Summary and General Discussion

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

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

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

CT Calcium imaging and CT angiography in stable angina

Chapter 3 focused on the clinical use of cardiac CT in stable ambulatory patients with a suspicion of obstructive CAD. At four centers in the Rijnmond region we randomized 350 patients [CRESCENT Trial] with stable chest pain between a tiered cardiac CT protocol and standard functional testing. The protocol started with a calcium scan and ruled out CAD in low-intermediate probability patients with a negative calcium scan(11). Patients with a very high calcium score underwent functional testing. Coronary CTA was performed in the remaining 49% of patients. Standard care started with an exercise ECG in the majority of patients. After one year fewer patients randomized to CT reported anginal symptoms in comparison to the functional testing group. This can be explained by a higher diagnostic performance of CT and subsequently more appropriate management of cardiac as well as non-cardiac conditions, although differences in experienced reassurance from cardiac CT by patients and physicians may have played a role as well. Although the study was not powered to demonstrate differences in mortality or myocardial infarction, cardiac CT did result in a lower combined event rate that included death, myocardial infarction, stroke, late revascularizations and unplanned cardiac evaluations (3.3% vs.10.2%). The use of X-rays represents a drawback of CT, although by applying the calcium scan, contemporary CT equipment and dose reducing techniques, the cumulative radiation dose exceeded the functional testing group by less than 10%. Cardiac CT achieved a conclusive diagnostic result faster, required fewer additional tests, did not significantly increase catheterization rates, and was less expensive, compared to functional testing (€369 versus €440). In conclusion: a tiered cardiac CT protocol that includes a CT calcium scan, is safe, avoids contrast medium in 39% of patients, reduces exposure to radiation, and appears cost-effective compared to standard functional testing.

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

The diagnostic management of women with suspected CAD is challenged by underrecognition due to differences in presentation, pathophysiology such as the higher prevalence of vasospasm and microvascular angina in women (14, 15), a lower performance of standard noninvasive tests resulting in equivocal test results and missed diagnoses (16-19) and a paradoxically low diagnostic yield of invasive angiography for angiographic CAD, due to a relative overuse, perhaps fueled by the limited confidence in noninvasive tests (20, 21). Based on the hypothesis that direct visualization of CAD by cardiac CT may be particularly effective in women, in **Chapter 4** we investigated gender differences in the performance of cardiac CT compared to functional testing in the evaluation of stable chest pain, and found that cardiac CT was more efficient in women than men in terms of time needed to reach the final diagnosis and downstream testing. In the previously published sub-analysis of the PROMISE trial women were less likely to have a positive CTA than a positive exercise ECG or nuclear stress test result, even after adjusting for clinical factors, which may be the result of false-positive stress test results(22). Interestingly, in the CRESCENT trial no evident differences were observed between the sexes with regard to the exercise tolerance or achieved heart rate during exercise testing. Contrary to PROMISE and SCOT-HEART, in the CRESCENT trial cardiac CT was not associated with an increase in the number of cardiac catheterizations in women(12, 13). The reduced catheterization referral rate after CT may be explained by the use of the calcium scan, or a higher accuracy by newer CT equipment, but may as well be the result of differences in management following the CT scan, compared to previous studies.

Enhancement of the coronary lumen is essential for the detection of CAD on CTA. Contrast media vary in terms of iodine concentration and osmolarity. Until recently the goal in coronary CTA was to achieve maximum lumen opacification, to overcome limitations related to residual motion and vessel calcifications, by injecting high-concentration contrast media (up to 400mg I/ml) or high injection rates. With more powerful roentgen tubes and iterative reconstruction techniques, many patients can be scanned at a lower tube potential (80kVp), which reduces overall radiation exposure. Because of a greater photoelectric effect and less Compton scattering, imaging at a lower kV also increases attenuation differences between iodine and soft tissue(23). As a result, sufficient coronary contrast can be achieved with less iodine injected in to the body. Iso-osmolar contrast media with an osmolarity equal to plasma were demonstrated to cause less heart rate acceleration and arrhythmia, which should be of potential benefit for CT image quality(24-28). In terms of opacification and image quality comparisons between iso-osmolar and low-osmolar contrast media have demonstrated mixed results, which may in part be related to the lower iodine concentration of iso-osmolar contrast media (26, 29, 30). In the IsoCOR trial, **in Chapter 5**, we randomized 306 patients scheduled for coronary CTA at 3 centers in the Rijnmond region, between iso-osmolar iodixanol-270mg I/ml (Visipaque) and low-osmolar iopromide 300mg I/ml (Ultravist) injected at the same iodine delivery rate. When injected at a similar iodine delivery rate, we found that coronary lumen opacification by iodixanol-270 was not inferior to iopromide-300 (476 ± 160 Hounsfield Units (HU) vs 454 ± 158 HU). Contrary to earlier studies that suggested that iso-osmolar contrast media cause less heart rate acceleration and arrhythmia with potential benefits to cardiac imaging (24, 27, 31, 32), we found that although in the iodixanol-270 group patients experienced less heat discomfort (72% vs. 86%), no differences in heart rate, heart rhythm, or image quality were observed.

