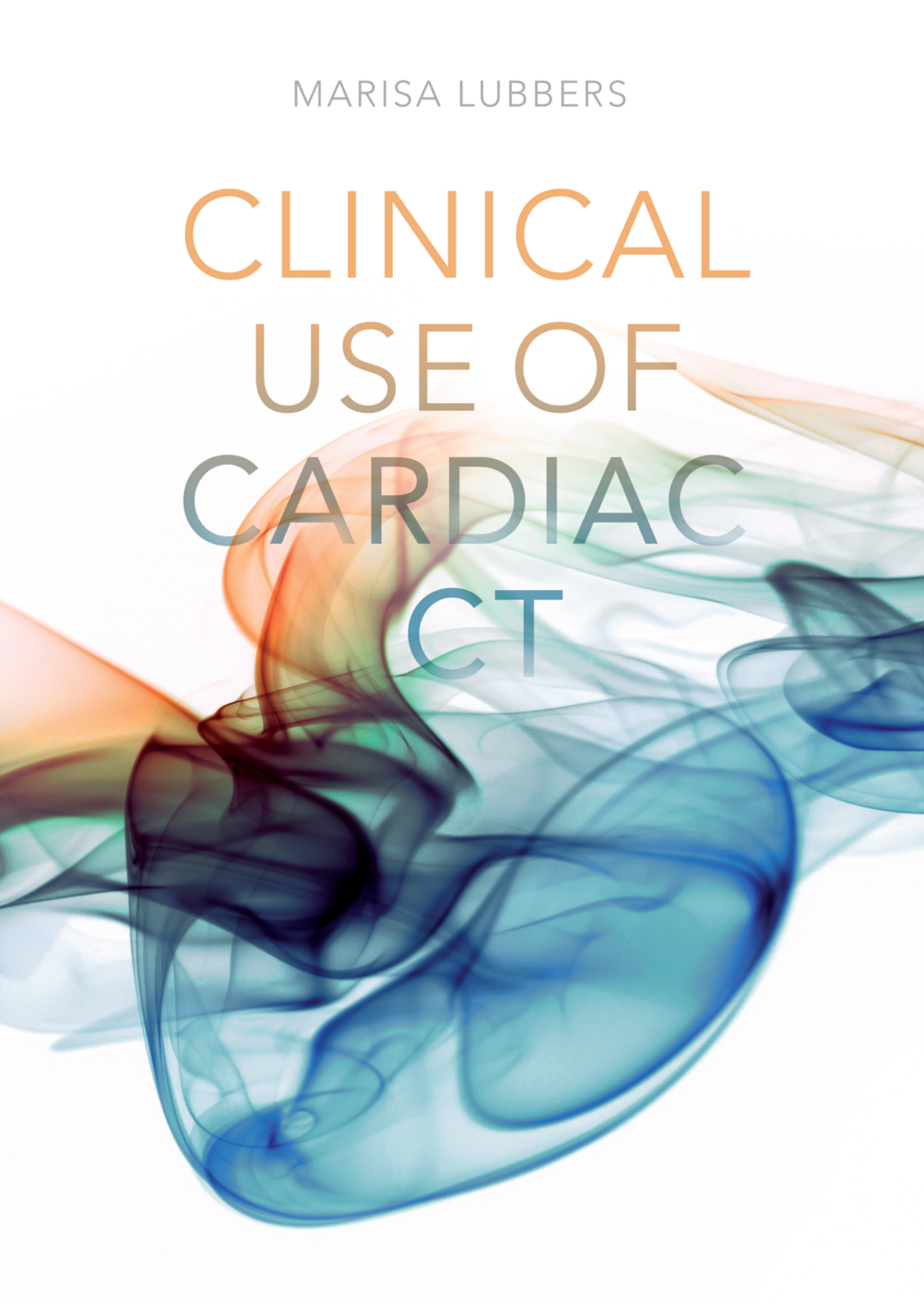
MARISA LUBBERS

CLINICAL USE OF CARDIAC CT



Clinical Use of Cardiac CT

Klinische toepassingen van cardiale CT

Marisa Marjolein Lubbers

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Pap, deze is voor jou

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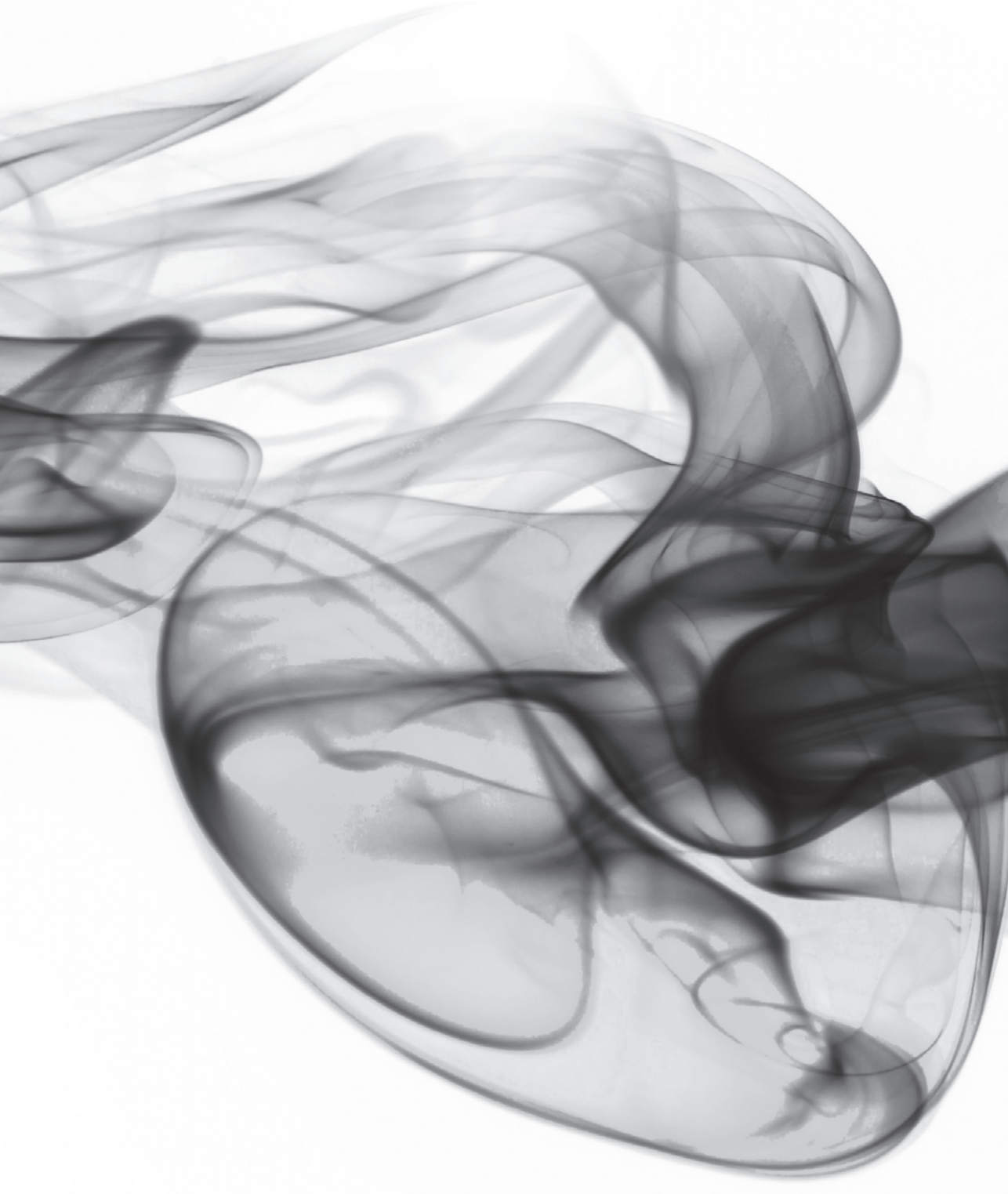

Part 1

Prologue

Chapter 1

General Introduction and Outline of the Thesis

GENERAL INTRODUCTION

Coronary artery disease

Coronary artery disease is one of the leading causes of morbidity and mortality worldwide(1). Common risk factors for atherosclerosis include high blood pressure, high cholesterol levels, smoking, obesity, diabetes mellitus and a family history of cardiovascular disease (2). Atherosclerosis of the coronary artery wall, results in vessel lumen narrowing, limiting the ability to increase blood flow and supply of oxygen to the myocardium at instances of increased demand. This often presents with angina pectoris, a clinical syndrome characterized by discomfort of the chest, provoked by physical or emotional stress and relieved by rest or nitroglycerin. In case a developed atherosclerotic lesion suddenly ruptures, acute luminal thrombosis causes partial or complete occlusion of the coronary artery resulting in ischemia of the myocardium. The term acute coronary syndrome (ACS) refers to the group of clinical symptoms compatible with acute myocardial ischemia.

Usual care of stable angina

The current guidelines recommend exercise electrocardiography (XECG) as first line diagnostic test for patients with suspected coronary artery disease (3, 4). While considered cost effective, the XECG is also known for its modest diagnostic accuracy(5-8). Stress myocardial perfusion imaging (SPECT) and stress echocardiography have a better diagnostic accuracy for detecting obstructive coronary artery disease(9). However, these stress imaging tests also have practical and logistical drawbacks, are relatively expensive, are not 100% accurate, and only reserved for patients with higher probability of disease (3, 4). Equivocal stress test results lead to multiple testing, including invasive angiography (ICA). The greatest advantage of ICA is high spatial resolution and the possibility of directly performing an intervention if needed. However, a US registry reported that only 37% of ICAs resulted in (mechanical) treatment illustrating that the non-invasive work-up fails as a gatekeeper to ICA (10). Since publication of the results of the COURAGE and FAME trial there is growing consensus that (surgical) revascularization does not benefit every patient with angiographic CAD, but should be reserved for those with objective myocardial ischemia. Invasive angiography, without proper ischemia testing, leads to over-treatment(11, 12).

Cardiac CT

Cardiac CT has emerged as an alternative modality for investigation of suspected CAD. It has been increasingly used over the past years, and rapid technological developments have led to improvement of spatial and temporal resolution. With the introduction of 64-slice CT scanners high diagnostic accuracy has been achieved and the reliability to

detect and particularly to exclude significant CAD against ICA has been confirmed in numerous studies(13, 14).

A cardiac CT examination often starts with a CT assessment of the calcium score. With a non-contrast enhanced scan calcium deposition can be detected and quantified non-invasively using the Agatston method (15). Calcium scores are highly associated with the degree and severity of CAD, and thus assist in predicting the probability of future cardiac events(16-18). While calcium imaging is still mostly used for risk stratification in asymptomatic individuals, the high sensitivity and negative predictive value, makes it an excellent diagnostic examination to rule out coronary artery disease in the evaluation of chest pain, avoiding contrast media and reducing costs and radiation exposure (19). Registry studies repeatedly showed that in low to intermediate risk patients with a negative calcium scan, severe CAD is rare(8, 20, 21).

During coronary computed tomography angiography (CCTA) radiodens iodinated contrast medium is injected into the vascular system of the patient to enhance the lumen of the coronary artery, revealing the presence and degree of atherosclerosis. It has a high sensitivity and negative predictive value for the detection of angiographic stenoses (22, 23), thereby allowing for reliable exclusion of coronary artery disease (3). However, it is limited in its ability to assess the hemodynamic importance of CAD. Because anatomical lesion severity is a poor predictor of hemodynamic significance, functional evaluation of intermediate stenoses is recommended for therapeutic decision making(3, 24). CT myocardial perfusion imaging (CT-MPI) could complement the anatomical information from CCTA by providing functional information and prognostic relevance. During myocardial hyperemia by adenosine infusion the myocardial blood flow can be measured from the differences in contrast inflow between normally and hypo-perfused myocardium (25). It has been validated in single center studies and shown to have diagnostic accuracy at least comparable to SPECT, with similar radiation dose and with the advantage of providing information on coronary stenosis. Hereby it can function as a gatekeeper for ICA in patients without hemodynamically significant CAD (25-29).

Aims

The aim of this thesis was to investigate the optimal diagnostic strategy for patients presenting with stable angina and unstable angina and ACS. A better diagnostic strategy, ultimately leads to a better outcome for patients with suspected CAD.

OUTLINE OF THE THESIS

Chapter 2 gives an overview of current use of cardiac CT, including the acquisition methods, evaluation of images, and the potential clinical applications of cardiac CT.

The first part of this thesis focuses on cardiac CT in stable angina patients. We designed and performed the multicentre, randomized controlled CRESCENT trial to evaluate a cardiac CT work up, consisting of a calcium scan and selective CT angiography with standard functional testing in patients with suspected CAD. The results are presented in **chapter 3**. In a sub analysis of this trial (**chapter 4)** we investigate the gender differences in the performance of cardiac CT compared to functional testing. **Chapter 5** shows the results of the randomized controlled IsoCOR trial comparing two contrast media with different osmolarity. The hypothesis was that if iso-osmolar contrast media is injected with a comparable iodine-delivery rate to low-osmolar contrast media, the coronary opacification is similar as with low-osmolar contrast media.

The second part of this thesis provides information on CT myocardial perfusion imaging in stable angina patients. In **chapter 6** we investigate the diagnostic value of transmural perfusion ratio for the detection of hemodynamically relevant coronary artery stenosis compared to quantified myocardial blood flow. In **chapter 7** we present the results of the multicenter randomized controlled CRESCENT-II trial comparing a tiered cardiac CT protocol, consisting of the selective performance of a CT-calciumscan, CT-angiography and CT-myocardial perfusion imaging, with functional testing in patients with suspected coronary artery disease.

The third part of the thesis focuses on CT angiography in unstable angina and acute coronary syndromes. In the randomized BEACON trial (**chapter 8**)we investigated whether a diagnostic strategy supplemented by early coronary CT angiography was superior to contemporary standard optimal care (SOC) encompassing high-sensitivity troponin assays (hs-troponins) for patients with suspected acute coronary syndrome in the emergency department. In **chapter 9** we describe the sex-associated differences in the performance of coronary CT angiography in an emergency setting. In **chapter 10** we assessed the image quality of coronary CT angiography performed during office hours and outside office hours in the emergency department.

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CHAPTER 2

Cardiac CT for Coronary Imaging

Marisa Lubbers
Koen Nieman

Cardiac CT, PET and MR, 2nd edition.
Edited by Vasken Dilsizian and Gerry Pohost.

INTRODUCTION

Cardiac CT allows for practically motion-free imaging of the heart and detailed visualization of the coronary arteries. Over the past decade noninvasive coronary angiography by cardiac CT has become a valuable technique for the diagnostic triage of patients with (suspected) coronary artery disease in various settings.

Data Acquisition and Evaluation

Cardiac CT scan modes

A fundamental step in the technical development of cardiac CT has been the removal of the physical connection between the rotating and stationary scanner elements. So-called slip-ring technology allows transfer of energy and data between the rotating tube-detector and the stationary unit without cables that necessitate unwinding after a few scanner rotations. Continuous rotation allows continuous data acquisition, which was crucial for the development of cardiac CT. The first widely applied scan mode for cardiac imaging using multislice CT systems was the spiral scan mode. A spiral CT scan is performed using continuous table advancement and data acquisition. From the table's perspective the path of the rotating elements has the shape of a helix or spiral, hence the name spiral or helical CT. By expanding the number of detector rows coverage speed could be improved significantly. While a 4-slice cardiac CT scan required up to 40 seconds, 64-slice CT systems and beyond can complete the acquisition in a few heart beats or less, which allows for a much more comfortable breath-hold. While the spiral scan mode with retrospective ECG synchronization is a very robust technique it has the drawback of a relatively high radiation exposure. In an effort to reduce radiation exposure the axial scan mode was re-introduced, though with continuous scanner rotation, and has by now become the default scan mode. Scanners with sufficient detector-collimation width to cover the entire heart do not require movement of the table during the examination.

ECG-Synchronization

For most scanners the width of the combined detector rows is insufficient to cover the heart at once. Therefore several stacks of data need to be acquired over several heart cycles to image the complete heart (figure 1). In order to create a comprehensible CT angiogram the acquisition or reconstruction of images needs to be synchronized to the heart cycle. Displacement of the coronary arteries varies throughout the cardiac cycle and is generally least during mid-diastole or end-systole. Therefore, ECG-synchronization is important both to create images without motion artifacts as well as phase consistency between images acquired during different heart cycles. There are two approaches to

acquire ECG-synchronized CT images. The original spiral CT protocols used only retrograde ECG-gating, which implies that after the acquisition of CT data a recorded rhythm tracing was used to select phase-consistent data to reconstruct images. This approach requires that each table position is scanned for the duration of at least one heart cycle. The advantage is that retrospectively any cardiac phase can be reconstructed. The downside is that the radiation dose to the patient is fairly high. The alternative approach is prospective ECG-triggering, in which case the data acquisition (and radiation exposure) is limited to a pre-specified window within the heart cycle based on the live ECG trace. The axial scan mode is performed using prospective ECG triggering: each set of images is acquired in sequence, triggered by the ECG, with repositioning of the table in between scans. Nowadays, ECG-gated spiral scans can be combined with prospectively ECG-triggered variation of the roentgen tube output to lower exposure during phases that are not expected to be needed for image interpretation. Alternatively, contemporary axial scan protocols can be performed with an extended exposure window to allow for reconstruction of more cardiac phases.

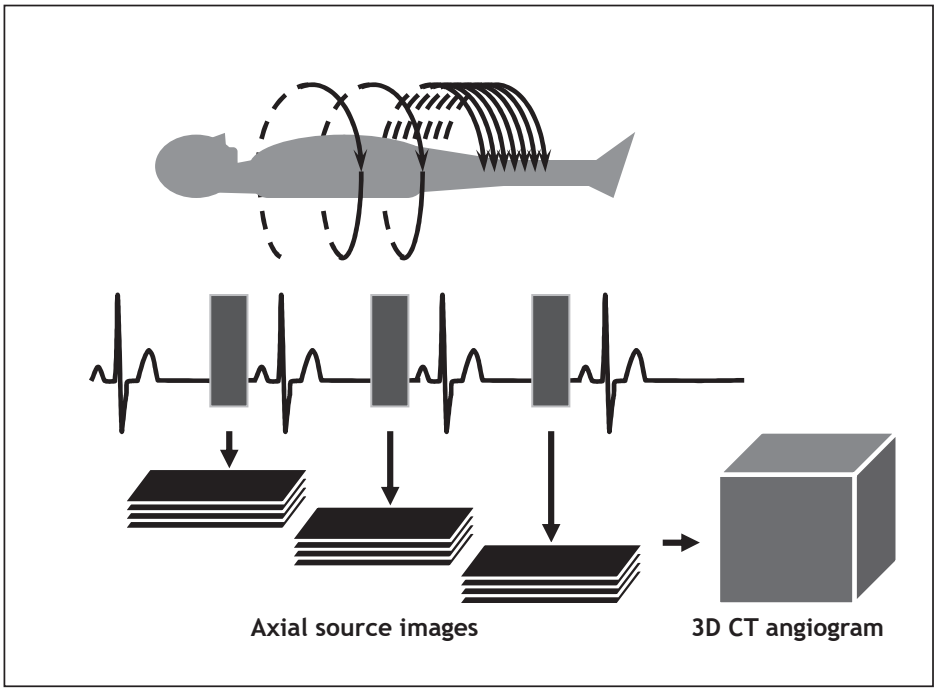

Figure 1. ECG-gated spiral CT image reconstruction. Overlapping data is acquired during a spiral CT scan. Using the recorded ECG, images are reconstructed from phase-consistent data acquired during each consecutive heart cycle. Together the reconstructed images from several heart cycles become a complete 3D data set of the heart during a single phase of contraction.

Temporal Resolution

While the scan time refers to the duration of the entire CT acquisition, the temporal resolution relates to the time needed to acquire a single image. The temporal resolution is comparable to the shutter time of a camera, and needs to be as short as possible to avoid motion blurring on the images. The fundamental temporal resolution of CT is determined by the rotation speed of the system, the image reconstruction algorithm, as well as the number of tube-detector units on the scanner. Standard partial scan reconstruction algorithms require approximately half of a rotation of projection data to create an image, so the temporal resolution is about half of the rotation time of the scanner. Alternatively, multisegmental reconstruction algorithms combine scan data from consecutive heart cycles to reconstruct images. Theoretically, the temporal resolution could be a fraction of the number of cycles combined (generally between two and four). In reality the effective temporal resolution is improved to a lesser magnitude, depending on the heart rate in relation to the scanner rotation time. Another limitation of multisegmental reconstruction algorithms is the requirement that each table position needs to be scanned during at least two or more heart cycles. For this reason these algorithms are generally only applied in case of a fast heart rate. For slower heart rates the table speed would need to be lowered, which would prolong the scan time and increase the radiation exposure. Depending on the rotation speed currently available single-source CT scanners offer a temporal resolution between 140 and 200 ms. To improve the relative temporal resolution modification of the heart rate by beta-blockers is common practice, and essential in patients with a faster heart rate. Alternatively calcium channel blockers or sinus node blockers may be used. Dual-source CT scanners are equipped with two tube-detector units mounted at an angular offset of 90°. Instead of a 180° rotation dual-source CT can acquire the same number of projections from a 90° rotation, which improves the temporal resolution by a factor of two (75-83 ms) independent of the heart rate. In the vast majority of patients with an acceptable heart rate current CT technology allows virtually motion-free imaging of the coronary arteries during phases of the heart cycle where the displacement of the heart is small, i.e., the mid-diastolic phase just before atrial contraction and/or the end-systolic phase.

Radiation Exposure

CT cannot be performed without exposure to roentgen, which is potential harmful for patients. The radiation dose of a cardiac scan generally exceeds that of non-ECG-synchronized CT scans. ECG-gated spiral CT requires multiple sampling to ensure availability of data at each table position during at least one entire heart cycle. Additional contributing factors to the relatively high radiation dose of cardiac CT are the need for fast rotation and thin detector collimation, and the location of the coronary arteries deep inside the chest. The actual radiation dose a patient receives during a given examination varies

substantially, and is determined by the scanner type, patient characteristics (body size) and the scan protocol. Initially, more powerful CT scanners resulted in a gradual increase in radiation doses associated with cardiac examinations. Without dose saving measures the dose of a 64-slice CT coronary angiogram varies between 8 and 20 mSv [1–4].

General measures to reduce the radiation exposure include narrowing of the scan range, lowering of the tube voltage, and lowering of the tube current, particularly in smaller patients (table 1) [1,5]. Contemporary scanners with powerful roentgen generators allow for imaging at tube potentials as low as 70 or 80kV in smaller patients. In patients with a regular heart rhythm ECG-triggered tube modulation is an effective means to reduce total dose for spiral CT acquisitions, without sacrificing image quality [1] (figure 2).With prospectively triggered axial scanning image acquisition (and radiation exposure) is limited to the phase of interest, which significantly reduces patient dose. Iterative reconstruction techniques, which largely replaced filtered back projection over the past few years, improve image quality with effective reduction of image noise. Iterative reconstruction techniques lead to dose reductions, when usual noise levels are accepted while images are acquired at lower tube current settings. The most recent generations of dual-source CT scanners have the capability of performing a prospectively ECG-triggered high-pitch spiral CT scan. This scan mode allows for complete data acquisition covering the entire heart within a single heart cycle, despite a maximum detector collimation of 5-7 cm. This scan protocol avoids potential stack artifacts that are typically seen for scans acquired over several heart cycles, but also further decreases the radiation dose. Because only a single heart-phase can be acquired, and a longer period within the heart cycle is needed to acquire all images, a low heart rate is important for good image quality. In general practice, state-of-the-art CT scanners perform coronary CT angiography at an average radiation exposure below 5 mSv. Using more cutting-edge technology the radiation dose can be less than 1 mSv in selected patients.

Table 1. Dose-reduction measures.

General tube current reduction
Geometry dependent (attenuation-based) tube current modulation
Tube voltage reduction
Tighter scan ranges
Table speed adjusted to the heart rate
ECG-triggered roentgen tube output modulation
ECG-triggered axial scan mode
ECG-triggered high-pitch spiral scan mode
Anatomic tube modulation
Iterative reconstruction algorithms (indirectly)

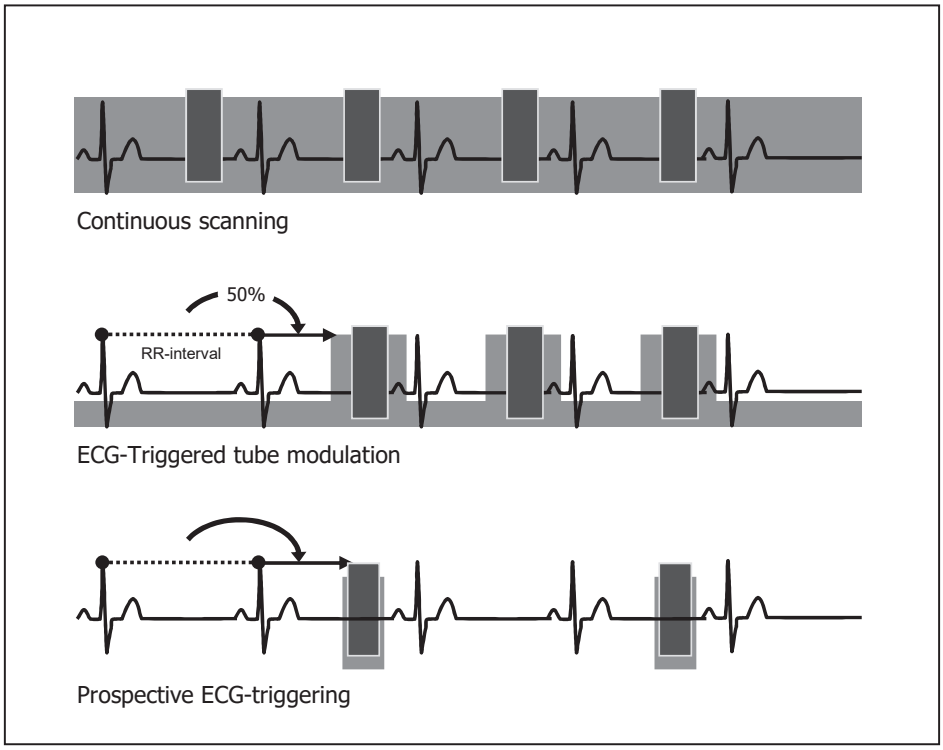

Figure 2. ECG-triggered tube modulation. Originally, tube output would be continuous during the data acquisition. Using ECG-triggered tube modulation the roentgen tube output can be alternated during the heart cycle. Based on the previous heart cycles the anticipated phase for reconstruction is predicted, at which time the tube output is elevated to the nominal level. For the remaining of the cycle the tube current is maintained at a very low level. For prospectively ECG-triggered, axial CT imaging the table is stationary during data acquisition. After each consecutive acquisition the table moves to the next position, which generally requires the time of two heart cycles, during which time no roentgen is emitted.

Image Reconstruction and Post-processing

As mentioned before images are acquired or reconstructed using ECG synchronization, and depending on the scan protocol different phases can be reconstructed afterwards, which may be helpful in case of motion artifacts. Images can be reconstructed using the filtered back-projection, or using the more recently introduced iterative reconstruction algorithms, which have become more or less the current standard. The slice thickness is adjustable, but generally selected in accordance with the detector width at around 0.4-0.75 mm. Overlapping slices can be reconstructed to improve the (subjective) longitudinal spatial resolution. The smoothness or sharpness of the images can be adjusted by using different reconstruction filters (kernels). Generally the field of view for the reconstruction is planned to include the entire heart. Given the fixed image matrix dimensions, reconstruction of a larger field of view will reduce the spatial resolution of the images.

To facilitate the evaluation of the large numbers of CT images postprocessing tools have been developed (figure 3). Cross-sectional images through the CT angiogram can be created in any position or orientation. These multiplanar reformations (MPR) can be flat cross-sectional planes, or they can be created along the (tortuous) trajectory of a vessel to demonstrate the entire course of that vessel in a single image. Thin-slab maximum intensity projections (MIP) are 2D displays of the highest attenuation values, usually contrast medium, calcium or metal, within a given slab. It provides greater overview of the vessel with better contrast between the lumen and the surrounding tissues. Because of the higher attenuation of metal and calcium, MIP is less effective in case of stented or severely calcified vessels. These postprocessing tools can be very helpful in combination with the axial source images, to assess the coronary lumen and detect coronary artery disease. Although not intended for the initial coronary evaluation three-dimensional (3D) volume-rendered images are an attractive means to summarize and communicate findings. Dedicated postprocessing tools have been developed for specific applications, including quantification of stenosis, differentiation of atherosclerotic plaque components, myocardial enhancement or contractile function.

CORONARY LUMENOGRAPHY

Detection of Coronary Stenosis

With the introduction of 64-slice CT systems coronary CT has emerged rapidly as a reliable diagnostic modality to detect coronary artery disease. (figure 4). Multiple studies comparing CT angiography with invasive angiography have shown that for the assessment of individual coronary segments, the sensitivity to detect significant coronary artery stenosis is around 94%. Calcified coronary disease causes blooming artifacts on CT, which increases the apparent stenosis severity of a lesion. CT angiography cannot assess the hemodynamic severity of CAD. Depending on the selected stenosis threshold the reported specificity of coronary CTA for detecting hemodynamically significant stenosis is 64-90%. The negative predictive value of CT has been consistently high in all studies, with a pooled average of 98%. Because of the excellent negative predictive value, coronary CTA is very effective for ruling out obstructive coronary artery disease [6,7,8].

Generally, the confidence and accuracy to assess stenosis is better in larger branches and in the absence of extensive coronary calcification (figure 5). Additionally, obesity decreases the signal to noise and the ability to assess coronary obstruction. An irregular heart rate, in particular atrial fibrillation, causes discontinuity between the consecutive acquisitions and negatively affects interpretation of the images, although contemporary technology does provide sufficient image quality in selected cases. As discussed previously image quality is better in patients with a low heart rate, for single-source CT preferably below 60–65/minute.

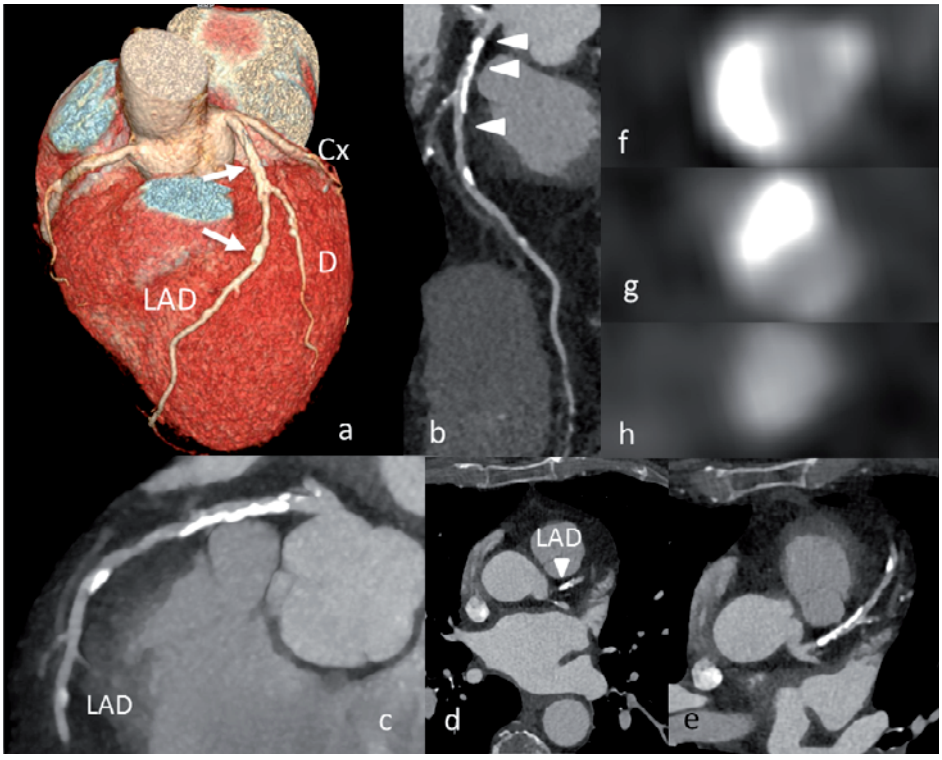

Figure 3. Image postprocessing. Use of different postprocessing tools in the same data set, which shows multiple calcified lesions in the left anterior descending coronary artery (LAD)(b and e). A complete 3D reconstruction of the heart (a) shows the highly calcified lesions in the LAD (arrows). Only a small section of the LAD can be visualized on a single axial slice (d), while multiplanar reformations can be created to demonstrate a longer section of the vessel (c). Curved multiplanar reformations (b) and maximum intensity projections (c) can be used to show the entire vessel in a single image. Panels (f–h) show cross-sections of the LAD at the proximal reference, the suspected stenosis and the distal reference level (arrowheads), respectively. D, diagonal branch; MO, marginal branch.

The development of contemporary CT systems with up to 320 detector rows for fast coverage, or double source-detector configuration for optimal temporal resolution, have improved the diagnostic performance of coronary CT further. However, to perform CTA with an optimal visualization of the coronary arteries it requires experienced operators, readers and sufficient preparations. Nitroglycerin expands the coronary lumen and beta-blockers improve image quality by reducing the heart rate. The challenge to rule out coronary artery disease is more difficult in patients with a high calcium burden, or otherwise higher pre-test probability of coronary artery disease. Because the spatial resolution of coronary CTA is lower than for invasive angiography, angiographic disease is classified in categories of diameter stenosis: normal in the absence of plaque, <25%, 25-49%, 50-69%, 70-99%, and occluded [9].

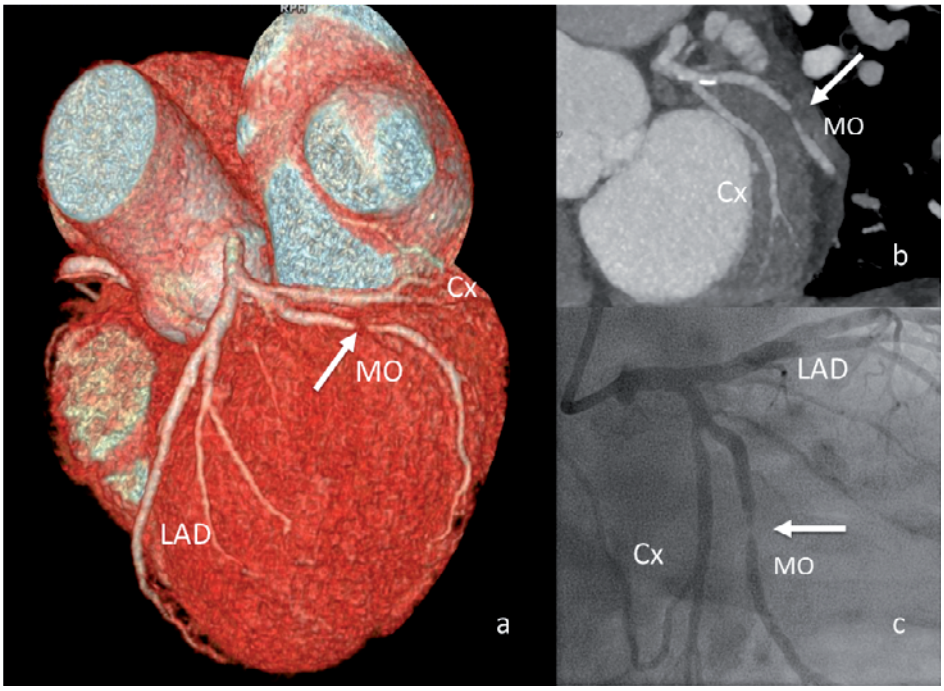

Figure 4. Severe coronary stenosis. CT shows a severe stenosis of a large obtuse-marginal branch (MO) of >70% (arrow). Maximum intensity projection of the circumflex artery (Cx) and the MO showing the severe stenosis (arrow) (b). Invasive angiography showing the left coronary system and stenosis (arrow)(c).

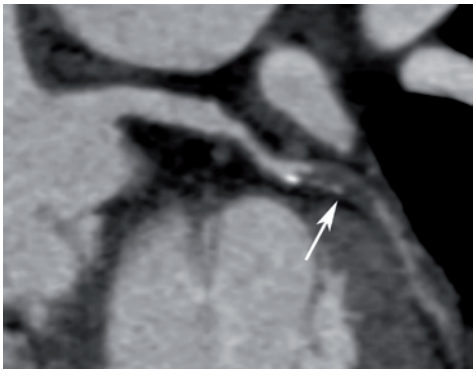

Figure 5. CT angiography shows an occluded left circumflex coronary artery, which appears to consist of thrombus on top of a partially calcified plaque. The plaque contains plaque with low attenuation values as well as spots of calcium. The vessel is also outwardly remodeled, all of which are features associated with rupture-prone plaque.

Coronary CTA is unable to directly assess the functional severity of coronary artery disease. To determine whether a lesion detected by cardiac CT causes ischemia may require a subsequent stress test or invasive FFR. Recently, CTA derived FFR (CTA-FFR) was introduced, which is a new technique that applies computational fluid dynamics to a coronary/myocardial model derived from the cardiac CT exam. Without the need for additional scans or stress medication (adenosine) aorta-coronary pressure gradients under simulated

hyperemia can be calculated throughout the coronary artery tree (figure 6). The good diagnostic performance of CTA-FFR in comparison with conventional invasive FFR has been demonstrated in several trials [10,11]. On-site performed CTA-FFR have recently become available, which also shows promising performance in single center studies[12,13].

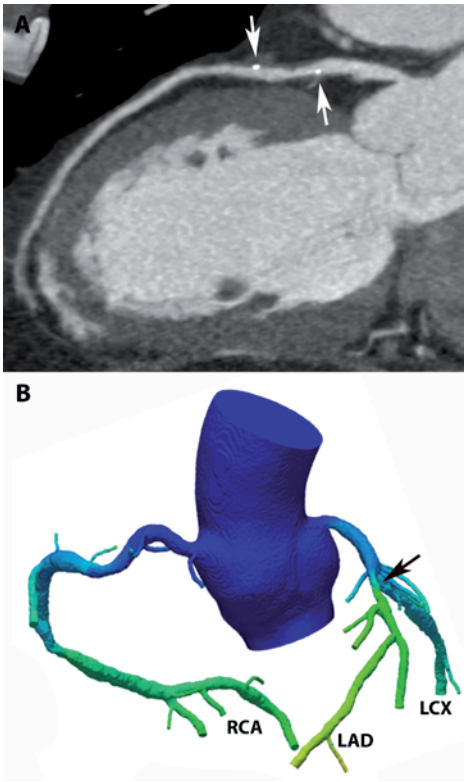

Figure 6. CTA shows moderate re-stenosis after placement of a bio-resorbable scaffold in the left anterior descending coronary artery (LAD) (A). The three-dimensional rendering of the CTA-derived fractional flow reserve (FFR) simulation displays calculated FFR values as a color map (B). While a change in shading from blue to green over the treated LAD indicates a change in FFR values, the distal CTA-FFR does not drop below 0.80, and is therefore not regarded as hemodynamically significant.

Clinical Applications

Coronary CTA is characterized by an excellent negative predictive value for confident exclusion of coronary stenosis, especially in patients with a low to intermediate probability of coronary artery disease. Based on the 2013 ESC guidelines on stable coronary artery disease coronary CTA is suitable for patients with a low to intermediate probability of disease (15-50% using the Genders prediction rule [14]) and an equal alternative compared to functional testing, under the condition that the patient is a suitable candidate for CT and if adequate technology and local expertise is available. (Class IIa, level of evidence C). [15] In addition, coronary CTA can be used for patients with inconclusive functional test results (Class IIa, level of evidence C). The ACC/AHA guidelines for stable ischemic heart disease consider coronary CTA as an alternative diagnostic option when functional testing is not possible or leads to inconclusive test results (Class IIa).

Use of coronary CTA recommended by current ESC Guidelines

- Coronary CTA should be considered as an alternative to stress imaging techniques for ruling out stable coronary artery disease in patients within the lower range of intermediate PTP for stable CAD in whom good image quality can be expected (class IIa, level of evidence C).
- Coronary CTA should be considered in patients within the lower range of intermediate PTP for stable coronary artery disease after a non-conclusive exercise ECG or stress imaging test, or who have contraindications to stress testing in order to avoid otherwise necessary invasive coronary angiography, if fully diagnostic image quality of coronary CTA can be expected (class IIa, level of evidence C).
- Coronary calcium detection by CT is not recommended to identify individuals with coronary artery stenosis (class III, level of evidence C).
- Coronary CTA is not recommended in patients with prior coronary revascularization. (class III, level of evidence C)
- Coronary CTA is not recommended as a 'screening' test in asymptomatic individuals without clinical suspicion of coronary artery disease (class III, level of evidence C).
- Coronary CTA should be considered as an alternative to invasive angiography to exclude ACS when there is a low to intermediate likelihood of CAD and when cardiac troponin and/or ECG are inconclusive (class IIa, level of evidence A).

After publication of these guidelines a few comparative effectiveness trials have been published (table 2). The pragmatic PROMISE trial randomized an impressive 10.003 patients with new stable chest pain between CT angiography and functional testing (mostly nuclear imaging) for evaluation of suspected coronary artery disease. The study demonstrated that there was no difference in adverse cardiac events after 2 years. [16] Although after CT more patients underwent invasive angiography and more were revascularized, the number of invasive angiograms without obstructive coronary artery disease was reduced. In the SCOT-HEART trial, the addition of coronary CTA to standard care was investigated in 4146 patients with stable angina. [17] The investigators demonstrated improved certainty of the diagnosis of angina pectoris caused by ischemic heart disease, but no effect on frequency of the diagnosis of angina due to coronary artery disease. After 1.7 years, there was a close to statistically significant 38% reduction in hard events in favor of patients in the CT group. The smaller CRESCENT trial randomized 350 patients between cardiac CT, consisting of a calcium scan and selective coronary CTA, and functional testing [18]. This study showed that after CT, more patients reported complete relief of anginal symptoms and resulted in fewer adverse events. CT was more often able to confidently rule out coronary artery disease and therefore the final diagnosis was reached faster, requiring fewer downstream noninvasive tests without a significant increase in invasive angiograms.

Table 2. Randomized controlled trials comparing coronary CTA and standard care in stable chest pain

	PROMISE (2015)		SCOT-HEART(2015)		CRESCENT (2016)	
N	10003		4146		350	
Risk	D&F: 53 ± 21%		ASSIGN 10-year CHD risk: 17 ± 12%		D&F: 45 ± 29%	
Follow up (yrs)	2.1		1.7		1.2	
	USA		Scotland		The Netherlands	
	CT	**Standard**	**Standard+ CT**	**Standard**	**CT**	**Standard**
Additional testing					25%*	53%*
Cath angiography	12.2%	8.1%	12%	13%	12%	11%
Revascularizations	8.8%*	3.9%*	11.2%	9.7%	9%	7%
Adverse events**	3.3%	3.0%	14%	15.7%	3%*	10%*
Total cost (€)					369*	440*
Mean cumulative radiation dose (mSv)	12.0*	10.1*			6.6	6.1

* Significant results ** PROMISE including all-cause death, nonfatal MI, hospitalization for unstable angina and major procedural complications. SCOT-HEART including all-cause death, non-fatal MI and stroke and hospitalizations for chest pain. CRESCENT including all-cause death, non-fatal MI and stroke, late revascularization procedures (>90days) and unplanned cardiac ED evaluations.

Besides diagnosing stable CAD, coronary CTA also has a role in suspected acute coronary syndromes in the emergency department, which has been investigated over the recent years (table 3). The CT-STAT trial compared coronary CTA with nuclear imaging as initial test in the management of patients with acute chest pain. They reported a 54% reduction in time to diagnosis and 38% lower costs of ED care with CT [19]. The ACRIN-PA trial demonstrated that low-risk patients could be safely discharged with early CT angiography twice as often, and CAD was more likely to be diagnosed with CT. [20] The ROMICAT2 trial showed a reduction in length of hospital stay and a 4-fold higher discharge rate from the ED after CT. [21] The results of these trials contributed to a class IIa recommendation (level of evidence A) for the use of coronary CTA in low-intermediate risk patients with non-conclusive ECG and biomarker results to avoid invasive angiography. [22] Since these trials were completed, the introduction of high sensitivity-troponin has changed standard care at the ED considerably and may reduce the efficiency benefits of CT substantially, as was demonstrated recently in the BEACON trial. [23] It showed that CT was safe, less expensive, with less subsequent diagnostic testing. However, CT did not identify more patients with significant CAD requiring revascularization and did not reduce the length of stay nor allowed more expedited discharge. The role of coronary CTA may shift towards the assessment of patients with low-elevated troponin levels, which become more frequent with the use of more sensitive troponin assays.

Table 3. Randomized controlled trials comparing coronary CTA and standard care in acute chest pain

	ACRIN (2012)		ROMICAT II (2012)		BEACON (2016)	
N	1370		985		500	
Risk	TIMI score 0-2		Low–intermediate risk		Average GRACE 83	
	USA		USA		The Netherlands	
Troponin assay	Conventional		Conventional		High-sensitivity	
	CT Angio	**Controls**	**CT Angio**	**Controls**	**CT Angio**	**Controls**
ACS diagnosis	1%	1%	9%	6%	9%	7%
ED discharge	50%*	23%*	47%*	12%*	65%	59%
Cath angiography	5%	4%	12%	8%	17%	13%
Revascularizations	3%	1%	6%	4%	9%	7%
Length of stay (hrs)	18*	25*	23*	31*	6.3	6.3
1-month MACE	0%	0%	0.4%	1.2%	10%**	9%**
Total cost			$4026	$3874	€337*	€511*

* significant results; ** including revascularizations. Acute coronary syndrome (ACS); emergency department (ED); major adverse cardiovascular events (MACE)

Imaging of Stents

The high roentgen attenuation of the metal in standard coronary stents causes artifacts that complicate evaluation of the coronary lumen within the stent, particular close to the stent struts. The magnitude of these artifacts vary depending on the material and the stent design, i.e., the strut thickness [24]. The effect on visualization of the in-stent lumen is most severe in smaller stent [25]. Comparative studies have shown a very reasonable accuracy for in-stent stenosis in comparison to conventional angiography, although a substantial number of stent were excluded because of insufficient image quality [26–28]. Accuracy is better in larger stent and is more accurate for detection of occlusion compared to stenosis [29]. Guidelines recommend CT angiography after coronary stenting in symptomatic patients and in asymptomatic patients with a prior left main stent with a diameter ≥ 3mm [9]. On an individual basis CT can be considered to rule out severe obstruction of stents in larger proximal coronary branches of bypass grafts [30]. Even more than in nonstented patients acquisition of high-quality data, with application of dedicated filters for image reconstruction is recommended to achieve interpretable image quality (figure 7). Recently bioresorbable scaffolds have been introduced. The metal-free struts allow unrestricted coronary CT angiography both at the time of implantation, as well as after resorption (figure 8).

Bypass Graft Imaging

Because of their large diameter, limited calcification and relative immobility bypass grafts, and particularly saphenous vein grafts, are well visualized by CT, although surgical material may cause artifacts (figure 9). Even with earlier generations of CT graft occlu-

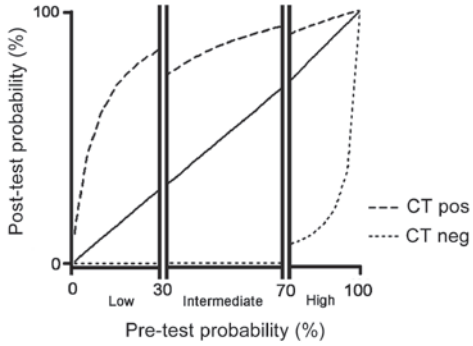

Figure 7. Diagnostic value of CT coronary angiography. Pretest and post-test probability of significant coronary artery disease after CT coronary angiography, confirmed by catheter coronary angiography. In the low-to-intermediate pretest probability group CT virtually excludes significant coronary artery disease, while a positive CT scan increases the probability of coronary artery disease to 68 and 88% for low and intermediate pretest probability patients. (Adapted from Meijboom *et al*. [6].)

