Coronary CT in Acute Cardiac Care

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Voor mijn dierbaren

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CHAPTER 1

General Introduction and Outline of the Thesis

Derived from the ancient Greek words 'tomos (τόμος)' and 'graphein (γράφειν), meaning 'slice' and 'to write', tomography stands for "to write (or describe) in slices [1]. One of the earliest reports of computed tomography can be traced back to publications in the beginning of 1960s by Allan M. Cormack, who described a scan of an aluminium phantom ring filled with Lucite and two aluminium disks, representing two tumors [2,3]. At that time, little attention was paid to his work, because the technique was time-consuming and involved complicated calculations. In the same period, Godfrey N. Hounsfield came up with a concept that if multiple X-ray measurements are taken through a body from different directions it could be possible to reconstruct its internal structure. From here on, it took several years of dedicated work before he developed the first clinical CT scanner at the Atkinson-Morley Hospital in September 1971 (Figure 1) [4]. For their pioneer work in the field of computed tomography, both G. Hounsfield and A.M. Cormack received the Nobel Prize of Physiology or Medicine in 1979.

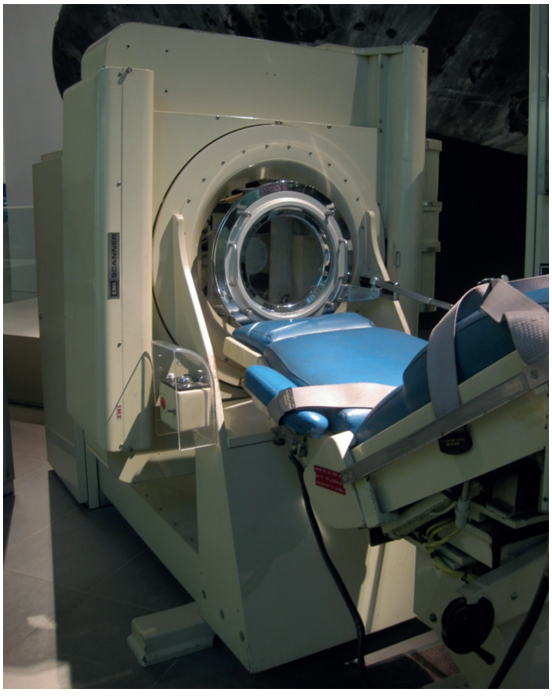

Figure 1 | EMI Brain Scanner. Museum of Science, London, UK. The EMI scanner produced detailed pictures of patients' brains for the first time. Godfrey Hounsfield invented the technique, called computed tomography, which constructed a picture from a series of 28.800 measurements made by a paired X-ray source and detector rotating around the patient. Previously, X-rays could only image the brain after hazardous injections of air or special liquids.

In his Nobel lecture Cormack referred to his early publications: "There was virtually no response. The most interesting request for a reprint came from the Swiss Center for Avalanche Research. The method would work for deposits of snow on mountains if one could get either the detector or the source into the mountain under the snow!".

Nowadays medical care is impossible to imagine without the aid of computed tomography. In computed tomography, X-ray beams are transmitted by an X-ray source on one side through

a patient and registered on the opposite side by detectors. While passing through a patient, different tissues allow X-ray beams to pass in different degrees, also called attenuation. Tissue like bone or calcification inhibit the passage of X-rays beams and are called radiodense, while air allows for passage of all X-ray beams and is called radiolucent. The X-ray source and the detectors are situated on opposite sides of each other. As they rotate around the patient, attenuation profiles of the transversed tissues are acquired as X-ray beams fall through the patient on the detectors. By using attenuation profiles from multiple radial points, we can transform them into images of the organ that is being radiated using advanced computer reconstruction techniques (Figure 2). As the patient is moved axially through the rotating gantry, images are constructed in slices. First-generation scanners took several minutes to perform one scan making them very susceptible for patient movement. In second generation scanners, multiple beam-detector matches instead of one were implemented to reduce scan times. Initial narrow X-ray beams were replaced by fan-beam technology in third generation scanners, reducing scan times even more. At that time, X-ray tube and detectors were connected by cables to the rest of the scanner and after a number of rotations they had to stop and reverse direction. These interscan delays were an important limitation for cardiac imaging, where a fast acquisition time is a prerequisite as the heart is a moving organ.

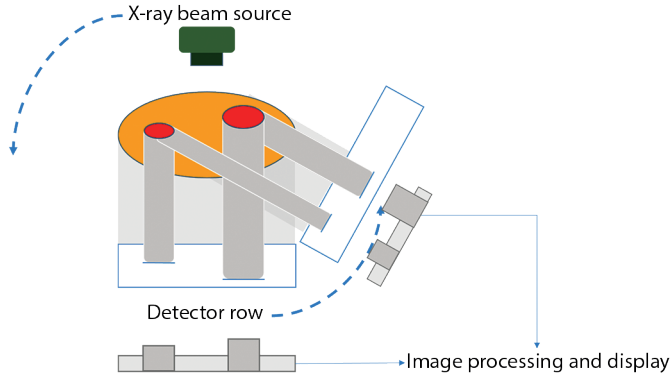

Figure 2 | A rotating X-ray source emits X-ray beams which are, after being attenuated as they pass through a patient, detected on the opposite of side. The detectors transform the incoming attenuation profiles in electronic information which is used by a supercomputer to manufacture an image.

Also, a long acquisition time made good contrast enhancement of the coronary arteries very hard. Two different types of scanners were developed in response, more suitable for cardiac imaging. The electron beam CT scanner, liberated from a mechanically rotating X-ray tube, used an electromagnetically guided electron beam over a tungsten target ring to acquire a slice (tomogram) within 100 milliseconds [5]. Although promising, cost issues and limitations in image quality prevented general acceptance of electron beam CT scanners. Focus was redirected to a different type of scanner, the helical multi-detector scanner with slip-ring technology, precursor of the current

multi-slice scanners, first released in 1992. Slip-ring technology allowed data between the rotating and stationary components in a scanner to be exchanged without fixed connections, eliminating interscan delays. A slip ring is a drum or annulus with grooves along which electrical contact brushes slide (similar to bumper cars). Helical scanners became immensely popular and they improved with increased volume coverage, improved spatial resolution and higher temporal resolution in the years that followed.

To obtain angiographic images, iodinated contrast medium, which is very radiodens, is injected into the vascular system of the patient to enhance the lumen of a blood vessel of interest, revealing the presence and degree of atherosclerosis. Scans without contrast enhancement scans do not allow to differentiate between vessel wall, lumen and atherosclerosis, but can be used to detect and quantitate calcium in coronary arteries, which signifies the presence of atherosclerosis [6]. To date, the coronary calcium score remains a valuable screening tool used next to contrast enhanced coronary computed tomography angiography [7]. In **chapter 2** of this thesis, further technological aspects of cardiac CT imaging, acquisition protocols and their associated radiation exposure are discussed. We also touch upon studies assessing the diagnostic accuracy of coronary CT angiography and some potential clinical applications are discussed.

Soon after the introduction of coronary CT angiography in clinical practice it became evident that this modality was a good angiographic non-invasive alternative for the diagnosis of coronary artery disease, exceeding in the ability to exclude important coronary artery disease [8-10]. Having the ability to reliably exclude coronary artery disease might be of particular benefit to patients who present at the emergency department with suspected coronary artery disease. Although the majority of them have a benign cause for their complaints, missing an acute coronary syndrome can have grave consequences. We investigated the value of coronary CT angiography in patients presenting to the emergency department suspected of an acute coronary syndrome (**part 2).** First, **Chapter 3** provides a systematic review on the diagnostic performance of the most used diagnostic modalities at that time (echocardiography, radionuclide myocardial perfusion imaging and coronary CT angiography) for patients presenting to the emergency department suspected of an acute coronary syndrome. In **chapter 4**, the results of our single-centre, blinded, observational study are presented, which was designed to examine the safety, feasibility and accuracy of coronary CT angiography in this clinical setting. In a sub study, described in **chapter 5,** coronary CT angiography is compared with copeptin, a novel biomarker, released very early in the case of hemodynamic stress. Finally, we designed and performed a multicentre, randomised controlled trial to compare a diagnostic strategy supplemented by early coronary CT angiography with standard optimal care, incorporating new high-sensitivity troponins. The results are presented in **chapter 6**.

While it is becoming evident that coronary CT angiography is a reliable diagnostic modality, expanding to several clinical scenarios, it has been suggested that the presence and degree of coronary artery disease detected by coronary CT angiography also might provide information regarding adverse events in the future.

In **part 3**, we examined the ability of coronary CT angiography to identify patients at higher risk of future adverse events. In **chapter 8**, we compared exercise electrocardiography and coronary

calcium scanning, both minimally invasive tests, as gatekeepers for additional testing. **Chapter 9** describes the prognostic value of coronary CT angiography and the coronary calcium score in high-risk patients without symptoms of coronary artery disease. **Chapter 10** covers the prognostic value of coronary CT angiography in patients with stable angina pectoris and how it compares to that of exercise electrocardiography. Finally, the prognostic implications of non-culprit lesions detected by coronary CT angiography in patients presenting with an acute coronary syndrome is described in **chapter 11**.

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CHAPTER 2

Non-invasive Study of Coronary Stenoses with Multidetector Computed Tomography

Koen Nieman, Admir Dedić, Pim J. de Feyter

Coronary Stenosis Imaging, Structure and Physiology.
Escaned J. & Serruys P.W. Europe Edition, Toulouse. 2nd Edition 2015. p296

Summary

ECG-synchronised computed tomography with intravenously injected contrast medium allows visualisation of the coronary anatomy, detection of luminal obstruction and evaluation of atherosclerotic plaque in the vessel wall. The current state of technology allows routine use of CT angiography, either as the initial test or as an alternative to functional testing, to exclude obstructive coronary artery disease. The high negative predictive value of CT angiography permits reliably exclusion of coronary artery disease. CT angiography may reveal coronary stenoses, which is difficult to visualise with conventional angiography. Combined CT and radionuclide imaging can potentially ascertain the haemodynamic effect of visualised stenoses. Contrary to catheter coronary angiography, CT angiography also images atherosclerotic plaque. Imaging of coronary plaque could improve risk stratification and perhaps lead to optimised risk modification.

Introduction

Despite the impressive quality and versatility of various invasive coronary imaging technologies described elsewhere in this book, there is both a clinical and scientific need for noninvasive imaging of coronary artery disease. The current availability of noninvasive coronary angiography by computed tomography (CT) is the result of an extraordinary technological development, which took place over the past 15 years. While initially electron-beam CT (EBCT) with its high temporal resolution seemed best suited to image the fast moving coronary arteries [1], eventually mechanical, multislice spiral CT emerged as the most widespread CT coronary imaging technique. The feasibility of mechanical (spiral) CT coronary angiography, though still challenging in its performance and interpretation, was demonstrated using 4-slice scanner technology [2,3]. At the present time, 64–320 slice CT scanners deliver reliable coronary imaging on a routine basis, allowing widespread clinical application of this exciting diagnostic modality. Further innovation in terms of scan speed, coverage and radiation dose saving is offered by the latest technology, with development of new applications, including stress imaging.

Principles of Cardiac CT

CT images are created by calculation of the spatial roentgen attenuation throughout a plane from a large number of radial roentgen attenuation projections acquired while the roentgen tube and opposed roentgen detectors rotate around the object. Roentgen attenuation is different for various tissues depending on the atomic mass and density of the material the photons pass through. The ability of CT to differentiate natural tissues is limited, and can be summarised as air containing tissues (lungs), fat tissue, soft tissues and bone.

To create contrast (an attenuation difference) between blood and the surrounding tissues CT angiography requires injection of a (iodine containing) contrast medium. The minimum number of projections needed to reconstruct a cross-sectional image is acquired during an approximate 180 degrees of scanner rotation. Displacement of the object during this half rotation will result in image degradation. To image a continuously moving organ it is crucial to perform this half rotation as fast as possible. The temporal resolution of the CT scanner is determined by the rotation speed of the scanner, but can be further improved by special reconstruction algorithms (multi-segmental reconstruction), or by equipping scanners with more than one tube and detector array (dual-source CT). Additionally, acquisition or reconstruction needs to be performed when cardiac motion is as minimal as possible, usually the mid-diastolic or end-systolic phase of cardiac contraction. Finally, cardiac motion may be reduced by administration of medication to slow the heart rate.

Because the CT scanner does not correct for displacement of the entire heart during acquisition, patients are required to hold their breath during the scan and remain motionless.

The use of spiral CT acquisition, i.e., continuous scanning and uninterrupted patient advancement, and multidetector technology allowed high-resolution CT angiography of the moving heart within the duration of a single breath hold.

Current CT Technology

State-of-the-art CT technology is equipped to simultaneously acquire at least 64 slices and scan the entire heart in no more than a few seconds. Meanwhile, scanners with wider detector collimation have been introduced by most vendors, which further shortened the scan time. Recently 320-detector row CT technology has become available with the advantage of complete coverage of the heart without the need for table movement during imaging of the heart. Cardiac motion artifacts on CT images can be challenging, particularly for patients with a high heart rate. The rotation time of most scanners is around 300 ms, resulting in a temporal resolution of 150 ms. Despite their limitations in efficiency, multi-segmental reconstruction algorithms can improve the effective temporal resolution by combining data from different heart cycles. Alternatively, dual-source CT technology, i.e., scanners are equipped with two sets of roentgen tubes and detectors mounted at a 90 degree angle, allows simultaneous acquisition of two complementary sets of 90-degrees projection data instead of a single 180-degrees dataset. This cuts the acquisition time per slice in half, temporal resolution of 70 ms at a scanner rotation time of 280 ms, irrespective of the heart rate of the patient. Concerns regarding radiation exposure have resulted in hardware and software modifications that have reduced the radiation exposure significantly. While conventional spiral CT acquisition protocols exposed the patient throughout the heart cycle, despite the fact that generally only mid-diastolic images were used for reconstruction of the coronary images, prospectively ECG-triggered tube modulation restricts full output to the cardiac phase of interest. Reintroduction of sequential or step-and-shoot CT imaging has reduced radiation doses to below 5 mSv [4,5,6], which can be further reduced by scanning at a lower tube voltage (80–100 kV) in smaller sized patients [7,8] (Table 1). Wide-detector, single-phase CT imaging is also associated with a lower radiation exposure compared to 64-slice spiral CT [9,10]. Finally, high-pitch, single-phase spiral imaging can bring the exposure below 1 mSv [11,12] (Figure 1).

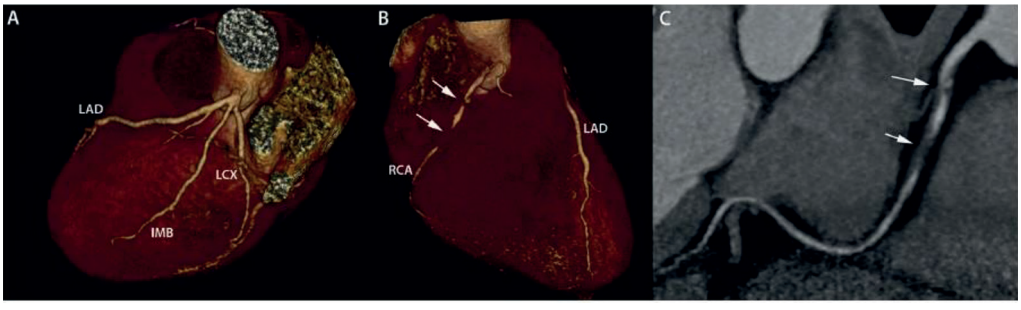

Figure 1 | High-pitch, single-phase cardiac CT angiography. Prospectively ECG-triggered, high-pitch spiral CT angiogram, with 3D volume-rendered (**A**, **B**) and curved-plane reconstruction (**C**), demonstrating severely obstructive coronary artery disease in the right coronary artery (RCA). Left anterior descending coronary artery (LAD), intermediate branch (IMB) and left circumflex coronary artery (LCX).

Table 1 |

CT acquisition techique	Range of average dose (mSv)
Conventional 64-slice spiral CT	12–18
ECG-triggered tube output modulation	8–12
Prospective (step-and-shoot) CT*	2.8–4.2 [4-6]
Lowed tube voltage*	1.5–3.8 [7,8]
320-detector CT	3.9–6.0 [9,10]
High-pitch spiral CT*	0.9 [11,12]

*Selected patients

Imaging Coronary Artery Obstruction

Initial studies comparing four-slice CT angiography and catheter angiography reported promising results, but also exposed the limitations of this technology in terms of temporal resolution, spatial resolution and scan duration [2,3]. In these comparative studies up to a third of the coronary branches needed to be excluded from evaluation as a result of insufficient image interpretability. Many of these excluded branches were affected by motion artifacts. Faster sixteen-slice CT scanners combined with routine use of betablockers to lower the heart rate clearly improved diagnostic performance, while 64-slice CT technology provided the level of image quality and examination convenience that paved the way to widespread clinical use of the noninvasive coronary angiography (Figure 2, Figure 3 and Table 2). The diagnostic performance of (64-slice) CT has been the topic of various meta-analyses, which reported per-patient sensitivities of around 98% and specificities of around 90% to detect "significant" >50% obstructive coronary artery disease [13]. The ability to exclude obstructive disease is very high, as reflected by the excellent per-segment negative predictive value of CT (range 95–100%). On the other hand, overestimation of stenosis severity on CT is common, hence the moderate positive predictive value in most comparative studies, ranging from 44% to 93% on a per segment basis. This tendency for overestimation particularly occurs in the presence of calcifications, which appear enlarged as a result of blooming. Furthermore, the subjective stenosis severity is increased by visualisation of plaque and outward vessel remodelling, which combined with an often defensive diagnostic approach in order not to miss any disease, contributed to the relatively high number of false positive diagnoses. As scanners have become faster and scan duration shorter, diagnostic performance is better with more advanced CT technology. Because motion artifacts occur less in patients with lower heart rates, beta-blockers are routinely administered in patients with heart rates over 65/min to improve image quality. As mentioned, diagnostic performance is better for patients with a low calcium score. Due to limitations in spatial resolution, diagnostic accuracy is better for larger proximal vessels in comparison to smaller branches. In obese patients, image quality is affected by increased levels of image noise, which can affect image quality dramatically. Because most scanners require several heart cycles to collect images, arrhythmia that results in a variable heart cycle duration causes misalignment and potentially missing data between the consecutive stacks of images, which negatively affects image interpretation.

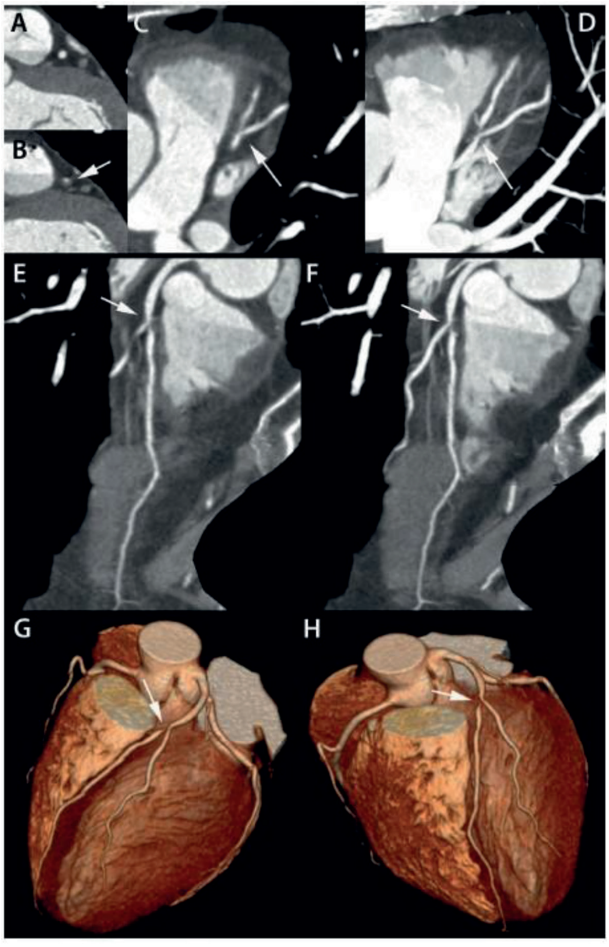

Figure 2 | CT angiography and secondary reconstruction techniques. Obstructive lesion (arrow) in the left anterior descending coronary artery (LAD) imaged by CT angiography and demonstrated using various secondary reconstruction techniques: double-oblique multi-planar imaging along the short (**A**, **B**) and long axis (**C**), maximum-intensity projection (MIP, **D**), curved multiplanar reformation (**E**) and maximum intensity projection (**F**) along the course of the entire LAD, three-dimensional volume-rendered reconstruction (**G**, **H**).

Table 2 |

	N	CAD	Sensitivity	Specificity	PPV	NPV
Miller, et al. [17]	291	56%	85%	90%	91%	83%
Budoff, et al. [18]	230	24%	95%	83%	64%	99%
Meijboom, et al. [19]	360	68%	99%	64%	86%	97%

Since the introduction of 64-slice cardiac CT, technical development has diverged between different CT manufacturers. Dual-source CT technology, which improves the temporal resolution and reduces motion artifacts, has demonstrated improved image quality even without routine use of heart rate modifying mediation [14-16]. All CT manufacturers continue to expand the number of detector rows on CT scanners to shorten the scan time, ranging from 128–320 detector rows. Studies using

320-detector CT, which allows complete coverage of the heart without the need for table movement, demonstrated good diagnostic performance [9,10].

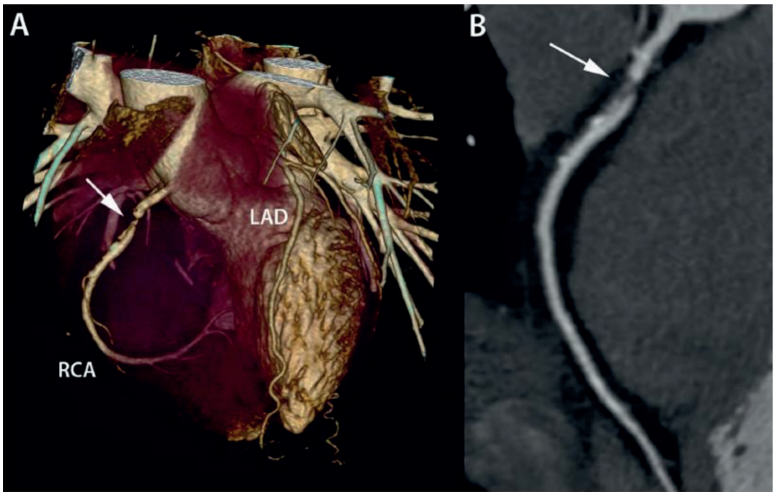

Figure 3 | CT angiography revealing RCA obstruction. Volume rendering and planar curve reconstruction of a severely obstructed right coronary artery (RCA).

Quantitative CT angiography tools are widely available and potentially improve diagnostic accuracy, reproducibility and diagnostic confidence. Despite good correlation, variability between individual quantitative CTA and catheter angiography measurements remains considerable. Given the limited spatial resolution of CT (0.4 mm at best) and the vulnerability of quantitative software to motion, calcium and other artifacts, automatic stenosis severity quantification may be misleading without consideration of the image quality.

Thus far, tools for automatic quantitative stenosis severity assessment, as compared to visual estimation, have not convincingly improved the diagnostic performance of coronary CT [10]. The use of categories of visual obstruction severity, normal, minimal obstructive (<25%), mildly obstructive (<50%), moderately obstructive (50–70%), severely obstructive (>70%) and occluded (100%), are currently recommended.

While CT angiography (CTA) and invasive angiography generally show good correlation, both angiographic techniques show only modest comparability with various invasive and noninvasive functional tests (Figure 4). Several comparisons between CTA and various noninvasive stress tests have been published, which demonstrated that an abnormal CTA does not necessarily imply (detectable) myocardial ischaemia. Myocardial ischaemia in the absence of obstructive disease on CTA is much less likely, although it does occur in clinical practice [21,22,23,24,25].

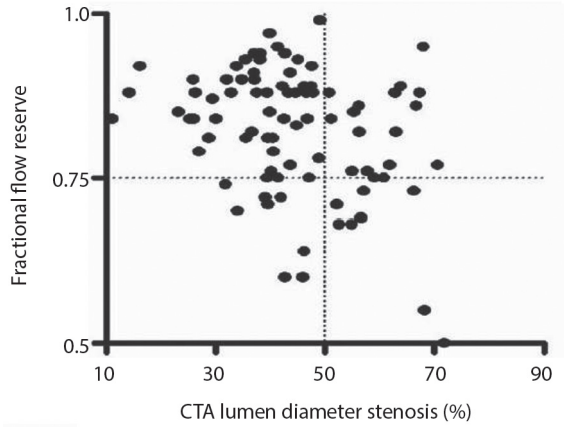

Figure 4 | CTA versus fractional coronary flow reserve. Correlation between CT angiography stenosis severity and intracoronary flow measurements, adapted form Meijboom et al. [20].

Clinical Applications

From the comparative studies between CTA and catheter angiography as well as functional tests we can conclude that CTA has a low detection threshold to coronary artery disease with a tendency to overestimate obstructive severity.

On the other hand CTA rarely misses significant disease as represented by the high sensitivity and negative predictive value in comparison to other techniques. The accuracy to confirm normal or minimally affected coronary arteries is much better than the accuracy to establish the extent of obstructive disease when atherosclerotic, and particularly calcified disease is abundant. In that perspective CTA appears to be particularly useful for exclusion of coronary artery disease in patients without a high pre-test probability of significant coronary artery disease. Although CTA is effective in excluding obstructive coronary artery disease in very low risk patients, the fact that these individuals have an excellent prognosis and may be managed without extensive testing needs consideration. Published consensus documents state that CTA is an acceptable diagnostic option in patients with symptoms, a low to intermediate probability of CAD (15–50%), provided that sufficient expertise is available and the patients lacks characteristics that make the CT exam unreliable (arrhythmia, obesity, contrast allergies, renal dysfunction) [26,27,75,76]. CTA is considered appropriate, particularly when a stress test is not feasible (abnormal resting ECG, inability to exercise), not diagnostic (insufficient exercise performance) or non-conclusive (moderately abnormalities or suboptimal test results). Considering the less than perfect diagnostic performance of stress tests, and particularly exercise electrocardiography with a sensitivity of merely 50–70%, there is a debate whether CTA is preferable as the initial test, reserving stress testing for patients with non-conclusive CTA results. While the recent multicentre PROMISE trial could not demonstrate superiority in terms of hard cardiovascular outcomes, CTA appears to perform equivalently in comparison to established functional test strategy [77].

While CTA is mostly used in patients with stable chest pain complaints, the use of noninvasive coronary angiography to exclude obstructive coronary artery disease also shows promise prior to non-coronary cardiac surgery, (assumed) non-ischaemic heart failure and in the setting of (low-risk)

acute chest pain. Many patients presenting with or after sudden chest pain symptoms and negative initial test (ECG and blood markers) will be admitted for observation, while only a minority will eventually be diagnosed with an acute myocardial infarction or obstructive coronary artery disease. Immediate exclusion of obstructive coronary artery disease makes an acute coronary syndrome unlikely, although observational studies observed a number of events in patients without significant obstructive disease. In the absence of any detectable atherosclerotic disease the odds of an acute coronary syndrome are extremely low; however, this lower threshold will decrease the specificity of the test considerably [28,78]. Randomised controlled trial between CTA and myocardial perfusion imaging in low-risk patients showed that CTA was safe and potentially cost-effective [29,79,80]. Of added value is the ability of CT to exclude other life threatening conditions such as aortic dissection and pulmonary embolism.

An important recommendation, which was explicitly expressed in the ESC consensus document, is that CTA should only be performed when interpretable image quality can be achieved [75]. Conditions that reduce the likelihood of a conclusive examination include arrhythmia, tachycardia, high calcium score, coronary stents, obesity, uncooperativeness.

Registry data from our own institution showed that when the coronary calcium score was more than 400 all but a few CTAs turned out positive, whether true of false, for obstructive coronary artery disease (Figure 5). Considering the limited quantitative correlation between CTA and catheter angiography, and the limited value of anatomical stenosis severity and myocardial ischaemia, clinical use of repeated CTA for monitoring obstructive coronary artery disease progression seems inappropriate.

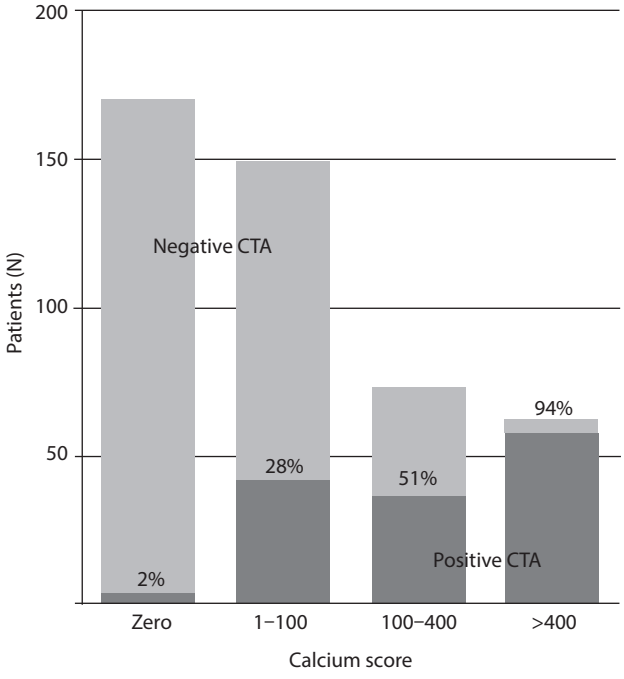

Figure 5 | Calcium score versus CT angiography. Number and percentage of positive CTAs (dark bars, any >50% lumen obstruction) versus the number of negative CTAs (bright bars), stratified by calcium score categories. Obstructive CAD on CT angiography is an infrequent finding when the calcium score is negative. On the other hand, obstructive disease is unlikely to be excluded by CTA in patients with a very high calcium score. Data from Nieman et al. [30].

CTA after Myocardial Revascularisation

As metal attenuates roentgen more than any natural tissue stents are generally well visible as bright structures on conventional greyscale CT images. This strong roentgen attenuation is also the cause of artifacts, which can complicate the assessment of the in-stent lumen. Blooming artifacts, referring to the apparent expansion of the stent strut dimensions on CT, is caused by partial volume effects (related to the spatial resolution of CT) and convolution filters used during reconstruction [31]. These stent artifacts become more severe combined with cardiac motion artifacts. Depending on the stent alloy, the stent design, its diameter size, the scanner and the reconstruction algorithm up to half of the in-stent lumen is affected by these artifacts [32].

Comparative studies between CTA and invasive angiography for the assessment of in-stent restenosis have demonstrated variable results [33,34,35,36,37,38,39] (Figure 6). For instance, the exclusion rate varied between none and 42%, while the sensitivity and specificity varied between 33–100% and 74–98%, respectively (Table 3). A meta-analysis calculated the pooled exclusion rate, sensitivity and specificity of 64-slice CT for the detection of restenosis per stent as, 11%, 82% and 91% [40]. While differences in patients selection and the number of completely occluded stents will be partially responsible for the differences in diagnostic performance between studies, the accuracy of CT is also associated with the earlier mentioned stent diameter size and alloy, and the use of sharp kernels for image reconstruction. Stainless steel is one of the more permissive metal alloys that produce relatively limited artifacts, while cobalt, tantalum and gold cause much more severe artifacts. At the current stage, use of CTA after PCI is restricted to patients with large stents,

in who excellent image quality can be expected [27]. Bioresorbable scaffolds with non-metal backbones interfere much less with interpretation by CTA. In several studies on the performance of a bioresorbable scaffold made of polylactic acid cardiac CT was applied for noninvasive angiographic follow-up [41,81].

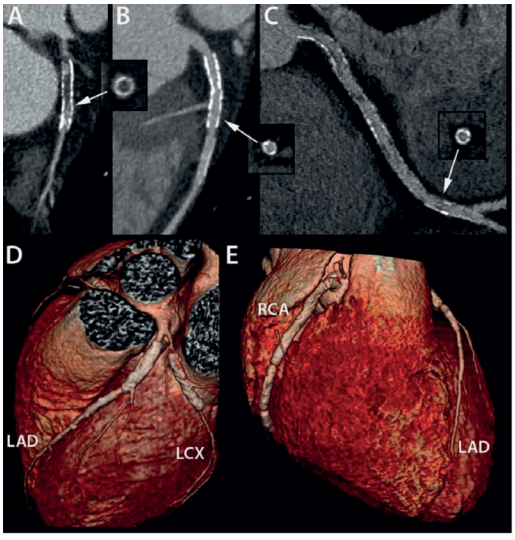

Figure 6 | CT angiography after three-vessel stenting. CT coronary angiography of a patient with stents in all three coronary arteries. The stent in the left circumflex coronary artery (LCX) is occluded (**A**), the two stents in the left anterior descending coronary artery (LAD) are completely patent, and the stents in the right coronary artery (RCA) show various degrees of narrowing (**C**), as confirmed by conventional catheter angiography.

Table 3 |

	N	Stents	ISR	Excl.	Sens	Spec	PPV	NPV
Van Mieghem et al. [33]	64	162	6%	21%	100%	91%	67%	100%
Cademartiri et al. [34]	182	192	11%	7%	95%	93%	63%	99%
Rixe et al. [35]	64	102	12%	42%	89%	98%	86%	98%
Pugliese et al. [36]	100	178	39%	5%	94%	92%	77%	98%
Ehara et al. [37]	81	125	20%	12%	91%	93%	77%	98%
Hecht et al. [38]	67	132	13%	–	94%	74%	39%	99%
Wykrzykowska et al. [39]	52	75	0	36%	33%	92%	57%	81%

CTA after Bypass Graft Surgery

Because bypass grafts have a large diameter with modest displacement during cardiac contraction they can be imaged well by cardiac CT (Table 4, Figure 7). Compared to venous bypass grafts, arterial grafts are smaller in diameter size with more metal clips, which potentially complicate evaluation of the CTA images. Assessment of graft occlusion does not require advanced CT technology and could be performed reliably even with more dated equipment [42,43], although complete coverage

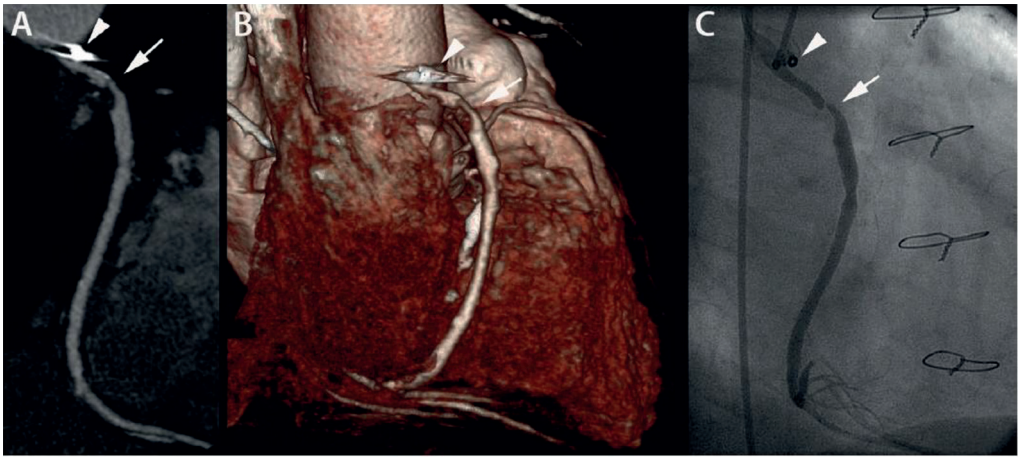

Figure 7 | Occluded LIMA and vein graft disease. Severe obstruction (arrows) of a venous graft to the right coronary artery by CT angiography (**A** and **B**) and conventional angiography (**C**). The animated 3D volume rendered angiogram also shows a string of high-density vascular clips along the anterior surface of the heart, which indicate the trajectory of an occluded left internal mammary grafts to the left anterior descending coronary artery. The metal indicator (arrow heads) near the proximal graft anastomosis causes severe beam hardening artefacts on CTA.

Table 4 |

	Total occlusion				Stenos (50–99%)		
Study	**N**	**Excl**	**Sens**	**spec**	**Excl**	**Sens**	**Spec**
Pache et al.[a] [44]	31	6%	98%	89%			
Malagutti et al. [45]	52	0%	96%	100%	0%	100%	94%
Ropers et al. [46]	50	0%	100%	100%	0%	100%	94%
Meyer et al.[b] [47]	138				2%	97%	97%
Onuma et al.[b] [48]	53				1–10%	100%	91–98%

of the proximal left anterior mammary artery grafts would require a 40 to 50 seconds breath-hold. Imaging of graft stenosis, particularly close to the more motion sensitive coronary anastomoses, has benefited from more advanced CT technology [44,45,46,47,48]. The challenge of imaging patients after coronary artery bypass graft surgery (CABG), however, are not the grafts, but the native coronary branches and the clinical interpretation of detected obstructions. Postsurgical patients often have advanced atherosclerotic disease with extensive deposition of calcium. For this reason, diagnostic performance of CTA of the coronary branches after CABG is inferior to patients without prior surgery [43,45,46,48]. In the presence of diffuse coronary artery disease, developed collateral vasculature and potentially long-standing (subclinical) graft thrombosis, it may be difficult to assess which (if any) stenoses are responsible for the patients complaints, without performing some sort of stress test. In certain situations, CT imaging of the grafts can avoid, simplify or shorten invasive

procedures. CTA can also provide important anatomical information in post-CABG patients (again) undergoing thoracic surgery.

CT Guided Percutaneous Coronary Interventions

Although in the near future CT angiography is unlikely to replace invasive catheter angiography as the roadmap for coronary interventions, there may be complementary use to CT imaging in specific situations. While CTA is inferior to catheter angiography in terms of spatial and temporal resolution, it has practical advantages and outperforms projectional lumenography where three-dimensional orientation and visualisation of the vessel wall are concerned.

Without the requirement of selective ostial engagement, CTA effectively images obstructive disease in proximal coronary branches, as well as anomalous coronary arteries and occluded grafts (Figure 8). Because CT is not a projectional technique the exact angle between branches can be determined, which can be helpful prior to revascularisation of bifurcation stenoses (Figure 9). Recanalisation of chronic total occlusions remains a challenge. CTA can provide additional information with regard to the length of the occlusion, calcifications within the occluded vessel segment, which predicts and potentially positively affects success of the revascularisation procedure [49,50] (Figure 10). Finally, the CT angiogram may be integrated as a roadmap for advanced revascularisation techniques, such as magnet navigated revascularisation procedures [51].

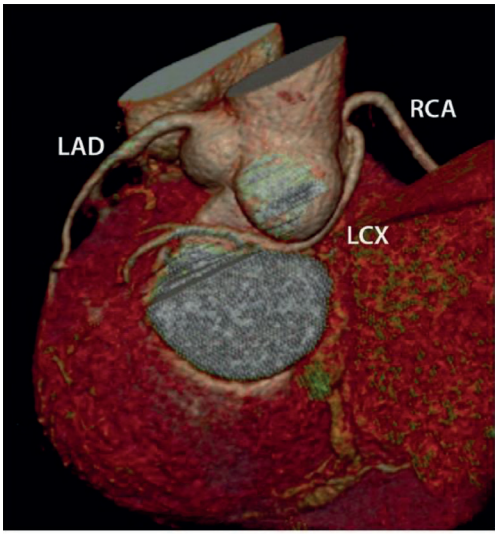

Figure 8 | Anomalous origin of the left circumflex coronary artery. 3D CT angiogram with a posterior view of the heart after removal of the left atrium, shows the anomalous origin of the left circumflex coronary artery from the right sinus of Valsalva, and its trajectory behind the aortic root towards the left interventricular groove.