CT myocardial perfusion imaging in stable angina

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

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

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

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

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

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

Coronary CT angiography in suspected acute coronary syndrome

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

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

The previously published CT-STAT trial compared coronary CT angiography with nuclear myocardial perfusion imaging as initial tests in the management of patients with acute chest pain(51). Investigators reported a reduction of 54% in time to diagnosis and 38% lower costs of ED care with CT. In the ACRIN-PA trial investigators left decisions to perform a diagnostic test in the standard care group to the discretion of the treating physicians(53). The study demonstrated that low-risk patients could be safely discharged with early coronary CT angiography twice as often and CAD was more likely to be diagnosed with CT. The ROMICAT-2 trial, also included a cost-analysis, demonstrating a reduction of the median length of hospital stay from 26.7 to 8.6 hours with early coronary CT angiography and a 4-fold higher discharge rate from the ED without increasing medical expenditure(52). Since the completion of these trials standard optimal care has changed considerably with the introduction of high sensitive troponin assays. These new assays are more sensitive and reach negative predictive values of >97% for myocardial infarction within three hours (9, 10). Hs-troponin allows fast and accurate exclusion of ACS in a substantial proportion of low to intermediate risk patients, obviating the need for prolonged observation and in-hospital diagnostic testing in the absence of elevated high sensitivity cardiac biomarkers or suggestive ECG abnormalities (55-58).

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

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

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

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

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

FUTURE PERSPECTIVES

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

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

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

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

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

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

Technical developments of functional assessments in cardiac CT

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

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

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

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

REFERENCES

1. Ghoshhajra BB, Takx RAP, Staziaki PV, Vadvala H, Kim P, Neilan TG, et al. Clinical implementation of an emergency department coronary computed tomographic angiography protocol for triage of patients with suspected acute coronary syndrome. Eur Radiol. 2017;27(7):2784-93.
2. Sun Z, Ng KH. Diagnostic value of coronary CT angiography with prospective ECG-gating in the diagnosis of coronary artery disease: a systematic review and meta-analysis. Int J Cardiovasc Imaging. 2012;28(8):2109-19.
3. Meijboom WB, Meijs MF, Schuijf JD, Cramer MJ, Mollet NR, van Mieghem CA, et al. Diagnostic accuracy of 64-slice computed tomography coronary angiography: a prospective, multicenter, multivendor study. J Am Coll Cardiol. 2008;52(25):2135-44.
4. Mowatt G, Cook JA, Hillis GS, Walker S, Fraser C, Jia X, et al. 64-Slice computed tomography angiography in the diagnosis and assessment of coronary artery disease: systematic review and meta-analysis. Heart. 2008;94(11):1386-93.
5. Salavati A, Radmanesh F, Heidari K, Dwamena BA, Kelly AM, Cronin P. Dual-source computed tomography angiography for diagnosis and assessment of coronary artery disease: systematic review and meta-analysis. J Cardiovasc Comput Tomogr. 2012;6(2):78-90.
6. Guo SL, Guo YM, Zhai YN, Ma B, Wang P, Yang KH. Diagnostic accuracy of first generation dual-source computed tomography in the assessment of coronary artery disease: a meta-analysis from 24 studies. Int J Cardiovasc Imaging. 2011;27(6):755-71.
7. Task Force M, Montalescot G, Sechtem U, Achenbach S, Andreotti F, Arden C, et al. 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. Eur Heart J. 2013;34(38):2949-3003.
8. Fihn SD, Gardin JM, Abrams J, Berra K, Blankenship JC, Dallas AP, et al. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. Circulation. 2012;126(25):e354-471.
9. Reichlin T, Hochholzer W, Bassetti S, Steuer S, Stelzig C, Hartwiger S, et al. Early diagnosis of myocardial infarction with sensitive cardiac troponin assays. N Engl J Med. 2009;361(9):858-67.
10. Keller T, Zeller T, Peetz D, Tzikas S, Roth A, Czyz E, et al. Sensitive troponin I assay in early diagnosis of acute myocardial infarction. N Engl J Med. 2009;361(9):868-77.
11. Diamond GA, Forrester JS. Analysis of probability as an aid in the clinical diagnosis of coronary-artery disease. N Engl J Med. 1979;300(24):1350-8.
12. Douglas PS, Hoffmann U, Patel MR, Mark DB, Al-Khalidi HR, Cavanaugh B, et al. Outcomes of Anatomical versus Functional Testing for Coronary Artery Disease. N Engl J Med. 2015;372:1291-300.
13. investigators S-H. CT coronary angiography in patients with suspected angina due to coronary heart disease (SCOT-HEART): an open-label, parallel-group, multicentre trial. Lancet. 2015;385:2383-91.
14. Shaw LJ, Bairey Merz CN, Pepine CJ, Reis SE, Bittner V, Kelsey SF, et al. Insights from the NHLBI-Sponsored Women's Ischemia Syndrome Evaluation (WISE) Study: Part I: gender differences in traditional and novel risk factors, symptom evaluation, and gender-optimized diagnostic strategies. J Am Coll Cardiol. 2006;47(3 Suppl):S4-S20.