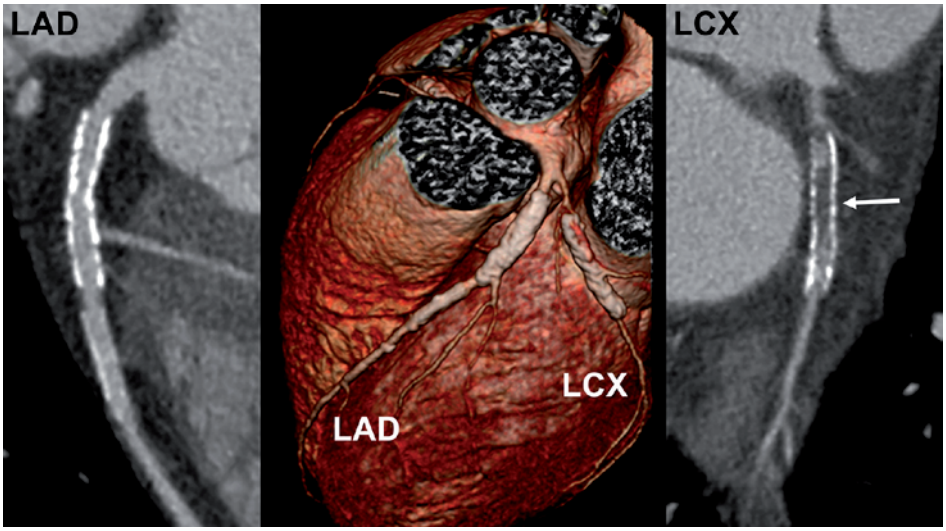

Figure 8. CT stent imaging. Two patent stents in the left anterior descending coronary artery (LAD). The different intensity of the stent struts on CT suggests they are stents of a different type. A septal branch is preserved after stenting. A third stent has been implanted in the left circumflex branch (LCX). The low-density material within the stent suggests occlusion (arrow). Distally the LCX is opacified, likely due by collateral supply.

sion or patency can be differentiated with very good accuracy. Current CT technology detects graft occlusion, as well as significant stenosis with an accuracy of approximately 95% (table 4) [31-35]. However, ischemic symptoms in patients after bypass surgery can be caused by obstruction of bypass grafts, or by progression of disease in the native coronary arteries. Longer after surgery obstruction of the non-grafted coronary arteries or distal coronary run-offs is in fact more likely than graft failure as the cause of recurrent complaints [36]. Therefore, evaluation cannot be limited to the bypass grafts alone, but should include the coronary arteries as well. The latter however proves to be more complicated due to often diffuse coronary disease and excessive presence of coronary

calcification [37]. Although results have improved using contemporary technology: sensitivity and specificity of approximately 90%, diagnostic performance is still inferior to the published results in patients without previous bypass graft surgery [32,33,35]. Because of the chronic nature of atherosclerotic disease in these patients luminal obstruction may be diffuse and extensive. Occluded grafts may exist for years without causing symptoms because of maintained coronary flow or development of collateral vessels [38]. Even more than in nonsurgical patients, functional information concerning the presence and localization of ischemic myocardium is important to identify the culprit coronary or graft lesion. As a consequence CT is often not fully conclusive in patients presenting with symptoms late after surgery. It can be of use in specific situations when one is (exclusively) interested in the condition of the bypass grafts. CT imaging of the grafts can be performed prior to catheterization to shorten the time spent in the catheterization laboratory, particularly when the location of the grafts is challenging or unknown.

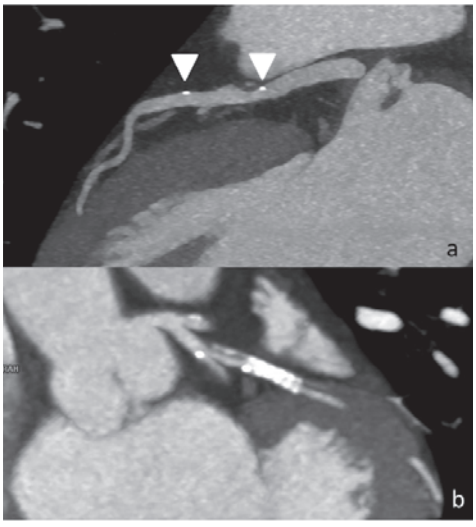

Figure 9. Bioresorbable scaffold in the left anterior descending artery (LAD). Remnant platinum markers (arrowheads) indicate the location of the previous scaffold placement. After the proximal marker noncalcified plaque results in a <50% stenosis (a). A patient with a previous bioresorbable scaffold placement from the proximal circumflex artery (Cx) into the marginal obtuses (MO) side branch. There is some intima hyperplasia visible causing stenosis up to 50%. A metal stent was placed distally from the bioresorbable scaffold. (b)

Table 4. Diagnostic performance of CT to detect significant bypass graft disease.

	N	*Excl.(%)*	*Sens.(%)*	*Spec.(%)*	*PPV(%)*	*NPV(%)*
Pache *et al*. [24]	31	6	98	89	90	98
Malagutti *et al*. [25]	52	0	99	96	95	99
Ropers *et al*. [26]	50	0	100	94	76	100
Meyer *et al*. [27]	138	0	97	97	93	99
Onuma *et al*. [28]	54	2	100	91	74	100

Number of patients (*N*), exclusion rate (Excl.), sensitivity (Sens.), specificity (Spec.), positive predictive value (PPV) and negative predictive value (NPV) to detect >50% luminal obstruction.

IMAGING OF CORONARY ATHEROSCLEROSIS

Coronary Calcium

Because of the roentgen attenuating properties of calcium in comparison to other tissues, calcium can be imaged without the need for contrast medium. While most clinical data has been gathered using electron-beam CT, calcium imaging can be performed with MSCT using either prospectively ECG-triggered scanning or retrospectively ECG-gated image reconstruction [35,36]. Finding calcium is evidence of coronary atherosclerosis. Most patients with flow-limiting disease have a positive calcium score. In symptomatic patients the positive predictive value of a positive calcium score for the presence of coronary stenosis is about 50%, and without symptoms even lower. The absence of coronary calcium does not exclude the presence of (noncalcified) atherosclerosis, although severe coronary artery disease will be unlikely in this case.

The (semi-)quantitative amount of coronary calcium is a surrogate measure for the total coronary plaque burden. Several studies have shown that the coronary calcium score [37] predicts adverse coronary events independently of conventional risk factors [38–42]. The St Francis Heart Study showed that the calcium score outperformed the Framingham Risk Score for the prediction of coronary events [39]. According to published guidelines calcium scoring is reasonable to better classify patients at an intermediate risk of cardiovascular events [43]. Patients with an Agatston score below 100 have a annular CV risk well below 1% and can be considered low-risk. Those with a score >400 have a CV risk equal to for instance diabetics and are entitled to more intensive preventive treatment. Whether this will reduce their risk, and whether calcium scoring as such improves clinical outcome still needs to be established.

The current ESC guidelines state that a "zero" calcium score cannot be used to rule out coronary artery stenosis in symptomatic individuals, especially when young and with acute symptoms (class III, level of evidence C). However, for asymptomatic adults at intermediate risk for CAD or with diabetes and 40 years of age and older, the use of coronary calcium scanning should be considered for CV risk assessment (class IIa, level of evidence B).

Contrast-Enhanced Plaque Imaging

On contrast-enhanced CT scans noncalcified plaque can be identified in addition to calcified lesions (figure 10). In comparative studies with IVUS CT detects most of the plaque in the proximal coronary vessels, particularly when some calcium is present [44,45]. Because the outer vessel wall is poorly defined, with user-dependent measurements affected by display settings, plaque quantification remains difficult [46,47]. Measured CT attenuation (Hounsfield units) within plaques has been compared with histology and IVUS [46,48–51]. Calcified plaques have a significantly higher attenuation than noncalci-

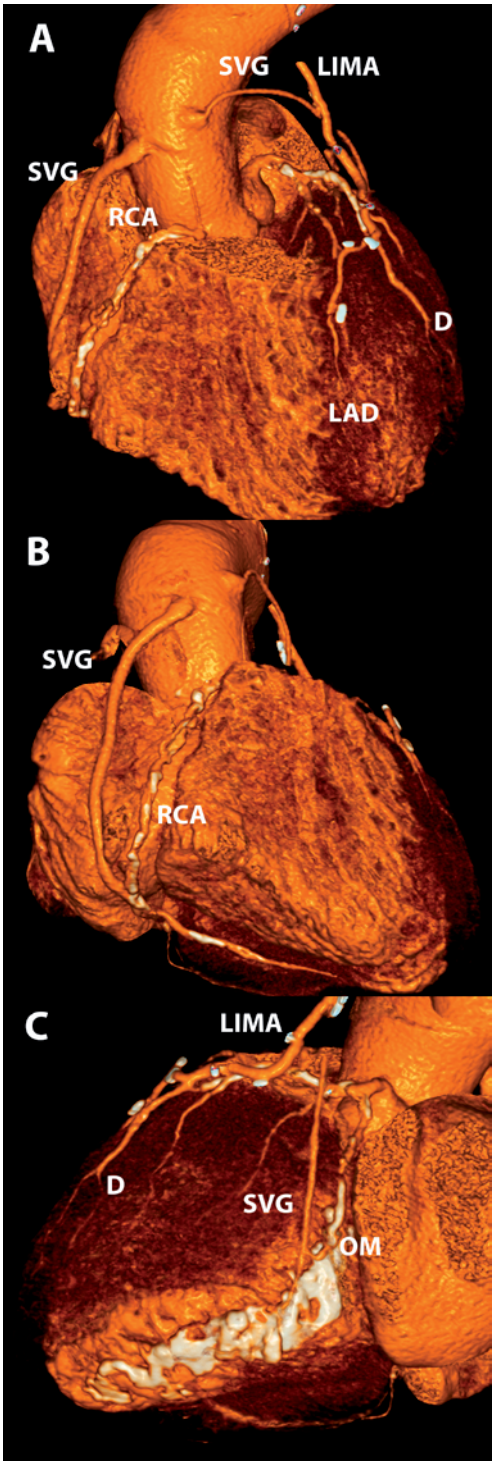

Figure 10. Graft imaging. Three-dimensional reconstruction of a CT angiogram of a patient with a left internal mammary artery graft (IMA) connected to the middle segment of the left anterior descending coronary artery (LAD) and a venous graft from the ascending aorta with an anastomosis to a diagonal branch (D), a posterolateral branch and a posterior descending branch (not shown). While the grafts are well visualized, assessment of the native coronary arteries, particularly the LAD, is more complicated.

fied plaques. Differentiation of lipid-rich and fibrous plaque, or hypo- and hyper-echo dense plaques has proven to be more difficult. Lipid-rich plaques have significantly lower attenuation values, but with significant overlap with measured values in fibrous plaques, particularly between studies. Similar to IVUS studies, CT has shown that culprit plaques in patients with an acute coronary syndrome tend to be larger with positive vessel remodeling. Unstable lesions contain smaller overall quantities of calcium, but with a more spotty distribution, as well as more low-density plaque in comparison to stable coronary plaques [52–56]. Recent years more research is conducted into high-risk plaques in coronary CTA. High risk plaque features are considered to be:

- low attenuation (HU) plaques, defined as <30 HU corresponding with plaques with a lipid core
- Positive remodeling, defined as a remodeling index >1.1, which is calculated as the ratio of the diameter of the plaque relative to diameters of the average proximal and distal reference diameters
- Spotty calcification, defined as calcification measuring <3mm in diameter surrounded by non-calcified plaque
- Napkin-ring sign, defined as a ring of peripheral high attenuation surrounding a low attenuation (necrotic) core

Further research and technical developments are necessary to develop CT-based plaque analysis in the future. [56,57,58].

SUMMARY

- ECG-synchronized cardiac CT allows noninvasive visualization of the heart and coronary arteries. Beta-blockers are often used to lower the heart rate and minimize motion artifacts.
- Contemporary scanner technology and scan protocols, combined with operator awareness, can reduce the radiation dose of cardiac CT considerably.
- The diagnostic accuracy of coronary angiography using the latest generation CT is good in comparison to conventional catheter angiography, and permits exclusion of significant coronary obstruction in the majority of patients. Challenges in coronary CT imaging include calcified vessels, stents, small vessel pathology, arrhythmia, tachycardia, and obese patients.
- Coronary CT is considered a diagnostic option in patients with chest pain, a low-intermediate probability for coronary artery disease, particularly when exercise tests are unavailable or nonconclusive. Other applications include the triage of patients

with recent/acute chest pain at low to intermediate risk without ECG changes or elevated blood markers.

- Coronary calcium scoring can improve risk stratification, and may be considered for individuals at intermediate risk. Imaging of noncalcified plaque by CTA is a field of intensive research and expectations.

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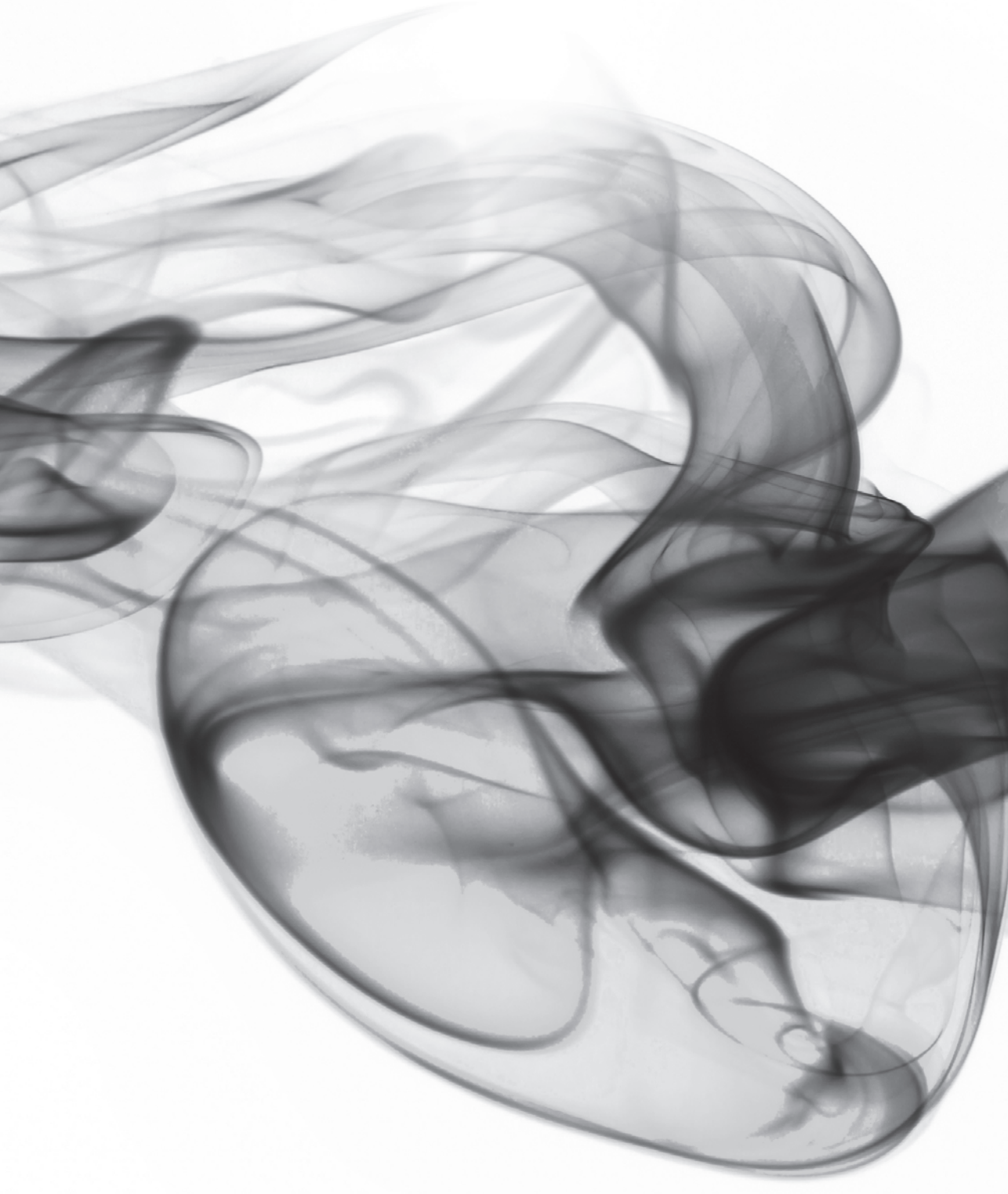

Part 2

CT Calcium imaging and CT angiography in stable angina

CHAPTER 3

Calcium imaging and selective CT angiography in comparison to functional testing for suspected coronary artery disease: the multicenter, randomized CRESCENT trial

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ABSTRACT

Aims To compare the effectiveness and safety of a cardiac CT algorithm with functional-testing in patients with symptoms suggestive of coronary artery disease (CAD).

Methods and Results Between April 2011 and July 2013 350 patients with stable angina, referred to the outpatient clinic of four Dutch hospitals, were prospectively randomized between cardiac CT and functional-testing (2:1 ratio). The tiered cardiac CT protocol included a calcium scan followed by CT angiography if the Agatston calcium score was between 1 and 400. Patients with test specific contra-indications were not excluded from study participation. By one year, fewer patients randomized to cardiac CT reported anginal complaints (p=0.012). The cumulative radiation dose was slightly higher in the CT group (6.6±8.7mSv versus 6.1±9.3mSv; p<0.0001). After 1.2 years, event-free survival was 96.7% for patients randomized to CT and 89.8% for patients randomized to functional-testing (p=0.011). After CT the final diagnosis was established sooner (p<0.0001), and additional downstream testing was required less frequently (25% vs 53%, p<0.0001), resulting in lower cumulative diagnostic costs (€369 versus €440; p<0.0001).

Conclusion For patients with suspected stable CAD, a tiered cardiac CT protocol offers an effective and safe alternative to functional-testing. Incorporating the calcium scan into the diagnostic workup was safe and lowered diagnostic expenses and radiation exposure.

INTRODUCTION

Diagnostic testing of coronary artery disease (CAD) is annually performed in 20 million patients worldwide.(1) Despite concerns about accuracy (2), exercise ECG remains the first performed test in many parts of the world,(3-5) while stress imaging is reserved for patients with a higher probability of disease.(3) Cardiac CT has emerged as an alternative diagnostic test for CAD, characterized by an excellent negative predictive value for confident exclusion of CAD. Recently, two large randomized studies reported on the value of coronary CT angiography for evaluation of stable angina (6, 7). In the Computed Tomography versus Exercise Testing in Suspected Coronary Artery Disease (CRESCENT) randomized-controlled trial we assessed the effectiveness and safety of a tiered cardiac CT protocol, consisting of a calcium scan and selective performance of CT angiography, in comparison to functional-testing.

METHODS

Study Design

The CRESCENT trial is a pragmatic randomized-controlled trial comparing the clinical effectiveness of a tiered cardiac CT approach and a standard diagnostic workup using functional-testing. At four hospitals in the Rotterdam region of the Netherlands, 350 patients with stable chest pain, who had been referred for evaluation of suspected CAD, were prospectively enrolled. The study was approved by the medical ethics committees of the central coordinating centre and participating sites. The CRESCENT trial is registered at the US National Institutes of Health (ClinicalTrials.gov), number NCT01393028.

Study participants

Patients aged 18 years or older with stable chest pain or angina equivalent symptoms potentially caused by obstructive CAD were study eligible. Exclusion criteria were known CAD or invasive angiography or stress test performed within the last year. Renal impairment, contrast allergy, atrial fibrillation, or other test specific contra-indications did not preclude study participation.

Study procedures

Participants who consented in writing were randomly assigned to CT or functional-testing in a 2:1 ratio because of the established performance of the standard protocol. After the standard outpatient clinic visit, all participants filled out the Seattle Angina Questionnaire (SAQ), EuroQol-5D-5L (EQ-5D) and Short-Form-36 (SF-36) for quality-of-life assessment, and a cost questionnaire. All subsequent testing was performed at the recruiting center.

Patients were contacted after one year for ascertainment of trial endpoints and health status measurements (questionnaires). Performance and results of downstream diagnostic and therapeutic procedures were collected. All procedures were confirmed through review of medical records.

Cardiac CT strategy

For the CT algorithm, detailed in figure 2, all patients first underwent a calcium scan. Absence of calcium excluded CAD and required no further testing, except for patients with a high pre-test probability of CAD (>70% by Diamond and Forrester criteria (8)). Patients with a calcium score between 1 and 400 (and patients without calcium but a >70% pre-test probability), underwent contrast-enhanced coronary CT angiography to detect obstructive CAD. Those with CT contra-indications, a calcium score >400, or non-conclusive CT angiogram (non-interpretable or intermediate obstructive disease), underwent stress testing or invasive angiography at the discretion of the treating physician. CT angiography results were classified as normal or CAD<50%, low-risk CAD>50%, or high-risk CAD. High-risk CAD was defined as left main stenosis, three-vessel disease or proximal LAD stenosis (>50%). All recruiting sites had previous cardiac CT experience, and were equipped with 64-slice or more advanced CT technology, with radiation minimizing measures depending on local practices and patients characteristics.

Functional-test strategy

Most patients randomized to standard care underwent a symptom-limited exercise ECG. The target heart rate was defined as 85% of the maximum predicted heart rate based on age. Based on exercise tolerance, ST-segment changes and symptoms the Duke Treadmill Score (DTS) was calculated to assist further management. Myocardial perfusion imaging or stress echocardiography were performed in case of contraindications to exercise ECG, or non-interpretable or equivocal results. All functional- imaging tests were interpreted for the presence of inducible ischemia, and assessed risk of adverse outcome applying established criteria for each respective test.(9, 10)

Both CT and functional tests were performed and interpreted by local physicians, who also made the subsequent clinical management decisions. Patients considered to be at high-risk based on test results and clinical interpretation, or those with refractory symptoms despite optimal medical treatment, were generally referred to invasive coronary angiography.

Outcomes

The primary outcome was the clinical effectiveness, defined as the absence of chest pain complaints after one year. Additionally, SAQ, SF-36 and EQ-5D questionnaire responses were compared between baseline and one year follow-up. Pre-specified secondary outcomes included the diagnostic yield, defined as the proportion of patients undergoing

revascularization after invasive angiography. Efficiency outcomes included the time to diagnosis, defined as the period from presentation until the first test that led to the final diagnosis, or the final test that ruled out obstructive CAD. Downstream testing included all non-invasive testing (exercise-ECG, cardiac CT, stress echocardiography and perfusion imaging) and invasive angiography to detect CAD after the initial test. The diagnostic costs included all tests performed until one year. Average costs per test were based on a previously published cost analyses.(11) Based on the frequency of tests performed in each group, a formula for calculation of the overall downstream procedural costs was constructed, which allows recalculation using alternative procedural charges.

Survival analysis was based on a composite endpoint of all-cause mortality, non-fatal myocardial infarction, major stroke, unstable angina pectoris with objective ischemia and/or requiring revascularization, unplanned cardiac evaluations and late coronary revascularization procedures. Nonfatal myocardial infarction was defined as biomarker elevations in a concordant clinical context. Late revascularizations were defined as performed beyond 90 days. Unplanned cardiac evaluations were defined as non-elective hospital visits and admissions for acute complaints suspected to be of a cardiovascular nature. Events were counted once for each patient in the hierarchical order listed above. Each suspected clinical endpoint and a random 10%-sample of the remaining patients were reviewed by two external, independent reviewers, blinded to randomization, with discordance resolved by a third reviewer.

The cumulative effective radiation dose (mSv) included all tests and interventions involving roentgen. For cardiac CT a conversion factor of 0.017 was used. For SPECT and catheterization conversion factors of 0.0085mSv/millibecquerel and 0.24mSv/Gy*cm^2 were used.(12, 13)

Statistical analyses

Insufficient funding prevented us from testing the original endpoint, which was the proportion of patients undergoing catheter angiography followed by revascularization and required 1128 patients to demonstrate an 8%-points difference (alpha 0.05; power 0.80). For the alternative endpoint, 294 patients were required to demonstrate an 8%-points difference in reported chest pain (alpha significance level 0.05; power 0.80). The secondary power analysis was performed shortly after patient recruitment had started.

Continuous data are presented as means±SD or medians with interquartile ranges. Groups were compared using an independent-sample t-test or Mann-Whitney U-test for continuous variables, and chi-square or Fisher's exact-test for categorical variables. Differences in the SAQ-questionnaire mean scores between baseline and follow-up were analysed with a paired-t-test. The probability of event-free survival was estimated by Kaplan-Meier survival analysis with comparisons performed with the log-rank statistic. A Cox-proportional hazards model was employed to estimate the relative hazard of events

by randomized test strategy, deriving hazard ratios and 95% confidence intervals (CIs). A two-sided p-value of <0.05 was considered statistically significant. Statistical analyses were performed using SPSS (version 21, IBM Corp, Armonk NY, USA), according to the intention-to-treat principle.

RESULTS

Study population

Between April 2011 and July 2013, 463 eligible patients were approached, of whom 93 (20%) declined participation and 20 (4%) were unable to provide written consent. Of the 350 enrolled patients, 242 were randomly assigned to CT and 108 to standard care based on functional-testing. All patients were included in the intention-to-treat analysis (figure 1). Overall, 293 of 350 participants (84%) had complete one-year follow-up. The original records for hospital visits and events were available in 347 of 350 (99%) patients. The mean age was 55±8 years, 55% were women, and most had an intermediate probability of CAD. While there were no significant differences in baseline characteristics, the estimated cardiovascular risk (SCORE) appeared slightly higher in the functional-testing group (table 1) (14). In 28 patients (8%) a final diagnosis of obstructive CAD was made by invasive angiography.

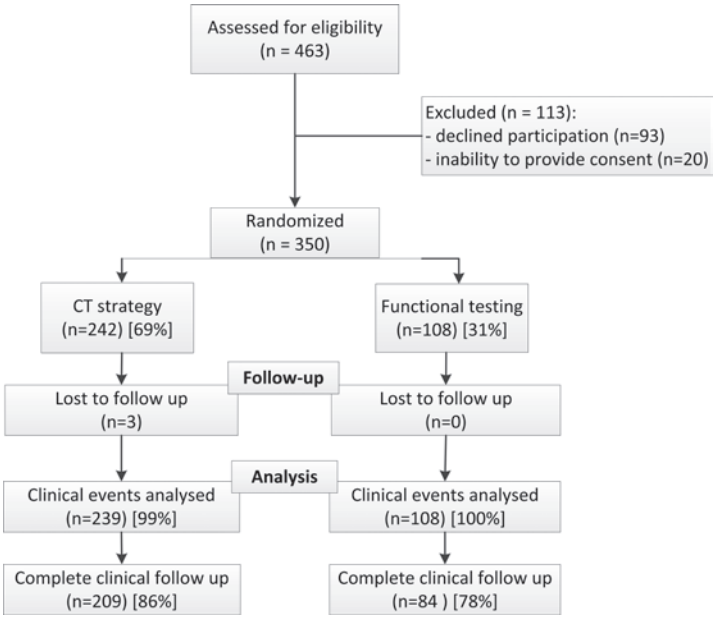


Figure 1. Patient flow diagram with disposition by randomized arm. Complete clinical follow-up defined as both clinical event information and questionnaires available at one year.

Table 1. Patient characteristics

	Cardiac CT (n=242)	Functional testing (n=108)
Mean age (years)	55±10	55±10
Female sex (%)	55	56
Systolic/diastolic blood pressure (mmHg)	138/84	138/84
Median body-mass index	28±5	28±5
History (%)		
Coronary disease	0	0
Stroke	3.3	7.4
Peripheral artery disease	3.7	6.5
Atrial fibrillation	0.4	1.9
Renal impairment*	3.7	4.6
Renal failure*	1.7	1.9
Cardiac risk factors (%)		
Current/past smoker	34	36
Hypertension	52	52
Dyslipidaemia	54	61
Diabetes mellitus	17	16
Family history of ischemic heart disease	38	37
Presenting chest pain symptoms (%)		
Typical angina	24	23
Atypical angina	53	51
Non-anginal complaints	23	24
Pre-test probability (%)**	45±29	45±29
Median cardiovascular risk (SCORE*)**	4.0(2.0;13.8)	6.0(2.0;12.0)
Baseline medications (%)		
ACE inhibitor or AT II blocker	23	25
Beta-blocker	23	30
Calcium channel blocker	11	17
Aspirin or other antiplatelet agent	29	29
Statin or other lipid lowering medication	47	49
Vitamin K antagonists	3	7
Nitrates, oral or sublingual	7	12
Diuretics	11	9

Patient characteristics presented as mean±SD, percentage or median and interquartile range. There are no significant differences between both groups. Dyslipidaemia: total cholesterol >5mmol/L, low-density lipoprotein >3mmol/L, or on lipid-lowering medication. *Renal impairment: GFR<90 ml/min/1.73m^2; renal failure: GFR <30 ml/min/1.73m^2 **Diamond and Forrester criteria(8, 14). ***Estimated annual risk of cardiovascular death by Systematic Coronary Risk Evaluation.(14)

Test results

In the functional testing group exercise ECG could not be performed in five patients (5%) because of left bundle branch block (n=2) or the inability to exercise (n=3). The exercise ECG was considered abnormal in 11%. In 50% of patients, including those with contra-indications to exercise ECG, further testing was required by myocardial perfusion imaging (29%), stress echocardiography (7%), cardiac CT (6%) and invasive angiography (11%).

In the CT group, the median calcium score was 4.0(0-61), and 100 patients had no detectable calcium. In 26 (11%) the calcium score was high (>400), for most of whom clinicians ordered further testing: nuclear imaging (n=8), stress echocardiography (n=3), exercise ECG (n=6), and invasive angiography (n=13). While CT angiography was indicated for 117 patients, one scan was inappropriately performed in a patient with a high calcium score, while the scan was not performed in 9 patients (8%) with renal failure (n=4), severe contrast allergy (n=4), or anxiety (n=1). Significant stenosis was absent in 75% of patients, 17% had >50% low-risk CAD, 6% had high-risk CAD, and 3% of the scans were non-diagnostic (figure 2).

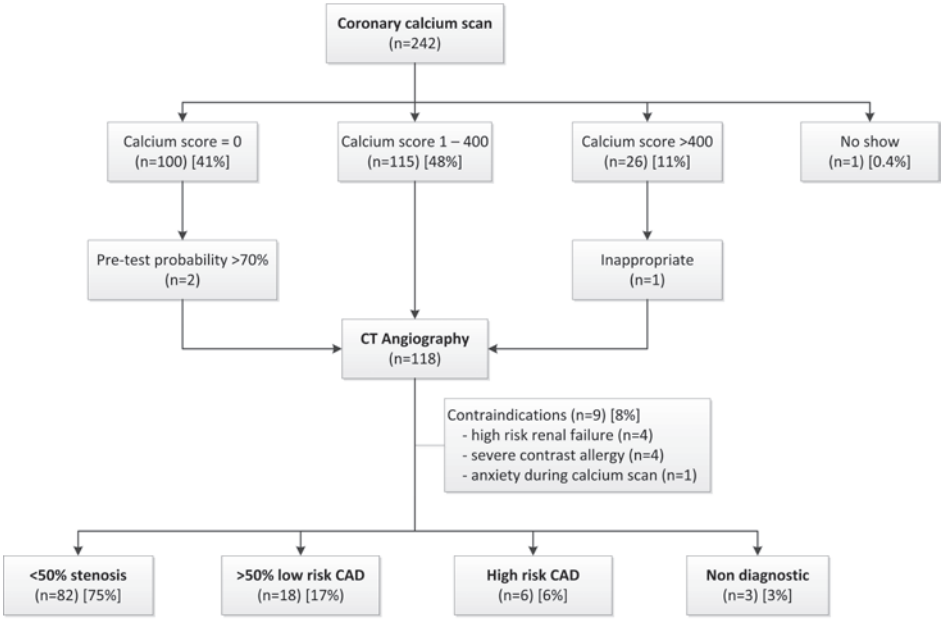


Figure 2. Cardiac CT algorithm and results. Coronary calcium by Agatston method. Pre-test probability of coronary disease (CAD) by Diamond and Forrester criteria(8). High-risk CAD defined as left main stenosis, three-vessel disease or proximal LAD stenosis (all >50%).

Clinical effectiveness

After one year fewer patients randomized to CT reported anginal symptoms in comparison to the functional-testing group (39% vs 25%, p=0.012), although the proportion of patients with similar or worsened symptoms was comparable (26% vs 29%, p=0.595) (figure 3). For the SAQ-subscales, the CT group had a lower angina frequency at one year follow-up (p=0.012). Other SAQ-subscales showed a statistically non-significant trend toward more improvement over one year for the CT group (table 2). Quality-of-life improvement, measured with the five dimensions of the EQ-5D-questionnaire did not differ between the groups (p=0.759)(appendix 1). The mean VAS scale increased in the CT group from 67.6 into 72.5, and in the functional-testing group from mean 66.8 to 69.4 (p=0.237). All SF-36-subscales were similar between both groups (appendix 2).

The diagnostic yield of invasive angiography, i.e. catheterizations followed by a revascularization procedure, was 72% after CT, compared to 58% in the functional-testing group (p=0.469)(table 3). The prevalence of >50% coronary disease was similar between groups (8.8% CT, 6.5% functional-testing; p=0.384), as well as the proportion of high-risk CAD (4% and 3%, respectively (p=0.703), and the proportion undergoing revascularization (table 3).

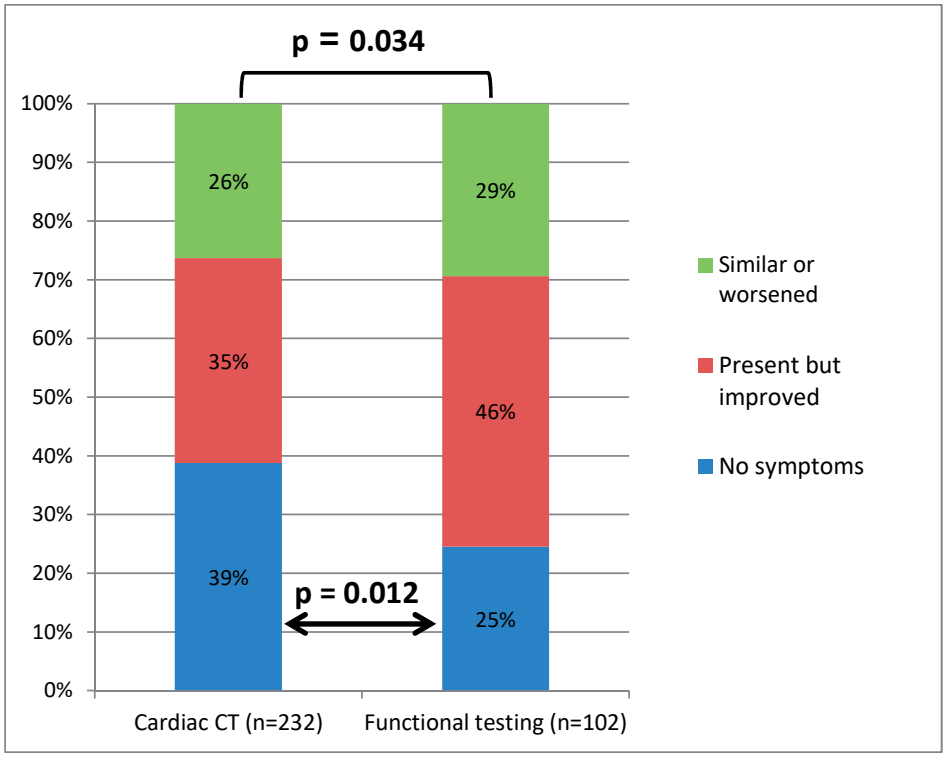


Figure 3. Angina status one year after randomization.

Table 2. SAQ results and subgroups at baseline (BL) and one-year follow-up (FU). The Seattle angina questionnaire consists of 17 questions. For every question points can be scored on an incremental scale. Every question contributes to one of the five SAQ-subscales. Scores are shown as means. A higher score indicates better angina health state.

	Cardiac CT			Functional-testing			Improvement		
	BL	FU	p-value	BL	FU	p-value	CT	FT	p-value
Physical limitations	37.3	39.7	<0.0001	37.0	38.8	0.09	2.30	1.80	0.630
Angina stability	3.1	4.1	<0.0001	3.0	3.9	<0.0001	0.93	0.95	0.948
Anginal frequency	9.2	10.9	<0.0001	9.6	10.6	<0.0001	1.68	1.05	0.012
Treatment satisfaction	17.2	17.8	0.070	17.0	17.2	0.731	0.63	0.23	0.598
Disease perception	3.3	4.1	<0.0001	3.3	4.0	0.001	0.86	0.62	0.209
Total SAQ	64.7	75.0	<0.0001	63.6	73.1	<0.0001	10.28	9.47	0.668

Table 3. Diagnostic yield defined as proportion of invasive angiograms followed by revascularization

	Cardiac CT (n=239)	Functional-testing (n=108)	p-value
Invasive angiography	29 (12.1%)	12 (11.1%)	0.843
No CAD>50%	8 (3.3%)	5 (4.6%)	0.384
Low-risk CAD>50%	12 (5.0%)	4 (3.7%)	0.635
High-risk CAD>50%	9 (3.8%)	3 (2.8%)	0.703
Revascularization	21 (8.8%)	7 (6.5%)	0.384
Percutaneous coronary intervention	15 (6.2%)	7 (6.5%)	0.703
Coronary bypass graft surgery	6 (2.5%)	0 (0%)	0.092
Diagnostic yield	21/29 (72%)	7/12 (58%)	0.469
Days to revascularization	31 (18-67)	46 (30-198)	0.243
Late revascularization(>90 days)	3 (1.2%)	3 (2.8%)	0.144

Table 4. Adverse events

	Cardiac CT (n=239)	Functional testing (n=108)	p-value
All-cause death	2 (1%)	2 (2%)	0.413
Non-fatal myocardial infarction	1 (0%)	1 (1%)	0.564
Unstable angina	1 (0%)	1 (1%)	0.564
Non-fatal stroke	0 (0%)	1 (1%)	0.137
Late revascularizations	2 (1%)	2 (2%)	0.413
Unplanned cardiac evaluations	2 (1%)	4 (4%)	0.058
Acute chest pain at emergency department	1 (0%)	3 (3%)	0.057
Palpitations at emergency department	1 (0%)	1 (1%)	0.564
Total adverse events	8 (3%)	11 (10%)	0.004

Diagnostic efficiency

For most patients the final clinical diagnosis was achieved on the same day in both groups, but more often in the cardiac CT group: median duration until final diagnosis 0(0;0) days by CT and 0(0;44) by functional-testing (p<0.0001). Overall, 25% of patients randomized to CT underwent another test after the baseline test, compared to 53% in the functional-testing group (p<0.0001)(figure 4). Invasive angiography was similarly frequent after CT (12%) and functional-testing (11%, p=0.775). Although index testing costs were higher, cumulative diagnostic expenses were 16% lower for CT €369 versus €440, p<0.0001) (appendix 3).

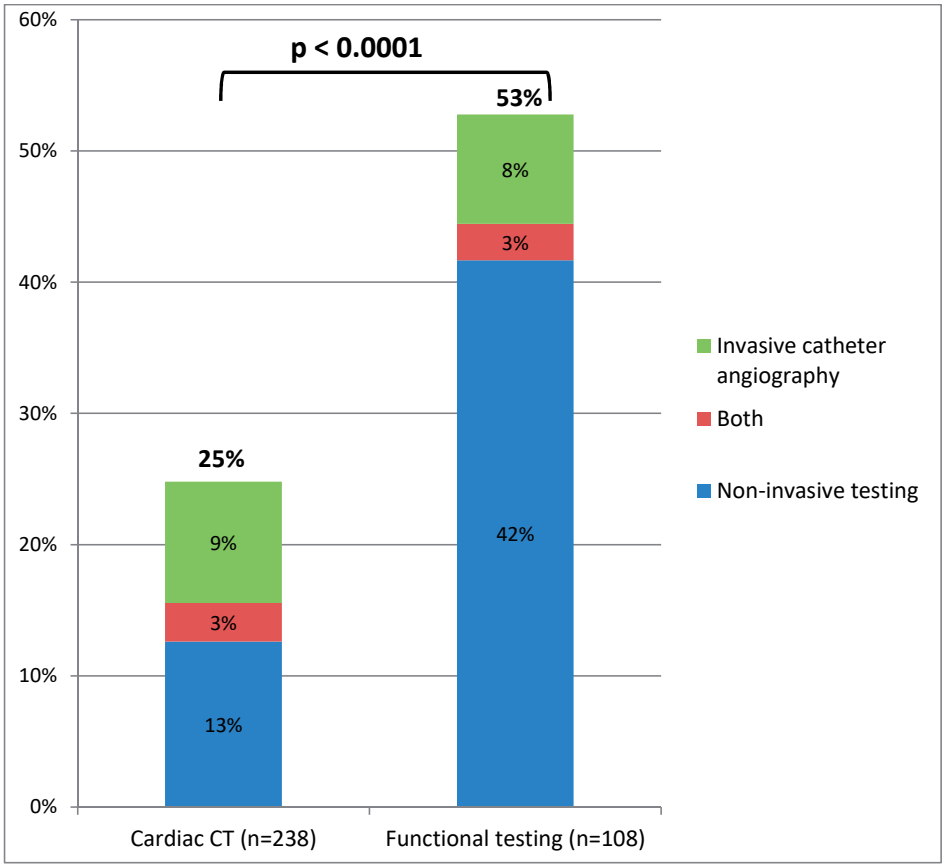
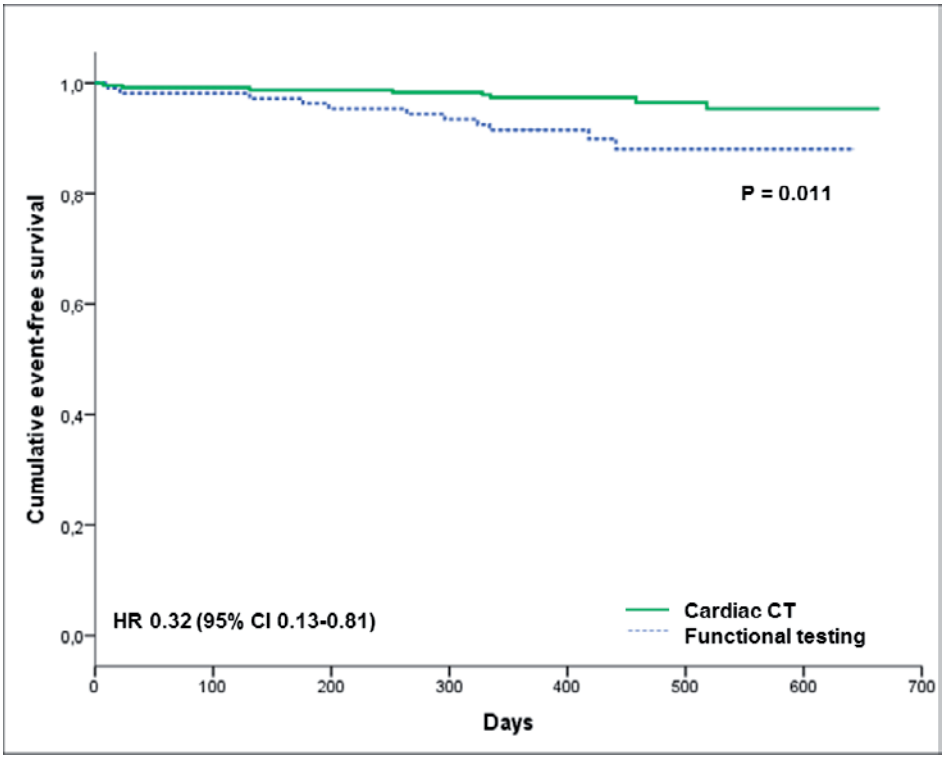


Figure 4. Downstream testing. Proportion of patients requiring further non-invasive and/or invasive testing.

Safety

Observed clinical events (19) included four deaths, two nonfatal infarctions, two cases of unstable angina requiring revascularization, one nonfatal major stroke, four late re-vascularizations and six other unplanned cardiac evaluations, reported in 347 patients



Number at risk

Days	0	100	200	300	400	500	600	664
Functional	108	104	101	98	58	42	33	0
Cardiac CT	239	236	234	228	137	89	69	0

Figure 5. Kaplan-Meier curves of event-free survival. Events counted once per patient in the hierarchical order of all-cause mortality, non-fatal myocardial infarction, major stroke, unstable angina with objective ischemia and/or requiring revascularization, unplanned cardiac evaluations and late revascularizations.

(table 4). The unplanned evaluations in the emergency department included two cases of palpitations and four cases of acute chest pain, four (3.7%) in the standard care group and two after CT (0.8%, p=0.058). At an average follow-up of 446 days (1.2 years), event-free survival was 96.7% for patients randomized to CT and 89.8% for patients randomized to standard care (p=0.011)(figure 5). The hazard ratio for adverse events was 0.32 (95%CI 0.13-0.81) for the CT group compared with the standard care group (p=0.015).

Cumulative radiation dose

All but one patients in the CT group (99.6%), but only 46 of 108 (43%) patients assigned to standard evaluation received radiation exposure from an imaging test. Hence, the cumulative radiation dose was higher in the CT group (6.6 ± 8.7mSv) compared to the

standard care group (6.1 ± 9.3mSv, p<0.0001). The mean radiation dose from only the calcium score scan was 1.3 ± 1.1mSv, for a complete cardiac CT examination 4.1 ± 4.4mSv, for myocardial perfusion scintigraphy 14.0 ± 2.3mSv and for invasive angiography 14.0 ± 14.3mSv.

Calcium scan based rule out of coronary disease

In 98 patients (39%) CAD was ruled out based on a zero calcium score. During follow-up none of these patients underwent further testing, and no adverse events occurred. Anginal symptoms were reported less frequently after a zero calcium scan, compared to when CAD was ruled out based on CT angiography or functional-testing (p=0.042). Only 2 patients (2%) without calcium had a >70% pre-test probability of CAD. CT angiography revealed single-vessel disease in one of these, eventually treated by stenting when symptoms persisted despite medical treatment.

DISCUSSION

This prospective, multicentre, randomized trial was designed to assess whether a tiered cardiac CT protocol based on calcium imaging and selective performance of CT angiography would be effective and safe for the management of suspected CAD, in comparison to functional-testing. To improve the overall applicability patients with test-specific contra-indications were not excluded from study participation, and data were evaluated by an intention-to-diagnose approach. After cardiac CT more patients reported complete relief of anginal symptoms after one year. Fewer adverse events occurred in the CT group. The cumulative radiation exposure was nearly 10% higher. Cardiac CT was more often able to confidently rule out CAD. Therefore the final diagnosis was reached faster, requiring fewer additional tests, and subsequently lower diagnostic expenses.