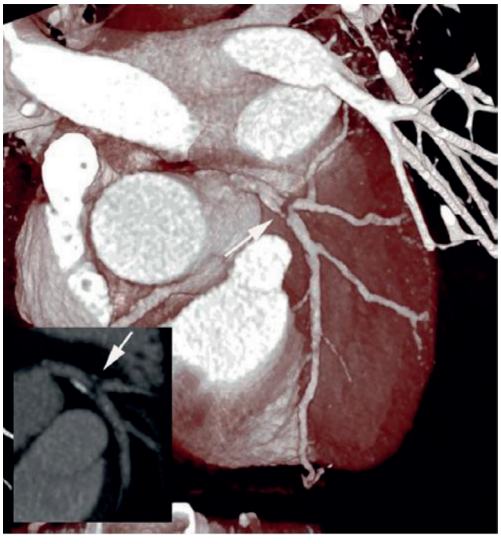

Figure 9 | Left main coronary artery bifurcation stenosis. Severe stenosis of the left main bifurcation caused by plaque of mixed composition on opposite sides of the distal left main coronary artery.

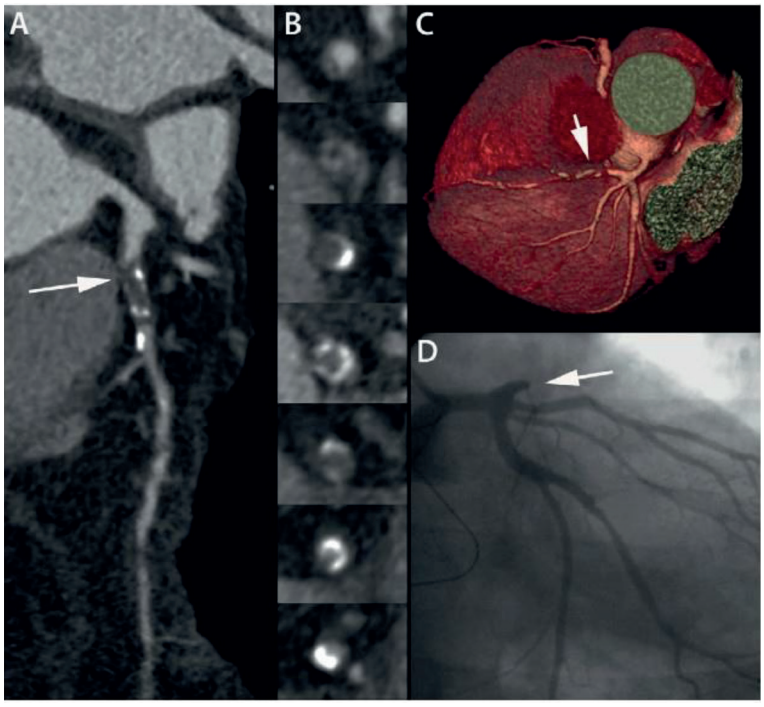

Figure 10 | Chronic LAD occlusion. CT angiography (**A**, **B** and **C**) prior to recanalisation of a chronically occluded left anterior descending coronary artery. Contrary to the catheter angiogram (**D**), CT visualises the length of the occlusion, its content in terms of calcium or non-calcified tissue, and the presence and location of side branches. Panels B are consecutive cross-sections of the middle segment of the LAD.

Functional Assessment of Coronary Artery Disease

At the current time, cardiac CT is predominantly used for assessment of coronary lumen stenosis. Similar to invasive angiography, cardiac CT is not easily able to differentiate haemodynamically significant from non-significant luminal narrowing. There are various means to overcome this limitation. The diagnostic performance of CT allows confident exclusion of (haemodynamically) significant coronary artery disease in the majority of patients. In case of coronary lumen narrowing, CT may be followed by a (noninvasive) stress test, for instance myocardial perfusion imaging or merely an exercise ECG, to assess whether myocardial ischaemia can be induced. Alternatively, multidetector CT can be physically combined with a myocardial perfusion imaging modality, for instance single-photon-emission computed tomography or positron emission tomography, to correlate coronary obstruction and inducible myocardial ischaemia in a single examination.

As a third alternative stress myocardial perfusion imaging may be performed using CT itself. Dynamic perfusion imaging has been performed in the past using electron-beam computed tomography [52]. Recently, as a result of wider longitudinal coverage and low-dose scan techniques, adenosine stress perfusion imaging using mechanical cardiac CT has been revisited. The least demanding stress perfusion methodology involves the acquisition of a single CT dataset during

myocardial enhancement during hyperemia by intravenous infusion of adenosine or another vasodilator. Feasibility of the technique and the potential for incremental diagnostic accuracy, has been demonstrated in several single and multicentre studies [53,54,82,83]. Alternatively, repeated scans can be performed during injection of contrast medium to acquire time-attenuation curves of the myocardium and calculate the myocardial blood flow. The latter technique, known as dynamic perfusion imaging, requires more advanced CT technology with extended coverage and is associated with a higher radiation dose. Advantages include the ability of absolute flow calculation and the apparent lower susceptibility to beam hardening artifacts (Figure 11).

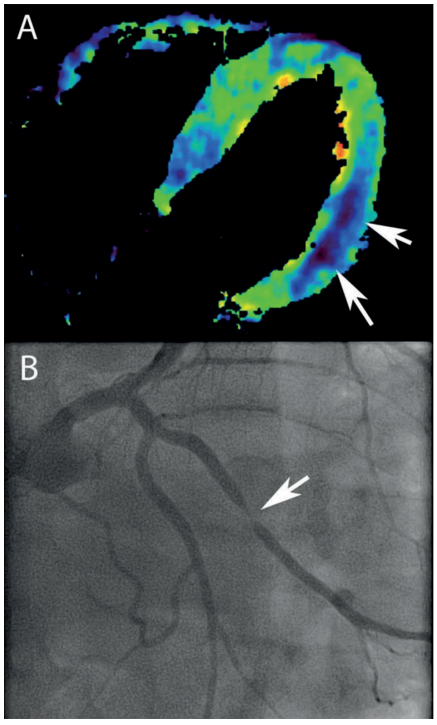

Figure 11 | CT myocardial perfusion imaging. Dynamic myocardial perfusion imaging after adenosine vasodilation using a third generation dual-source CT system. The calculated myocardial blood flow is lower, displayed as blue (arrows), in the lateral wall (**A**), corresponding to a stenosis (arrow) in the marginal branch of the left circumflex coronary artery (**B**).

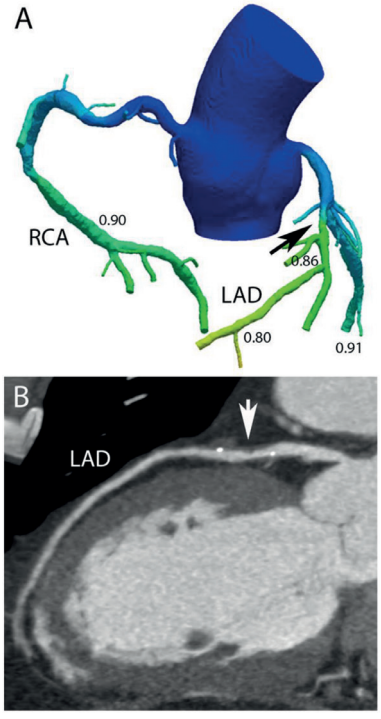

Figure 12 | CTA derived fractional flow reserve. Three-dimensional display of the coronary anatomy, and superimposed in colour the spatially distributed fractional flow values as calculated from the CT angiogram using computational fluid dynamics (**A**). CT angiography follow-up after implantation of a bioresorbable coronary scaffold in the left anterior descending coronary artery (LAD), as indicated by the two platinum indicator, which shows moderate angiographic obstruction. CTA based fractional flow reserve shows that the FFR decreases to 0.86 distal to the scaffolded segment, but not reach 0.80 until very distally.

Smaller studies have demonstrate the feasibility and incremental diagnostic value of the technique over CTA, although large multicentre trials have not yet been performed [84,85].

An new method to assess the hemodynamic severity of coronary artery disease is the calculation of fractional flow reserve from CT images using computational fluid dynamics (Figure 12). Similar to applications used in the aviation industry, the modelling of flow in interaction with form can be simulated for the coronary arteries. Using these models flow and pressure can be calculated throughout the coronary arteries, including the calculation of the fractional flow reserve, but without the need for injection of vasodilator [86]. In controlled studies CTA based fractional flow reserve performs well and provides incremental diagnostic value over CTA alone [87]. In addition to remote services for CTA-FFR calculation, also locally performed interpretations of functional severity based on CT anatomy are currently developed [88]. Both myocardial perfusion imaging and CTA based fractional flow reserve represent promising new techniques that add valuable functional information for therapeutic decision.

Infarct Imaging

The permanent consequences of coronary artery disease to the myocardium can also be visualised using cardiac CT. Without adenosine stress perfusion defects may be observed in patients with severe myocardial ischaemia and more frequently after suffering myocardial infarction (Figure 13). On CT chronic myocardial infarction is associated wall thinning, dilatation and quite frequently fatty infiltration (with very low CT attenuation values) [55]. Similar to magnetic resonance imaging (MRI), infarcted myocardium displays increased contrast enhancement approximately 10 minutes after contrast administration, as a result of delayed wash-in and wash-out of contrast medium within the necrotic or fibrotic myocardium, of acute or chronic myocardial infarction, respectively [56,57,58,59]. Although the quality of CT delayed enhancement imaging is still regarded inferior to MRI, there are clinical situations (pacemakers, claustrophobia) where CT could be a useful alternative. If during a CT scan data are acquired continuously throughout the cardiac cycle, which is no longer routinely done, reconstruction of sequential cardiac phases allows evaluation of the left ventricular function. Global parameters of LV function: end-diastolic and end-systolic LV volumes, stroke volume and ejection fraction, by CT correlate well with other imaging techniques. In addition, regional wall motion can be displayed by viewing consecutive CT reconstructions in motion (Figure 14).

Coronary Plaque Imaging

Visualisation and quantification of calcified plaque perhaps was the first coronary applications of computed tomography. Because of the inherent high attenuation of calcium it can be imaged without the need for injection of contrast medium. Coronary calcium is almost exclusively the result of coronary atherosclerosis, but not necessarily in association with luminal obstruction. Neither does the absence of detectable calcium exclude the presence of atherosclerotic plaque, although the probability of severely obstructive coronary disease will very low in most populations [30]. On the other hand, a high calcium score does increase the probability of obstructive disease, particularly in symptomatic populations [60]. Quantification of the coronary calcium burden correlates with the overall extent of atherosclerosis, and is associated with adverse cardiovascular events [60,62].

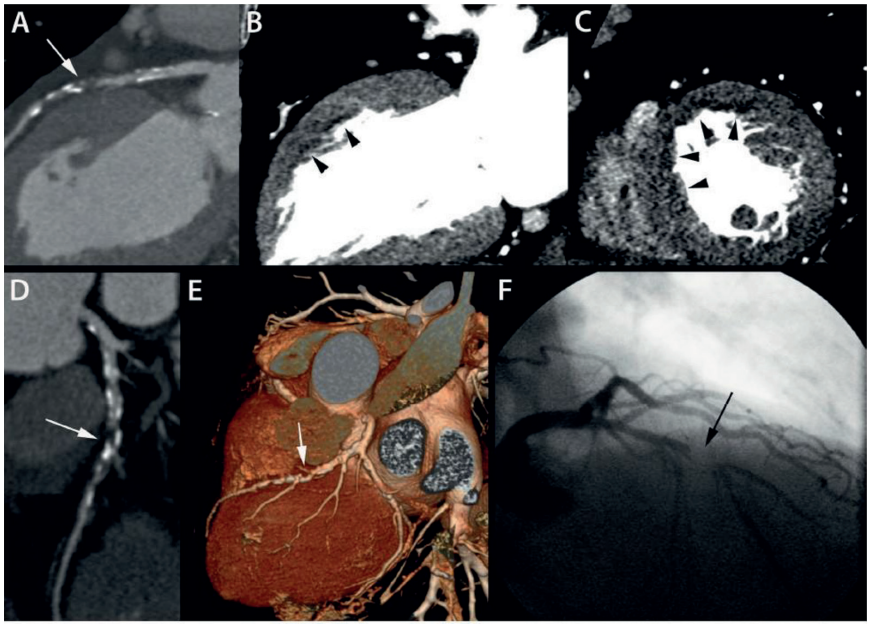

Figure 13 | Myocardial ischaemia by cardiac CT. CT angiography (panels **A**, **D** and **E**) and invasive angiography (panel **F**) showing severe obstruction of the left anterior descending coronary artery (arrow). In addition, the anterior wall shows decreased enhancement (arrow heads) of the subendocardial myocardium on the CT angiogram (**B** and **C**).

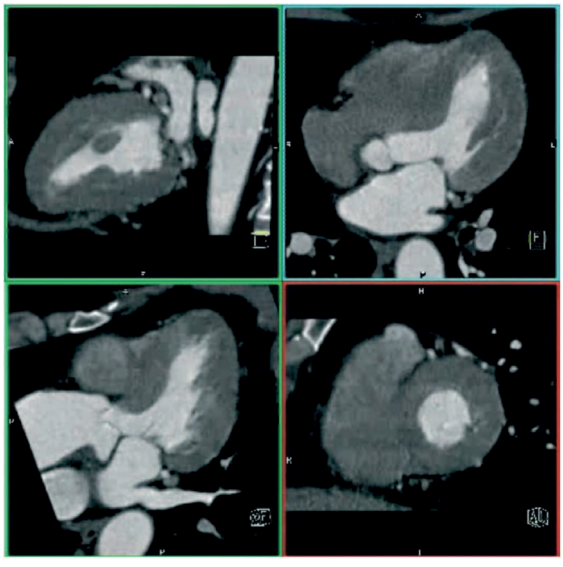

Figure 14 | Assessment of left ventricular function with CT. Assessment of left ventricular function and regional wall motion can be performed with using consecutive CT reconstructions.

For this reason, calcium scanning can be used for (further) risk stratification of asymptomatic individuals, particularly those at intermediate risk by traditional risk factors [63].

Contrary to invasive catheter angiography, contrast-enhanced CT angiography can visualise the atherosclerotic coronary wall and distinguish calcified and non-calcified plaque material (Figure 15 and Figure 16). While on average lipid-rich plaques have lower measured attenuation values (CT number in Hounsfield units) compared to fibrous plaque [64,65,66], differentiation of individual plaques remains difficult as the measured values are affected by the limited spatial resolution, residual coronary motion, reconstruction filtering and the contrast intensity of the adjacent coronary lumen [67].

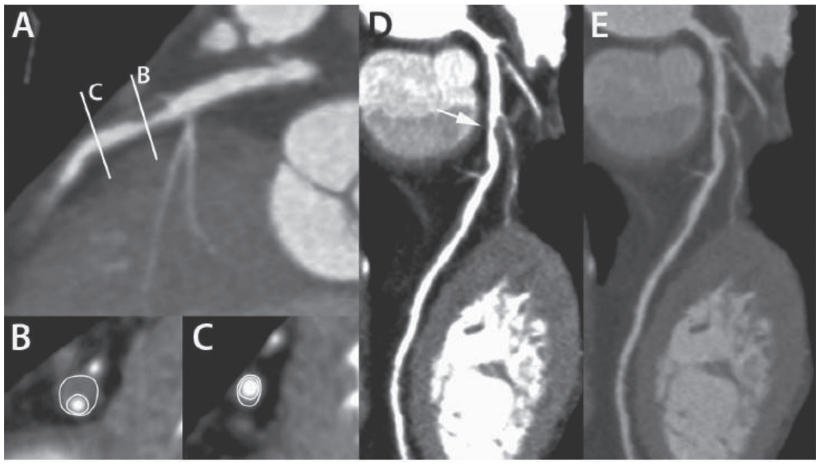

Figure 15 | Non-calcified coronary plaque. Symptomatic male with moderately obstructive coronary artery disease. The left anterior descending coronary artery shows (**A**) noncalcified plaque at several locations, with evident outward vessel remodelling in the proximal LAD (cross-sections **B** and **C**). Better visualisation of noncalcified plaque requires optimisation of the display settings (window level and width, **D**, **E**).

Quantification of coronary plaque on CT correlates fairly well with invasive coronary imaging techniques [68,69]. Limited reproducibility of total plaque quantification [68,69], predominantly the result of poor delineation of the outer vessel border, may be overcome by more standardised acquisition techniques and automatic quantification tools. In one study the average annual progression of overall plaque on CT in a selected population was reported as 22% (95% confidence interval 15–30%) [70]. In addition to the presence of low-density plaque, CT studies in patients who suffered an acute coronary syndrome have revealed various other parameters associated with plaque instability, including large plaque size, outward vessel remodelling (Figure 15), and spotty calcifications [71,72,73]. Finally, preliminary data suggests that low-density plaque and outward vessel remodelling on coronary CTA predict adverse cardiovascular events [74].

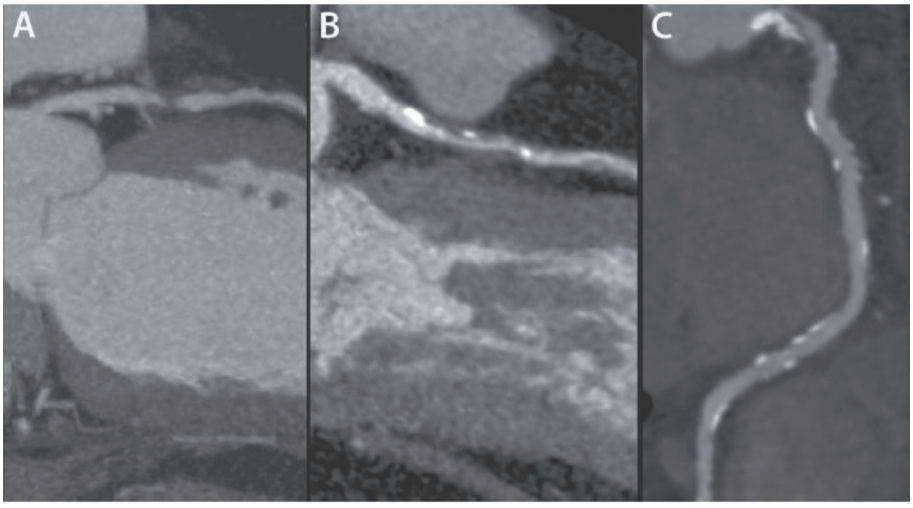

Figure 16 | Coronary plaque by CT angiography. Examples of noncalcified, severely obstructive, coronary plaque in the left anterior descending coronary artery (**A**), plaque of mixed composition also in the left anterior descending coronary artery (**B**), and predominantly calcified plaque in the right coronary artery (**C**).

Conclusions

- Contemporary CT technology allows for diagnostic noninvasive coronary angiography in the majority of patients with symptoms of coronary artery disease.
- High image quality requires patient cooperation and often heart rate modulation.
- Interpretability of the CT images is negatively affected by arrhythmia, obesity, extensive calcification, and previous revascularisation procedures.
- CT angiography is effective for exclusion of obstructive coronary artery disease in patients with a low-intermediate probability, or when functional testing cannot be performed or rendered inconclusive results.
- Evaluation of haemodynamic significance and the need for revascularisation of (moderately) obstructive coronary disease by CTA often requires further invasive or noninvasive functional testing.
- New CT applications for evaluation of the functional severity of coronary artery disease include stress myocardial perfusion imaging and CTA based computation of fractional flow reserve.
- •While invasive angiography remains superior in many ways, CT angiography has practical advantages and can provide complementary information concerning the three-dimensional coronary anatomy, ostial and bifurcation disease, chronic total occlusion of coronary arteries and bypass grafts, as well as plaque imaging.
- Although the CT plaque imaging is limited by spatial and contrast resolution, this non-invasive modality does allow for differentiation of calcified and non-calcified plaque and assessment of outward vessel remodelling, which has prognostic value.

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Part 2

Coronary CT Angiography in Suspected Acute Coronary Syndrome

CHAPTER 3

Imaging Strategies for Acute Chest Pain in the Emergency Department

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Objective

Echocardiography, radionuclide myocardial perfusion imaging (MPI), and coronary CT angiography (CTA) are the three main imaging techniques used in the emergency department for the diagnosis of acute coronary syndrome (ACS). The purpose of this article is to quantitatively examine existing evidence about the diagnostic performance of these imaging tests in this setting.

Conclusion

Our systematic search of the medical literature showed no significant difference between the modalities for the detection of ACS in the emergency department. There was a slight, positive trend favoring coronary CTA. Given the absence of large differences in diagnostic performance, practical aspects such as local practice, expertise, medical facilities, and individual patient characteristics may be more important.

The entity acute coronary syndrome (ACS) encompasses the conditions unstable angina pectoris and myocardial infarction (MI) with or without ST-segment elevation. MI is a diagnosis based on patient symptoms, ECG changes, and markers of myocardial necrosis in the blood [1]. Unstable angina pectoris, on the other hand, indicates myocardial ischemia without biochemical evidence of cardiac myocyte death [2].

Patients with ACS frequently present with atypical chest pain complaints, unremarkable findings on physical examination, and an ECG that either is difficult to interpret or has normalized at presentation [3]. Cardiac biomarkers are often normal during the initial phase and patients with unstable angina may not show a rise of these markers at all. In these patients, ACS cannot be ruled out on the basis of an initial assessment alone, which generally requires clinical observation and sequential testing. Optimal triage re-quires a quick noninvasive test that is cost-effective and is readily available to identify all patients with ACS. Moreover, a triage test should also be able to accurately identify patients in whom significant coronary artery disease (CAD) can be excluded and who can thus safely be discharged. This article quantitatively examines the existing evidence about the diagnostic performance of imaging tests in this setting.

Background and Importance

Acute chest pain is a common diagnostic dilemma in the emergency department and its impact on the health care system is substantial, with an estimated annual cost of sever-al billions of dollars in the United States [4]. Emergency department physicians and cardiologists are commonly required to make a decision whether to admit a patient with chest pain based on little more than clinical judgment and a rough estimation of risk but without conclusive evidence whether ACS is developing. Most patients presenting to the emergency department with sudden chest pain do not suffer from ACS and many are, in fact, free of CAD [5]. In the majority of cases, chest pain can be explained by other causes such as gastroesophageal diseases and chest wall syndromes [6]. Nevertheless, the risk of overlooking an underlying ACS has major consequences, which is why most patients are hospitalized to undergo additional stress testing and even invasive coronary angiography (CAG) to rule out ischemic heart disease. The results of a large multicenter study showed that although most patients with suspected ACS were hospitalized for further evaluation, only 17% was ultimately diagnosed with ACS [7]. Despite this defensive approach, the literature suggests that an estimated 2–6% of the patients discharged from the emergency department were found to have ACS [8-12]. Patients with ACS who are mistakenly discharged from the emergency department generally have a worse prognosis than appropriately managed patients, partly because of their risk for sudden cardiac death but also because of the delay in implementing treatments that are known to be beneficial for ACS [8,11]. In the United States, an estimated 25% of the lawsuits concerning emergency care involves errors in the diagnosis of MI [13].

Synopsis and Synthesis of Evidence

Echocardiography, radionuclide myocardial perfusion imaging (MPI), and coronary CT angiography (CTA) are the three main imaging techniques used in clinical practice for the diagnosis of ACS. Echocardiography and MPI are functional imaging modalities used to assess wall motion abnormalities (WMAs) and myocardial perfusion. Performed while the patient is resting, these modalities are used to identify ACS. They can also be performed during or after stress to detect inducible ischemia. Coronary CTA is an anatomic technique that can depict atherosclerotic plaque in the coronary tree and provide information about its composition and the degree of stenosis. A discussion of each technique follows, with a summary of these imaging techniques shown in Table 1.

Table 1 | Major Advantages and Disadvantages of Imaging Techniques for the Detection of Acute Coronary Syndrome

Imaging Technique	Major Advantages	Major Disadvantages
Echocardiography	Readily accessible	Poor sensitivity
	Portable	Operator and reader dependent
	Safe	
	Less expensive than MPI and CTA	Poor thoracic window in at least 10% of patients
	Allows assessment of many nonischemic causes of acute chest pain	
Radionuclide MPI	High sensitivity and high specificity	Logistic barrier
		Radiation exposure
		Expensive
Coronary CTA	High sensitivity and high specificity	Radiation exposure
	Identification of noncoronary conditions	
	Fast	

Note—MPI = myocardial perfusion imaging, CTA = CT angiography.

Echocardiography

Echocardiography is a noninvasive, portable, and relatively inexpensive bedside imaging technique that is available in most hospitals. It can assess both left ventricular systolic function and regional WMAs and therefore provides valuable diagnostic as well as prognostic information. Because of the close relationship between wall motion and myocardial blood flow (MBF), echocardiography is a very useful tool in patients with suspected ACS. Development of WMAs is preceded by considerable reductions in MBF. Echocardiography is also useful in the assessment of many nonischemic causes of acute chest pain such as perimyocarditis, valvular heart disease, cardiomyopathy, pulmonary embolism, or aortic dissection. It is the preferred imaging method for detecting complications of acute infarction including myocardial free wall rupture, acute ventricular septal defect, and mitral regurgitation secondary to papillary muscle rupture or ischemia.

Rest Echocardiography

When echocardiography is performed soon after a patient arrives at the emergency department or during a chest pain episode, WMAs are detected in up to 90% of the cases [14]. However, chest pain has subsided in most patients at the time of evaluation and the resting echocardiogram may be completely normal. Investigators of a large study reported rest echocardiographic findings of 901 patients with acute chest pain but no clinical manifestations of acute myocardial infarction (AMI) as part of protocol-driven care along with serial myocardial bound creatine kinase measurements and continuous ECG monitoring. Rest echocardiography was associated with high specificity (99%, 873/882) but unsatisfactory sensitivity (47%, 9/19) for adverse events within 30 days, including MI, revascularization, or unstable angina [15]. Smaller studies have shown similar results [16,17]. Di Pasquale et al. performed rest echo-cardiography in 280 patients presenting with chest pain of suspected cardiac origin but normal initial CK-MB levels and no evidence of ST-elevation or new left bundle branch block on ECG. The presence of WMAs was used to predict significant stenosis (>50% left main coronary stenosis or >70% stenosis in other branches) on invasive CAG. In this high-risk population, with significant CAD present in 50% of patients, the authors found, once again, not only a high specificity of 91% (84/92) but also a high sensitivity of 93% (170/182).

Contrast-enhanced Echocardiography

Microbubble contrast agents enhance delineation of endocardial borders, which facilitates wall motion assessment (Figure 1). Imaging using these agents also provides important information about myocardial perfusion and viability [19]. In a prospective analysis of 114 patients with cardiac chest pain and no clinical manifestations of AMI, Kang et al. found that the addition of contrast material improved the sensitivity of echocardiography from 49% (43/87) to 77% (67/87), whereas specificity was similar, 78% (74/95) versus 73% (69/95), for the detection of ACS at the index visit. In a large observational study, 1017 patients underwent contrast-enhanced echocardiography in addition to routine clinical evaluation. For the detection of a composite endpoint of CAD within 48 hours of presentation, the authors reported a high sensitivity of 89% (148/166) and a modest specificity of 57% (485/851) [20].

Stress Echocardiography

Generally excluding only MI will not be sufficient to safely discharge patients. Patients may have myocardial ischemia with unstable angina pectoris, putting them at risk of adverse events. As soon as serial cardiac markers and rest imaging have excluded the presence of AMI, stress echocardiography, which is performed during pharmacologic stress or exercise, may be used to visualize inducible ischemia. Trippi and colleagues investigated the diagnostic performance of stress echocardiography in 163 patients with normal initial markers and normal findings on resting echocardiography. They reported a sensitivity of 89% (17/19) and specificity of 89% (128/144) for the detection of AMI or significant CAD (>50% stenosis) on invasive angiography [21]. In another study, investigators compared stress echocardiography with stress MPI in 503 patients without evidence of AMI after 6 hours of observation and initial workup [22]. The authors used a composite endpoint consisting of ≥50% coronary stenosis on invasive CAG or cardiac events during a follow-up of 6 months.

Echocardiography had sensitivity and specificity of 85% (80/94) and 95% (390/409), respectively, and MPI had a sensitivity and specificity of 86% (81/94) and 90% (369/409).

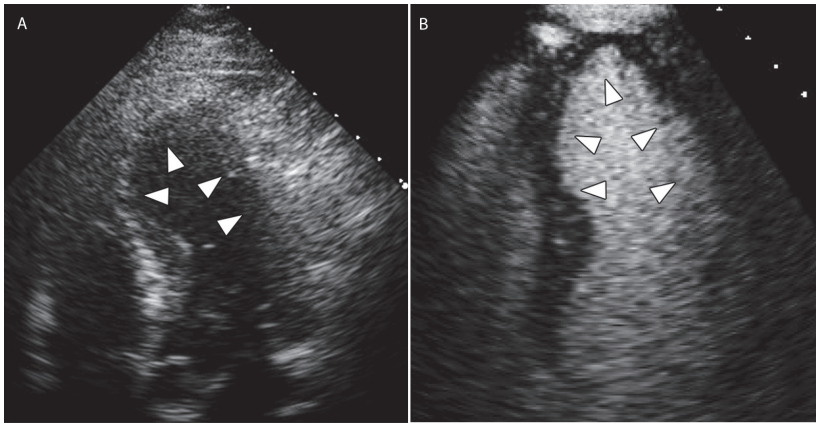


Figure 1 | A 67-year-old man suspected to have myocardial ischemia who was referred for echocardiography. (**A**) Microbubble contrast agents were used to enhance delineation of endocardial borders. Arrowheads in A indicate endocardial borders on unenhanced echocardiography, and arrowheads in B indicate improved delineation of endocardial borders by using contrast agents. (**B**) Microbubble contrast agents were used to enhance delineation of endocardial borders. Arrowheads in A indicate endocardial borders on unenhanced echocardiography, and arrowheads in B indicate improved delineation of endocardial borders by using contrast agents.

Limitations

There are some key concerns regarding the use of echocardiography in the ED. Evaluation of remains a subjective and difficult skill to master. Interpreters should there-fore be experienced readers. Second, a considerable number of patients have a poor thoracic imaging window resulting in indeterminate findings in at least 10% [23]. Discriminating between existing WMAs and newly developed WMAs is difficult, and both conditions may even coexist in the same patient. AMI should be excluded before performing stress echocardiography by measuring serial cardiac markers or performing rest imaging. This step results in a longer diagnostic workup.

Myocardial Perfusion Imaging

Radionuclide MPI provides a direct assessment of MBF and is used for identification of ischemia or infarction. The injected radionuclide agents are transported through the coronary vasculature and eventually accumulate in the myocardium. At the moment of MBF impairment, MPI shows perfusion defects that allow early detection of obstructive CAD. Pioneer work from four decades ago showed that impaired myocardial uptake of 201Tl could be visualized on planar images in patients with MI [24]. By now, 201Tl has largely been replaced by 99mTc-based agents, which are associated with less scatter and blurring. Images could be acquired over a longer time because of slow myocardial

clearance, overcoming some logistic barriers [25]. Replacements of planar imaging by SPECT have resulted in improved visualization of the location as well as extent of disease [26]. Last, introduction of gated reconstructions permits assessments of regional and global ventricular function [27].

Rest myocardial Perfusion Imaging

The value of rest MPI in the patient with acute chest pain has been studied extensively. Numerous studies have reported sensitivities of more than 90% for the detection of MI ac-companied by specificities of 50–80% [28-30]. One study conducted at the Medical College of Virginia in 620 patients with suspected ACS reported a sensitivity of 92% (54/59) and a specificity of 67% (376/561) for the detection of AMI. Among the 59 patients with AMI, five patients with an enzymatic small infarction had normal findings on rest MPI. The diagnostic performance to predict the need for revascularization was some-what lower: a sensitivity of 81% (47/58) and a specificity of 74% (416/562). In a randomized trial, Udelson et al. re-ported that the addition of rest MPI to standard care decreased the number of unnecessary ad-missions without an increase in inadvertent discharge of patients with acute cardiac ischemia.

Stress Myocardial Perfusion Imaging

Conti and colleagues evaluated the implementation of exercise MPI in the early triage of 306 patients with suspected ACS and nor-mal findings on an initial workup (Figure 2). The sensitivity and specificity to predict significant CAD or adverse events within 6 months were 94% (45/48) and 77% (198/258), respectively. A large observational study of 805 patients with low to intermediate risk of CAD compared the diagnostic performance of rest MPI with stress MPI. In that study, investigators evaluated the sensitivity and specificity for diagnosing the following events within 30 days of MPI: AMI, revascularization, stenosis of more than 70% on invasive CAG not amenable to revascularization, life-threatening complication, or cardiac death. The sensitivity and specificity of rest MPI, 71% (109/153) and 73% (476/652), respectively, were significantly lower than the sensitivity and specificity of stress MPI, 97% (148/153) and 88% (574/652) [33]. In 2007, investigators com-pared stress MPI with CTA in a randomized trial of low-risk patients without evidence of AMI [34]. They found that the diagnostic performance of MPI and CTA was comparable, but there were reductions in the time-to-diagnosis and cost in the CTA group.

Limitations

The limited availability of nu-clear facilities in some hospitals and transportation of patients to the nuclear medicine department may form a barrier to the use of MPI. Physicians should be aware of possible false-negative results of rest images in patients with subsided chest pain or balanced ischemia caused by three-vessel disease [35]. AMI should be excluded before performing stress MPI by measuring serial cardiac markers or performing rest imaging. The need to exclude AMI results in a longer diagnostic workup. Finally, there is concern about the increasing radiation exposure from diagnostic imaging procedures and the potential risk of cancer [36].

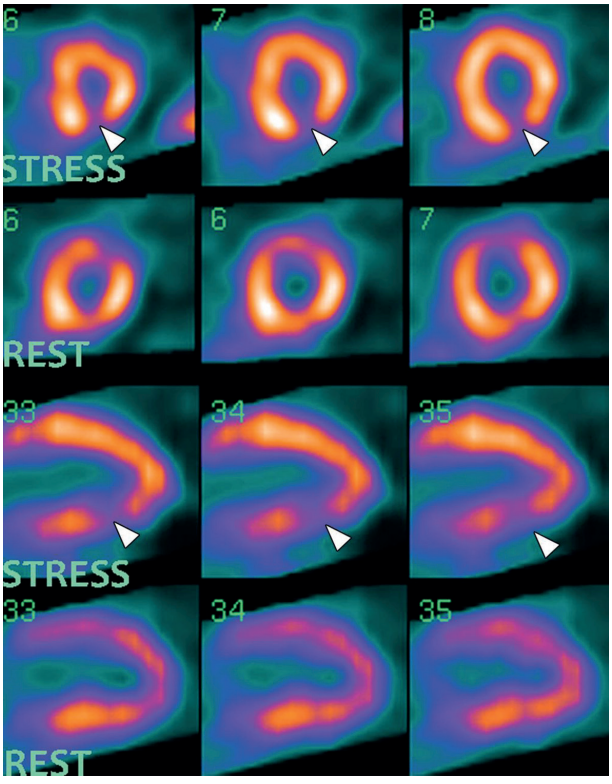


Figure 2 | 51-year-old woman who presented with acute chest pain in emergency department. Short-axis and long-axis stress and rest nuclear perfusion scans show ischemia of inferior left ventricular wall. Arrowheads indicate diminished perfusion of inferior wall during stress acquisition.

Coronary CT Angiography

Coronary CTA can provide high-quality images of the heart and coronary vasculature and requires minimal patient cooperation (Figure 3). Coronary CTA provides accurate information about the degree of stenosis as well as certain characteristics of plaque, such as spotty calcification and low attenuation, that are associated with a higher risk of future ACS [37,38].

Image acquisition with coronary CTA can be performed in minutes. Widely available dedicated software for automated post-processing makes interpretation quick and undemanding. In the past years, numerous articles about the diagnostic performance of coronary CTA have been published. In recent reviews, investigators reported sensitivities of greater than 95% and specificities of 90% or greater [39,40]. In a large observational study in an emergency department setting, Hoffmann et al. reported that the sensitivity of CTA for the detection of ACS was high and that the absence of atherosclerosis was associated with an excel-lent 6-month outcome. The results of that study confirmed the results of some earlier, smaller studies [42-44]. Recently, a large multicenter randomized trial (CT-STAT) focused on the cost-effectiveness of CTA versus nuclear imaging. Low-risk patients were randomly allocated to undergo CTA (n=361) instead of rest and stress MPI (n=338) [45]. The CTA strategy reduced time-to-diagnosis by 54% and costs of care by 38%. The occurrence

of major ad-verse cardiac events (MACEs) was similar for CTA and nuclear imaging. However, that study was powered to detect a difference in the primary endpoint – that is, the time-to-diagnosis – and it may be underpowered to detect a difference in MACEs.

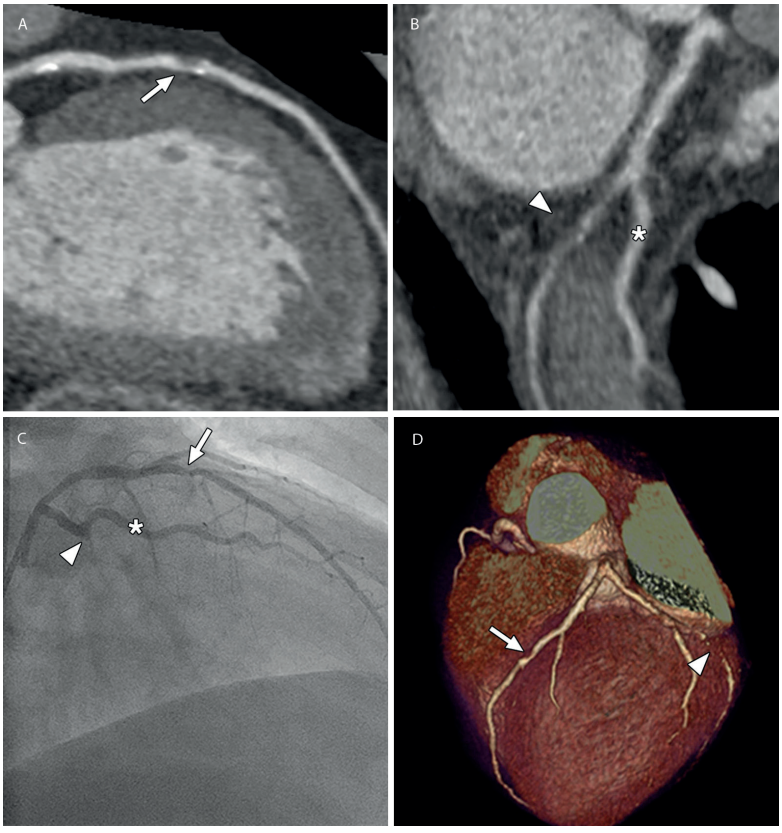


Figure 3 | 59-year-old man who presented with acute chest pain. Coronary CT angiography (CTA) was performed in emergency department. (**A**) CTA images show obstructive disease of left anterior descending artery (arrow, A) and occlusion of left circumflex artery (arrowhead, B). First marginal branch (asterisk, B) is shown. (**B**) CTA images show obstructive disease of left anterior descending artery (arrow, A) and occlusion of left circumflex artery (arrowhead, B). First marginal branch (asterisk, B) is shown. (**C**) Catheter angiogram shows lesions in left anterior descending (arrow) and left circumflex arteries (arrowhead). Occlusion of left circumflex artery (asterisk) is denoted by abrupt filling of contrast material after bifurcation of first marginal branch. (**D**)Three-dimensional volume-rendered image shows lesions in lieft anterior descending (arrow) and left circumflex (arrowhead) arteries.