15. Douglas PS, Ginsburg GS. The evaluation of chest pain in women. N Engl J Med. 1996;334(20):1311-5.
16. Kwok Y, Kim C, Grady D, Segal M, Redberg R. Meta-analysis of exercise testing to detect coronary artery disease in women. Am J Cardiol. 1999;83(5):660-6.
17. Shaw LJ, Mieres JH, Hendel RH, Boden WE, Gulati M, Veledar E, et al. Comparative effectiveness of exercise electrocardiography with or without myocardial perfusion single photon emission computed tomography in women with suspected coronary artery disease: results from the What Is the Optimal Method for Ischemia Evaluation in Women (WOMEN) trial. Circulation. 2011;124(11):1239-49.
18. Mieres JH, Shaw LJ, Arai A, Budoff MJ, Flamm SD, Hundley WG, et al. Role of noninvasive testing in the clinical evaluation of women with suspected coronary artery disease: Consensus statement from the Cardiac Imaging Committee, Council on Clinical Cardiology, and the Cardiovascular Imaging and Intervention Committee, Council on Cardiovascular Radiology and Intervention, American Heart Association. Circulation. 2005;111(5):682-96.
19. Detry JM, Kapita BM, Cosyns J, Sottiaux B, Brasseur LA, Rousseau MF. Diagnostic value of history and maximal exercise electrocardiography in men and women suspected of coronary heart disease. Circulation. 1977;56(5):756-61.
20. Patel H, Rosengren A, Ekman I. Symptoms in acute coronary syndromes: does sex make a difference? Am Heart J. 2004;148(1):27-33.
21. Shaw LJ, Shaw RE, Merz CN, Brindis RG, Klein LW, Nallamothu B, et al. Impact of ethnicity and gender differences on angiographic coronary artery disease prevalence and in-hospital mortality in the American College of Cardiology-National Cardiovascular Data Registry. Circulation. 2008;117(14):1787-801.
22. Pagidipati NJ, Hemal K, Coles A, Mark DB, Dolor RJ, Pellikka PA, et al. Sex Differences in Functional and CT Angiography Testing in Patients With Suspected Coronary Artery Disease. J Am Coll Cardiol. 2016;67(22):2607-16.
23. Leschka S, Stolzmann P, Schmid FT, Scheffel H, Stinn B, Marincek B, et al. Low kilovoltage cardiac dual-source CT: attenuation, noise, and radiation dose. Eur Radiol. 2008;18(9):1809-17.
24. Becker CR, Vanzulli A, Fink C, de Faveri D, Fedeli S, Dore R, et al. Multicenter comparison of high concentration contrast agent iomeprol-400 with iso-osmolar iodixanol-320: contrast enhancement and heart rate variation in coronary dual-source computed tomographic angiography. Invest Radiol. 2011;46(7):457-64.
25. Chartrand-Lefebvre C, White CS, Bhalla S, Mayo-Smith WW, Prenovault J, Vydareny KH, et al. Comparison of the effect of low- and iso-osmolar contrast agents on heart rate during chest CT angiography: results of a prospective randomized multicenter study. Radiology. 2011;258(3):930-7.
26. Nakazato R, Arsanjani R, Shalev A, Leipsic JA, Gransar H, Lin FY, et al. Diagnostic Accuracy, Image Quality, and Patient Comfort for Coronary CT Angiography Performed Using Iso-Osmolar versus Low-Osmolar Iodinated Contrast: A Prospective International Multicenter Randomized Controlled Trial. Acad Radiol. 2016;23(6):743-51.
27. Svensson A, Ripsweden J, Ruck A, Aspelin P, Cederlund K, Brismar BT. Heart rate variability and heat sensation during CT coronary angiography: Low-osmolar versus iso-osmolar contrast media. Acta Radiol. 2010;51(7):722-6.
28. Christensen JD, Meyer LT, Hurwitz LM, Boll DT. Effects of iopamidol-370 versus iodixanol-320 on coronary contrast, branch depiction, and heart rate variability in dual-source coronary MDCT angiography. AJR Am J Roentgenol. 2011;197(3):W445-51.