Diagnostic management of suspected coronary artery disease

Because prospective outcome data are sparse, diagnostic testing recommendations for stable CAD are predominantly based on technical performance studies, registry data and expert opinion, with discordant recommendations between guidelines.(3-5) In many centres the routine non-invasive diagnostic approach consists of stress testing, with the applied test modality depending on pre-test probability, patient characteristics, local availability and expertise. The exercise-ECG is the most widely available and least expensive functional test, but has a modest diagnostic performance. Although functional imaging more accurately detects angiographic CAD, its superiority over the exercise ECG has not been convincingly demonstrated in prospective clinical trials.(15)

Performance and safety

While the negative predictive value and ability to exclude CAD are high, coronary CT angiography has a tendency to overestimate both the angiographic and hemodynamic severity of CAD, which may necessitate further functional-testing for management decisions. Because the prevalence of obstructive CAD is low in real-world populations with stable chest pain symptoms, cardiac CT could be an efficient and cost-effective first-line test (6, 8, 15, 16). In our study cardiac CT allowed immediate exclusion of CAD in 75% of patients, compared to 47% in the functional-testing group. While CT angiography does not assess the hemodynamic severity, excluding high-risk angiographic CAD often allows for reassured medical treatment without further testing required at that moment. While there was a notable numerical difference in the proportion of catheterizations followed by revascularization in favour of patients randomized to CT (72 vs 58%), this result did not reach statistical significance, and it is not possible to conclude whether this higher diagnostic yield affected clinical outcome. The proportion of patients with complete relief of angina was higher after CT. While this can be explained by a higher diagnostic performance of CT followed by more appropriate management of cardiac as well as non-cardiac conditions, perceived symptoms and further need for diagnostic tests may also be affected by differences in experienced reassurance of patients and physicians by the test results.

Importantly, cardiac CT appears a safe strategy. The total adverse event rate was in fact lower in the CT group, although these results should be considered of an explorative nature given the population size and inclusion of softer endpoints. No statistically significant difference in the occurrence of death or myocardial infarction could be demonstrated between the two groups. The use of X-rays represents a drawback of CT, although by applying the calcium scan, contemporary CT equipment and dose reducing techniques, the cumulative exposure exceeded doses in the functional-testing group by no more than 10%.

Diagnostic efficiency

In this population with a relatively low CAD prevalence, the cardiac CT strategy achieved a conclusive diagnostic result much faster than functional-testing. In the functional-imaging group, further testing was required twice more frequent. Contrary to our expectations, cardiac CT did not increase the rate of referral to invasive angiography. Despite higher initial costs, after one year the CT approach was less expensive, decreasing overall diagnostic costs by 16% as calculated within our cost accounting system. Appendix 3 contains a formula for calculation of the overall downstream procedural costs based on frequency of performed tests, which allows recalculation using alternative procedural charges.

Calcium imaging to rule out CAD

Calcium imaging is still mostly used for risk stratification in asymptomatic individuals. While data from high-risk symptomatic populations suggest a non-negligible rate of obstructive CAD in the absence of detectable calcium, (17) registry data from more representative lower-risk cohorts have repeatedly demonstrated that severe CAD is rare and no more than 1% of patients with a negative calcium scan ultimately undergo PCI or bypass graft surgery.(18, 19) Given the excellent negative predictive value of the calcium scan, perhaps better than any other test, we decided its incorporation was justified in the CT algorithm, thereby avoiding contrast medium in 39% of patients, as well as an overall reduction in radiation exposure and costs in the CT group. Although groups are small, our results show no indication that implementation of the calcium scan in patients with a low-intermediate probability is unsafe.

CRESCENT in light of recently published trials

Recently two randomized controlled trials were published that examined whether CCTA would be more clinically effective than standard care. The pragmatic PROMISE trial randomized an impressive 10,003 patients between CT angiography and functional testing (67% nuclear imaging) for evaluation of suspected CAD, and reported no difference in adverse cardiac events after two years.(6) Although more patients underwent invasive angiography within the first 90 days, CT was associated with fewer invasive angiograms without obstructive CAD. Differences between our study and PROMISE include the use of calcium imaging in the CT strategy, and less frequent use of functional imaging in the control group (27% in CRESCENT vs approximately 90% in PROMISE).

In the SCOT-HEART trial, the addition of CCTA to standard care was investigated in 4146 patients with stable angina.(7) The investigators demonstrated improved certainty, but no effect on frequency of the diagnosis of angina due to coronary heart disease if CCTA was included in the diagnostic evaluation. After 1.7 years there was a close to statistically significant 38% reduction in the composite endpoint of death related to coronary heart disease and myocardial infarction (p=0.0527). The design of SCOT-HEART differs from our study, or PROMISE, for the fact that CT did not replace functional testing, but was added to a standard care protocol with XECG for most.

The low prevalence of CAD and the generally benign clinical outcome of patients with stable chest complaints in these studies, has raised questions concerning the need for advanced and expensive imaging tests. In this respect our randomized trial, albeit much smaller in population size, adds to the evidence from PROMISE and SCOT-HEART by demonstrating that a tiered approach including calcium imaging can mitigate the potential risks and costs of cardiac CT, while achieving at least comparable performance in comparison to a functional test approach without predominance of stress imaging.

Contrary to previous trials we did not exclude patients based on contraindications to specific test, thereby widening the applicability of our results.

In all these trials with a relatively low CAD prevalence, the individual probability of disease was overestimated by conventional prediction rules.(6, 7) Depending on the criteria the disease prevalence in CRESCENT was 8%, while the predicted probability by the Diamond and Forrester method was 45%. Similarly, in PROMISE the average probability was 53%, while the observed disease prevalence was 8.8%. In 2013, which was after the study had started, the new ESC guidelines recommended a different prediction rule(3, 20). Retrospective implementation of these Genders criteria lowered the pre-test probability of CAD from 45% to 37%, but still substantially overestimating the true observed disease burden.

In line with contemporary guidelines(3), in the CRESCENT trial patients with angiographically significant, but otherwise low-risk CAD on CT angiography were often treated medically before considering further testing or revascularization. This relatively conservative approach may have affected the downstream use of stress imaging, invasive angiography and revascularization procedures in comparison to previous trials.

Limitations

Although it was not possible to blind caregivers and patients to the test results, participants were treated by multiple physicians without direct involvement in the study. Although our trial demonstrated benefit of cardiac CT on several aspects, the modest population prevented us from drawing firm conclusions on some of the other endpoints. The follow up rate of clinical questionnaires (SAQ, EQ-5D, SF-36) was slightly higher for the CT group (86% vs 78%, p=0.06), which may have influenced results. We compared cardiac CT to a functional strategy starting with exercise ECG in the majority of patients. Performance of the functional approach might have been different if stress imaging techniques had been applied more frequently. In addition, outcome of the diagnostic strategy is indirectly measured, based on the assumed benefit of therapeutic choices based on those test results. Although the study was performed at several sites, appropriateness of extrapolation of our results to other centres will depend on comparability of the clinical setting in terms of current diagnostic care, available technology, cost-accounting systems and therapeutic management attitudes. Further research is necessary to establish the value of cardiac CT in terms of hard endpoints and in comparison to other diagnostic strategies.

CONCLUSION

In the workup of suspected, stable coronary artery disease, cardiac CT represents a safe and effective diagnostic strategy in comparison to functional testing, with potential benefits in terms of cost-efficiency.

APPENDICES

Appendix 1. EQ-5D results. VAS scale is the respondent's self-rated health on a vertical, visual analog scale where the endpoints are labelled best and worst imaginable health state. A higher score indicates a better health state. Mean (± SD). P value of the improvement in the reported quality of life scale at one year follow-up between the CT and functional-testing group.

	Baseline		One year follow-up		p-value
	Cardiac CT (n=219)	Functional testing (n=93)	Cardiac CT (n=208)	Functional testing (n=85)	
Mobility					0.325
No problems walking about	116 (53%)	53 (57%)	132 (63%)	47 (55%)	
Slight problems walking about	40 (18%)	18 (19%)	39 (19%)	25 (29%)	
Some problems walking about	43 (20%)	16 (17%)	21 (10%)	9 (11%)	
A lot of problems walking about	20 (9%)	6 (6%)	12 (6%)	4 (5%)	
Confined to bed	0 (0%)	0 (0%)	4 (2%)	0 (0%)	
Self-care					0.911
No problems with self-care	189 (86%)	79 (85%)	190 (91%)	74 (87%)	
Slight problems washing or dressing	20 (9%)	7 (8%)	7 (3%)	8 (9%)	
Some problems washing or dressing	7 (3%)	5 (5%)	8 (4%)	2 (2%)	
A lot of problems washing or dressing	2 (1%)	2 (2%)	3 (1%)	1 (1%)	
Unable to wash or dress	1 (0%)	0 (0%)	0 (0%)	0 (0%)	
Usual activities					0.670
No problems with usual activities	96 (44%)	43 (46%)	118 (57%)	40 (47%)	
Slight problems with usual activities	70 (32%)	21 (23%)	54 (26%)	26 (31%)	
Some problems with usual activities	42 (19%)	18 (19%)	24 (12%)	16 (19%)	
A lot of problems with usual activities	9 (4%)	11 (12%)	8 (4%)	2 (2%)	
Unable to perform usual activities	1 (0%)	0 (0%)	3 (1%)	1 (1%)	
Pain/discomfort					0.736
No pain or discomfort	43 (20%)	21 (23%)	74 (36%)	29 (34%)	
Slight pain or discomfort	97 (44%)	37 (40%)	87 (42%)	30 (35%)	
Moderate pain or discomfort	62 (28%)	27 (29%)	36 (17%)	20 (24%)	
A lot of pain or discomfort	14 (6%)	6 (6%)	8 (4%)	6 (7%)	
Extreme pain or discomfort	1 (0%)	2 (2%)	3 (1%)	0 (0%)	
Anxiety/depression					0.623
Not anxious or depressed	110 (50%)	41 (44%)	118 (57%)	45 (53%)	
Slightly anxious or depressed	76 (35%)	32 (34%)	63 (30%)	26 (31%)	
Moderately anxious or depressed	26 (12%)	15 (16%)	14 (7%)	10 (12%)	
Very anxious or depressed	6 (3%)	4 (4%)	9 (4%)	3 (4%)	
Extremely anxious or depressed	0 (0%)	1 (1%)	4 (2%)	1 (1%)	
Total EQoL					0.759
VAS scale	67.6 (±16.9)	66.8 (±19.5)	72.5 (±17.6)	69.4 (±19.1)	0.237

Appendix 2. Short Form 36 results. SF-36 quality-of-life questionnaire subdivided into eight subscales. A higher score indicates a better health state. Mean (±SD). P-values for change in SF-36 subscale scores from baseline to follow-up between the CT and functional-testing group.

	Baseline		One year follow-up		
	Cardiac CT (n=219)	Functional testing (n=93)	Cardiac CT (n=208)	Functional testing (n=85)	p-value
Physical functioning	668 (±256)	640 (± 258)	717(±278)	775 (±223)	0.699
Role limitations due to physical health	194 (±168)	210 (± 177)	278(±163)	256 (±160)	0.136
Role limitations due to emotional problems	195 (±125)	196 (±121)	216(±119)	209 (±117)	0.941
Energy/fatigue	201 (±81)	190 (±91)	220 (±90)	219 (±80)	0.991
Emotional well being	337 (±92)	334 (±94)	347(±100)	359 (±82)	0.941
Social functioning	140 (±49)	140 (±53)	154 (±51)	162 (±43)	0.962
Pain	122 (±42)	123 (±45)	147 (±52)	152 (±47)	0.391
General health	218 (±86)	208 (±90)	223 (±95)	218 (±96)	0.209

Appendix 3. Downstream diagnostic costs

Total costs	Cardiac CT	Functional testing	p value
Mean (SD)	369 (± 501)	440 (± 474)	p<0.0001
Median (25th, 75 percentile)	270 (64, 270)	159 (106, 651)	
Cost estimates (euros)[1]			
Exercise tolerance test	106		
Coronary calcium score	64		
CT coronary angiography	206		
Stress echocardiography	105		
Single photon emission CT	545		
Catheter-based coronary angiography	1,394		

Appendix 3. Shows the cost estimates for diagnostic testing, based on Genders et al. (11) and the downstream procedural costs for standard care compared with CT. Results are shown in euros.
Formula for the calculation of the total diagnostic costs of a workup of patients with suspected CAD with functional-testing and the comprehensive cardiac CT workup:

- **Costs in functional-testing group** = (0.94 * € exercise ECG) + (0.29 * € SPECT) + (0.06 * € CCTA) + (0.07 * € Stress echo) + (0.11 * € Cath)
- **Costs in CT group** = (1 * € CAC-score) + (0.46 * € CCTA) + (0.07 * € SPECT) + (0.05 * € exercise ECG) + (0.01 * € Stress echo) + (0.12 * € Cath)

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CHAPTER 4

Sex differences in the performance of cardiac CT compared with functional testing in evaluating stable chest pain: sub-analysis of the multicenter, randomized CRESCENT trial

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ABSTRACT

Background - Cardiac CT represents an alternative diagnostic strategy for women with suspected CAD, with potential benefits in terms of effectiveness and cost-efficiency.

Methods and Results - the CRESCENT trial prospectively randomized 350 patients with stable angina (55% women; 55±10 years), mostly with an intermediate CAD probability, between cardiac CT and functional testing. The tiered cardiac CT protocol included a calcium-scan followed by CT-angiography if the Agatston calcium score was between 1-400. Patients with test specific contraindications were not excluded from study participation. Gender differences were studied as a pre-specified sub-analysis. Enrolled women presented more frequently with atypical chest pain and had a lower pre-test probability of CAD compared to men. Independently of this differences, cardiac CT led in both sexes to a fast final diagnosis as compared functional testing, while the effect was larger in women (p-interaction=0.01). The reduced need for further testing after CT, compared to functional testing, was most evident in women (p-interaction=0.009). However, no gender interaction was observed with respect to changes in angina and quality of life, cumulative diagnostic costs, and applied radiation dose (all p-interactions≥0.097).

Conclusions – Cardiac CT is more efficient in women than men in terms of time to reach the final diagnosis and downstream testing. However, overall clinical outcome showed no significant difference between women and men after one year.

INTRODUCTION

In industrialized countries, coronary artery disease (CAD) is the leading cause of death among women and associated with a worse outcome compared to men [1, 2]. Due to a frequently different presentation of complaints ischemic heart disease is thought to be under-recognized in women [3, 4]. The prevalence of vasospasm and microvascular angina is higher in women, which may partly explain the differences in symptoms between women and men [4]. Conventional first-line non-invasive diagnostic tests are thought to be less accurate in women, further contributing to under-diagnosis, and potentially under-treatment [5, 6]. On the other hand, women have higher rates of indeterminate exercise ECG results, but also more false positive results due to nonspecific ST-T changes. The lower sensitivity of nuclear imaging is thought to result from the smaller size of the female heart, while false-positive diagnoses may be introduced by breast attenuation artifacts [7, 8]. Paradoxically, there appears to be an relative overuse of invasive angiography (ICA) in women, perhaps fueled by the limited confidence in noninvasive tests, resulting in a rather low diagnostic yield for obstructive CAD [9, 10].

Cardiac CT is a non-invasive imaging modality with an excellent diagnostic accuracy for the detection of CAD in both men and women [11]. Recently, three multicenter randomized trials showed that cardiac CT is at least as effective and safe as standard diagnostic testing for patients with suspected CAD [12-14].Given the uncertain diagnostic accuracy of functional tests in women, direct visualization of CAD by cardiac CT may be particularly effective in women.

In this pre-specified sub-analysis of the recently published CRESCENT trial (Calcium imaging and selective CT angiography in comparison to functional testing for suspected coronary artery disease), we investigated whether sex affects the effectiveness and safety of cardiac CT compared to standard functional testing in patients with symptoms suggestive of CAD.

METHODS

Study design and participants

CRESCENT is a multicenter randomized controlled clinical effectiveness trial. From the cardiology outpatient clinics at four hospitals in the Rotterdam region of the Netherlands, 350 patients with stable chest pain and suspected CAD were enrolled in the study. The study design, inclusion and exclusion criteria, and primary results have been reported previously [12]. Briefly, all adult patients with stable chest pain or angina equivalent symptoms potentially caused by obstructive CAD were considered for study participation. Exclusion criteria were a history of known CAD, invasive coronary angi-

ography or stress test performed less than one year ago, or inability or unwillingness to provide informed consent. Renal impairment, contrast allergy, atrial fibrillation, or other test specific contra-indications did not preclude study participation. The study was approved by the medical ethics committees at each participating site and all participants provided informed consent. The CRESCENT trial is registered at the US National Institutes of Health (ClinicalTrials.gov), number NCT01393028.

Randomization and study procedures

Patients were randomized in a 1:2 ratio between standard functional testing as dictated by local caregivers and the investigational CT algorithm. For the CT algorithm, all patients first underwent a calcium scan. Absence of calcium excluded CAD and obviated the need for further testing, except for patients with a high pre-test probability of CAD (>70% by Diamond and Forrester criteria [15]). Patients with a calcium score between 1 and 400, as well as patients without calcium but a >70% pre-test probability, underwent contrast-enhanced coronary CT angiography to detect obstructive CAD. Those with CT contra-indications, a calcium score >400, or non-conclusive CT angiogram (non-interpretable or intermediate obstructive disease), underwent stress testing or invasive angiography at the discretion of the treating physician. All participating sites had prior experience in performing cardiac CT before initiation of the trial. Image acquisition was performed on a 64-slice or more advanced CT system with radiation minimizing measures depending on local practices and patients characteristics. For the standard arm the functional test was chosen and interpreted by the local physician, based on clinical guidelines [16, 17]. Observed disease by CTA and XECG test results were recorded and compared between both sexes. A heart rate below 85% of the predicted heart rate, and a maximum workload below 100% of the predicted exercise capacity were classified as insufficient. A positive XECG was defined as >1-mm ST deviation. A negative XECG was defined as without >1-mm ST deviation, provided that the target heart rate and workload were achieved. CT scans were classified as negative calcium scan, <50% stenosis on CTA, not high-risk >50% CAD, and high-risk >50% CAD (left main stenosis, three-vessel disease or >50% proximal LAD stenosis).

All patients were contacted after 12 months for ascertainment of trial endpoints and health status measurements. The occurrence and results of downstream procedures (exercise ECG, cardiac CT, stress echocardiography, perfusion imaging, catheter angiography and revascularization) were collected during follow-up. All diagnostic procedures were confirmed through review of the patients' medical records. This pre-specified secondary analysis focused on differences between women and men with regard to the effectiveness and safety of a cardiac CT strategy versus standard functional testing in patients with suspected CAD.

Endpoints

The primary outcome was the clinical effectiveness, defined as the absence of chest pain complaints after one year. Additionally, Seattle Angina Questionnaire (SAQ), EuroQol-5D-5L (EQ-5D) and Short-Form-36 (SF-36) for quality-of-life responses were compared between baseline and one-year follow-up. Pre-specified secondary outcomes included the diagnostic yield, defined as the proportion of patients undergoing revascularization (PCI or CABG) after invasive angiography. Efficiency outcomes included the time to diagnosis, defined as the period from presentation until the first test that led to the final diagnosis, or the final test that ruled out obstructive CAD. Downstream testing included all non-invasive testing and invasive angiography to detect CAD after the initial test. The diagnostic costs included all tests performed during one year follow up. Average costs per test were based on a previously published cost analysis [18]. The safety outcomes included the event-free survival using the composite endpoint of all-cause mortality, non-fatal myocardial infarction or major stroke, unstable angina pectoris with objective ischemia and/or requiring revascularization, unplanned cardiac evaluations and late coronary revascularization procedures, defined as more than 90 days after the first presentation in the outpatient clinic. The cumulative radiation dose was defined as radiation exposure from all tests and interventions from the first outpatient clinic visit until 1 year of follow up, including CT, perfusion imaging and catheter angiography, calculated in millisieverts (mSv) using standard methods [19, 20], applying a conversion factor kappa (κ) of 0.017 for cardiac CT scans.

Statistical analysis

Continuous data are presented as means±SD or medians with interquartile ranges. Groups were compared using an independent-sample t-test or Mann-Whitney U-test for continuous variables, and chi-square or Fisher's exact-test for categorical variables. We used logistic regression to test the interaction between sex and randomization strategy for binary outcomes and linear regression for continuous outcome, as appropriate. Logistic regression variables with more than two outcomes, were transformed into dichotomous variables. For adjusted analysis of sex interaction and randomization strategy on the angina improvement we used multivariable models and controlled for age, cardiac risk factors (hypertension, dyslipidemia, smoking, diabetes and family history of premature CAD), as well as for other covariates that were found to be different between men and women (diastolic blood pressure, type of angina and pre-test probability). While the cumulative diagnostic costs are not normally distributed, costs are presented as means, as it better reflects the overall financial burden of each approach. The probability of event-free survival was calculated by the Kaplan-Meier method for each of the end points, and impact of randomization strategy in man and women was analyzed with the log-rank test. A Cox-proportional hazards model with treatment assignment, sex, as

well as their interaction were used to test the hypothesis that sex interacts with clinical adverse events. A two-sided p-value <0.05 was considered statistically significant. Statistical analysis were made using SPSS (version 21, IBM Corp, Armonk NY, United States of America), according to the intention-to-treat principle.

RESULTS

Study population

There were 192 (55%) women and 158 (45%) men. Women more often presented with atypical chest pain compared to men (58% vs. 46%, p=0.029), and had a lower pre-test probability of CAD, as determined using the Diamond and Forrester criteria (p<0.001). While cardiovascular risk factors were similar between sexes, except for a lower diastolic blood pressure, the Systematic Coronary Risk Evaluation [21] was lower in women (p<0.001) (table 1). Neither for women nor men were there differences in baseline characteristics between the two diagnostic strategies (all p>0.05).

Test results

Women had a median calcium score of 1.0(0-43.5), compared to 17.0(0-143.5) in men (p=0.159). CAD was excluded based on the absence of calcium in 48% of women and 35% of men (p=0.036). In women CT angiography demonstrated obstructive CAD in 7% and 13% of men (p=0.279) The technical test results are summarized in figure 1. There were no significant differences between women and men for the exercise test result, which showed comparable rates of insufficient heart rate or exercise capacity (figure 1). Overall, 41 patients (12%) underwent invasive angiography. In women that underwent CT the revascularization rate was 62% (8/13), compared to 50% (4/8) in the functional test group (p=0.604). For men 81% (13/16) were revascularized after CT, compared to 75% (3/4) after revascularization (p=0.780).

Clinical effectiveness

After one year 40% of women randomized to CT reported no anginal symptoms in comparison to 22% of women in the functional testing group (p=0.026). For men 36% reported no symptoms after CT compared to 30% after functional testing (p=0.466). However, significant interactions by sex on the outcome of resolved angina could not be demonstrated (p-interaction=0.286) (Figure 2). For the Seattle angina questionnaire (SAQ) and the quality of life questionnaires (EQ-5D and SF-36), however, there were no significant differences in improvement between CT and functional testing, neither for women and men (table 2).

Table 1. Baseline characteristics of patients by sex

	Women			Men		
	All women	Cardiac CT	Functional testing	All men	Cardiac CT	Functional testing
n	192 (55)	133 (55)	59 (55)	158 (45)	109 (45)	49 (45)
Demographics						
Age, years†	56 ± 10	56 ± 10	55 ± 10	54 ± 10	53 ± 10	55 ± 10
Systolic blood pressure (mmHg)†	139 ± 22	139 ± 23	136 ± 20	138 ± 20	137 ± 20	139 ± 21
Diastolic blood pressure (mmHg)†	82 ± 12*	82 ± 11	81 ± 13	87 ± 11*	86 ± 11	88 ± 10
Mean body mass index (kg/m^2)†	28 ± 6	28 ± 6	28 ± 6	28 ± 5	28 ± 5	28 ± 5
Cardiovascular risk factors						
Former or current smoker	65 (34)	43 (32)	22 (37)	55 (35)	39 (36)	16 (33)
Hypertension	95 (49)	68 (51)	27 (46)	85 (54)	56 (51)	29 (59)
Dyslipidemia	104 (54)	70 (53)	34 (58)	91 (58)	59 (54)	32 (65)
Diabetes mellitus	32 (17)	22 (17)	10 (17)	26 (16)	19 (17)	7 (14)
Family history of ischemic heart disease	79 (41)	54 (41)	25 (42)	53 (34)	38 (35)	15 (31)
History of stroke	6 (4)	6 (5)	4 (7)	10 (5)	2 (2)	4 (8)
History of peripheral artery disease	7 (4)	4 (3)	3 (5)	9 (6)	5 (5)	4 (8)
Presenting chest pain symptoms						
Typical angina	40 (21)	29 (22)	11 (19)	41 (26)	28 (26)	13 (27)
Atypical angina	110 (58)*	77 (58)	33 (56)	72 (46)*	49 (45)	23 (47)
non-anginal complaints	40 (21)	26 (20)	14 (24)	42 (27)	30 (28)	12 (25)
None	1 (1)	1 (1)	0	2 (1)	1 (1)	1 (2)
Pre-test probability†	38 ± 28*	39	36	54 ± 28*	53	55
10 years Cardiovascular risk ‡ (SCORE)	7 ± 9*	3 [1-10]	4 [1-10]	12 ± 13*	6 [3-17]	8 [4-18]

Unless otherwise specified, data are numbers of patients, with percentages in parentheses. †Data are means ± standard deviations. ‡ Data are medians, with interquartile ranges in parentheses. *Significant difference between men and women. Diabetes mellitus is defined as plasma glucose >11.0mmol/L or treated with either diet regulation or medication. Dyslipidemia defined as a total cholesterol level >5mmol/L, low-density lipoprotein level >3mmol/L, or on lipid-lowering medication. Hypertension defines as >150mmHg systolic or >90mmHg diastolic or treated. Pretest probability based on Diamond and Forrester criteria [15]. Estimated 10-year risk of cardiovascular death was done using SCORE[21] . SCORE = Systematic Coronary Risk Evaluation.

Diagnostic efficiency

In women additional diagnostic testing over the subsequent year was less often needed after cardiac CT compared to standard care (16% vs. 57%, p<0.001). The reduced need for further testing after CT was significantly better in women compared to men (p-interaction=0.009), in whom the secondary diagnostic testing rate just failed to reach statistical significance (27% vs. 41%, p=0.057)(figure 3). Women had lower downstream diagnostic costs after CT compared to functional testing (one-year mean cumulative costs for women in CT group: €326 ± 470 vs. functional testing: €478 ± 493, p<0.001; men: €421 ± 534 for CT vs. €394 ± 451, p=0.329). However, a sex-specific difference could

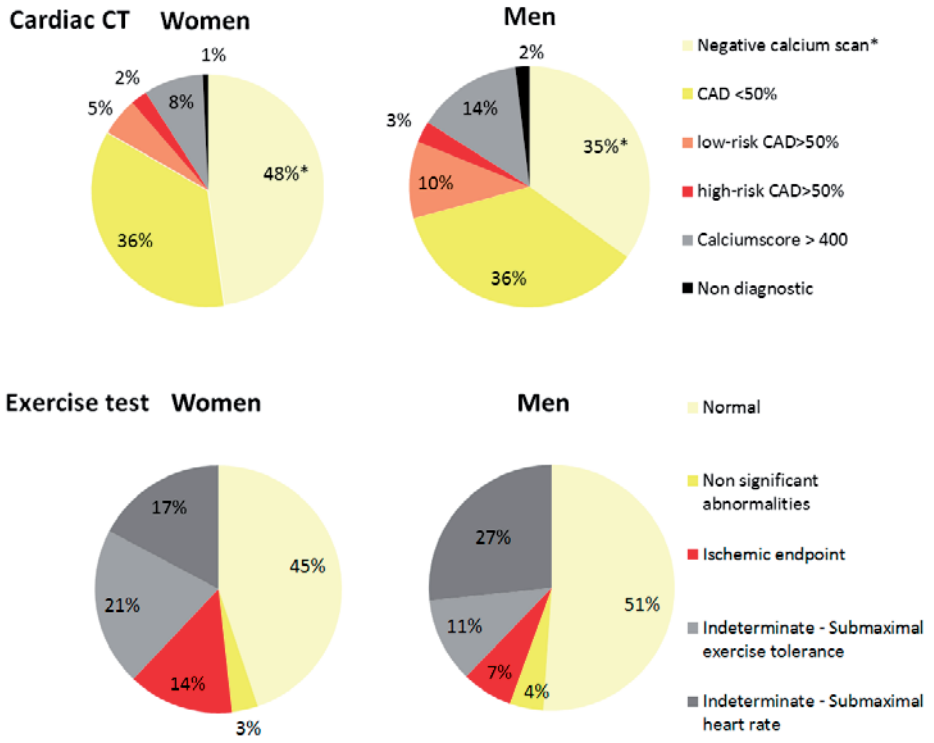

Figure 1. Cardiac CT and exercise test results stratified by sex
CT results based on calcium scan or CTA, classified as absent calcium, calcium score >400, <50% CAD on CTA, and CTA>50% subdivided in high-risk or not (left main stenosis, three-vessel disease or proximal LAD stenosis). A negative calcium scan was more frequent in women (*p=0.036). XECG test results were classified as ischemic (>1 mm ST-deviation in ≥2 leads), non-significant (0.5-1 mm), normal, insufficient heart rate response, or insufficient exercise capacity. No significant XECG result differences were observed between women and men. These technical classifications did not necessarily correspond with clinical interpretations.

not be statistically confirmed (p-interaction=0.120). For women the final diagnosis could be made on the same day in 86% after CT, compared to 44% of women after functional testing (median time to final diagnosis 0(0;0) vs. 10(0;57) days, p<0.001). While the diagnosis was also reached faster in men after cardiac CT (0(0;0) vs. 0(0;29), p=0.011), the improvement was more in women (p-interaction=0.012).

Safety

During an average of 1.2 years of follow-up (median follow up time: 1.2 IQR [1.0;1.7] years) a total of 19 clinical events were recorded, 8 (4%) in women and 11 (7%) in men (p=0.344) (table 3). The event-free survival was 97.7% for women randomized to CT and 91.5% for functional testing (log rank p=0.061). For men randomized to CT the event-

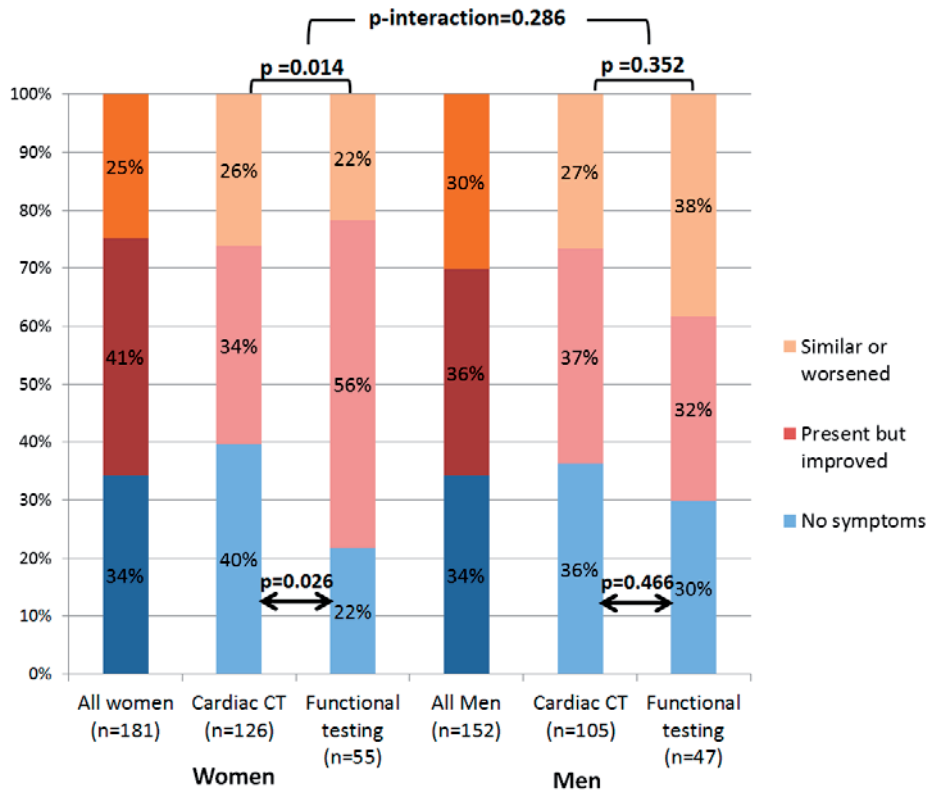

Figure 2. Anginal symptoms

Anginal status at one year, stratified by randomized diagnostic strategy and sex. P-values between the blue stack bars signify differences between the cardiac CT and functional group with regard to the absence of angina symptoms after one year, left part of the graph for women and right for men. P-values above the stacked bars signify differences in the total distribution of anginal complaints between CT and functional testing. Above is the p-interaction signifying the interaction between sex and randomization strategy on anginal symptoms, which was not significant (0.286).

free survival was 95.4% and for functional testing 87.8% (log rank p=0.083) (figure 4). Sex was not a significant predictor of clinical adverse events (p-interaction=0.759).

Radiation exposure

The median radiation dose for the complete cardiac CT examination was 1.7 mSv [0.8;4.7] in women, and 2.6 mSv [1.0;6.8] in men (p=0.179), while the mean doses were 3.7±4.2 mSv in women and 4.6±4.8 mSv in men. Because of the skewed cumulative dose distribution for women in the functional testing group, of whom a minority received relatively high radiation exposure from nuclear imaging and angiography, the median effective dose was 0 mSv [0;12.5], compared to 4.7 mSv [0.9;7.9] in the CT group (p=0.005). Similarly,

Table 2. Questionnaire derived changes in angina and quality of life

	Women			Men			
	Cardiac CT	**Functional testing**	**p-value**	**Cardiac CT**	**Functional testing**	**p-value**	**p-interaction**
Responders (n)	81 (108)	66 (39)		85 (93)	69 (34)		
SAQ	10.3 ± 15.5*	9.9 ± 14.6*	0.874	10.3 ± 12.8*	9.0 ± 12.8*	0.628	0.896
EQ-5D total	0.005 ± 0.331	-0.020 ± 0.384	0.670	-0.017 ± 0.305	-0.016 ± 0.371	0.982	0.743
EQ-5D VAS score	3.4 ± 15.8*	3.9 ± 15.2	0.868	5.9 ± 15.2*	-0.24 ± 16.4	0.063	0.118
SF-36	272 ± 619*	207 ± 672	0.668	369 ± 618*	305 ± 662*	0.685	0.997

Change in questionnaire score after one year. Responders are percentages, with numbers in parentheses. *Significant improvement in score from first outpatient clinic visit to one year follow up. A higher score indicates a better health status. Mean (±SD). P value signifies differences in improvement between CT and functional testing. P-interaction for sex-dependent differences. SAQ; Seattle Angina Questionnaire. EQ-5D total; EuroQol-5D-5L total quality of life score. EQ-5D VAS score; EuroQol-5D-5L quality of life respondent's self-rated health on a vertical, visual analog scale from 0-100 scale; SF-36; Short-Form-36 quality of life questionnaire.

Table 3. Adverse events

	Women			Men		
	All	**Cardiac CT**	**Functional testing**	**All**	**Cardiac CT**	**Functional testing**
All-cause death	0 (0)	0 (0)	0 (0)	2.5 (4)	1.8 (2)	4.1 (2)
Non-fatal myocardial infarction	0.5 (1)	0 (0)	1.7 (1)	0.6 (1)	0.9 (1)	0 (0)
Unstable angina	0.5 (1)	0 (0)	1.7 (1)	0.6 (1)	0.9 (1)	0 (0)
Non-fatal stroke	0.5 (1)	0 (0)	1.7 (1)	0 (0)	0 (0)	0 (0)
Late revascularizations	1 (2)	0.8 (1)	1.7 (1)	1.3 (2)	0.9 (1)	2.0 (1)
Unplanned cardiac evaluations	1.6 (3)	1.5 (2)	1.7 (1)	1.9 (3)	0 (0)	6.1 (3)
All events	**4.2 (8)**	**2.3 (3)**	**8.5 (5)**	**7.0 (11)**	**4.6 (5)**	**12.2 (6)**

Data are percentages, with numbers in parentheses. No significant differences as stratified for sex

Table 4. Cumulative radiation dose

	Cardiac CT	**Functional testing**	**p-value**
Women	Median: 4.7[0.9;7.9] Mean: 5.3 ± 5.5	Median: 0[0;12.5] Mean: 6.3 ± 10.3	0.005
Men	Median: 4.7 [1.1;11.5] Mean: 8.2 ± 11.2	Median: 0[0;14.0] Mean: 5.8 ± 8.1	<0.001
p-value	0.014	0.791	0.097*

Cumulative radiation dose in mSv. *p-interaction value

in men the median cumulative dose was 4.7 mSv [1.1;11.5] in the CT group, compared to 0 mSv [0;14.0] in the functional testing group (p<0.001; p-interaction=0.097)(table 4). If calcium scans had not been included in the decision making, and all patients had

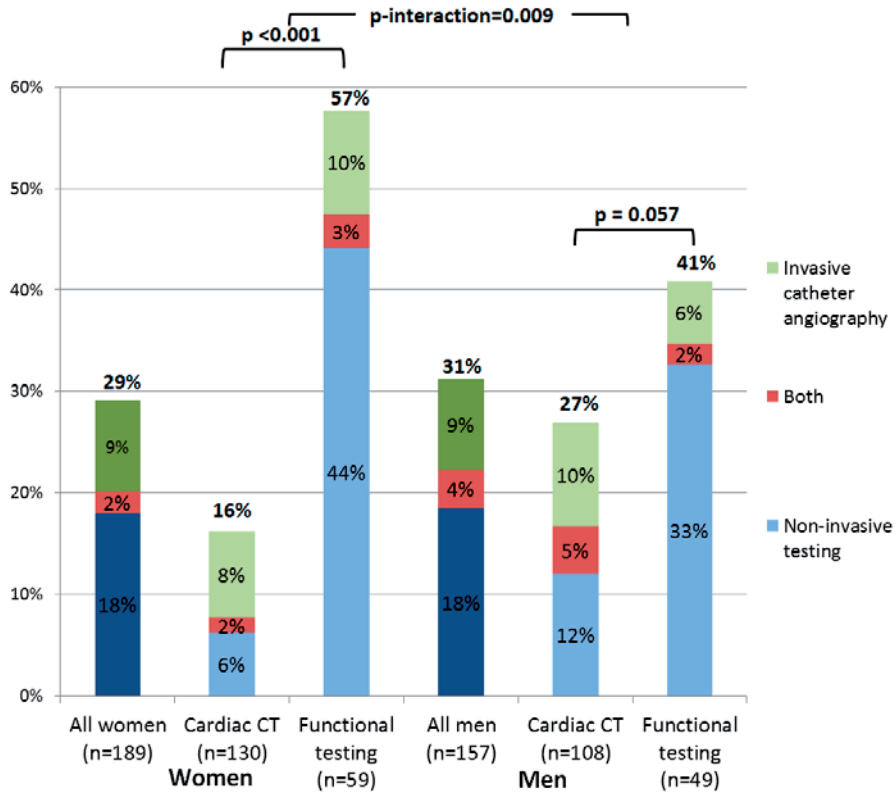

Figure 3. Downstream diagnostic testing stratified by sex
Proportion of patients requiring further non-invasive and/or invasive testing. P-values signify differences in total number of downstream diagnostic testing in the CT arm versus the functional testing arm. P-interaction (0.009) indicates no significant interaction by sex and randomization strategy.

undergone CTA instead, the estimated median radiation exposure from the CT exam might have increased to 4.7 mSv [3.7;10.7] (mean 7.5±8.6 mSv). In women below 60 years (59%), in whom CAD was ruled out based on a negative calcium scan in 71%, the median cumulative radiation dose was 1.1 mSv [0.8;1.5] (mean 1.4±1.3mSv).

DISCUSSION

In this pre-specified sub-analysis of the CRESCENT trial we compared the performance of cardiac CT and functional testing between women and men. Apart from previously described differences in disease prevalence the main findings of our study are that cardiac CT performs well in women with stable chest pain complaints. In women cardiac CT

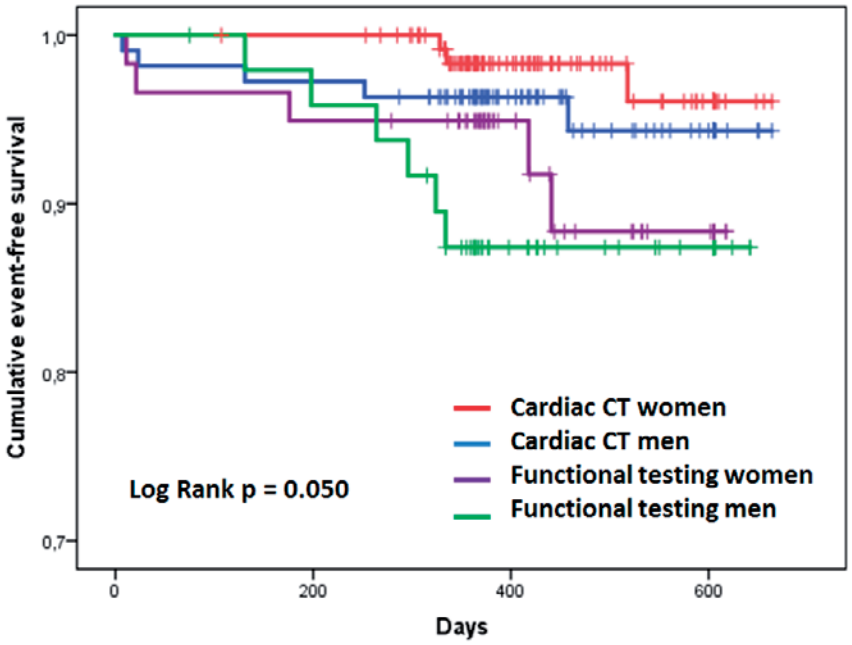

Figure 4. Event-free survival
Kaplan-Meier curves of event-free survival stratified by randomized diagnostic strategy and by sex. There was a difference in event rate between randomization strategy (p=0.011), but not between sexes.

resulted in more resolution of chest pain, a lower need for further testing and diagnostic expenses, however with a higher median radiation exposure. In terms of the need for further testing and time to reach the final diagnosis, women had significantly more benefit from cardiac CT compared to men.

Symptoms and disease prevalence

In concordance with prior observations, women in the CRESCENT trial more often had atypical symptoms (57% vs. 46%, p=0.032) and lower rates of focal, epicardial CAD than men[4]. All trials, including this cohort, had a low CAD prevalence with overestimation of the individual probability of disease by conventional prediction rules for both men and women [13, 14, 22]. In CRESCENT the CAD prevalence was 9% in women, while the predicted probability by the Diamond and Forrester method was 38%. For men the prevalence was 12%, while the predicted probability was 54%. In PROMISE the pre-test probability of CAD was 53% by Diamond & Forrester criteria, while the observed disease prevalence was approximately 9%.

Sex differences in the performance of diagnostic testing

In many centers the routine diagnostic work-up of patients with suspected CAD includes stress testing. The recommended test modality depends on the patient's pre-test probability of CAD, clinical characteristics, technical availability and local expertise. In women, exercise testing is thought to be less helpful due to a lower diagnostic accuracy and high rate of indeterminate test results [7]. In the previously published subanalysis of the PROMISE trial women were less likely to have a positive CTA than a positive exercise ECG or nuclear stress test result, even after adjusting for clinical factors, which may be the result of false-positive stress test results [23]. Interestingly, in the CRESCENT trial no differences were observed between sexes with regard to the exercise tolerance or achieved heart rate during exercise testing, possibly caused by the small population size. Both in women and men cardiac CT reached a final diagnosis faster, requiring fewer additional tests. In 47% of women randomized to functional testing additional testing was ordered by the treating physician, compared to only 8% after cardiac CT. Contrary to PROMISE and SCOT-HEART, in this study cardiac CT was not associated with an increase in the number of cardiac catheterizations in women [13, 14]. The reduced catheterization referral rate after CT may theoretically be explained by the use of the calcium scan, or a higher accuracy by newer CT equipment, but may as well be the result of differences in management following the CT scan, compared to previous studies. Conservative management of low-risk CAD and functional confirmation before revascularization may have avoided premature catheterization referral in CRESCENT, although it is unknown if these treatment practices were different in other pragmatic trials. Alternatively, equivalent catheterization rates may also be explained by a higher referral rate in the control group resulting from different stress test decisions. While in PROMISE more revascularizations and catheterizations were performed after CTA, costs were comparable after 90 days and 3 years[24]. In CRESCENT, women had lower downstream diagnostic costs after CT compared to functional testing.

In women, as well as the cohort as a whole[12], cardiac CT more often resulted in resolved anginal symptoms after one year in comparison to functional testing. This can be explained by a higher diagnostic performance of CT, followed by more appropriate management of cardiac as well as non-cardiac conditions. Perceived symptoms and further need for diagnostic tests may also be affected by differences in reassurance of patients and physicians by the test results. However, for the SAQ and quality of life questionnaires there were no significant differences between CT and functional testing for either sex. Similar equivalidity was found in the PROMISE trial[25], while the PLATFORM trial observed more improvement in QoL scores after CT (including FFR_{CT}), in comparison to a strategy with usual noninvasive testing[26].

Safety

Cardiac CT is in both women and men associated with a higher median cumulative radiation dose, compared to functional testing, however significant interaction by sex could not be demonstrated (p-interaction=0.097). In the functional testing group the cumulative radiation exposure increased because of more nuclear imaging tests (mean 14±2mSv) and invasive angiography (mean 14±14mSv) after the initial functional test. We incorporated the calcium scan into the CT algorithm because of its excellent negative predictive value. By not performing CTA in patients with a negative calcium scan, contrast medium and additional radiation could be avoided in 48% of women. Young women are relatively more vulnerable to radiation exposure, but we observed that with the incorporation of the calcium scan the cumulative radiation dose in this group was very low. While it is possible that severe but non-calcified lesions may be missed if CT angiography is not performed, the clinical course of patients who did not undergo CTA was uneventful over the first 6 months.

Similar to other CT studies in populations with stable CAD the overall event rate was low. While for the entire population cardiac CT was associated with lower event rates [12-14], no significant differences were found between sexes.

Diagnostic management of suspected CAD in women and men

While exercise-ECG has a modest diagnostic performance, especially in women, both American and European guidelines recommend it as the first choice test in patients with a low to intermediate pre-test probability, interpretable resting ECG and ability to exercise[27, 28]. PROMISE and SCOT-HEART, as well as CRESCENT, have demonstrated that cardiac CT is equally or more effective and safe as standard diagnostic testing for patients with suspected CAD [12-14]. This sub analysis underlines the notion that cardiac CT is more efficient in women in terms of less downstream testing and a speedier diagnosis, compared to functional testing.

Limitations

This subgroup analysis was hampered by the small sizes of subgroups, which was particularly relevant for the comparison of the diagnostic yield of ICA as well as some other secondary endpoints. Observed differences in diagnostic performance may reflect in part differences in disease prevalence between men and women. While we performed adjusted analysis to correct for potential confounders, other relevant confounders may have remained unidentified. Although it was not possible to blind caregivers and patients to the test results, participants were treated by multiple physicians without direct involvement in the study. We compared cardiac CT to a functional strategy starting with exercise ECG in the majority of patients. Performance of the functional approach might have been different if stress imaging techniques had been applied more frequently.

Although the study was performed at several sites, appropriateness of extrapolation of our results to other centers will depend on comparability of the clinical setting in terms of current diagnostic care, available technology, cost-accounting systems and therapeutic management practices.

CONCLUSION

Cardiac CT is more efficient in women than men in terms of time to reach the final diagnosis and downstream testing. However, overall clinical outcome showed no significant difference between women and men after one year.

