of the patients. CCTA was less often performed than expected, because of (relative) contra-indications.

Disclosure

Dr. Engbers, Dr. Timmer, Dr. Ottervanger, Dr. Mouden, Dr. Oostdijk, Dr. Knollema, and Dr. Jager have nothing to disclose.

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