29. Achenbach S, Paul JF, Laurent F, Becker HC, Rengo M, Caudron J, et al. Comparative assessment of image quality for coronary CT angiography with iobitridol and two contrast agents with higher iodine concentrations: iopromide and iomeprol. A multicentre randomized double-blind trial. Eur Radiol. 2016.
30. Andreini D, Pontone G, Mushtaq S, Bartorelli AL, Conte E, Bertella E, et al. Coronary stent evaluation with coronary computed tomographic angiography: comparison between low-osmolar, high-iodine concentration iomeprol-400 and iso-osmolar, lower-iodine concentration iodixanol-320. J Cardiovasc Comput Tomogr. 2014;8(1):44-51.
31. Chinnaiyan KM, McCullough PA. Optimizing outcomes in coronary CT imaging. Rev Cardiovasc Med. 2008;9(4):215-24.
32. Ozbulbul NI, Yurdakul M, Tola M. Comparison of a low-osmolar contrast medium, iopamidol, and an iso-osmolar contrast medium, iodixanol, in MDCT coronary angiography. Coron Artery Dis. 2010;21(7):414-9.
33. Rossi A, Papadopoulou SL, Pugliese F, Russo B, Dharampal AS, Dedic A, et al. Quantitative computed tomographic coronary angiography: does it predict functionally significant coronary stenoses? Circ Cardiovasc Imaging. 2014;7(1):43-51.
34. Techasith T, Cury RC. Stress myocardial CT perfusion: an update and future perspective. JACC Cardiovasc Imaging. 2011;4(8):905-16.
35. Kurata A, Mochizuki T, Koyama Y, Haraikawa T, Suzuki J, Shigematsu Y, et al. Myocardial perfusion imaging using adenosine triphosphate stress multi-slice spiral computed tomography: alternative to stress myocardial perfusion scintigraphy. Circ J. 2005;69(5):550-7.
36. Bischoff B, Bamberg F, Marcus R, Schwarz F, Becker HC, Becker A, et al. Optimal timing for first-pass stress CT myocardial perfusion imaging. Int J Cardiovasc Imaging. 2013;29(2):435-42.
37. Rochitte CE, George RT, Chen MY, Arbab-Zadeh A, Dewey M, Miller JM, et al. Computed tomography angiography and perfusion to assess coronary artery stenosis causing perfusion defects by single photon emission computed tomography: the CORE320 study. Eur Heart J. 2014;35(17):1120-30.
38. Bettencourt N, Ferreira ND, Leite D, Carvalho M, Ferreira Wda S, Schuster A, et al. CAD detection in patients with intermediate-high pre-test probability: low-dose CT delayed enhancement detects ischemic myocardial scar with moderate accuracy but does not improve performance of a stress-rest CT perfusion protocol. JACC Cardiovasc Imaging. 2013;6(10):1062-71.
39. Blankstein R, Shturman LD, Rogers IS, Rocha-Filho JA, Okada DR, Sarwar A, et al. Adenosine-induced stress myocardial perfusion imaging using dual-source cardiac computed tomography. J Am Coll Cardiol. 2009;54(12):1072-84.
40. Bamberg F, Becker A, Schwarz F, Marcus RP, Greif M, von Ziegler F, et al. Detection of hemodynamically significant coronary artery stenosis: incremental diagnostic value of dynamic CT-based myocardial perfusion imaging. Radiology. 2011;260(3):689-98.
41. Jin KN, De Cecco CN, Caruso D, Tesche C, Spandorfer A, Varga-Szemes A, et al. Myocardial perfusion imaging with dual energy CT. Eur J Radiol. 2016;85(10):1914-21.
42. Danad I, Szymonifka J, Schulman-Marcus J, Min JK. Static and dynamic assessment of myocardial perfusion by computed tomography. Eur Heart J Cardiovasc Imaging. 2016;17(8):836-44.
43. Duncker DJ, Koller A, Merkus D, Canty JM, Jr. Regulation of coronary blood flow in health and ischemic heart disease. Prog Cardiovasc Dis. 2015;57(5):409-22.
44. Bache RJ, Schwartz JS. Effect of perfusion pressure distal to a coronary stenosis on transmural myocardial blood flow. Circulation. 1982;65(5):928-35.
45. George RT, Arbab-Zadeh A, Miller JM, Kitagawa K, Chang HJ, Bluemke DA, et al. Adenosine stress 64- and 256-row detector computed tomography angiography and perfusion imaging: a pilot