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AD, TG, JA, TB, BK, PM, MO, AL, AN, PF: none declared

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CHAPTER 5

Iodixanol versus Iopromide at coronary CT angiography: lumen opacification and effect on heart rhythm - the randomized IsoCOR trial

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ABSTRACT

Purpose: Demonstrate that using contemporary cardiac CT protocols equal coronary lumen opacification can be achieved with iso-osmolar and low-osmolar contrast media, when injected at the same iodine delivery rate. In addition, we investigate the cardiovascular effect of iso-osmolar contrast media, and achieved image quality.

Materials and Methods: Institutional review board approval was obtained. Written informed consent was obtained from all subjects. Between November 2015 and August 2016 306 patients (167 (55%) women) at least 18 years old and weight between 50-125kg, were prospectively randomized between iso-osmolar iodixanol-270 (Visipaque) and low-osmolar iopromide-300 (Ultravist). All coronary segments were assessed for intraluminal opacification and image quality and compared using a student T-test. Heart rate, arrhythmia, patients discomfort and adverse events were also monitored.

Results: Measured coronary attenuation values were comparable between both contrast media (469 ± 167 HU vs 447 ± 166 HU, p=0.241, 95% CI: -15.1 -60.0), including subanalyses. Adjusted for the lower iodine concentration, the mean iodixanol-270 bolus was higher compared to iopromide-300 (76.8 ± 11.6 ml vs. 69.7 ± 10.8 ml, p<0.001). The higher injection rate was associated with a higher pressure (111 ± 44 PSI vs 90 ± 36 PSI, p<0.001). Although in the iodixanol-270 group patients experiences less heat discomfort (72% vs. 86% p<0.001), no differences in heart rate or rhythm were observed.

Conclusion: If injected at comparable iodine delivery rates, the iso-osmolar contrast medium iodixanol-270 is not inferior to low-osmolar contrast medium iopromide-300 in terms of coronary opacification (body weight 50-125 kg). Iodixanol-270 was associated with less heat discomfort, but did not affect heart rate differently compared to iopromide-300.

INTRODUCTION

Coronary computed tomography angiography (CTA) is an established test in the diagnostic work up of patients with stable angina pectoris and allows for reliable exclusion of coronary artery disease (1). As a result of continued scanner development and iterative reconstruction algorithms contemporary CT systems allow for coronary imaging at lower tube voltages (kV). Nowadays many patients can be scanned using 80kV, lowering overall radiation exposure. Because of greater photoelectric effect and decreased Compton scattering, imaging at a lower kV also increases the attenuation differences between iodine and soft tissue (2). Because current technology allows comparable opacification at lower intra-coronary iodine concentrations, the iodine delivery rate can be reduced, permitting application of contrast media with lower iodine concentrations. When osmolality increases, the viscosity as well as opacification of the contrast agent increases but the tolerance power of the patients decreases. Sensations of heat, discomfort or even pain are directly related to the osmolality of the contrast medium(3).

Most roentgen contrast media have an osmolarity higher than blood plasma, which is responsible for various clinical effects, such as sensations of heat, discomfort and even pain(4). Invasive coronary angiography studies suggest that arrhythmia occur more frequently with low-osmolar contrast media. Iso-osmolar contrast agents, with an osmolarity equal to plasma, cause less heart rate acceleration and arrhythmia, which should be of potential benefit for CT image quality (3, 5-8). In terms of opacification and image quality comparisons between iso-osmolar and low-osmolar contrast media have demonstrated mixed results (6, 9, 10). Because many studies compared protocols of identical injection rates of contrast media, but unequal iodine concentrations, observations may be affected by differences in the net iodine delivery rates(3, 5-12). It remains unclear how an iso-osmolar contrast medium affects the opacification of the coronary arteries when identical iodine fluxes are applied. Also the effect on heart rate, arrhythmia, and subsequent image quality in case of identical iodine fluxes has not yet been evaluated in a randomized trial.

The aim of the Isocor randomized-controlled trial was to demonstrate that using contemporary cardiac CT protocols equal coronary lumen opacification can be achieved with iso-osmolar and low-osmolar contrast media, when injected at the same iodine delivery rate. In addition, we investigate the cardiovascular effect of iso-osmolar contrast media, and achieved image quality.

MATERIALS AND METHODS

Study Design

The Isocor trial is a non-inferiority, multicentre, double-blinded randomized-diagnostic validation trial comparing the opacification between an iso-osmolar (iodixanol) and a low-osmolar (iopromide) contrast medium. Patients referred for coronary CTA were prospectively enrolled at three hospitals in Rotterdam. The study was conducted in accordance with the Declaration of Helsinki and international standards of Good Clinical Practice and was approved by the medical ethics committees of the central coordinating centre and both participating sites. Written informed consent was obtained from each participating patient. The Isocor trial is registered at the EU Clinical trials register (www.clinicaltrialsregister.eu), EUdract-number 2014-000681-22. GE Healthcare, the manufacturer of iodixanol, provided unrestricted financial and material support (iodixanol contrast medium). The authors had full control of the data and information submitted for publication.

Study participants

Patients aged 18 years or older, body weight between 50-125kg, and referred for coronary CT-angiography in the context of suspected coronary artery disease (CAD) were study eligible. Exclusion criteria were pregnancy, renal dysfunction (eGFR<45ml/min/1.73m^2), allergies to iodine contrast media, manifest thyrotoxicosis, arrhythmia including atrial fibrillation/flutter, 2nd or 3rd degree atrioventricular block, frequent ectopic beats prior to the exam (discretion of referrer), prior coronary artery bypass graft surgery or percutaneous coronary intervention with stents.

Randomization and blinding

From an electronically created randomization list, allocation results were placed in numbered envelopes, which were opened just prior to the CT scan when an eligible patient consented to the study. The allocation was unknown to the patient and to the reader of the images. For practical reasons (different injection rates) the CT technicians performing the examination were not blinded with regard to allocation.

Contrast material and injection

Iodixanol-270 mg iodine per ml (Visipaque, GE Healthcare, Amersham, UK) and iopromide-300 mg iodine per ml (Ultravist, Bayer Healthcare, Berlin, Germany) were stored and administered in a similar, clinically standard manner, in accordance with the summary of product characteristics (SPC). Bottles of contrast media were stored at the CT suite at 37° Celsius. Using a disposable system, contrast medium was transferred to a dual-head power injector, with external heating element. The power injector was then connected

to an 18-gauge IV canula in the antecubital vein. All participating hospitals used the same contrast injector type (Medrad® Stellant® CT Injection System, Bayer Medical Care Inc., Indianola, PA, USA). Contrast media were injected to achieve a net iodine delivery rate of 1.5gI/s (bodyweight 50-100kg), or 1.75gI/s for larger patients (bodyweight 100-125kg) to maintain sufficient concentrations of iodine in the bloodstream and the coronary arteries at higher anticipated cardiac output. Iodixanol-270 was injected at 5.6ml/s (body weight 50-100kg) or 6.5ml/s (100-125kg), iopromide-300 was injected at 5.0ml/s (50-100kg) or 5.8ml/s (100-125kg). The total contrast volume was calculated by [estimated scan duration + 8 seconds] * [flow rate], followed by a 40cc saline bolus chaser at same flow rate. The pressure limit of the power injector was 325 PSI.

CT examination

All CT angiograms were performed by standard contemporary protocols using 2nd or 3rd generation dual-source CT systems (Somatom Definition Flash and SOMATOM Force, Siemens Healthineers, Forchheim, Germany). If indicated (heart rate >65 bpm) and clinically tolerable, beta-blockers were administrated. All patients received sublingual nitroglycerin just before scanning. First a non-enhanced calcium scan was performed to measure the Agatston score. The median total Agatston calcium score was 4 [0;89]. The scan parameters are summarized in table 2. In both groups the majority was imaged using the prospectively ECG-triggered axial scan mode (92% vs 94%, p=0.473), with an exposure window during diastole and/or systole depending on the heart rate. . Automatic tube current modulation and tube voltage selection based on the scout images were employed. The tube settings were optimized to achieve sufficient signal to noise. The system automatically selected the lowest possible *tube* voltage that still be supported by the tube current in a given patient and application, in order to achieve sufficient image quality at the lowest possible dose. The tube current was 70 or 80kV in 51% of patients in the iodixanol-270 group and 53% in the iopromide-300 group (table 2). The dose-length-product (DLP) and effective dose (k=0.017) was 160±119Gycm and 2.7±2.0mSv in the iodixanol group, and 174±160mGycm and 3.0±2.7msV (p=0.387) in the iopromide group. Iterative reconstruction (Strength-3) was used. The reconstructed slice thickness was 0.6mm, reconstruction increment 0.4mm, reconstructed area dimensions 180x180mm.

Image evaluation

All CTA images were assessed by an independent, experienced reader (ML, 4 years of cardiac CT experience), blinded to the patients' clinical characteristics and the contrast medium used. The mean attenuation (Hounsfield units,HU) and standard deviation were measured in the proximal, mid and distal part of the right coronary artery (RCA), left anterior descending artery (LAD) (13), and left circumflex artery (LCX). The attenuation

measurements were performed on the axial images in vessel segments with a minimal diameter of 2mm and good or diagnostic image quality, by placing a circular region-of-interest (ROI) with a minimum number of 10 image elements (pixels) in the center of the vessel at a location of sufficient image quality. Attenuation was also measured in the middle of the atrial and ventricular cavities, the middle of the ventricular septum (myocardium) and the ascending and descending aorta. For each coronary segment subjective image quality was classified on a 3-point scale as good, diagnostic, or poor. Image noise, signal-to-noise ratio, and contrast-to-noise ratio were determined for all scans (see formulas). The image noise was derived from the averaged SDs of the CT attenuation values sampled using two large regions of interest in the proximal segments of both the left and right coronary arteries. The signal intensity was defined as the mean attenuation values derived from the same 2 regions of interest. The signal-to-noise ratio was calculated as mean CT attenuation values of the left and right coronary arteries divided by image noise. The contrast-to-noise ratio was defined as the difference between the mean CT attenuation values of the proximal coronary arteries and the mean density of the left ventricular wall, which was divided by image noise.

$$Contrast-to-noise\ ratio = \frac{([attenuation]LCA + [attenuation]RCA\ /2) - [attenuation]LV\ wall}{[attenuation\_SD]LCA + [attenuation\_SD]RCA\ /2}$$

Clinical effects and safety

The cardiovascular response to the contrast injection was monitored by measuring the mean heart rate. The heart rate was measured over 15 seconds before scanning (free breathing), at the time of the calcium scan (without contrast injection, but breath holding), and during CTA (after contrast injection and with breath holding), calculated from the ECG traces during data acquisition. Also the number of ectopic beats on the ECG recordings during CT-angiography were recorded, as well as the occurrence of atrial fibrillation. All adverse events, such as contrast extravasation, severe arrhythmia with hemodynamically significance, allergic reactions and renal failure were reported. The physical complaints during contrast injection were evaluated using a 5-point scale ranging from 0(no complaints) to 4(worst thinkable).

Outcomes

The primary outcome was the coronary lumen opacification, defined as the averaged attenuation values (Hounsfield Units, HU) sampled in the middle segment of the LAD, the middle segment of the RCA, and proximal segment of the LCX, demonstrating non-inferiority. Secondary outcome measures of image quality were the contrast attenuation values in the proximal, middle and distal coronary arteries, respectively, the signal-to-noise ratio (SNR), the contrast-to-noise ratio (CNR), and the scaled subjective image

quality per coronary segment. Clinical outcome measures included adverse events, heart rate, arrhythmia, and patient reported sensations.

Statistical analyses

For 80%-power at a one-sided p-value of 0.025 we needed to recruit at least 272 patients to detect a difference of 30HU in coronary opacification, which was pre-specified and considered relevant for image interpretation. Anticipating a drop-out of up to 10%, we aimed to recruit 300 patients.

The primary endpoint to assess coronary opacification, the sampled and averaged attenuation values in the mid-segment of the RCA and LAD and proximal Cx, is a continuous variable with normal distribution reported as means ±SD. The hypothesis would be rejected if coronary opacification by iodixanol-270 were >30HU lower than by iopromide-300. Non-inferiority can be concluded when the lower bound of the confidence interval of the difference in attenuation does not exceed the non-inferiority margin(-Δ) of -30HU. Unavailable or technically failed scans were excluded. To meet the intention-to-treat principle, we corrected for missing data due to poor image quality. Missing values were replaced by the lowest measured mean coronary opacification (142HU). Results between the groups were compared using a student t-test. To correct for potential confounders influencing the opacification we also performed an analysis of covariance (ANCOVA).

Secondary, continuous measures (attenuation measures, SNR, CNR, contrast injection parameters) and categorical parameters (subjective quality, artifacts, adverse events) were compared using the student-t and Chi-square tests. The heart rate and change in heart rate in patients were compared using Wilcoxon signed-ranks test. Data distribution was tested with the Shapiro-Wilk test. Multi-variable linear regression analysis was performed to assess potentially confounding parameters towards the vessel opacification, which were pre-specified and included age, gender, height, weight, BMI, heart rate, left ventricular function (determined by cardiac echocardiography, registered from patient records if available), IV gauge location, as well as other covariates found to be different between the randomization groups (gender and systolic blood pressure). To test whether injection rate was an effect modifier of contrast agent on opacification an ANCOVA model was performed with the interaction term contrast injection rate x randomization. A two-sided p-value of <0.05 was considered statistically significant. Statistical analyses were performed using SPSS (version 21, IBM Corp, Armonk NY, USA), according to the intention-to-treat principle.

RESULTS

Study population

Between November 2015 and August 2016 329 eligible patients were approached, of whom 9(3%) declined participation, 4(1%) had atrial fibrillation, 3(1%) had a known contrast allergy, 2(1%) were unable to consent, 2(1%) had a body weight >125kg, 2(1%) were excluded because of technical reasons, and 1(0.3%) was excluded because of renal dysfunction (figure 1). Of the 306 enrolled patients, 154(50%) were randomly assigned to iodixanol-270 and 152(50%) to iopromide-300. No scans were excluded because of overall non-diagnostic image quality. All patients were included in the intention-to-treat analysis (figure 1). The mean age was 56±12 years. There were more women randomized to iopromide-300 (61% vs 48%, p=0.022), and also the mean systolic blood pressure was higher in this group (143±21 mmHg vs 136±20 mmHg, p=0.008). Otherwise there were no significant differences in clinical symptoms and cardiovascular risk factors (table 1). Most patients presented with chest pain complaints (90% vs 89%, p=0.896).

Table 1. Patient characteristics

	Iodixanol-270 (n=154)	Iopromide-300 (n=152)
Mean age (years)	56±12	56±11
Female sex	74 (48%)*	93 (61%)*
Systolic blood pressure (mmHg)	136±20*	143±21*
Diastolic blood pressure (mmHg)	82±11	82±12
Length (cm)	172±11	172±10
Weight (kg)	82±15	81±16
Body-mass index (kg/m^2)	27±4	27±5
eGFR (ml/min/1.73m^2)	76±16	75±16
Cardiovascular risk factors		
Current/past smoker	34 (22%)	22 (14%)
Hypertension	49 (32%)	49 (32%)
Dyslipidaemia	39 (25%)	36 (24%)
Diabetes mellitus	16 (10%)	14 (9%)
Family history of ischemic heart disease	33 (21%)	39 (26%)
History of obesity (BMI ≥30kg/m^2)	45 (30%)	37 (25%)

Patient characteristics presented as mean ± standard deviation or n (%), or median and interquartile range. Hypertension: >150 systolic or >90 diastolic mmHg or using tension-lowering medication. Dyslipidaemia: total cholesterol >5mmol/L, low-density lipoprotein >3mmol/L, or on lipid-lowering medication. Diabetes Mellitus: plasma glucose >11.0mmol/L, or treated with diet regulation or medication. * Significant difference (p<0.05).

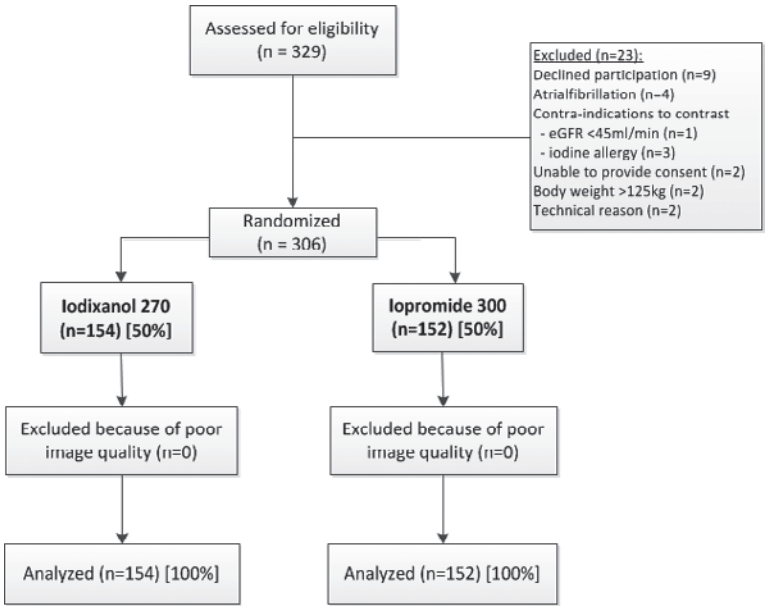

Figure 1. Enrolment and randomization of patients. There were no patients with a poor image quality of all the coronary arteries, so no scans were excluded based on poor image quality.

Quantitative and qualitative image quality

The primary endpoint coronary lumen opacification, averaged in the middle segment of the RCA, LAD and proximal LCx, was 469 ± 167 using iodixanol-270 and 447±_166 using iopromide-300 (p=0.241)(95% CI: -15.1 – 60.0) (appendix 1). Corrected for potential confounders (age, gender, BMI and injection rate) the mean coronary lumen opacification in the iodixanol-270 group was 471 ± 450, compared to 439 ± 417 in the iopromide-300 group (p=0.037, 95% CI: 1.9 – 62.7). Comparisons on a segmental level, summarized for proximal, middle and distal coronary segments, and averaged per patient showed no differences (iodixanol-270 462±155 HU vs iopromide-300 440±150 HU, p=0.220). Interestingly, attenuation values in the interventricular septum were higher in the iopromide-300 group (110±29 vs 117±33, p=0.034). Coronary opacification was positively influenced by female gender (55.9 HU higher in women; 95% CI 12.0,100.0; p=0.013). Opacification was positively affected by age (4.0 HU increase per year of age; 95% CI 2.0,5.9; p<0.001). Opacification was negatively influenced by BMI (-20.6 HU per 1kg/m^2; 95% CI -24.8,-16.5, p<0.001), weight (-6.3 HU per kg; 95% CI -7.2,-5.5, p<0.001) and length (B -4.6 lower per cm; 95% CI -6.2,-2.9, p<0.001). LV function, systolic blood pressure, heart rate before and during contrast administration and the location of the IV canula did not affect mean attenuation values. In a multivariate analysis the remaining predictor of coronary opacification was age (+3.1 HU per year; 95% CI 0.05,6.19, p=0.046). There were no differences in attenuation between both contrast media through the

sequential vasculature from right atrium to the distal aorta (appendix 2). The effect of contrast agent on opacification was not depended on the injection rate (p=0.652). A case example of the coronary opacification with both contrast agents is shown in figure 2. The signal-to-noise ratio and contrast-to-noise ratio did not differ between the groups (SNR: iodixanol-270: 22.3±9.3 HU vs 23.5±10.9 HU, p=0.290)(CNR: iodixanol-270: 17.2±7.7 HU vs 17.5±8.4 HU, p=0.729) (appendix 1). The subjectively assessed image quality was good in 86% and 85% of all coronary segments and did not differ between iodixanol-270 and iopromide-300 (p=0.283, appendix 3).

Concordant with the different iodine concentrations the contrast volume was higher in the iodixanol-270 group to achieve similar iodine delivery rates (mgI/sec) to the iopromide-300 group (76.8±11.6 ml vs 69.7±10.8 ml, p<0.001), and at higher injection pressures (111±44 PSI vs 90±36 PSI, p<0.001)(table 2).

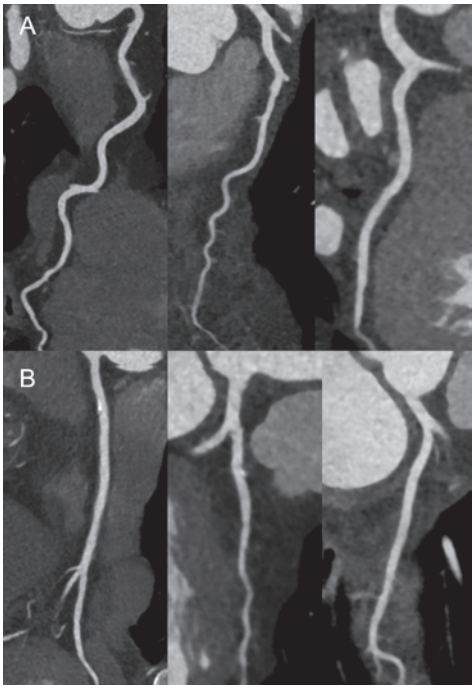

Figure 2. Coronary lumen opacification performed with both contrast agents. Both patients were men of 54 years old and a BMI of 25. Patient A was scanned with iodixanol-270, at a heartrate of 63bpm and had a calciumscore of 0. Patient B was scanned with iopromide-300 at heartrate 56bpm and had a calciumscore of 68. From left to right the right coronary artery (RCA), left anterior descending artery (LAD) and left circumflex artery (LCx) are shown.

Effect on heart rhythm

Beta-blockers were administrated in nearly half of the patients. For both groups combined, the heart rate decreased during the breath-held calcium scan from 64.8±9.9 bpm to 63.4±10.5 bpm (p<0.001). During contrast-enhanced CT-angiography the heart rate remained virtually unchanged in the iodixanol-270 (+0.01±4.56, p=0.986) and the iopromide-300 group (+0.32±5.37; p=0.473), without a difference between both groups

(p=0.588) (figure 3). Ectopic beats occurred in 3(2%) of iodixanol-270 patients, compared to 6(4%) of iopromide-300 patients (p=0.334). No atrial fibrillation occurred in either group before or after contrast injection.

Table 2. Scan characteristics

	Iodixanol-270 (n=154)	Iopromide-300 (n=152)	p-value
Heart rate			
Before scanning (bpm) (mean±SD) [range]	65 ± 9 [45-98]	65 ± 11 [44-115]	0.638
During calcium scan (bpm) (mean±SD) [range]	63 ± 10 [45;98]	63 ± 11 [46-118]	0.887
During CTA(bpm) (mean±SD) [range]	63 ± 11 [43-98]	64 ± 11 [42-114]	0.590
Heart rate change* (bpm) (mean±SD)	0.01 ± 4.56	0.32 ± 5.37	0.588
Ectopic beats during and after contrast injection	3 (2%)	6 (4%)	0.334
Occurrence of atrial fibrillation	0	0	1.000
Pre medication			
B-blockers	70 (46%)	65 (43%)	0.646
Contrast injection			
Contrast bolus (cc) (mean±SD) [range]	76.8 ± 11.6 [48-100]	69.7 ± 10.8 [45-95]	<0.001
Iodine delivery rate, patients 50-100kg (gI/s)	1.5	1.5	
Iodine delivery rate, patients 100-125kg (gI/s)	1.75	1.75	
Maximal injection pressure (PSI)	111 ± 44	90 ± 36	<0.001
Scanning technique			0.473
Retrospectively gated spiral scan mode	13 (8%)	9 (6%)	
Prospectively triggered axial scan mode	117 (76%)	124 (82%)	
Prospectively triggered high-pitch spiral scan mode	24 (16%)	19 (13%)	
Tube current (mAs) (mean±SD) [range]	341 ± 103 [88-600]	345 ± 103 [108-568]	0.716
Tube voltage (kV) (median, IQR)	80 (80;100)	80 (80;100)	0.796
Scan time (seconds) (mean±SD)	4.6 ± 2.4	4.9±2.3	0.264
Radiation dose			
Dose-length product (mGycm) (mean±SD) [range]	160 ± 119 [19;561]	174 ± 160 [25;1038]	0.387
Total calcium score (mean±SD) [range]	118 ± 348 [0;3429]	123 ± 308 [0;2765]	0.897

Patient characteristics presented as mean ± standard deviation and range, or n (%), or median and interquartile range. The heart rate before scanning was a mean over 15 seconds. *Difference in heart rate recorded during the calcium scan and the contrast-enhanced CTA. Number of patients with ectopic beats throughout the ECG recording during and after contrast injection. B-blockers are oral and intravenous. The maximum contrast injection pressure measured in pound-force per square inch (PSI). Dose-length product (DLP) in mGycm for CT-angiography.

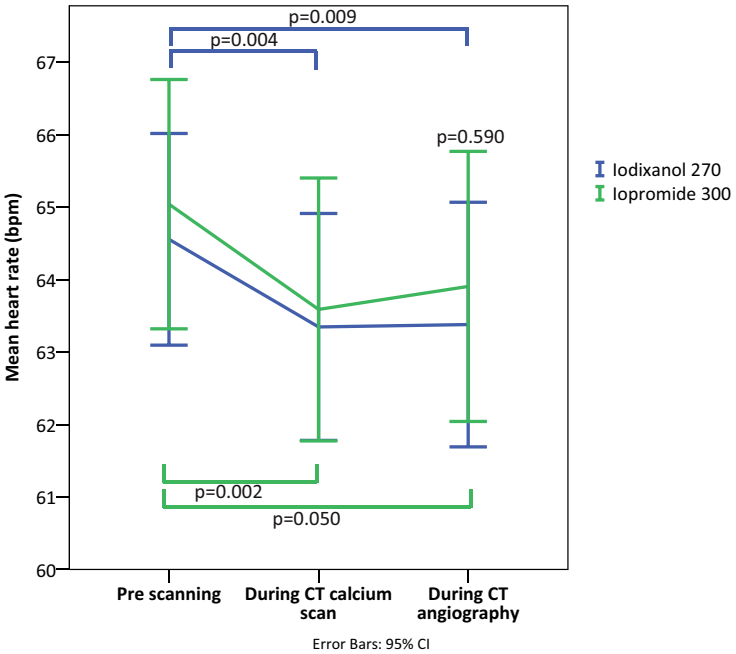

Figure 3. Change in heart rate. The mean heartrate (beats per minute), before the CT exam, calcium scan, and CT-angiography. Compared to measurements before the CT scan, heart rates decreased during both the calcium scan (iodixanol-270: p=0.004, iopromide-300: p=0.002) and CT-angiography (iodixanol-270: p=0.009, iopromide-300: p=0.050). The heart rate during CT angiography was not significantly different between the iodixanol-270 and iopromide-300 group (p=0.590).

Clinical effect and safety

In the iodixanol-270 group fewer patients experienced heat discomfort during the scan compared to iopromide-300 group (72% vs 86%, p<0.001)(figure 4). Other symptoms and sensations were observed in similarly low rates between both groups. One patient in the iodixanol-270 group experienced contrast extravasation. In the iopromide-300 group two patients experienced mild allergic reactions (sneezing and urticaria, respectively), and one experienced blurred vision <2hours after the scan, all of which resolved shortly without treatment. No arrhythmias or renal failure occurred.

DISCUSSION

This multicentre, randomized trial was designed to assess whether iso-osmolar contrast medium with a low iodine concentration provides comparable coronary opacification to low-osmolar contrast media, if injected at a similar iodine delivery rate. We found that 1) coronary lumen opacification by iso-osmolar contrast (iodixanol) is not inferior

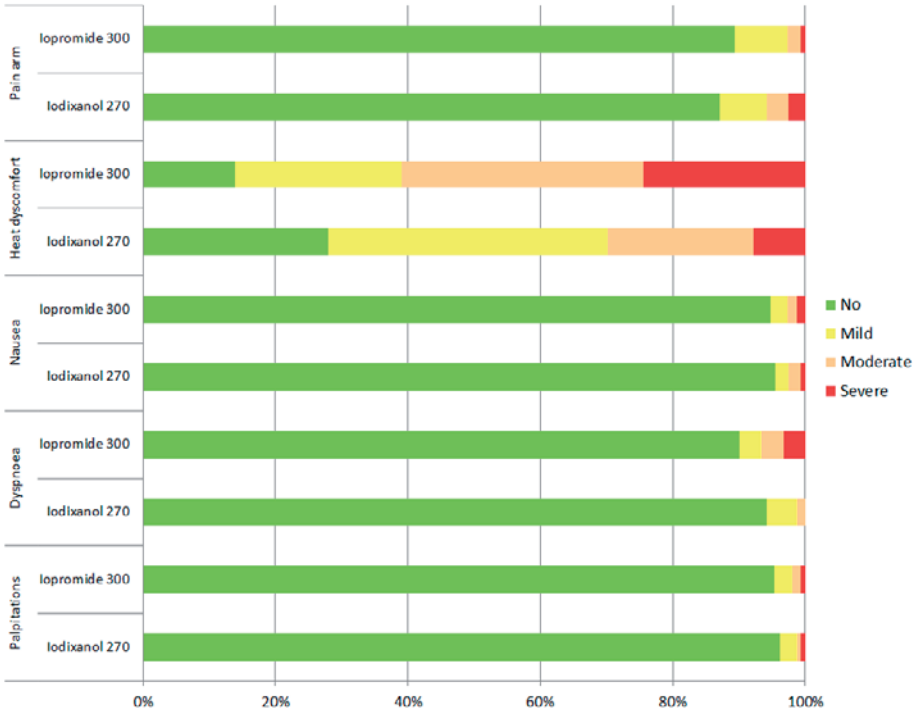

Figure 4. Clinical effect. All symptoms were classified as no symptoms, mild, moderate or severe. The iodixanol-270 group experienced less heat discomfort during contrast administration compared to the iopromide-300 group (72% vs 86%, p<0.001). There were no significant differences in other symptoms and sensations between both groups.

to a low-osmolar contrast (iopromide), 2) while iopromide-300 was associated with more frequent heat sensations, heart rate was not affected differently between the two groups, 3) objective and subjective measures of image quality were similar between iodixanol-270 and iopromide-300.

In this study we found that if contrast media are injected at comparable iodine delivery rates, by injecting the iso-osmolar contrast medium at a higher injection rate, coronary opacification by iodixanol-270 is not inferior to iopromide-300. In terms of coronary arterial opacification and image quality comparisons between iso-osmolar and low-osmolar contrast media have demonstrated mixed results. While some studies demonstrated comparable coronary opacification between iso-osmolar and low-osmolar contrast (6, 9), there is also data showing significantly lower opacification of low-osmolar contrast compared to high iodine-osmolality (5, 10). However, in these trials contrast media were injected with unequal iodine delivery rates.

Using an iodine delivery rate of 1.5 gI/s in both arms (body weight <100kg), we measured average attenuation values well above 400HU, with acceptable noise and image

quality. The injection rate of iodixanol-270 was 5.6 - 6.5 ml/s. Until recently achieving sufficient coronary opacification at reasonable contrast injection rates required contrast media with a high iodine concentration of up to 400mgI/ml. High attenuation values partially compensated for some of the limitations of cardiac CT related to residual motion and calcifications. Technological innovation, in particular improved temporal resolution and iterative image reconstruction techniques, allow for reliable coronary assessment at a lower coronary opacification. In addition, desired attenuation values can be achieved with lower intra-coronary iodine concentration by using more powerful roentgen tubes operated at lower tube voltages. Iterative reconstruction algorithms reduce image noise and improve SNR and CNR while keeping intravascular attenuation values homogenous (2, 14).

The osmolarity of contrast media is associated with several clinical effects, such as sensations of heat, discomfort and pain. Low-osmolar contrast media may increase heart rate, and thereby reduce image quality in coronary CT angiography. In the Isocor trial we found that the mean heart rate did not increase in either group. Multiple studies in stable patients evaluating suspected coronary artery disease, suggest that iso-osmolar contrast media cause less heart rate acceleration and arrhythmia (5, 7, 11, 15). Low heart rate and absent arrhythmia positively affect image quality in ECG-synchronized CT-angiography. However, other studies that compared iso-osmolar and low-osmolar contrast media in abdominal CT reported no difference in heart rate (12, 16). It should be noted that nearly half of the patients in this study received additional beta-blockers prior to scanning, but at comparable proportion in both groups.

In the Isocor study we found no significant differences in terms of coronary opacification, nor for several other objective parameters of image quality. Previously, some investigators demonstrated similar diagnostic accuracy, coronary attenuation and subjective image quality of CTA using either iso-osmolar or low-osmolar contrast (6, 9), while other studies demonstrated better coronary enhancement and fewer inadequately visualized segments using high-iodine concentration low-osmolar contrast protocols (5).

There were a few occurrences of contrast extravasation and mild allergy, and a single incidence of blurred vision, which is a known side-effect of both contrast agents. Maximal injection pressure was higher for iodixanol (PSI 111 ± 44) compared to iopromide (PSI 90 ± 36, <0.001) as a result of higher injection rates and higher viscosity (6.3cP vs 4.9cP at 37°C) for iodixanol, but never exceeded the safety threshold (PSI 325).

There are limitations to the study that require consideration. Because of the different injection rates the CT technicians could not be blinded towards the study allocation. However, this should not have affected the independent, blinded reading and establishment of the primary outcome. Although unlikely given the comparable image quality parameters, we cannot exclude differences in diagnostic accuracy related to the contrast media. Except for heart rate no other hemodynamic parameters were monitored. A sys-

tematic assessment of renal function after contrast exposure was not performed, however, no differences in CIN risk between iodixanol-270 and iopromide-300 have been reported in the past (19, 20). Comparison between the iso-osmolar contrast medium iodixanol was compared to only a single low-osmolar contrast medium, which may not be representative for the entire class.

In conclusion, if injected at comparable iodine delivery rates, the iso-osmolar contrast medium iodixanol-270 is not inferior to low-osmolar contrast medium iopromide-300 in terms of coronary opacification (body weight 50-125 kg). Iodixanol-270 was associated with less warmth discomfort during contrast injection, but did not affect heart rate or image quality compared to iopromide-300.

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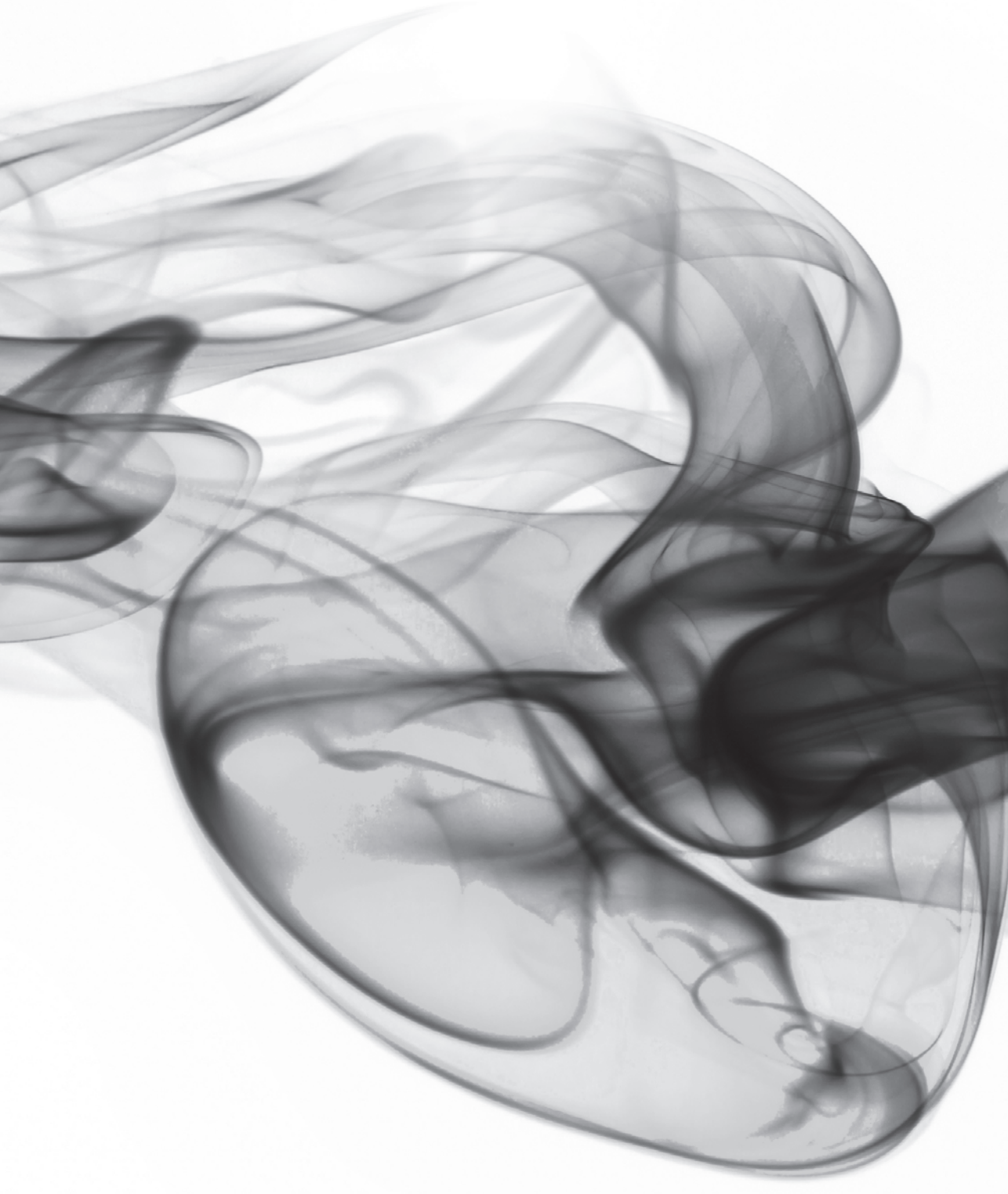

Part 3

CT myocardial perfusion imaging in stable angina

CHAPTER 6

Diagnostic Value of transmural perfusion ratio derived from dynamic CT-based myocardial perfusion imaging for the detection of hemodynamically-relevant coronary artery stenosis

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Eur Radiol. 2017 Jun;27(6):2309-2316.

ABSTRACT

Aims: To investigate the additional value of transmural perfusion ratio (TPR) in dynamic CT myocardial perfusion imaging for detection of hemodynamically significant coronary artery disease, compared with fractional flow reserve (FFR).

Methods: Subjects with suspected or known coronary artery disease were prospectively included and underwent a CT-MPI examination. From the CT-MPI time-point data absolute myocardial blood flow values (MBF) were temporally resolved using a hybrid deconvolution model. An absolute MBF value was measured in the suspected perfusion defect. TPR was defined as the ratio between subendocardial and subepicardial MBF. TPR and MBF results were compared with invasive FFR using a threshold of 0.80.

Results: Forty-three patients and 94 territories were analyzed. The area under the receiver operator curve was larger for MBF (0.78) compared with TPR (0.65, *P*=0.026). No significant differences were found in diagnostic classification between MBF and TPR with a territory based accuracy of 77% (67-86%) for MBF, compared with 70% (60-81%) for TPR. Combined MBF and TPR classification did not improve diagnostic classification.

Conclusion: Dynamic CT-MPI based transmural perfusion ratio predicts hemodynamically significant coronary artery disease. However, diagnostic performance of dynamic CT-MPI derived TPR is inferior to quantified MBF and has limited incremental value.

INTRODUCTION

Dynamic computed tomography myocardial perfusion imaging (CT-MPI) is based on sequential scanning of the myocardium during the first pass of a contrast bolus. The dynamic imaging of the contrast medium allows for a non-invasive quantification of myocardial blood flow (MBF), until now mainly performed with either magnetic resonance imaging or positron emission tomography [2; 3]. With recent developments in CT scanners this technique also became available for CT imaging [4; 5]. The diagnostic performance of CT-MPI compared with fractional flow reserve is good [6-8]. However, possible underestimation of absolute MBF values by CT-MPI is a potential concern [5; 9].

Reduced myocardial perfusion due to coronary artery disease (CAD) tends to be more pronounced in the subendocardium [10]. The high spatial resolution of CT allows for distinguishing of the subendocardium and subepicardium. A method to utilize the susceptibility of the subendocardium for ischemia is the transmural perfusion ratio (TPR) [11]. TPR is the ratio between subendocardium and subepicardium perfusion. As TPR is a relative index we hypothesized it would be less influenced by lower absolute MBF values and improve diagnostic performance of CT-MPI.

In this study TPR and MBF based on dynamic CT-MPI are investigated individually and in combination, and compared with invasive fractional flow reserve [1].

METHODS

Study Design

The local institutional review board approved this prospective study. Written informed consent was obtained from all patients. This study included cases from a previous study investigating the diagnostic performance of CT-MPI [8]. Patients with suspected or known CAD referred for invasive angiography were prospectively recruited. Included patients underwent a dynamic CT-MPI examination 1-14 days before invasive angiography.

This study was designed to investigate the ability of CT-MPI to detect ischemia, therefore only territories with an FFR measurement in the associated coronary artery were included. Territories associated with a (sub)total occluded coronary artery were no FFR measurement could be performed were not included in the analysis.

Recruitment and Population

Patients with suspected or known coronary artery dished referred for invasive angiography were recruited in the time period December 2010 till December 2014.. Exclusion criteria: younger than 40 years old, impaired renal function (serum creatinine >120

μmol/L), possible pregnancy or breast feeding, body weight over 120 kg, use of clopidogrel, contra-indications for iodine contrast medium, or contra-indications for adenosine.

CT-MPI Acquisition

All patients were requested to withhold from caffeine intake 24-hours prior to the examination. In both arms 18-gauge cannulas were inserted in the antecubital veins. Blood pressure and ECG were monitored during the examination. Forty patients were scanned with a second-generation dual-source CT scanner, and three patients with a third-generation dual-source CT scanner (SOMATOM Definition Flash and SOMATOM Force, Siemens Medical Solutions, Forchheim, Germany). Adenosine was infused at a rate of 140μgram/kg/min. CT-MPI acquisition was started three minutes after start of adenosine infusion.

The acquisition protocol consisted of coronary CT angiography, a non-contrast scan and the dynamic CT-MPI scan. The non-contrast scan was acquired during end-systole, and served for planning of the CT-MPI. Before the CT-MPI acquisition all patients received sublingual nitroglycerine. Intravenous beta blockers were used in patients with high heart rates prior to the coronary CT angiography, but very infrequently (N=3) as these potentially affect the CT-MPI performance. After 3 minutes of adenosine infusion, 50 ml of contrast medium (Ultravist, 370 mgI/ml; Bayer, Berlin, Germany) was injected at 6 ml/s, followed by a saline bolus of 40 ml. All CT-MPI studies were made with an axial scan mode at 250 ms after the R wave (end-systolic). To sufficiently cover the left ventricle the myocardial acquisition was performed in alternating cranial and caudal table positions (shuttle-mode), acquiring two slightly overlapping data-sets [4]. CT-MPI acquisition was started 5 seconds after start of the contrast medium injection. Patients were asked to hold their breath during the entire dynamic CT-MPI acquisition (30-35 seconds). The number of time points acquired varied per patient depending on the heart rate: 1 patient had 9 cranial and caudal time points, 11 patients had 10, 6 patients had 11, 12 patients had 12, 9 patients had 13, and 4 patients had 14 time points.

The second-generation dual-source CT scanned used the following scan parameters: collimation 2×64×0.6mm detector collimation with flying z-spot technique [12], gantry rotation time 280ms, temporal resolution 75ms, tube voltage/current 100kVp/ 300mAs, shuttle-mode coverage 73mm.

The third-generation dual-source CT scanner used the following scan parameters: collimation 2×96×0.6mm detector collimation with flying z-spot technique. Gantry rotation time 250ms, temporal resolution 66ms, Care-Kv [13] was used with reference settings for tube voltage/current: 80kVp/300mAs, shuttle-mode coverage 102mm.

Post Processing

The CT-MPI images were reconstructed using a dedicated kernel for reduction of iodine beam hardening artifacts (b23f, Qr36), and transferred to a CT-MPI analysis software package (Volume Perfusion CT body, Syngo Somaris/7; Siemens, Germany). Motion correction was applied if necessary to correct for breathing displacement. The motion correction algorithm uses a time point selected by the user (with contrast in the left and right ventricle and smooth connection between the cranial and caudal section), and then registers the other time points to the selected time point using non-rigid registration. The left ventricle is segmented by combining thresholding and peak enhancement [14]. The change of attenuation in the myocardium over time was computed by creating time-attenuation curves (TAC). For quantification of the MBF the influx of contrast bolus was measured with an arterial input function [15]. The AIF was measured by placement of a ROI in the descending aorta in the CT-MPI images. Precision of the AIF was increased by including both the cranial and caudal sections (double sampling). For quantification of the MBF the myocardial TACs were coupled with the AIF using a hybrid deconvolution model. The model generates perfusion model curve based on the change in attenuation using a simplified impulse residue function for modeling the interaction between intra- and extracellular compartments. The MBF was computed on a per voxel basis by dividing the maximal slope of the model curve for the myocardial tissue by the maximum AIF [4; 5; 16]. MBF data-sets were reconstructed with a 512×512 matrix resulting in a pixel size of 0.35×0.35 mm and were reconstructed as a stack of color-coded maps with a slice thickness of 3mm and an increment of 1.5 mm.

Image Analysis

MBF and TPR were individually evaluated by readers with previous experience in dynamic CT-MPI examinations. Both readers were provided with the color-coded CT-MPI datasets. For each patient a list of vessels investigated by FFR was provided. To ensure correct territory-vessel correspondence left or right coronary dominance was provided for each patient. All readers were asked to measure MBF or TPR value corresponding to the vessel where the FFR measurements were performed. Each independent reader was blinded to all other medical information.

Within the MBF short axis slice interpreted as representing the myocardium dependent on the vessel in which the FFR was made, a freehand ROI was placed surrounding the suspected perfusion defect (Syngo Via 2.0, Siemens AG, Germany). The freehand ROI had a minimal area of 50 mm^2. Careful considerations were made to prevent inclusion of artifacts in the ROI.

For TPR the CT-MPI color-coded maps were visually assessed to identify the slice most representative for a subendocardial/subepicardial ratio. The section of interest was loaded onto a dedicated image analysis application (ImageJ 1.48, National Institutes of

Health, USA).[17] To measure the transmural differences in MBF a series of linear samples perpendicular to the myocardial surface were taken at 0.4mm equal intervals (Figure 2). The mean MBF values from the pixels under the line are projected in the transmural MBF profile curve. Care was take not to sample too close to the LV lumen and epicardial border as the MBF absolute values are unreliable due to displacement artifacts. From the short-axis MBF image and the MBF profile curve the user selected the endocardial and epicardial position. The TPR was calculated by dividing the subendocardial by the subepicardial MBF.

Invasive Angiography and Fractional Flow Reserve

Invasive coronary angiography was performed according to local clinical standards. Prior to the invasive angiography intracoronary nitroglycerine was given, as is the standard in our center. Invasive FFR was performed in all vessels with a visual stenosis grade between 30-90% by invasive angiography. By protocol, an FFR pressure wire (PressureWire Aeris/Certus, St. Jude Medical, St. Paul, USA or Prime/Combo Wire, Volcano, San Diego, USA) was placed distal to the stenosis of interest, after which hyperemia was induced by intravenous infusion of adenosine at 140 µg/kg/min. An invasive FFR ≤0.80 was considered hemodynamically significant.