Additionally, coronary CTA allows evaluation of important non-coronary cardiac findings. Depending on the scanning protocol, conditions such as acute aortic syndromes, pulmonary embolism, or esophageal abnormalities may be detected. Incidental findings may increase down-stream testing

(e.g., CT for the workup and follow-up of pulmonary nodules). Studies that account for the costs of this additional testing are needed to evaluate the implications for the cost-effectiveness of coronary CTA.

High-attenuation structures such as calcified plaques or stents appear enlarged (or "bloomed") as a result of partial volume and beam-hardening effects. These artifacts obscure the adjacent lumen and may result in false-positive results. In response to the concern about the potential risk related to radiation exposure, several radiation dose reduction protocols have recently been developed and validated, including ECG-dependent tube modulation, prospective ECG gating, adaptive iterative reconstruction, and high-pitch helical acquisition [46-48]. When these techniques are applied, bearing in mind that prospective ECG gating may not be applicable for imaging patients with high heart rates, the radiation dose of coronary CTA compares favorably with current rest and stress MPI protocols [40,49] (Figure 4).

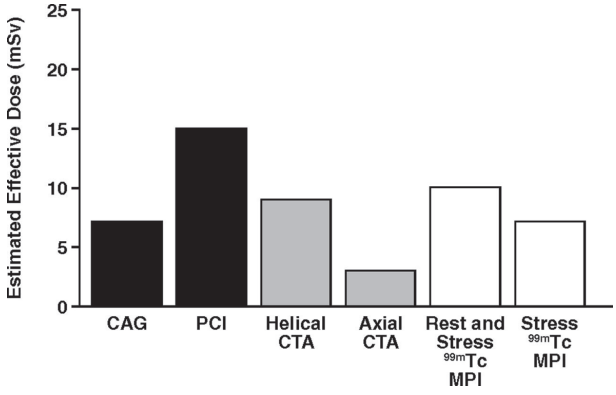


Figure 4 | Bar graph shows estimated effective doses for invasive coronary angiography. (CAG), percutaneous coronary intervention (PCI), coronary CT angiography (CTA), and myocardial perfusion imaging (MPI). Both helical and axial image acquisitions are with tube current modulation. MPI was performed with 99mTc using rest and stress protocols or stress-only protocol [49,60].

Systematic Review

To summarize the available literature on this topic, we formulated the following question: In patients with acute chest pain suggestive of ACS, what is the diagnostic performance of echocardiography, radionuclide MPI, and coronary CTA? A systematic search of the English-language literature in PubMed was performed to identify studies that addressed this clinical question leading to 219 citations; search details are provided in Appendix 1. Subsequently, all systematic reviews and meta-analyses that were found with the original search were reviewed to identify additional articles (Figure 5). One reviewer extracted all relevant data from each included study. A second reviewer checked the results obtained for accuracy and completeness. Discrepancies were resolved by consensus. Summaries of the relevant articles categorized by imaging modality are included in Tables 2 and 3.

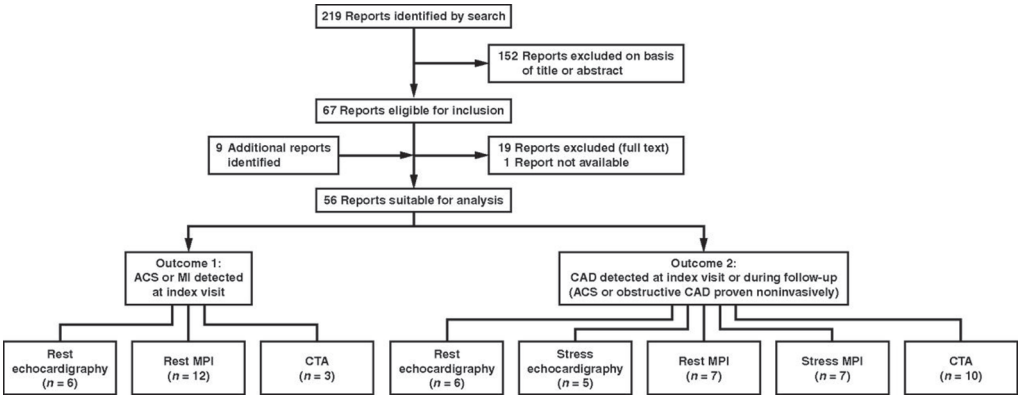
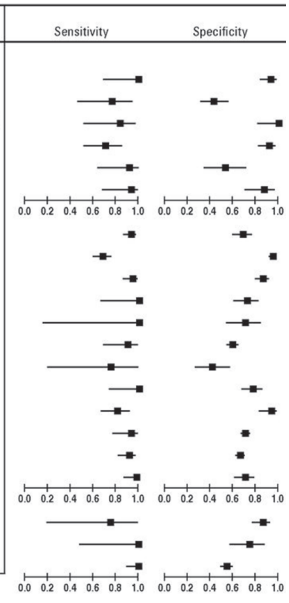


Figure 5 | **Flow diagram illustrates review process.** ACS = acute coronary syndrome, MI = myocardial infarction, CAD = coronary artery disease, MPI = myocardial perfusion imaging, CTA = CT angiography.

Table 2 | **Relevant Articles Evaluating Diagnostic Performance of Rest Echocardiography.** Rest Myocardial Perfusion Imaging (MPI), and Coronary CT Angiography (CTA) for the Detection of Acute Coronary Syndrome (ACS) or Myocardial Infarction (MI) During Index Visita

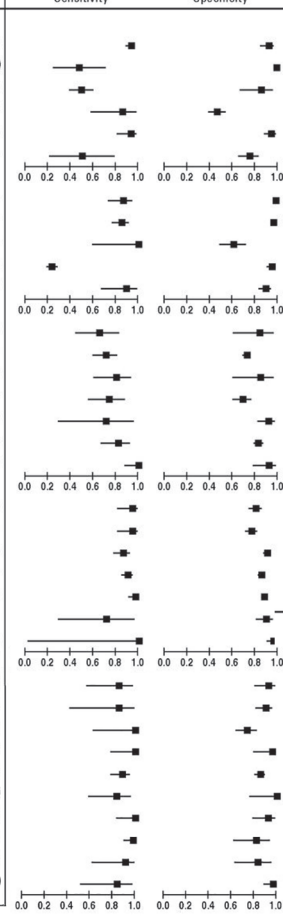
First Author [Reference No.]	Year[b]	Mean Age (y)	Male Patients (%)	Outcome	No. of Patients	Sensitivity (%)[c]	Specificity (%)[c]
Echocardiography							
Atar [61]	2004	50	80	Not defined	70	100 (69–100)	93 (84–98)
Hickman [62]	2004	64	78	MI (CK-MB)	80	77 (46–95)	43 (31–56)
Loh [63]	1982	62	37	MI (CK-MB)	30	83 (52–98)	100 (81–100)
Mohler [17]	1998	56	62	MI (troponin)	92	71 (52–86)	92 (82–97)
Peels [64]	1990	53	74	MI (undefined)	43	92 (64–100)	53 (34–72)
Sasaki [65]	1986	—	—	MI (undefined)	46	93 (68–100)	87 (70–96)
MPI							
Berman [66]	1977	64	72	MI (undefined markers and ECG)	235	93 (86–97)	69 (60–77)
Codini [67]	1979	61	71	MI (undefined markers and ECG)	436	68 (59–76)	95 (91–98)
Cowley [68]	1977	—	—	MI (undefined)	203	94 (86–98)	86 (79–92)
Duca [69]	1999	59	40	MI (undefined)	75	100 (66–100)	73 (60–83)
Forberg [70]	2009	55	50	MI (undefined)	40	100 (16–100)	71 (54–85)
Heller [29]	1998	—	56	MI (undefined)	357	90 (68–99)	60 (54–65)
Henneman [71]	1992	56	55	MI (undefined)	47	75 (19–99)	42 (27–58)
Hilton [30]	1994	57	59	MI (undefined)	102	100 (74–100)	78 (68–86)
Kan [72]	1977	—	—	MI (undefined markers and ECG)	91	81 (67–92)	94 (83–99)
Kontos [73]	1997	55	45	MACE	532	93 (76–99)	71 (67–75)
Kontos [28]	1999	56	46	MI (undefined)	620	92 (81–97)	67 (63–71)
van der Wieken [74]	1983	58	59	MI (undefined)	149	97 (87–100)	71 (61–79)
CTA							
Hansen [75]	2010	56	63	MI (troponin)	89	75 (19–99)	86 (77–92)
Hoffmann [76]	2006	57	53	ACS (clinical consensus)	40	100 (48–100)	74 (57–88)
Hoffmann [41]	2009	53	61	ACS (clinical consensus)	368	100 (89–100)	54 (49–60)



Note— Dash (—) indicates data were not reported. CK-MB = myocardial bound creatine kinase; MACE = major adverse cardiac event (death, myocardial infarction, coronary revascularization).
[a]Diagnosis group 1.
[b]Year of publication.
[c]Data in parentheses are 95% CIs.

Table 3 | Relevant Articles Evaluating Diagnostic Performance of Rest and Stress Echocardiography. Rest and Stress Myocardial Perfusion Imaging (MPI), and Coronary CT Angiography (CTA) for the Detection of Coronary Artery Disease With or Without Follow-Up.

First Author [Reference No.]	Year[b]	Mean Age (y)	Male Patients (*n*)	Outcome	Follow-Up	No. of Patients	Sensitivity (%)[c]	Specificity (%)[c]
Echocardiography (rest)								
Di Pasquale [18]	2004	60	182	> 70% or > 50% LM on CAG	Index	280	93 (89–97)	92 (85–96)
Gibler [15]	1995	—	—	MACE	30 d	901	47 (24–71)	99 (98–100)
Kang [16]	2005	60	73	ACS, coronary revascularization	Index	114	49 (39–60)	85 (66–96)
Kontos [77]	1998	—	133	MI, coronary revascularization	Index	260	86 (57–98)	46 (39–54)
Muscholl [78]	2002	56	91	MACE	30 d	132	93 (81–99)	94 (88–98)
Weston [23]	2004	54	63	Death, MI, myocardial ischemia	Index	108	50 (21–79)	75 (65–83)
Echocardiography (stress)								
Bedetti [79]	2005	58	321	Cardiac death, ACS	13 mo	552	87 (73–95)	98 (96–99)
Conti [22]	2005	60	321	CAG or MACE and UAP	6 mo	503	85 (76–92)	95 (93–97)
Geleijnse [80]	2000	57	51	MACE	Index	80	100 (59–100)	60 (48–72)
Iglesias-Garriz [81]	2005	64	272	CAG > 50%	Index	487	24 (19–29)	94 (90–97)
Trippi [21]	1997	50	85	MI or CAG	30 d	163	89 (67–99)	89 (83–94)
MPI (rest)								
Bilodeau [82]	1991	58	24	CAG > 50%	Index	45	65 (44–83)	84 (60–97)
Fesmire [33]	2001	54	431	MACE	30 d	805	71 (59–81)	73 (69–76)
Gregoire [83]	1990	58	24	CAG > 50%	Index	45	81 (61–93)	84 (60–97)
Kaul [84]	2004	62	138	MACE	Index	203	74 (55–88)	69 (60–77)
Kosnik [85]	1999	56	30	MACE	12 mo	69	71 (29–96)	92 (82–97)
Tatum [86]	1997	51	215	MACE	Index	438	82 (66–92)	83 (79–87)
Varetto [87]	1993	58	35	MI, CAG, SPECT	Index	64	100 (87–100)	92 (78–98)
MPI (stress)								
Conti [88]	2001	59	478	MI, CAG, SPECT	6 mo	231	94 (81–99)	81 (74–86)
Conti [32]	2003	60	321	MI, CAG, SPECT	6 mo	306	94 (83–99)	77 (71–82)
Conti [22]	2005	60	321	CAG or MACE and UAP	6 mo	503	86 (78–92)	90 (87–93)
Conti [89]	2008	62	157	CAG or MACE and UAP	12 mo	798	90 (84–95)	85 (82–88)
Fesmire [33]	2001	54	431	MACE	30 d	805	97 (90–100)	88 (85–90)
Gallagher [90]	2007	49	45	CAG, SPECT	30 d	85	71 (29–96)	90 (81–95)
Goldstein [34]	2007	51	56	CAG, CTA, SPECT	6 mo	98	100 (3–100)	96 (90–99)
CTA								
Chow [91]	2010	53	32	CAG, SPECT	Index	55	86 (57–98)	93 (80–98)
Gallagher [90]	2007	49	45	CAG, SPECT	30 d	85	86 (42–100)	90 (81–96)
Goldstein [34]	2007	48	42	CAG, CTA, SPECT	6 mo	99	100 (63–100)	74 (63–82)
Johnson [92]	2008	64	78	CAG > 50%	6 mo	109	100 (78–100)	96 (89–99)
Kim [93]	2010	58	146	Clinical judgment	30 d	296	89 (78–95)	85 (80–89)
Olivetti [94]	2006	59	19	CAG > 50%	Index	31	83 (59–96)	100 (75–100
Rubinshtein [44]	2007	56	37	MI, CAG, SPECT	15 mo	58	100 (83–100)	92 (79–98)
Tsai [42]	2007	61	55	CAG > 50%	Index	78	98 (90–100)	81 (62–94)
Ueno [95]	2009	66	19	CAG, SPECT	30 d	36	92 (62–100)	83 (63–95)
White [43]	2005	51	35	CAG, SPECT, stress echocardiography, CTA	30 d	69	83 (52–98)	96 (88–100)



Note—Dash (—) indicates data were not reported. LM = left main coronary artery; CAG = invasive coronary angiography; MACE = major adverse cardiac event, defined as death, myocardial infarction, coronary revascularization; ACS = acute coronary syndrome, MI = myocardial infarction, UAP = unstable angina pectoris, CTA = CT angiography.
[a]Diagnosis group 2.
[b]Year of publication.
[c]Data in parentheses are 95% CIs.

Statistical Analysis

To obtain summary estimates of sensitivity and specificity and account for a possible correlation between sensitivities and specificities, we used a bivariate random-effects model to perform the meta-analysis [50]. In the bivariate random-effects model, it is assumed that the logit-transformed true sensitivity and specificity in each study follow a bivariate normal distribution across studies, allowing a possible correlation between sensitivities and specificities. The random-effects model produces estimates of the mean logit-transformed sensitivity, logit-transformed specificity, log-

transformed positive predictive value (PPV), and log-transformed negative predictive value (NPV) with their standard errors. Sensitivity, specificity, PPV, and NPV estimates with their 95% CIs were reported. All analyses were performed using statistics software (SAS version 9.2, SAS Institute).

All studies were divided over two diagnosis groups according to the endpoint used as the reference standard for calculating diagnostic performance. Studies appointed to diagnosis group 1 used MI or ACS during the index visit based on clinical presentation, serial cardiac marker results, or ECG results as the reference standard. Studies appointed to diagnosis group 2 used the composite endpoint "CAD" (a combination of proven ACS, angiographic evidence of obstructive CAD, obstructive CAD proven by noninvasive tests, and information from follow-up) as the reference standard. For diagnosis group 1, we compared coronary CTA, rest echocardiography, and rest MPI. For diagnosis group 2, we compared coronary CTA, rest and stress echocardiography, and rest and stress MPI (Figure 5).

Results (Diagnostic Performance)

For the detection of MI or ACS during the index visit (diagnosis group 1), the pooled sensitivities of coronary CTA, rest echocardiography, and rest MPI were as follows: 0.94 (95% CI, 0.74–0.99), 0.86 (0.72–0.93), and 0.91 (0.85–0.95), respectively. The pooled specificity was 0.73 (0.46–0.90), 0.82 (0.65–0.91), and 0.76 (0.64–0.85), respectively. The summary receiver operating characteristic (SROC) curves for group 1 are displayed in Figure 6. For the detection of CAD (diagnosis group 2), rest echocardiography and rest MPI had a pooled sensitivity of 0.76 (0.58–0.89) and 0.80 (0.64–0.90), respectively. The pooled specificity was 0.89 (0.78–0.95) and 0.83 (0.70– 0.91). Stress echocardiography and stress MPI had a pooled sensitivity of 0.78 (0.57–0.90) and 0.92 (0.84–0.97). Their corresponding pooled specificity was 0.92 (0.83–0.96) and 0.88 (0.78–0.94), respectively. Coronary CTA showed a pooled sensitivity of 0.93 (0.84–0.97) and a pooled specificity of 0.90 (0.83– 0.95), which are comparable to its diagnostic performance for the detection of MI or ACS (diagnosis group 1). The SROC curves for group 2 are displayed in Figure 7.

Evidence-Based Guidelines

The current guidelines from the 2011 American College of Radiology Appropriateness Criteria consider combined rest and stress MPI as the preferred test in patients with intermediate to high risk of ACS. A reasonable alternative is rest and stress echocardiography, especially because it does not require radiation exposure. Combined rest-stress protocols are considered more appropriate than single protocols. Coronary CTA is regarded as an appropriate alternative in low- to intermediate-risk patients [51]. Patients with a high likelihood of CAD would benefit most from invasive angiography. The current analysis incorporated several recently published articles with coronary CTA in which diagnostic performance was reported to be excellent. Compared with the guidelines, our findings are more in favor of using coronary CTA than in using MPI or echocardiography.

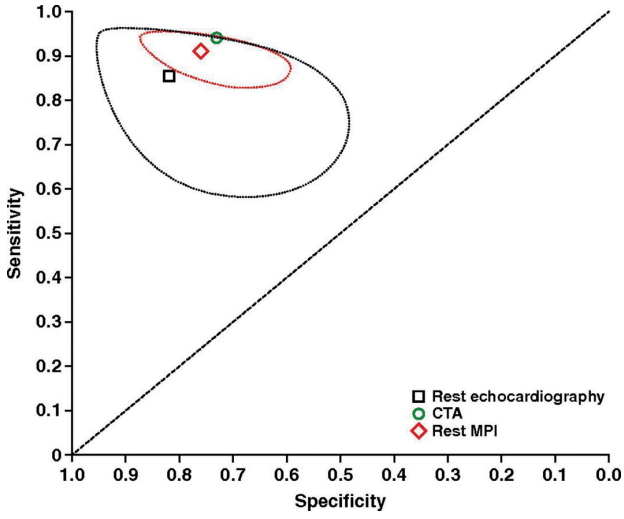


Figure 6 | Summary receiver operating characteristic curves for diagnosis group 1. Rest myocardial perfusion imaging (MPI) and CT angiography (CTA) are encircled by 95% CIs. No 95% CI could be calculated for CTA because of small number of studies.

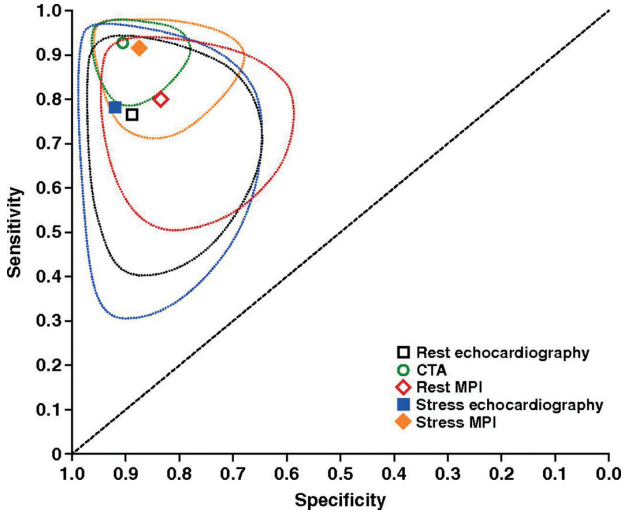


Figure 7 | Summary receiver operating characteristic curves for diagnosis group 2. Rest echocardiography, stress echocardiography, rest myocardial perfusion imaging (MPI), stress MPI, and CT angiography (CTA) are encircled by their 95% CIs.

Outstanding Issues That Warrant Research

Heterogeneity

The diagnostic performance of the three modalities showed large variation across studies. This variation is, in part, because of differences in patient populations but is mainly because different clinical endpoints were used as the reference standard to calculate diagnostic performance. These endpoints ranged from cardiac markers to angiographic results or adverse events during follow-

up. Some studies used combined endpoints, which may be misleading because they may not truly reflect the ability to correctly risk-stratify patients with suspected ACS.

Technical Advancements

Three-dimensional volumetric imaging is a promising application of echocardiography that shortens acquisition time, reduces operator dependency, and provides more accurate assessment of ventricular volumes. However, for assessment of WMAs, this technique seems less applicable than conventional 2D echocardiography and its use is further held back because of lower spatial and temporal resolutions compared with conventional 2D echocardiography and multiple-beat acquisition artifacts [52,53]. The use of 3D echocardiography does not preclude convention-al 2D imaging and these techniques can be used side by side to reinforce each other.

In nuclear perfusion imaging, reduced imaging time and better diagnostic information will be possible because of improved camera designs, iterative reconstruction methods, and new acquisition protocols (stress-only acquisitions, dynamic imaging, and so on) [54]. Also, radionuclide agents with "ischemic memory" could help identify patients with acute chest pain and subsided ischemia in the future [55].

In search of the functional significance of plaques seen on coronary CTA, new techniques such as CT myocardial perfusion and computational fluid dynamics are being investigated and show very promising results [56,57].

Summary

Recommendations for Best Practice

Our systematic search of the medical literature showed no significant differences among the three modalities for the detection of both ACS and CAD with or without follow-up. There was a slight, nonsignificant positive trend favoring coronary CTA in both analyses.

It is important to keep in mind that the optimal imaging strategy is determined not only by the diagnostic performance of a modality but also by local practice, expertise with imaging techniques, medical facilities, and individual patient characteristics. Given the absence of large differences in diagnostic performance, these practical aspects may be even more important.

Because the diagnostic performance of CTA is excellent and the test can be performed quickly, we advocate performing coronary CTA of low- to intermediate-risk patients pro-vided the test and expertise to interpret the results are readily available in emergency situations. For institutions with nuclear imaging expertise and rapid access to nuclear facilities, MPI will generally be the first choice for imaging low- to intermediate-risk patients, despite the fact that recent trials suggest it is more costly and time-consuming than CTA. Rapid screening with echocardiography for the presence of many nonischemic conditions as well as for the assessment of hemodynamic status remains a vital part of the standard workup of all patients with acute chest pain. However, extensive imaging seems less suitable for diagnosing ACS or CAD than for diagnosing other cardiac abnormalities. In

concordance with the current guidelines, we believe high-risk patients would benefit most from an invasive strategy [58,59].

Recommendations for Future Research

The lack of robust evidence to identify the optimal test is partially caused by substantial heterogeneity across studies. The studies identified by our systematic search used various clinical endpoints to calculate diagnostic performance. To date, there seems to be no general agreement about which clinical endpoint – cardiac markers, angiographic results, or these combined with follow-up data – should be used for validation. In addition, there is still a limited number of comparative studies between imaging strategies. For a better understanding of the optimal imaging strategy for patients with acute chest pain, large randomized trials with generally accepted clinical endpoints are needed.

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Appendix 1 | Criteria for Study Selection

Search Details

Studies were included if they met all of the following criteria:

1. The study population was composed of patients with acute chest pain suggestive of acute coronary syndrome (ACS);
2. The study reported operating characteristics of echocardiography, nuclear myocardial perfusion imaging (MPI), or coronary CT angiography (CTA); and
3. The reference standard was the presence of ACS based on cardiac markers or ECG; clinical consensus based on invasive angiography or proven obstructive coronary artery disease on additional tests (not consisting of the index test); or cardiac events during follow-up.

Studies were excluded if they met one of the following criteria:

1. Article was a review, guideline, or cost-effectiveness analysis;
2. Study population consisted of patients with stable angina, asymptomatic patients, or patients with proven myocardial infarction (MI) at baseline;
3. Study population consisted of patients with ST-segment elevation MI; or
4. Study population overlapped with previous publications.

Articles not accessible or not written in English were excluded from the analysis.

Search Strategy

("myocardial infarction" [MeSH] OR "myocardial ischemia" [MeSH] OR "angina, unstable" [MeSH] OR "acute coronary syndrome" [MeSH terms] OR "coronary disease" [MeSH] OR "coronary artery disease" [MeSH] OR "chest pain" [MeSH])

AND

("acute disease" [MeSH] OR "emergency service, hospital" [MeSH] OR "emergency medical services" [MeSH] OR "emergency treatment" [MeSH] OR "emergencies" [MeSH] OR "emergency medicine" [MeSH])

AND

("echocardiography" [MeSH] OR "radionuclide imaging" [MeSH] OR "technetium Tc 99m sestamibi" [MeSH] OR "tomography, X-ray computed" [MeSH])

AND

("coronary angiography" [MeSH] OR "consensus" [MeSH] OR "acute coronary syndrome" [MeSH] OR "angina, unstable" [MeSH] OR "myocardial infarction" [MeSH] OR "myocardial ischemia" [MeSH])

AND

("sensitivity and specificity" [MeSH] OR sensitivity [tw] OR specificity [tw] OR "predictive value of tests" [MeSH] OR "ROC curve" [MeSH] OR ("positive predictive" [tw] AND value* [tw]) OR ("negative predictive" [tw] AND value* [tw]) OR (false [tw] AND nega-tive* [tw]) OR (false [tw] AND positive* [tw]) OR (true [tw] AND negative* [tw]) OR (true [tw] AND positive* [tw]) OR misdiagnosis [tw] OR misdiagnoses OR "diagnostic errors" [MeSH] OR (diagnost* [tw] AND (accuracy [tw] OR error* [tw] OR efficacy [tw])

AND

(English [lang] NOT (animals [MeSH] NOT humans [MeSH]) OR Editorial [Publication type] OR Comment [Publication type] OR Letter [Publication type] OR Case Reports [Publication type])

Note: MeSH refers to "Medical Subject Headings," which is the National Library of Medicine's controlled vocabulary thesaurus. tw = text word, * = MeSH concept that is the main point of the article.

CHAPTER 4

Coronary CT Angiography Outperforms Calcium Imaging in the Triage of Acute Coronary Syndrome

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Abstract

Background: In this prospective study we determine the diagnostic value of coronary CT angiography (CTA) and calcium imaging in low to intermediate risk acute chest pain patients.

Methods: One hundred and eleven consecutive patients (57±11 years, 71 males) presenting to the emergency department with chest pain suggestive of acute coronary syndrome (ACS), but without indication for immediate catheter angiography, underwent both coronary CTA and calcium imaging without disclosure of the findings to the treating physicians.

Results: ACS was diagnosed in 19 patients (17%). Coronary calcium was present in 71 patients (64%). Coronary CTA identified 74 (67%) patients with coronary plaque and 36 (32%) patients with obstructive (≥50%) plaque. The sensitivity and specificity of the calcium scan were: 89% and 41%. The sensitivity and specificity of coronary CTA were: 100% and 40% based on the presence of any plaque and 89% and 79% based on the presence of >50% stenosis. C-statistics of the GRACE risk score (0.77 [95% CI 0.66–0.89]) improved after addition of coronary CTA (0.93 [0.88–0.98], pb0.01), though not after addition of calcium scores (0.81 [0.71–0.91], p=0.52). Follow-up at 3 months revealed four late revascularizations (no deaths or myocardial infarctions), all of whom had obstructive CAD with calcium on CT at presentation.

Conclusions: Coronary CTA outperforms calcium imaging in the triage of patients suspected of developing ACS. Absence of plaque on coronary CTA allows safe discharge. Coronary CTA has incremental value to clinical risk scores and has the potential to reduce unnecessary hospital admissions.

Introduction

Acute chest pain (ACP) represents a major diagnostic challenge in emergency care [1]. The differential diagnosis is broad varying from benign causes to life-threatening conditions. Observational studies report that an estimated 2–8% of myocardial infarctions (MI) are missed [2,3]. Patients mistakenly discharged from the emergency department have a worse prognosis than properly managed patients, partly because of the risk for sudden death but also because of the delay in implementing treatment known to be effective for acute coronary syndrome (ACS) [2,4]. In fear of missing life-threatening conditions, a large proportion of patients with ACP is admitted for clinical observation and serial testing to rule out ACS, of whom only a fraction turn out to have a MI, resulting in substantial resource utilization.

Coronary CT angiography (CTA) readily provides high quality non-invasive images of the heart, great vessels, and coronary vasculature [5,6]. While registry data is available, only a few blinded prospective studies have evaluated the feasibility of coronary CTA in the emergency room so far, and none of these studies included a direct comparison of coronary CTA and calcium imaging. In this prospective study we determine and compare the diagnostic value of coronary CTA and calcium imaging in low to intermediate risk ACP patients.

Methods

Patient Population

A consecutive cohort of patients without a history of coronary artery disease (myocardial infarction or coronary revascularization) presenting to the emergency department with chest pain during the past 24 h, suggestive of ACS, were planned to undergo both coronary CTA and calcium imaging without disclosure of findings to the treating physicians. Patients older than 40 years, without ST-segment elevation, hemodynamic instability or highly elevated cardiac troponin (>0.15 µg/l) were eligible for participation. Exclusion criteria included severe arrhythmia, impaired renal function and contrast allergies. Enrolment was conducted during weekdays between 7:00 h and 19:00 h.

Patient demographics, presence of risk factors and type of medical treatment were prospectively collected and used to calculate traditional risk estimators (TIMI risk score and the GRACE risk score) for the occurrence of in-hospital mortality or myocardial infarction [7,8].

Treating physicians were blinded to the results of cardiac CT imaging. The decision to admit patients for observation, including serial ECGs and cardiac biomarkers was clinically driven. Subsequent cardiac testing, i.e. exercise testing, stress perfusion imaging or cardiac catheterization was performed at the clinician's discretion. The study complies with the Declaration of Helsinki, the local ethics committee approved the research protocol and all patients provided written informed consent.

Coronary Computed Tomography

A standard prospectively ECG-triggered axial coronary calcium scan was per-formed with the following parameters: 120 kV tube voltage, 70 mAs tube current-time product and 3-mm slice thickness. Quantification was performed using the Agatston method with a standard 130-HU attenuation threshold [9].

Coronary CTA was performed on a dual-source 128-slice (Siemens Definition Flash, Forchheim, Germany) or a single-source 128-slice (Siemens Definition AS+, Forchheim, Germany), depending on availability, using the spiral mode with ECG gating and ECG-modulated tube output modulation in 20, and prospectively ECG-triggered axial imaging in 91 patients. Further scan parameters: 100–120 kV tube volt-age, 320–370 or 160–188 mAs tube current-time product depending on patient size, detector row width 0.6 mm, rotation times 280 and 300 ms, temporal resolutions 75 and 150 ms, respectively. Iopromide 90 to 100 ml (Ultravist 370 mgI/ml, Bayer Schering Pharma, Berlin, Germany), followed by a 45 ml saline bolus chaser, was peripherally injected at 5.0 to 5.5 ml/s. A bolus tracking technique was used to synchronize data acquisition with contrast delivery. Patients with high heart rates received intravenous beta-blockade (n=36, metoprolol up to 10 mg), while sublingual nitroglycerin was administered routinely. Median effective radiation dose for coronary CTA was 4.9 mSv (IQR 3.1–8.1) and for calcium scan 0.69 mSv (0.41–1.16).

Coronary branches were evaluated on axial images, multiplanar reformations, and maximum intensity projections. The presence of coronary atherosclerotic plaque and the degree of stenosis was determined using a 16-segment AHA classification by two experienced readers (AM, MO), who were blinded with regard to the patients' clinical information, in a joint reading [10]. If consensus could not be reached, a third reader was consulted.

Coronary atherosclerotic plaque was classified either as noncalcified, partially cal-cified or calcified. Stenosis grade was quantified either as no stenosis, less than 20%, 20–50%, 50–70%, >70% stenosis or occluded.

Diagnostic accuracy for the calcium scan was calculated on a per-patient level using the following threshold: absence vs. presence of any calcium. Diagnostic accuracy for coronary CTA was calculated on a per-patient level using the following thresholds: presence vs. absence of any plaque; presence of minimal plaque (b20% stenosis) vs. substantial plaque (>20% stenosis) and the presence of non-obstructive plaque (≤50% stenosis) vs. obstructive plaque (>50% stenosis). By intention to diagnose non-evaluable segments on CT were classified positive for plaque and obstructive CAD.

Follow-up

Follow-up was performed at 3 months using a standardized telephone interview or questionnaire for the occurrence of myocardial infarction and coronary revascularization (percutaneous coronary intervention or coronary artery bypass graft surgery), after consulting the national death registry (CBS). All events were confirmed with death records and medical records.

Clinical Endpoints

Two cardiologists (KN, TG), blinded for the cardiac CT scan, independently reviewed patient data and hospital records to establish clinical outcome. In case of disagreement, consensus was reached by a

joint reading. ACS was defined as either a myocardial infarction: myocardial ischemia resulting in a rise and fall of cardiac bio-markers (>99th percentile of the upper limit of normal); or unstable angina: chest pain with altered frequency or character, suspicious for ACS with documented ischemia on the ECG, stress testing or invasive angiography (ICA) [11,12]. At follow-up major adverse cardiovascular events were defined as cardiac death, non-fatal myocardial infarction or revascularization.

Statistical Analysis

Categorical variables are presented as proportions; continuous variables are expressed as mean (±SD) or median (±IQR), as appropriate. Differences between independent groups were compared using the 2-sided unpaired t test, chi-square test or Wilcoxon rank-sum test, as appropriate. Differences between dependent groups were compared using the paired t test,Wilcoxon rank-sumtest or McNemar's test, as appropriate. Conventional parameters of diagnostic accuracy, i.e. sensitivity, specificity, positive predictive value and negative predictive value, were calculated with their corresponding 95% confidence intervals. To account for the skewed distribution, calcium scores were transformed by taking the natural logarithm of the calcium score +1.

Receiver operating characteristics (ROC)-curves with their corresponding areas under the curve (i.e. c-statistic) were constructed to assess the discriminative performance of the GRACE risk score alone and in combination with calcium scores or the degree of stenosis on coronary CTA (0, <20%, 20–50%, 50–70% and >70%) on a per-patient level.

To assess the potential impact of coronary CTA on clinical management in terms of hospital admission and additional testing the following assumptions were made: 1) no or minimal plaque (<20%) on a per-patient level allows for immediate discharge from the emergency department, 2) an observation period with serial enzyme measurements and ECG monitoring is needed in the presence of a 20–50% stenosis, 3) the presence of a 50–70% stenosis on CT requires stress testing, of whom eventually 50% will ultimately require ICA, 3) ICA is required in the presence of a >70% stenosis. The number of admissions and investigations was compared to actual clinical management. All probability values refer to 2-tailed tests of significance; a value <0.05 was considered significant. Statistical analyses were performed using SPSS software (version 17.0, SPSS Inc, Chicago, Ill).

Results

Of the 191 patients who met the inclusion criteria; 39 patients had a contraindication for CTA (20%), 25 were unwilling to participate (13%), and in 10 patients (5%) the CT scan could not be performed because of claustrophobia (1), language problems (3) or unavailability of the scanner (6). Scan failure occurred in 6 patients (5%), because of severe patient movement (4), incorrect scan timing (1) and extravasation of contrast media (1). Consequently, our study population consisted of 111 patients (mean age 57±11 and 64% male; Table 1).

Table 1 | Baseline characteristics.

	All (n=111)	ACS+ (n=19)	ACS– (n=92)	*p* value
Age (years)	57±11	61±11	56±10	0.06
Male gender	71 (64)	13 (68)	58 (63)	0.80
Smoking	47 (42)	8 (42)	39 (42)	1.00
Hypertension	68 (61)	11 (58)	57 (62)	0.80
Diabetes mellitus	23 (21)	7 (37)	16 (17)	0.07
Statin use	36 (32)	12 (63)	24 (26)	0.003
Family history	34 (31)	7 (37)	27 (29)	0.59
TIMI score *	5 (5–8)	13 (8–13)	5 (5–8)	<0.001
GRACE score †	5 (4–7)	8 (6–14)	4 (3–7)	<0.001
Low	96 (87)	11 (58)	85 (93)	
Intermediate	10 (9)	5 (26)	5 (5)	
High	5 (5)	3 (16)	2 (2)	
ICA performed	31 (28)	18 (95)	13 (14)	<0.001
Calcium imaging				
Calcium score	19 (0–195)	256 (63–721)	2 (0–123)	<0.001
No detectable calcium	40 (36)	2 (11)	38 (41)	0.02
Coronary CT angiography				
Plaque absent	37 (33)	0	37 (40)	
Plaque present	74 (67)	19 (100)	55 (60)	0.001
Non-calcified	6 (8)	3 (16)	3 (5)	
Partially calcified	43 (58)	14 (74)	29 (53)	
Calcified	23 (31)	2 (10)	21 (38)	
Non-evaluable segment	2 (3)	0 (0)	2 (4)	
≤20% stenosis	50	0	50 (54)	
20–50% stenosis	25	2 (10)	23 (25)	
50–70% stenosis	20	7 (37)	13 (14)	
>70% stenosis	16	10 (53)	6 (7)	<0.001

Unless otherwise specified, the data are presented as numbers of patients (percentage) or mean ± standard deviation. * Risk of in hospital death, myocardial infarction or urgent revascularisation, median (inter-quartile range) [6].† Risk of in hospital death or myocardial infarction, median (inter-quartile range) [7]. ICA = invasive catheter angiography.

Early Clinical Outcome

The diagnosis of ACS was established in 19 patients (17%): 13 had myocardial infarction and 6 had unstable angina pectoris (Figures 1 and 2). According to the GRACE risk score, 11 (58%) of these patients were low risk, 5 (26%) intermediate risk and 3 (16%) high risk. Seventy-nine patients were admitted for observation and 62 underwent stress testing. Based on the initial evaluation 31

(28%) patients underwent ICA, followed by coronary artery bypass graft surgery in two (2%), and percutaneous coronary intervention in 18 (16%) patients.

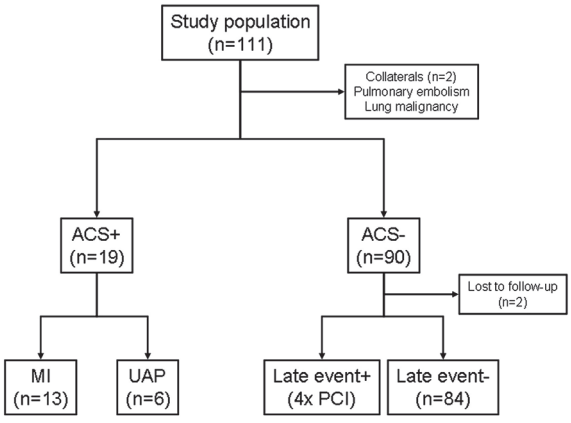

Figure 1 | Clinical outcome in the study population.

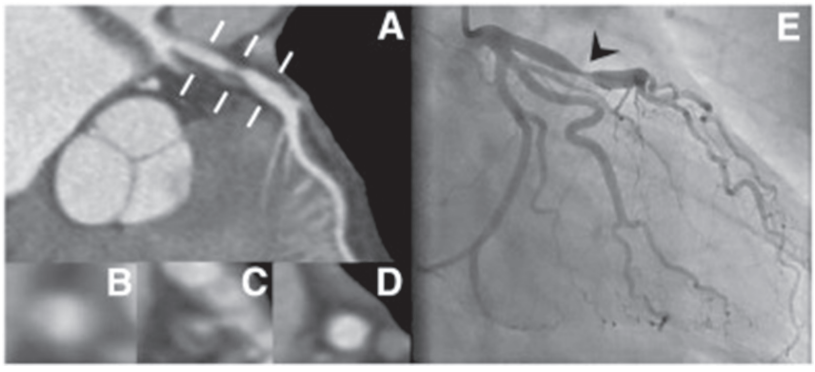

Figure 2 | Acute coronary syndrome in the absence of detectable calcium in a 46 year-old man presenting with acute chest pain in the emergency department. (**A)** Coronary CTA shows high grade stenosis of the proximal LAD with post-stenotoic dilatation. (**B-D)** Cross sections proximal, local and distal to the stenosis. (**E)** This lesion was confirmed on ICA (black arrowhead) and subsequent percutaneuos coronary intervention was performed.