study evaluating the transmural extent of perfusion abnormalities to predict atherosclerosis causing myocardial ischemia. Circ Cardiovasc Imaging. 2009;2(3):174-82.
46. Yang DH, Kim YH, Roh JH, Kang JW, Han D, Jung J, et al. Stress Myocardial Perfusion CT in Patients Suspected of Having Coronary Artery Disease: Visual and Quantitative Analysis-Validation by Using Fractional Flow Reserve. Radiology. 2015;276(3):715-23.
47. De Bruyne B, Pijls NH, Kalesan B, Barbato E, Tonino PA, Piroth Z, et al. Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. N Engl J Med. 2012;367(11):991-1001.
48. Tonino PA, De Bruyne B, Pijls NH, Siebert U, Ikeno F, van' t Veer M, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. N Engl J Med. 2009;360(3):213-24.
49. Lubbers M, Dedic A, Coenen A, Galema T, Akkerhuis J, Bruning T, et al. Calcium imaging and selective computed tomography angiography in comparison to functional testing for suspected coronary artery disease: the multicentre, randomized CRESCENT trial. Eur Heart J. 2016;37(15):1232-43.
50. Jorgensen ME, Andersson C, Norgaard BL, Abdulla J, Shreibati JB, Torp-Pedersen C, et al. Functional Testing or Coronary Computed Tomography Angiography in Patients With Stable Coronary Artery Disease. J Am Coll Cardiol. 2017;69(14):1761-70.
51. Goldstein JA, Chinnaiyan KM, Abidov A, Achenbach S, Berman DS, Hayes SW, et al. The CT-STAT (Coronary Computed Tomographic Angiography for Systematic Triage of Acute Chest Pain Patients to Treatment) trial. J Am Coll Cardiol. 2011;58(14):1414-22.
52. Hoffmann U, Truong QA, Schoenfeld DA, Chou ET, Woodard PK, Nagurney JT, et al. Coronary CT angiography versus standard evaluation in acute chest pain. N Engl J Med. 2012;367(4):299-308.
53. Litt HI, Gatsonis C, Snyder B, Singh H, Miller CD, Entrikin DW, et al. CT angiography for safe discharge of patients with possible acute coronary syndromes. N Engl J Med. 2012;366(15):1393-403.
54. Cury RC, Feuchtner GM, Batlle JC, Pena CS, Janowitz W, Katzen BT, et al. Triage of patients presenting with chest pain to the emergency department: implementation of coronary CT angiography in a large urban health care system. AJR Am J Roentgenol. 2013;200(1):57-65.
55. Reichlin T, Schindler C, Drexler B, Twerenbold R, Reiter M, Zellweger C, et al. One-hour rule-out and rule-in of acute myocardial infarction using high-sensitivity cardiac troponin T. Arch Intern Med. 2012;172(16):1211-8.
56. Haaf P, Drexler B, Reichlin T, Twerenbold R, Reiter M, Meissner J, et al. High-sensitivity cardiac troponin in the distinction of acute myocardial infarction from acute cardiac noncoronary artery disease. Circulation. 2012;126(1):31-40.
57. Body R, Carley S, McDowell G, Jaffe AS, France M, Cruickshank K, et al. Rapid exclusion of acute myocardial infarction in patients with undetectable troponin using a high-sensitivity assay. J Am Coll Cardiol. 2011;58(13):1332-9.
58. Haaf P, Reichlin T, Twerenbold R, Hoeller R, Rubini Gimenez M, Zellweger C, et al. Risk stratification in patients with acute chest pain using three high-sensitivity cardiac troponin assays. Eur Heart J. 2014;35(6):365-75.
59. Schoen C, Osborn R, Squires D, Doty MM. Access, affordability, and insurance complexity are often worse in the United States compared to ten other countries. Health Aff (Millwood). 2013;32(12):2205-15.
60. Schafer W, Kroneman M, Boerma W, van den Berg M, Westert G, Deville W, et al. The Netherlands: health system review. Health Syst Transit. 2010;12(1):v-xxvii, 1-228.