Statistics

Absolute variables are represented as total and percentage, continuous variables as mean and standard deviation (±). The mean values for MBF and TPR for normal and ischemic territories were compared with an unpaired two-sided independent t-test. Pearson coefficient correlation was calculated for respectively MBF and TPR against invasive FFR. The receiver-operator characteristic (ROC) curves including area under the curve (AUC) were presented for MBF and TPR. To investigate the combine diagnostic performance for MBF and TPR an ROC curve was also plotted for a new combined variable MBF multiplied by TPR (MBF×TPR). The optimal threshold for MBF and TPR diagnostic accuracy was calculated using the Youden index[18]. A sub-analysis was made for territories with an intermediate MBF between 50-100 ml/100ml/min, as these represent territories with MBF values close to the diagnostic threshold [6; 8]. Diagnostic performance was evaluated as sensitivity, specificity, positive predictive value, negative predictive value and accuracy, with their corresponding 95% confidence intervals (CI). The 95% confidence intervals were corrected for within subject clustering of data using variance adjustment[1]. MBF and TPR were displayed against each other with territories classified as normal or ischemic. Inter-observer variability was determined for 72 (75%) randomly selected territories by intra-class correlation coefficient for absolute MBF and TPR, diagnostic classification was compared using Kappa statistics. Results were reported on a per-territory and per patient basis and in accordance with the STARD initiative (Standard

for Reporting Diagnostic accuracy) [19]. Most statistical analysis were made using SPSS (version 21, IBM Corp, Armonk NY, United States of America), while MedCalc (version 13.0; MedCalc Software, Ostend, Belgium) was used to compare the AUCs by using the method of DeLong et al [20].

RESULTS

53 patients were recruited, 10 patients were excluded of whom 8 due to a lack of invasive FFR measurements (Figure 1). Resulting in a study population consisting of 43 patients, in whom 94 vessels were analyzed by invasive FFR (Table 1). The mean FFR was 0.79±0.17, of which 48 vessels were considered hemodynamically significant with an FFR ≤0.80. The mean dose-length product for the CT-MPI acquisition was 640±135 mGy-cm, resulting in an effective dose of 9.0±1.9 mSv applying a conversion factor of 0.014.

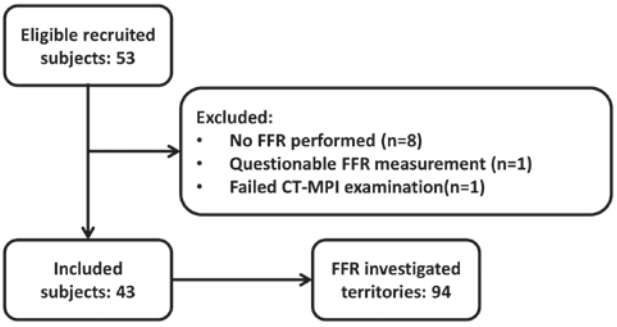

Figure 1. Inclusion flow chart

The mean MBF for FFR confirmed ischemic territories was 71.3±24.3 ml/100ml/min, and for normal territories 92.2±21.6 ml/100ml/min (Figure 3). Pearson correlation coefficient was 0.55 for MBF directly compared with invasive FFR. The area under the curve (AUC) was 0.78 (Figure 4). Optimal threshold for diagnostic classification was ≤76 ml/100ml/min. The territory based accuracy for MBF was 77% (67-86%) (Table 2).

The mean TPR for ischemic territories was 0.85±0.31 (Figure 3). Pearson correlation between TPR and invasive FFR was 0.37. The AUC for TPR was 0.65 and significantly smaller than MBF (P=0.026). The optimal threshold for diagnostic classification was ≤0.82 (Figure 4). The territory based accuracy of TPR was 70% (60-81%) (Table 2).

The AUC for the MBF and TRP combined was 0.71 significantly higher than TPR alone (P=0.032), the difference with MBF just failed to reach statistical significance (P= 0.070). To further investigate the incremental value of TPR a combined interpretation is shown in Figure 5. Concordance between MBF and TPR diagnostic classification was present in the majority of the territories (74%). For territories with concordant abnormal MBF and

Table 1. Patient Characteristics

Number of patients, *n*	43
Age (years)	62.6±8.7
Male gender, *n* (%)	36 (84)
Body mass index (kg/m^2)*	20.1±2.3
Body surface area (m^2)*	2.0±0.14
Cardiovascular risk factors, *n* (%)	
Hypertension	27 (63)
Dyslipidaemia	20 (47)
Diabetes	7 (16)
Family history of CAD	17 (40)
Smoking within the last year	10 (22)
Prior myocardial infarction, *n* (%)†	8 (19)
Prior PCI, *n* (%)†	5 (12)
Agatston coronary calcium score‡	628 (265-1450)
Heart rate during rest	63.4±12.9
Heart rate during hyperemic CT-MPI.	83.0±13.7

Values are reported as mean and ± standard deviation or absolute number *n* and percentage (%). CAD, coronary artery disease; PCI, percutaneous coronary intervention.
* In four patients length and weight data were not available.
† Not in the vessel territories interrogated by invasive FFR.
‡ Represented in median and (quartiles).

TPR a trend towards an increase positive predictive value was observed. A combined classification did not yield significant improvement in diagnostic accuracy, not for all territories, and neither for the territories with an intermediate MBF between 50-100 ml/100ml/min (Table 2).

The inter-observer variability for TPR was moderate to good with an intra-class correlation coefficient of 0.77 and a Kappa of 0.66. For MBF reproducibility was better with an intra-class correlation of 0.84 and a Kappa of 0.77.

Only three patients were scanned with a 3rd generation DSCT. Reanalysis after exclusion of these cases did not affect the results (data not shown).

DISCUSSION

The main findings of this study are 1) Transmural perfusion ratio from dynamic CT-MPI predicts functionally flow limiting CAD. 2) Transmural perfusion ratio based on dynamic CT-MPI myocardial blood flow maps is inferior to quantified myocardial blood flow.

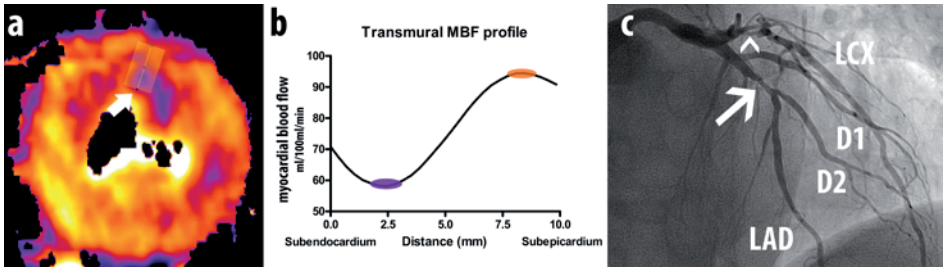

Figure 2. TPR case example: 65-years-old man presenting after exertional collapse. a) Short-axis CT-MPI image with the transmural perfusion line placed in the anterior-lateral segment. (white arrow). b) The transmural MBF profile. The subendocardial MBF was 58ml/100ml/min (purple marker), and 91ml/100ml/min in the subepicardium (orange marker). The TPR was 0.64 (58/91), and thus considered positive for ischemia. c) Invasive angiography showing a stenosis in the proximal LAD with an FFR of 0.69. A subtotal stenosis was directly stented in the LCX (arrow head), as such no FFR measurement was performed. In panel a however a perfusion defect with a transmural perfusion ratio can be seen in the territory associated with the LCX. The RCA was normal with an FFR of 0.91. RCA: right coronary artery, LAD: left anterior descending artery, LCX: left circumflex artery, TPR transmural perfusion ratio, MBF: myocardial blood flow, FFR: fractional flow reserve.

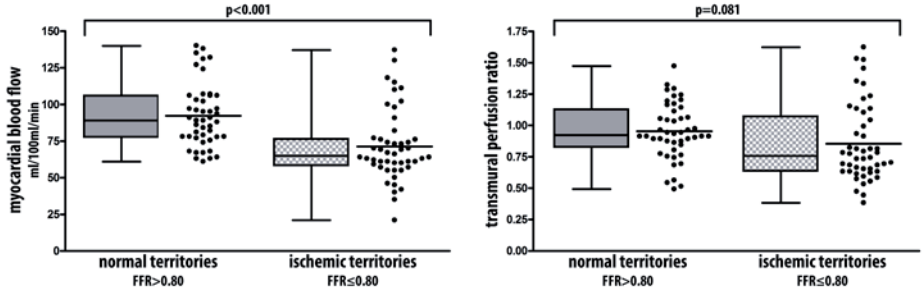

Figure 3. MBF and TPR: Median and mean myocardial blood flow and transmural perfusion ratio in 94 territories for normal (n=46) and ischemic (n=48) territories. Normal territory defined as invasive FFR >0.80, and ischemic territories as FFR ≤0.80. FFR: fractional flow reserve.

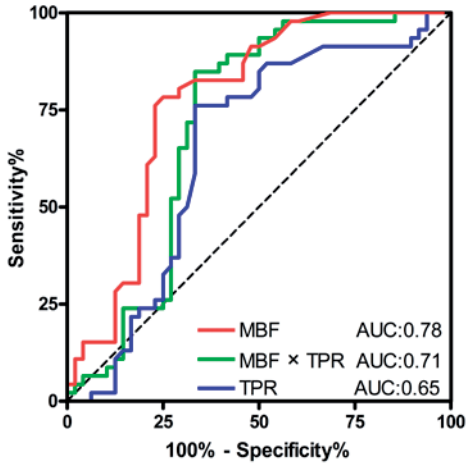

Figure 4. ROC: Receiver operator curves for MBF and TPR validated against FFR using a threshold of 0.80 for hemodynamically significance. Area under the curve for MBF was 0.78 (95% CI:0.67-0.87), for TPR 0.65 (95% CI:0.53-0.77), and for MBF×TPR 0.71 (95% CI:0.60-0.82) . The optimal diagnostic threshold was calculated at 76 ml/100ml/min for MBF and 0.82 for TPR. MBF: myocardial blood flow, TPR: transmural perfusion ratio, FFR fractional flow reserve, CI: confidence interval.

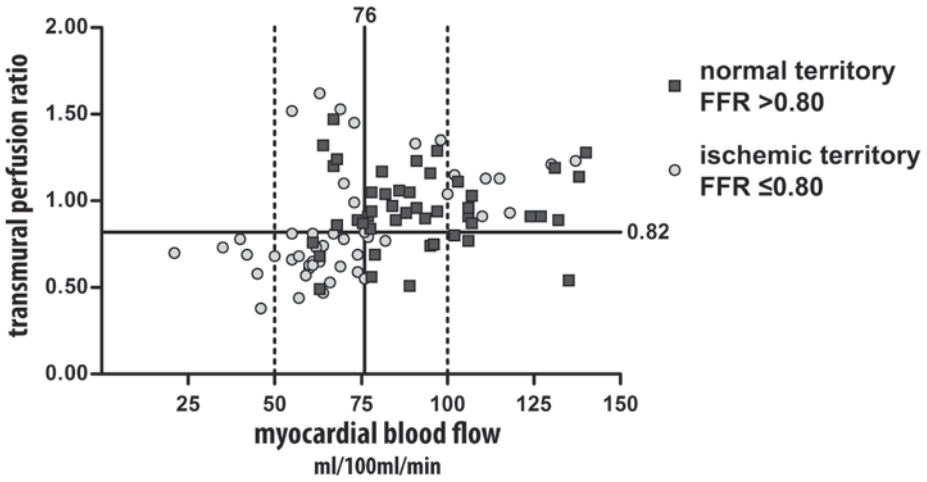

Figure 5. Classification by MBF and TPR: Scatterplot showing the combined classification by MBF and TPR. The solid lines represent the diagnostic threshold for MBF (76) and TPR (0.82). A larger proportion of ischemic territories was observed in the bottom left quarter, representing territories with a concordant abnormal MBF and TPR. The area between the two vertical dashed lines represent the territories with an intermediate MBF between 50 and 100 ml/100ml/min. TPR: transmural perfusion ratio, MBF: myocardial blood flow, FFR: fractional flow reserve.

The subendocardial layer is more susceptible for ischemia, which is thought to be due to a reduction in the diastolic perfusion time-interval, higher contractile intra-myocardial tissue pressures, and differences in coronary microvasculature [10; 21]. By comparing the subendocardial and subepicardial perfusion the susceptibility of the endocardium for ischemia can be used as a diagnostic criteria.

Barmeyer et al. found that subendocardial/subepicardial ratio using stress MRI perfusion was associated with functional CAD in comparison with coronary flow reserve, however measurements taken only in the subendocardial layer showed superior diagnostic performance [22]. Using oxygen positron emission tomography MPI a similar association between TPR and functional stenosis measurement was found, however similar to our study TPR was inferior to quantified myocardial perfusion measurements [23]. The high spatial resolution of CT is well suited for differentiating the myocardial layers, and identification of subendocardial perfusion differences. George et al. showed the potential of transmural perfusion ratio using static CT-MPI to detect ischemia, validated by a combination of quantitative angiography analysis and SPECT [11]. In another static CT-MPI study validated by SPECT a good diagnostic performance of a transmural perfusion gradient was found [24]. Ko et al. found static rest and stress CT-MPI assets visually was of incremental value to coronary CT angiography [25]. More recently Yang et al. published visual static CT-MPI assessment performed better than transmural perfusion

ratio, validated by FFR [26]. In these studies a segmental based TPR was calculated while for the epicardial layer the entire circumferential attenuation was averaged. In our study we used the epicardial myocardial blood flow at the location of the suspected perfusion defect. Because calculated MBF values vary between different regions of the heart, even in the absence of CAD, we compared the subendocardial MBF values against the adjutant subepicardial layer.

Several studies showed good diagnostic performance of dynamic CT-MPI to identify hemodynamically significant coronary artery disease compared with fractional flow reserve [6-8; 27]. A potential concern are the relative low absolute myocardial blood flow values computed with dynamic CT-MPI [5; 28; 29]. We hypothesized that a relative endocardial/epicardial perfusion ratio would be less vulnerable to individual variations in global MBF values and would be more sensitive in the identification of subtle perfusion defects.

This study shows that the transmural perfusion ratio identifies hemodynamically relevant coronary artery disease. However, no significant incremental value of TPR on top of MBF was found. In patients with an abnormal MBF, addition of TPR could reclassify a number of false positive results, however a statistical significant improvement could not be demonstrated in this modestly sized cohort. There are several possible explanations for the negative outcome in this study: The TPR methodology in this study is different from methods previously used in static CT-MPI. In dynamic CT-MPI the endocardial zone directly adjacent to the left ventricle cavity is prone to artifacts related to myocardial displacement, beam hardening and partial voluming potentially obscuring subtle perfusion defects. Future research related to improving MBF reconstruction in the endocardial layer adjacent to the ventricle cavity, is of importance as the endocardial layer is more susceptible to myocardial ischemia and perfusion imaging defects.[30]

Limitations

These results are based on a limited number of patients recruited over a relatively long period of time (4 years) from a single-center study. As a result of the study complexity, as well as logistic factors such as availability of researchers and competing competitive research, only a fraction of the potentially eligible patients were recruited in this study. While the non-consecutive enrolment was mostly based on these logistic factors, some degree of selection bias cannot be excluded. In a clinical setting CT-MPI will most likely be performed in conjunction with coronary CTA. However, this study focused on the diagnostic performance of CT-MPI specifically. As the diagnostic performance of dynamic CT-MPI using manual sampling of absolute MBF values is already good, a larger sample size might be needed to demonstrate an incremental value of other parameters. Motion correction algorithms were used if indicated, however especially around the edge of the MBF color-coded images myocardium displacement artifacts can still be present. In

several cases these artifacts result in high MBF values directly next to the left ventricle lumen. Even though care was taken to avoid these artifacts they may have negatively affected the performance of TPR. In this study preference was given to a robust, relatively user-independent transmural MBF profile curve as base for TPR. However, a more flexible freehand ROI in the endocardial and epicardial layer might affect TPR.

CONCLUSION

Transmural perfusion ratio measurements are feasible from dynamic CT-MPI and can identify functional obstructive CAD. Transmural perfusion ratio, as investigated in this study, from dynamic CT-MPI is inferior to and has limited incremental value on top of absolute myocardial blood flow measurements. In the future other myocardial flow parameters may be investigated to enhance the diagnostic performance of dynamic CT-MPI to identify myocardial ischemia.

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CHAPTER 7

Comprehensive Cardiac CT with Myocardial Perfusion Imaging versus Functional Testing in Suspected Coronary Artery Disease: the multicenter, randomized CRESCENT-II trial

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ABSTRACT

Objectives: To assess the effectiveness, efficiency and safety of a tiered, comprehensive cardiac CT protocol in comparison to functional-testing.

Background: While CT angiography accurately rules out coronary artery disease (CAD), incorporation of CT myocardial perfusion imaging as part of a tiered diagnostic approach could improve the clinical value and efficiency of cardiac CT in the diagnostic workup of patients with angina pectoris.

Methods: Between July 2013 and November 2015 268 patients (mean age 58 years; 49% female) with stable angina (mean pretest-probability 54%) were prospectively randomized between cardiac CT and standard guideline-directed functional-testing (95% exercise-ECG). The tiered cardiac CT protocol included a calcium scan, followed by CT-angiography if calcium was detected. Patients with ≥50% stenosis on CT-angiography underwent CT-myocardial perfusion imaging.

Results: By six months, the primary endpoint, the rate of invasive coronary angiograms without an ESC class-I indication for revascularization, was lower in the CT group than the functional-testing group (2/130 (1.5%) vs. 10/138 (7.2%), p=0.035), while the proportion of invasive angiograms with a revascularization indication was higher (88% vs 50%, p=0.017). The median duration until the final diagnosis was 0(0;0) days in the CT group and 0(0;17) in the functional-testing group (p<0.001). Overall, 13% of patients randomized to CT required further testing, compared to 37% in the functional-testing group (p<0.001). The adverse event rate was similar (3% vs 3%, p=1.000), though the median cumulative radiation dose was higher for the CT group (3.1mSv [IQR: 1.6;7.8] vs 0mSv [0;7.1], p<0.001).

Conclusions: In patients with suspected stable CAD, a tiered cardiac CT protocol with dynamic perfusion imaging offers a fast and efficient alternative to functional-testing.

Clinical Trial: US National Institutes of Health (ClinicalTrials.gov): NCT02291484

INTRODUCTION

Coronary computed tomography angiography (1) has become an established, reliable diagnostic test in the management of coronary artery disease (CAD). Two large randomized studies demonstrated that coronary CTA performs at least equally well as functional tests for the evaluation of stable angina(2,3). In the CRESCENT-I trial we found that incorporation of a calcium scan in a tiered CT strategy is safe and effective(4). Although coronary CTA effectively rules out coronary disease, it is limited in its ability to assess the hemodynamic importance of angiographic lesions. Because anatomical lesion severity is a poor predictor of hemodynamic significance, functional evaluation of intermediate stenoses is recommended for therapeutic decision-making(5,6). The performance of myocardial perfusion imaging (MPI) by CT has been validated in a large number of studies(6-11). A comprehensive cardiac CT examination, combining CTA and CT-MPI, could provide all essential information for clinical decision-making in CAD, and avoid invasive coronary angiography (ICA) in patients without hemodynamically significant CAD(7-9,12).

In the Comprehensive Cardiac CT versus Exercise Testing in Suspected Coronary Artery Disease (CRESCENT-II) randomized-controlled trial we assessed the effectiveness, efficiency and safety of a tiered cardiac CT protocol, consisting of a calcium scan with selective performance of CTA and CT-MPI, in comparison to functional-testing.

METHODS

Study design

The CRESCENT-II trial is a pragmatic randomized-controlled trial comparing the effectiveness, efficiency and safety of a comprehensive, tiered cardiac CT approach with a standard diagnostic workup using functional-testing. At four hospitals in the Netherlands, 268 patients referred with stable chest pain and suspected CAD were prospectively enrolled. Medical ethics committees at each of the sites approved the study. The CRESCENT-II trial is registered at the US National Institutes of Health (ClinicalTrials.gov): NCT02291484.

Study participants

Patients ≥18 years with chest pain symptoms suspicious of obstructive CAD, and CAD probability >10% were study eligible(13). Exclusion criteria were prior myocardial infarction or revascularization procedure, renal failure (eGFR<60ml/min/1.73m^2), iodine allergy, contra-indications to adenosine or known pregnancy.

Study procedures

After an outpatient clinic assessment, participants provided written informed consent and were randomly assigned to either the CT group or the functional-testing group. All participants filled out the Seattle Angina Questionnaire(SAQ), EuroQol-5D-5L(EQ-5D) and Short-Form-36(SF-36) for quality-of-life assessment, and a cost questionnaire. All testing was performed at the recruiting center. For ascertainment of trial endpoints at six months, results of downstream diagnostic and therapeutic procedures were collected from the medical records, and patients completed again the questionnaires for ascertainment of angina complaints, quality of life and health status.

Cardiac CT strategy

In the CT group all patients first underwent a non-contrast-enhanced calcium scan (Somatom Definition Flash and Force, Siemens Healthineers, Forchheim, Germany). In patients with a low-intermediate probability of CAD (10-80% by Diamond and Forrester) (13), the absence of calcium excluded obstructive CAD and obviated the need for further testing. Patients with a zero calcium score but >80% pre-test probability, and all patients with a positive calcium score (>0) underwent contrast-enhanced coronary CTA.

All patients received sublingual nitroglycerin before CTA studies. If indicated (HR>65/min) and clinically acceptable, beta-blockers were administrated. The prospective electrocardiographically triggered axial scan mode was used, with an exposure window during diastole and/or systole depending on the heart rate. Tube current and tube voltage were selected semi-automatically on the basis of body size. A test bolus acquisition was performed using 15-ml of contrast medium followed by a 40-ml saline chaser. For the CT angiogram, a contrast bolus of 50-60 ml (depending on iodine concentration) was injected to achieve an iodine delivery rate of 2.2-g/s, followed by a 40-ml saline bolus chaser. Images were reconstructed with a medium-smooth kernel (B26, Bv40), slice thickness of 0.5-mm, and an increment of 0.3-mm. The CTA was immediately assessed, and all patients with >50% stenosis underwent an adenosine-stress dynamic myocardial perfusion CT scan (CT-MPI) during the same session. All recruiting sites had previous cardiac CT experience.

Dynamic CT myocardial perfusion imaging

Detailed descriptions of the dynamic myocardial perfusion imaging protocol were published previously (8,11). In brief, CT perfusion started 10 minutes after CTA for washout of contrast media. Myocardial hyperemia was achieved by adenosine infusion (≥3 minutes, 140µg/kg/min) over a second venflon. To avoid interference with adenosine patients abstained from caffeine-containing beverages 24-hours prior to their appointment. A 50-ml contrast bolus (Ultravist, 370mgI/ml; Bayer, Germany) and 40 ml saline were injected at 6ml/s. Using an alternating table positions (shuttle mode) for complete

myocardial coverage, systolic images were acquired every second heart cycle while the patient maintained a 35-s inspiratory breath hold.

The following scan parameters were used for the second-generation dual-source scanner: 2×64×0.6-mm collimation, 280-ms gantry rotation time, 75-ms temporal resolution, 100-kV and 300-mA or 80-kV and 370-mA tube voltage and current per rotation, and shuttle-mode with 73-mm total z-axis coverage; for the third-generation dual-source scanner: 2×96×0.6-mm collimation, 250-ms gantry rotation time, 66-ms temporal resolution, 80-kV tube voltage and 300-mA current (Care-kV as a reference), and 102-mm shuttle-mode z-axis coverage.

From a series of 12-15 consecutive datasets, myocardial attenuation was plotted against time. A parametric deconvolution technique based on a 2-compartment model was used to fit the time-attenuation curves (Volume Perfusion CT body, Siemens). Myocardial blood flow (MBF, ml/100ml/min) was computed by dividing the convoluted maximal slope of the myocardial time-attenuation curve by the maximum arterial input function (aorta). By calculating MBF on a per-voxel basis, 3D-MBF maps were reconstructed with a slice thickness of 3.0-mm and an increment of 1.5-mm, which were used for interpretation of hypoperfusion in relation to angiographic obstructions (figure 1). Patients without (substantial) myocardial ischemia were treated medically. Patients with substantial myocardial ischemia (visually ≥10% LV) were referred for invasive angiography, in accordance with international guidelines(5).

Functional test strategy

The functional-testing strategy was selected by the treating physicians in accordance with international guidelines(5). Most underwent a symptom-limited exercise-ECG, with a target heart rate defined as 85% of the age-defined maximum-predicted heart rate. The main diagnostic ECG criterion for ischemia consists of a horizontal or down-sloping ST-segment depression ≥0.1mV, persisting for at least 0.06–0.08s after the J-point, in one or more ECG leads. SPECT MPI or stress echocardiography were performed in case of contraindications to exercise-ECG, or non-interpretable or equivocal results. Criteria for the presence of ischemia were reversible perfusion defects on SPECT MPI (≥10% ischemia, based on a segment difference score of 7 or higher) or the presence of new wall motion abnormalities on echocardiography. All functional imaging tests were interpreted for the presence of inducible ischemia and risk of adverse outcome, applying established criteria for each respective test (14,15).

Interpretation of CT and functional test results, using all available clinical data, as well as subsequent clinical management decisions, were performed by local physicians. Patients considered to be at high risk based on test results and clinical interpretation, or those with refractory symptoms despite optimal medical treatment, were generally referred to invasive coronary angiography.

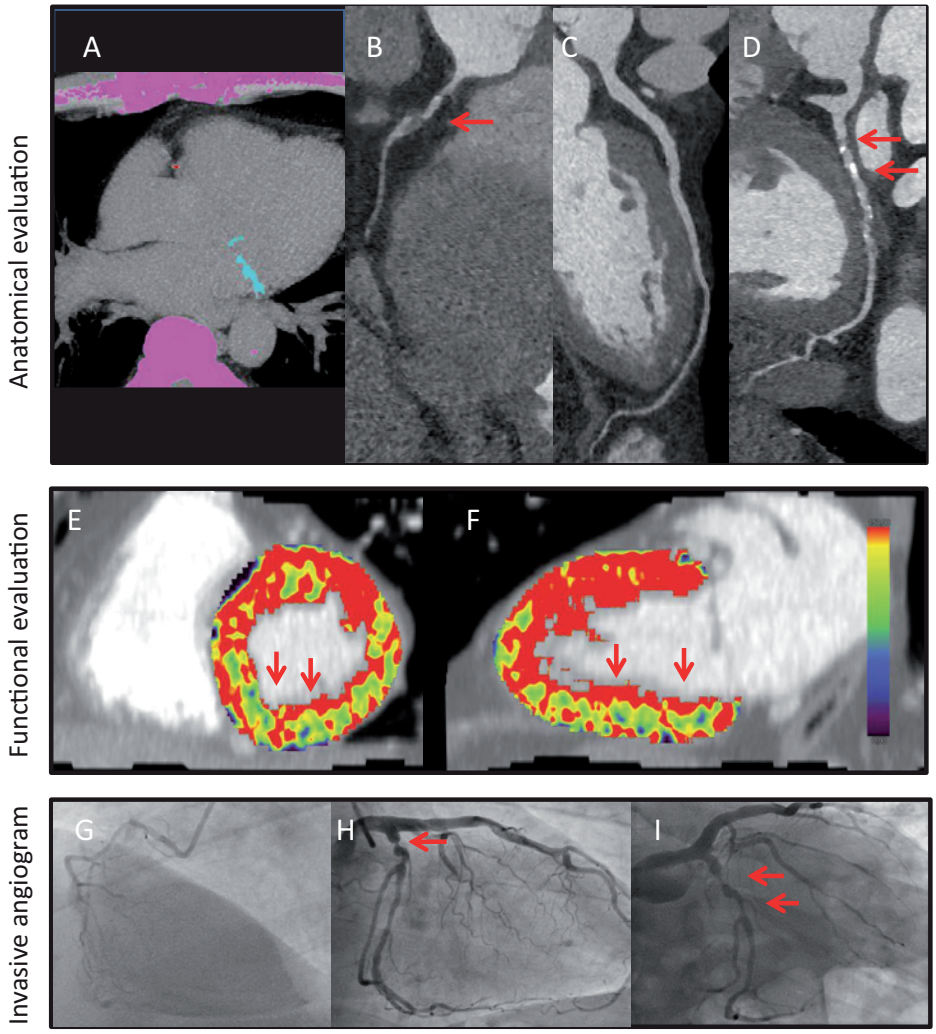

Figure 1. Case example of the comprehensive cardiac CT protocol. 52-years-old man with atypical angina, randomized to cardiac CT. Agatston score: 338.6 (A). CT-angiography: diffuse narrowing (50-70%) in the proximal, small RCA (arrow)(B), normal LAD (C), two 50-70% stenoses in the Cx(D). CT-MPI: low myocardial blood flow (0.55-0.73ml/min/g) in inferior wall (green-blue, arrows)(E,F). Invasive angiography: confirmed Cx lesions (H-I) were percutaneously treated(H-I), RCA regarded too small for revascularization(G).

Outcomes

The primary outcome was the *negative invasive angiography rate*, defined as the number of angiograms without a class I indication for revascularization based on ESC guidelines(16), as a proportion of the total number of patients. Class I indication for revascularization were: left main >50% with objective ischemia, proximal LAD >50% with ischemia, two or three-vessel disease with impaired LV function and ischemia, proven

large area of ischemia (>10% LV), >50% stenosis with limiting angina unresponsive to optimal medical treatment(16). An external, independent reviewer reassessed revascularization criteria, irrespective of clinical decisions by the treating physician.

Pre-specified secondary outcomes included the *positive yield of invasive coronary angiography*: proportion of invasive angiograms leading to a class I revascularization indication. Clinical effectiveness was defined by persistent or recurrent *anginal symptoms* and quality of life at 6 months. Efficiency outcomes included *time to diagnosis* from first outpatient visit until the first test that led to the final diagnosis, or the final test that ruled out obstructive CAD. *Downstream testing* included all non-invasive tests and invasive angiography to diagnose CAD after the initial test. *Diagnostic costs* included all tests to diagnose CAD over the first six months. Costs per test were based on previously published cost analyses(17).

Major adverse events included death, non-fatal myocardial infarction, unstable angina, urgent revascularization and stroke. For the survival analysis, events were counted once for each patient in the hierarchical order listed above. The *cumulative effective radiation dose* (mSv) included all tests and interventions applying radiation. For cardiac CT a conversion factor of 0.017 was used. For SPECT and invasive angiography conversion factors of 0.0085mSv/millibecquerel and 0.24mSv/Gy*cm^2 were used(18,19).

Statistical analyses

Based on registry data, an angiography without class I indication for revascularization rate of 1.2% in the CT group and 10.9% in the control group were predicted(20). For 80% power at a two-sided p-value of 0.05 at least 250 patients were required to detect a similar difference in invasive angiograms without a class I revascularization indication. Continuous data are presented as means±SD or medians with interquartile ranges. Groups were compared by independent-sample t-test or Mann-Whitney U-test for continuous variables, and chi-square or Fisher's exact-test for categorical variables. The invasive angiography without class I indication for revascularization rate was compared using a Fisher exact test. The event-free survival probability was estimated by Kaplan-Meier survival analysis and log-rank statistic. A Cox-proportional hazards model was employed to estimate the relative hazard of events by randomized test strategy, deriving hazard ratios and 95% confidence intervals (CIs). A two-sided p-value of <0.05 was considered statistically significant. Statistical analyses were performed using SPSS (version 21, IBM Corp, Armonk NY, USA), according to the intention-to-treat principle.

RESULTS

Study population

Between July 2013 and November 2015, out of 352 potential candidates 268 patients (age 58±11years, 49% women) could be enrolled and randomized between cardiac CT (138) and functional-testing (138) (table 1; figure 2). All patients were included in the intention-to-treat analysis. Pre-test CAD probability was 54±30% based on Diamond&Forrester(13). Invasive angiography demonstrated >50% CAD in 28 patients (8%). At 6-months follow-up original records of hospital visits and events were available in 266 of 268 (99%) patients.

Table 1. Patient characteristics

	Cardiac CT (n=130)	**Functional testing (n=138)**
Mean age (years)	58±11	58±11
Female sex (%)	49	56
Systolic/diastolic blood pressure (mmHg)	136±19/84±11	137±18/83±9
Median body-mass index	28±5	28±5
History (%)		
Transient ischemic attack or stroke	6	7
Peripheral artery disease	2	4
Cardiac risk factors (%)		
Current or past smoker	33	42
Hypertension	52	52
Dyslipidemia	38	40
Diabetes mellitus	18	18
Family history of ischemic heart disease	36	38
Presenting chest pain symptoms (%)		
Typical angina	38	36
Atypical angina	45	51
Non-anginal complaints	18	14
Pre-test probability – Diamond&Forrester (%)(13)	56±30	53±30

Patient characteristics as mean±SD, percentage, or median and interquartile range. No significant differences between both groups. Hypertension: systolic >150mmHg, diastolic >90mmHg, or medication. Dyslipidemia: total cholesterol>5mmol/L, low-density lipoprotein>3mmol/L, or medication. Diabetes mellitus: plasma glucose>11.0mmol/L, or medication.

Test results

In the functional-testing group the first test was exercise-ECG in 131 (95%) and nuclear imaging in 7 patients (5%), with a result interpreted as positive in 12 (9%), negative in 77 (56%), inconclusive in 47/138 (34%), while 2 patients did not undergo their scheduled

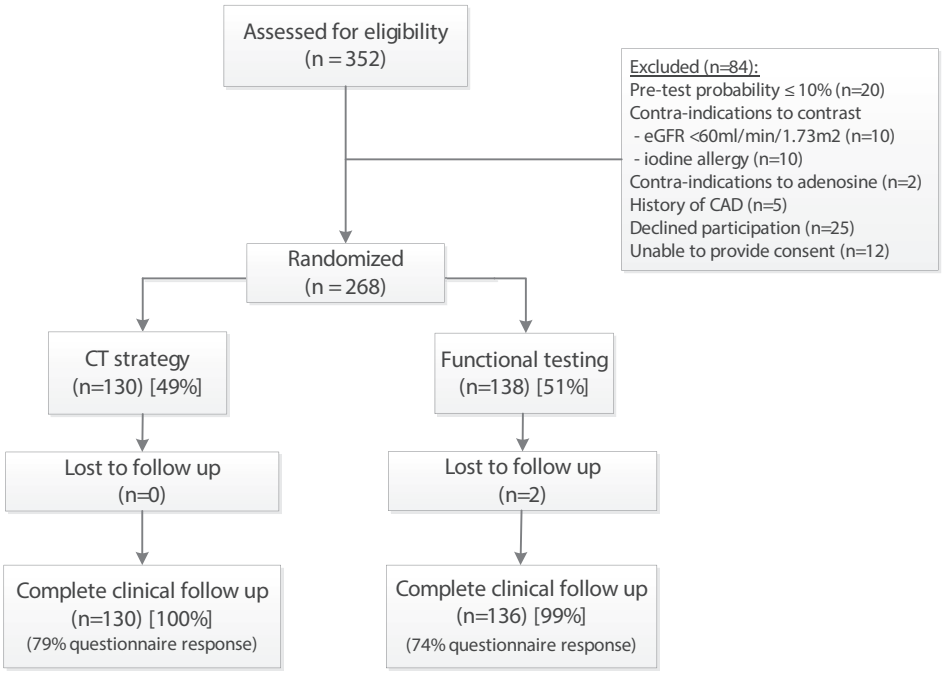

Figure 2. Enrolment, randomization, follow-up. Patient flow diagram with disposition by randomized arm. Complete clinical follow-up: clinical events at 6-months. Questionnaire response at 6 months: SAQ, EQ-5D and SF-36 questionnaires.

examination. Additional testing, and multiple tests in some patients, included: SPECT-MPI (n=24), stress echocardiography (n=4), cardiac CT (n=11), exercise-ECG (n=1) and invasive angiography (n=20)(figure 3). Of 20 patients undergoing invasive angiograms, 10 required revascularization.

In the CT group, the median calcium score was 5 (0-146), and 50 (39%) patients had no detectable calcium. CT-angiography was performed in 79 (61%) patients with a positive calcium scan, and 5 patients with a zero calcium score but >80% pre-test probability. Out of 29 patients with >50% stenosis, 19 (66%) showed myocardial ischemia on perfusion imaging (figure 3). Concordant ischemia was demonstrated by CT-MPI in 7/12 (58%) vessels of patients with three-vessel disease (n=4), 3/4 (75%) with left main or proximal left anterior descending coronary disease, and 13/25 (52%) vessels of patients with other one- or two-vessel disease (n=21) by CT-angiography. Concordant ischemia was demonstrated by CT-MPI in 11/12 (92%) patients with >70% maximum stenosis and 8/17 (47%) patients with 50-70% maximum stenosis by CT angiography. Of 19 patients with myocardial ischemia, 14 underwent invasive angiography, and 13 were revascularized. Two patients with a normal CT-MPI later underwent PCI because of insufficient symptomatic relief, one in the setting of unstable angina.

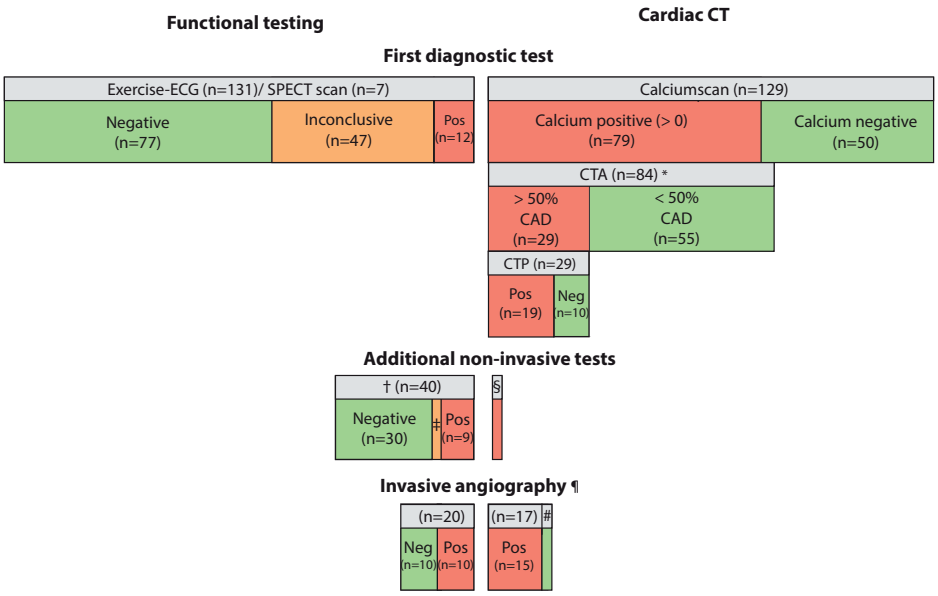

Figure 3. Flowchart of diagnostic testing. Flowchart showing the first and additional diagnostic tests and their outcome, per randomization arm.
* Including 5 patients without calcium but high pretest probability
(>80 by Diamond & Forrester).
† SPECT-MPI (n=24), CTA (n=11), stress echocardiography (n=4), exercise-ECG (n=1).
‡ Inconclusive SPECT-MPI scan (n=1).
§ Positive SPECT-MPI (n=1).
¶ Independent review of class I indication for revascularization, based on the 2010 ESC guidelines.
# Invasive angiography without class I indication for revascularization (n=2).

Table 2. Diagnostic yield of invasive angiography

	Cardiac CT (n=130)	Functional testing (n=138)	p-value
Invasive angiograms	17 (13.1%)	20 (14.5%)	0.860
Class I indication for revascularization[1]	15 (11.5%)	10 (7.2%)	0.294
Left main >50% with objective ischemia	1	1	
Proximal LAD >50% with ischemia	4	0	
2 or 3-vessel disease with impaired LV function and ischemia	1	2	
Proven large area of ischemia (≥10% of LV)	6	2	
Any stenosis >50% with limiting anginal symptoms unresponsive to OMT	3	5	
Without class I indication	2	10	0.035
Positive diagnostic yield of invasive angiography	15/17 (88.2%)	10/20 (50.0%)	0.017

1. Cardiac catheterizations with class I indication for revascularization(16). OMT: optimal medical treatment

Diagnostic effectiveness

Fewer invasive angiograms without class I indication for revascularization were observed in the CT group (2/130, 1.5%), compared to the functional-testing group (10/138, 7.2%, p=0.035)(table 2). At a comparable rate of invasive angiograms (p=0.860), the positive yield was higher after CT (15/17, 88%), compared to functional-testing (10/20, 50%; p=0.017). The independently assigned class I revascularization indications were concordant with the clinically performed revascularization procedures.

Diagnostic efficiency

In both groups the majority of patients reached the final clinical diagnosis the same day at the outpatient clinic, though most frequently in the cardiac CT group (87% vs. 64% of functional-testing group, p<0.001)(figure 4). Further testing was needed in 13% of patients randomized to CT, compared to 37% after functional-testing (p<0.001)(figure 5). Although index testing costs were higher for CT, the mean cumulative diagnostic expenses were comparable for CT €435 [range: €64- €2439] and functional-testing €450 [range: €106- €2015] (p=0.827).

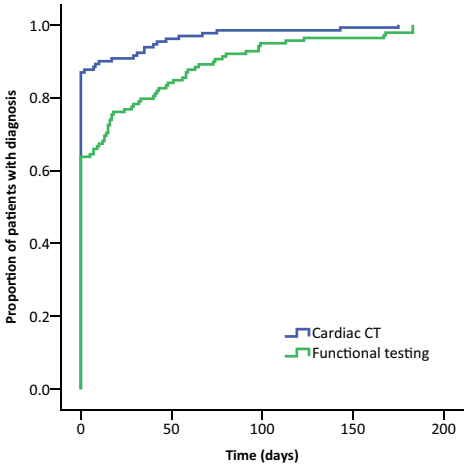

Figure 4. Time to diagnosis. Proportion of patients with a diagnosis plotted against time. P<0.001.

Anginal symptoms and quality of life

After six months 38% of patients in the CT group reported absent anginal symptoms, in comparison to 28% in the functional-testing group (p=0.118). In both groups comparable improvements in SAQ-subscales were observed (appendix 1). Quality-of-life improvement by EQ-5D-questionnaire did not differ (p=0.245)(appendix 2). The improvement in QoL-VAS scale for CT was from 66.8 to 73.7 (p<0.001) compared to 68.9 to 72.4 (p=0.042) for functional testing, this numerical difference failed to reach statistical significance (p=0.168)(appendix 3).

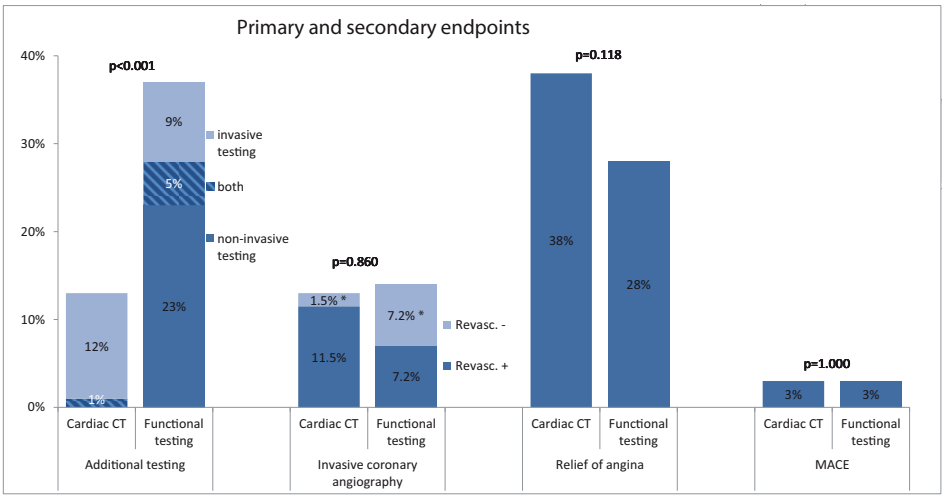

Figure 5. Primary and secondary outcomes. Additional tests after the first diagnostic test, divided into non-invasive, invasive or both. Invasive angiography: followed by revascularization (+), or no revascularization (-). Angiography without class I indication for revascularization rate was the primary endpoint and was significantly different (*) between CT and functional testing (1.5% vs 7.5%, p=0.035). Relief of angina at 6 months. MACE: death, myocardial infarction and stroke.

Safety

After an average follow up of 250±95 days (8±3 months) three non-cardiac deaths, four nonfatal infarctions, and one case of unstable angina requiring revascularization, were observed in 266 patients (CT 4 vs. functional 4 events, p=1.000). Event-free survival was similar (CT 96.9% vs. functional 97.1%, p=0.929) with an adverse event hazard ratio of 1.07 (95%CI 0.27-4.26) for CT compared to standard care (p=0.929).

No adverse events occurred in the 45 patients (35%) in whom CAD was ruled out based on a zero calcium score. One patient later presented with acute chest pain and ECG changes, though biomarkers were negative and invasive angiography revealed no abnormalities. Amongst the five patients without calcium, but >80% pre-test probability, CT-angiography revealed single-vessel CAD with ischemia on CT-MPI in one case.

In the functional-test group only 51 patients (37%) were exposed to radiation, which resulted in a lower median cumulative dose (CT 3.1mSv [1.6;7.8] vs 0mSv [0;7.1], p<0.001). The mean dose of the cardiac CT exam was 5.6±6.3mSv. The mean dose was 1.3±0.7mSv for the calcium scan, 3.5±3.0mSv for CT-angiography, and 10.6±6.3mSv for CT-MPI.

DISCUSSION

In this multicenter randomized clinical trial, a comprehensive cardiac CT examination that involved a stepwise performance of a calcium scan, CT-angiography and CT myocardial perfusion imaging, was compared to the current standard of functional-testing for suspected CAD. The main findings are that a tiered cardiac CT protocol improves the efficiency of invasive angiography without increasing overall catheterization rates. The combined CT protocol achieved a diagnosis faster, and removed the need for additional noninvasive testing.

Diagnostic management of stable angina

While there are many noninvasive techniques for diagnosing CAD, the low diagnostic yield of invasive angiography suggests lack of effectiveness by current diagnostic practices(21). Although stress imaging is more sensitive to the detection of angiographic CAD, without evident clinical outcome benefit(22), the ACC/AHA guidelines maintain exercise ECG as the first-choice test in suitable patients with a low-intermediate CAD probability(23). CT-angiography is a relatively new diagnostic option with a high sensitivity for the detection of CAD. In a very large cohort the PROMISE trial demonstrated equivalent clinical outcome for CT-angiography and stress testing(2). Meta-analyses, however, indicate that CT-angiography may increase catheterization and revascularization rates, of which clinical benefit remains yet unproven(24,25). Functional tests can differentiate patients more likely to benefit from revascularization, although the prospective evidence for this is stronger for fractional flow reserve than noninvasive functional tests. In SCOT-HEART, which demonstrated improved outcome from CT-angiography, cardiac CT was combined with an exercise ECG in the majority of patients(3,26). This supports the idea that both anatomical and functional information are required for therapeutic decisions that affect clinical outcome. Another observation from these trials is the low, but often overestimated CAD prevalence, as well as a low adverse event rate in real-world populations with stable chest pain(2-4), fueling a paradoxical debate on the value of extensive testing in low-risk populations(27).

Comprehensive cardiac CT protocol

The objective of the CRESCENT-II trial was to test a tiered comprehensive cardiac CT protocol that would allow safe rule-out of CAD by relatively simple means, while at the same time incorporating functional measures of CAD for well-informed decisions and avoidance of premature invasive procedures. Calcium imaging in symptomatic patients is controversial due to the possibility of non-calcified obstructions. Supported by CONFIRM and other registries in real-world populations(28-32), and the low CAD prevalence in recent trials (2-4), we concluded that triage by calcium imaging in lower-risk patients

would be a safe opportunity to reduce radiation exposure and save resources. Similar to CRESCENT the present study suggest an uneventful intermediate-term outcome when CAD is excluded based on a negative calcium scan(4). Restriction to patients with detectable calcium or a high CAD probability increased the positive yield of CT-angiography to more than a third.