Diagnostic Performance of the Calcium Scan

Coronary calcium was detected in 71 patients (64%), with a median Agatston score of 19 (IQR 0–195). ACS (1 MI; 1 UAP) was established in 2/40 patients (5%) with a negative calcium scan: sensitivity 89%, specificity 41% (Table 2).

Table 2 | Diagnostic accuracies on a per-patient level of calcium imaging (no vs. any calcium) and coronary CTA with different thresholds: no plaque vs. any detectable plaque; minimal (<20% stenosis) vs. substantial plaque (>20%) and non-obstructive (<50% stenosis) vs. obstructive plaque (≥50% stenosis).

Test	Sensitivity	Specificity	NPV	PPV
Calcium	89 (65–98)	41 (31–52)	95 (82–99)	24 (15–36)
Any plaque	100 (79–100)	40 (30–51)	100 (88–100)	26 (17–37)
Minimal plaque (>20%)	100 (79–100)	54 (44–65)	100 (91–100)	31 (20–44)
Stenosis (>50%)	89 (65–98)	79 (69–87)	97 (90–100)	47 (31–64)

Data presented as percentages with 95% confidence intervals in parentheses. NPV = Negative predictive value, PPV = positive predictive value.

Diagnostic Performance of Coronary CTA

Coronary plaque was present in 74 patients (67%, Table 1). None of the 37 (33%) patients without plaque had ACS: sensitivity and negative predictive value of 100%. Specificity and positive predictive values were lower: 40% and 26%, respectively. For the patients with an ACS, the culprit lesion consisted of non-calcified plaque in 3 (16%) patients, partially calcified plaque in 14 (74%) patients and calcified plaque in 2 (10%) patients. Five patients (5%) had one or more non-evaluable segments and were classified as positive for obstructive CAD, of whom none experienced an ACS or a late adverse event.

Obstructive CAD (>50% diameter reduction) was present in 31 (28%) patients of whom 17 were diagnosed with ACS. The sensitivity for this threshold was 89% and specificity 79%. Two patients with a ≤50% stenosis had a non-ST elevation myocardial infarction. The characteristics of patients with ACS and no calcium or non-obstructive plaque (<50%) are summarized in Table 3.

No or minimal plaque (<20% stenosis on a per-patient level) was present in 50 patients (45%). Using absent or minimal plaque as the discriminator, ACS could be diagnosed with a sensitivity of 100% and specificity of 54%.

Receiver operating characteristics showed that combining the GRACE risk score with coronary CTA improved the diagnostic accuracy (c-statistic of 0.93 [95% CI 0.88–0.98], $p<0.01$) compared to the GRACE score alone (0.77 [0.66–0.89]; Figure 3). In the case of calcium scores, the additional value to the GRACE score was modest (0.81 [0.71–0.91], $p=0.52$).

Two patients had significant non-cardiac disease twice (lung malignancy and pulmonary embolism), which were disclosed to the treating physician.

Table 3 | **Acute coronary syndrome in patients with no detectable calcium or non-obstructive (<50%) plaque.**

Subject	Initial ECG	Initial Trop T	CCS	CTA	Outcome	Stress test	ICA	Peak Trop T
Woman (49 yrs)	Non specific	0.05	0	LCX 50–70%	NSTEMI	None	LCX >50%	0.08
Man (46 yrs)	Minimal ST depression	Normal	0	LAD >70%	UAP	Typical angina + ST elevation	LAD >50%	Normal
Woman (60 yrs)	Non-specific T-wave changes	0.03	15	LCX 20–50%	NSTEMI	None	LCX >50%	0.70
Man (64 yrs)	Non specific T-wave changes	0.06	225	RCA 20–50%	NSTEMI	None	RCA >50%	0.17

CCS = Coronary calcium score, Trop T = Troponine T (ug/l), ICA= Invasive catheter angiography (degree of stenosis measured with QCA) LCX = left circumflex coronary artery, LAD = Left anterior descending coronary artery, RCA = Right coronary artery, NSTEMI = Non ST-elevation myocardial infarction, UAP = Unstable angina pectoris.

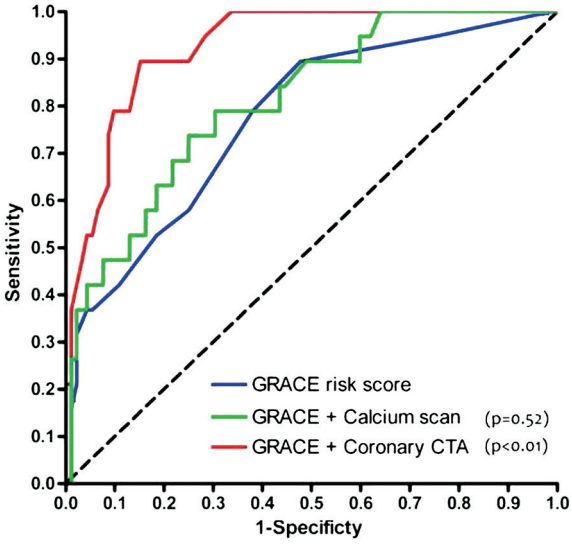

Figure 3 | ROC-curve of the GRACE risk score (c-statistic 0.77 [95% CI 0.66–0.89]). Additional value of calcium scores (c-statistic 0.81 [0.71-0.91], *p*=0.52) and the degree of stenosis on coronary CTA (0, <20%, 20–50%, 50–70% and >70%) for identification of ACS (c-statistic 0.93 [95% CI 0.88–0.98], *p*>0.01).

Late Adverse Events

After 3 months no deaths occurred in the entire group. Further follow-up was complete for 109 patients (98%), of whom four (all without an initial diagnosis of ACS) had undergone coronary revascularization. The CT scan had shown obstructive disease at presentation, as well as a positive calcium scan in all four cases. One patient with earlier diagnosed ACS had a recurrent myocardial infarction and another was hospitalized because of unstable angina pectoris.

Anticipated Clinical Impact of Coronary CTA

Assuming that all patients with no or minimal plaque (<20% stenosis on a per-patient level) can be discharged from the emergency department, only 61 (55%) patients would have needed admission (versus 78 (70%) in actuality, *p*<0.01). Stress testing in case of moderately obstructive disease on CTA would be required in 20 (18%) patients (versus 62, *p*<0.01), while ICA was estimated to be performed in 26 (23%) patients (versus 31, *p*=0.06), in case of >70% stenosis on CTA or an abnormal stress test following an abnormal CT scan.

Discussion

The main findings of the this study are that 1) in patients at low to intermediate risk the absence of coronary plaque on CTA excludes ACS and seems to guarantee an event-free short-term outcome; 2) because coronary CTA visualizes all plaques as well as the severity of stenosis, it outperforms calcium imaging in terms of diagnostic ac-curacy; 3) coronary CTA has incremental predictive value to traditional risk estimators; 4) coronary CTA has the potential to reduce the number of unnecessary hospital admissions and stress tests; 5) the use of contemporary scan techniques in this study

resulted in a lower radiation exposure in comparison to previous reports, without compromise to image quality.

Coronary CTA in the Emergency Department

Proof of concept studies, using 64-slice scanners, showed very acceptable diagnostic accuracies for the detection of ACS [13]. Studies that also included patients with a known history of CAD confirmed these results; however the positive predictive value was hampered by blooming artifacts caused by stents, metal clips or highly calcified lesions [14]. In a comparison with stress nuclear imaging, CTA was at least as effective in detecting or excluding ACS in low risk emergency department patients [15]. However, for most of the earlier observations, CTA was performed as part of the clinical management, introducing an unavoidable selection bias. In 2009, Hoffmann et al. published the ROMICAT study, which was performed in a low-risk group of consecutive patients presenting with acute chest pain [16]. The authors demonstrated in a blinded manner excellent diagnostic accuracy of coronary CTA, confirming some early modestly sized studies (Table 4). In our study, which also did not disclose CT results, we could confirm the good performance of coronary CTA in a Europe-an clinical setting, in a population at higher risk. As in ROMICAT, the absence of stenosis did not entirely exclude ACS in our population. The absence of plaque did exclude ACS and was found in a third of this high risk population. Our data show that ACS is also rare in patients with minimal plaque. Using this criterion, the specificity of CTA can be improved without sacrificing sensitivity.

Table 4 | Earlier studies assessing the feasibility of coronary CTA in the emergency department, performed in a blinded manner.

Author	N	Outcome	Age (mean)	Male (%)	Prevalence ACS (%)	CTA threshold	Sensitivity (%)	Specificity (%)
Soon, et al. (2007) [31]	34	ICA / Stress test	54	76	23	>=50%	100	80
Ueno, et al. (2009) [32]	36	ICA / S tress test	66	53	31	>=50%	92	83
Hoffmann, et al. (2009) [15]	368	Clinical consensus	53	61	8	Any plaque	100	54
						>=50%	77	87
Chow, et al. (2010) [33]	55	ICA / Stress test	53	58	25	>=50%	86	93
Dedic, et al. (2012)	111	Clinical consensus	57	64	17	Any plaque	100	40
						>=50%	89	79

Data is presented as number of patients. ICA = invasive catheter angiography. Clinical consensus = Consensus between two independent physcians after assessment of all available clinical information and tests.

Risk stratification (GRACE or TIMI) is important to allow for those at high risk to undergo early invasive therapy [17]. However, in our population more than half of the patients (58%) ultimately diagnosed with ACS, would be classified as low risk using the GRACE score. Our study demonstrates that coronary CTA, which showed plaque or stenosis in all patients with ACS, has incremental value to traditional risk stratification, particularly in the low risk patients.

Because the absence of obstructive (epicardial) CAD despite elevated cardiac markers is quite frequently encountered [18], and is likely to increase in frequency with the introduction of high-sensitive troponin essays [19], we allowed (stabilized) patients with minor elevations of serum troponin T to undergo CT. While most of these showed obstructive CAD (67%), or non-obstructive plaque (22%), there was also one patient with left ventricular hypertrophy, who presented with chest pain and slightly elevated troponins after exercise, but had completely normal coronary arteries by angiography (Figure 4).

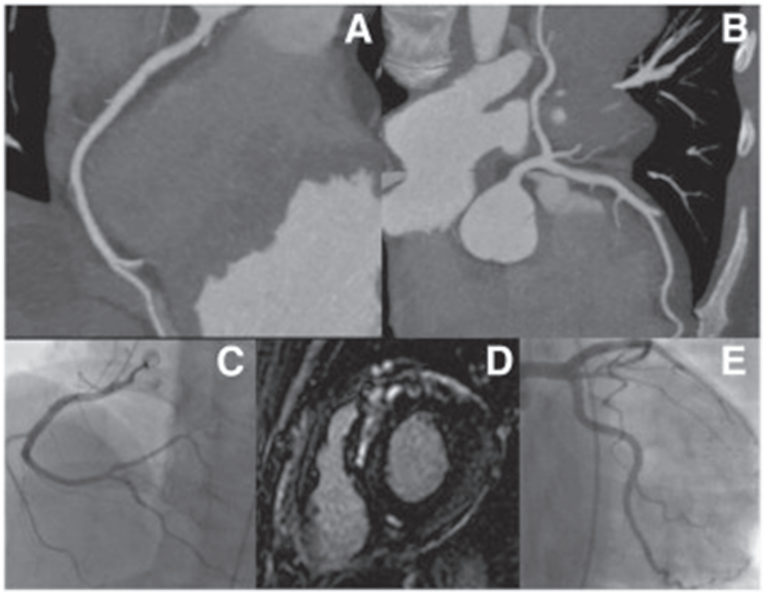

Figure 4 | A 41 year-old woman presented with acute chest pain after exercise. Initial work-up at the emergency department revealed abnormal troponins (0.10). (**A,B)** Coronary CTA showed no coronary artery disease. (**C,E)** This was confirmed on ICA. (**D)** Further diagnostic work-up with cardiac MRI showed left ventricular hypertrophy with myocardial fibrosis.

Coronary Calcium Imaging

Coronary artery calcification is considered to be a marker of atherosclerotic plaque [20,21]. Calcium imaging is a widely used diagnostic modality and it has been studied extensively for improvement of risk stratification [22,23]. It is associated with minimal radiation exposure and therefore often

incorporated in scan protocols. However, whether calcium imaging can reliably be used to exclude ACS in the emergency department remains a subject of debate [24,25]. Several studies suggest that noncalcified plaques play an important role in ACS [26,27] but at the same time there is evidence that a negative calcium scan in low risk ED patients has excellent negative predictive value [28]. In our study, we added a calcium scan to the CT protocol for direct comparison with contrast-enhanced angiography. The absence of calcium did not exclude ACS and its overall diagnostic performance was comparable to the commonly used GRACE risk score (Figure 3).

Clinical Implications

In clinical practice, patients with no or minimal CAD (no more than 20% stenosis plaque in one or more vessels) and resolved symptoms, which was nearly half of our population, could be safely discharged from the emergency department. In case of mild disease (20–50% stenosis) safe discharge is still possible after a short period of observation and negative serial markers, without the logistic and economic consequences of in-hospital stress testing and/or ICA. Using contemporary high-sensitivity troponins this observation period could be as short as three hours [19]. Less than half of patients with moderate CAD (50–70% stenosis) on CT angiography had ACS and/or required a revascularization procedure. In these patients, an observation period and a stress test should point out the need for ICA in our opinion. Given the heterogeneous pathophysiology of acute coronary disease, including spasm, emboli, resolved thrombus and micro-vascular disease, it should be emphasized that clinical management should not be dictated by a single test result [29].

Future Directions

The presented data are promising and confirm previous studies. Expectations of coronary CTA in the emergency room are high [30], but largely based on registry data. However, before cardiac CT can be recommended in general clinical guidelines its performance needs to be compared to existing and emerging strategies for triage of acute chest pain, including clinical decision algorithms, novel biomarkers and other stress/imaging tests and should consider economic consequences. Recently, Raff and colleagues published the results of the multicenter CT-STAT trial, which compared the performance of cardiac CT and nuclear imaging in very low risk patients, and demonstrated that both tests safely rule out coronary artery disease with a 38% reduction in costs at the emergency room for cardiac CT as a result of shorter length of stay [31]. Future research is needed to confirm whether these findings can be extrapolated to patients at higher risk, in varying clinical settings and different standards of care.

Strengths and Limitations

Strengths of our study are the blinded fashion in which the CT scans were performed and reviewed and the absence of a verification bias. Radiation exposure remains an important limitation of cardiac CT. The use of contemporary scan techniques in this study resulted in a lower radiation exposure in comparison to previous reports, without compromise to image quality.

It should be recognized that coronary CTA is useful for a selected group of patients with ACP. In this study 25% of all eligible patients could not participate because of CTA related exclusion criteria.

In addition, in 6 (5%) patients imaging acquisition failed, while 5 (5%) patients had scan that was not reliably interpretable. While certain contra-indications inherent to contrast-enhanced CT will remain, growing experience with coronary CTA and ongoing scanner development is expected to meet some of the present day challenges of imaging patients in the emergency department.

Potential other limitations are the fact that the total population size was relatively small, and enrolled at a single university medical center. Clinical management was left to the discretion of the treating clinicians, while ICA and intracoronary imaging was not available for the majority of patients. The projected effect on clinical management should be regarded as hypothesis generating, and further investigated in a formal randomized controlled clinical trial. New applications, such as perfusion imaging and computational fluid dynamics, are developing rapidly, which may further contribute to the triage of patients with acute chest pain [32,33].

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CHAPTER 5

Copeptin in Acute Chest Pain: Identification of Acute Coronary Syndrome and Obstructive Coronary Artery Disease on Coronary CT Angiography

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Abstract

Objective: To determine the diagnostic accuracy of copeptin in patients with suspected acute coronary syndrome (ACS) and its correlation with obstructive coronary artery disease (CAD) on coronary CT angiography (CTA).

Methods: Copeptin was measured at arrival in 65 consecutive patients (56±10 years, 45 men) suspected of ACS and no indication for immediate invasive angiography. All patients underwent coronary CTA without disclosure of the results to the treating physician, and outcomes were classified as obstructive CAD (>50% stenosis) or no obstructive CAD (≤50%) in one or more vessel.

Results: The final diagnosis of ACS was established in 10 (15%) patients, 6 myocardial infarctions and 4 unstable angina pectoris. Coronary CTA detected obstructive CAD in all patients with ACS and in 10 (15%) patients with no ACS. Copeptin concentrations were higher in patients with ACS (median 7.42 pmol/l (IQR 3.71–18.72)) vs patients with no ACS (3.40 pmol/l (1.13–6.27), p=0.02). Copeptin was not higher in patients with obstructive CAD on coronary CTA (4.87 pmol/l (2.90–8.51) vs 3.60 pmol/l (1.21–6.23), p=0.20) compared with patients with no obstructive CAD.

Conclusions: Copeptin seems to be elevated in patients with ACS while there is no strong correlation with obstructive coronary disease on CTA.

Introduction

Management of patients suspected of acute coronary syndrome (ACS) is a daily challenge for the clinician in the emergency department (ED) [1]. The majority presents with subsided chest pain, and the ECG is often normal or displays unspecific changes [2,3]. Current cardiac markers take several hours to convert, or do not rise at all in the case of unstable angina [4]. The arginine-vasopressin (AVP) hormone plays an important role in the retention of body fluids and regulation of vascular resistance, and is rapidly released in conditions with haemodynamic stress [5,6]. The peptide copeptin is secreted alongside AVP by the neurohypophysis, and its concentrations adequately represent AVP levels.

Copeptin can be measured more easily, making it suitable as a clinical marker [7,8]. Haemodynamic stress arising from myocardial infarction results in an increase in copeptin levels, detectable within 3 h after onset [9].

Recently, coronary CT angiography (CTA) has been introduced as a novel diagnostic modality in the ED. Several studies have demonstrated that coronary CTA has high negative predictive value. On the other hand, not all patients with acute chest pain and obstructive lesions on CTA turn out to have myocardial infarction. Their complaints might, however, be explained by the presence of ischaemia without onset of myocardial necrosis. In patients with obstructive coronary artery disease (CAD) on their CTA, copeptin might help to discriminate between those with and without ischaemia.

In this study, we determine the diagnostic accuracy of copeptin in suspected ACS patients, and examine the association between CAD on CTA and copeptin levels.

Methods

Study Population

Patients with chest pain in the last 24 h were enrolled consecutively at the ED of Erasmus University Medical Centre from November 2009 to February 2011 [10]. Eligible for participation were patients older than 40 years, without ST segment elevation, haemodynamic instability or highly elevated cardiac troponin T (>0.15 µg/l). Exclusion criteria included severe arrhythmia, impaired renal function and contrast allergies. Information on patient demographics, presence of risk factors, and type of medical treatment were prospectively collected and used to determine the Thrombolysis In Myocardial Infarction risk score (TIMI) risk assessment score [11]. The study complied with the Declaration of Helsinki; the local ethics committee approved the research protocol, and all patients provided written informed consent.

Biochemical Analysis

A specimen of venous blood was drawn at arrival in the ED from a catheter inserted into the antecubital vein. The sample was taken at a median of 3 h after the complaints had started. The samples were collected in plastic tubes containing EDTA. They were placed on ice and centrifuged at

3000 g. Plasma was frozen at -80°C until assay. Copeptin concentrations were determined by using a sandwich immunoluminometric assay (LUMITEST CT-pro AVP, BRAHMS AG, Germany).

Coronary CTA

Coronary CTA was performed, without disclosure of the results to the treating physician, either on a dual-source 128-slice (Siemens Definition Flash, Forchheim, Germany) or a single-source 128-slice (Siemens Definition AS+, Forchheim, Germany), depending on availability. The following scan parameters were used: 100–120 kV tube voltage, 320–370 or 160–188 mAs tube current-time product depending on patient size, detector row width 0.6 mm, rotation times 280 and 300 ms, temporal resolutions 75 and 150 ms, respectively. Followed by a 45 ml saline bolus chaser, 90–100 ml Iopromide (Ultravist 370 mgI/ml, Bayer Schering Pharma, Berlin, Germany) was injected at 5.0–5.5 ml/s. Coronary branches were evaluated on axial images, multiplanar reformations and maximum intensity projections. The presence of coronary atherosclerotic plaque and the degree of stenosis was determined using a 16-segment American Heart Association (AHA) classification by two experienced readers in a joint reading [12]. Stenosis grade was quantified either as no stenosis, less than 20%, 20–50%, 50–70%, >70% stenosis or occluded on a per-patient level. Non-evaluable segments were classified as obstructive CAD using the intention-to-treat principle.

Clinical Diagnosis of ACS

Patient data and hospital records were reviewed independently by two cardiologists to establish the presence of ACS. Both were blinded for the results of copeptin and coronary CTA. In case of disagreement, consensus was reached by a joint reading. ACS was defined as either myocardial infarction or unstable angina pectoris. Myocardial infarction was diagnosed when there was evidence of myocardial necrosis in a clinical setting consistent with myocardial ischaemia (rising and/or falling pattern of troponin T, with at least one value >99th percentile). Unstable angina was diagnosed when there was chest pain with altered frequency or character, suspicious for ACS with documented ischaemia on the ECG, stress testing or invasive angiography [13,14].

Statistical Analysis

Continuous variables are presented as means (±SD) or medians (with IQR), categorical variables as proportions. Differences between groups were compared using the analysis of variance test (ANOVA) or Kruskal-Wallis one-way ANOVA test as appropriate. Parameters of diagnostic accuracy in terms of sensitivity and specificity were calculated with their corresponding 95% CIs using an optimal Receiver Operating Characteristics (ROC) curve cut-off value. The optimal ROC curve cut-off value was selected with the intention to optimise sensitivity and restrict false negative results. All probability values refer to 2-tailed tests of significance; a value <0.05 was considered significant. Statistical analyses were performed using SPSS software (V.17.0, SPSS Inc, Chicago, Illinois, USA) and STATA software (V.12.0, StataCorp, College Station, Texas, USA).

Results

Patient Characteristics

The study population consisted of 65 patients with a mean age of 56±10 years and 45 (69%) men. Baseline characteristics are shown in table 1. According to the TIMI risk score, 53 (82%) patients had low, 11 (17%) intermediate, and 1 (2%) high risk. The final diagnosis of ACS was established in 10 (15%) patients, 6 patients with myocardial infarctions and 4 with unstable angina pectoris. The sensitivity and specificity of using an obstructive lesion (>50% stenosis) on coronary CTA to detect ACS was 100% (95% CI 65% to 100%) and 82% (69% to 90%) (Table 2).

Table 1 | Baseline characteristics.

Characteristic	All patients (n=65)
Age (years)	56±10
Male gender	45 (69)
Smoking	31 (48)
Hypertension	36 (55)
Diabetes mellitus	13 (20)
Statin use	16 (25)
Family history	22 (34)
Peripheral artery disease	10 (15)
Heart rate (beats/min)	74±11
Systolic blood pressure (mmHg)	146±26
Diastolic blood pressure (mmHg)	82±18
Glucose (mmol/L)	6.2 (5.7–7.6)
Kreatinine (µmol/L)	75±14
CRP (mg/l)	1.5 (1.0–4.0)
TIMI score *	5 (5–8)
Low	53 (82)
Intermediate	11 (17)
High	1 (2)
Between time of onset (hrs) †	3.0 (1.5–12)
Coronary CTA‡	
≤20% stenosis	31 (48)
20–50% stenosis	14 (22)
50–70% stenosis	11 (17)
>70% stenosis	9 (14)
Acute coronary syndrome	10 (15)
Myocardial infarction	6 (9)
Unstable angina pectoris	4 (6)

Data are presented as numbers (%), mean ±standard deviation or median (interquartile range). * Risk of in hospital death, myocardial infarction or urgent revascularisation, median (inter-quartile range). † Time between onset of symptoms and blood sampling. ‡ Maximal obstruction on coronary CTA on a per-patient level.

Table 2 | Acute coronary syndrome detection with coronary CT angiography.

	Coronary CT angiography	
	Obstructive CAD (n=20)	No obstructive CAD (n=45)
Acute coronary syndrome (n=10)	10	0
No acute coronary syndrome (n=55)	10	45

Copeptin in ACS

Copeptin concentrations were higher in patients with ACS (median 7.42 pmol/l (IQR 3.71–18.72)) as compared with patients with no ACS (3.40 (1.13–6.27) pmol/l in those without (p=0.02, Figure 1). By using an ROC-derived optimal cut-off value of 3.27 pmol/l, we found a sensitivity of 90% (95% CI 54% to 99%) and specificity of 49% (36% to 63%) for the detection of ACS.

Obstructive CAD on CTA

Coronary CTA revealed no or minimal (<20%) stenosis in 31 (48%) patients, 20–50% stenosis in one or more vessels in 14 (22%), 50–70% stenosis in 11 (17%) and >70% stenosis in 9 (14%) (Table 1). Patients with obstructive CAD (>50% stenosis) had a median copeptin concentration of 4.87 (IQR 2.90–8.51), and those with no obstructive CAD 3.60 (1.21–6.23) (p=0.20, Figure 2).

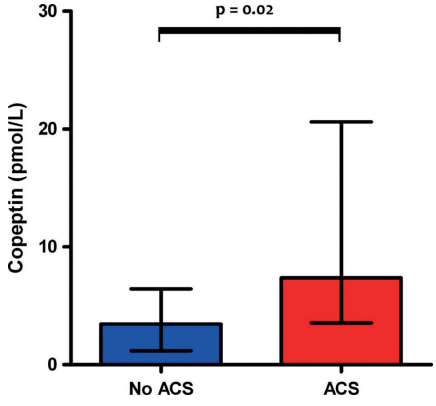

Figure 1 | Copeptin concentrations in patients with ACS (median 7.42 pmol/L [IQR 3.71–18.72]) vs. no ACS (3.40 [1.13–6.27]) (p=0.02).

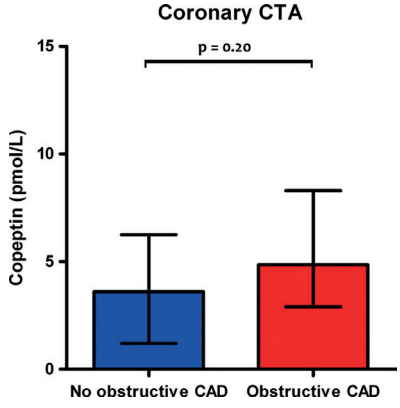

Figure 2 | Copeptin concentrations in patients with obstructive CAD on coronary CTA (median 4.87 [IQR 2.90–8.51] vs. no obstructive CAD (3.60 [1.21–6.23]).

Discussion

In this prospective study of patients with acute chest pain, we report the following findings: (1) serum copeptin concentrations at arrival were higher in patients with ACS; (2) in this population, no significant correlation between copeptin and obstructive CAD on coronary CTA could be demonstrated.

Since its introduction, copeptin has been studied in different populations as a potential clinical maker of haemodynamic stress [15]. Reichlin et al. [9] as well as Keller et al. demonstrated that copeptin allowed identification of patients with acute myocardial infarction, with incremental value to troponin T. However, more recent observations by Karakas et al suggested that the diagnostic performance of copeptin might be less in patients with low risk ACS [17]. Our results confirm previous larger studies and suggest rapid release of copeptin in patients with ACS.

While the role of copeptin in suspected ACS appears to be limited in light of the rapidly expanded implementation of high-sensitivity troponins, which also identify myocardial injury within 3–6 h [18,19] ongoing research suggests diagnostic performance may still be improved with addition of copeptin to these new-generation troponin essays [20,21].

Copeptin and Coronary CTA

Coronary CTA is increasingly employed in patients with suspected ACS, to allow safe and early discharge of those without CAD [22,23]. In our population, we could not detect an association between copeptin and the presence of obstructive CAD on CTA. Given the small sample size, a truly existing difference might be concealed due to lack of statistical power. However, our results are in agreement with earlier observations [17]. Coronary CTA has modest positive predictive value, that is, the exact severity of stenosis and degree of ischaemia cannot be assessed [24]. In patients with modest obstructive lesions on CTA (50–70% stenosis), copeptin could complement imaging by identifying patients with haemodynamic stress resulting from myocardial ischaemia. With increasing use of imaging as well as cardiac biomarkers, there is a demand for research with prespecified protocols combining new biomarkers with imaging modalities, like coronary CTA, to guide future clinical practice.

Study Limitations

There are several limitations that need to be acknowledged. First of all, this is a single-centre study, and is based on a population of modest size. Conclusions should be made with caution and are not necessarily generalizable to other populations. Nevertheless, the results of this explorative study indicate a discriminative role for copeptin in patients suspected of ACS. Second, the use of a data-derived ROC curve threshold in this study will overestimate diagnostic accuracy. Finally, the study was conducted in a selected population, because all patients also had to undergo coronary CTA. Those with an impaired renal function, previous coronary revascularization, arrhythmias, history of allergy to iodine, presence of contra-indication to β-blocker administration or clinical instability were excluded.

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CHAPTER 6

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

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Abstract

Background: It is uncertain whether a diagnostic strategy supplemented by early coronary computed tomography angiography (CCTA) is superior to contemporary standard optimal care (SOC) encompassing high-sensitivity troponin assays (hs-troponins) for patients suspected of acute coronary syndrome (ACS) in the emergency department (ED).

Objectives: 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.

Conclusions: 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)

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/m^2.

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 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

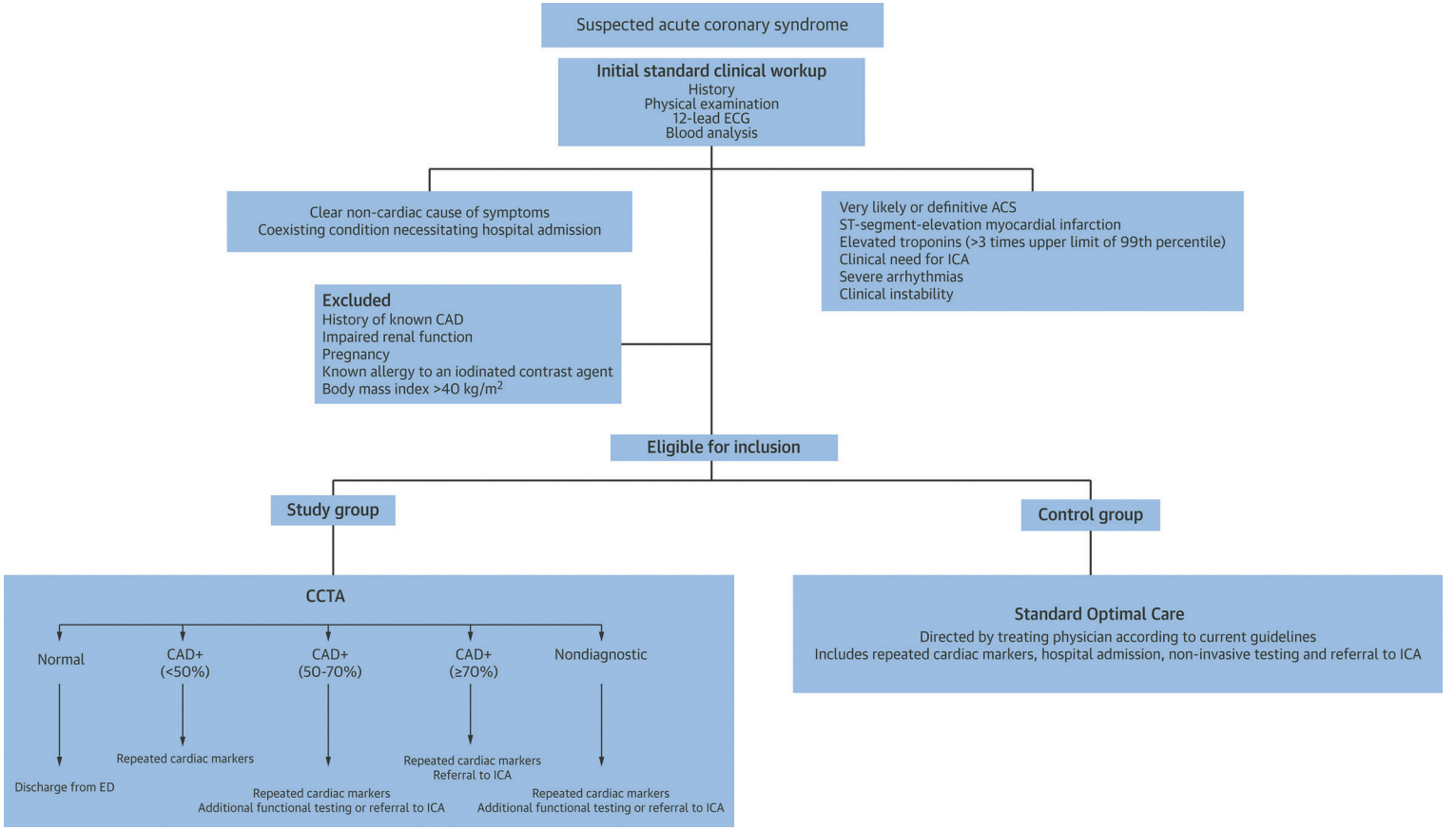


Figure 1 | Trial profile. In the study group, CCTA results were reported at the point of care, with imaging-based recommendations as displayed. However, the final decision regarding clinical work-up was left to the discretion of the treating physicians. Impaired renal function was classified as an estimated 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.

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/Gycm^2 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 (additional information in the Supplemental Appendix). 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.

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.

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

Table 1 | Baseline Characteristics *(Continued).*

	CCTA (n=250)	SOC (n=250)	*p* value
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)	
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.

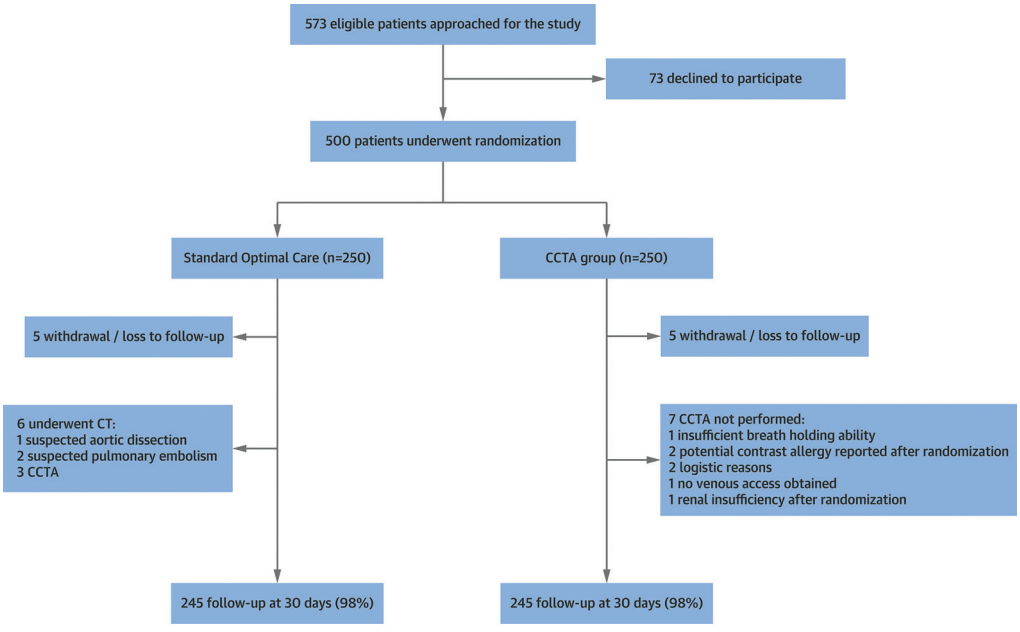


Figure 2 | Enrollment, Randomization, and Follow-up of Study Participants. CT = computed tomography; ACS = acute coronary syndrome; CAD = coronary artery disease; CCTA = coronary computed tomography angiography; ICA = invasive coronary angiography.

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).

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. CCTA = coronary computed tomography angiography; CVA = cerebrovascular accident; SOC = standard optimal care; TIA = transient ischemic attack; TIMI = Thrombosis in Myocardial Infarction. *Includes procedures at index visit.

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 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).

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. CCTA = coronary computed tomography angiography; CVA = cerebrovascular accident; SOC = standard optimal care; TIA = transient ischemic attack; TIMI = Thrombosis in Myocardial Infarction.

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 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 (Central Illustration).

CCTA in the ED

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].

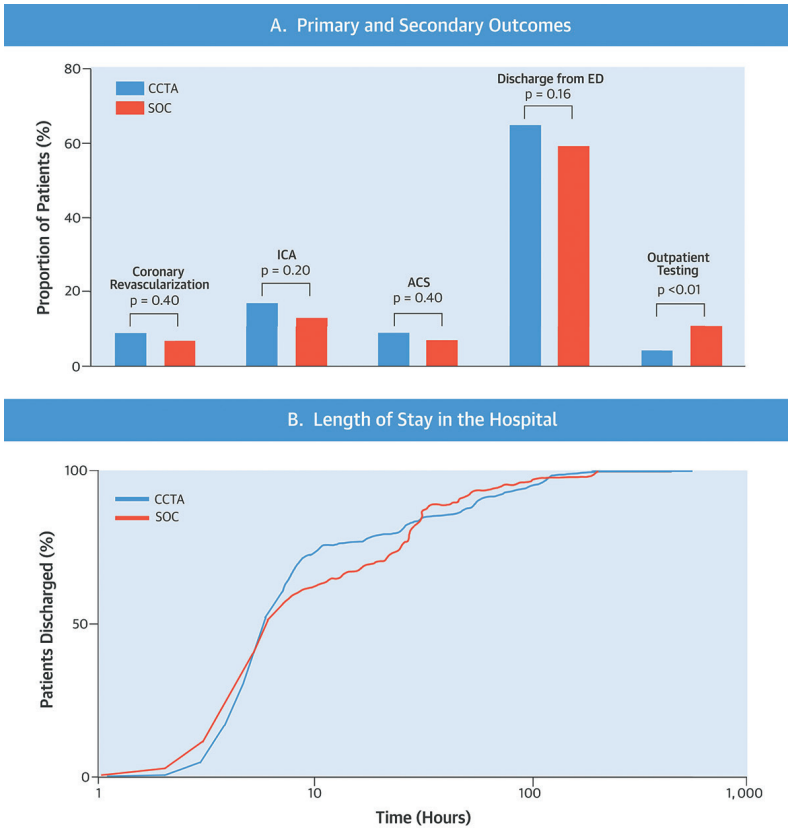
Since these trials were completed, the introduction of hs-troponin has changed SOC considerably. These new assays are more sensitive and reach negative predictive values of >97% for myocardial infarction within 3 h [11,12]. Early observations indicated that hs-troponins would allow fast and accurate 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 3). However, the length of stay in our SOC group was substantially lower (median 6.3 hours), underlining the vigorous improvement of SOC after the introduction of hs-troponins, and also making it harder to achieve an improvement with early CCTA.



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

Figure 3 | CCTA for Triage of Suspected Acute Coronary Syndrome: Outcomes and Length of Stay. (**A**) Primary and secondary outcomes in the early CCTA group and SOC group. B. Length of stay and proportion of patients discharged. angiography. ACS = acute coronary syndrome; CCTA = coronary computed tomography angiography; ED = emergency department; ICA = invasive coronary angiography; SOC = standard optimal care.