61. Sun BC, Hsia RY, Weiss RE, Zingmond D, Liang LJ, Han W, et al. Effect of emergency department crowding on outcomes of admitted patients. Ann Emerg Med. 2013;61(6):605-11 e6.
62. Hemingway H, Langenberg C, Damant J, Frost C, Pyorala K, Barrett-Connor E. Prevalence of angina in women versus men: a systematic review and meta-analysis of international variations across 31 countries. Circulation. 2008;117(12):1526-36.
63. Truong QA, Hayden D, Woodard PK, Kirby R, Chou ET, Nagurney JT, et al. Sex differences in the effectiveness of early coronary computed tomographic angiography compared with standard emergency department evaluation for acute chest pain: the rule-out myocardial infarction with Computer-Assisted Tomography (ROMICAT)-II Trial. Circulation. 2013;127(25):2494-502.
64. Reiter M, Twerenbold R, Reichlin T, Benz B, Haaf P, Meissner J, et al. Early diagnosis of acute myocardial infarction in patients with pre-existing coronary artery disease using more sensitive cardiac troponin assays. Eur Heart J. 2012;33(8):988-97.
65. Ferencik M, Hoffmann U, Bamberg F, Januzzi JL. Highly sensitive troponin and coronary computed tomography angiography in the evaluation of suspected acute coronary syndrome in the emergency department. Eur Heart J. 2016;37(30):2397-405.
66. Shaw LJ, Bugiardini R, Merz CN. Women and ischemic heart disease: evolving knowledge. J Am Coll Cardiol. 2009;54(17):1561-75.
67. Magid DJ, Wang Y, Herrin J, McNamara RL, Bradley EH, Curtis JP, et al. Relationship between time of day, day of week, timeliness of reperfusion, and in-hospital mortality for patients with acute ST-segment elevation myocardial infarction. JAMA. 2005;294(7):803-12.
68. Jneid H, Fonarow GC, Cannon CP, Palacios IF, Kilic T, Moukarbel GV, et al. Impact of time of presentation on the care and outcomes of acute myocardial infarction. Circulation. 2008;117(19):2502-9.
69. Boden WE, O'Rourke R A, Teo KK, Hartigan PM, Maron DJ, Kostuk W, et al. The evolving pattern of symptomatic coronary artery disease in the United States and Canada: baseline characteristics of the Clinical Outcomes Utilizing Revascularization and Aggressive DruG Evaluation (COURAGE) trial. Am J Cardiol. 2007;99(2):208-12.
70. Hussain ST, Paul M, Plein S, McCann GP, Shah AM, Marber MS, et al. Design and rationale of the MR-INFORM study: stress perfusion cardiovascular magnetic resonance imaging to guide the management of patients with stable coronary artery disease. J Cardiovasc Magn Reson. 2012;14:65.
71. Danad I, Raijmakers PG, Driessen RS, Leipsic J, Raju R, Naoum C, et al. Comparison of Coronary CT Angiography, SPECT, PET, and Hybrid Imaging for Diagnosis of Ischemic Heart Disease Determined by Fractional Flow Reserve. JAMA Cardiol. 2017;2(10):1100-7.
72. Group ITR, Maron DJ, Hochman JS, O'Brien SM, Reynolds HR, Boden WE, et al. International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA) trial: Rationale and design. Am Heart J. 2018;201:124-35.
73. Higgins JP, Higgins JA, Williams G. Stress-induced abnormalities in myocardial perfusion imaging that are not related to perfusion but are of diagnostic and prognostic importance. Eur J Nucl Med Mol Imaging. 2007;34(4):584-95.
74. Feuchtner G, Goetti R, Plass A, Wieser M, Scheffel H, Wyss C, et al. Adenosine stress high-pitch 128-slice dual-source myocardial computed tomography perfusion for imaging of reversible myocardial ischemia: comparison with magnetic resonance imaging. Circ Cardiovasc Imaging. 2011;4(5):540-9.
75. Min JK, Leipsic J, Pencina MJ, Berman DS, Koo BK, van Mieghem C, et al. Diagnostic accuracy of fractional flow reserve from anatomic CT angiography. JAMA. 2012;308(12):1237-45.