While there are multiple more established stress imaging techniques, CT-MPI may have practical advantages, as it can be performed in conjunction with CT-angiography, and allows for a comprehensive assessment of anatomy and function. Contrary to CRESCENT(4), the addition of CT-MPI virtually removed the need for a separate functional test after CT (1% in CRESCENT-II vs 16% in CRESCENT).

Overall, cardiac CT increased the diagnostic yield of invasive angiography (88% vs 50%, p=0.017), but without affecting the overall catheterization rate. All except one patients referred for invasive angiography after a positive CT-angiogram and CT-MPI (19/29) required revascularization. CRESCENT-II was not large enough to assess differences in adverse events, or in a statistically significant manner reproduce the symptomatic relief after CT, as observed in the previous trial(4).

While anatomical imaging as the first step appears to be most efficient in our cohort with a low prevalence of CAD and no history of CAD, this may be different in population with a history or truly high prevalence of CAD.

Safety

The use of contemporary CT technology, and restricting CT-MPI to the highest-risk patients, resulted in a median overall effective dose of 3.1mSv (including diagnostic tests after cardiac CT), compared to a median cumulative dose of 10.0mSv in PROMISE, and a 4.1mSv median dose for CT-angiography alone in SCOT-HEART.

In patients with a low CAD probability, often younger and female, calcium imaging and new CT technology lowered doses in those most vulnerable to radiation exposure. However, radiation exposure was lowest in the functional-testing group, of whom most underwent exercise testing without nuclear imaging.

Future outlook

As scanner and data processing technology further develop, the comfort of use and radiation exposure of dynamic CT-MPI will likely improve. Apart from dynamic CT-MPI, and well-known established functional modalities, several other CT-based functional assessment techniques have emerged. Static myocardial perfusion imaging (7,12,33), potentially with dual-energy protocols, or hybrid systems that combine CT with PET or SPECT, also offer functional interpretation in conjunction with CT-angiography. CTA based FFR (CT-FFR) computes coronary flow parameters from conventional CT angiograms(34,35). While CT-FFR is not a direct physiological measurement, and relies on

sufficient CT quality, the lack of additional testing and radiation exposure are obvious advantages. The PLATFORM study demonstrated how CTA combined with CT-FFR can improve the diagnostic yield of invasive angiography(36). The few direct comparisons published to date suggest a comparable and partially complementary performance of CT-MPI and CT-FFR (37-39).

Limitations

Although this study allowed several relevant observations, the cohort size does not permit conclusive results in terms of clinical outcome. Similar to other pragmatic diagnostic trials, the CRESCENT-II trial did not apply a predefined management protocol. While blinding of caregivers and patients was not possible, participants were treated by multiple physicians without direct involvement in the study. We designed a specific CT algorithm, and compared performance with a control group that mostly underwent exercise ECG. While the use of exercise ECG is supported by guidelines and part of standard practice in many parts of the world, extrapolation of the results may not be possible to settings with substantially different diagnostic as well as therapeutic practices. More stress imaging would be expected to improve diagnostic accuracy, but could also increase cost(22). Although dynamic CT-MPI was validated in multiple studies, the technique requires specific CT equipment and is not yet widely practices. Implementation of the tiered algorithm requires scheduling flexibility and immediate reading, which can pose practical challenges.

CONCLUSION

In patients with stable angina and a typically low CAD prevalence the challenge is to accurately rule out CAD in the majority by relative simple means, while comprehensively assessing those who may benefit from revascularization. A tiered, comprehensive cardiac CT protocol, including dynamic perfusion imaging, appears to be a fast and efficient alternative to standard functional-testing in these patients.

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ROLE OF THE FUNDER/SPONSOR

The funder had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

CONFLICT OF INTEREST

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Appendix 1. Seattle Angina Questionnaire results

	Cardiac CT		
	Baseline	**Follow-up**	**p-value**
Physical limitations	71.8 ± 23.2	81.4 ± 21.9	<0.001
Angina stability	49.2 ± 27.5	77.6 ± 23.9	<0.001
Anginal frequency	71.9 ± 13.9	90.5 ± 12.0	<0.001
Treatment satisfaction	81.9 ± 15.4	81.2 ± 16.2	0.720
Quality of life	55.8 ± 29.6	77.5 ± 28.2	<0.001
Total SAQ	324.8 ±403.7	403.7 ±78.1	<0.001

	Functional testing		
	Baseline	**Follow-up**	**p-value**
Physical limitations	67.9 ± 26.3	78.4 ± 23.0	<0.001
Angina stability	47.2 ± 24.3	71.2 ± 23.9	<0.001
Anginal frequency	71.7 ± 17.4	87.4 ± 13.6	<0.001
Treatment satisfaction	78.4 ± 18.9	75.9 ± 17.1	0.245
Quality of life	55.4 ± 26.9	73.3 ± 26.4	<0.001
Total SAQ	317.1 ± 78.0	378.0 ±83.3	<0.001

	Improvement from baseline to follow-up		
	Cardiac CT	**Functional testing**	**p-value**
Physical limitations	9.6 ± 23.2	10.5 ±24.3	0.782
Angina stability	28.4 ± 32.0	24.0 ±30.2	0.325
Anginal frequency	18.6 ± 15.4	15.7 ±18.8	0.225
Treatment satisfaction	-0.7 ± 19.6	-2.4 ±21.5	0.538
Quality of life	21.7 ± 31.9	17.9 ±28.7	0.373
Total SAQ	78.9 ± 81.5	60.9 ±87.0	0.121

SAQ results and subgroups at baseline and six months follow-up. The Seattle angina questionnaire consists of 17 questions. For every question points can be scored on an incremental scale from 0-100. Every question contributes to one of the five SAQ-subscales. Scores are shown as means ±SD. A higher score indicates better angina health state.

Appendix 2. EQ-5D results

	Cardiac CT		
	BL	**FU**	**p-value**
Total EQ-5D score	0.711±0.243	0.818± 0.134	<0.001
VAS scale	66.8±16.9	73.7±13.6	<0.001

	Functional testing		
	BL	**FU**	**p-value**
Total EQ-5D score	0.736±0.213	0.805±0.165	0.003
VAS scale	68.9±17.7	72.4±15.5	0.042

	Improvement		
	CT	**FT**	**p-value**
Total EQ-5D score	0.107±0.240	0.069±0.223	0.245
VAS scale	6.8±16.6	3.5±16.9	0.168

Total EQ-5D quality of life score at baseline (BL) and 6-months follow up (FU). The EQ-5D questionnaire consists of 5 questions, questioning problems with mobility, self-care, usual activities, pain and anxiety. Combined this creates the total EQ-5D score between 0 (worst QoL) and 1 (best QoL). The last question is the VAS scale, it is the respondent's self-rated health on a vertical, visual analog scale where the endpoints are labelled best and worst imaginable health state, ranging from 0-100. A higher score indicates a better health state. Scores are shown as means ± SD.

Appendix 3. Short Form 36 results

	Cardiac CT		
	BL	**FU**	**p-value**
Physical functioning	653 ± 238	756 ± 229	<0.001
Role limitations due to physical health	211 ± 178	275 ± 169	0.001
Role limitations due to emotional problems	214 ± 122	223 ± 115	0.499
Energy/fatigue	203 ± 78	237 ± 77	<0.001
Emotional well being	351 ± 90	369 ± 90	0.038
Social functioning	111 ± 23	105 ± 20	0.046
Pain	122 ± 41	151 ± 45	<0.001
General health	197 ± 60	211 ± 70	0.079

	Functional testing		
	BL	**FU**	**p-value**
Physical functioning	634 ± 242	708 ± 242	0.001
Role limitations due to physical health	221 ± 173	266 ± 168	0.002
Role limitations due to emotional problems	191 ± 128	215 ± 127	0.070
Energy/fatigue	210 ± 77	223 ± 75	0.090
Emotional well being	352 ± 84	356 ± 95	0.665
Social functioning	108 ± 24	110 ± 24	0.659
Pain	125 ± 42	149 ± 45	<0.001
General health	208 ± 67	221 ± 73	0.154

	Improvement		
	CT	**FT**	**p-value**
Physical functioning	103 ± 211	75 ± 222	0.365
Role limitations due to physical health	64 ± 180	45 ± 138	0.426
Role limitations due to emotional problems	9 ± 133	25 ± 133	0.412
Energy/fatigue	34 ± 81	12 ± 70	0.052
Emotional well being	18 ± 86	4 ± 81	0.227
Social functioning	- 6 ± 29	2 ± 35	0.108
Pain	29 ± 48	23 ± 51	0.449
General health	14 ± 77	13 ± 86	0.225

SF-36 quality of life scores at baseline (BL) and 6-months follow up (FU). SF-36 quality-of-life questionnaire subdivided into eight subscales. A higher score indicates a better health state. Scores are shown as means ± SD.

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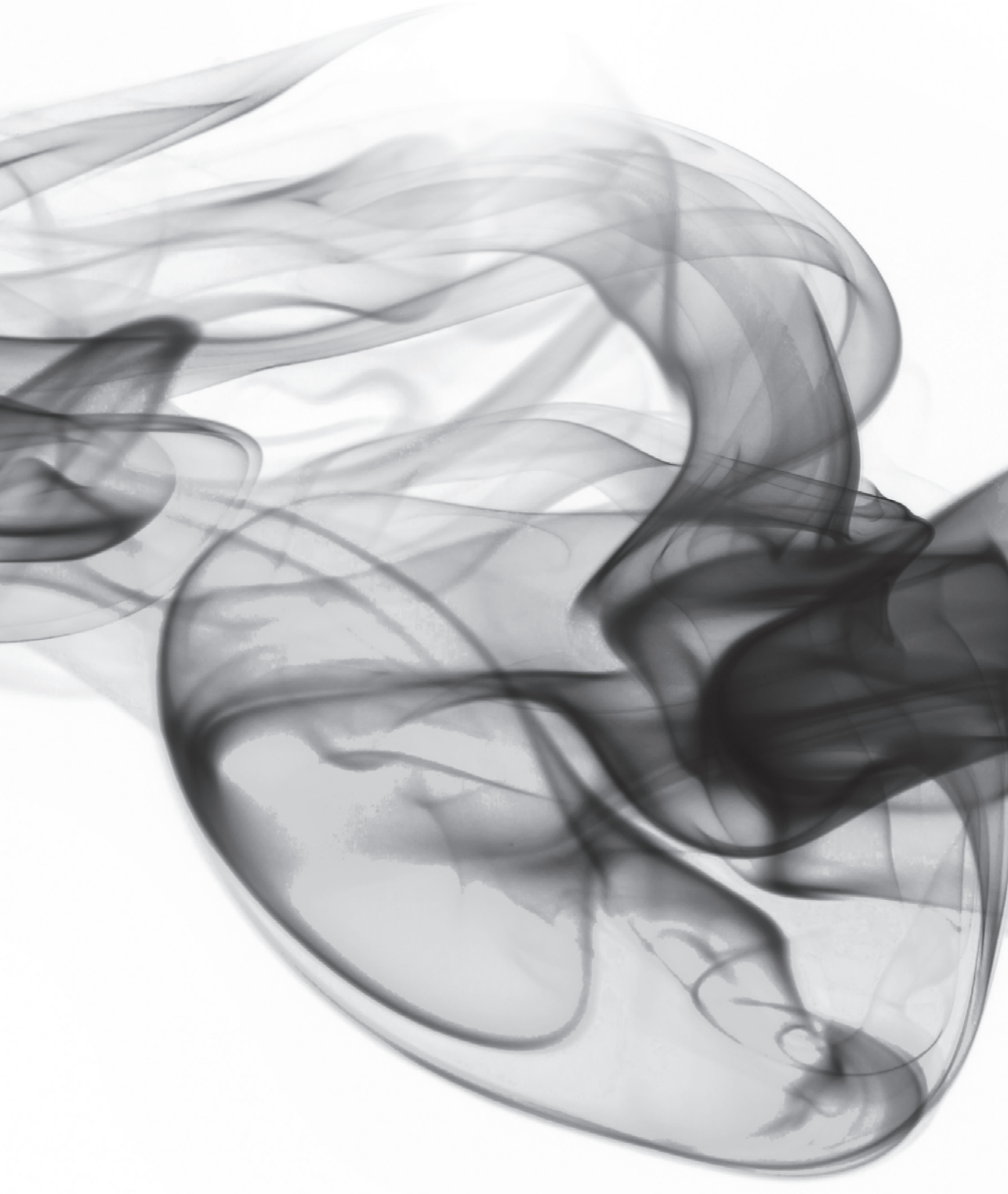

Part 4

Coronary CT angiography in suspected acute coronary syndrome

CHAPTER 8

Coronary CT Angiography for Suspected ACS in the Era of High-Sensitivity Troponins: Randomized Multicenter Study

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ABSTRACT

Aims - This study assessed whether a diagnostic strategy supplemented by early CCTA improves clinical effectiveness compared with contemporary SOC.

Methods - In a prospective, open-label, multicenter, randomized trial, we enrolled patients presenting with symptoms suggestive of an ACS at the ED of 5 community and 2 university hospitals in the Netherlands. Exclusion criteria included the need for urgent cardiac catheterization and history of ACS or coronary revascularization. The primary endpoint was the number of patients identified with significant coronary artery disease requiring revascularization within 30 days.

Results - The study population consisted of 500 patients, of whom 236 (47%) were women (mean age 5410 years). There was no difference in the primary endpoint (22 [9%] patients underwent coronary revascularization within 30 days in the CCTA group and 17 [7%] in the SOC group [p = 0.40]). Discharge from the ED was not more frequent after CCTA (65% vs. 59%, p = 0.16), and length of stay was similar (6.3 h in both groups; p = 0.80). The CCTA group had lower direct medical costs (€337 vs. €511, p < 0.01) and less outpatient testing after the index ED visit (10 [4%] vs. 26 [10%], p < 0.01). There was no difference in incidence of undetected ACS.

Conclusion - CCTA, applied early in the work-up of suspected ACS, is safe and associated with less outpatient testing and lower costs. However, in the era of hs-troponins, CCTA does not identify more patients with significant CAD requiring coronary revascularization, shorten hospital stay, or allow for more direct discharge from the ED. (Better Evaluation of Acute Chest Pain with Computed Tomography Angiography [BEACON]; NCT01413282)

INTRODUCTION

Acute chest pain can herald severe cardiovascular conditions, such as an acute coronary syndrome (ACS) (1). However, the differential diagnosis of acute chest pain is broad, and the consequences of misdiagnosis can be detrimental (2–4). Physicians confront this diagnostic dilemma daily. Coronary computed tomography angiography (CCTA) allows noninvasive visualization of the coronary arteries (5). Because of its high accuracy in ruling out coronary artery disease (CAD), CCTA has been proposed for better decision making in the emergency department (ED), allowing for rapid discharge of patients without important CAD and, possibly, more appropriate referral for coronary revascularization (6,7). Early CCTA as a diagnostic strategy in low- to intermediate-risk patients suspected of ACS is considered safe and may provide logistic and economic benefits (8–10). Meanwhile, high-sensitivity troponin assays (hs-troponins) have become standard practice in many institutions, allowing for more accurate and faster rule-out of ACS (11,12). Whether hs-troponins will erode the potential clinical, logistic, and economic benefits of CCTA has not yet been investigated. The BEACON (Better Evaluation of Acute Chest Pain with Coronary Computed Tomography Angiography) trial is a European randomized trial comparing a diagnostic strategy supplemented by early CCTA with standard optimal care (SOC) for patients suspected of ACS in the era of hs-troponins.

METHODS

STUDY DESIGN

The BEACON study is a prospective, open-label, multicenter, randomized trial. Patients were enrolled at 2 university and 5 community hospitals in the Netherlands. Enrollment was performed during working hours, except at the Erasmus Medical Center University Medical Centre, where patients were included around the clock. The study complied with the CONSORT 2010 Statement and Declaration of Helsinki, and was approved by the institutional ethics committees of each participating center. All patients provided written informed consent.

PARTICIPANTS

Patients with acute chest pain or symptoms suggestive of ACS warranting further diagnostic evaluation, as determined by the treating physician, were eligible for inclusion. We included patients 30 years of age and older, with a maximum age of 75 years for men and 80 years for women. Patients were excluded if symptoms were clearly of noncardiac origin or a coexisting condition already necessitated hospital admission. Exclusion criteria also included a history of known CAD, clinical need for urgent invasive coronary

angiography (ICA), clinical instability, serum troponin levels above 3 times the upper limit of the 99th percentile of the local assay, impaired renal function (estimated glomerular filtration rate <60% of age-corrected normal values), pregnancy, known allergy to an iodinated contrast agent, severe arrhythmias, and body mass index >40 kg/m2.

RANDOMIZATION

Trial participants were randomly assigned to a CCTA-based diagnostic strategy or SOC (1:1). For allocation, a computer-generated block randomization sequence was used, stratified by participating center. An independent physician at the coordinating center extracted the randomization schedule from an electronic randomization tool and codes were sent in sealed, sequentially numbered, opaque envelopes to the participating centers.

PROCEDURES

The initial standard clinical work-up at the ED included a 12-lead electrocardiogram (ECG) and blood analysis. If the initial clinical work-up did not reveal either an evident ACS or an evident noncardiac cause, eligible and consenting patients were randomized between a CCTA-guided strategy and SOC. In the intervention group, CCTA was performed after the initial clinical work-up at the ED. In both groups, hs-troponins were available (supplemental table 1). Image acquisition was performed on 64-slice or a more advanced computed tomography (CT) system, using ECG-synchronized axial or spiral scan protocols combined with radiation minimizing measures, depending on local practices, available technology, and patient characteristics. Results of CCTA were reported by certified radiologists with a minimum of 2 years of experience reading CCTA. Treating physicians were informed directly at the point of care regarding the result of CCTA and imaging-based recommendations were issued. Final medical management decisions were, however, left to the treating physicians (Figure 1). In the SOC group, the attending physicians made clinical decisions regarding further testing, including repeated cardiac marker assessment, hospital admission, noninvasive tests, and referral to ICA, according to current guidelines (13,14). Participants from both groups who were discharged from the ED, without prolonged observation (<8 h) were asked to return to the outpatient clinic after 48 to 72 hours for repeated measurement of cardiac biomarkers and a 12-lead ECG. All participants were followed-up at the outpatient clinic or contacted by telephone after 30 days.

OUTCOME MEASURES

The pre-defined primary endpoint of the study was the number of patients identified with significant CAD requiring coronary revascularization, as interpreted by the clinical operators, within the follow-up period of 30 days. This outcome parameter was chosen on the basis of the hypothesis that a CCTA-driven strategy would identify more

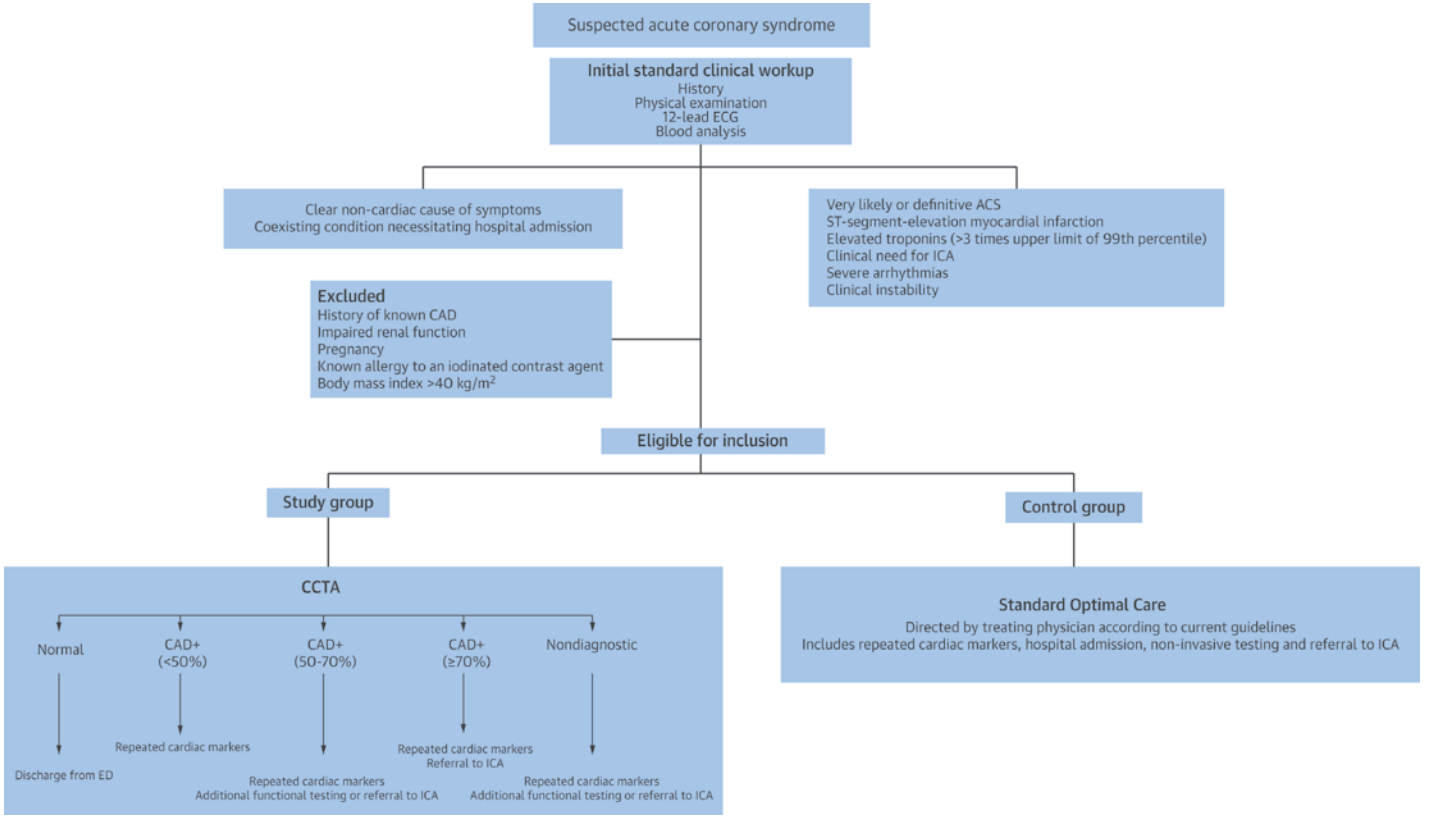


Figure 1. Trial profile.
In the study group, CCTA results were reported at the point of care, with imaging-based recommendations as displayed. However, the final decision regarding clinical work-up was left to the discretion of the treating physicians. Impaired renal function was classified as an estimated glomerular filtration rate <60% of the age-corrected normal values. ACS = acute coronary syndrome; CAD = coronary artery disease; CCTA = coronary computed tomography angiography; ICA = invasive coronary angiography.

clinically important CAD, as suggested by the results of our single-center pilot study, which could effectuate a prognostic benefit (15). The use of fractional flow reserve for ischemia-proven coronary revascularization was encouraged, but not mandatory. This study was set up as a pragmatic clinical trial focusing on initial ED management without protocol-mandated medical management during the remaining clinical course. Secondary endpoints included expedited discharge rate from the ED, length of hospital stay, undetected ACS, cumulative radiation exposure, direct medical costs, and repeat visits to the ED or re-hospitalization for recurrent chest pain within 30 days of follow-up. We defined expedited discharge as discharge within 8 h from the ED, and length of stay as the time from presentation in the ED until hospital discharge. The treating physician made the decision to discharge. ACS was defined as either unstable angina pectoris or myocardial infarction, according to current guidelines (16). The diagnosis of ACS was not on the basis of the CCTA results. The occurrence of undetected ACS was assessed at both the safety follow-up within 72 hours and the general follow-up at 30 days. Cumulative radiation exposure was expressed in millisieverts (mSv) and defined as radiation exposure from all tests and interventions undergone within the first 30 days, including CCTA, single-photon emission computed tomography (SPECT) myocardial perfusion imaging, and ICA. Effective radiation dose was derived by multiplying the dose-length product by a conversion factor of 0.014 for CCTA, 0.0085 mSv/mBq for SPECT and 0.22 mSv/Gycm2 for ICA. To estimate the radiation dose of procedures without reported exposure data, the median radiation dose per procedure was used. Direct medical costs during the index visit and within the follow-up period of 30 days were assessed using reports from the Erasmus MC University Medical Centre cost-accounting system in 2013 in Euros. Finally, we compared the occurrence of total major adverse cardiac events within 30 days, defined as death, ACS, and coronary revascularization. Information on clinical events, repeat visits to the ED, re-hospitalization for recurrent chest pain, diagnostic testing, or interventions was verified by medical records. An adjudication committee consisting of 2 certified, independent cardiologists reviewed medical records of patients with clinically relevant events and a random 10% sample of patients without a diagnosis of cardiac disease.

STATISTICAL ANALYSIS

Statistical analyses were performed on the basis of an intention-to-treat analysis. Continuous data are presented as mean SD or medians with interquartile ranges. Independent samples Student t test or Mann-Whitney U test were used for between-group comparisons for continuous variables, and chi-square or Fisher exact test was used for categorical variables. A 2-sided p value <0.05 was considered to indicate statistical significance. For statistical analyses, we used SPSS version 20.0.

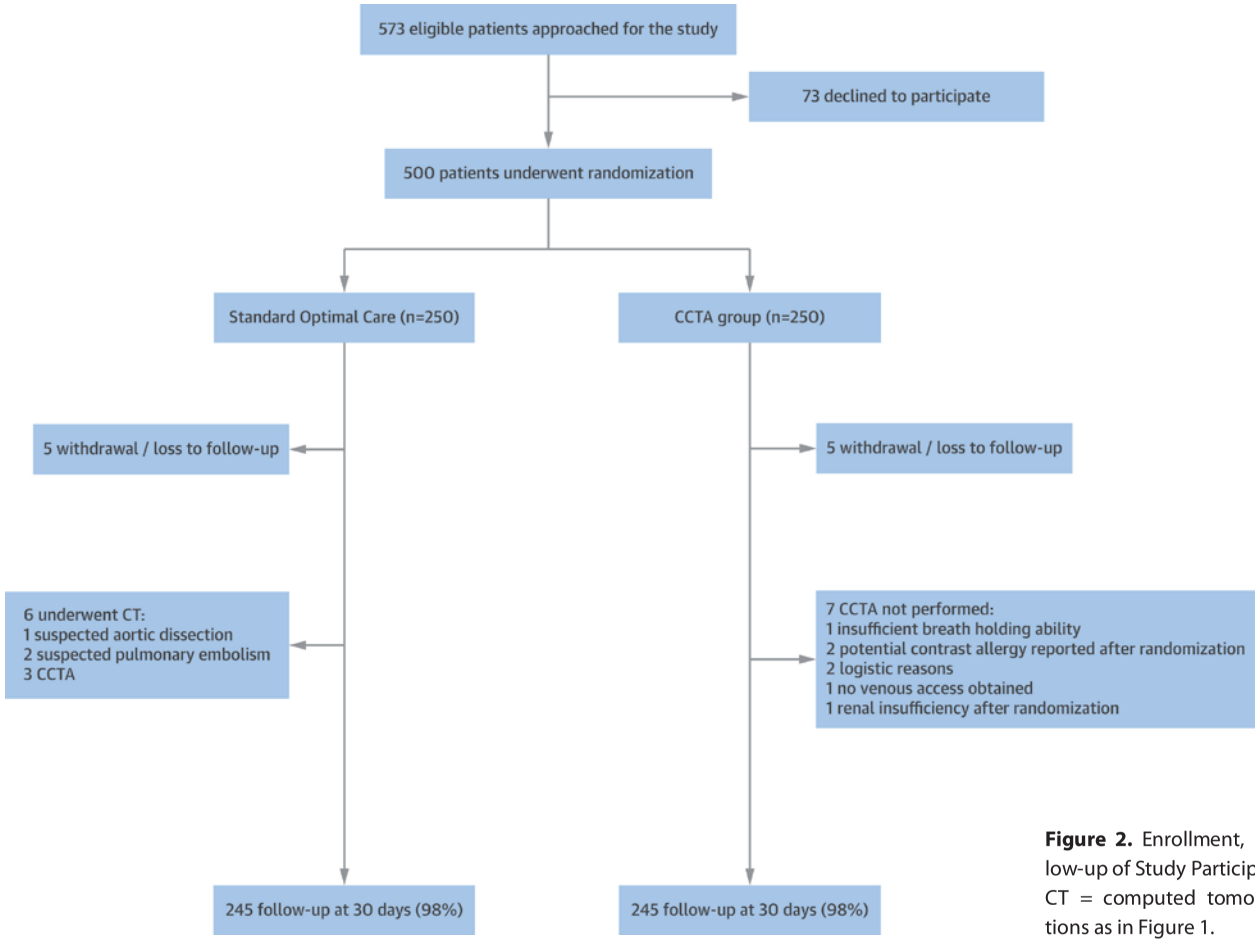


Figure 2. Enrollment, Randomization, and Follow-up of Study Participants
CT = computed tomography; Other abbreviations as in Figure 1.

Table 1. Baseline Characteristics

	CCTA (n = 250)	SOC (n = 250)	p-value
Age, yrs*	55 ± 10	53 ± 9	0.07
Sex, female	123 (49)	113 (45)	0.37
Medication			
Statin	65 (26)	51 (20)	0.14
Aspirin	48 (19)	35 (14)	0.12
Beta-blocker	41 (16)	40 (16)	0.90
ACE inhibitor	29 (12)	29 (12)	1.00
Angiotensin-receptor blocker	18 (7)	17 (7)	0.86
Calcium-channel blocker	18 (7)	19 (8)	0.86
Diuretic agent	36 (14)	23 (9)	0.07
Oral antidiabetic agent	22 (9)	24 (10)	0.76
Insulin	6 (2)	3 (1)	0.31
Cardiovascular risk factors			
Diabetes mellitus	31 (12)	33 (13)	0.79
Hypertension			0.95
>150 mm Hg systolic or >90 mm Hg diastolic	43 (17)	43 (17)	
Treated	66 (26)	69 (28)	
Hypercholesterolemia			0.31
Total cholesterol >5 mmol/l	25 (10)	35 (14)	
Treated	65 (26)	52 (21)	
Smoking			0.26
Current	93 (37)	78 (31)	
Stopped >1 yr	25 (10)	22 (9)	
History of cardiovascular disease			0.95
Peripheral artery disease	8 (3)	7 (3)	
TIA/CVA	16 (7)	17 (7)	
Family history	112 (45)	98 (39)	0.21
Blood pressure (mm Hg)			
Systolic*	140 ± 19	141 ± 20	0.67
Diastolic*	82 ± 12	82 ± 11	0.63
Heart rate* (beats/min)	72 ± 14	72 ± 13	0.86
TIMI risk score (39)†	1 (0-2)	1 (0-2)	0.31
0	74	83	
1	84	91	
≥2	92	76	
Grace risk score (40)†	85 (70–100)	81 (67–98)	0.28
Low	211 (84)	208 (83)	0.20
Intermediate	31 (12)	39 (16)	

Table 1. Baseline Characteristics (continued)

	CCTA (n = 250)	SOC (n = 250)	p-value
High	8 (3)	3 (1)	
Ischemic ECG abnormalities	60 (24)	44 (18)	0.08
Baseline troponins			
Elevated‡	11 (4)	13 (5)	0.67

Unless otherwise specified, data are numbers of patients, with percentages in parentheses. *Data are means ± SD. †Data are medians, with interquartile ranges in parentheses. Diabetes mellitus is defined as plasma glucose >11.0 mmol/l or treated with either diet regulation or medication. Ischemic ECG abnormalities defined as Q-wave or ST-T-segment alterations suggestive of ischemia. ‡Elevated within 3 times the upper limit of the 99th percentile. CCTA = coronary computed tomography angiography; CVA = cerebrovascular accident; SOC = standard optimal care; TIA = transient ischemic attack; TIMI = Thrombosis in Myocardial Infarction.

Table 2. Primary Outcome and Clinical Endpoints Within 30 Days After Index Visit

	CCTA	SOC	p-value
Invasive coronary angiography*	41 (17)	31 (13)	0.20
Invasive coronary angiography at index visit	34 (14)	25 (10)	0.21
Coronary revascularization*	22 (9)	17 (7)	0.40
Percutaneous coronary intervention	22 (9)	13 (5)	
Coronary artery bypass graft surgery	0	4 (2)	
Acute coronary syndrome at discharge	22 (9)	17 (7)	0.40
Unstable angina	8 (3)	3 (1)	0.64
Myocardial infarction	14 (6)	14 (6)	
Repeat emergency department visit	13 (5)	19 (8)	0.27
Repeat hospital admission	7 (3)	14 (6)	0.12
Undetected acute coronary syndrome	1 (0)	3 (1)	0.62
Major adverse cardiac event	25 (10)	21 (9)	0.54
All-cause mortality	1 (0)	0	1.0

Unless otherwise specified, data are numbers, with percentages in parentheses. Major cardiac adverse event includes all-cause mortality, myocardial infarction and coronary revascularization. Abbreviations as in **Table 1**. *Includes procedures at index visit.

On the basis of our previous observational data, we anticipated an absolute 9% increase in the number of coronary revascularizations if the results of CCTA were to be incorporated (15). Considering an $\alpha = 0.05$ and $\beta = 0.8$ with an intervention versus control group enrollment ratio of 1:1, and allowing a loss to follow-up of approximately 10%, we would require 500 participants to detect a difference in the number of patients requiring revascularization of relevant CAD.

RESULTS

Between July 11, 2011, and January 30, 2014, 573 eligible patients were approached for the study; 73 (13%) declined to participate (Figure 2). In total, 7 patients in the CCTA group did not have a CT scan, and 6 patients in the SOC group eventually under-went a CT examination to exclude either CAD or other vascular conditions. At 30 days, 5 patients in each group had withdrawn from the study, resulting in complete follow-up in 490 (98%) patients.

STUDY POPULATION

Table 1 shows patient demographics, clinical characteristics, and medical treatment at baseline. The mean age of the study population was 54 ± 10 years and 236 (47%) participants were women. Baseline characteristics and clinical status were similar between the 2 groups. In the intervention group, CCTA identified 106 (42%) patients with no detectable CAD. Among the patients with CAD on CCTA, 71 (28%) had atherosclerotic plaque with <50% luminal narrowing, 35 (14%) had 50% to 70% luminal narrowing in 1 or more coronary arteries, and 13 (5%) had >70% luminal narrowing in 1 or more coronary arteries. The scan was considered non-diagnostic in 18 patients (7%). The mean radiation dose in the CCTA group was 7.3 ± 6.6 mSv versus 2.6 ± 6.5 mSv in the SOC group.

PRIMARY OUTCOME AND CLINICAL ENDPOINTS

For the primary outcome, the number of patients requiring revascularization within 30 days, no difference was observed between the CCTA group and SOC, that is, 22 (9%) versus 17 (7%) ($p = 0.40$) (Table 2). Also, the total number of ICAs performed within 30 days was similar. At hospital discharge, 22 (9%) patients in the CCTA group and 17 (7%) in the SOC group were diagnosed with ACS($p = 0.40$). Repeat visits to the ED occurred in 13 (5%) patients in the CCTA group, compared with 19 (8%) in the SOC group ($p = 0.27$). At 30 days, a similar incidence of total major adverse cardiac events, that is, 25 (10%) in the CCTA group and 21 (9%) in the SOC group was observed ($p = 0.54$).

SAFETY ENDPOINTS

Undetected ACS occurred once (0.5%) in the CCTA group and 3 times (1%) in the SOC group within the 30-day follow-up period ($p = 0.62$). In the CCTA group, 1 patient had recurrent chest pain with ECG changes suggestive of myocardial ischemia at his safety visit. In the SOC group, 1 patient returned with recurrent complaints, and underwent coronary revascularization following an abnormal exercise electrocardiography (ExECG) result. Another patient reported intermittent chest pain at his safety visit within 72 hours and his laboratory tests showed elevated cardiac biomarkers. The third patient returned after 5 days with recurrent complaints and elevated cardiac biomarkers. One patient in

Table 3. Diagnostic Testing and Resource Utilization

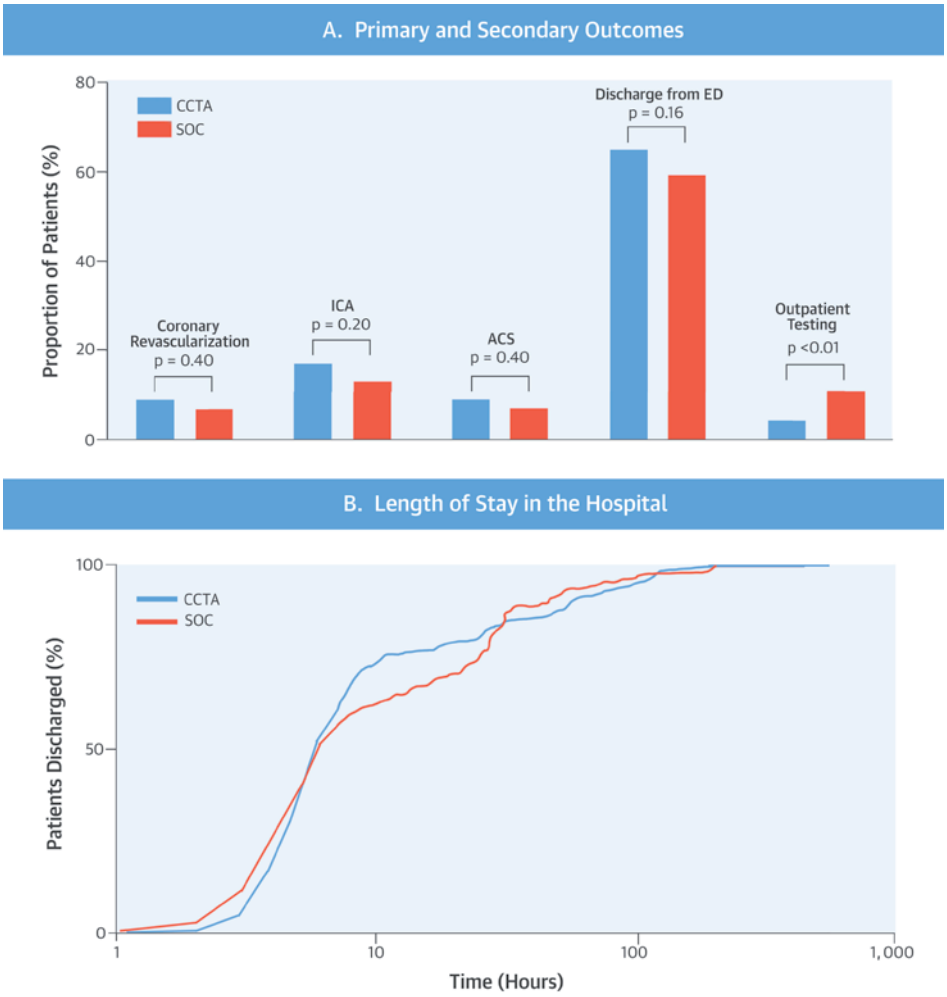
	CCTA	SOC	p-value
Length of stay (h)*	6.3 (4.8–11.1)	6.3 (4.5–25.5)	0.80
Discharge status			0.16
Discharge from emergency department	159 (65)	144 (59)	
Admitted to hospital	86 (35)	101 (41)	
ExECG at index visit	23 (9)	130 (53)	<0.01
ExECG<30 days	32 (13)	143 (58)	<0.01
SPECT at index visit	2 (1)	7 (3)	0.18
SPECT <30 days	2 (1)	16 (7)	<0.01
CMR at index	1 (0)	1 (0)	1.0
CMR <30 days	1 (0)	3 (1)	0.62
CCTA after index visit	1 (0)	2 (1)	1.0
Outpatient diagnostic testing <30 days†	10 (4)	26 (11)	<0.01
Cost (€)*	337 (337–932)	511 (309–916)	<0.01

Unless otherwise specified, data are numbers of patients, with percentages in parentheses. *Data are medians, with interquartile ranges in parentheses. †Total of ExECG, SPECT, CMR, and CCTA in an outpatient setting after index ED visit. CMR = cardiac magnetic resonance imaging; ExECG = exercise electrocardiography; SPECT = *single-photon emission computed tomography* myocardial perfusion imaging. Other abbreviations as in **Table 1**.

the CCTA group died of a hemorrhagic stroke following emergency thrombolysis for occlusive peripheral artery disease 11 days after the index ED visit. Nine CCTA examinations (4%) had minor com-plications: 3 patients had self-limiting, transient increases in their creatinine levels, 4 patients experienced contrast medium extravasation without clinical consequences, and 2 had mild, medically treated allergic skin reactions. In the SOC group, 1 patient who was discharged early had a transient increase in the creatinine level at his safety visit.

DIAGNOSTIC TESTING AND RESOURCE UTILIZATION

More patients were discharged immediately from the ED after CCTA (159 [65%] vs. 144 [59%]), although this difference did not reach statistical significance (p = 0.16) (Table 3). The median length of stay was similar in both groups. ExECG was the most commonly performed alternative noninvasive diagnostic test. In the CCTA group, 32 (13%) patients underwent ExECG within 30 days: 3 (9%) were suspected of ischemia and 10 (31%) were non-diagnostic. In the SOC group, 143 (58%) patients underwent ExECG within 30 days: 9 (6%) were suspected of ischemia and 39 (27%) were non-diagnostic (supplemental table 2). Outpatient testing was less frequently performed in the CCTA group (10 [4%] vs. 26 [11%]; p < 0.01), and direct medical costs after 30 days were lower (€337 [€337 to €932] vs. €511 [€309 to €916]; p < 0.01).



Dedic, A. et al. J Am Coll Cardiol. 2016; 67(1):16-26.

Figure 3. Central illustration
A. Primary and secondary outcomes in the early CCTA group and SOC group.
B. Length of stay and proportion of patients discharged.
ACS = acute coronary syndrome; CCTA = coronary computed tomography angiography; ED = emergency department; ICA = invasive coronary angiography; SOC = standard optimal care.

DISCUSSION

In this prospective, open-label, multicenter, randomized trial, we compared a diagnostic strategy supplemented by early CCTA with contemporary SOC encompassing hs-troponins. In a European setting, early CCTA was safe, less expensive, with less sub-sequent outpatient testing than SOC alone. However, a diagnostic strategy supplemented

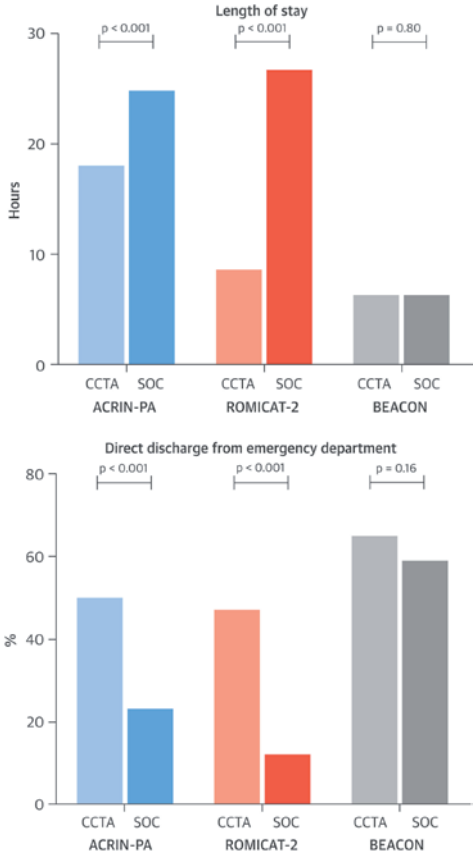


Figure 4. Length of Stay and Discharge Rate From the Emergency Department in the ACRIN-PA, ROMICAT-2, and BEACON trials
Reported data are medians. Abbreviations as in Figure 1.

by early CCTA did not identify more patients with significant CAD requiring coronary revascularization, reduce the length of stay, or allow more expedited discharge from the ED (Figure 3).

CCTA IN THE EMERGENCY DEPARTMENT

Initial observational studies showed that CCTA was feasible and could safely be performed in the ED (19,20). The ROMICAT (Rule Out Myocardial Infarction using Computer Assisted Tomography) study, where 50% of patients with acute chest pain were free from any CAD, demonstrated high negative predictive value and underlined the potential of CCTA in this setting (6). Because CCTA identifies the presence of nonobstructive coronary atherosclerotic plaque, it also may provide the basis for preventive therapeutic medical measures, as opposed to SPECT or ExECG, which detect the presence of existing myocardial ischemia (21). In the current study, non-obstructive coronary atherosclerosis was found in 28% of patients, warranting preventive management, which would be overlooked with SOC.

Shortly after these initial studies, randomized controlled trials were initiated to examine whether a CCTA-based strategy would be more clinically effective than current practice. The CT-STAT trial compared CCTA with nuclear myocardial perfusion imaging as initial tests in the management of patients with acute chest pain (10). Investigators reported a 54% reduction in time to diagnosis and 38% lower costs of ED care with CCTA. In the ACRIN-PA (American College of Radiology Imaging Network-Pennsylvania) trial, investigators left decisions to perform diagnostic tests in the SOC group to the discretion of the treating physicians (9). The study demonstrated that low-risk patients could be safely discharged with early CCTA twice as often, and CAD was more likely to be diagnosed with CCTA. The ROMICAT-2 trial also included a cost analysis, demonstrating a reduction of the median length of hospital stay from 26.7 to 8.6 hours with early CCTA and a 4-fold higher discharge rate from the ED (47% vs. 12%) without increasing medical expenditure (8).

Since these trials were completed, the introduction of hs-troponin has changed SOC considerably. These new assays are more sensitive and reach negative predictive values of >97% for myocardial infarction within 3 h (11,12). Early observations indicated that hs-troponins would allow fast and accurate exclusion of ACS in a substantial proportion of low- to intermediate-risk patients, obviating the need for prolonged observation and in-hospital diagnostic testing in the absence of elevated high-sensitivity cardiac biomarkers or precarious ECG abnormalities (22–24).

CURRENT RESULTS IN PERSPECTIVE

The BEACON trial was designed to compare the clinical effectiveness of a diagnostic strategy supplemented by early CCTA with contemporary SOC encompassing hs-troponins. The current study included a population with a higher prevalence of obstructive CAD on CCTA (19%) compared with previous randomized trials. The majority of patients were referred by a general practitioner, deferring very low-risk patients or those with non-cardiac conditions from the ED. Furthermore, as mandated by the study protocol, only patients with acute chest pain or symptoms suggestive of an ACS warranting further diagnostic evaluation, as determined by the treating physician, were eligible for inclusion. Finally, the inclusion of patients with mildly elevated troponins probably led to an increased prevalence of CAD.

A diagnostic strategy supplemented by early CCTA was inclined to detect more patients with significant CAD requiring coronary revascularization in our study; however, this was not of statistical significance. The results of our logistic endpoints differ from previous trials, as early performance of CCTA did not shorten the length of stay, nor reduce the number of hospital admissions in our study. The length of stay with early CCTA in this study is com-parable or even lower than previously reported (Figure 4). However, the length of stay in our SOC group was substantially lower (median 6.3 hours), underlin-

ing the vigorous improvement of SOC after the introduction of hs-troponins, and also making it harder to achieve an improvement with early CCTA.