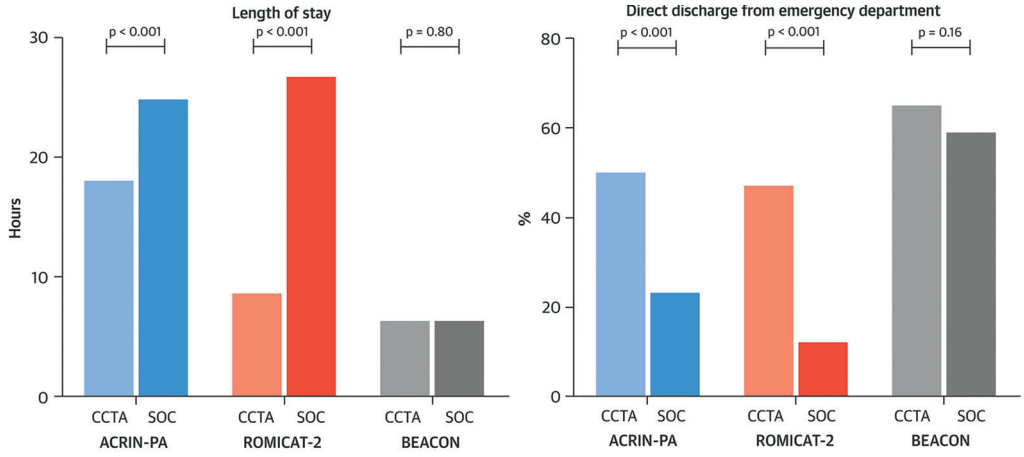


Figure 4 | Length of Stay and Discharge Rate From the Emergency Department in the ACRIN-PA, ROMICAT-2, and BEACON trials. Reported data are medians. ACS = acute coronary syndrome; CCTA = coronary computed tomography angiography; ED = emergency department; ICA = invasive coronary angiography; SOC = standard optimal care.

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 increase 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).

Conclusions

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	392 (78)	50	Serial measurement (3h interval).	14–50	5	14	13
Roche Elecsys			Value above the pre-defined threshold or a significant rise is regarded as infarction				
TnT Gen 4	87 (17)	30	Serial measurement (6h interval).	10–30	10	10	30
Roche Elecsys			Value above the pre-defined threshold is regarded as infarction				
cTnI	13 (3)	50	Serial measurement (6h interval).	28–50	10	28	32
Abbott ARCHITECT			Value above the pre-defined threshold is regarded as infarction				
hs-cTnI	4 (1)	34	Serial measurement (3h interval)	16–34	1.2	16	3
Abbott ARCHITECT			Value above the pre-defined threshold or a significant rise is regarded as infarction				
AccuTnI	4 (1)	60	Serial measurement (6h interval)	40–60	10	40	60
Gen 3 enhanced Beckman Coulter			Value above the pre-defined threshold is regarded as infarction				

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

	Standard optimal care			Coronary CT angiography				
	TIMI 0	TIMI 1	TIMI ≥2	No CAD	<50%	50–70%	>70%	Non-diagnostic
	(83)	(91)	(76)	(106)	(71)	(35)	(13)	(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.

Interbellum

CHAPTER 7

Transcatheter Closure of a Traumatic Ventricular Septum Defect Resulting from a Stab Wound

A. Dedić, K. Nieman, A.J.J.C. Bogers and M. Witsenburg

Eur Heart J Acute Cardiovasc Care. 2015 Feb;4(1):96-9.

Abstract

A 25-year-old man with a ventricular septal defect resulting from a stab wound to his chest was admitted to our hospital. Because of extensive comorbidity and favorable location, transcatheter closure with an Amplatzer device was preferred over surgical repair. Ventricular septal defects are an uncommon complication of cardiac trauma, but when they do occur from this cause, they often have more dramatic consequences. Transcatheter closure is an attractive, less invasive alternative in patients with increased surgical risk, multiple previous surgical interventions, or poorly accessible defects.

Introduction

Ventricular septal defects (VSD) are a common presentation of congenital heart disease (30–40% at birth) and the majority will close spontaneously before patients reach adulthood [1]. A less common cause of VSD is cardiac trauma, but when they do occur from this cause, they often have more dramatic consequences and mortality rates of up to 80% have been reported [2]. Cardiac trauma can be divided in two groups; blunt and penetrating injury, according to the causing mechanism. Ventricular defects may arise from direct lacerations, cardiac contusion, or myocardial infarction as a result of a coronary artery tear [3]. Defects can arise at any part of the septum and can become apparent hours or days after the original injury.

Case

A 25-year-old man with no history of heart disease was brought to the emergency room of a community hospital after sustaining a stab wound to the chest. His clinical situation deteriorated quickly necessitating emergency thoracotomy performed by the local general surgeon. A left lung laceration was stapled and a perforation of the left ventricle was directly sutured. Echocardiography revealed a large VSD, and the patient was subsequently transported to the intensive care unit (ICU) of our hospital. Transesophageal echocardiography showed a VSD of approximately 1.1×1.3 cm (Figure 1). CT angiography confirmed the presence of the defect (diameter of 8×16 mm in diastole) (Figure 2). His stay on the ICU was complicated by recurrent intrathoracic hemorrhages requiring re-thoracotomy on two occasions. In relation to the initial hemodynamic instability, the patient suffered multiple intracranial infarcts. During the intensive care treatment, a rectal canula resulted in bowel perforation, for which he underwent resection of his ileum and rectosigmoid. These complications delayed treatment of the VSD with a clinically impressive left to right shunt.

Once the patient had reached a stable clinical situation, transcatheter closure was attempted under general anaesthesia and systemic heparization. Antibiotics were given periprocedurally. Vascular access for cardiac catheterization was attained through the right femoral artery and the jugular vein. The VSD was crossed with a JR catheter (Cordis, Miami, FL, USA) and an arteriovenous loop was created by snaring a wire from the right jugular vein (Figure 3). Because of uncertainty about the size of the slit-like defect, balloon sizing was performed with a 25-mm PTS balloon, measuring a VSD diameter of 16 mm. A long sheath (AGA Medical, Plymouth, MN, USA) was placed from the jugular vein through the VSD and a 20-mm Amplatzer post-myocardial infarction VSD occluder (St Jude Medical, St Paul, MN, USA) was positioned under continuous echocardiographic control. The position of the occluder was checked for 20 min and was found to be stable with minimal residual flow. A check 30 min after release showed a stable position of the device and the procedure was ended. An immediate remarkable rise in the systemic blood pressure was seen with an aortic pressure, from 80/55 mmHg before placement to 121/78 mmHg after. Clinical observation after treatment showed normalization of both respiratory and heart rate. The patient was transferred to a rehabilitation centre for further recovery. Four years later, the patient is still in a stable condition and has no cardiac complaints.

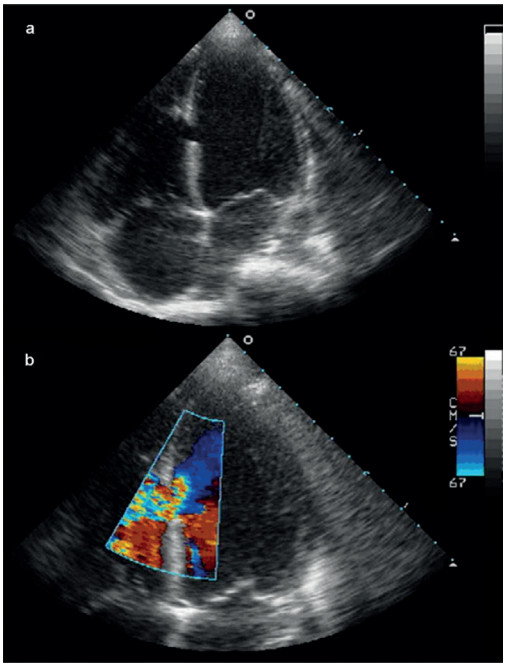

Figure 1 | Transthoracic echocardiogram. (**a**) Four-chamber view showing a midseptal ventricular defect; (**b**) colour Doppler recording with left to right shunting.

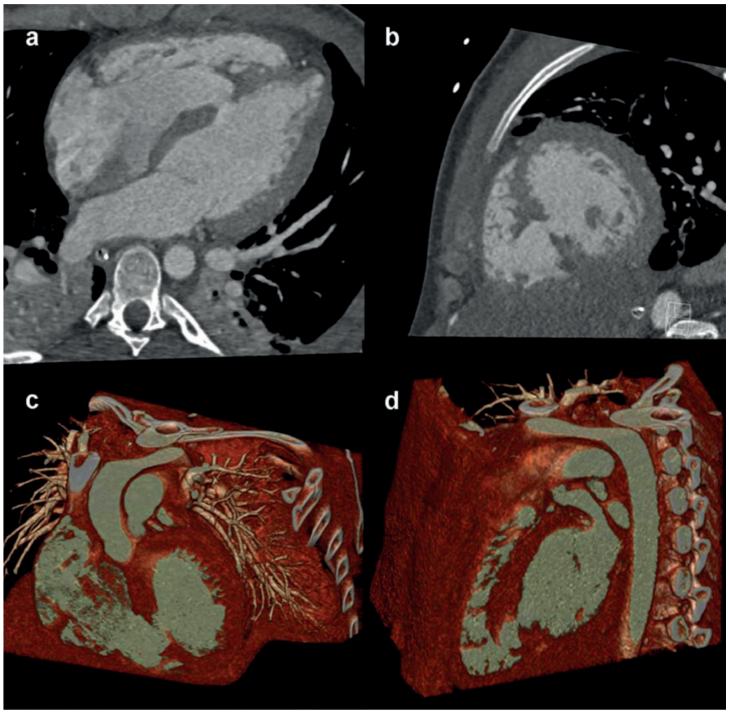

Figure 2 | Computed tomography angiogram. (**a**) Multiplanar four chamber and (**b**) short axis views visualizing the midseptal ventricular defect; (**c**, **d**) volume-rendered images with anterior (**c**) and lateral orientation (**d**).

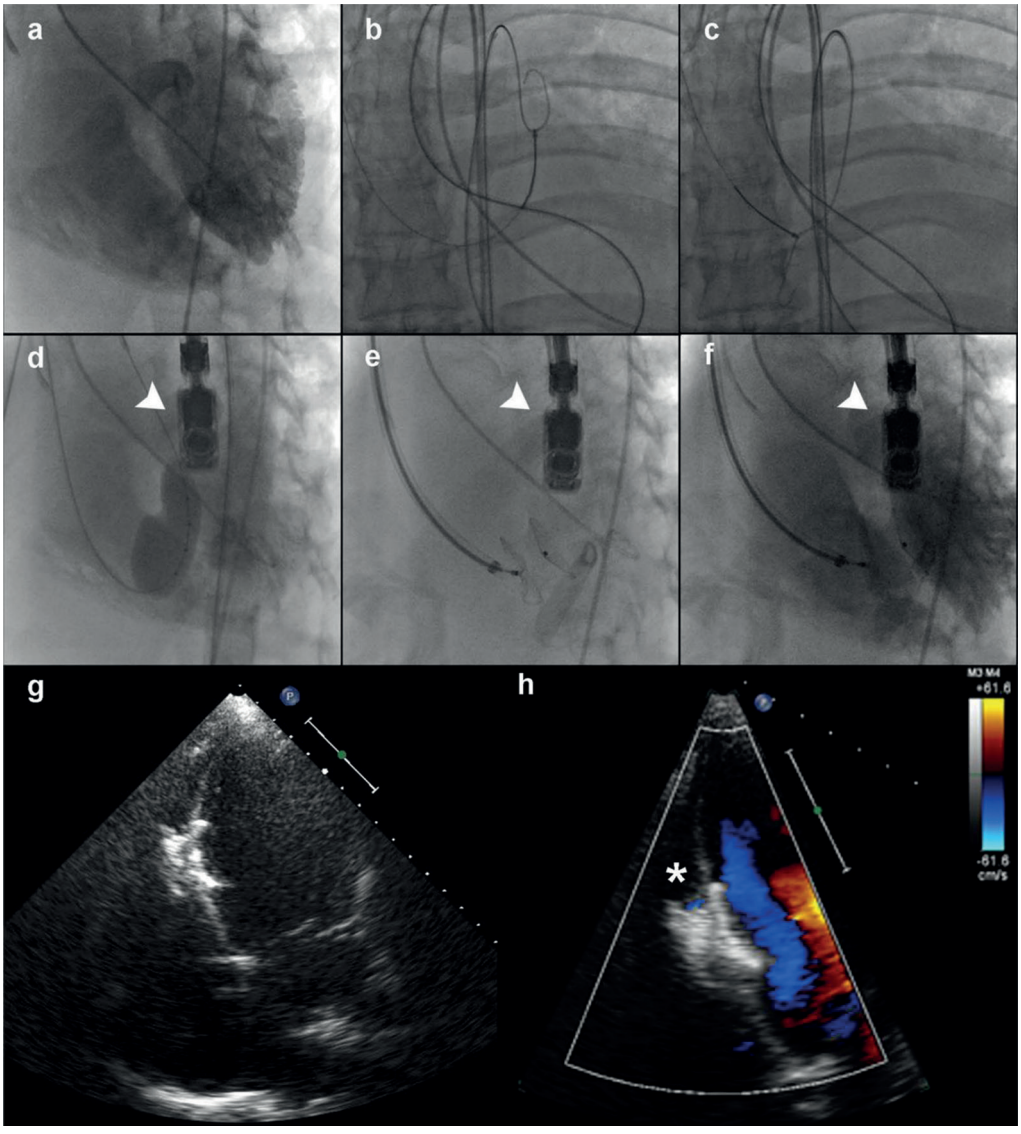

Figure 3 | Transcatheter closure of the ventricular septal defect. (**a**) Angiographic image before closure. (**b**, **c**) The VSD was crossed by a JR catheter (Cordis, Miami, Florda) and an arteriovenous loop was created by snaring a wire from the right jugular vein. (**d**) Sizing with a 25-mm PTS balloon, measuring a diameter of 16 mm. (**e**) A long sheath was placed from the jugular vein through the VSD and a 20-mm Amplatzer post-myocardial infarction VSD occluder was positioned under continuous echocardiographic control (arrowheads). (**f**) A check 30 min after release showed a stable position of the device. (**g**, **h**) Control echocardiography shows placement of the occluder with minimal residual flow (asterisk).

Discussion

Mostly seen after myocardial infarction, VSD associated with cardiac trauma are uncommon but not rare with an estimated incidence of 5% [4,5]. Echocardiography is a reliable non-invasive tool to establish the presence of such a VSD and therefore first choice for diagnosis [6]. The technique can be performed rapidly allowing the examiner to identify pericardial effusion, recognize septal defects, evaluate cardiac wall motion and examine valvular integrity. Alternatively, CT angiography, not limited by acoustic angles, allows a detailed morphological appreciation of the defect with depiction of other intrathoracal structures [7].

The timing of closure remains a subject of debate and while spontaneous closure of traumatic VSDs has been reported on several occasions, patients are often symptomatic necessitating closure [8,9]. Because of extensive experience in adult congenital disease, surgical repair has been the benchmark for treating acquired VSDs.10 More recently, transcatheter techniques have been introduced as a less-invasive alternative [11-13]. Patients with increased surgical risk, multiple previous surgical interventions or poorly accessible defects for surgical closure are suitable candidates for transcatheter closure [1,14]. In this patient, we preferred the transcatheter approach over surgery because of the extensive comorbidity and favorable location, distant from any valve. In addition, a lower risk of necrosis sur-rounding the defect was expected compared to post-myocardial infarction VSDs.

The most commonly described technique in transcatheter closure is the creation of an arteriovenous loop by retrograde approach from the aorta and exteriorization of a wire tip through the femoral or the jugular vein. A possible complication with this technique is injury to all structures that are in direct contact with the wire loop, including the aorta, ventricles, and valves. Other techniques are the trans-septal approach or crossing the defect from the right ventricular side without the need to exteriorize [15]. With interventional closure, continuous echocardiographic monitoring is recommended to visualize any remaining defects or damage to surrounding structures. The reported success rates are high in adult congenital VSDs (>90% closure); however, there is limited experience in traumatic VSDs [13,16]. Complications have been reported in 1–3% of the cases, including device embolization, rhythm and conduction abnormalities, haemolysis, valve injury, cardiac tamponade, and endocarditis [15]. This case illustrates that in selected patients transcatheter repair of a traumatic VSD can be successful and may be preferred over surgery as a less-invasive type of treatment.

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Part 3

Risk stratification with Coronary CT Angiography

CHAPTER 8

First-line Evaluation of Coronary Artery Disease with Coronary Calcium Scanning or Exercise Electrocardiography

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Abstract

Background: Although conventional (CAG) and computed tomography angiography (CTA) are reliable diagnostic modalities for exclusion of obstructive coronary artery disease (CAD), they are costly and with considerable exposure to radiation and contrast media. We compared the accuracy of coronary calcium scanning (CCS) and exercise electrocardiography (X-ECG) as less expensive and non-invasive means to rule out obstructive CAD.

Methods: In a rapid-access chest pain clinic, 791 consecutive patients with stable chest pain were planned to undergo X-ECG and dual-source CTA with CCS. According to the Duke pre-test probability of CAD patients were classified as low (<30%), intermediate (30–70%) or high risk (>70%). Angiographic obstructive CAD (>50% stenosis by CAG or CTA) was found in 210/791 (27%) patients, CAG overruling any CTA results.

Results: Obstructive CAD was found in 12/281 (4%) patients with no coronary calcium and in 73/319 (23%) with a normal X-ECG ($p<0.001$). No coronary calcium was associated with a substantially lower likelihood ratio compared to X-ECG; 0.11, 0.13 and 0.13 vs. 0.93, 0.55 and 0.46 in the low, intermediate and high risk group. In low risk patients a negative calcium score reduced the likelihood of obstructive CAD to less than 5%, removing the need for further diagnostic work-up. CCS could be performed in 754/756 (100%) patients, while X-ECG was diagnostic in 448/756 (59%) patients ($p<0.001$).

Conclusions: In real-world patients with stable chest pain CCS is a reliable initial test to rule out obstructive CAD and can be performed in virtually all patients.

Introduction

Angina pectoris is a common and disabling condition that affects millions of people worldwide. The diagnostic evaluation and subsequent management of patients suspected of coronary artery disease (CAD) is aimed at reducing complaints and improving prognosis. Although invasive coronary angiography (CAG) remains the gold standard for the diagnosis of obstructive CAD, coronary computed tomography (CTA) has emerged as a reliable non-invasive alternative, with an excellent accuracy for ruling out obstructive CAD [1-4]. However increasing concern about the costs, radiation exposure and contrast agents involved with either angiographic modalities justifies exploration of alternative approaches [5-8].

Exercise electrocardiography (X-ECG) is a widely available, well-established and cost-effective means to assess ischemic heart disease, despite its limited diagnostic accuracy and substantial rate of inconclusive test results [9]. Alternatively, coronary calcium scanning (CCS) is inexpensive, fast, operator-independent, associated with a much lower radiation exposure and without need for contrast media [10,11]. In this study we compared the ability of CCS and X-ECG as an initial test to rule out obstructive CAD in a large group of patients with stable angina from a rapid-access chest pain clinic. According to pre-test probabilities of obstructive CAD patients were assigned to low, intermediate and high risk groups.

Methods

Study Population

From September 2006 to April 2010 we evaluated 791 consecutive patients with stable chest complaints and no history of CAD at our rapid-access chest pain clinic. Patients were planned to undergo both dual-source CTA and X-ECG, in addition to a clinical examination and blood analysis. Referral to CAG was clinically driven. Using the Duke Clinical Score (DCS), based on the type of chest discomfort, age, gender and cardiovascular risk factors, patients were classified as having a low (<30%), intermediate (30–70%) or high (>70%) pre-test probability of obstructive CAD [12]. Chest pain was classified using the three categories by Diamond: typical angina pectoris, atypical angina pectoris and non-anginal chest pain [13].

Angiographic obstructive CAD was found in 210/791 (27%) patients, defined as the presence of >50% stenosis in ≥1 coronary branches by CAG or CTA (CAG overruling any CTA result). Obstructive CAD was absent in 546/791 (69%) patients, defined as none or >50% coronary stenosis by CAG (overruling any CTA result) or CTA.

In total 27/791 (3%) patients, without sufficient cause for invasive angiography, did not undergo CTA, because of renal failure, contrast allergy, patient preference, Parkinson disease, patient willingness to cooperate, failed venous access and severe obesity. Because of premature scan initiation or movement during scan 8 (1%) scans were considered non-diagnostic. The mean age in the study population was 56±10 years, with significantly more elderly patients in higher risk groups. Males were at higher risk for obstructive CAD, although overall the gender was evenly

divided (369/756=49% female) (Table 1). There were fewer smokers, diabetics and patients with dyslipidemia in the low risk group. There were more patients with hypertension and a history of vascular disease in the high risk group. The study complied with the Declaration of Helsinki and the ethical committee at our institution approved the study. Informed consent was obtained from all patients.

Table 1 | Baseline characteristics.

	Overall (n=756)	Low[a] (n=284)	Intermediate[a] (n=270)	High[a] (n=202)	*p* value[b]
Age (years)	56±10	52±9	56±9	62±9	<0.001
Women	369 (49%)	220 (78%)	122 (45%)	27 (13%)	<0.001
Nicotine abuse	198 (26%)	49 (17%)	91 (34%)	58 (29%)	<0.001
Hypertension	404 (53%)	141 (50%)	139 (52%)	124 (61%)	0.04
Diabetes mellitus	129 (17%)	27 (10%)	49 (18%)	53 (26%)	<0.001
Dyslipidemia	451 (60%)	125 (44%)	187 (69%)	139 (69%)	<0.001
Family history of cardiovascular disease	357 (47%)	146 (51%)	138 (51%)	73 (36%)	0.001
History of vascular disease	83 (11%)	22 (8%)	27 (10%)	34 (17%)	0.04
Body-mass index	28±5	28±5	27±5	28±5	0.63
CCS performed	754 (100%)	284 (100%)	268 (99%)	202 (100%)	0.25
CTA performed	753 (100%)	284 (100%)	268 (99%)	201 (100%)	0.39
X-ECG performed	675 (89%)	259 (91%)	241 (89%)	175 (87%)	0.22
Inconclusive X-ECG	227 (30%)	72 (25%)	90 (33%)	65 (32%)	0.06
Catheter angiography	180 (24%)	24 (9%)	69 (26%)	87 (43%)	<0.001
Revascularisation	112 (15%)	11 (4%)	32 (12%)	69 (34%)	<0.001
PCI	87 (12%)	10 (4%)	26 (10%)	51 (25%)	<0.001
CABG	25 (3%)	1 (<1%)	6 (2%)	18 (9%)	<0.001

CCS = coronary calcium scanning, CTA = computed tomography angiography, X-ECG = exercise electrocardiography, PCI = percutaneous coronary intervention, CABG = coronary artery bypass graft surgery. [a] Duke clinical score: pre-test probability of significant CAD. Low: ≤30%; intermediate: 30–70%; high: >70%. [b] ANOVA or nonparametric test.

Non-enhanced Coronary Calcium Scan

The calcium scan was performed using an ECG-triggered sequential scan mode, with 120-kV tube voltage, 78±26-mAs tube current and 3-mm slice thickness. Quantification was performed by the Agatston method with a standard 130-HU attenuation threshold. The absence of detectable calcium was considered as a negative CCS result. Patients with detectable coronary calcium were divided in two groups: moderate (1–400) and severe (>400 Agatston units) [14,15].

Contrast-enhanced CT Angiography

Computed tomography angiography was performed in the absence of the following contraindications: pregnancy, renal dysfunction or known allergy to iodine contrast media.

Image acquisition was conducted using a dual-source CT: Siemens Definition (Forchheim, Germany) from September 2006 to April 2009 and Siemens Flash from April 2009 to April 2010. Technical details regarding image acquisition are summarized in Table 2. Before the scan patients received a sublingual dose of nitroglycerine but no additional beta-blockers. Effective radiation doses for CCS and CTA were 0.8±0.2 mSv (range 0.4 to 1.6) and 8.5±3.4 mSv (range 0.5 to 17.8). Readers were blinded for patients' symptoms or exercise test results. Data was sent to an offline workstation for image analysis. All coronary segments were evaluated on axial images, multiplanar reformations, and maximum intensity projections according to readers' preferences. In a joint session, two readers evaluated the coronary anatomy, and vessels were qualitatively scored as normal, not significantly stenosed (<50% stenosis) or significantly stenosed (>50% stenosis).

Table 2 | Scan parameters.

	64-slice DSCT [a]	128-slice DSCT [b]
Patients (n)	527	234
Conventional spiral mode (n)	527	35
Sequential mode (n)	0	169
High pitch spiral mode (n)	0	30
Collimation (mm) [c]	64 (32x2)	128 (64x2)
Gantry rotation time (ms)	0.33	0.28
Effective temporal resolution (ms) [d]	83	75
Pitch (conventional spiral mode)	0.2–0.53	0.2–3
Tube voltage (kV)	120	100–120
Tube current (ma) [e]	370–412	320–412

Scan parameters of patients undergone CTA (761/791) using dual source computed tomography (DSCT): Siemens Definition[a] and Flash[b], Forchheim, Germany; [c]by alternating focal spot (Z-sharp®), [d]using a single-segmental reconstruction algorithm, [e]depending on patient size.

Exercise Electrocardiography

Bicycle X-ECG was performed by standardized protocol, with established criteria for performance and exercise discontinuation. Criteria for myocardial ischemia included horizontal or down sloping ST-segment depression or elevation ≥0.1 mV during or after exercise or typical, increasing angina during exercise. In case of established contra-indications patients did not perform an X-ECG [16]. A non-diagnostic result was defined by discontinuation without evidence of myocardial ischemia before reaching 85% of the target heart rate.

Coronary Angiography

Clinically indicated quantitative coronary angiography (QCA) was performed using standard techniques, with assessment of the most severe obstruction from ≥2 orthogonal projections using quantitative software (CAAS, Pie Medical, Maastricht, The Netherlands).

Statistical Analysis

Statistical analyses were performed using SPSS software (version 15.0, SPSS Inc, Chicago, Ill). Categorical variables are presented as proportions. Continuous variables are expressed as mean (±SD) or median (±IQR) as appropriate. All probability values refer to 2-tailed tests of significance; a probability value <0.05 was considered significant. Differences between groups were compared using 2-sided unpaired t test, chi-square test, or analysis of variance, as appropriate. Diagnostic performance parameters in terms of sensitivity and specificity were calculated with 95% confidence intervals. Post-test probabilities were calculated for low, intermediate and high risk patients using likelihood ratios.

Because of the known high number of not performed or inconclusive tests, we also analyzed X-ECG results using an intention-to-diagnose approach, considering inconclusive tests as positive tests.

Additionally, we hypothesized that a calcium threshold slightly above the conventional zero calcium would reduce the false positive results without significant sacrifice on the negative predictive value. A ROC analysis was performed to find calcium scores optimally discriminating angiographic obstructive CAD in our study population.

Results

Coronary Calcium Scanning

In two patients CCS was not performed because of patient preference or severe obesity. There was no detectable coronary calcium in 281/756 (37%) patients, 152 (54%) in the low, 99 (37%) in the intermediate and 30 (15%) in the high risk group (Figure 1). Angiographic obstructive CAD was found in 10/281 (4%) patients with no calcium, 2/152 (1%) with low risk, 4/99 (4%) with intermediate risk and 4/30 (13%) with high risk. In comparison, these patients did not differ in age (55 vs. 56 years, p=0.67), gender (30 vs. 49%, p=0.21), smoking (30 vs. 26% p=0.75), hypertension (50 vs. 54% p=0.82), dyslipidemia (60 vs. 59% p=0.94), family history (60 vs. 47% p=0.41) or BMI (27 vs. 28 p=0.66). However, none had a prior history of vascular disease or diabetes mellitus. A ROC analysis with consideration for pre-test probability of CAD revealed calcium thresholds of 2, 2.5 and 15 Agatston units in low, intermediate and high risk group, respectively, to optimally differentiate patients with or without obstructive CAD (Figure 2).

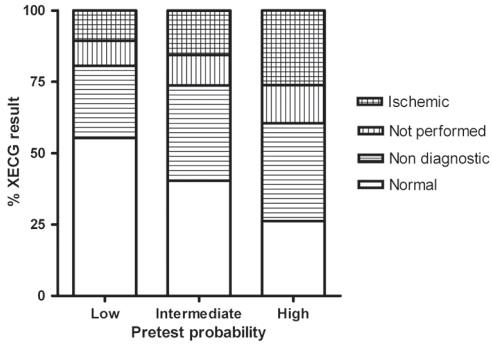

Figure 1 | Distribution of groups with no detectable calcium, intermediate calcium scores and high calcium scores considering pre-test probability of CAD.

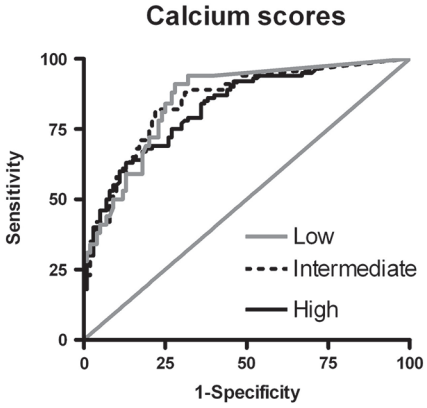

Figure 2 | ROC-curve of coronary calcium scores predicting obstructive coronary disease considering pre-test probabilities.

Exercise Electrocardiography

In 81 (11%) patients X-ECG could not be performed because of inability to cycle, resting ECG abnormalities, pulmonary disease and combined or unspecified reasons. In 227 (30%) patients X-ECG did not yield a diagnostic result, mostly because the target heart rate was not reached. A normal X-ECG was found in 319/756 (42%) patients, 157 (49%) in the low, 109 (34%) in the intermediate and 53 (17%) in the high risk group (Figure 3). A normal X-ECG was found in 55/319 (17%) patients with angiographic obstructive CAD, 15/157 (10%) with low risk, 17/109 (16%) with intermediate risk and 23/53 (43%) with high risk.

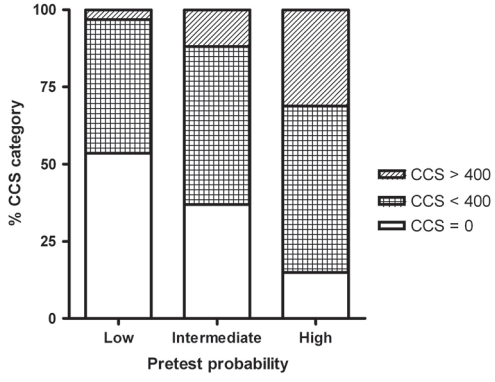

Figure 3 | Distribution of exercise electrocardiography results considering pre-test probability of CAD.

Coronary Angiography

Invasive coronary angiography was performed in 180 patients (24%), with subsequent need for coronary revascularization in 112 (15%) patients: 87 (12%) percutaneous coronary intervention, 25 (3%) coronary bypass surgery.

Comparison of Diagnostic Performance

Overall CCS showed significantly higher negative predictive value compared to X-ECG, 96% (95% CI 93–98) vs. 83% (95% CI 78–87), regardless of pre-test probability of disease. In patients with low and intermediate risk we found excellent negative predictive values of 99% (95–100) and 96% (89–99), respectively (Table 3). No detectable calcium was associated with a likelihood ratio of 0.11 (0.03–0.4), 0.13 (0.05–0.3) and 0.13 (0.05–0.3) in the low, intermediate and high risk group. A normal XECG was associated with a likelihood ratio of 0.93 (0.7–1.2), 0.55 (0.4–0.8) and 0.46 (0.3–0.6) in the low, intermediate and high risk group, respectively.

By increasing the calcium threshold to 2, 2.5 and 15 Agatston units, respectively, based on the previous ROC analysis, the specificity of CCS increased from 60% (53–66), 47% (40–54) and 29% (20–39) to 68% (62–74), 52% (45–59) and 46% (36–57) in the low, intermediate and high risk group, respectively (Table 3). Excluding non-diagnostic results, X-ECG was significantly more specific: overall 82% (77–86) vs. 50% (45–54), regardless of pre-test probabilities. However, using an intention-to diagnose approach, assuming non-diagnostic tests to be positive, the specificity decreased to a value comparable to CCS.

Discussion

From our results we concluded that the absence of calcium rules out angiographic obstructive CAD reliably in real-world patients, particularly in those with low to intermediate risk of CAD, outperforming X-ECG in this setting. No calcium was found in 281/756 (37%) patients and 319/756 (42%) patients had a normal X-ECG result. Patients without detectable calcium were substantially less likely to have obstructive CAD (Figure 4) in comparison to a normal X-ECG result: 10 (4%) vs. 55 (17%) (pb0.001).

Clinical Implications

Recently a large US registry reported on the low yield of obstructive coronary artery disease by invasive coronary angiography, recommending a more effective non-invasive diagnostic workup [17]. While CCS has been used for exclusion of CAD in asymptomatic and symptomatic individuals for the past decade [15,18], its capacity to rule out obstructive CAD was recently questioned in a paper assessing patients referred for invasive catheterisation [19]. According to the Bayes' theorem test performance is influenced by the pre-test probability of the population. Patients selectively referred for catheterization generally have a higher likelihood of obstructive CAD compared to our outpatient cohort presenting with stable chest pain. Our results demonstrate that the negative predictive value of the calcium scan is excellent in subgroups with low disease prevalence. In line

with the observations by Gottlieb et al., the rate of patients with obstructive CAD and no detectable calcium gradually increases concomitantly with their pre-test probability.

Table 3 | Operating characteristics.

	Sensitivity % (95% CI)	Specificity % (95% CI)	LR+ (95% CI)	LR– (95% CI)
Overall				
CCS (>0)	95 (91–98)	50 (45–54)	1.9 (1.7–2.1)	0.1 (0.05–0.2)
Optimal CCS	94 (89–96)	58 (54–63)	2.3 (2.0–2.5)	0.1 (0.06–0.2)
X-ECG	56 (47–65)	82 (77–86)	3.1 (2.4–4.1)	0.5 (0.4–0.7)
X-ECG-itd	70 (63–76)	54 (49–58)	1.5 (1.3–1.7)	0.6 (0.5–0.7)
Low				
CCS (>0)	94 (78–99)	60 (53–66)	2.3 (1.9–2.8)	0.1 (0.03–0.4)
Optimal CCS	94 (78–99)	68 (62–74)	2.9 (2.4–3.6)	0.1 (0.02–0.3)
X-ECG	21 (7–46)	85 (78–89)	1.4 (0.5–3.5)	0.9 (0.7–1.2)
X-ECG-itd	44 (26–64)	61 (55–67)	1.1 (0.7–1.8)	0.9 (0.6–1.3)
Intermediate				
CCS (>0)	94 (84–98)	47 (40–54)	1.8 (1.5–2.0)	0.1 (0.05–0.3)
Optimal CCS	94 (84–98)	52 (45–59)	2.0 (1.7–2.3)	0.1 (0.02–0.3))
X-ECG	55 (38–71)	81 (73–88)	3.0 (1.8–4.8)	0.5 (0.4–0.8)
X-ECG-itd	73 (60–83)	51 (44–59)	1.5 (1.2–1.9)	0.5 (0.4–0.8)
High				
CCS (>0)	96 (90–99)	29 (20–39)	1.3 (1.2–1.5)	0.1 (0.05–0.3)
Optimal CCS	94 (87–97)	46 (36–57)	1.7 (1.4–2.1)	0.1 (0.06–0.3)
X-ECG	67 (54–77)	73 (57–85)	2.5 (1.5–4.2)	0.5 (0.3–0.6)
X-ECG-itd	76 (65–84)	37 (27–49)	1.2 (1.0–1.5)	0.7 (0.4–1.0)

CCS = coronary calcium scanning, Optimal CCS = ROC-based calcium thresholds, X-ECG = exercise electrocardiography, X-ECG-itd = exercise electrocardiography with an intention-to-diagnose approach, LR+ = positive likelihood ratio, LR– = negative likelihood ratio.

In low risk patients (0–30%) a negative calcium score reduced the likelihood of obstructive CAD <5% (Figure 5), removing the need for further diagnostic work-up in a substantial proportion of patients (19%). For intermediate risk patients (30–70%) the likelihood decreased to 5–25%, reducing the need for further testing, particularly in those with a post-test probability of <10%. In high risk patients (N70%) neither CCS nor X-ECG excluded angiographic obstructive CAD, although a negative X-ECG may be more helpful to exclude hemodynamically relevant lesions and guide patient management.

Furthermore, we found that a cut-off value above the conventional zero calcium score reduced false positive results without sacrifice on the high negative predictive value in patients with a low to intermediate probability.

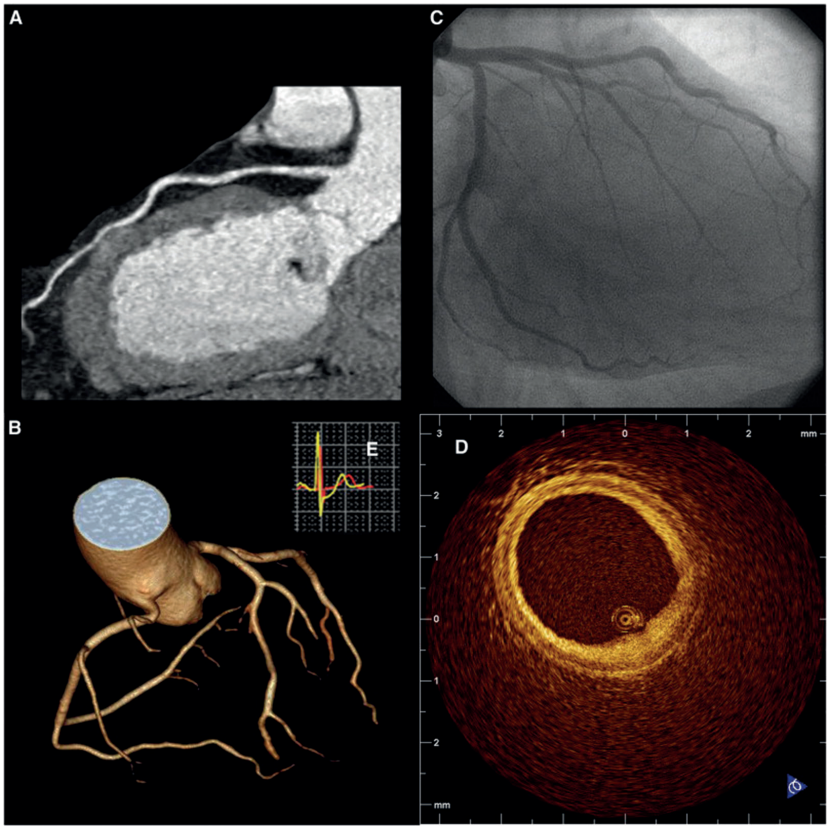

Figure 4 | 52 year old female with typical angina pectoris, positive family history and recent cessation of smoking. **A**, **B**: There was no detectable calcium on the non-enhanced CT-scan. CTA curved MPR and volume rendering show a non-obstructive, non calcified plaque in the mid left anterior descending (LAD) coronary artery. **C**: CAG revealed no significant obstructions. **D**: Optical Coherence Tomography (OCT) (Lightlab Imagewire®, Lightlab Imaging, Westford, MA, USA) confirmed the presence of a non-obstructive, non calcified plaque in the LAD. The eccentric intimal thickening is visible from 12–6 o'clock. The 3-layered appearance of the vessel is well visible: the inner endoluminal yellow, bright layer corresponds with the intima, the dark middle layer corresponds with the media and the outer, bright layer corresponds with the adventitia. E: X-ECG was borderline positive with slight ST-deviation of ±1 mm in V4-V6.