76. Norgaard BL, Leipsic J, Gaur S, Seneviratne S, Ko BS, Ito H, et al. Diagnostic performance of noninvasive fractional flow reserve derived from coronary computed tomography angiography in suspected coronary artery disease: the NXT trial (Analysis of Coronary Blood Flow Using CT Angiography: Next Steps). J Am Coll Cardiol. 2014;63(12):1145-55.
77. Douglas PS, De Bruyne B, Pontone G, Patel MR, Norgaard BL, Byrne RA, et al. 1-Year Outcomes of FFRCT-Guided Care in Patients With Suspected Coronary Disease: The PLATFORM Study. J Am Coll Cardiol. 2016;68(5):435-45.
78. Coenen A, Rossi A, Lubbers MM, Kurata A, Kono AK, Chelu RG, et al. Integrating CT Myocardial Perfusion and CT-FFR in the Work-Up of Coronary Artery Disease. JACC Cardiovasc Imaging. 2017.
79. Ko BS, Cameron JD, Meredith IT, Leung M, Antonis PR, Nasis A, et al. Computed tomography stress myocardial perfusion imaging in patients considered for revascularization: a comparison with fractional flow reserve. Eur Heart J. 2012;33(1):67-77.
80. Redberg RF. Coronary CT angiography for acute chest pain. N Engl J Med. 2012;367(4):375-6.

NEDERLANDSE SAMENVATTING

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

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

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

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

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

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

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

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

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

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

CT-myocard perfusie bij patiënten met stabiele angina pectoris

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

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

Het doel van het uitvoeren van niet-invasieve diagnostische onderzoeken in patiënten met een verdenking op een vernauwing in de kransslagaders is om op een betrouwbare wijze vernauwingen uit te sluiten. Een invasieve katheterisatie (angiografie) waarbij uiteindelijk géén vernauwingen zichtbaar blijken te zijn, beschouwen we als een falende poortwachters functie van de diagnostische testen die hieraan vooraf zijn gegaan. In de CRESCENT-II studie was het primaire eindpunt het aantal invasieve katheterisaties zónder significant vernauwde kransslagaders (13), dit aantal bleek significant lager in de CT groep vergeleken met de standaard functionele test (1.5% vs 7.2%). In 34% van de patiënten met een >50% vernauwing in één van de kransslagaders op CCTA werd myocard ischemie toch uitgesloten door middel van een perfusie scan (CT-MPI). Hiermee heeft CT-MPI een belangrijke rol in de CT-strategie als "poortwachter" voor doorverwijzing naar invasieve katheterisatie. In tegenstelling tot onze verwachtingen was het aantal invasieve katheterisaties niet verhoogd in de CT groep, daarnaast bleken in de CT groep een hoger aantal invasieve katheterisaties mét significante vernauwingen opgespoord te worden (88% vs 50%) (26-28). Tenslotte bleek een CT strategie sneller tot een diagnose te leiden en waren daar minder extra diagnostische testen voor nodig. Een nadeel van cardiale CT is de straling, met name CT-MPI gaat gepaard met een hogere stralingsdosis. In onze studie was de gemiddelde stralingsdosis van CT-MPI 10.6±6.3mSv. Maar omdat CT-MPI enkel nodig was in 22% van de CT patiënten, was de gemiddelde cumulatieve stralingsdosis in de CT groep 5.6±6.3mSv. Dit was hoger vergeleken met de functionele test groep, waarin de meesten primair een fietstest ondergingen en uiteindelijk slechts 37% een tweede test nodig had die straling betrof (nucleaire SPECT scan, danwel katheterisatie). De conclusie van de CRESCENT-II studie was dat bij patiënten met verdenking op vernauwde kransslagaders een cardiale CT, met stapsgewijze uitvoering van CT-calciumscan, CCTA, en CT-MPI, een snel, veilig en efficiënt alternatief is voor de functionele test.