Similarly, as many as 59% of patients in the SOC group could be discharged from the ED, a proportion 2 to 4 times higher than reported in previous randomized trials with physician-directed standard care as a comparator. Differences in the Netherlands and U.S. health care systems may be responsible, to some extent, for the contrast between our observations and those from previously published studies from the United States. In the Netherlands, primary care physicians, who are easily accessible and fully covered by medical insurance, have an important gatekeeper role and can defer patients at very low risk or with probable non-cardiac etiology from the ED, which avoids overcrowding and likely increased the overall coronary disease prevalence in our population (25,26). Furthermore, coverage by Dutch insurance companies is comparable for elective and emergency care, and financial incentives that stimulate outpatient work-up and testing are in place (27,28). In the United States, delays in access to care, social differences, and insurance coverage problems in-crease the number of patients seeking care in the ED (29,30). In addition, although guidelines allow for outpatient testing in 48 to 72 hours after discharge from the ED, U.S. physicians are more inclined to achieve a conclusive work-up for the presence of CAD before discharge because of the availability of the testing, poor follow-up, and vulnerability to litigation (31–34). Testing is typically available only during working hours, leading to prolonged hospital stays. Nonetheless, we believe that the contrasting findings are largely explained by the profound effect of the introduction of hs-troponins in the work-up of suspected ACS (11,12,35).

An attractive consequence of early CCTA in our study was the reduced number of subsequent outpatient testing and lower medical costs at 30 days. Outpatient testing was mostly driven by the preference of the treating physician to assess the presence of CAD as the cause of symptoms, which was no longer necessary if CCTA had been performed at first presentation. Although direct comparison of absolute costs between studies is difficult, the shorter length of stay, more frequent use of exercise testing instead of nuclear imaging, and relatively lower cost of CCTA likely reduced general medical expenditure in this study (36). When comparing costs between the 2 groups in our study, some important aspects should be taken into account. According to the applied hospital cost-accounting system, CCTA was only slightly more expensive than ExECG. Nuclear myocardial imaging, which is substantially more costly than either CCTA or ExECG in the Netherlands, was more frequently performed in the SOC group. Finally, the higher costs in the SOC group can likely be attributed to the higher proportion of admitted patients. The median cost per patient in the SOC group was not affected by the unbalanced coronary artery bypass graft distribution.

CLINICAL IMPLICATIONS

There is growing evidence that patients with hs-troponin values below the 99th percentile of the upper reference limit have a very low likelihood of ACS. These patients have a very good prognosis and very often have a normal functional or CCTA test (37–39). However, those with levels above the 99th percentile might benefit from additional testing (i.e., CCTA or a functional test) where (especially in those with low clinical risk profile) a negative test would make the occurrence of cardiovascular events in the short term very unlikely and the need for immediate further testing unnecessary. In this light, it would be of interest for future studies to assess the value of a tiered approach, where application and timing of CCTA or test of choice is directly guided by risk profiles and biomarker results.

STUDY LIMITATIONS

The majority of patients were enrolled during office hours, and round-the-clock implementation of CCTA in the ED poses practical challenges. In real-world clinical practice, SOC might prove more efficient than CCTA for 24-hours use. Extrapolation of our results may be affected by differences in CT technology, imaging expertise, local practices, and cost-accounting systems. The overall observed incidence of the primary endpoint was lower than anticipated on the basis of experiences from our observational study. Although speculative, we believe that the exceptional sensitivity of hs-troponins, allowing early and precise detection of ACS, reduced the incidence of the primary endpoint in both groups, resulting in an underpowered sample size. Earlier troponin elevations and expedited catheterization procedures rendered a proportion of high-risk patients ineligible for study inclusion. In addition, a substantial proportion of patients (50%) with obstructive CAD on CCTA were ultimately not referred for catheterization. Without elevated troponins, these lesions were probably considered stable, which would justify optimal medical treatment on the basis of large coronary revascularization outcome trials (40). Given the low incidence of undetected ACS, this strategy does not appear to have affected safety. Inherent to the nature of diagnostic trials, blinding of patients and treating physicians was not possible, although study participants were treated by physicians who aimed for optimal clinical care, and had no direct involvement in the design and realization of this study. The effect of an early CCTA strategy on long-term downstream testing, resource utilization, and clinical outcome has yet to be determined. Although the majority of patients were evaluated with hs-troponins, 21% entered the study when these assays were not yet available at a number of centers. Finally, an important and noteworthy disadvantage of CCTA is the exposure of patients to radiation. However, use of more innovative CT technology and dose-saving protocols resulted in lower radiation exposure compared with earlier trials (7.3 vs. 14.3 mSv).

CONCLUSION

CCTA, applied early in the work-up of suspected ACS, is safe and associated with less outpatient testing and lower costs. However, in the era of hs-troponins, CCTA does not identify more patients with significant CAD requiring coronary revascularization, nor does CCTA shorten hospital stay or allow for more immediate discharge from the ED.

ACKNOWLEDGMENTS

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SUPPLEMENTAL MATERIAL

Direct medical costs

Based on the costs of the initial ED evaluation (including fee of physician, costs of laboratory tests and ECG), proportions of diagnostic tests, costs of hospital admission, and costs of repeat ED evaluation and readmission, an estimation of costs for the two arms can be compared for other settings and prices using the following formula:

Average cost per patient in the CCTA group = [cost of initial ED evaluation] + [cost CCTA] + 0.13 * [cost XECG] + 0.01 * [cost SPECT] + 0.004 * [cost CMR] + 0.17 * [cost ICA] + 0.09 [cost PCI] + 0 * [cost CABG] + 0.05 [cost repeat ED evaluation] + 0.03 [repeat hospital admission]

Average cost per patient in the SOC group = [cost of initial ED evaluation] + 0.58 * [cost XECG] + 0.07 * [cost SPECT] + 0.01 * [cost CMR] + 0.13 * [cost ICA] + 0.05 [cost PCI] + 0.02 * [cost CABG] + 0.08 [cost repeat ED evaluation] + 0.06 [repeat hospital admission]

Supplemental Table 1. Detailed information on the troponin assays used.

Assay	N (%)	Infarction threshold (ng/L)	Management	Interm. range (ng/L)	Level of detection (ng/L)	99th percentile (ng/L)	10% Coeff. of variation (ng/L)
hs-cTnT Roche Elecsys	39 (78)	50	Serial measurement (3h interval). Value above the pre-defined threshold or a significant rise is regarded as infarction	14-50	5	14	13
TnT Gen 4 Roche Elecsys	87 (17)	30	Serial measurement (6h interval). Value above the pre-defined threshold is regarded as infarction	10-30	10	10	30
cTnI Abbott ARCHITECT	13 (3)	50	Serial measurement (6h interval). Value above the pre-defined threshold is regarded as infarction	28-50	10	28	32
hs-cTnI Abbott ARCHITECT	4 (1)	34	Serial measurement (3h interval) Value above the pre-defined threshold or a significant rise is regarded as infarction	16-34	1.2	16	3
AccuTnI Gen 3 enhanced Beckman Coulter	4 (1)	60	Serial measurement (6h interval) Value above the pre-defined threshold is regarded as infarction	40-60	10	40	60

Supplemental Table 2. Clinical care in the SOC and CCTA group.

	Standard optimal care			Coronary CT angiography				
	TIMI 0 (83)	**TIMI 1 (91)**	**TIMI ≥2 (76)**	**No CAD (106)**	**<50% (71)**	**50-70% (35)**	**>70% (13)**	**Non-diagnostic (18)**
Exercise ECG	51 (61)	47 (52)	32 (42)	4 (4)	1 (1)	11 (31)	2 (15)	5 (28)
SPECT MPI	1 (1)	5 (5)	1 (1)	0	0	0	0	2 (7)
Invasive angiography	4 (5)	4 (4)	17 (22)	0	4 (6)	13 (37)	11 (85)	6 (33)
Revascularization	1 (1)	1 (1)	10 (13)	0	0	6 (17)	11 (85)	2 (7)

Numbers of patients are shown with percentages between parentheses. Tests performed within 30 days from initial presentation. Standard optimal care (SOC) arm sub-classified by Thrombolysis In Myocardial Infarction score (TIMI) (1). Coronary CT angiography (CCTA) arm, sub-classified by most severe obstructive lesion per patient. SPECT MPI = *single-photon emission computed tomography* myocardial perfusion imaging.

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CHAPTER 9

Coronary CT Angiography for Suspected Acute Coronary Syndrome in the Era of High-Sensitivity Troponins: Sex–associated Differences

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ABSTRACT

Background: The optimal diagnostic test in the work-up of suspected acute coronary syndrome (ACS) might differ between men and women. The aim of this study was to compare the clinical effectiveness of early coronary CT angiography (CCTA) in women and men.

Methods: 500 patients presenting with symptoms suggestive of an ACS at the emergency department (ED) were randomized between a diagnostic strategy supplemented by early CCTA or standard optimal care (SOC) with high-sensitivity troponins (hs-troponins) available in both groups. Interactions between sex and diagnostic group were assessed using regression analysis.

Results: ACS was diagnosed less often in women (5% versus 10%, p=0.03). No significant interaction was found for the number of hospital admissions, length of stay, repeat ED visits or outpatient testing between sexes and diagnostic groups (all p-interactions >0.05).

Conclusions: Women had a lower prevalence of CAD, were less often admitted and had a shorter length of stay. The results of our study suggest that CCTA provides no additional benefit for women compared to men who have normal hs-troponin levels.

Clinical Trial Registration - www.clinicaltrials.gov NCT01413282

SHORT REPORT

INTRODUCTION

The burden of coronary artery disease (CAD) in women may still be under-recognized [1]. This might be the result of distinct pathophysiological differences or disease perception by patients and physicians [2]. The optimal diagnostic test in the work-up of suspected acute coronary syndrome (ACS) might therefor differ between men and women [3]. In this pre-specified sub-analysis of the Better Evaluation of Acute Chest Pain with Coronary Computed Tomography Angiography (BEACON) trial, we compare the clinical effectiveness of early coronary CT angiography (CCTA) in women and men.

METHODS

The study design, criteria for enrolment, and primary results have been reported previously [4]. Briefly, in the BEACON-trial, we randomized 500 patients suspected of ACS (47% women) at the emergency departments (ED) of 7 hospitals to either a diagnostic strategy supplemented by early CCTA or standard optimal care (SOC) with high-sensitivity troponins (hs-troponins) available in both groups. Patients with the need for urgent cardiac catheterization were excluded. The results of the main study showed that CCTA, applied early in the work-up of suspected ACS, is safe and associated with less outpatient testing and lower costs. To assess interactions between sex and diagnostic group we used logistic regression analysis for binary outcomes and linear regression analysis for continuous outcomes.

RESULTS

In the BEACON-trial, women were generally older, i.e. 56 ± 10 versus 53 ± 10 years ($p<0.01$) and less often active smokers, i.e. 28% versus 40% men (Table 1, $p<0.01$). Type of chest pain at presentation was not different between sexes, with atypical chest pain as the most frequent type in both groups (52% of women and 51% of men, $p= 0.62$ for trend). Obstructive coronary artery disease (CAD) on CCTA (>50% luminal narrowing) was less frequent in women than in men (14% versus 29%, $p<0.01$). No significant difference was observed for results of exercise electrocardiography ($p=0.42$), which was the most frequently used diagnostic test in the SOC group. Regardless of randomization, women were admitted less often (33% versus 43%, $p=0.02$) and had a shorter length of stay than

Table 1. Baseline characteristics and study outcomes

	Women (n=236)	Men (n=264)	*p-value*	*p interaction*
Age, years ± SD†	56 ± 10	53 ± 10	<0.01	
Diabetes mellitus	25 (11)	39 (15)	0.16	
Hypertension	102 (43)	119 (45)	0.68	
Dyslipidemia	76 (32)	101 (38)	0.15	
Smoking	65 (28)	106 (40)	<0.01	
Family history	101 (43)	109 (41)	0.73	
Chest Pain			0.62	
Non-anginal	40 (17)	44 (17)		
Atypical	120 (51)	134 (51)		
Typical	76 (32)	84 (32)		
Diagnostic test				
Coronary CT angiography			<0.01	
<50% CAD	95 (86)	82 (71)		
≥50% CAD	15 (14)	33 (29)		
Exercise-ECG			0.42	
Normal	45 (40)	51 (38)		
Inconclusive	21 (19)	18 (13)		
Ischemic	5 (4)	4 (3)		
Coronary angiography	27 (11)	45 (17)	0.07	0.92
Coronary revascularization	15 (6)	24 (9)	0.25	0.94
ACS diagnosis at discharge	12 (5)	27 (10)	0.03	0.93
Hospital admission	77 (33)	113 (43)	0.02	0.81
Length of stay‡	6.1 (4.5-15)	7.0 (4.7-24.5)	0.04	0.80
Repeat ED visit	17 (7)	15 (6)	0.49	0.36
Outpatient testing	18 (8)	18 (7)	0.74	0.31

Table 1. Unless otherwise specified, data are numbers of patients, with percentages in parentheses. †Data are means ± standard deviations. ‡ Data are medians, with interquartile ranges in parentheses. Diabetes mellitus is defined as plasma glucose >11.0mmol/L or treated with either diet regulation or medication. Hypertension defines as >150mmHg systolic or >90mmHg diastolic or treated. Dyslipidemia defined as a total cholesterol level >5mmol/L, low-density lipoprotein level >3mmol/L, or on lipid-lowering medication. CAD, coronary artery disease; ACS, acute coronary syndrome; ED, emergency department

men (p=0.04). At discharge, ACS was diagnosed less often in women (5% versus 10%, p=0.03). The use of coronary angiography and the rate of coronary revascularization was not statistically different for women regardless of diagnostic strategy. Moreover, no significant interaction was found for the number of hospital admissions, length of stay, repeat ED visits or outpatient testing between sexes and diagnostic groups (all p-interactions >0.05).

DISCUSSION

Previously, it has been shown that early CCTA may be a more efficient work-up for suspected ACS, especially in women [5]. Women are thought to have a general lower risk of CAD and that they might benefit more than men from CCTA, which is known for its excellent negative predictive value. However, at the same time concerns exist about radiation associated cancer in young women resulting from increased exposure to radiation from medical testing [6]. Our results show indeed a lower incidence of obstructive CAD and ACS in women, however no additional benefit of CCTA could be demonstrated. We believe that there are two important reasons that can explain current findings. Novel to prior reports was the availability of hs-troponins for clinical decision making in both groups. The majority of patients in the current study (>90%) had normal hs-troponin levels (<99th percentile of the upper limit of normal). It has been shown that these patients have a very low risk of ACS [7]. Further advanced testing, in the form of CCTA, might therefor not be needed for them, and this is regardless of sex [8]. Secondly, it is believed that less classical causes of angina such as endothelial dysfunction and microvascular disease are more relevant in women, while epicardial CAD is more prevalent in men [9]. Consequently, it is likely that CCTA as a anatomic modality would provide less benefit in women following this pathophysiological hypothesis.

CONCLUSION

In conclusion, women had a lower prevalence of CAD, were less often admitted and had a shorter length of stay. Obstructive CAD on CCTA was more often found in men and they were more likely to undergo invasive angiography. The results of our study suggest that CCTA provides no additional benefit for women compared to men who have normal hs-troponin levels.

DISCLOSURES

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CHAPTER 10

Round-the-clock Performance of Coronary CT Angiography for Suspected Acute Coronary Syndrome – results from the BEACON trial

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ABSTRACT

Objective - To assess the image quality of coronary CT-angiography for suspected Acute Coronary Syndrome (ACS) outside office hours.

Methods - Patients with symptoms suggestive of an ACS underwent coronary CT-angiography (CCTA) at the emergency department 24-hours, 7 days a week. A total of 118 patients, of whom 89 (75%) presented during office hours (weekdays between 07:00 and 17:00) and 29 (25%) outside office hours (weekdays between 17:00 and 07:00, weekends and holidays) underwent CCTA. Image quality was evaluated per coronary segment by two experienced readers and graded on an ordinal scale ranging from 1 to 3.

Results - There were no significant differences in acquisition parameters, beta-blocker administration or heartrate between patients presenting during office hours and outside office hours. The median quality score per patient was 30.5 [interquartile range 26.0-33.5] for patients presenting during office hours in comparison to 27.5 [19.75-32.0] for patients presenting outside office hours (p=0.043). The number of non-evaluable segments was lower for patients presenting during office hours (0 [0-1.0] vs. 1.0 [0-4.0], p=0.009).

Conclusion – Image quality of CCTA outside office hours in the diagnosis of suspected ACS is diminished.

INTRODUCTION

The optimal diagnostic work-up of suspected acute coronary syndrome (ACS) remains a topic of controversy (1). Recently, several trials have demonstrated that coronary CT angiography (CCTA) is a safe and potentially more efficient diagnostic option for the triage of patients with acute chest pain (2-7). While patients with acute chest pain may seek medical attention at any time during the day, most medical centers offer CCTA only during office hours. A round-the-clock CCTA service poses various challenges, in terms of the availability of scanners and experienced staff, as well as patient characteristics and severity of disease. (8, 9). It is currently unknown whether the time of the day affects the image quality of CCTA. In this pre-specified sub-analysis of the Better Evaluation of Acute Chest Pain with Computed Tomography Angiography (BEACON) trial, we investigated the feasibility of CCTA outside office hours.

MATERIALS AND METHODS

Study design and participants

In the multicenter randomized BEACON trial, we compared a diagnostic strategy with early CCTA to standard optimal care in patients suspected of acute coronary syndrome. At one institution, patients were enrolled 24 hours, 7 days a week. The study design, inclusion and exclusion criteria, and primary results have been reported previously (5). Briefly, we enrolled patients with symptoms suggestive of an ACS at the emergency department (ED). Exclusion criteria included the need for urgent cardiac catheterization and history of ACS or coronary revascularization.

Study participants were divided into patients presenting during regular office hours (weekdays between 07:00 and 17:00) and outside office hours (weekdays between 17:00 and 07:00, weekends and holidays). Information regarding clinical characteristics, time of presentation, time between presentation and CT angiography, image quality, presence of coronary artery disease and clinical outcome were collected prospectively.

Procedures

After initial workup at the ED, consisting of a clinical evaluation including an ECG and laboratory tests, patients underwent CCTA. Image acquisition was performed on either a 128-slice single source scanner, present at the ED or a dual-source system, situated at the radiology department depending on physician preference and availability. We used ECG-synchronized axial or spiral scan protocols combined with radiation minimizing measures. During the day CT scans were performed by a cardiac dedicated technician team. At night the examinations were performed by a broader group of technician,

although all were trained to perform cardiac CT. If indicated and clinically acceptable, beta-blockers were administrated. All patients received sublingual nitroglycerin one minute before scanning. First a coronary calcium scan was performed, and the Agatston calcium score calculated. Subsequent CCTA was evaluated according to SCCT criteria (10). For clinical decision making CCTAs were assessed at the point of care by cardiologists and radiologists with at least 5 years of experience in cardiac CT.

Image evaluation

Image quality was evaluated per segment in accordance with the American Heart Association (AHA) classification (10), by two independent observers (A.K. and A.D., each with more than 3 years' experience), blinded to the time of acquisition. Data sets were transferred offline and evaluated for quality purposes at a later time. If necessary, multiple data sets were used for the quality assessment in sequential and retrospective spiral scans. Artefacts were defined as stack, motion, breathing, blooming, noise or streak. Small segments with a diameter of less than 1.5 mm were excluded from analysis. Image quality was graded on an ordinal scale ranging from 1 to 3. Segments scored as 1 representing poor image quality due to major artefacts and diagnostic evaluation was deemed impossible. In segments scored as 2 there were artefacts present, but image quality was adequate for diagnostic evaluation, and segments scored as 3 had no artefacts with good image quality. Image quality was assessed for all segments of each coronary artery (left main coronary artery, left anterior descending coronary artery, left circumflex coronary artery, and right coronary artery) and then averaged for every patient. Image quality comparison was performed using several approaches: 1) the median quality score per patient; 2) the median quality score per patient of the proximal coronary segments (segments 1,2,5-7 and 11); 3) the number of non-evaluable segments per patient; and 4) the number of non-evaluable proximal coronary segments per patient.

Values for effective radiation dose (mSv) were calculated by multiplying the dose-length product (DLP) with a conversion factor for cardiac CT of $\kappa = 0.017$ mSv/mGy x cm (11).

Statistical analysis

Continuous data are presented as means ± SD or medians with interquartile ranges as appropriate, and categorical variables as frequencies or percentages. Groups were compared using an independent-sample t-test or Mann-Whitney U-test for continuous variables, and chi-square or Fisher's exact-test for categorical variables. A two-sided p-value of <0.05 was considered statistically significant. Statistical analyses were performed using SPSS (version 21, IBM Corp, Armonk NY, USA).

RESULTS

Study population

A total of 118 patients with suspected acute coronary syndrome underwent CCTA. 89 (75%) presented during office hours and 29 (25%) outside office hours. Baseline characteristics are shown in table 1. The mean age was 54 ± 10, 47% were women and the majority had a low GRACE risk score. Aside from ischemic ECG abnormalities (mostly T-wave abnormalities), which were seen more frequently in patients presenting during office-hours patients, no differences were found in other baseline characteristics.

Table 1. Baseline characteristics

	Office hours (n=89)	Outside office hours (n=29)	p-value
Age, years	54 ± 10	55± 11	0.749
Sex, female	42 (47)	15 (52)	0.671
Blood pressure, systolic, mm Hg	140 ± 16	143 ± 16	0.332
Blood pressure, diastolic, mm Hg	84 ± 12	86 ± 10	0.456
Cardiovascular risk factors			
Diabetes mellitus	8 (9)	3 (10)	0.330
Hypercholesterolemia	25 (28)	10 (34)	0.612
Smoking	41 (46)	18 (62)	0.187
Family history	34 (38)	13 (45)	0.663
Hypertension	39 (44)	14 (48)	0.798
TIMI risk score	1 (0-2)	1 (1-2)	0.259
0	29 (33)	5 (17)	
1	33 (37)	12 (41)	
≥ 2	27 (30)	12(41)	
Grace risk score	85 [70-98]	96 [72-121]	0.131
Low	76 (85)	21 (72)	
Intermediate	12 (13)	6 (21)	
High	1 (1)	2 (7)	
Ischemic ECG abnormalities	26 (29)	15 (52)	0.042
Baseline hs troponins elevated[a]	36 (40)	13 (45)	0.829

Values are mean ± SD, n (%), or median [interquartile range]. Diabetes mellitus is defined as plasma glucose >11.0 mmol/l or treated with either diet regulation or medication. Hypertension is defined as >150 mmHg systolic or >90 mm Hg diastolic or treated with medication. Ischemic ECG abnormalities are defined as Q-wave or ST-T segment alterations suggestive of ischemia. [a] Elevated within 3 times the upper limit of the 99th percentile.

The median Agatston calcium score was 1 [0-30] in patients presenting during office hours and 4 [0-48] in patients presenting outside office hours. CCTA identified 40 (45%) patients presenting during office hours with no detectable CAD, compared to 11 (38%) of patients presenting outside office hours. Obstructive CAD (>50% luminal narrowing) was found in 13 (15%) patients presenting during office-hours and 5 (17%) presenting outside office hours. The scan was considered non-diagnostic in 5 (6%) of patients presenting during office-hours and in 2 (7%) of patients presenting outside office-hours (all p>0.05) (figure 1). The mean radiation dose for CT-angiography was 4.2 ± 3.7 mSv for patients presenting during office-hours and 4.2 ± 2.8 mSv for patients presenting outside office-hours (p=0.957).

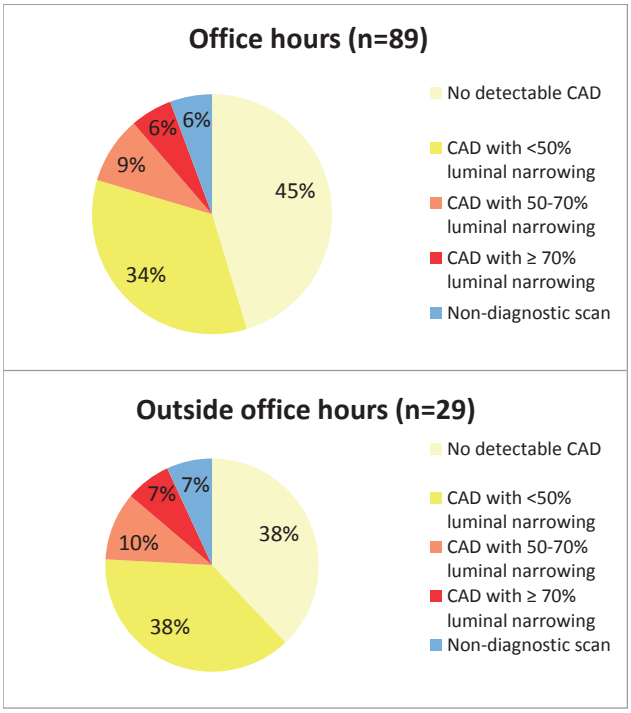

Figure 1. CT results stratified for patients presenting during and outside office hours. All p>0.05. CAD, coronary artery disease.

CT acquisition

Scan acquisition parameters are shown in table 2. There were no significant differences in acquisition parameters between patients presenting during office hours and outside office hours. The number of patients receiving intravenous beta-receptor antagonists prior to the scan was similar between the office- and outside office hours presenting patients, as well was the dose (table 2). The mean heart rate was higher in the group presenting outside office hours although not reaching statistical significance (64 ± 13 vs. 69 ± 13, p=0.095).

Table 2. Scan acquisition parameters

	Office hours (n=89)	Outside office hours (n=29)	p-value
Type CT scanner			0.340
Single Source 128-slice	67 (75)	19 (66)	
Dual Source 128-slice	22 (25)	10 (34)	
Heart rate /min. during scanning (range)	64 ± 13 (38-100)	69 ± 13 (50-98)	0.095
Scan protocol			0.183
Axial	76(85)	28 (97)	
Spiral	13 (15)	1 (3)	
Beta blocker administration			0.590
Yes	47 (53)	13 (45)	
No	19 (21)	7 (24)	
Missing	23 (26)	9 (31)	
Beta blocker dose	5 [5-6.5]	5 [5-6.25]	0.371
Tube voltage, kV	100 [100-120]	120 [100-120]	0.361
Tube current-time product, mAs	194 [144-332]	322 [146-307]	0.562
Dose Length Product (DLP)	280 ± 245	271 ± 198	0.851

Values are n (%), median [interquartile range], or means ± standard deviation

Image quality

The total quality score per patient was higher for patients presenting during office hours in comparison to patients presenting outside office hours (30.5 [26.0 - 33.5] vs. 27.5 [19.75 - 32.0], p=0.043, table 3). The total per-patient quality score of the proximal coronary segments (segments 1,2,5-7 and 11) was higher for patients presenting during office hours (16.0[14.0 - 17.0] vs. 15.0[10.5 - 17.0], p=0.014). The number of non-evaluable segments was lower for patients presenting during office hours (0[0 – 1] vs. 1[0 – 4], p= 0.009), as well as the number of non-evaluable proximal coronary segments (0[0 – 0] vs. 0[0 – 2], p=0.021). An example of image quality is shown in figure 2.

Table 3. Median quality score

	Office hours (n=89)	Outside office hours (n=29)	p-value
Total quality score of all segments	30.5 [26.0-33.5]	27.5 [19.75-32.0]	0.043
Quality of all proximal segments[a]	16.0 [14.0-17.0]	15.0 [10.5-17.0]	0.014
Total number of unevaluable segments	0 [0-1.0]	1.0 [0-4.0]	0.009
Number unevaluable proximal segments[a]	0 [0-0]	0 [0-2.0]	0.021

Image quality was graded on an ordinal scale ranging from 1 to 3, 1 representing poor image quality due to major artefacts, no diagnostic evaluation possible, 2 artefacts present, but image quality was adequate for diagnostic evaluation, and grade 3, no motion artefacts present, good image quality. [a] Proximal segments included segment 1,2,5-7 and 11.

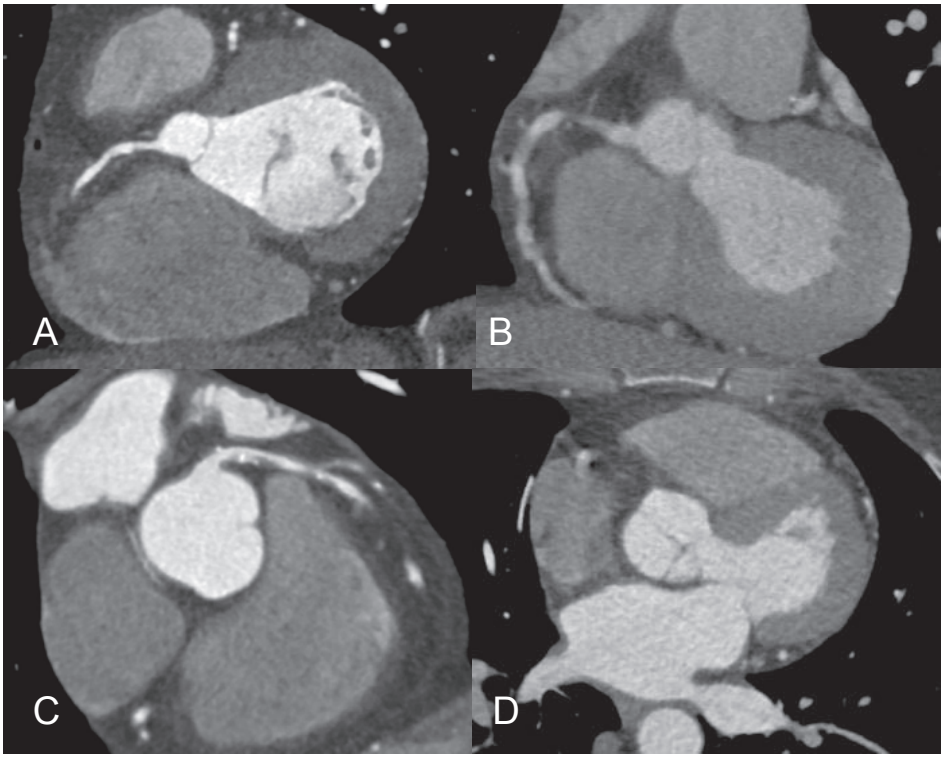

Figure 2. Example of image quality in patient presenting during office hours (A and B), and outside office hours (C and D). Showing a good image quality, with a good coronary enhancement, no motion or other artefacts of the right coronary artery (A – during office hours), and a well-defined lumen with partly calcified and partly non-calcified plaque in the left main coronary artery and left anterior descending (C – outside office hours).
Poor image quality due to motion artefacts and low contrast enhancement of the right coronary artery are shown (B – during office hours). Poor image quality mainly due to major motion artefacts (D – outside office hours), made diagnostic evaluation deemed impossible.

Clinical outcome and downstream testing

From the group of patients presenting during office hours, 22 (25%) patients were admitted, in comparison to 12 (41%) patients that presented outside office hours (p=0.085). The overall number of major adverse cardiac events (including all-cause mortality, myocardial infarction, and coronary revascularization) within 30 days after the index visit was low, and comparable between groups (9(10%) vs 3(10%), p=0.320)). In addition, there was no difference in the rate of invasive coronary angiography and the rate of coronary revascularization between patients presenting during and outside office hours (table 4). The length of stay at the ED was significantly longer for patients presenting outside regular office hours (4.8 [4.0-7.5] vs 6.4 [5.5 - 22.9] hours, p=0.005).

Table 4. Clinical outcome and downstream testing within 30 days after index visit

	Office hours (n=89)	Outside office hours (n=29)	p-value
Admitted to hospital [a]	22 (25)	12 (41)	0.085
Length of ED stay, hours	4.8 [4.0-7.5]	6.4 [5.5 – 22.9]	0.005
Major adverse cardiac events	9 (10)	3 (10)	0.320
Invasive coronary angiography[b]	13 (15)	5 (17)	0.749
Coronary revascularization[b]	8 (9)	2 (7)	0.714

Values are n (%) or median [interquartile range]. [a] Admission to hospital is defined as at least 8 hours in hospital. Major cardiac adverse events includes all-cause mortality, myocardial infarction, and coronary revascularization. [b] Includes procedures at index visit. ED; emergency department.

DISCUSSION

In this pre-specified sub-analysis of the BEACON trial, we assessed the feasibility of CCTA outside office hours. Our results show that image quality of CCTA outside office hours is slightly lower than during office hours. While no worse clinical outcome was observed after 30 days, patients presenting outside office hours had a longer length of stay and were more likely to be admitted to hospital.

CCTA performance

To the best of our knowledge, this is the first study to investigate round-the-clock utilization of CCTA for suspected ACS. We found image quality of CT scans made outside office hours to be sufficient in the majority of patients. There is a small, but statistically significant difference in image quality and non-assessable scans in favour of examinations performed during office hours. An explanation for this difference was not immediately evident from the clinical characteristics, type of scanner or acquisition parameters, which were largely comparable between the two groups. However, there was a trend towards higher heart rates in patients presenting outside office hours, which might partly explain the difference in heart rate. A relative small sample size may have obscured any existing difference in clinical characteristics or acquisition parameters. Also, other unidentified confounders or a combination of factors may explain the lower image quality of CT scans acquired outside office hours. While not investigated, experience of the technician and workflow pressure in the emergency ward during off-hours could have played a role as well.

Differences in clinical outcome

Patients presenting outside office hours had a longer length of stay with the tendency to be admitted more often, which is consistent with previous observations (8, 9). Logistic reasons, such as the accessibility to testing and staffing, next to unfavourable clinical

characteristics are suggested as possible reasons for this difference. In our study, the clinical profiles were unexpectedly comparable between patients presenting outside or within office hours. Their short-term prognosis, expressed in major adverse cardiac events, was also not different. While the difference was small, lower image quality and subsequent less reliability of CCTA outside office hours might have contributed to a longer hospital stay. Also, logistic reasons and the inclination of physicians to admit patients more easily during night hours, rather than clinical profiles, may also play a role.

24/7 implementation of CCTA at the emergency department

While CCTA is becoming an accepted diagnostic tool in the workup of low- to intermediate-risk patients presenting with suspected acute coronary syndrome, round-the-clock performance of CCTA at the emergency department has not yet been widely implemented (12). CCTA is still one of the more demanding CT examination that requires state-of-the-art scanner technology, sufficiently trained staff and time for preparation and optimization of the procedure. Also, it is important that CT readers at the ED are well trained in assessing CCTA. These conditions are difficult to achieve 24 hours per day, seven days per week, which is why most centres opt to limit the cardiac CT service to regular office hours. Some of the current barriers towards full-time implementation may be overcome in the future with further improved technology, lowering the complexity and lessening need for premedication, as well as remote expert reading.

Limitations

There are some study limitations that need to be addressed. The current sub-analysis comprises a relatively small number of patients from a single centre. The proportion of patients enrolled outside office hours (25%) was lower than expected. Screening of all potential study candidates by the medical team may not have been concordant during regular hours and shifts. Quality of CCTA depends on the available technology and personnel. Therefore extrapolation of our results to other centres may be limited. Larger studies with patients enrolled in different centres are needed to thoroughly address the performance of CCTA outside office hours.

CONCLUSION

Image quality of CCTA outside office hours in the diagnosis of suspected ACS is diminished.

CONFLICT OF INTEREST DISCLOSURE

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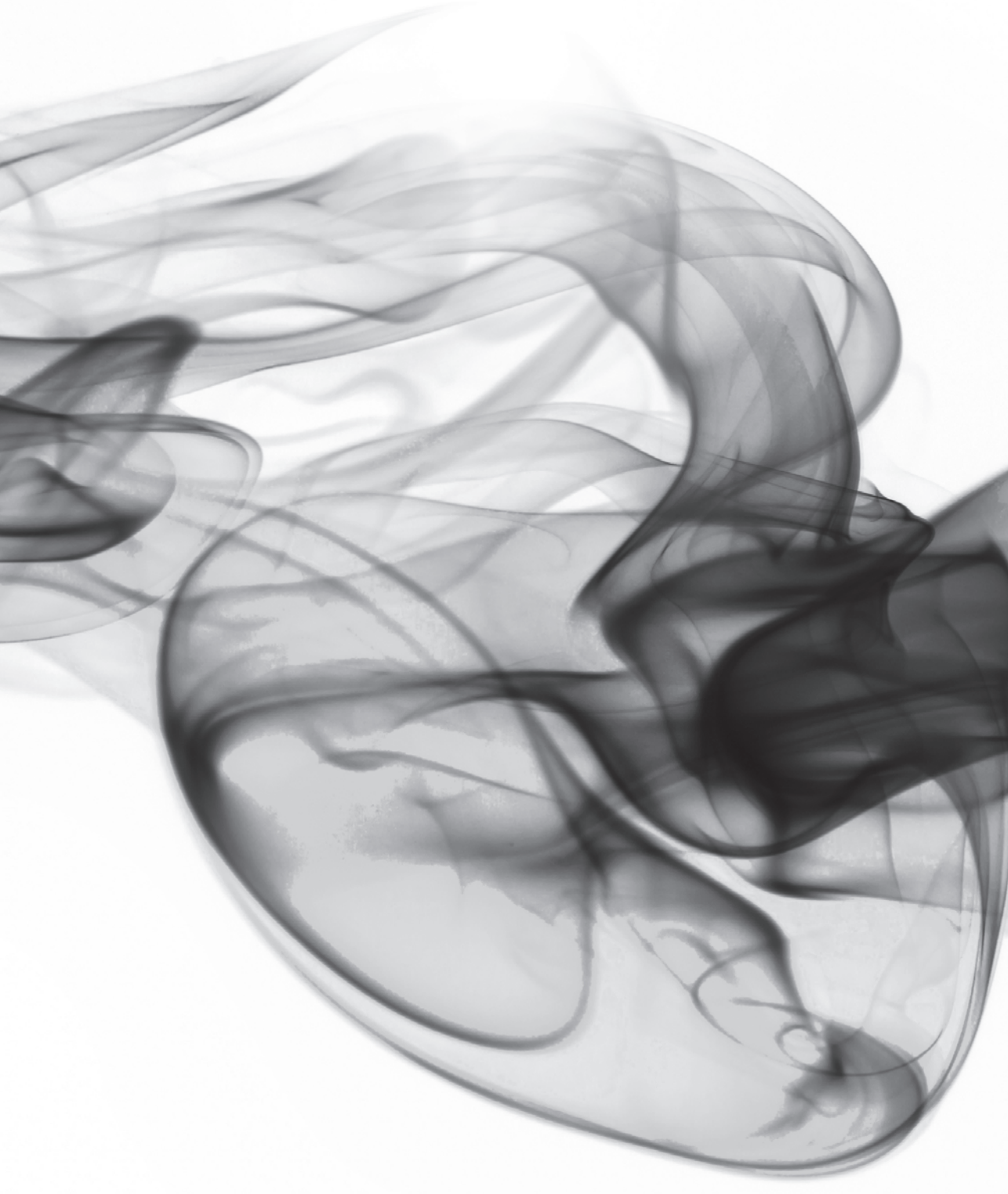

Part 5

Epilogue

CHAPTER 11

Summary and General Discussion

SUMMARY AND GENERAL DISCUSSION

Over the past decade non-invasive coronary angiography using cardiac CT has become a valuable technique for the diagnostic triage of patients with suspected coronary artery disease (CAD) in various settings. Multiple studies have shown that coronary CT angiography (coronary CTA) (1) has a high sensitivity and an excellent negative predictive value for the detection of obstructive CAD, allowing confident exclusion of CAD (2-6). Despite the limited accuracy of exercise ECG for the detection of CAD, in many parts of the world this test remains the first choice for patients with stable chest pain and a low-intermediate probability of CAD (7, 8). In patients with a higher probability of disease stress imaging is often performed (7, 8). Large randomized trials demonstrated equivalence between coronary CTA and standard functional tests, but did not investigate the role of calcium imaging or the value of new CT applications for interpretation of the hemodynamic severity of CAD. In case of acute chest pain, several studies have shown that coronary CTA has clinical, logistic and economic benefits to rule out an acute coronary syndrome (ACS). Since these studies were published, high-sensitivity troponin assays (hs-troponins) have become standard practice in Europe, which allow for accurate and fast rule-out of ACS, leaving uncertainty about the role of cardiac CT in the ED(9, 10).

In this thesis, we assessed the value of cardiac CT in patients with suspected CAD. We investigated the effectiveness, (cost-) efficiency and safety of cardiac CT in comparison to standard functional testing. In this discussion, we will address our research questions and discuss the outcomes against the background of published literature. We will end this chapter with a brief discussion on future perspectives.

In **chapter 2** we provided an in-depth description of the technical background of cardiac CT imaging, to understand how images are acquired, post-processed and interpreted. In addition, an overview of the diagnostic accuracy and the current recommendations for clinical use are presented.

CT Calcium imaging and CT angiography in stable angina

Chapter 3 focused on the clinical use of cardiac CT in stable ambulatory patients with a suspicion of obstructive CAD. At four centers in the Rijnmond region we randomized 350 patients [CRESCENT Trial] with stable chest pain between a tiered cardiac CT protocol and standard functional testing. The protocol started with a calcium scan and ruled out CAD in low-intermediate probability patients with a negative calcium scan(11). Patients with a very high calcium score underwent functional testing. Coronary CTA was performed in the remaining 49% of patients. Standard care started with an exercise ECG in the majority of patients. After one year fewer patients randomized to CT reported anginal symptoms in comparison to the functional testing group. This can be explained by a higher diagnostic performance of CT and subsequently more appropriate manage-

ment of cardiac as well as non-cardiac conditions, although differences in experienced reassurance from cardiac CT by patients and physicians may have played a role as well. Although the study was not powered to demonstrate differences in mortality or myocardial infarction, cardiac CT did result in a lower combined event rate that included death, myocardial infarction, stroke, late revascularizations and unplanned cardiac evaluations (3.3% vs.10.2%). The use of X-rays represents a drawback of CT, although by applying the calcium scan, contemporary CT equipment and dose reducing techniques, the cumulative radiation dose exceeded the functional testing group by less than 10%. Cardiac CT achieved a conclusive diagnostic result faster, required fewer additional tests, did not significantly increase catheterization rates, and was less expensive, compared to functional testing (€369 versus €440). In conclusion: a tiered cardiac CT protocol that includes a CT calcium scan, is safe, avoids contrast medium in 39% of patients, reduces exposure to radiation, and appears cost-effective compared to standard functional testing.

Two randomized controlled trials that compared the effectiveness of coronary CTA standard care to standard testing were published just before the CRESCENT trial. The pragmatic PROMISE trial randomized 10,003 US patients between coronary CT angiography and functional testing (67% nuclear imaging) for evaluation of suspected CAD, and reported no difference in adverse cardiac events after two years(12). Cardiac CT lead to more invasive angiograms, but fewer (angiographically) negative invasive angiograms. Differences between CRESCENT and PROMISE include the use of calcium imaging and the less frequent use of functional imaging in the control group (27% in CRESCENT vs ~90% in PROMISE). The SCOT-HEART trial demonstrated in 4146 patients with stable angina that the addition of coronary CTA to standard care improved the certainty of the diagnosis, but not the frequency of the diagnosis of *angina due to coronary heart disease* (13). After 1.7 years there was a close to statistically significant 38% reduction in the composite endpoint of death related to coronary heart disease and myocardial infarction (p=0.0527). Contrary to CRESCENT and PROMISE, in the SCOT-HEART trial coronary CTA did not replace functional testing, but was added to a standard care protocol with exercise ECG in most cases. The low prevalence of CAD and the generally benign clinical outcome of patients with stable chest complaints in these studies, has raised questions concerning the need for advanced and expensive imaging tests in these patients. In this respect our randomized trial, albeit much smaller in population size, adds to the evidence from PROMISE and SCOT-HEART by demonstrating that a tiered approach including calcium imaging can mitigate the potential risks and costs of cardiac CT, while achieving comparable if not better performance to a functional test approach.

The diagnostic management of women with suspected CAD is challenged by underrecognition due to differences in presentation, pathophysiology such as the higher prevalence of vasospasm and microvascular angina in women (14, 15), a lower performance of standard noninvasive tests resulting in equivocal test results and missed

diagnoses (16-19) and a paradoxically low diagnostic yield of invasive angiography for angiographic CAD, due to a relative overuse, perhaps fueled by the limited confidence in noninvasive tests (20, 21). Based on the hypothesis that direct visualization of CAD by cardiac CT may be particularly effective in women, in **Chapter 4** we investigated gender differences in the performance of cardiac CT compared to functional testing in the evaluation of stable chest pain, and found that cardiac CT was more efficient in women than men in terms of time needed to reach the final diagnosis and downstream testing. In the previously published sub-analysis of the PROMISE trial women were less likely to have a positive CTA than a positive exercise ECG or nuclear stress test result, even after adjusting for clinical factors, which may be the result of false-positive stress test results(22). Interestingly, in the CRESCENT trial no evident differences were observed between the sexes with regard to the exercise tolerance or achieved heart rate during exercise testing. Contrary to PROMISE and SCOT-HEART, in the CRESCENT trial cardiac CT was not associated with an increase in the number of cardiac catheterizations in women(12, 13). The reduced catheterization referral rate after CT may be explained by the use of the calcium scan, or a higher accuracy by newer CT equipment, but may as well be the result of differences in management following the CT scan, compared to previous studies.

Enhancement of the coronary lumen is essential for the detection of CAD on CTA. Contrast media vary in terms of iodine concentration and osmolarity. Until recently the goal in coronary CTA was to achieve maximum lumen opacification, to overcome limitations related to residual motion and vessel calcifications, by injecting high-concentration contrast media (up to 400mg I/ml) or high injection rates. With more powerful roentgen tubes and iterative reconstruction techniques, many patients can be scanned at a lower tube potential (80kVp), which reduces overall radiation exposure. Because of a greater photoelectric effect and less Compton scattering, imaging at a lower kV also increases attenuation differences between iodine and soft tissue(23). As a result, sufficient coronary contrast can be achieved with less iodine injected in to the body. Iso-osmolar contrast media with an osmolarity equal to plasma were demonstrated to cause less heart rate acceleration and arrhythmia, which should be of potential benefit for CT image quality(24-28). In terms of opacification and image quality comparisons between iso-osmolar and low-osmolar contrast media have demonstrated mixed results, which may in part be related to the lower iodine concentration of iso-osmolar contrast media (26, 29, 30). In the IsoCOR trial, **in Chapter 5**, we randomized 306 patients scheduled for coronary CTA at 3 centers in the Rijnmond region, between iso-osmolar iodixanol-270mg I/ml (Visipaque) and low-osmolar iopromide 300mg I/ml (Ultravist) injected at the same iodine delivery rate. When injected at a similar iodine delivery rate, we found that coronary lumen opacification by iodixanol-270 was not inferior to iopromide-300 (476 ± 160 Hounsfield Units (HU) vs 454 ± 158 HU). Contrary to earlier studies that suggested that iso-osmolar contrast media cause less heart rate acceleration and arrhyth-

mia with potential benefits to cardiac imaging (24, 27, 31, 32), we found that although in the iodixanol-270 group patients experienced less heat discomfort (72% vs. 86%), no differences in heart rate, heart rhythm, or image quality were observed.