Limitations

Because not all patients had a clinical indication for invasive angiography, a composite diagnostic endpoint including CT angiography was used. Given the well-established diagnostic accuracy of CTA, especially its negative predictive value, performing invasive CAG in every patients would be unethical [20]. However, limiting the study to patients with QCA would have resulted in loss of the real-world character of this study. In this study we focused on reliability of CCS or X-ECG to rule

out CAD. We believe that using a composite endpoint of CTA next to invasive angiography does not jeopardize our conclusions. Nevertheless to anticipate overestimation of CTA we performed a sensitivity analysis using a composite diagnostic endpoint of >50% coronary stenosis by CAG (overruling any CTA result) and >50% left main or three-vessel disease or >70% one or two-vessel stenosis by CTA. By excluding patients with intermediate coronary stenosis on one or two vessels, we obtained no significantly different diagnostic performances of CCS and X-ECG.

There was no comparison of CCS to more advanced functional imaging tests, nor was the hemodynamic significance of the coronary lesions routinely determined. Assessment of myocardial ischemia has prognostic consequences and is important for clinical decision making. The incremental value of stress testing applies mostly to those with angiographic coronary disease, and less to patients in whom CAD has been excluded (by CTA or QCA), which involves the majority of patients presenting in a chest pain clinic. Recent work from Esteves et al. demonstrated that the absence of coronary calcium also excludes ischemia on functional testing [21]. In addition, patients with no detectable calcium show slow progression of CAD over time [22].

Nevertheless, clinical outcome studies are needed to evaluate the value of CCS as a tool for exclusion of obstructive CAD, in comparison to functional tests.

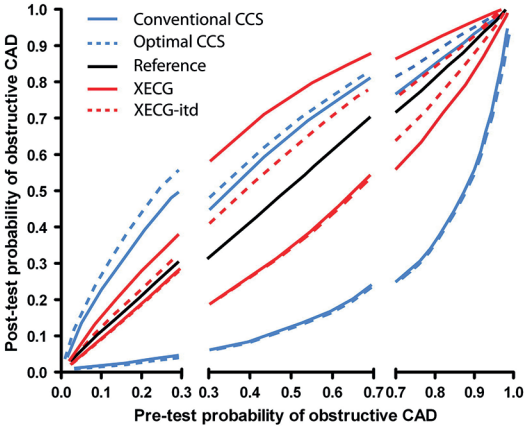

Figure 5 | Post test probability of obstructive coronary artery disease (CAD) considering pre-test probability. Conventional CCS = coronary calcium scanning regarding zero calcium as negative result, exercise electrocardiography, optimal CCS = coronary calcium scanning with ROC analysis based thresholds, XECG = exercise electrocardiography, XECG-itd = exercise electrocardiography with an intention-to-diagnose approach.

Conclusions

Coronary calcium scanning is a reliable initial test in real-world patients with stable chest pain to rule out obstructive CAD and it can be performed in virtually all patients. In low risk patients without detectable coronary calcium further diagnostic work-up seems redundant as the post-test probability of obstructive CAD is less than 5% for these patients. In the group of patient with intermediate risk of obstructive CAD the likelihood decreased to 5–25% after a negative CCS, reducing the need for further testing, particularly in those with a post-test probability of <10%. High risk patients do not seem to benefit from neither CCS nor X-ECG to exclude angiographic obstructive

CAD, although a normal X-ECG may be more helpful to exclude hemodynamically relevant lesions and guide management.

Acknowledgment

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CHAPTER 9

Prognostic Value of Coronary Computed Tomography Imaging in Patients at High Risk Without Symptoms of Coronary Artery Disease

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Abstract

At present, traditional risk factors are used to guide cardiovascular management of asymptomatic subjects. Intensified surveillence may be warranted in those identified as high risk of developing cardiovascular disease (CVD). This study aims to determine the prognostic value of coronary computed tomography (CT) angiography (CCTA) next to the coronary artery calcium score (CACS) in patients at high CVD risk without symptoms suspect for coronary artery disease (CAD). A total of 665 patients at high risk (mean age 56±9 years, 417 men), having at least one important CVD risk factor (diabetes mellitus, familial hypercholesterolemia, peripheral artery disease, or severe hypertension) or a calculated European systematic coronary risk evaluation of >10% were included from outpatient clinics at 2 academic centers. Follow-up was performed for the occurrence of adverse events including all-cause mortality, nonfatal myocardial infarction, unstable angina, or coronary revascularization. During a median follow-up of 3.0 (interquartile range 1.3 to 4.1) years, adverse events occurred in 40 subjects (6.0%). By multivariate analysis, adjusted for age, gender, and CACS, obstructive CAD on CCTA (≥50% luminal stenosis) was a significant predictor of adverse events (hazard ratio 5.9 [CI 1.3 to 26.1]). Addition of CCTA to age, gender, plus CACS, increased the C statistic from 0.81 to 0.84 and resulted in a total net reclassification index of 0.19 ($p<0.01$). In conclusion, CCTA has incremental prognostic value and risk reclassification benefit beyond CACS in patients without CAD symptoms but with high risk of developing CVD.

Introduction

In the general population, the annual incidence of sudden cardiac death is estimated from 50 to 100 cases per 100,000 adults, both in Europe and North America, accounting for approximately 50% of all cardiac deaths [1,2]. In at least half of these cases, sudden cardiac death is the first and only manifestation of cardiovascular disease (CVD) in an otherwise asymptomatic individual [3]. Autopsy data show that >80% of these subjects had anatomically important, subclinical coronary artery disease (CAD) [4]. At present, traditional risk factors are used to guide cardiovascular management of asymptomatic subjects [5]. Patients without symptoms or signs of CAD, but with diabetes mellitus (DM), familial hyper-cholesterolemia (FH), peripheral artery disease (PAD), severe hypertension, or a calculated European systematic coronary risk evaluation of >10% are considered at high risk of developing a cardiovascular event. Therefore, optimal primary prevention is required including preventive pharmacologic treatment and screening for organ damage [6]. Studies have shown that the coronary artery calcium score (CACS) is useful for refined risk stratification in these patients at high risk, in particular, in those with DM [7,8]. It has been postulated that asymptomatic patients at high risk might benefit from increased medical surveillance [9]. Coronary computed tomography (CT) angiography (CCTA) offers a more detailed assessment of subclinical CAD and could be of incremental prognostic value, as previously demonstrated in symptomatic patients [10-12]. The aim of this observational multicentre study was to determine whether CCTA improves risk prediction beyond CACS in patients without symptoms of CAD but at high risk of developing CVD.

Methods

Eligible patients (aged between 45 and 70 years) were clinically referred to the outpatient clinics of 2 academic hospitals by general practitioners or other physicians for optimized cardiovascular management and primary prevention according to current guidelines [5]. For this observational study, we collected patients prospectively and retrospectively, who were considered at high risk of developing CVD, because of the presence of a markedly elevated single cardiovascular risk factor, such as DM, FH, PAD, severe hypertension, or a calculated European systematic coronary risk evaluation of >10% [5].

Diabetes mellitus was defined as fasting glucose levels >7.0 mmol/L or >11.1 mmol/L 2 hours after an oral glucose tolerance test [13]. FH was defined as the presence of a documented low-density lipoprotein receptor mutation or a low-density lipoprotein cholesterol level above the gender and age corrected 95th percentile in combination with typical clinical characteristics in the patient or a first-degree relative [14]. Severe hypertension was defined as a systolic blood pressure level >160 mm Hg or a diastolic blood pressure >100 mm Hg [5]. PAD was defined as a history of targeted surgical, percutaneous, or medical treatment of atherosclerosis in a noncoronary artery.

All patients were receiving intense lifestyle counseling and/or medical therapy at baseline, and strict compliance was ensured by regular outpatient clinic visits. Exclusion criteria included a history of CAD, renal dysfunction (serum creatinine >120 mmol/L), contrast allergy, irregular heart rhythm,

severe chronic obstructive pulmonary disease, or known pregnancy. The study complies with the Declaration of Helsinki, and the study protocol was approved by the institutional review boards. A waiver was obtained for the use of retrospective data. A proportion of patients was enrolled prospectively and provided written informed consent.

Image acquisition was performed on multidetector row CT scanners with 64 rows. Detection of coronary artery calcium was performed using an electrocardiogram-triggered axial scan and measured using the Agatston method [15]. Patients were stratified in groups according to the extent of coronary artery calcification: 0, 1 to 100, 101 to 400, and >400 CACS. CCTA was performed during a single inspiration using an electrocardiogram-triggered axial scan with X-ray tube current modulation and tube voltage reduction when clinically feasible. A 17-segment coronary artery tree model (as recommended by the American Heart Association) was used to describe the presence, extent, and severity of CAD [16]. In the case of severe movement or inappropriate contrast delivery, resulting in non-diagnostic image quality of >1 coronary artery or important proximal segments, the entire scan was considered non-diagnostic.

Stenosis grade was visually classified either as <29%, 30–49%, 50–69%, ≥70% luminal narrowing or occluded (100%). We used commonly applied methods of measuring extent of CAD [17]. First, subjects were categorized in groups by most severe CAD lesion: 'obstructive CAD' (≥1 plaques with ≥50% luminal stenosis), 'non-obstructive CAD' (<49% luminal stenosis), or 'absence of CAD'. Secondly, patients were classified by the number of coronary arteries with obstructive CAD, into '3-vessel or left main obstructive CAD', '2-vessel obstructive CAD', 'single-vessel obstructive CAD', 'non-obstructive CAD' or 'absence of CAD'. In addition, to determine the overall coronary artery plaque burden a segment stenosis score was calculated: <29% stenosis: score 0; 30–49%: score 1; 50–69%: score 2; ≥70%: score 3. Finally, the number of segments with CAD ≥30% stenosis was determined.

The primary outcome measure was a combination of adverse events including all-cause mortality, nonfatal myocardial infarction (MI), unstable angina, or coronary revascularization beyond 90 days after the index CCTA. All-cause mortality was confirmed using the Dutch National Mortality Registry. Information regarding clinical events was acquired through questionnaires, outpatient visits, or electronic patient records. Nonfatal MI and unstable angina were defined according to current guidelines [18].

Statistical analyses were performed using SPSS software (SPSS Inc, Chicago, Illinois) and SAS software (SAS Institute, Cary, North Carolina). Categorical variables are presented as proportions and continuous variables are expressed as mean (SD) or median (interquartile range), as appropriate. The cumulative incidence of adverse events over time was estimated according to the Kaplan-Meier method, whereas the log-rank test was applied to evaluate differences. Univariate Cox regression analysis was applied to assess associations between clinical characteristics or imaging results and incidence of adverse events. Cox regression models including CACS and CCTA, adjusted for age and gender, were used to determine adjusted hazard ratios with 95% CIs. Improvement in discriminative model performance and reclassification was assessed by calculating C statistics and net reclassification index (NRI) at 2.5 years. NRI is a measure of correctly reclassified patients penalized for those incorrectly classified [19]. Because no validated risk score is available to determine baseline

risk in this population, required for the calculation of NRI, we used a binary regression model with age and gender to substratify patients to low (<1%), intermediate (1% to 5%), or high baseline risk (>5%). Subsequently, CACS and CCTA information was added to calculate NRI. In addition, we examined the association between CCTA findings and incidence of adverse events in patients with zero, intermediate, and high CACS. All probability values refer to 2-tailed tests of significance and a *p* value <0.05 was considered significant.

Results

A total of 665 subjects were included between September 2006 and March 2013. The mean age was 56±9 years and 417 (63%) were male (Table 1). Most patients received medical therapy, and statins (492 [74%] patients) were the most frequently prescribed medication. No coronary artery calcium was detected in 174 (27%) patients, while 127 (19%) patients had an Agatston score >400. On CCTA, 126 (19%) patients had no detectable CAD, 337 (51%) had non-obstructive CAD and obstructive CAD was noted in 192 (29%) patients. We observed CAD on CCTA in 66 (38%) patients with zero CACS (Figure 1). The median radiation dose of the calcium scan was 1.0 [IQR 0.7–1.4] mSv and 5.3 [3.4–8.4] mSv for CCTA using a conversion factor (k) of 0.014.

Follow-up was obtained for 620 (95%) patients with an interpretable scan during a median follow-up period of 3.0 (1.3–4.1) years. All-cause mortality was checked for all patients. The composite outcome occurred in 40 (6.0%) patients with an estimated annual incidence of 2.0% after a median period of 3 years. All-cause mortality was recorded in 9, non-fatal MI in 3, unstable angina in 3 and late coronary revascularisation in 25 individuals. The annual incidence of adverse events in patients with zero CACS (0.4% [CI 0.1–1.3%]) was significantly lower compared to patients with CACS >400 (6.8% [CI 4.8–9.4%]) (Figure 2). Patients with obstructive CAD on CCTA (6.0% [CI 4.4–8.0%]) had a significantly higher incidence of adverse events compared to patients without (0.5% [CI 0.2 – 1.9%]) or non-obstructive CAD (0.5% [CI 0.2–1.2%]) (Figure 3).

Table 1 | Patient baseline characteristics.

Variable	All patients (n=665)
Age, mean ± SD	56±9
Men	417 (63%)
Cardiovascular risk factors	
Smoker	150 (23%)
Blood pressure >130/80 mmHg	333 (50%)
Dyslipidemia*	423 (64%)
Diabetes mellitus	378 (57%)
Positive family history of CAD	295 (44%)
Body Mass Index >30 kg/m^2	173 (26%)
Medication	
Statin	492 (74%)
Oral antidiabetics	236 (35%)
Insulin	207 (31%)
ACE inhibitor	169 (25%)
Aspirin	162 (24%)
Beta-blocker	151 (23%)
AR-blocker	129 (19%)
Calcium channel blocker	78 (12%)
Coronary artery calcium score	
0	174 (27%)
1-100	239 (37%)
100-400	115 (18%)
>400	127 (19%)
Coronary Computed Tomography Angiography	
No Coronary Artery Disease	126 (19%)
Non-obstructive Coronary Artery Disease	337 (51%)
Obstructive Coronary Artery Disease (≥50% diameter stenosis)	192 (29%)
1	103 (15%)
2	59 (9%)
3 or left main disease	30 (5%)
Segment stenosis score, median (IQR)	6 (2–12)
Segment involvement score, median (IQR)	4 (1–7)

CT data were not available in 10 patients. * Dyslipidemia was defined as either known familial hypercholesterolemia, on statin treatment or measured serum LDL-C levels >190 mg/dL. AR = angiotensin receptor.

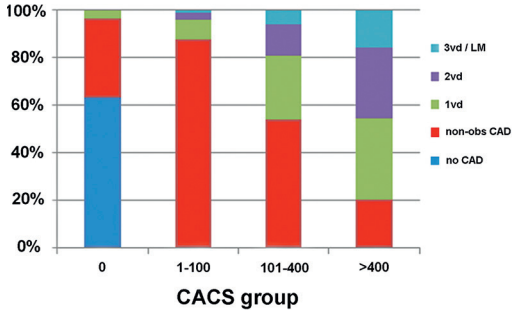

Figure 1 | Distribution of coronary artery disease (CAD) detected by coronary CT angiography across different coronary artery calcium score (CACS) groups. Non-obs CAD = non-obstructive coronary artery disease (1-49% luminal stenosis) in ≥1coronary vessels. 1vd = presence of 1-vessel obstructive (≥50% luminal stenosis) disease. 2vd = presence of 2-vessel obstructive disease. 3vd = presence of 3-vessel obstructive disease. LM = presence of left main obstructive disease.

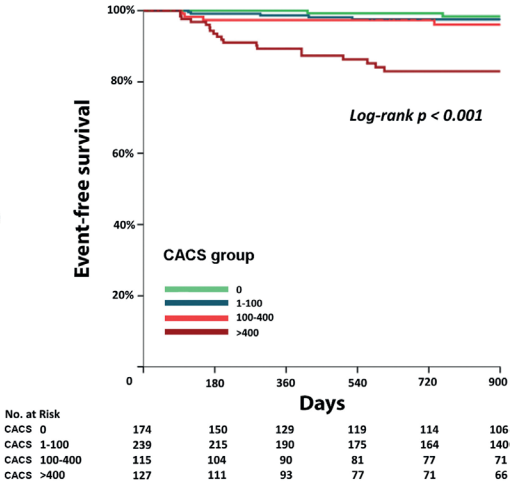

Figure 2 | Unadjusted survival for different coronary artery calcium score (CACS) groups. Log-rank p<0.001 for any difference.

Univariable Cox regression analysis identified age, male gender, and DM as significant predictors of the composite outcome (Table 2). There was a positive correlation between the occurrence of adverse events and CACS. Also, patients with obstructive CAD on CCTA had a higher incidence of adverse events compared to patients without obstructive CAD. The semi-quantitative measures of plaque burden, segment stenosis score or number of segments with CAD were significant predictors of adverse events. In multivariable Cox regression analysis, accounting for age, gender and CACS, obstructive CAD on CCTA remained a significant predictor of adverse events (Figure 4).

Most adverse events, that is, 32 (8.5%) in 378 patients, was observed in patients with DM, where the incidence of CAD detected with CCTA was also higher compared with patients without diabetes (Supplementary Material). The prognostic performance of both CCTA and CACS in these patients was equally well compared to the total study population.

The addition of CACS to a model with age and gender increased the C statistic to 0.81; subsequent addition of obstructive CAD increased the C statistic to 0.84 (Table 3). With the addition of CACS, we observed an NRI of 0.35 (p<0.01). There was an additional reclassification observed with the addition of CCTA to age, gender plus CACS with an NRI of 0.19 (p<0.01).

Table 2 | Univariable Cox regression analysis.

Variable	Hazard ratio (95% Confidence Interval)	*p* value
Age, per year	1.05 (1.01–1.09)	0.01
Man	2.83 (1.25–6.40)	0.01
Cardiovascular risk factors		
Smoker	1.84 (0.95–3.59)	0.07
Blood pressure >130/80 mmHg	1.80 (0.95–3.43)	0.07
Dyslipidemia*	0.83 (0.43–1.57)	0.56
Diabetes mellitus	4.49 (2.05–9.81)	<0.001
Positive family history of CAD	0.77 (0.41–1.44)	0.41
Body Mass Index >30 kg/m^2	1.18 (0.59–2.36)	0.65
Coronary artery calcium score		
0	Reference	NA
1-100	1.84 (0.36–9.50)	0.47
101-400	5.55 (1.18–26.17)	0.03
>400	17.56 (4.16–74.20)	<0.001
Coronary Computed Tomography Angiography		
No Coronary Artery Disease	Reference	NA
Non-obstructive Coronary Artery Disease	0.87 (0.17–4.46)	0.86
Obstructive Coronary Artery Disease (≥50% diameter stenosis)	11.23 (2.69–46.80)	0.001
Number of coronary arteries with ≥50% diameter stenosis		
None	Reference	NA
1	5.09 (1.10–23.65)	0.04
2	14.54 (3.25–65.06)	<0.001
3	26.12 (5.82–117.22)	<0.001
Segment stenosis score (per point)	1.13 (1.09–1.18)	<0.001
Segment involvement score (per point)	1.21 (1.13–1.30)	<0.001

* Dyslipidemia was defined as either known familial hypercholesterolemia, on statin treatment or measured serum LDL-C levels >190 mg/dL.

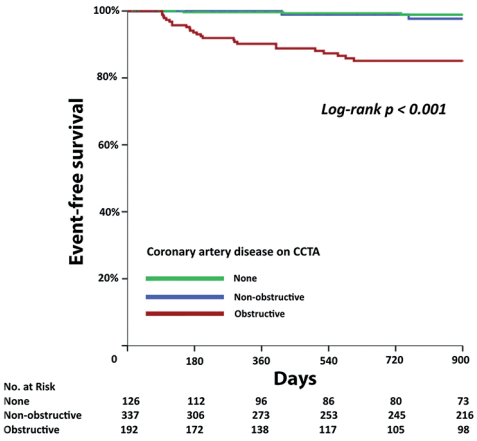

Figure 3 | Unadjusted survival for obstructive coronary artery disease (≥50% luminal stenosis) versus none and non-obstructive coronary artery disease on coronary CT angiography (CCTA). Log-rank $p<0.001$ for any difference.

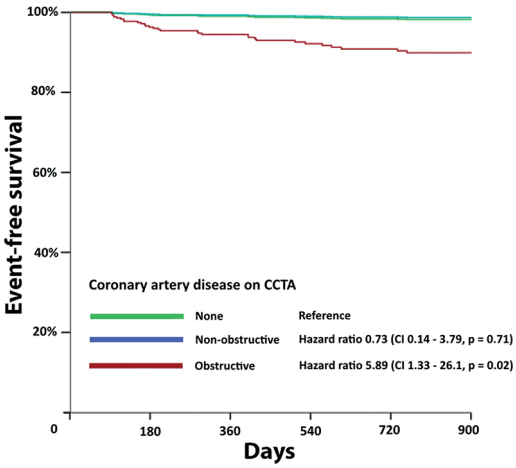

Figure 4 | Risk-adjusted survival for obstructive coronary artery disease (≥50% luminal stenosis) versus none and non-obstructive coronary artery disease, corrected for age, gender and coronary artery calcium scores. CCTA = coronary CT angiography. CI = Confidence interval.

Table 3 | **Model discriminative performance and reclassification index.**

Model	C Statistic (95% Confidence Interval)	Total NRI	Proportion of non- events correctly reclassified	Proportion of events correctly reclassified
Model I: Age and gender	0.66 (0.58–0.75)			
Model II: Model I + CACS	0.81 (0.74–0.87)	0.35*	0.32*	0.02
Model III: Model II + CCTA	0.84 (0.78–0.90)	0.19*	0.16*	0.02

CACS = Coronary artery calcium score. CCTA = Coronary computed tomography angiography, classified as either presence or absence of obstructive coronary artery disease (≥50% luminal stenosis). NRI = Net Reclassification Index. * = ($p<0.01$)

There were 2 patients (1%) with zero CACS who had an adverse event during follow-up. In 1 patient, who was free from any CAD on CCTA as well, the cause of death was unknown; the other patient, with a <29% stenosis on CCTA, underwent late coronary revascularization (Table 4). Obstructive CAD in the absence of coronary artery calcium was rare (3%), and none of these patients experienced an adverse event. In patients with CACS 1 to 100, the event rate was higher in those with obstructive CAD compared with those with non-obstructive CAD. In contrast, in patients with CACS 100 to 400, there were no differences in event rates between obstructive or non-obstructive CAD. Finally, in patients with CACS >400, none with non-obstructive CAD had an adverse event as opposed to 25 patients with obstructive CAD ($p=0.002$).

Table 4 | Distribution of adverse events across different coronary artery calcium score groups in relation to the presence of non-obstructive or obstructive coronary artery disease on coronary computed tomography angiography.

Coronary Computed Tomography Angiography		Coronary artery calcium score			
		0	1–100	100–400	>400
Non-obstructive Coronary Artery Disease	Adverse event-	156 (96%)	193 (87%)	56 (50%)	26 (21%)
	Adverse event+	2 (1%)	1 (0.5%)	4 (4%)	0
Obstructive Coronary Artery Disease (≥50% diameter stenosis)	Adverse event-	5 (3%)	24 (11%)	47 (42%)	73 (59%)
	Adverse event+	0	4 (2%)	4 (4%)	25 (20%)

Discussion

The main findings of this observational multicenter CT imaging study of patients at high risk for developing CVD, but without CAD symptoms, can be summarized as follows. First, the incidence of adverse events during a median follow-up period of 3 years was low, annually 2.0%. Second, both CACS and CCTA independently predicted adverse events. Third, CCTA had incremental prognostic value over baseline clinical risk factors and CACS as demonstrated by an improved risk reclassification, mainly through correctly shifting patients without any CAD from the substratified high-risk group to a lower risk group. Finally, patients with zero CACS were found to have an excellent prognosis, and these patients may not require further imaging with CCTA, whereas in patients with a positive CACS, CCTA is useful to discriminate patients who are likely to experience an adverse event.

The prognostic value of CACS has been clearly demonstrated in large prospectively enrolled, unselected asymptomatic cohorts [20-22], where increasing CACS were associated with increasing incidence of all-cause mortality. Current guidelines consider CACS an acceptable option (class IIa) for primary screening of patients at intermediate risk [5]. Although CACS is a good reflection of the extent of CAD, it does not equate with the evaluation of CAD by CCTA, which provides more detailed information about atherosclerotic plaque and stenosis severity. In our study, CCTA identified CAD in 38% of patients with zero CACS.

The question whether CCTA has incremental value next to CACS in asymptomatic subjects was addressed in the Coronary CT Angiography Evaluation For Clinical Out-comes International Multicenter (CONFIRM) registry, including a mix of 7,590 subjects at low to high-risk without CAD symptoms who were followed for a median period of 24 months [23]. This study demonstrated that both CACS and CCTA were predictors of all-cause mortality and a composite end point of all-cause mortality and nonfatal MI. However, CCTA did not improve risk stratification beyond CACS. The CONFIRM registry then presented results from a subanalysis, focusing on 400 asymptomatic patients with diabetes only, where addition of CCTA did have incremental value next to CACS, improving the C statistic of a model with age, gender, and CACS from 0.64 to 0.77 [24]. Likewise, when 3,217 asymptomatic patients from the same registry were stratified according to the magnitude of their

CACS, CCTA did provide incremental value in patients with a CACS >100 [25]. In line with these observations, our study demonstrates that CCTA has additional risk reclassification benefit next to CACS in a prespecified high-risk population.

In the present study, we enrolled a prespecified high-risk population, where CAD was found to have a high prevalence (81% of patients with any CAD on CCTA). However, we encountered an unexpectedly low rate of adverse events. Although speculative, the low incidence of adverse events may be the consequence of a stringent primary prevention program, including intensive pharmacologic therapy. This low event rate is in line with other large scale follow-up studies [20-22]. The rate of cardiac death or nonfatal MI in subjects studied to assess the predictive value of CACS including the Multi-Ethnic Study of Atherosclerosis, Heinz Nixdorf Recall, and the Rotterdam studies ranged from 0.4% to 0.7% per year. The annual rate of cardiac death or nonfatal MI in the Detection of Ischemia in Asymptomatic Diabetics study was 0.6%. This study included 1,123 asymptomatic patients with DM with a follow-up of 4.8 years [26]. In the previously mentioned CONFIRM registry, all-cause mortality was 1.2% per year in 7,590 patients without CAD symptoms [23]. This reported low incidence of adverse events makes it difficult to accurately establish the predictive value of clinical scores, biomarkers, or imaging techniques. In the randomized, multicenter Screening For Asymptomatic Obstructive Coronary Artery Disease Among High-Risk Diabetic Patients Using CT Angiography Following Core 64 (FACTOR-64) trial, investigators aimed to assess whether incorporation of CCTA findings into management of asymptomatic patients at high risk would improve patient outcome. This study included 900 asymptomatic patients with diabetes, who were followed for a mean follow-up time of 4 years and showed that CCTA-guided management was not better than standard care intervention in terms of pre-venting mortality, MI, or unstable angina requiring hospitalization [27]. The investigators of the FACTOR-64 trial stated that the rate of adverse events was also unexpectedly low, which may have obscured a potential benefit of CCTA.

CCTA has relevant drawbacks that must be taken into account. In our study, CCTA was associated with a fivefold higher radiation dose compared with CACS. Using contemporary CT technology and radiation hygienic Coronary Artery Disease/Primary Screening with Cardiac CT 5 protocols, the CCTA dose can be reduced to <1 mSv in selected patients, whereas with the most recent technology this may be even as low as 0.21 mSv [28]. However, the need for iodinated contrast medium remains and the impact of incidental findings on downstream testing should not be overlooked.

The main purpose of our study was to examine whether CCTA has incremental value next to CACS to justify its use in screening a high-risk asymptomatic population. However, patients with zero CACS are known to be have an excellent prognosis [29], and another approach would be to exclude them from further imaging with CCTA, thereby obviating the additional exposure with ionizing radiation and the use of iodinated contrast medium in a substantial number of patients. Also in our study, zero CACS is associated with an excellent prognosis and addition of CCTA was not helpful in this particular group. This is in contrast to the group of patients with CACS 1 to 100, where CCTA could discriminate between patients who experienced adverse events. Patients with high CACS (>400) experienced the highest incidence of adverse events and those with additional obstructive CAD on CCTA had the worst prognosis. Therefore, in patients with a positive CACS, CCTA is useful to discriminate patients who are likely to experience an adverse event.

Several limitations of the present study deserve attention. First, the rather low adverse event rate requires caution to the interpretation of the predictive power of CCTA. Larger study populations and/or longer follow-up times, expecting to yield higher incidences of adverse events, should provide more robust outcomes. The incorporation of late coronary revascularization in addition to all-cause mortality and nonfatal MI may be a limitation as late revascularization is a less hard outcome. However, by incorporating late coronary revascularization as part of our composite outcome, we attempted to investigate whether CCTA findings are associated with CAD that is prone to progress, causing symptoms and eventually the need for coronary revascularization. Also, late coronary revascularization was incorporated into our composite outcome, as is it is often included as an outcome of other comparable imaging studies focused on prognosis.

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Supplementary Files

Table 1 | Supplemental material. Baseline characteristics of patients with diabetes mellitus.

Variable	Diabetes Mellitus (n=378)
Age, mean±SD	56±9
Men	221 (59%)
Cardiovascular risk factors	
Smoker	84 (22%)
Blood pressure >130/80 mmHg	225 (60%)
Dyslipidemia*	224 (59%)
Positive family history of CAD	137 (36%)
Body Mass Index >30 kg/m^2	129 (34%)
Coronary artery calcium score	
0	101 (27%)
1-100	130 (34%)
100-400	66 (18%)
>400	79 (21%)
Coronary Computed Tomography Angiography	
No Coronary Artery Disease	86 (23%)
Non-obstructive Coronary Artery Disease	168 (44%)
Obstructive Coronary Artery Disease (≥50% diameter stenosis)	124 (33%)
Number of coronary arteries with ≥50% diameter stenosis	
1	62 (16%)
2	36 (10%)
3 or left main disease	26 (7%)
Segment stenosis score, median (IQR)	6 (2–11)
Segment involvement score, median (IQR)	4 (1–7)

SD = Standard deviation, IQR = interquartile range. * Dyslipidemia was defined as either known familial hypercholesterolemia, on statin treatment or measured serum LDL-C levels >190 mg/dL.

Table 2 | Supplemental material. Univariable and multivariable Cox regression analysis in patients with diabetes mellitus.

Variable	Univariable		Multivariable	
	Hazard ratio (95% CI)	*p* value	Hazard ratio (95% CI)	*p* value
Age, per year	1.05 (1.00–1.09)	0.04		
Man	3.30 (1.35–8.04)	0.01		
Cardiovascular risk factors				
Smoker	2.40 (1.15–5.00)	0.02		
Blood pressure >130/80 mmHg	1.28 (0.62–2.68)	0.51		
Dyslipidemia*	0.99 (0.48–2.04)	0.98		
Positive family history of CAD	0.85 (0.41–1.75)	0.66		
Body Mass Index >30 kg/m^2	0.75 (0.35–1.63)	0.47		
Coronary artery calcium score				
0	Reference	NA		
1-100	3.86 (0.45–33.14)	0.22		
101-400	10.67 (1.31–86.96)	0.03		
>400	27.34 (3.65–205.03)	0.001		
Coronary Computed Tomography Angiography				
No Coronary Artery Disease	Reference	NA	Reference	NA
Non-obstructive Coronary Artery Disease	2.01 (0.23–18.03)	0.53	0.95 (0.78–11.72)	0.97
Obstructive Coronary Artery Disease (≥50% diameter stenosis)	22.07 (2.98–162.83)	0.002	9.46 (0.86–104.23)	0.07
Number of coronary arteries with ≥50% diameter stenosis				
None	Reference	NA	Reference	NA
1	8.64 (2.89–25.86)	<0.001	6.74 (2.16–21.03)	0.001
2	19.79 (6.67–58.72)	<0.001	14.74 (4.72–46.01)	<0.001
3 or left main disease	16.01 (5.17–50.11)	<0.001	11.95 (3.65–3916)	<0.001
Segment stenosis score (per point)	1.14 (1.09–1.19)	<0.001	1.13 (1.07–1.18)	<0.001
Segment involvement score (per point)	1.28 (1.13–1.33)	<0.001	1.19 (1.09–1.30)	<0.001

* Dyslipidemia was defined as either known familial hypercholesterolemia, on statin treatment or measured serum LDL-C levels >190 mg/dL.

CHAPTER 10

Stable Angina Pectoris: Head-to-Head Comparison of Prognostic Value of Cardiac CT and Exercise Testing

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Abstract

Purpose: To determine and compare the prognostic value of cardiac computed tomographic (CT) angiography, coronary calcium scoring, and exercise electrocardiography (ECG) in patients with chest pain who are suspected of having coronary artery disease (CAD).

Materials and Methods: This study complied with the Declaration of Helsinki, and the local ethics committee approved the study. Patients (n=471) without known CAD underwent exercise ECG and dual-source CT at a rapid assessment outpatient chest pain clinic. Coronary calcification and the presence of 50% or greater coronary stenosis (in one or more vessels) were assessed with CT. Exercise ECG results were classified as normal, ischemic, or non-diagnostic. The primary outcome was a major adverse cardiac event (MACE), defined as cardiac death, nonfatal myocardial infarction, or unstable angina requiring hospitalization and revascularization beyond 6 months. Univariable and multivariable Cox regression analysis was used to determine the prognostic values, while clinical impact was assessed with the net reclassification improvement metric.

Results: Follow-up was completed for 424 (90%) patients; the mean duration of follow-up was 2.6 years. A total of 44 MACEs occurred in 30 patients. Four of the MACEs were cardiac deaths and six were nonfatal myocardial infarctions. The presence of coronary calcification (hazard ratio [HR], 8.22 [95% confidence interval {CI}: 1.96, 34.51]), obstructive CAD (HR, 6.22 [95% CI: 2.77, 13.99]), and non-diagnostic stress test results (HR, 3.00 [95% CI: 1.26, 7.14]) were univariable predictors of MACEs. In the multivariable model , CT angiography findings (HR, 5.0 [95% CI: 1.7, 14.5]) and non-diagnostic exercise ECG results (HR, 2.9 [95% CI: 1.2, 7.0]) remained independent predictors of MACEs. CT angiography findings showed incremental value beyond clinical predictors and stress testing (global χ^2, 37.7 vs 13.7; $p<.001$), whereas coronary calcium scores did not have further incremental value (global χ^2 , 38.2 vs 37.7; $p=.40$).

Conclusion: CT angiography findings are a strong predictor of future adverse events, showing incremental value over clinical predictors, stress testing, and coronary calcium scores.

Introduction

Over the past decade, cardiac computed tomographic (CT) angiography has emerged as a valuable diagnostic tool to evaluate coronary artery disease (CAD) and has found use as an anatomic alternative to functional testing and a noninvasive alternative to conventional (catheter-based) coronary angiography [1,2]. Functional assessment of CAD severity with exercise electrocardiography (ECG) is well established, and its prognostic value has been studied extensively [3,4]. Although evidence regarding the prognostic value of CT angiography findings is emerging [5-7], the question remains if this angiographic modality holds incremental prognostic value beyond functional evaluation with exercise ECG. In this study, in a prospectively enrolled population, we sought to determine and compare the prognostic value of cardiac CT angiography, coronary calcium scoring (CCS), and exercise ECG in patients with chest pain who were suspected of having CAD.

Materials and Methods

From September 2006 to December 2008, 471 consecutive patients without a history of CAD were evaluated at our rapid assessment outpatient chest pain clinic (mean age, 56 years ± 10 [standard deviation]; age range, 18–84 years; 244 men) [8]. They had been referred by their general practitioner because of chronic complaints of chest pain potentially caused by CAD to undergo additional testing with exercise ECG, CT angiography, and CCS. Information on risk factors was prospectively acquired, and clinical risk estimators – that is, the Systematic Coronary Risk Evaluation (SCORE) [9] and Diamond and Forrester metrics [10] – were calculated from these data. According to the SCORE, 291 patients had a 10-year risk of less than 5% of developing fatal cardiovascular disease, 130 patients had a risk of 5%–10%, and 50 patients had a risk of greater than 10%.

The study complied with the Declaration of Helsinki, and the local ethics committee approved the study.

CCS Protocol

Calcium detection was performed with an ECG-triggered step-and-shoot acquisition mode, by using a 120-kV tube voltage, a mean tube current of 78 mAs ± 26, and a section thickness of 3 mm. The coronary calcium score was assessed by using dedicated software (Syngo CaScore; Siemens, Forchheim, Germany) and was quantified with the Agatston method with a standard 130-HU attenuation threshold [11]. To account for the skewed distribution, all calcium scores were transformed by taking the natural logarithm of the calcium score +1.

CT Angiographic Parameters

Contrast material-enhanced dual-source multisection CT (Definition; Siemens) was performed by using the following parameters: number of detector rows, 32; section thickness, 0.6 mm; 64-channel acquisition by z-axis focal spot alternation; rotation time, 330 msec; temporal resolution, 83 msec; spiral acquisition mode with prospectively ECG-triggered tube modulation depending on the heart

rate regularity; tube volt-age, 120 kV; tube current, 380–412 mAs depending on patient size; and variable pitch depending on the heart rate. Iopromide 70–100 mL (Ultravist, 370 milligrams of iodine per milliliter; Schering, Berlin, Germany), followed by a 40-mL saline bolus chaser, was peripherally injected at 5.0–5.5 mL/sec. Patients received sublingual nitroglycerin before the examination but no additional β-blockers. Effective radiation doses for CCS and CT angiography were 0.8 mSv ± 0.2 (range, 0.4–1.6 mSv) and 11.0 mSv ± 3.5 (range, 4.7–17.8 mSv), respectively.

The coronary arteries were evaluated on axial images, multiplanar reconstructions, and maximum intensity projections according to readers' preferences. Readers (including A.M., with 5 years of experience), who were assisted by research fellows with a minimum of 1 year of experience in coronary imaging, were blinded to patients' symptoms and exercise ECG results. Vessels were qualitatively scored as significantly stenosed (≥50% diameter narrowing) or less than significantly stenosed (<50%) or free from plaque. To assess the prognostic value of CT angiography, we constructed a model comparing obstructive plaque to non-obstructive plaque. In a second model, we assessed the prognostic value of obstructive and non-obstructive plaque versus no plaque.

Exercise ECG

Patients underwent stress testing on a bicycle ergometer by using a standardized protocol. Use of any β-blockers was ceased 72 hours before stress testing, if possible. During continuous ECG registration and 12-lead printing at 1-minute intervals, the workload was increased from 40 W in 20-W increments at 1-minute intervals. Blood pressure was measured every 2 minutes. In cases of established contraindications, patients did not undergo exercise ECG [12]. Criteria for myocardial ischemia included horizontal or downsloping ST-segment depression or elevation of 0.1 mV or greater during or after exercise or typical, increasing angina during exercise. A non-diagnostic test was defined as when there was an inability to perform the test or the test was discontinued without evidence of myocardial ischemia before reaching 85% of the predicted maximum heart rate [12]. Additionally, for every patient, we approximated the Duke Treadmill Score by using a standardized formula as follows: DE − (5 · STD) − (4 · TAI), where DE is duration of exercise in minutes, STD is maximum net ST-segment deviation during or after exercise in millimeters, and TAI is treadmill angina index (where a score of 0 = no complaints, a score of 1 = non-limiting angina, and a score of 2 = angina requiring discontinuation) [3].