CT myocardial perfusion imaging in stable angina

Although coronary CT angiography effectively rules out coronary artery disease, it is limited in its ability to assess the hemodynamic importance of angiographic lesions. Because anatomical lesion severity is a poor predictor of hemodynamic significance, functional evaluation of stenosis with intermediate severity is recommended for therapeutic decision making(7, 33). Recent developments in CT technology have created the technical prerequisites for the application of stress CT myocardial perfusion imaging (CT-MPI) for the evaluation of CAD. Thereby CT provides not only anatomical information, but it also allows to determine the functional relevance of coronary stenosis, rendering it a potential "one stop shop" procedure for the diagnosis and management of CAD(34). Pioneered by Kurata et al. in 2005 (35), static CT-MPI acquires a single CT dataset during the first pass of contrast medium through the heart, to visualize differences in myocardial enhancement at a single time point. The assessment of perfusion defects is qualitative and hypo-enhanced regions are compared with normal remote myocardial segments -, comparable to nuclear imaging techniques- potentially disguising globally reduced myocardial perfusion. While advantages of the static perfusion technique are the relatively simple scan acquisition and a full heart coverage with any scanner, a drawback lies in the assessment of only one sample of data and potentially incorrect timing of the contrast bolus missing the peak attenuation resulting in poor contrast-to-tissue ratios (36) its susceptibility to artefacts.

While most experience exists with static CT-MPI(37-39), newer scanners with wider detector coverage also allow for dynamic CT-MPI with total coverage of the left ventricular myocardium. Dynamic CT-MPI was performed in our studies with myocardial hyperemia achieved by infusion of adenosine (≥3 minutes, 140µg/kg/min). At alternating table positions (shuttle mode) systolic images were acquired every second heart cycle while the patient maintained an inspiratory breath-hold. From a series of 12-15 low-resolution datasets the changes in myocardial enhancement during contrast medium passage could be plotted over time, from which the myocardial blood flow could be calculated using a previously described methodology(40). In contrast to static CT-MPI, dynamic CT-MPI allows for calculation of absolute myocardial blood flow(33, 40, 41). Furthermore the differentiation between true perfusion abnormalities and various artefacts is easier by evaluating the time course of the myocardial enhancement. However, because of the acquisition of different data points over time, the scan technique is more challenging and more time consuming compared to static CT-MPI, and is associated with a higher radiation dose (40, 42).

Reduced myocardial perfusion due to CAD tends to be more pronounced in the sub-endocardium(43). This is thought to be due to a reduction in diastolic perfusion time-interval, higher contractile intra-myocardial tissue pressures, and differences in coronary microvasculature(43, 44). The high spatial resolution of CT allows the distinction between sub-endocardium and sub-epicardium. A method to utilise the susceptibility of the sub-endocardium for ischaemia is the transmural perfusion ratio (TPR). TPR is the ratio between sub-endocardium and sub-epicardium perfusion. Since it is a relative index, we hypothesized that this ratio could improve the diagnostic performance of dynamic CT-MPI, because this relative index of perfusion could be less sensitive to the variation of absolute myocardial blood flow values between patients. In **chapter 6** we evaluated the accuracy of TPR alone in comparison to regular myocardial blood flow (MBF) values by dynamic CT-MPI for the detection of haemodynamically significant CAD. We found an area under the receiver operator curve that was significantly larger for MBF (0.78) compared with TPR (0.65), concluding that dynamic CT-MPI derived TPR is inferior to quantified MBF and has limited incremental value. Also no significant incremental value of TPR on top of MBF was found. While some studies showed the potential of TPR to detect ischemia(45), recently other studies demonstrated that visual assessment performed better than TPR(46).

Anatomical and functional parameters are both essential for clinical decision-making in patients with CAD(47, 48). While CT angiography is reliable for ruling out CAD, angiographic and hemodynamic severity may be overestimated with CT angiography alone. A comprehensive stepwise cardiac CT examination, combining calcium scoring, CT angiography and CT-MPI, could provide all essential information for clinical decision making in CAD, and avoid invasive coronary angiography in patients without hemodynamically significant CAD(37, 38, 40). In **chapter 7** we presented the CRESCENT-II randomized-controlled trial performed at 4 centers in the Netherlands, in which 268 patients with stable angina were randomized between cardiac CT and standard guideline-directed functional testing between July 2013 and November 2015. The tiered cardiac CT protocol included a calcium scan, followed by CT angiography if calcium was detected. Patients with significant stenosis on CT angiography underwent CT-MPI. The functional testing strategy was selected by the treating physicians in accordance with international guidelines (initial test 95% exercise ECG)(7).

The purpose of noninvasive testing is to accurately rule out coronary disease and invasive angiograms without coronary artery disease are considered a failure of that gatekeeper function. In CRESCENT II the rate of negative invasive coronary angiograms (primary endpoint) was lower in the CT group than the functional test group (1.5% vs 7.2%). Myocardial ischemia was excluded in 34% of patients with >50% CAD on CT angiography. Hereby, CT-MPI improved the performance of cardiac CT as a gatekeeper to invasive angiography and did not increase catheterization rates (13% vs. 14%).

Presently, patients evaluated and treated for suspected CAD are characterized by a low but overestimated CAD prevalence and overall benign outcome. This was observed in the PROMISE and SCOT-HEART trials, as well as the CRESCENT trials(12, 13, 49). The objective of the CRESCENT-II trial was to test a diagnostic strategy that would allow safe rule-out of CAD by relatively simple means, while at the same time incorporating functional measures of CAD for well-informed decisions and avoiding unnecessary invasive procedures. Incorporation of CT-MPI in CRESCENT-II resulted in a higher diagnostic yield for invasive angiography (88% vs 50%) (compared to 72% in CRESCENT-I), while only 13% of cardiac CT patients required further testing, compared to 37% in the functional testing group(12, 38, 50). In the CRESCENT-II trial the complete cardiac CT protocol, with an examination time of up to 30 minutes, provided a conclusive diagnosis on one day in 87% of patients, achieved a conclusive diagnostic result faster and required fewer additional tests. Although results should be confirmed in larger populations, these findings suggest a promising role for a tiered, comprehensive cardiac CT protocol. A drawback of CT and especially CT-MPI is the radiation dose. By using dynamic CT-MPI the radiation exposure is higher compared to static perfusion imaging protocols (42). The mean radiation dose for dynamic CT-MPI in our trial was 10.6±6.3mSv. But because CT-MPI was only necessary in 22% of CT patients the average cumulative dose in the CT group was 5.6±6.3mSv. X-ray exposure was higher compared to the functional test group, in whom exercise-ECG was the predominant initial test, and only 37% required (secondary) testing involving nuclear imaging and invasive angiography. We concluded that, In patients with suspected stable CAD, a tiered cardiac CT protocol that involved a stepwise use of a calcium scan, CTA and CT-MPI offers a fast, safe and efficient alternative to functional testing.

Coronary CT angiography in suspected acute coronary syndrome

Patients presenting to the emergency department (ED) with symptoms suggestive of an acute coronary syndrome remain a diagnostic challenge. While it is important to reliably rule out an acute coronary syndrome (ACS) or any other life-threatening condition, a clinical efficient work-up is needed as many of these patients are not suffering any serious illness.

Recently, several trials have demonstrated that coronary CT angiography is a safe and potentially more efficient diagnostic procedure for the triage of patients with acute chest pain(51-54).

The previously published CT-STAT trial compared coronary CT angiography with nuclear myocardial perfusion imaging as initial tests in the management of patients with acute chest pain(51). Investigators reported a reduction of 54% in time to diagnosis and 38% lower costs of ED care with CT. In the ACRIN-PA trial investigators left decisions to perform a diagnostic test in the standard care group to the discretion of the treating physicians(53). The study demonstrated that low-risk patients could be safely

discharged with early coronary CT angiography twice as often and CAD was more likely to be diagnosed with CT. The ROMICAT-2 trial, also included a cost-analysis, demonstrating a reduction of the median length of hospital stay from 26.7 to 8.6 hours with early coronary CT angiography and a 4-fold higher discharge rate from the ED without increasing medical expenditure(52). Since the completion of these trials standard optimal care has changed considerably with the introduction of high sensitive troponin assays. These new assays are more sensitive and reach negative predictive values of >97% for myocardial infarction within three hours (9, 10). Hs-troponin allows fast and accurate exclusion of ACS in a substantial proportion of low to intermediate risk patients, obviating the need for prolonged observation and in-hospital diagnostic testing in the absence of elevated high sensitivity cardiac biomarkers or suggestive ECG abnormalities (55-58).

In **chapter 8** the results of the prospective, multicenter randomized BEACON trial are described in which 500 patients presenting with symptoms suggestive of an ACS were enrolled at the emergency departments of five community and two university hospitals in the Netherlands. Patients in need of urgent revascularization were excluded. Patients were randomized to either a diagnostic strategy supplemented by early coronary CT angiography or standard optimal care. In both groups hs-troponins were available. We found that a diagnostic strategy supplemented by early coronary CT angiography was safe, less expensive and prevented downstream testing in the outpatient setting. However, in the era of hs-troponins, coronary CT angiography did not identify more patients requiring coronary revascularization, nor did it shorten hospital stay or allow for more direct discharge from the ED.

The results of the BEACON trial differ from previous trials as early coronary CT angiography did not shorten the length of stay, nor reduce the number of hospital admissions. We found that the length of stay using an early CT exam was comparable or even lower than reported in previous trials. However, the length of stay in our standard care group was substantially shorter, underlining the substantial improvement of standard care after the introduction of hs-troponins. Similarly, the proportion of discharged patients in the standard care group was 2 to 4 times higher compared to previous trials, however compared to our CT group this was not significantly different. Other differences between healthcare systems in previously published trials from the United States and the Netherlands, such as the important gatekeeper role of the general practitioner and delays in access to care, social differences and insurance coverage problems, may also influence the patient population, and could be responsible for the different results(59-61). The BEACON trial demonstrated that early coronary CT angiography reduced the need for subsequent outpatient testing if CT was performed at first presentation. Additionally, we found lower medical costs at 30 days. This was caused by a combination of shorter length of stay and the more frequent use of exercise ECG instead of nuclear imaging.

The burden of CAD in women may still be under-recognized(62). This might be the result of distinct pathophysiological differences or disease perception by patients and physicians(15). The optimal diagnostic test in the work-up of suspected ACS might therefor differ between men and women. In **chapter 9** we compared the clinical effectiveness of an early coronary CT angiography strategy on the ED in women and men. Women were found to have a lower prevalence of CAD and were at discharge less frequently diagnosed with ACS compared to men. In terms of efficiency women were less often admitted and had a shorter length of stay after CT, however there was no significant interaction by sex. In conclusion, we found that the performance of coronary CT angiography was comparable in women and men who have normal hs-troponin levels. In contrast, it has previously been shown that early CT may be a more efficient work-up for suspected ACS, especially in women(63). The different findings in the BEACON trial can be explained by the novel availability of hs-troponins for clinical decision making. The majority of patients (>90%) in our study had normal hs-troponin levels, and it has been shown that these patients have a very low ACS risk (64). The logistic benefit of early advanced diagnostic testing may therefore be of limited value in this context, regardless of sex(65). Secondly, it is believed that less classical causes of angina such as endothelial dysfunction and microvascular disease are more frequent in women, while epicardial CAD is more prevalent in men(66). Consequently, it is likely that coronary CT angiography as an anatomic modality would provide less benefit in women.

The presentation of patients with acute chest pain is not limited to office hours and if coronary CT angiography is considered for triage in the ED it is important to investigate its performance around the clock. A 24/7 availability of a cardiac CT service poses various challenges, in terms of the availability of scanners and experienced staff, as well as patients characteristics and severity of disease(67, 68). As one of the participants in the BEACON trial, the Erasmus MC recruited patients 24-hours a day, 7 days a week. In this population, consisting of 118 patients, of whom 75% presented during office hours and 25% outside office hours, we investigated the image quality of coronary CT angiography during and outside office hours **(chapter 10).** We found that image quality was lower in patients presenting outside office hours, and the number of non-evaluable segments due to artefacts was significantly higher. This could not be explained by differences in clinical characteristics, type of scanner, acquisition parameters or beta-blocker administration. Probably other unidentified confounders, or a combination of factors may explain the lower image quality of CT scans acquired outside office hours. A trend towards higher heart rates in the group seen outside office hours was found (64 vs 69 bpm, p=0.095), or maybe the experience of technicians and workflow pressure in the ED during off-hours, could have played a role in the image quality as well.

Besides the finding that image quality of CT scans acquired during off-hours was lower, we found that patients presenting outside office hours had a longer length of

stay with the tendency to be admitted more frequently (67, 68). This was consistent with previous observations and can be explained by logistic reasons, such as the accessibility to testing and staffing, next to unfavourable clinical characteristics of patients presenting outside office hours (67, 68). The 24/7 implementation of coronary CT angiography on the ED is a challenge, and requires state-of-the-art scanner technology, sufficiently trained staff and time for preparation and optimization of the procedure.

FUTURE PERSPECTIVES

The COURAGE and FAME trials (47, 48, 69) showed that revascularization does not benefit every patient with angiographic CAD, but should be reserved for those with objective myocardial ischemia. Invasive angiography, without proper ischemia testing leads to over-treatment. In the field of non-invasive ischemia testing there are multiple modalities available. Functional assessment with CT-MPI may have practical advantages, as it can be performed in conjunction with CTA, and allows for a comprehensive assessment of anatomy and function like we showed in this dissertation. The high radiation dose, relatively complicated scan protocol and the requirement of specific CT equipment for a dynamic CT-MPI scan can slow down the implementation in daily practice of the regular cardiology clinic. However, as scanner and data processing technology further develop, the comfort of use and radiation exposure of dynamic CT-MPI will likely improve and will become easier accessible.

Besides functional assessment with CT, there are more established stress imaging techniques available. For example, cardiovascular magnetic resonance (MR) perfusion imaging has demonstrated the highest accuracy of all non-invasive testing. In the MR-INFORM trial, Nagel et al [in press](70) showed that MR-perfusion guided management of patients with stable angina is non inferior for MACE at one year compared with invasive angiography and FFR. This was the first trial to show that MR-perfusion imaging could guide patient management in a high-risk population with the same effectiveness as invasive angiography with FFR. The advantages of an MR-based work up are the absence of radiation, as well as gaining potentially relevant information on anatomy, contractile function and myocardial structure in a single session. However, MR-perfusion is a time-consuming technique of which the cost-effectiveness still needs to be investigated.

Another non-invasive testing modality for myocardial ischemia is PET imaging. Danad et al determined the diagnostic value of CTA, SPECT and PET imaging compared against invasive FFR(71). They found that PET yielded the highest diagnostic accuracy, outperforming CTA and SPECT and unexpectedly a hybrid diagnostic approach, combining anatomy and functional assessment did not improve accuracy compared to PET alone. However, before PET can be used as standard gatekeeper in the work up of stable CAD, some drawbacks need to be overcome. The image quality with the currently used isotope is not sufficient to perform a standard segmental perfusion analysis and also the

high costs and duration of a PET exam are not ideal for a gatekeeper function in large groups of patients.

There is still ongoing debate what is the best non-invasive gatekeeper that provides anatomical and functional information and accurately predicts significant flow impairment compared with the gold-standard invasive FFR. While the technical strengths and weaknesses of each technique are known, as well as the diagnostic accuracy and prognostic power, there are also other important variables influencing the choice of a test, some of which are availability and waiting times, local expertise and radiation exposure. Another very important variable is the cost of each test which varies tremendously between countries and is very difficult to standardize. Long-term cost-effectiveness is difficult to establish, depends on the local conditions and may conflict with the economic incentives within health care systems. Patients are different and it is unlikely that one specific test is the best choice for each patient in every clinical context.

So what is the next step from here? The important and clinically relevant question for the practicing physicians is how to match each patient with its own clinical characteristics with each test to improve clinical care. Thus, the important challenge for clinical research would be to develop well-defined patient groups for which physicians can be advised about the best test choice based on group's clinical characteristics, the diagnostic accuracy of the test, and the specific data required from the test. Robust trial evidence is needed to find the best non-invasive imaging test for each patient. Conversely, we are not likely to see many large-scale randomized controlled trials in imaging because of the high cost of performing them and non-imaging factors that contribute to outcomes, including downstream use of test information and less than optimum post-test patient care strategies, are difficult to control. It is therefore likely that we will see more pragmatic trials with varied clinical endpoints. But it will be challenging to compare the different clinical endpoints for their effectiveness, safety, or efficiency.

Currently an international landmark trial named ISCHEMIA has recently completed recruitment and the results will be published in the upcoming years(72). Five thousand patients with stable angina and at least moderate ischemia were randomized between invasive angiography or optimal medical treatment and followed for four years. The primary aim is to determine if an initial strategy with invasive angiography and revascularization together with medical therapy will reduce events compared to a strategy of medical therapy alone (with cath lab referral reserved for failed medical treatment). Where prior trials in stable CAD showed that an index strategy of optimal medical therapy alone was safe and equally effective as PCI with optimal medical therapy, this trial will possibly offer great opportunities for imaging to be a core component and decision trigger for the clinical management of stable CAD and may potentially provide evidence to alter the current evaluation strategy.

Technical developments of functional assessments in cardiac CT

The possibility of imaging myocardial enhancement during hyperemia using CT has been demonstrated repeatedly(35, 39, 45, 73), but only with the introduction of wider detector-row CT systems has it become feasible to perform dynamic MPI in clinical practice(33, 40). Up to now dynamic CT-MPI had only been tested in single-center studies (33, 40), however the international multicenter SPECIFIC trial is currently recruiting patients referred for invasive angiography and performs dynamic CT-MPI before invasive angiography. The aim is to determine the diagnostic accuracy of dynamic CT-MPI for the detection of hemodynamically relevant coronary stenosis as determined by invasive FFR. Results are expected in 2019. Meanwhile cardiac CT technology is developing and the latest CT systems provide higher temporal resolution, wider detector coverage, better tissue resolution and lower radiation doses. Whether these improvements in scanner technology, as well as the development of user-independent tools for interpretation, will benefit the performance and applicability of CT-MPI will need to be further investigated.

Apart from dynamic CT-MPI, and well-known established functional modalities, several other CT-based functional assessment techniques have emerged. For static CT-MPI the diagnostic performance and incremental value over CTA has been demonstrated in single- and multicenter trials (35, 37-39, 45, 74), with potential for diagnostic improvement using dual-energy techniques (41), or hybrid systems that combine CT with PET or SPECT.

An alternative approach to estimating the functional severity of angiographic CAD is by model-based calculation of the fractional flow reserve (FFR) using computational fluid dynamics. CTA based FFR (CT-FFR) computes coronary flow parameters from conventional CT angiograms(75, 76). While CT-FFR is not a direct physiological measurement, and relies on sufficient CT quality, the lack of additional testing and radiation exposure are obvious advantages, that can make it a fruitful functional tool in the future. The PLATFORM study demonstrated how CTA combined with CT-FFR can improve the diagnostic yield of invasive angiography(77). The few direct comparisons published to date suggest a comparable and partially complementary performance of CT-MPI and CT-FFR (46, 78, 79). In the future, the simultaneous assessment of coronary anatomy and functional severity of CAD has the potential to function as a reliable "one stop shop". With further advancements of cardiac CT, such as improved diagnostic accuracy, radiation reduction, artifact reduction, reduced susceptibility to motion artifacts, a wider acceptance of cardiac CT in the work-up of suspected stable CAD can be expected.

While work presented in this theses answered many questions, undoubtedly it raised even more questions as mentioned in this chapter. The coming years will reveal how the above mentioned different non-invasive testing modalities of suspected CAD have moved forward.

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NEDERLANDSE SAMENVATTING

Cardiale CT ("computed tomography") heeft zich het afgelopen decennium ontwikkeld tot een volwaardige diagnostische test in het opsporen van mogelijke vernauwingen in de kransslagaders ("coronair lijden"). Cardiale CT is de overkoepelende naam voor een aantal CT onderzoeken van het hart. Vaak begint het CT onderzoek met een CT-calciumscore. Dit is een "blanco" CT scan zonder contrastmiddel, waarbij de calciumafzetting in de vaatwanden gedetecteerd en vervolgens gekwantificeerd kan worden volgens de Agatston-methode(1). Calciumscores zijn sterk geassocieerd met de graad en ernst van aderverkalking(2-4) en worden tegenwoordig het meest gebruikt als risico-stratificatie bij asymptomatische patiënten. Maar de hoge sensitiviteit en negatief voorspellende waarde van de CT-calciumscore maken de test ook uitermate geschikt om bij patiënten met pijn op de borst klachten vernauwingen in de kransslagaders mee uit te sluiten. Een voordeel van deze methode is dat er geen contrasttoediening nodig is en de stralingsdosis en kosten zo lager zijn(5). Meerdere observationele studies hebben aangetoond dat in patiënten met een laag tot intermediair risico op coronair lijden een negatieve calciumscore, ernstige aderverkalking zeer zeldzaam is(6-8).

Na een CT-calciumscore kan een coronair CT angiografie (CCTA) volgen. Tijdens de CCTA wordt jodiumhoudend contrastmiddel in de bloedvaten van de patiënt geïnjecteerd om zo de binnenkant van de kransslagaders zichtbaar te maken en daarmee de ernst van de aderverkalking en vernauwingen te beoordelen. CCTA heeft een hoge sensitiviteit en negatief voorspellende waarde voor het detecteren van angiografische vernauwingen(9, 10). CCTA is echter beperkt in zijn vermogen om het hemodynamisch belang van vernauwingen in de kransslagaders te beoordelen.

De anatomische ernst van een vernauwing is een slechte voorspeller van de hemodynamische ernst van een vernauwing, daarom wordt in de richtlijnen een functionele beoordeling van intermediaire vernauwingen aanbevolen(11, 12). CT-myocardiale perfusie (CT-MPI) is een derde CT techniek waarmee naast de anatomische informatie van de CCTA ook functionele informatie verkregen kan worden. CT-MPI wordt uitgevoerd onder toediening van adenosine, waardoor toegenomen bloedtoevoer (hyperemie) naar het hartspierweefsel ontstaat(13). Door verschillen in contrast-toevoer in het myocard tussen gebieden achter een vernauwde kransslagader die minder goed doorbloed worden, en gebieden die normaal doorbloed worden, kan een perfusie (doorbloedings-) defect opgespoord worden(14). Hiermee kunnen de hemodynamische consequenties van een anatomische vernauwing in een kransslagader beoordeeld worden, dit noemen we een functionele beoordeling. Deze perfusie techniek is gevalideerd in single-center studies en heeft een diagnostische nauwkeurigheid die ten minste vergelijkbaar is met een nucleaire SPECT scan. Daarnaast is ook de stralingsdosis vergelijkbaar met een SPECT scan, met als voordeel dat CT ook anatomische informatie over de kransslagaders geeft.

Hierdoor kan cardiale CT een belangrijke rol als "poortwachters functie" vervullen voor patiënten zonder hemodynamisch belangrijke aderverkalking en zo doorverwijzing naar invasieve katheterisatie (angiografie) voorkomen.

Het doel van dit proefschrift was het onderzoeken van de waarde van cardiale CT bij patiënten met een verdenking op vernauwingen in de kransslagaders. We beschreven de effectiviteit, de (kosten-) efficiëntie en veiligheid van cardiale CT als diagnostische test om vernauwingen in de kransslagaders op te sporen en vergeleken deze met de momenteel standaard functionele test methode.

Hoofdstuk 1 is de algemene inleiding van dit proefschrift waarin het doel en de indeling ervan worden beschreven. In **hoofdstuk 2** wordt een overzicht van de technische aspecten van cardiale CT beschreven. Onder andere de acquisitie, de evaluatie van data en de klinische toepassingen van CT zoals beschreven in de huidige richtlijnen komen aan bod.

CT-calciumscan en coronair CT-angiografie bij patiënten met stabiele angina pectoris

Hoofdstuk 3 is gericht op de klinische toepassing van cardiale CT in poliklinische patiënten met pijn op de borst klachten met een verdenking op vernauwingen in de kransslagaders. In 4 ziekenhuizen in regio Rijnmond werden 350 patiënten met stabiele pijn op de borst gerandomiseerd tussen een cardiale CT-scan of een standaard functionele test volgens de huidige richtlijnen (de CRESCENT studie). Het cardiale CT protocol startte met een CT-calciumscan en in patiënten met vooraf een laag tot intermediair risico op vernauwde kransslagaders sloot de afwezigheid van calcium vernauwingen in de kransslagaders uit(15). Patiënten met een hoge calcium score (>400) ondergingen daarna een functionele test. In de standaard test groep ondergingen de meeste patiënten een fietstest. De belangrijkste bevinding was dat in de CT groep na één jaar meer patiënten van hun pijn op de borst klachten af waren. Dit werd mogelijk verklaard door de betere diagnostische kwaliteiten van CT, waardoor een meer passende behandeling gekozen konden worden, waardoor de klachten sneller en beter verdwenen. Mogelijk speelt tevens mee dat artsen en mogelijk ook patiënten meer gerustgesteld waren na een negatieve CT scan, in vergelijking met een negatieve functionele test. Ondanks dat de studie niet berekend was op het aantonen van verschillen in mortaliteit of hartinfarcten, werd in de CT groep opgeteld een lager aantal dood, hartinfarct, beroerte, late revascularisaties en ongeplande ziekenhuisbezoeken gevonden (3.3% vs 10.2%). Een nadeel van CT is het gebruik van röntgen straling, echter door het gebruik van de CT-calciumscan als triage middel voor de volgende testen en tevens de hedendaagse CT-apparatuur en dosis verlagende technieken was de cumulatieve stralingsdosis niet meer dan 10% hoger vergeleken met de functionele test groep. Op het gebied van efficiëntie bleek na CT de diagnose sneller bereikt, waren hier minder diagnostische onderzoeken

voor nodig, waaronder ook geen stijging van het aantal invasieve katheterisaties en waren de kosten lager vergeleken met de standaard functionele test.

Vrouwen en hart en vaatziekten is de laatste jaren een controversieel onderwerp, onder andere omdat blijkt dat de mortaliteit onder vrouwen hoger is (16). Dit heeft te maken met een vaak niet-typische presentatie bij vrouwen, een hogere prevalentie van verkrampingen in de kransslagvaten (vasospasmen) en meer ziekte in de kleine haarvaatjes van het hart (microvasculair vaatlijden), evenals de minder accurate diagnostische functionele testen bij vrouwen. Hierom lijkt cardiale CT, waarbij de aanwezigheid van aderverkalking direct gevisualiseerd wordt, een uitermate geschikte test voor vrouwen. **Hoofdstuk 4** breidt voort op hoofdstuk 3 en beschrijft de verschillen tussen man en vrouw in de prestatie van cardiale CT in vergelijking met de functionele diagnostische test. Cardiale CT bleek meer efficiënt bij vrouwen wat betreft een kortere tijd tot de uiteindelijke diagnose en daarbij bleken minder extra diagnostische testen nodig.

In **hoofdstuk 5** presenteren we de prospectieve, multicenter, gerandomiseerde IsoCOR studie. Door technische ontwikkelingen kunnen de kransslagaders van het hart tegenwoordig gescand worden met lagere "buis spanningen" (kV). Hierdoor is de stralingsdosis verlaagd, maar het vergroot ook de aankleuring (attenuatie)-verschillen tussen jodium en de weke delen. Hierdoor kan contrastmiddel met een lagere jodium concentratie geïnjecteerd worden en hiermee voldoende contrastaankleuring verkregen worden. Iso-osmolaire contrast middelen, dus met een osmolariteit gelijk aan bloedplasma, veroorzaken minder hartritme versnellingen en aritmiëen, wat uiteindelijk zou kunnen zorgen voor een betere CT beeldkwaliteit (17-21). In de IsoCOR studie, werden 306 patiënten in de regio Rijnmond gerandomiseerd en vergeleken we de aankleuring van de kransslagaders door twee verschillende contrastmiddelen: iso-osmolair iodixanol-270 mg I/ml (Visipaque) en laag-osmolair iopromide 300mg I/ml (Ultravist). Beide contrast middelen werden met gelijke jodium aanvoersnelheden geinjecteerd en we vonden een aankleuring van de kransslagaders die met iodixanol-270 niet inferieur was aan iopromide-300 (476 ± 160 Hounsfield Units (HU) vs 454 ± 158 HU). Omdat de osmolariteit van contrastmiddel ook geassocieerd is met een aantal klinische effecten, zoals een gevoel van warmte, pijn, en hartritme versnellingen, werd dit in de IsoCOR studie ook onderzocht. Patiënten in de iodixanol-270 groep ervoeren significant minder warmte-discomfort (72% vs. 86%), maar er werden geen verschillen in hartritme geobjectiveerd. Er dient te worden opgemerkt dat bijna de helft van alle patiënten een bètablokker kregen toegediend voor de CT scan, maar in vergelijkbare aantallen in beide groepen. Tenslotte werd er geen verschil in beeldkwaliteit gevonden tussen beide contrastmiddelen.

CT-myocard perfusie bij patiënten met stabiele angina pectoris

Verminderde doorbloeding van de hartspier (myocardiale perfusie) veroorzaakt door vernauwingen in de kransslagaders blijkt meer uitgesproken te zijn in het subendocardium, de diepste laag van de hartspier (22). Dit wordt mogelijk verklaard door een vermindering in diastolische perfusie tijd, hogere weefsel drukken tijdens contractie in de hartspier ter plaatse, en verschillen in de coronaire haarvaatjes (microvasculatuur) (22, 23). De hoge spatiele resolutie van CT maakt het mogelijk onderscheid te maken tussen subendocard en subepicard. Een methode om de gevoeligheid van subendocard voor ischemie uit te drukken is de transmurale perfusie ratio (TPR). De hypothese van **hoofdstuk 6** was dat deze ratio de diagnostische prestatie van CT-MPI kon verbeteren, omdat de TPR minder gevoelig is voor lagere absolute bloedstroom, omdat het een relatieve index is. We vergeleken de additionele waarde van TPR alleen en in combinatie met de normale myocardiale bloedstroom (MBF) waardes in dynamische CT-MPI. Er werden 43 patiënten, en 94 myocardiale territoria geanalyseerd. De "area under the receiver operator curve" was significant groter voor MBF vergeleken met TPR, en ook de toevoeging van TPR aan MBF bracht geen toegevoegde waarde. Terwijl sommige studies de toegevoegde waarde van TPR aan het detecteren van ischemie laten zien(24), zijn er ook recentere studies die aantonen dat een visuele beoordeling van ischemie beter presteert dan TPR (25). Wij concludeerden dat TPR in dynamische CT-MPI geen toegevoegde waarde heeft. Deze negatieve uitkomst kan mogelijk verklaard worden doordat de endocardiale zone direct aangrenzend aan de linker ventrikel vatbaar is voor artefacten, zoals "beam hardening" en "partial voluming", wat subtiele perfusie defecten heeft kunnen vervagen.

In **hoofdstuk 7** presenteren we de CRESCENT-II studie: een prospectieve, multicenter, gerandomiseerde studie waarin de effectiviteit , de efficiëntie en de veiligheid van cardiale CT onderzocht werd in vergelijking met een standaard functionele test strategie. De CRESCENT-II studie verschilde van de CRESCENT-I studie wat betreft de CT-strategie. In CRESCENT-II werd er gestart met een CT-calciumscan, gevolgd door CCTA als er calcium gedetecteerd werd. Patiënten met een significante stenose op CCTA ondergingen ook een zogenaamde perfusie scan (CT-MPI) om de hemodynamische ernst van de vernauwing te bepalen. In de functionele test groep onderging 95% als eerste test een fietstest.

Het doel van het uitvoeren van niet-invasieve diagnostische onderzoeken in patiënten met een verdenking op een vernauwing in de kransslagaders is om op een betrouwbare wijze vernauwingen uit te sluiten. Een invasieve katheterisatie (angiografie) waarbij uiteindelijk géén vernauwingen zichtbaar blijken te zijn, beschouwen we als een falende poortwachters functie van de diagnostische testen die hieraan vooraf zijn gegaan. In de CRESCENT-II studie was het primaire eindpunt het aantal invasieve katheterisaties zónder significant vernauwde kransslagaders (13), dit aantal bleek significant lager in de CT groep vergeleken met de standaard functionele test (1.5% vs 7.2%). In 34% van

de patiënten met een >50% vernauwing in één van de kransslagaders op CCTA werd myocard ischemie toch uitgesloten door middel van een perfusie scan (CT-MPI). Hiermee heeft CT-MPI een belangrijke rol in de CT-strategie als "poortwachter" voor doorverwijzing naar invasieve katheterisatie. In tegenstelling tot onze verwachtingen was het aantal invasieve katheterisaties niet verhoogd in de CT groep, daarnaast bleken in de CT groep een hoger aantal invasieve katheterisaties mét significante vernauwingen opgespoord te worden (88% vs 50%) (26-28). Tenslotte bleek een CT strategie sneller tot een diagnose te leiden en waren daar minder extra diagnostische testen voor nodig. Een nadeel van cardiale CT is de straling, met name CT-MPI gaat gepaard met een hogere stralingsdosis. In onze studie was de gemiddelde stralingsdosis van CT-MPI 10.6±6.3mSv. Maar omdat CT-MPI enkel nodig was in 22% van de CT patiënten, was de gemiddelde cumulatieve stralingsdosis in de CT groep 5.6±6.3mSv. Dit was hoger vergeleken met de functionele test groep, waarin de meesten primair een fietstest ondergingen en uiteindelijk slechts 37% een tweede test nodig had die straling betrof (nucleaire SPECT scan, danwel katheterisatie). De conclusie van de CRESCENT-II studie was dat bij patiënten met verdenking op vernauwde kransslagaders een cardiale CT, met stapsgewijze uitvoering van CT-calciumscan, CCTA, en CT-MPI, een snel, veilig en efficiënt alternatief is voor de functionele test.

Coronair-CT angiografie bij patiënten met verdenking op een acuut hartinfarct (ACS)

Het laatste deel van het proefschrift gaat over CT (CCTA) bij patiënten met verdenking op een ACS ("hartinfarct"). Het is in deze patiënten groep op de spoedeisende hulp belangrijk om een ACS, of een andere levensbedreigende aandoening, met zekerheid uit te sluiten. Aan de andere kant is het belangrijk hierin een efficiënte strategie te hanteren, omdat er wereldwijd grote aantallen patiënten zich zo presenteren en vele daarvan blijken uiteindelijk geen hartinfarct of andere ernstige aandoening te hebben. Meerdere studies hebben recent aangetoond dat CT veilige en efficiëntere diagnostiek is op de spoedeisende hulp bij patiënten met acute pijn op de borst in vergelijking met de oude standaard (29-32). Echter zijn deze studies niet uitgevoerd ten tijde van de "high sensitivity troponines" (hs-troponine). Troponine is een stof die vrijkomt uit beschadigd hartspierweefsel, zoals tijdens een hartinfarct. De nieuwe hs-troponine zijn zeer gevoelig en kunnen daarmee hartspierschade nog sneller detecteren. In **hoofdstuk 8** worden de resultaten van de prospectieve, multicenter gerandomiseerde BEACON studie beschreven. 500 patiënten met acute pijn op de borst verdacht voor ACS werden gerandomiseerd tussen een diagnostische strategie aangevuld met CT, danwel de momenteel standaard optimale zorg. In beide groepen waren de hs-troponine beschikbaar. Belangrijkste exclusie criterium was de behoefte aan acute revascularisatie. We concludeerden dat een diagnostische strategie met CT op de spoedeisende hulp veilig

is en gepaard gaat met minder poliklinische diagnostische testen in een later stadium en lagere kosten. Echter, in de huidige tijd met de beschikbaarheid van hs-troponine worden er door CT niet meer patiënten geïdentificeerd die een revascularisatie behoeven, tevens verkort het de duur in het ziekenhuis niet en leidt het ook niet tot sneller ontslag van de spoedeisende hulp.

Zoals ook beschreven in hoofdstuk 4 worden hart en vaatziekten nog vaak onderkend in vrouwen. In **hoofdstuk 9** worden de verschillen tussen man en vrouw onderzocht in klinische effectiviteit tussen de CT en de standaard strategie in patiënten met acute pijn op de borst op de spoedeisende hulp. Vrouwen bleken minder vaak vernauwingen in de kransslagaders te hebben en werden minder vaak gediagnosticeerd met hartinfarcten (ACS) vergeleken met mannen. Wat betreft de effectiviteit, bleken er geen additionele voordelen aan een CT strategie te zitten voor vrouwen. In tegenstelling leken er in voorgaande studies wel voordelen te zitten aan een vroege CT-scan bij vrouwen met acute pijn op de borst (33). Het verschil in uitkomst kan te maken hebben met de nieuwe beschikbaarheid van de hs-troponine.

Nu voor patiënten met acute pijn op de borst CT op de spoedeisende hulp zich aan het ontwikkelen is als mogelijk nieuwe strategie, hebben we in **hoofdstuk 10** de verschillen in beeld kwaliteit van CT gedurende de dag en nacht beoordeeld. Het 24uur per dag bieden van de mogelijkheid tot cardiale CT op een spoedeisende hulp gaat namelijk gepaard met enige uitdagingen, zoals de beschikbaarheid van geavanceerde scanners en ervaren personeel, maar ook wat betreft patiënt karakteristieken en de ernst van ziekte (34, 35). In het coördinerend centrum van de Beacon studie, het Erasmus MC, werden patiënten 24uur per dag, 7 dagen per week geïncludeerd. Van deze 118 patiënten, waarvan 75% zich presenteerde tijdens normale kantoortijden, en 25% daarbuiten, hebben we de beeldkwaliteit van CT onderzocht. De beeldkwaliteit bleek significant lager in de diensten ten opzichte van de normale kantoortijden, tevens bleek het aantal niet-beoordeelbare segmenten tijdens diensten hoger. Dit werd niet verklaard door klinische karakteristieken, type scanner, acquisitie parameters of bètablokker toediening. Mogelijk dat een combinatie van andere onbekende "confounders" een rol hebben gespeeld in de lagere beeldkwaliteit tijdens diensturen. Er werd een trend naar een hogere hartfrequentie gezien tijdens de diensturen (64 vs 69, p=0.095), wat mogelijk meegespeeld heeft. Tevens kan de ervaring van de CT-laboranten en de werkdruk tijdens diensten op de spoedeisende hulp meegespeeld hebben, maar dit werd in deze studie niet onderzocht. Naast de mindere beeldkwaliteit tijdens diensten, bleek dat patiënten die zich buiten kantooruren presenteerden langer op de spoedeisende hulp verbleven en vaker in het ziekenhuis werden opgenomen. Dit is in lijn met eerdere studies en kan verklaard worden door logistieke redenen, zoals de beschikbaarheid van diagnostiek en personeel, naast de ongunstige klinische kenmerken van patiënten die zich buiten kantoortijden presenteren(34, 35). Om CT 24/7 beschikbaar te maken op

een spoedeisende hulp is state-of-the-art scanner technologie vereist, voldoende goed opgeleid personeel met verstand van cardiale CT en met tijd voor voorbereiding en optimalisatie van de procedure.

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LIST OF PUBLICATIONS

Papers

Marisa Lubbers, Adriaan Coenen, Marcel Kofflard, Tobias Bruning, Bas Kietselaer, Tjebbe Galema, Marc Kock, Andre Niezen, Marco Das, Marco van Gent, Ewout-Jan van den Bos, Leon van Woerkens, Paul Musters, Suze Kooij, Fay Nous, Ricardo Budde, Miriam Hunink, Koen Nieman. Comprehensive Cardiac CT with Myocardial Perfusion Imaging versus Functional Testing in Suspected Coronary Artery Disease: the multicenter, randomized CRESCENT-II trial.
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Marisa M. Lubbers, Admir Dedic, Akira Kurata, Marcel Dijkshoorn, Jeroen Schaap, Jeroen Lammers, Evert J. Lamfers, Benno J. Rensing, Richard L. Braam, Hendrik M. Nathoe, Johannes C. Post , Pleunie P. Rood, Carl J. Schultz, Adriaan Moelker, Mohamed Ouhlous, Bas M. van Dalen, Eric Boersma, Koen Nieman. Round-the-clock Performance of Coronary CT Angiography for Suspected Acute Coronary Syndrome – results from the BEACON trial.
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the Performance of Cardiac Computed Tomography Compared With Functional Testing in Evaluating Stable Chest Pain: Subanalysis of the Multicenter, Randomized CRESCENT Trial (Calcium Imaging and Selective CT Angiography in Comparison to Functional Testing for Suspected Coronary Artery Disease).
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Coenen A, **Lubbers MM**, Kurata A, Kono A, Dedic A, Chelu RG, Dijkshoorn ML, Rossi A, van Geuns RM, Nieman K. Diagnostic value of transmural perfusion ratio derived from dynamic CT-based myocardial perfusion imaging for the detection of haemodynamically relevant coronary artery stenosis.
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Kurata A, Coenen A, **Lubbers MM**, Nieman K, Kido T, Kido T, Yamashita N, Watanabe K, Krestin GP, Mochizuki T. The effect of blood pressure on non-invasive fractional flow reserve derived from coronary computed tomography angiography.
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Dedic A, Kurata A, **Lubbers M**, Meijboom WB, van Dalen BM, Snelder S, Korbee R, Moelker A, Ouhlous M, van Domburg R, de Feijter PJ, Nieman K. 'Prognostic implications of non-culprit plaques in acute coronary syndrome: non-invasive assessment with coronary CT angiography'.
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Marisa Lubbers, Admir Dedic, Adriaan Coenen, Tjebbe Galema, Paul Musters, Mohamed Ouhlous, Jurgen Akkerhuis, Ahno Liem, Tobias Bruning, Andre Niezen, Boudewijn Krenning, Miriam Hunink, Erik Boersma, Pim de Feijter, Koen Nieman. Calcium imaging and selective CT angiography in comparison to functional testing for suspected coronary artery disease: the multicentre, randomized CRESCENT trial.
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J Cardiovasc Comput Tomogr. 2016 Mar-Apr;10(2):105-13.

A. Dedic, **M.M. Lubbers**, J. Schaap, J. Lammers, E.J. Lamfers, B.J. Rensing, R.L. Braam, H.M. Nathoe, J.C. Post, T. Nielen, D. Beelen, M.C. le Cocq d'Armandville, P.P. Rood, C.J. Schultz, A. Moelker, M. Ouhlous, H. Boersma, K. Nieman. Coronary CT Angiography for Suspected ACS in the Era of High-Sensitivity Troponins – Randomised Multicenter Study.
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Kono AK, Coenen A, **Lubbers M**, Kurata A, Rossi A, Dharampal A, Dijkshoorn M, van Geuns RJ, Krestin GP, Nieman K. Relative myocardial blood flow by dynamic computed tomographic perfusion imaging predicts hemodynamic significance of coronary stenosis better than absolute blood flow.
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Eur Heart J Cardiovasc Imaging. 2014 Nov;15(11):1231-7.

A. Dedic, **M.M. Lubbers**, J. Schaap, J. Lammers, E.J. Lamfers, B.J. Rensing, R.L. Braam, H.M. Nathoe, J.C. Post, P.P. Rood, C.J. Schultz, A. Moelker, M. Ouhlous, H. Boersma, K. Nieman. Coronary CT Angiography for Suspected Acute Coronary Syndrome in the Era of High-Sensitivity Troponins: Sex–associated Differences.
Submitted

Book chapters

Marisa Lubbers, Koen Nieman. Cardiac CT for Coronary Imaging
Cardiac CT, PET and MR, 2nd edition. Edited by Vasken Dilsizian and Gerry Pohost. © 2017 Blackwell Publishing Ltd.

PHD PORTFOLIO

	Year	Workload (ECTS)
1. PhD training		
General academic and research skills		
Introduction to clinical research, NIHES Erasmus MC	2013	0.9
CCO2 Biostatistical methods I: basic principles, NIHES Erasmus MC	2013	5.7
Instellingsgebonden regelgeving en stralingshygiëne niveau 5A, Erasmus MC	2013	1.25
Open Clinica training	2014	0.3
English biomedical writing and communication course, Erasmus MC	2014	3.0
Diagnostic research, NIHES Erasmus MC	2014	0.75
Advanced decision making, NIHES Erasmus MC	2014	1.4
Photoshop and Illustrator CS6 workshop, Erasmus MC	2014	0.3
Research integrity course, Erasmus MC	2015	0.3
In-depth courses		
Cardiovascular imaging and diagnostics, COEUR Erasmus MC	2013	1.5
Cardiovascular pharmacology, COEUR Erasmus MC	2013	1.5
Cardiovascular medicine, COEUR Erasmus MC	2013	1.5
Translational electrophysiology, COEUR Erasmus MC	2013	0.4
Gender differences in cardiovascular disease	2013	0.4
Ercathan module1: functionele en toegepaste cardiale anatomie, Skillslab EMC	2013	0.3
Heart failure research, COEUR Erasmus MC	2014	1.5
Arrhythmia research methodology	2014	1.5
Webinar EACVI advanced cardiac CT, ESC EACVI	2015	0.3
Congenital heart disease	2015	1.5
Coeur PhD days	2014, 2016	0.8
Conferences and Symposia		
RSNA Annual Meeting	2014	1.2
ECR congress	2015, 2016	2.4
ESC congress	2015	1.5
Radiologen dagen	2015	0.6
NVVC congress	2015, 2016 (2x)	1.5
SCCT winter meeting	2016	0.9
ACC Scientific Sessions	2016	0.9
SCCT Annual Scientific Meeting	2016	0.9

2. Teaching

Lecturing

Basic + Advanced Cardiac CT workshop, K.Nieman/R.Budde Erasmus MC	2014, 2015 (2x), 2016	2.1
Siemens CT-User day, presentation about CT myocardial perfusion imaging	2016	0.3

Supervising practicals

Supervising research of 2nd year medical students	2014, 2016	0.6
TOTAAL		***38***

Oral presentations

2016 The Netherlands Society of Cardiology (NVVC) autumn congress, Papendal, The Netherlands

2016 American College of Cardiology (ACC) conference, Chicago, USA

2016 The Netherlands Society of Cardiology (NVVC) spring congress, Noordwijkerhout, The Netherlands

2016 European Congress of Radiology (ECR), Vienna, Austria

2016 Society of Cardiovascular Computed Tomography (SCCT) winter meeting, Istanbul, Turkey

2015 The Netherlands Society of Cardiology (NVVC) autumn congress, Papendal, The Netherlands

2015 Radiologen dagen, Rotterdam, The Netherlands

2015 European Society of Cardiology (ESC), London, UK

Moderated poster presentations

2016 Society of Cardiovascular Computed Tomography (SCCT), Orlando, USA

Poster presentations

2015 European Congress of Radiology (ECR), Vienna, Austria

2014 Radiological Society of North America (RSNA), Chicago, USA

Awards

2016 NVVC autumn, best presentation in session I: computed tomography / Cardiovascular magnetic resonance

2016 SCCT Istanbul, best abstract

2015 NVVC autumn, best presentation in session I: computed tomography / Cardiovascular magnetic resonance

ABOUT THE AUTHOR

Marisa Lubbers was born on April 14, 1987 in Haarlem, the Netherlands. After graduating at Atheneum College Hageveld in Heemstede, she started medical school at the Leiden University in 2005. During her medical study she went abroad for clinical internships to Cameroon and Thailand. January 2012 she obtained the degree of Medical Doctor. Subsequently, she started working as a resident (ANIOS) on the cardiology department of the Maasstad hospital in Rotterdam. Here her enthusiasm for cardiology was confirmed. Subsequently, she started her PhD project at the Erasmus MC Rotterdam, entitled: "Clinical use of cardiac CT" under the supervision of Professor F. Zijlstra (head of cardiology department) and Professor G.P. Krestin (head of radiology department) which resulted in this thesis. From January 2017 she was working as a resident (ANIOS) at the department of cardiology at the Erasmus MC, Rotterdam. In September 2017 she started her cardiology training (AIOS) at Erasmus MC in Rotterdam, started with internal medicine at the Maasstad hospital in Rotterdam.

Marisa married Frank Juijn on July 13, 2017 and on July 31, 2018 their daughter Myla was born.

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