Follow-up

Follow-up data were obtained by consulting the national death registry for the occurrence of mortality and through standardized telephone interviews, questionnaires, or hospital visits. All events were confirmed with death records, hospital records, or correspondence with treating physicians and hospitals. If patients experienced multiple events during follow-up, only the first event counted. Patients lost to follow-up were censored. All events were reviewed by an independent cardiologist (K.N., with 3 years of post-residency experience as a Cardiology Department staff member) who was blinded to both CT angiography and exercise ECG results.

Outcome Measures

The primary outcome measure was a composite of cardiac death, nonfatal myocardial infarction, unstable angina requiring hospitalization, and coronary revascularization (percutaneous coronary intervention or coronary artery bypass graft surgery). Cardiac death was defined as death caused by acute myocardial infarction, ventricular arrhythmia, refractory heart failure, or cardiogenic shock. Nonfatal myocardial infarction was defined as ischemia resulting in abnormal cardiac biomarkers (>99th percentile of the upper limits of normal). Unstable angina was defined as chest pain with altered frequency or character that was suspicious for acute coronary syndrome; a diagnosis of unstable angina also required ischemic ECG changes or significantly obstructive CAD at invasive conventional angiography [13]. Coronary revascularizations initiated as a result of the initial diagnostic work-up and performed within 6 months were not considered as an end point.

Statistical Analysis

Statistical analyses were performed by using SPSS (version 15.0; SPSS, Chicago, Ill) and STATA (version 11.1; Stata, College Station, Tex). All probability values refer to two-tailed tests of significance; $p<.05$ was considered to indicate a significant difference. Categoric variables are presented as proportions. Continuous variables are expressed as means±standard deviations or as medians±interquartile ranges (IQRs) as appropriate. Clinical patient characteristics are summarized by the SCORE 10-year cardiovascular mortality risk [9].

Univariable Cox regression analyses of each potential clinical predictor, as well as coronary calcification, CT angiography results, and exercise ECG results, were performed to evaluate their effect in predicting major adverse cardiac events (MACEs) during follow-up.

Cumulative event rates as a function over time were estimated according to the Kaplan-Meier method. Unadjusted comparison of survival between groups defined by the two CT angiography results, coronary calcium categories, and exercise ECG results was performed by using the log-rank test. Annual event rates were calculated by dividing the cumulative event rates by the median number of follow-up years.

A multivariable Cox proportional hazards model was used to assess the independent prognostic value of exercise ECG, CT angiography, and CCS. Risk adjustment for clinical characteristics was performed by using patients' SCORE results. To assess the incremental value of exercise ECG, CT angiography, and CCS, the global χ^2 values were compared between models with and those without the addition of each incrementally. Using logistic regression, receiver operating characteristic curves with estimates of the area under the receiver operating characteristic curve (AUC, or the C-statistic) were obtained to compare the discriminative performance of the different models.

To quantify the clinical impact of adding exercise ECG, CT angiography, and CCS to the model predicting MACE, we calculated the net reclassification improvement (NRI), which is a measure of correctly reclassified subjects that is penalized for those incorrectly classified. In this context, clinically relevant cutoff values for the risk of a MACE (ie, the thresholds of risk where reclassification to another category would influence clinical management) are absent. Thus, we used an extension of the traditional NRI that was recently introduced by Pencina et al. [14]. The so-called continuous NRI (or category-free NRI) does not depend on the existence of risk categories and allows NRI

estimation in the context of survival data. The continuous NRI is the weighted sum of the observed event rate increase among the individuals for whom the predicted risk goes up and observed event rate de-crease among those for whom the predicted risk goes down.

Results

Coronary CT could not be performed in 16 (3%) patients because of renal failure (n=2), known allergy to contrast material (n=1), patient preferences (n=8), Parkinson disease (n=1), patient noncooperation (n=1), lack of venous access (n=1), and severe obesity (n=2). Two examinations (0.4%) failed because of patient movement or premature scanning initiation. Three patients (0.6%) had mild to moderate allergic reactions.

Exercise ECG could not be performed in 48 (10%) patients because of orthopedic restraints (n=13), neurologic restraints (n=8), severe obesity (n=3), abnormalities at resting ECG (n=8), pulmonary disease (n=2), in-ability to bicycle (n=3), and a combination of these factors or an unspecified factor (n=11). Results were considered inconclusive in 140 (30%) patients, mostly because the target heart rate was not reached. These patients together (n=188) were considered to have had non-diagnostic tests in the survival analysis (Figure 1).

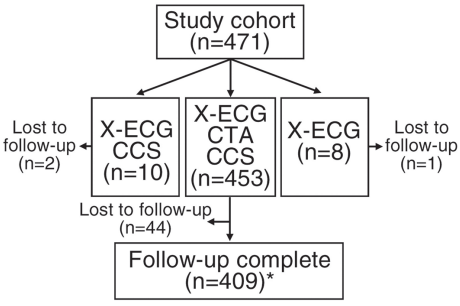

Figure 1 | Flowchart of patients included in the survival analysis. *Included in multivariable analysis. CTA = CT angiography, X-ECG = exercise ECG.

Follow-up

Follow-up data were obtained for 424 (90%) patients. Forty-four adverse cardiac events occurred in 30 patients. These events consisted of four cardiac deaths, six acute myocardial infarctions, 23 coronary revascularizations, and 11 instances of unstable angina pectoris. The occurrence of mortality was obtained for all patients, and, according to the national bureau of statistics, another four patients died of a non-cardiac cause – that is, respiratory failure, stroke, or malignancy (n=2). The median follow -up time was 2.6 years (IQR, 2.1–3.2 years). The overall rate of events was 3.2% per year.

Patients without follow-up were younger (p<.001) and more often smokers (p=.02). Lower coronary calcium scores and fewer abnormal CT angiography and exercise ECG results were

observed for patients without follow-up, although this did not reach statistically significance. There was no significant difference in Duke Treadmill Score between the patients with and those without follow-up (median score, 5 [IQR, 1–7] vs 5 [IQR, 0.5–7]). Only six patients were classified as having high risk, and they all completed follow-up.

Descriptive Analysis

Coronary calcium score | Patients with no coronary calcium had excellent prognoses. No cardiac deaths and no nonfatal myocardial infarctions were observed (Table 1). However, three hospitalizations for unstable angina occurred, and one late revascularization was performed.

Coronary CT | In the group of patients with obstructive CAD, 22 (17%) events occurred, consisting of three cardiac deaths (2%) and four myocardial infarctions (3%). Patients without obstructive CAD experienced significantly fewer total events (eight patients [3%]; $p<.001$), one cardiac death (0.4%), and two (0.7%) myocardial infarctions (Table 1). Patients who did not undergo CT angiography or in whom the study was non-diagnostic did not experience a MACE.

Exercise ECG | Patients with a normal exercise ECG result experienced seven (4%) events during follow-up, of which one (0.6%) was a myocardial infarction. An abnormal exercise ECG result was associated with the occurrence of four (5%) events, of which one (1%) was a myocardial infarction. We observed 19 (11%) events in the group of patients who were unable to perform the test or who had an inconclusive test; of these events, four (2%) were cardiac deaths and four (2%) were myocardial infarctions (Table 1).

Univariable Analysis

The clinical risk estimators SCORE and Diamond and Forrester score were both significant predictors of MACE (Table 2). Of the traditional risk factors, only sex was a statistically significant predictor. A typical angina presentation was associated with an HR of 3.86 (95% CI: 0.88, 16.87) compared with non-anginal complaints, while atypical presentation was associated with an HR of 1.91 (95% CI: 0.43, 8.47).

Detectable coronary calcium was a significant predictor of MACE (HR, 8.22 [95% CI: 1.96, 34.51]; $p=.004$), along with nondiagnostic exercise ECG results (HR, 3.00 [95% CI: 1.26, 7.14]; $p=.01$). Regarding CT angiography results, in the first model, obstructive CAD was associated with a significantly higher hazard (HR, 6.22 [95% CI: 2.77, 13.99]; $p<.001$). In the second model, the presence of non-obstructive plaque was also associated with a higher hazard (HR, 5.03 [95% CI: 0.62, 40.85]), although this did not reach statistical significance ($p=.13$), while obstructive CAD remained a significant predictor (HR, 20.80 [95% CI: 2.80, 154.33]; $p=.003$).

Table 1 | Baseline characteristics.

	Follow–up (n=424)	No follow–up (n=47)	*p* value
Age (yrs)	56 (10)	50 (11)	<0.001
Male sex (%)	219 (52)	25 (53)	0.88
Smoking (%)	116 (27)	22 (47)	0.01
Hypertension (%)	213 (50)	21 (45)	0.54
Diabetes (%)	58 (14)	10 (21)	0.19
Dyslipidemia (%)	251 (59)	29 (62)	0.88
Family history of CAD (%)	191 (45)	23 (49)	0.65
History of vascular disease (%)	30 (7)	1 (2)	0.35
Body mass index	26.8 (24.2–30.0)	26.9 (24.5–30.5)	0.58
Non-anginal chest pain (%)	66 (16)	8 (17)	0.31
Atypical chest pain (%)	222 (52)	29 (62)	
Typical chest pain (%)	136 (32)	10 (21)	
SCORE	3 (1–7)	1 (1–5)	0.02
Diamond & Forrester	54(32–79)	46 (13–59)	0.02
Calcium score	18(0–158)	0 (0–93)	0.06
0 (%)	151 (34)	24 (52)	0.04
0-10	45 (11)	3 (7)	
10-100	92 (22)	9 (20)	
100-400	66 (16)	8 (17)	
>400	63 (15)	2 (4)	
CT Angiography (%)	453 (96%)		0.12
Non-obstructive CAD (%)	277 (68)	35 (80)	
Obstructive CAD (%)	132 (32)	9 (20)	
Exercise ECG (%)	471 (100%)		0.76
Normal (%)	172 (41)	18 (38)	
Ischemic (%)	85 (20)	8 (17)	
Non-diagnostic (%)	167 (39)	21 (45)	
Duke treadmill score	5 (1–7)	5 (0.5–7)	0.95
Low risk (%)	190 (51)	24 (55)	
Intermediate risk (%)	181 (48)	20 (45)	
High risk (%)	6 (2)	0	

CAD = coronary artery disease, SCORE 10-year cardiovascular disease mortality risk [9], Diamond&Forrester [10].

Table 2 | Events sorted by test.

	N	MACE	Cardiac death	AMI	Late revascularization	UAP	Annual event rate
CCS=0	151	2 (1%)	0 (0%)	0 (0%)	1 (0.7%)	3 (2%)	0.5%
CCS>0	266	28 (11%)	4 (2%)	6 (2%)	22 (8%)	8 (3%)	4.2%
CTA <50%	277	8 (3%)	1 (0.4%)	2 (0.7%)	3 (1%)	3 (1%)	1.2%
CTA >50%	132	22 (17%)	3 (2%)	4 (3%)	20 (15%)	8 (6%)	6.8%
Normal X-ECG	172	7 (4%)	0 (0%)	1 (0.6%)	6 (4%)	3 (2%)	1.6%
Ischemic X-ECG	85	4 (5%)	0 (0%)	1 (1%)	5 (6%)	1 (1%)	1.9%
Nondiagn X-ECG	167	19 (11%)	4 (2%)	4 (2%)	12 (7%)	7 (4%)	4.6%

MACE = Major adverse cardiac event, AMI = acute myocardial infarction, UAP = unstable angina pectoris requiring hospitalizations, CCS = coronary calcium score, CTA = cardiac computed tomography angiography, X-ECG = exercise electrocardiography (Nondiagn = non-diagnostic result)

Survival Analysis

Unadjusted comparison between patients with and those without coronary calcium showed significantly higher event-free survival in the group with no calcium (Figure 2a) (*p*=.001). The annual event rate in patients without calcium was 0.5%.

Absence of obstructive CAD at CT angiography was associated with a significantly lower event rate than the presence of obstructive CAD at CT angiography (Figure 2b) (*P*<.001). The annual event rates were 6.8% versus 1.2% for obstructive versus non-obstructive CAD (Table 1).

Non-diagnostic exercise ECG results were associated with significantly higher event rates than normal or ischemic exercise ECG results (Figure 2c) (*P*=.016). The observed annual event rate for patients with non-diagnostic results compared with that for patients with normal or ischemic results was substantially higher (4.6% vs 1.6% and 1.9%, respectively).

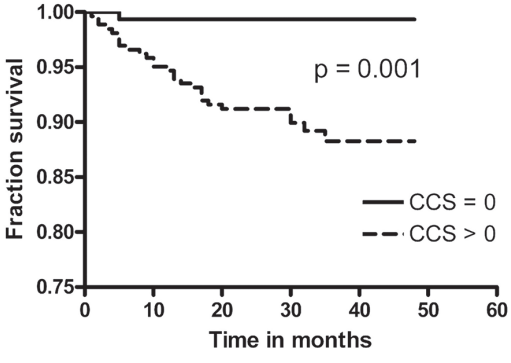

Figure 2a | Graphs show Kaplan-Meier estimates of survival as compared between **(a)** patients with and those without visible coronary calcium *(CCS)*, **(b)** patients with and those without obstructive CAD at CT angiography, and **(c)** patients with normal, those with ischemic, and those with non-diagnostic exercise ECG results.

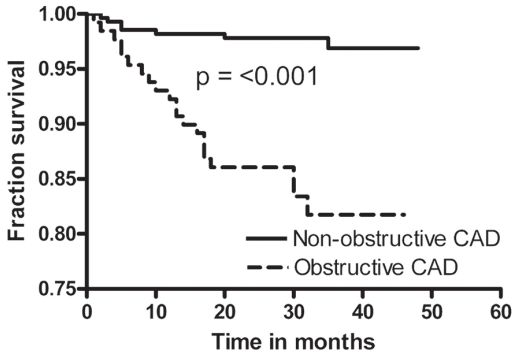

Figure 2b | Graphs show Kaplan-Meier estimates of survival as compared between **(a)** patients with and those without visible coronary calcium *(CCS)*, **(b)** patients with and those without obstructive CAD at CT angiography, and **(c)** patients with normal, those with ischemic, and those with non-diagnostic exercise ECG results.

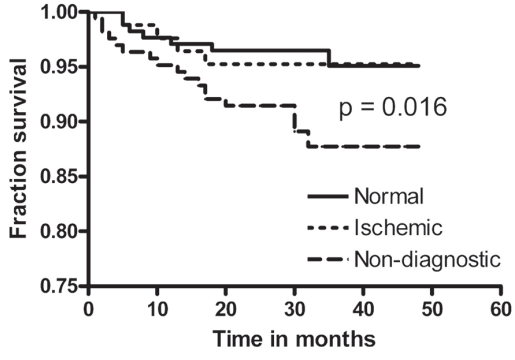

Figure 2c | Graphs show Kaplan-Meier estimates of survival as compared between **(a)** patients with and those without visible coronary calcium *(CCS)*, **(b)** patients with and those without obstructive CAD at CT angiography, and **(c)** patients with normal, those with ischemic, and those with non-diagnostic exercise ECG results.

Multivariable Risk-adjusted Analysis

In the multivariable Cox regression analysis, after adjusting for SCORE, the presence of obstructive CAD (HR, 6.61 [95% CI: 2.83, 15.43]) and non-diagnostic exercise ECG result (HR, 2.93 [95% CI: 1.23, 6.99]) remained independent predictors of MACE (Table 3). The addition of CCS led to a slight decrease in the HRs of CT angiography (HR, 5.00 [95% CI: 1.72, 14.52]) and exercise ECG (HR, 2.80 [95% CI: 1.17, 6.73]), whereas CCS itself was not an independent predictor (HR, 1.09 [95% CI; 0.89, 1.33]).

A statistically significant increase in the global χ^2 value was seen after adding CT angiography results to a risk-adjusted model with exercise ECG (global χ^2 value, 37.7 vs. 13.7; $p<.001$) but not with the subsequent addition of CCS (global χ^2 value, 38.2 vs 37.7; $p=.40$).

Detectable calcium was an independent predictor in a risk-adjusted model with exercise ECG alone (HR, 1.33 [95% CI: 1.13, 1.56]). Subsequent addition of CT angiography improved model performance significantly (global χ^2 value, 38.2 vs. 26.3; $p=.002$).

Table 3 | Cox univariable analysis.

	MACE (n=30)	No MACE (n=392)	Hazard ratio (95% CI)	*p* value
Age (yrs)	58±8	56±10	1.02 (0.99–1.06)	0.21
Male sex (%)	22 (73)	195 (50)	2.68 (1.19–6.02)	0.02
Smoking (%)	9 (30)	107 (27)	1.15 (0.53–2.52)	0.72
Hypertension (%)	20 (67)	193 (49)	1.99 (0.93–4.25)	0.08
Diabetes (%)	7 (23)	51 (13)	1.92 (0.82–4.47)	0.13
Dyslipidemia (%)	20 (67)	229 (58)	1.29 (0.60–2.76)	0.52
Family history of CAD (%)	16 (53)	173 (44)	1.39 (0.68–2.85)	0.37
History of vascular disease (%)	2 (7)	28 (7)	0.94 (0.22–3.94)	0.93
Body mass index	26.9	26.8	1.01 (0.94–1.08)	0.86
Non-anginal chest pain (%)	2 (7)	64 (16)	1	
Atypical chest pain (%)	13 (43)	207 (53)	1.91 (0.43–8.47)	0.39
Typical chest pain (%)	15 (50)	121 (31)	3.86 (0.88–16.87)	0.07
SCORE	6 (2.75–8.25)	3 (1–6)	1.06 (1.01–1.12)	0.03
Diamond & Forrester			1.02 (1.01–1.04)	0.003
Low (<22)	67 (53–92)	54 (28–79)	1	
Interm(22–78)			2.83 (0.64–12.47)	0.17
High (>78)			5.16 (1.17–22.70)	0.03
Calcium score (%)				
0	2 (7)	149 (39)	1	
0–10	2 (7)	43 (11)	3.19 (0.45–22.65)	0.25
10–100	10 (33)	82 (21)	8.45 (1.85–38.58)	0.006
100–400	7 (23)	59 (15)	8.50 (1.77–40.793)	0.008
>400	9 (30)	54 (14)	11.66 (2.52–54.01)	0.002
>0	28 (93)	238 (62)	8.22 (1.96–34.51)	0.004
CT Angiography model 1				
Non-obstructive CAD (%)	8 (27)	269 (71)	6.22 (2.77–13.99)	<0.001
Obstructive CAD (%)	22 (73)	108 (29)		
CT Angiography model 2				
No plaque (%)	1 (3)	114 (30)	1	
Non-obstructive plaque (%)	7 (23)	155 (41)	5.03 (0.62 – 40.85)	0.13
Obstructive plaque (%)	22 (73)	110 (29)	20.80 (2.80–154.33)	0.003
Exercise ECG				
Normal (%)	7 (23)	164 (42)	1	
Ischemic (%)	4 (13)	80 (20)	1.19 (0.35–4.08)	0.78
Non-diagnostic (%)	19 (63)	148 (38)	3.00 (1.26–7.14)	0.01

CAD = coronary artery disease, SCORE 10-year cardiovascular disease mortality risk(9), Diamond&Forrester(10), 95% CI = 95% confidence interval

Receiver Operating Characteristics

The obtained curves and their AUC estimates demonstrated that the combination of clinical characteristics and exercise ECG findings resulted in an AUC of 0.71 (95% CI: 0.63, 0.79) (Figure 3). A risk-adjusted model with CT angiography resulted in an AUC of 0.75 (95% CI: 0.67, 0.83), while clinical characteristics and CCS produced an AUC of 0.73 (95% CI: 0.65, 0.81).

When clinical characteristics, exercise ECG findings, and CT angiography findings were combined in a model, we found an AUC of 0.80 (95% CI: 0.72, 0.88). Insertion of CCS into this model did not improve its predictive value consider-ably (AUC, 0.81 [95% CI: 0.73, 0.88]).

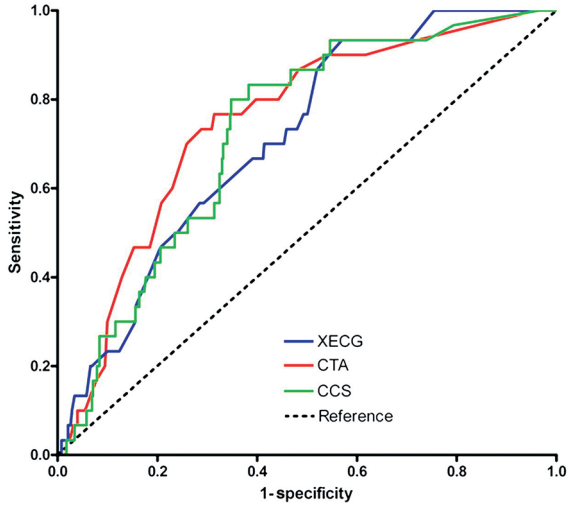

Figure 3a | Graphs show receiver operating characteristics curves of multivariable models of **(a)** exercise ECG (XECG), CCS, and CT angiography (CTA) and **(b)** incremental value of CT angiography and CCS beyond exercise ECG. The models are risk adjusted with the SCORE 10-year cardiovascular disease mortality risk metric [9].

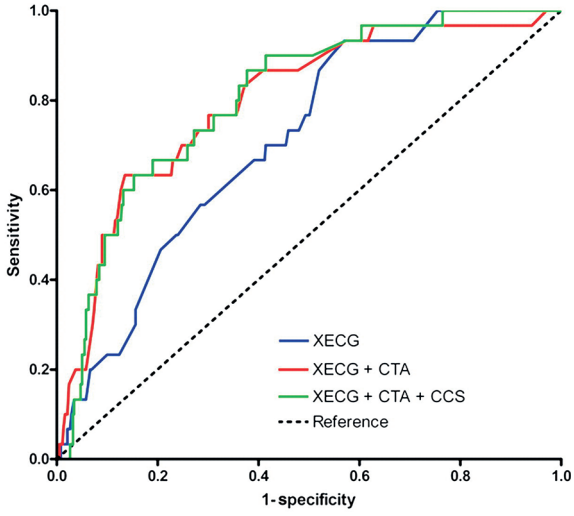

Figure 3b | Graphs show receiver operating characteristics curves of multivariable models of **(a)** exercise ECG (XECG), CCS, and CT angiography *(CTA)* and **(b)** incremental value of CT angiography and CCS beyond exercise ECG. The models are risk adjusted with the SCORE 10-year cardiovascular disease mortality risk metric [9].

NRI Results

The NRI was 54% (number of patients classified upward: 160; downward: 249) when exercise ECG was added to the clinical Cox proportional hazards model using only the SCORE. The addition of CT angiography to the model with both SCORE and exercise ECG resulted in a NRI of 80% (number of patients classified upward: 132; downward: 277). Finally, the full model that included CCS resulted in an NRI of 47% (number of patients classified upward: 182; down-ward: 227) (Table 3).

Table 4 | Cox multivariable analysis.

	Hazard ratio (95% CI)	p value	Global chi-square	Model comparison *p* value	AUC (95% CI)	Continuous NRI (%)
SCORE	1.06 (1.01–1.12)	0.03	5.1		0.66 (0.57–0.75)	reference
SCORE	1.07 (1.01–1.12)	0.02				
X-ECG-	1		13.7	0.01	0.71 (0.63–0.79)	54
X-ECG+	1.02 (0.29–3.52)	0.98				
X-ECG≠	2.96 (1.24–7.04)	0.01				
SCORE	1.02 (0.96–1.09)	0.54				
X-ECG-	1					
X-ECG+	0.69 (0.20–2.41)	0.57	37.7	<0.001	0.80 (0.72–0.88)	80
X-ECG≠	2.93 (1.23–6.99)	0.02				
CTA	6.61 (2.83–15.43)	<0.001				
SCORE	1.02 (0.95–1.08)	0.67				
X-ECG-	1					
X-ECG+	0.69 (0.20–2.39)	0.56	38.2	0.40	0.81 (0.73–0.88)	47
X-ECG≠	2.80 (1.17–6.73)	0.02				
CTA	5.00 (1.72–14.52)	0.003				
CCS	1.09 (0.89–1.33)	0.41				

SCORE 10-year cardiovascular disease mortality risk(9), X-ECG = exercise electrocardiography, CTA = cardiac computed tomography angiography (- normal, + ischemic and ≠ non-diagnostic), CCS = natural logarithm of the calcium score +1, AUC = area under the curve, 95% CI = 95% confidence interval, NRI = net reclassification improvement(14)

Table 5 | Cox multivariable analysis.

	Hazard ratio (95% CI)	*p* value	Global chi-square	Model comparison *p* value	AUC (95% CI)	Continuous NRI (%)
SCORE	1.06 (1.01–1.12)	0.03	5.1		0.66 (0.57–0.75)	reference
SCORE	1.07 (1.01–1.12)	0.02				
X-ECG-	1		13.7	0.01	0.71 (0.63–0.79)	54
X-ECG+	1.02 (0.29–3.52)	0.98				
X-ECG≠	2.96 (1.24–7.04)	0.01				
SCORE	1.02 (0.96–1.09)	0.57				
X-ECG-	1					
X-ECG+	0.79 (0.23–2.75)	0.71	26.3	<0.001	0.77 (0.70–0.85)	72
X-ECG≠	2.40 (1.00–5.79)	0.05				
CCS	1.33 (1.13–1.56)	0.001				
SCORE	1.02 (0.95–1.08)	0.67				
X-ECG-	1					
X-ECG+	0.69 (0.20–2.39)	0.56	38.2	0.002	0.81 (0.73–0.88)	15
X-ECG≠	2.80 (1.17–6.73)	0.02				
CCS	1.09 (0.89–1.33)	0.41				
CTA	5.00 (1.72–14.52)	0.003				

SCORE 10-year cardiovascular disease mortality risk(9), X-ECG = exercise electrocardiography, CTA = cardiac computed tomography angiography (- normal, + ischemic and ≠ non-diagnostic), CCS = natural logarithm of the calcium score +1, AUC = area under the curve, 95% CI = 95% confidence interval, NRI = net reclassification improvement(14)

Discussion

Our results show that the presence of obstructive CAD at CT angiography, the degree of exercise tolerance, and the extent of coronary calcification predict future adverse events in patients with stable symptoms of chest pain. After adjustment for clinical characteristics, CT angiography showed incremental value beyond exercise testing, whereas the additive prognostic value of CCS was limited compared with CT angiography.

For the past decades, exercise testing has been the diagnostic cornerstone for the evaluation of ischemic heart disease and can help identify patients at increased risk for adverse events [3,4]. Exercise tolerance is a powerful predictor of prognosis [15,16], which is confirmed in our study by the fact that inability to perform and complete exercise ECG predicted unfavorable outcome. Exercise capacity is an important predictor of adverse outcome, representing contractile left ventricular function as well as overall physical health. Most non-diagnostic exercise tests were the result of a low exercise capacity and consequent inability to reach the target heart rate.

Remarkably, ischemic ECG changes were not associated with increased event rates. Presumably, patients with these changes were treated more aggressively, explaining their better event-free survival. Second, patients developing ischemic ECG changes during exercise, but straining

themselves outstandingly, apparently tolerate ischemia well and may be in good general shape. The fact that only a minority of the study population was categorized as having high-risk disease according to the Duke Tread-mill Score supports this hypothesis.

Nonenhanced CT imaging can be used to help detect and quantify calcified CAD, and its findings have independent prognostic value in both symptomatic and asymptomatic individuals [17–21]. Also in our study, the presence of coronary calcium was associated with an adverse outcome. In particular, our results confirm the idea that patients with no detectable calcium have an excellent outcome (annual event rate, 0.5%).

More recently, CT coronary angiography has emerged as a noninvasive alternative for direct assessment of CAD. Evidence of its prognostic value is emerging [5–7], although results from some studies were affected by work-up bias, selected populations, and short follow-up periods [22-24]. In our consecutive population we can confirm the good predictive value of CT angiography for future adverse events.

Because of the nature of our diagnostic work-up, we could directly compare the prognostic value of the different diagnostic modalities in patients with stable chest pain and a low-to-intermediate probability of CAD. To the best of our knowledge, ours is the first study to evaluate the incremental predictive value of CT angiography over exercise ECG in a consecutive patient population.

In the risk-adjusted multivariable analysis, obstructive atherosclerosis at CT angiography and non-diagnostic exercise ECG results remained independent predictors of late cardiac adverse events, whereas coronary calcium did not remain a significant predictor. This finding is confirmed by a recent study [25] that reported no additive prognostic value of CCS next to CT angiography. It appears that the information obtained with calcium scanning largely overlaps with the information obtained with CT angiography, while the latter also provides such additional characteristics as total plaque burden and luminal obstruction.

The performance of the final model with clinical predictors, exercise ECG, and CCS improved significantly after the addition of CT angiography results. In addition, we assessed the potential clinical value of the considered predictors by calculating the continuous NRI, an extension of the traditional NRI that is independent of risk categories. Our results suggest that CT angiography is most effective in improving risk prediction, since the NRI was substantial. For CCS, the NRI was 47%, although the addition of CCS did not improve model performance in terms of the χ^2 value or AUC. This finding is explained by the fact that the continuous NRI does not take into account the magnitude of the increase (or decrease) in predicted risk. In other words, the predictions were not substantially influenced when CCS was added, but among patients with a higher predicted risk, the observed event rate increased compared with the overall mean. Similarly, for patients with a lower predicted risk, the observed event rate decreased compared with the overall mean. Finally, it should be noted that the continuous NRIs reported in the current study cannot be compared directly with the traditional NRIs that have been reported in other studies because of the differences in definition and calculation described earlier.

Although our study population consisted of prospectively enrolled “all-comers” with stable angina complaints, the limitations associated with an observational single-center study were still present. Therefore our results may not necessarily reflect populations or practices elsewhere. Because

of the limited number of hard events, we used a composite end point of cardiac death, nonfatal myocardial infarction, unstable angina requiring hospitalization, and coronary revascularization. The use of coronary revascularization as an end point could lead to overestimation of the prognostic value as a result of a potential work-up bias. Revascularizations performed within 6 months from the initial work-up were excluded to minimize this effect. Even though an experienced cardiologist, blinded to the initial test reports, evaluated all events, unstable angina requiring hospitalization can be a subjective end point.

Given the limited number of events, our analysis could be subject to overfitting. Current guidelines stating a minimum of 10 outcome events per predictor variable have been questioned [26]. In this view, our findings regarding the additive value of coronary calcium should be considered explanatory, and conclusions should be made with caution. To limit the number of variables in the multivariable analysis, we dichotomized CT angiography results.

Incomplete follow-up may result in underreporting of adverse events. However, the follow-up rate was substantial (90%), and no deaths occurred in the group without follow-up, as confirmed by the national death registry. Patients lost to follow-up appear to have been at lower risk, with fewer abnormal test results. Larger multicenter studies with longer follow-up, or meta-analyses of existing studies, are needed to fully comprehend the prognostic value of these modalities.

In conclusion, both functional and anatomic assessment of CAD has prognostic value. Coronary CT angiography findings are strong predictors of future adverse events, with incremental value over clinical predictors, stress testing, and coronary calcification.

Advances in Knowledge

- Coronary CT angiography has incremental prognostic value over exercise testing.
- Coronary calcium scoring seems to have no additive prognostic value beyond coronary CT angiography.
- Inability to perform a diagnostic exercise test is associated with unfavorable outcome.

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CHAPTER 11

Prognostic Implications of Non-culprit Plaques in Acute Coronary Syndrome: Non-invasive Assessment with Coronary CT Angiography

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Abstract

Aims: Non-culprit plaques are responsible for a substantial number of future events in patients with acute coronary syndrome (ACS). In this study, we evaluated the prognostic implications of non-culprit plaques seen on coronary computed tomography angiography (CTA) in patients with ACS.

Methods and results: Coronary CTA was performed in 169 patients (mean 59±11 years, 129 males) admitted with ACS. Data sets were assessed for the presence of obstructive non-culprit plaques (>50% luminal narrowing), segment involvement score, and quantitative measures of plaque burden, after censoring initial culprit plaques. Follow-up was performed for the occurrence of major adverse cardiovascular events (MACEs) unrelated to the initial culprit plaque; cardiac death, second ACS, or coronary revascularization after 90 days. After a median follow-up of 4.8 (IQR 2.6–6.6) years, MACE occurred in 36 (24%) patients: 6 cardiac deaths, 16 second ACS, and 14 coronary revascularizations. Dyslipidaemia (hazard ratio [HR] 3.1 [95% confidence interval 1.5–6.6]) and diabetes mellitus (HR 4.8 [2.3–10.3]) were univariable clinical predictors of MACE. Patients with remaining obstructive non-culprit plaques (HR 3.66 [1.52–8.80]) and higher plaque burden index (HR 1.22 [1.01–1.48]) had a higher risk of MACE. In multivariate analysis, with diabetes, dyslipidaemia, and plaque burden index, obstructive non-culprit plaques (HR 3.76 [1.28–11.09]) remained an independent predictor of MACE.

Conclusion: Almost a quarter of the study population experienced a new event arising from a non-culprit plaque during a follow-up of almost 5 years. ACS patients with remaining obstructive non-culprit plaques or high plaque burden have an increased risk of future MACE.

Introduction

Coronary computed tomography angiography (CTA) offers direct non-invasive assessment of atherosclerotic plaque throughout the entire coronary tree and has proved to be a reliable diagnostic tool in patients suspected of coronary artery disease with valuable prognostic information [1-5]. While several publications have evaluated the prognostic value of coronary CTA in patients with stable chest pain complaints [6-9], little is known about the prognostic implications of non-culprit plaques on coronary CTA in patients with acute coronary syndrome (ACS). Follow-up studies using intravascular imaging techniques in patients with ACS have shown that a substantial number of second events arise from these non-culprit plaques [10]. The aim of this study was to determine the prognostic implications of non-culprit plaques on coronary CTA in patients with ACS.

Methods

The study population consisted of patients admitted for ACS, including unstable angina pectoris, non-ST-segment elevation myocardial infarction (NSTEMI), and ST-segment elevation myocardial infarction (STEMI) according to the definitions of the European Society of Cardiology in the period between August 2004 and March 2011 [11]. Patients from three separate diagnostic studies with consecutive enrolment were pooled for the current study population; patients requiring urgent invasive intervention underwent coronary CTA after coronary angiography(CAG) [12-14]. Treating physicians were not informed regarding the findings on CTA.

Information on the presence of cardiac risk factors was prospectively collected. Hypertension was defined as a blood pressure of ≥140/90 mmHg or undergoing treatment for hypertension. Dyslipidaemia was defined as total cholesterol of >5.0 mmol/L or current statin treatment. Diabetes mellitus was defined as treatment with oral anti-diabetic medication or use of insulin. Smoking was considered as a risk factor if patients were current smokers and family history of cardiovascular disease was considered as positive if a first-degree relative (males <55 years or females <65 years) was diagnosed with cardiovascular disease [15,16]. The study complied with the Declaration of Helsinki and the institutional review board of Erasmus MC Rotterdam approved the study.

Image Acquisition

Image acquisition was performed using a multislice CT scanner (64-slice single source from August 2004 to September 2006, 64-slice dual source from September 2006 to April 2009, and 128-slice dual source from April 2009 to March 2011; Siemens, Forchheim, Germany) using the following scan parameters: 100–120 kV tube voltage, 850–960 mAs (64-slice single source), 370–412 mAs (64-slice dual source), and 320–412 mAs (128-slice dual source) tube current with X-ray tube modulation depending on patient size and variable pitch depending on the heart rate. A bolus of 80–100 mL of contrast material was injected intravenously followed by a 45-mL saline bolus chaser at a flow rate of 5.0–5.5 mL/s. A bolus-tracking technique was used to synchronize the arrival of contrast in

the coronary arteries. Patients received sublingual nitroglycerine before the scan and beta-blockers were administered in patients with high heart rates.

Follow-up

The national mortality registry was consulted for all patients. Questionnaires, standardized telephonic interviews, and information from hospital visits were additionally used to determine the occurrence and nature of potential events.

To determine the nature of the second event, an independent cardiologist, blinded for CT information, interpreted all clinical information, including ECG, echocardiography, and CAG at the time of the new event. Based on the ECG and angiographic findings at the time of the second event, the same physician identified the coronary segment most likely associated with the new event. The outcome measure was major adverse cardiac event (MACE) unrelated to the index culprit plaque: cardiac death, second ACS, and coronary revascularization after 90 days. Cardiac death was defined as death caused by acute myocardial infarction, ventricular arrhythmias, refractory heart failure, or cardiogenic shock. ACS was defined as either myocardial reinfarction with a rise and fall of cardiac biomarkers (>99th percentile of the upper limit of normal) or unstable angina requiring revascularization [17,18].

Image Evaluation

Coronary arteries were evaluated on axial images, multiplanar reconstructions (MPRs), and maximum intensity projections according to readers' preferences. All plaques deemed responsible for ACS at baseline were censored. The presence of coronary atherosclerotic plaque was determined using the 16-segment AHA classification by two experienced readers [19]. Stenosis grade was quantified as <20%, 20–50%, 50–70%, >70% stenosis or occluded. Segments of poor quality due to misalignment or movement artefacts and small segments (<1.5 mm) were excluded from analysis. After censoring for plaques causing ACS at baseline, we determined the segment involvement score: all lesions with a stenosis grade >20% [20]. Coronary atherosclerotic plaque was classified as non-calcified, partially calcified (≤50% calcium), or predominantly calcified (>50% calcium). Interobserver disagreements were resolved by a joint reading. With the semi-automated software (QAngioCT Research Edition, Medis Medical Imaging Systems, Leiden, the Netherlands), we determined total plaque volume and plaque burden index, as described previously [13]. In short, planimetry of the inner lumen and outer vessel areas was performed following a stepwise approach throughout the vessel. Plaque burden index was calculated by dividing the total plaque volume by the length of the evaluated vessel. Segments with chronic total occlusions or accountable for baseline ACS were not taken into account.

Morphological Evaluation

Plaques causing a second presentation with ACS were evaluated for their morphological features and compared with those that remained clinically silent in age- and gender-matched patients. The following characteristics were analysed by a blinded independent reader: percent area stenosis, plaque volume, remodelling index, minimal attenuation values, and presence of spotty calcifications.

For the evaluation of percent area stenosis, remodelling index, and minimal attenuation values, curved MPRs were created with perpendicular cross-sectional views using the dedicated software (Syngo.via; Siemens). Percent area stenosis was calculated by dividing the lumen are a at the site of maximal narrowing by the vessel area at the same cross-sectional view.

Remodelling index was calculated by dividing the cross-sectional vessel area at the site of maximal luminal narrowing by the cross-sectional vessel area in a reference segment. For reference we used segments without detectable plaque preferably proximal and as close as possible to the lesion. In the absence of a disease-free segment, the least diseased segment or a segment distally, before major bifurcations, and close to the investigated lesion was used. Minimal attenuation values were determined by placing a region of interest with a minimum size of 0.25 mm^2 in a region with the lowest attenuation assessed visually. Regions with extensive calcification or motion artefacts were avoided and fully calcified lesions were excluded. Spotty calcifications were defined as small calcified material <3 mm in size on MPRs, embedded in non-calcified material and one-sided on cross-sectional images.

Statistical Analysis

Statistical analyses were performed using the SPSS software (version 15.0, SPSS, Inc., Chicago, IL, USA) and STATA software (version 12.0, StataCorp, College Station, TX, USA). All probability values refer to two-tailed tests of significance; a p value of <0.05 was considered significant. Categorical variables are presented as proportions. Continuous variables are expressed as mean (±SD) or median (±IQR). Differences between independent groups were compared using the two-sided unpaired t test, χ^2 test, Wilcoxon rank-sum test or Fisher's exact test, as appropriate. Cox regression analysis was used to assess any associations between outcome and clinical characteristics or coronary CTA results. A second regression analysis was performed for the combined outcome cardiac death and ACS. Hazard ratios (HRs) were calculated with their corresponding 95% confidence intervals. Risk-adjusted models were corrected for significant (p<0.05) univariable clinical variables and used to create adjusted survival curves. The global χ^2 value was calculated to determine the incremental value of coronary CTA. Receiver operating characteristic (ROC) curves with estimates of the area under the curve (AUC) were obtained to compare discriminative model performances.

Results

The study population consisted of 169 ACS patients (mean age 59±11 years, 129 males) who underwent coronary CTA during their admission. Follow-up was obtained for 152 (90%) patients with a median follow-up time of 4.8 (2.7–6.6 years; Table 1). Diagnosis at the discharge of index hospitalization was unstable angina pectoris in 65 (43%) patients, NSTEMI in 59 (39%), and STEMI in 28 (18%) (Table 1). The composite endpoint MACE occurred in 36 (24%) patients, consisting of 6 cardiac deaths, 16 second ACS, and 14 late revascularizations unrelated to the plaque causing ACS at baseline. Coronary revascularization was driven by recurrent symptoms in 11 patients and by

ischaemia on non-invasive testing in 3 patients. The overall annual event rate was 4.9%. In addition, seven patients had died of a non-cardiac cause (all-cause mortality = 13 [9%]).

Table 1 | Baseline characteristics.

Characteristic	All (n=152)	MACE+ (n=36)	MACE- (n=116)	*p* value
Age, years[a]	58±10	58±10	59±10	0.56
Gender, male	116 (76)	30 (83)	86 (74)	0.26
Smoking	76 (50)	19 (53)	57 (49)	0.70
Hypertension	77 (51)	23 (64)	54 (47)	0.07
Dyslipidemia	81 (53)	27 (75)	54 (47)	0.003
Diabetes Mellitus	20 (13)	10 (28)	10 (9)	0.003
Positive Family History	74 (49)	18 (50)	56 (48)	0.86
Creatinin (µmol/L) [a]	84±14	86±16	84±14	0.33
Heart rate (/min) [a]	62±9	62±11	62±8	0.90
Index diagnosis				
Unstable angina	65 (43)	14 (39)	45 (39)	0.69
NSTEMI	59 (39)	17 (47)	48 (41)	
STEMI	28 (18)	5 (14)	23 (20)	
Index management				
Invasive angiography	143 (94)	35 (97)	108 (93)	0.36
PCI	126 (83)	34 (94)	92 (79)	0.04
CABG	8 (5)	0	8 (7)	0.68

Unless otherwise specified, data are numbers of patients, with percentages in parentheses. MACE = major adverse cardiac event (cardiac death, second ACS = and late coronary revascularization); NSTEMI = non-ST-segment elevation myocardial infarction; STEMI = ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; CABG = coronary artery bypass grafting. [a]Data are means±standard deviations.

Coronary CTA Results

A total of 2432 segments were evaluated; of which 87 (3.6%) were considered non-diagnostic, 317 (13.0%) too small for evaluation (,1.5 mm in diameter), and 172 (7.0%) were censored because of index ACS treatment. On a per-patient level, obstructive non-culprit plaques (>50% luminal narrowing) were more often seen in patients with MACE than in those without (83 vs. 52%, p=0.001, Table 2). A total of 263 non-calcified, 185 partially calcified, and 274 predominantly calcified plaques were seen in the whole group. Predominantly calcified plaques were more frequently seen in patients with MACE than in those without, although the difference did not reach statistical significance (p=0.08). Plaque burden index was significantly higher in patients with MACE, respectively, 8.4 vs. 7.2 mm2 (p=0.009).

Table 2 | Coronary CTA findings in patients with and without MACE.

	All (n=152)	MACE+ (n=36)	MACE- (n=116)	*p* value
Non-calcified plaques	1 (0-2)	1 (0-3)	1 (0-2)	0.37
Partially calcified plaques	1 (0-2)	1 (0-2)	1 (0-2)	0.87
Calcified plaques	1 (0-3)	2 (2-4)	1 (0-2)	0.08
SIS	6 (2–10)	10 (5–12)	5 (2–8)	0.002
Total plaque volume (mm^3)	1762 (1386–2278)	1803 (1427–2551)	1722 (1372–2253)	0.32
Plaque burden index (mm^2)	7.5 (6.1–8.7)	8.4 (6.8–9.2)	7.2 (5.6–8.6)	0.009
Obstructive non-culprit plaque (>50%)[a]	90 (59)	30 (83)	60 (52)	0.001

Unless otherwise specified, data are medians with interquartile ranges in parentheses. SIS = segment involvement score; MACE = major adverse cardiac event (cardiac death, second ACS, and late coronary revascularization). [a]Data are numbers of patients, with percentages in parentheses.

Prediction of Clinical Outcome

Patients with dyslipidaemia and diabetes mellitus experienced MACE more often during follow-up (Table 3). Obstructive non-culprit plaques and plaque burden index were significant predictors of MACE. For the combined outcome cardiac death and second ACS, both variables remained significant predictors. In multivariable analysis,correcting for dyslipidaemia and diabetes mellitus, the presence of obstructive non-culprit plaques on CT remained an independent predictor (Figure 1 and Table 4). Model discrimination performance increased with the addition of CTA to a clinical model consisting of dyslipidaemia and diabetes (Figure 2).

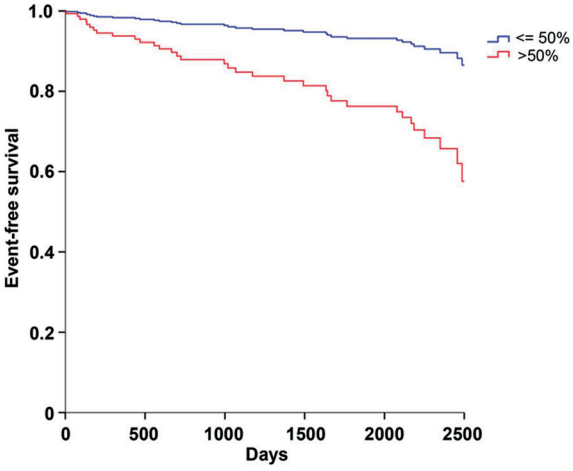

Figure 1 | Event-free survival in patients with or without obstructive (>50%) non-culprit plaque. Risk-adjusted, *p*=0.006 (controlling for dyslipidaemia and diabetes mellitus).

Table 3 | Univariable Cox regression analysis.

Characteristic	MACE HR (95% CI)	*p* value	Cardiac death and recurrent ACS HR (95% CI)	*p* value
Age, per year	1.01 (0.98–1.04)	0.61	1.01 (0.98–1.06)	0.46
Gender, male	2.00 (0.82–4.88)	0.13	1.82 (0.60–5.47)	0.29
Smoking	1.25 (0.65–2.40)	0.51	2.09 (0.89–4.95)	0.09
Hypertension	1.89 (0.94–3.81)	0.07	2.08 (0.85–5.10)	0.11
Dyslipidemia	3.10 (1.45–6.61)	0.003	3.49 (1.29–9.45)	0.01
Diabetes Mellitus	4.81 (2.25–10.27)	<0.001	5.01 (2.00–12.52)	0.001
Coronary CT angiography				
Non-calcified plaques	1.09 (0.98–1.22)	0.11	1.07 (0.92–1.24)	0.40
Partially calcified plaques	1.11 (0.89–1.39)	0.35	0.97 (0.71–1.32)	0.85
Calcified plaques	1.11 (0.97–1.26)	0.15	1.14 (0.97–1.34)	0.12
SIS	1.14 (1.06–1.23)	0.002	1.01 (1.00–1.21)	0.05
Plaque burden index	1.22 (1.01–1.48)	0.04	1.29 (1.01–1.65)	0.04
Obstructive non-culprit plaque (>50%)	3.66 (1.52–8.80)	0.004	4.11 (1.21–13.89)	0.02

MACE = major adverse cardiac event (cardiac death, second ACS, and late coronary revascularization); SIS = segment involvement score; ACS = acute coronary syndrome; CTA = computed tomography angiography; HR = hazard ratio.

Table 4 | Multivariable analysis.

	Risk-adjusted HR (95% CI)	p value
Model I		
SIS	1.03 (0.94–1.13)	0.49
Obstructive non-culprit plaque (>50%)	3.22 (1.10–9.43)	0.03
Model II		
Plaque burden index	1.16 (0.94–1.44)	0.19
Obstructive non-culprit plaque (>50%)	3.76 (1.28–11.09)	0.02

Risk-adjusted for dyslipidaemia and diabetes mellitus. SIS = segment involvement score.

Comparison with CAG

In this study, 143 patients underwent CAG with an obstructive non-culprit lesion visible in 24 cases. During the follow-up, 10 of these patients experienced MACE, while 26 patients who experienced MACE had no obstructive lesions on CAG after initial treatment.

In a model with CAG, CT remained a significant predictor (HR 3.60 [1.36–9.59], *p*=0.01 for MACE and HR 4.27 [1.24–14.71], *p*=0.02 for cardiac death and ACS).

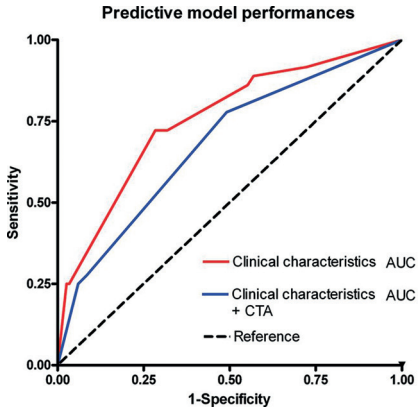

Figure 2 | ROC curves for clinical characteristics alone, i.e. dyslipidaemia and diabetes mellitus (red line AUC 0.68 [0.58–0.78]) and with obstructive non-culprit plaque on CTA (blue line AUC 0.76 [0.66–0.85]).

Morphological comparison

Second ACS occurred in 16 patients; among whom, a culprit lesion could be identified in 13 cases. Percent area stenosis (0.81% [0.76–0.88] vs. 0.71% [0.63–0.78], p=0.02) was significantly higher in plaques causing second ACS. Total volume of plaques causing second ACS was 175 mm^3 (IQR 95–254) and 120 mm^3 (IQR 101–151) of control plaques (p=0.22). No difference was found for remodelling index (1.11±0.42 in culprit plaques vs. 1.08 ± 0.16 in control plaques, p=0.83), minimal plaque attenuation (98 HU [65–147] vs. 104 HU [72–168], p=0.79), and presence of spotty calcification (5 vs. 3, p=0.67) types.

Discussion

During a follow-up of almost 5 years, almost a quarter of patients with ACS at baseline experienced a second event and patients with higher plaque burden or obstructive non-culprit plaques on CT had a significantly higher risk of MACE.

As a reliable gatekeeper for invasive angiography, coronary CTA has become a part of the diagnostic armamentarium for patients suspected of ACS [21-23]. Once patients have been diagnosed with ACS and treated accordingly, their risk of new cardiac events will determine future therapy. With intravascular imaging techniques, the natural history of coronary atherosclerosis in patients admitted with ACS has been evaluated thoroughly [10]. The investigators of the PROSPECT study detected high residual plaque burden even after the treatment of all angiographically significant lesions. Non-culprit plaques were responsible for a substantial number of second events and patients with higher plaque burden had an increased risk of MACE [24]. More recently, investigators of the PRAMI trial showed that preventive percutaneous coronary intervention (PCI) of non-culprit lesions with major stenoses significantly reduced the risk of adverse cardiovascular events in patients with STEMI and multivessel disease [25]. Although currently not recommended and without immediate suggestion in differentiation of post-ACS treatment, our intention was to perform an exploratory

study to understand the role of non-culprit lesions better. Looking beyond luminology, coronary CTA provides detailed information regarding total plaque burden, accounting for non-obstructive lesions as well, and specific plaque characteristics that might be important for understanding of the occurrence of second cardiac events in these patients. We found that remaining obstructive plaques and quantitatively measured higher plaque burden are associated with an increased risk of cardiac events. Also, CT remained an independent predictor of MACE next to CAG, suggesting that CT picks up lesions which do not look important on CAG, but over time do cause cardiac events, which might be due to the additional information provided by CT over sheer luminology.

Extensively studied in populations with stable complaints, CT has shown to be a strong predictor of mortality and cardiac-specific adverse outcomes [26-28]. However, there is a paucity of data in the group patients with ACS. In a study by Kristensen et al. [29], there was a significant correlation found between the total amount of non-obstructive plaque and adverse cardiac events in NSTEMI patients after 16 months. In the present study, we included all non-culprit plaques for quantitative measurement of plaque burden, confirming this correlation for a more heterogeneous ACS population.

Morphological plaque features are next to stenosis severity also determinates of plaque progression and rupture. Intravascular imaging techniques allow a more detailed assessment of plaques and can visualize specific characteristics like thin fibrous caps or large necrotic cores [10]. It has been postulated that a thin fibrous cap is a major determinant in discrimination between a vulnerable plaque and a stable plaque [30]. Limited by its spatial resolution, CT cannot detect thin-cap fiberoatheromas, but there are specific CT plaque features, such as low-attenuation, positive remodelling, and spotty calcifications (Figure 3), that are associated with a higher risk of future cardiac events [31-34]. In a sub-analysis, we examined morphological features of lesions causing ACS. Percent area stenosis was significantly higher in lesions causing second ACS compared with those that remained silent. There was no significant difference found for other morphological features, possibly because of the small sample size, limited observation time, or methods of measuring, and also due to the high-risk nature of the study population. All patients had already experienced ACS at baseline and high-risk features of interest might have been frequent in the control group as well.

Limitations

There are several limitations to the present study. First, this is a single-centre study of a retrospective nature. Therefore, our results may not necessarily reflect populations or practices elsewhere and may be subject to a selection bias. In this study, we reached considerable follow-up (90%); however, incomplete follow-up may result in underreporting of events. Allocation of deaths to cardiac or non-cardiac was made by an independent cardiologist, blinded for CT in-formation, who reviewed clinical records and information provided by the general practitioners. Autopsy was either not performed or results were not available in many patients who had died during follow-up and we cannot exclude that baseline ACS or its complications influenced or were the direct cause of subsequent cardiac deaths during follow-up. By censoring initial culprit lesions, we tried to minimize misclassification

of cardiac deaths. Most importantly, our goal was to exclude clear non-cardiac cases or those with clinical information suggesting a clear link between cause of death and index event. Considering the observational methodology and modest sized population, our results should be considered exploratory and we do not advocate regular use of CT in ACS patients. Finally, the sample size in the present study might lack power to detect existing associations between clinical characteristics, CT, and outcome.

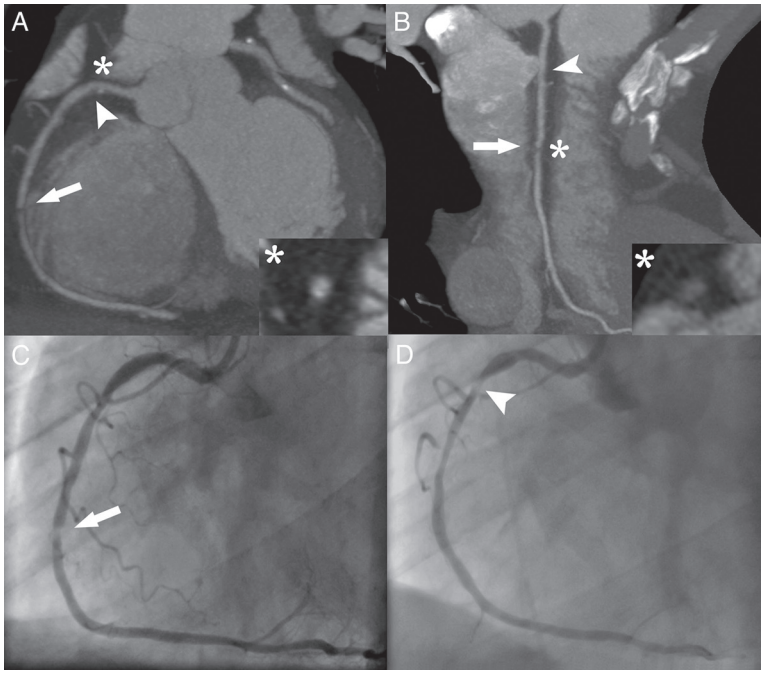

Figure 3 | (**A** and **B**) Coronary CTA in a 67-year-old male presenting with NSTEMI showing a severe lesion in the mid-right coronary artery (white arrows) and a moderate lesion proximally (white arrowhead). Cross-sectional views magnified in the right lower corner (asterisks). (**C**) The severe lesion was confirmed on invasive angiography (white arrow) and the patient subsequently underwent PCI. (**D**) After 6 years, the patients returned with a NSTEMI. Invasive angiography showed a significant lesion in the proximal right coronary artery (white arrowheads), on CT previously described as a moderately narrowing plaque with spotty calcification (A and B; white arrowheads).

Conclusions

Almost a quarter of the study population experienced a second event caused by a non-culprit plaque during 5-year follow-up. ACS patients with obstructive non-culprit plaques or high plaque burden have an increased risk of future MACE.

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Part 4

Epilogue

Summary and General Discussion

In this thesis, we explored new clinical applications of coronary CT angiography. Presently, considered an established diagnostic modality, coronary CT angiography has made tremendous progress since its first steps in the clinical field. Current guidelines by the European Society of Cardiology have adopted coronary CT angiography as a viable alternative non-invasive test in the diagnostic work-up of patients with stable coronary artery disease. Because of an excellent negative predictive value, it is the most effective non-invasive test in those cases where ruling out of important coronary artery disease is imperative [1].

In **Chapter 2**, we provide an in-depth description of the technical background of cardiac CT imaging, to understand how images are acquired, what determines image quality, and why the new generation scanners provide better diagnostic accuracy. In addition, an overview is presented of the diagnostic accuracy and clinical applications available today or under development.

Coronary CT angiography in suspected acute coronary syndrome

Patients presenting to the emergency department with symptoms suggestive of an acute coronary syndrome remain a diagnostic challenge. While physicians are understandably cautious not to miss an acute coronary syndrome or any other important condition, they strive to perform a clinical efficient work-up as these patients present in large numbers worldwide every year and many of them actually do not have any serious illness.

Chapter 3

In this chapter, we present a systematic review of the diagnostic accuracy of currently used imaging techniques (echocardiography, radionuclide myocardial perfusion imaging and coronary CT angiography) in the diagnostic work-up of patients suspected of an acute coronary syndrome. A meta-analysis of the currently available literature showed no significant difference in diagnostic accuracy between the three modalities. Pooled sensitivities ranged from 86%–94% and pooled specificities ranged from 73%–82%, with coronary CT angiography at the top-end of both. Based on these results, we conclude that all three modalities are suitable for the diagnostic work-up of patients suspected of an acute coronary syndrome. Practical aspects such as local practice, expertise, medical facilities, and individual patient characteristics should determine which modality to choose for.

Chapter 4

In a prospective, blinded observational study, we determined the diagnostic value of coronary CT angiography and the coronary calcium scan in 111 low- to intermediate-risk patients presenting to the emergency department with symptoms suggestive of an acute coronary syndrome. Absence of coronary atherosclerotic plaque on coronary CT angiography excluded an acute coronary syndrome and was associated with a benign short-term prognosis. In terms of diagnostic accuracy, coronary

CT angiography performed better than the coronary calcium scan and had incremental value over the GRACE risk score, a commonly used clinical risk prediction algorithm.

Chapter 5

Copeptin is a biomarker that is secreted very early during times of haemodynamic stress and can be measured in peripheral blood. In this study, we determined the diagnostic accuracy of copeptin in 65 suspected acute coronary syndrome patients, and examined the association between copeptin levels and coronary artery disease detected by coronary CT angiography. Patients that were eventually diagnosed with an acute coronary syndrome had higher copeptin levels, but no significant correlation between copeptin and obstructive coronary artery disease on coronary CT angiography could be found.

Chapter 6

In a prospective, open-label, multicentre, randomized trial, 500 patients presenting with symptoms suggestive of an acute coronary syndrome were enrolled at the emergency departments of five community and two university hospitals in the Netherlands. Patients were randomized to either a diagnostic strategy supplemented by early coronary CT angiography or standard optimal care. We found that a diagnostic strategy supplemented by early coronary CT angiography is safe, less expensive and averts outpatient testing. However, in the era of high-sensitivity troponins, coronary CT angiography does not identify more patients with requiring coronary revascularization, nor does it shorten hospital stay or allow for more direct discharge from the emergency department.

Risk stratification with coronary CT angiography

Gradually scientific evidence is accumulating to support the use of coronary CT angiography for prognostic purposes as well. The technique can discriminate between low- and high-risk patients providing more individually tailored clinical management.

Chapter 8

We compared the ability of the coronary artery calcium score and exercise electrocardiography as less expensive and cumbering tests to rule out obstructive coronary artery disease in 791 patients with stable angina pectoris. In low risk patients with a coronary calcium score of 0, further diagnostic work-up seems redundant as the post-test probability of obstructive coronary artery disease was less than 5%. In the group of patient with intermediate risk, both modalities were not able to sufficiently rule out obstructive coronary artery disease. High-risk patients also do not seem to benefit from either, although a normal exercise electrocardiography may be more helpful to exclude haemodynamically relevant lesions and guide management.

Chapter 9

At present, traditional risk factors guide cardiovascular management of asymptomatic individuals. High-risk asymptomatic patients may benefit from increased medical surveillance. In an observational multicentre study we aimed to determine whether the coronary artery calcium score and coronary CT angiography could be used for improved risk prediction. In this study 665 patients participated. During a follow-up period of 3 years, we found a generally low annual incidence of adverse events. Both modalities were found to be significant predictors of adverse cardiovascular events. Coronary CT angiography had incremental prognostic value over the coronary calcium scan. Importantly, in patients without detectable coronary calcium, which had an excellent prognosis, this incremental value was not seen.

Chapter 10

In this study, consisting of 471 consecutively enrolled patients with stable angina pectoris, we aimed to determine and compare the prognostic value of coronary CT angiography, the coronary artery calcium score, and exercise electrocardiography. We found that the extent of coronary calcification, the presence of obstructive coronary artery disease detected by coronary CT angiography, and the maximal exercise tolerance during exercise electrocardiography all predict future adverse events. Importantly, after adjustment for clinical characteristics and results of exercise electrocardiography, coronary CT angiography remained a predictor of future adverse events.

Chapter 11

Non-culprit plaques are responsible for a substantial number of future events in patients with an acute coronary syndrome. In this study, we evaluated the prognostic implications of non-culprit plaques seen on coronary CT angiography in 169 patients with an acute coronary syndrome. During a follow-up of nearly 5 years, almost a quarter of the study population experienced a second event, either cardiac death, second acute coronary syndrome, or coronary revascularisation after 90 days. Patients with higher plaque burden or obstructive non-culprit plaques on coronary CT angiography had a significantly higher risk of adverse events.

Future Directions

The growth of coronary CT angiography as a diagnostic and prognostic modality is evident. Although we strived to answer several questions in these thesis, several issues remain unresolved and at the same time new questions arise. In the field of acute cardiac care, where the sensitivity of hs-troponins seems impeccable, an unavoidable decrease in specificity has been noted, resulting in a substantial number of patients with slightly elevated troponins who do not suffer from an acute coronary syndrome. It would be important to investigate whether coronary CT angiography can guide management in these patients and defer those without important coronary artery disease from invasive angiography. Also, while coronary CT angiography is suitable to identify patients at higher risk of future adverse events, as demonstrated in this thesis, it still remains to be proven that

subsequent interventions based on findings from coronary CT angiography will actually prevent future adverse events.

In other fields, research groups are working relentlessly to answer outstanding issues and challenges. Much attention has been directed towards further improvement of the diagnostic accuracy, more precisely the specificity, which is still lagging behind to that of other non-invasive tests. This has partly already been accomplished because of the better temporal and spatial resolution of new generation scanners, increasing the specificity to 86% compared to 78% of the traditional 64-slice scanners [2]. However, two altogether new cardiac CT imaging techniques have emerged addressing this issue more directly: stress myocardial perfusion CT imaging and CT angiography derived fractional flow reserve. Initial experiences show that both improve specificity for functional significant stenosis substantially, bringing the dream of a one-stop-shop diagnostic modality very close [3].

On the other side, efforts are undertaken to decrease radiation exposure and the quantity of iodinated contrast medium needed per scan. Using new reconstruction algorithms with lower kV acquisition settings and modified contrast delivery protocols, complete scans can be attained for radiation doses of less than 1 mSV and a 30% decrease in the amount of contrast medium [4,5]. Lastly, it is still unclear how coronary CT angiography compares to other diagnostic tests in terms of cost-effectiveness. Considering the increasing medical expenditure in our society, partially the result of an aging population, it would be valuable to examine for what indication and which group of patients CT is cost-effective.

The coming years will reveal how the here above mentioned developing areas have moved coronary CT angiography as a diagnostic modality forward and what place it will have earned within the clinical field of cardiology.

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Nederlandse Samenvatting

Coronaire CT angiografie heeft zich in het afgelopen decennium ontwikkeld tot een volwaardige diagnostische test bij kransslagvat ziekte. **Hoofdstuk 1** geldt als een algemene inleiding van dit proefschrift, waarin een historisch perspectief geschetst wordt van deze ontwikkeling. Daarnaast worden hierin het doel en de opzet van dit proefschrift beschreven.

In **Hoofdstuk 2** worden de technologische aspecten van de cardiale beeldvorming met behulp van de CT beschreven, alsmede de mogelijke acquisitie protocollen en de bijbehorende stralingsbelasting. Tevens wordt een overzicht gepresenteerd van de huidige diagnostische nauwkeurigheid en de klinische toepassingen.

In **Hoofdstuk 3** wordt een overzicht gegeven van de bestaande literatuur over het gebruik van echocardiografie, nucleaire perfusie beeldvorming, en coronaire CT angiografie bij verdenking op een acuut coronair syndroom. In dit artikel hebben wij de diagnostische prestaties van deze beeldvormende technieken vergeleken door middel van een systematische zoektocht in de beschikbare medische literatuur. Hoewel een lichte positieve trend ten gunste van de coronaire CT angiografie naar voren kwam, was er geen statistisch significant verschil tussen de drie modaliteiten. Hieruit concludeerden wij dat gezien de afwezigheid van grote verschillen in diagnostische nauwkeurigheid, andere aspecten zoals de lokale praktijk, expertise, medische voorzieningen, en de individuele kenmerken van de patiënt de doorslag moeten geven in de keuze van de diagnostische modaliteit.

In **Hoofdstuk 4** wordt een prospectieve geblindeerde studie beschreven waarin de diagnostische nauwkeurigheid van de coronaire CT angiografie en de coronaire calcium score wordt vergeleken in 111 patiënten met symptomen verdacht voor een acuut coronair syndroom. De studie liet zien dat afwezigheid van kransslagvatziekte op de coronaire CT angiografie een acuut coronair syndroom volledig uitsloot en een zeer gunstige korte termijn prognose garandeerde. Daarnaast bleek dat coronaire CT angiografie superieur was aan de coronaire calcium score was op het vlak van de diagnostische nauwkeurigheid. Tenslotte had de coronaire CT angiografie toegevoegde waarde naast de GRACE-score, de meest gebruikte klinische algoritme voor risicoinschatting in deze patiëntengroep.

In **Hoofdstuk 5** wordt de diagnostische nauwkeurigheid van copeptin, een biomarker van cardiovasculaire stress, onderzocht en afgezet tegen de bevindingen bij coronaire CT angiografie. Deze studie omvatte 65 patiënten die verdacht worden van een acuut syndroom. Bij deze patiënten werd bij presentatie op de Spoedeisende Hulp copeptin bepaald. Daarnaast ondergingen zij een coronaire CT angiografie. Het bleek dat patiënten met een acuut coronair syndroom gemiddeld een hogere copeptin waarden hebben, maar dat er geen significante associatie was tussen copeptin waarden en de aanwezigheid van kransslagvatziekte op coronaire CT angiografie.

In **Hoofdstuk 6** wordt een prospectieve, gerandomiseerde, multicenter studie van 500 patiënten beschreven. Deze patiënten, die zich presenteerden met klachten verdacht voor een acuut coronair syndroom, werden op basis van willekeur verdeeld in twee groepen met verschillende diagnostische strategieën. De helft van de patiënten onderging de standaard optimale diagnostische strategie,

gedicteerd door hun behandelde arts. De andere groep onderging een diagnostische strategie waarin een vroege coronaire CT angiografie centraal stond. De belangrijkste bevinding van deze studie was dat een diagnostische strategie met coronair CT angiografie in een vroeg stadium, praktisch en veilig is, met lagere kosten en minder poliklinische onderzoeken nadien. Maar een diagnostische strategie met coronair CT angiografie kon niet meer patiënten met ernstige kransslagvatziekte vinden, noch kon het ziekenhuisopnames verkorten of zorgen dat meer patiënten meteen vanaf de spoedeisende-hulpafdeling ontslagen konden worden.

In **Hoofdstuk 8** hebben we de nauwkeurigheid van de coronaire calcium score en de fietsergometrie als een eventuele goedkopere, niet-invasieve test voor het screenen van ernstige kransslagvatziekte vergeleken. Beide testen werden in 791 patiënten met klachten van pijn op de borst verricht, gevolgd door een hartcatheterisatie of een coronaire CT angiografie als verificatie. Deze studie liet zien dat bij patiënten met een laag risico op basis van het klinisch profiel en verder geen verkalkingen van de kransslagvaten verdere diagnostiek onnodig lijkt omdat zij een kans van minder dan 5% op belangrijke kransslagvatziekte hebben. In de groep patiënten met een gemiddeld risico waren beide modaliteiten niet in staat om ernstig kransslagvatziekte uit te sluiten. Bij hoog risico patiënten lijkt de fietsergometrie bruikbaar om de prognose in te schatten.

In **Hoofdstuk 9** wordt onderzocht of coronaire CT angiografie een betere risico inschatting voor toekomstige cardiovasculaire aandoeningen kan geven dan de coronaire calcium score in individuen zonder klachten maar wel een hoog cardiovasculair risicoprofiel. In twee academische centra participeerden 665 patiënten aan deze studie. Zij werden gemiddeld 3 jaar gevolgd. Hoewel de patiënten gekenmerkt werden door een zeer ongunstig risicoprofiel, bleken zij over het algemeen na 3 jaar een lage incidentie van cardiovasculaire aandoeningen te hebben. Afwezigheid van verkalkingen van de kransslagvaten was geassocieerd met een zeer gunstige prognose. In diegene met verkalkingen van de kransslagvaten bleek coronaire CT angiografie toegevoegde waarde te hebben voor het voorspellen van cardiovasculaire aandoeningen.

In **Hoofdstuk 10** worden de voorspellende waarden van fietsergometrie, de coronaire calcium score en coronaire CT angiografie voor het optreden van toekomstige cardiovasculaire aandoeningen vergeleken. Aan deze studie participeerden 471 patiënten met klachten van stabiele angina pectoris. Zij ondergingen allemaal alle drie de testen. Deze studie liet zien dat hogere calcium scores, de aanwezigheid van belangrijke kransslagvatziekte op coronaire CT angiografie en de maximale inspanningstolerantie tijdens fietsergometrie allen voorspellend waren voor het optreden van cardiovasculaire aandoeningen in de toekomst. Als de drie modaliteiten worden vergeleken, blijkt de uitslag van de coronaire CT angiografie het meeste toegevoegde waarde te hebben.

In **Hoofdstuk 11** wordt een studie beschreven van patiënten die zich presenteren met een acuut coronair syndroom en ook coronaire CT angiografie ondergingen. Specifiek wordt gekeken naar de gevolgen van overig kransslagvatziekte, niet verantwoordelijk voor het huidige acuut coronair syndroom. In totaal ondergingen 169 patiënten coronaire CT angiografie en werden gevolgd in de tijd op het voorkomen van dood, een nieuw hartinfarct of een behandeling van de kransslagvaten. Gedurende 5 jaar bleek bijna een kwart van deze patiënten een van deze aandoening te hebben gehad. Patiënten met veel zogeheten overige kransslagvatziekte op coronair CT angiografie hadden een statistisch significant hoger risico op nieuwe cardiovasculaire aandoeningen in de toekomst.

List of publications

Manuscripts

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Presentations

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First-line evaluation of coronary artery disease with coronary calcium scanning or exercise electrocardiography.

European Society of Cardiology 2011
Stable angina pectoris: head-to-head comparison of prognostic value of cardiac CT and exercise testing.

European Society of Cardiology 2012
Coronary CT angiography outperforms calcium imaging in the triage of acute coronary syndrome.

European Society of Cardiology: Acute Cardiac Care 2012
Copeptin in acute chest pain: identification of acute coronary syndrome and obstructive coronary artery disease on coronary CT angiography.

European Society of Cardiology 2013
Prognostic implications of non-culprit plaques in acute coronary syndrome: non-invasive assessment with coronary CT angiography.

American College of Cardiology 2013
The effect of LDL-receptor negative genotype on aortic valve calcification using cardiac CT in asymptomatic statin treated patients with heterozygous familial hypercholesterolemia.

European Society of Cardiology: EuroEcho Imaging 2013
The time and place of cardiac CT in the emergency room.

Macedonian Cardiology Congress 2014
Cardiac CT: clinical value, new approaches.

European Society of Cardiology 2015
Prognostic value of coronary CT imaging in high-risk patients without symptoms of coronary artery disease.

American Heart Association 2015
Coronary CT Angiography for Suspected Acute Coronary Syndrome in the Era of High-Sensitivity Troponins – a Randomized Multicentre Study.

Curriculum vitae

Admir Dedic was born on September 7th 1984 in Sarajevo, Bosnia-Hercegovina.

He started Medical School in 2002 at Erasmus MC University Medical Center Rotterdam. In 2009, he obtained his medical degree. Following a year of internship at the department of Cardiology at the Erasmus MC University Medical Centre, he started his PhD under the supervision of Professor F. Zijlstra (Head of Department of Cardiology) and Professor G.P. Krestin (Head of Department of Radiology). His scientific efforts regarding the clinical application of coronary CT angiography are summarized in this PhD thesis. In October 2013 he started his specialisation in Cardiology at the Erasmus MC University Medical Center (supervisor Professor F. Zijlstra). The first two years of general internal medicine, he completed at the Sint Franciscus Gasthuis, Rotterdam (supervisor dr. A.P. Rietveld). At this moment, he is in training at the Amphia Ziekenhuis Breda (supervisor dr. A.M.W. Alings).

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PhD Portfolio

	Year	Workload (ECTS)
PhD training		
General Academic and Research Skills		
NIHES Biostatistical Wintercourse	2010	5.7
COEUR PhD Day	2010	0.4
Seminar Clinical Decision Making	2010	0.4
OpenClinica Training	2012	0.6
In-depth Courses		
ERCATHAN Functional Anatomy Masterclass	2010	0.3
COEUR Cardiovascular Imaging and Diagnostics	2010	1.5
COEUR Clinical Cardiovascular Epidemiology	2010	1.5
Molmed Imaging Workshop	2010	0.3
Course Radiation Protection level 5A/B	2010	0.6
Research Seminar Biomarkers for Risk prediction	2010	0.4
Seminar Detection of Early Atherosclerosis	2011	0.4
COEUR Intensive Care Research	2012	1.5
COEUR Pathophysiology of Ischemic Heart Disease	2012	1.5
COEUR Arrhythmia Research Methodology	2012	1.5
CVOI Cardiac Imaging	2012	0.3
Conferences and Symposia		
AHA – Chicago	2010	2.1
ICNC – Amsterdam	2011	0.9
Cardiac MRI & CT – Cannes	2011	0.9
Hypertrophic Cardiomyopathy – Rotterdam	2011	0.3
RSNA – Chicago	2011	2.1
NVVC – Arnhem	2011	0.3
ESC – Parijs	2011	1.5
Simoons de Doelen – Rotterdam	2011	1.2
ESC Acute Cardiac Care – Istanbul	2012	1.5
ESC – Munchen	2012	1.5
RSNA – Chicago	2012	2.1
ACC – San Francisco	2013	0.5
ESC EuroEcho – Istanbul	2013	1.5

	Year	Workload (ECTS)
Conferences and Symposia *(Continued)*		
ESC – Amsterdam	2013	1.2
Winter Meeting ESC Imaging Nucleus	2014	0.9
National Cardiology Convention Macedonia	2014	0.9
ESC – Londen	2015	1.2
AHA – Orlando	2015	1.2
Teaching Activities		
Supervising research of 2nd year medical students	2012	1.0
CT reading course	2012	0.6
CT reading course	2013	0.9
CT reading course	2014	0.3
CT reading course	2015	0.3
CT reading course	2016	0.3
Total ECTS		**42.1**

Abbreviations

ACP	=	Acute Chest Pain
ACS	=	Acute Coronary Syndrome
AHA	=	American Heart Association
AMI	=	Acute Myocardial Infarction
ANOVA	=	Analysis of Variance
AUC	=	Area Under the Curve
AVP	=	Arginine Vasopressin
CABG	=	Coronary Artery Bypass Graft surgery
CACS	=	Coronary Artery Calcium Score
CAD	=	Coronary Artery Disease
CAG	=	coronary Angiography
CCS	=	Coronary Calcium Scanning
CCTA	=	Coronary Computed Tomography Angiography
CI	=	Confidence Interval
CK-MB	=	Creatine Kinase Myocardial Band
CT	=	Computed Tomography
CTA	=	Computed Tomography Angiography
CTA-FFR	=	Computed Tomography Angiography based Fractional Flow Reserve
CVD	=	Cardiovascular Disease
DCS	=	Duke Clinical Score
DM	=	Diabetes Mellitus
ED	=	Emergency Department
EBCT	=	Electron-beam Computed Tomography
ECG	=	Electrocardiography
ExECG	=	Exercise Electrocardiography
FH	=	Familial Hypercholesterolemia
GRACE	=	Global Registry of Acute Coronary Events
HR	=	Hazard Ratio
Hs-troponins	=	High-sensitivity Troponins
ICA	=	Invasive Coronary Angiography
ICU	=	Intensive Care Unit
IQR	=	Interquartile Range
LAD	=	Left Anterior descending
LCX	=	Left Circumflex
LM	=	Left Main
LR	=	Likelihood Ratio
LV	=	Left Ventricle
MACE	=	Major Adverse Cardiac Event

MBF	=	Myocardial Blood Flow
MI	=	Myocardial Infarction
MPI	=	Myocardial Perfusion Imaging
MPR	=	Multiplanar Reconstruction
MRI	=	Magnetic Resonance Imaging
mSv	=	MiliSievert
NPV	=	Negative Predictive Value
NRI	=	Net Recalssification Index
NSTEMI	=	Non ST-segment Elevation Myocardial Infarction
PAD	=	Peripheral Artery Disease
PCI	=	Percutaneous Coronary Intervention
PPV	=	Positive Predictive Value
QCA	=	Quantitative Coronary Angiography
RCA	=	Right Coronary Artery
ROC	=	Receiver Operating Characteristics
SD	=	Standard Deviation
SIS	=	Segment Involvement Score
SOC	=	Standard Optimal Care
SPECT	=	Single-Photon Emission Computed Tomography
SROC	=	Summary Receiver Operating Characteristics
STEMI	=	ST-segment Elevation Myocardial Infarction
TIMI	=	Thrombolysis in Myocardial Infarction
UAP	=	Unstable Angina Pectoris
VSD	=	Ventricular Septal Defect
WMA	=	Wall Motion Abnormalities
X-ECG	=	Exercise Electrocardiography