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

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

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

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

REFERENTIES

1. Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M, Jr., Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. J Am Coll Cardiol. 1990;15(4):827-32.
2. Guerci AD, Spadaro LA, Goodman KJ, Lledo-Perez A, Newstein D, Lerner G, et al. Comparison of electron beam computed tomography scanning and conventional risk factor assessment for the prediction of angiographic coronary artery disease. J Am Coll Cardiol. 1998;32(3):673-9.
3. Keelan PC, Bielak LF, Ashai K, Jamjoum LS, Denktas AE, Rumberger JA, et al. Long-term prognostic value of coronary calcification detected by electron-beam computed tomography in patients undergoing coronary angiography. Circulation. 2001;104(4):412-7.
4. Budoff MJ, Shaw LJ, Liu ST, Weinstein SR, Mosler TP, Tseng PH, et al. Long-term prognosis associated with coronary calcification: observations from a registry of 25,253 patients. J Am Coll Cardiol. 2007;49(18):1860-70.
5. Shaw LJ, Giambrone AE, Blaha MJ, Knapper JT, Berman DS, Bellam N, et al. Long-Term Prognosis After Coronary Artery Calcification Testing in Asymptomatic Patients: A Cohort Study. Ann Intern Med. 2015;163(1):14-21.
6. Nieman K, Galema TW, Neefjes LA, Weustink AC, Musters P, Moelker AD, et al. Comparison of the value of coronary calcium detection to computed tomographic angiography and exercise testing in patients with chest pain. Am J Cardiol. 2009;104(11):1499-504.
7. Mouden M, Timmer JR, Reiffers S, Oostdijk AH, Knollema S, Ottervanger JP, et al. Coronary artery calcium scoring to exclude flow-limiting coronary artery disease in symptomatic stable patients at low or intermediate risk. Radiology. 2013;269(1):77-83.
8. Al-Mallah MH, Qureshi W, Lin FY, Achenbach S, Berman DS, Budoff MJ, et al. Does coronary CT angiography improve risk stratification over coronary calcium scoring in symptomatic patients with suspected coronary artery disease? Results from the prospective multicenter international CONFIRM registry. Eur Heart J Cardiovasc Imaging. 2014;15(3):267-74.
9. Sun Z, Ng KH. Diagnostic value of coronary CT angiography with prospective ECG-gating in the diagnosis of coronary artery disease: a systematic review and meta-analysis. Int J Cardiovasc Imaging. 2012;28(8):2109-19.
10. von Ballmoos MW, Haring B, Juillerat P, Alkadhi H. Meta-analysis: diagnostic performance of low-radiation-dose coronary computed tomography angiography. Ann Intern Med. 2011;154(6):413-20.
11. Task Force M, Montalescot G, Sechtem U, Achenbach S, Andreotti F, Arden C, et al. 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. Eur Heart J. 2013;34(38):2949-3003.
12. Rossi A, Papadopoulou SL, Pugliese F, Russo B, Dharampal AS, Dedic A, et al. Quantitative computed tomographic coronary angiography: does it predict functionally significant coronary stenoses? Circ Cardiovasc Imaging. 2014;7(1):43-51.
13. Task Force on Myocardial Revascularization of the European Society of C, the European Association for Cardio-Thoracic S, European Association for Percutaneous Cardiovascular I, Kolh P, Wijns W, Danchin N, et al. Guidelines on myocardial revascularization. Eur J Cardiothorac Surg. 2010;38 Suppl:S1-S52.
14. Rossi A, Merkus D, Klotz E, Mollet N, de Feyter PJ, Krestin GP. Stress myocardial perfusion: imaging with multidetector CT. Radiology. 2014;270(1):25-46.

15. Diamond GA, Forrester JS. Analysis of probability as an aid in the clinical diagnosis of coronary-artery disease. N Engl J Med. 1979;300(24):1350-8.
16. Lloyd-Jones D, Adams R, Carnethon M, De Simone G, Ferguson TB, Flegal K, et al. Heart disease and stroke statistics--2009 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation. 2009;119(3):480-6.
17. Becker CR, Vanzulli A, Fink C, de Faveri D, Fedeli S, Dore R, et al. Multicenter comparison of high concentration contrast agent iomeprol-400 with iso-osmolar iodixanol-320: contrast enhancement and heart rate variation in coronary dual-source computed tomographic angiography. Invest Radiol. 2011;46(7):457-64.
18. Chartrand-Lefebvre C, White CS, Bhalla S, Mayo-Smith WW, Prenovault J, Vydareny KH, et al. Comparison of the effect of low- and iso-osmolar contrast agents on heart rate during chest CT angiography: results of a prospective randomized multicenter study. Radiology. 2011;258(3):930-7.
19. Nakazato R, Arsanjani R, Shalev A, Leipsic JA, Gransar H, Lin FY, et al. Diagnostic Accuracy, Image Quality, and Patient Comfort for Coronary CT Angiography Performed Using Iso-Osmolar versus Low-Osmolar Iodinated Contrast: A Prospective International Multicenter Randomized Controlled Trial. Acad Radiol. 2016;23(6):743-51.
20. Svensson A, Ripsweden J, Ruck A, Aspelin P, Cederlund K, Brismar BT. Heart rate variability and heat sensation during CT coronary angiography: Low-osmolar versus iso-osmolar contrast media. Acta Radiol. 2010;51(7):722-6.
21. Christensen JD, Meyer LT, Hurwitz LM, Boll DT. Effects of iopamidol-370 versus iodixanol-320 on coronary contrast, branch depiction, and heart rate variability in dual-source coronary MDCT angiography. AJR Am J Roentgenol. 2011;197(3):W445-51.
22. Duncker DJ, Koller A, Merkus D, Canty JM, Jr. Regulation of coronary blood flow in health and ischemic heart disease. Prog Cardiovasc Dis. 2015;57(5):409-22.
23. Bache RJ, Schwartz JS. Effect of perfusion pressure distal to a coronary stenosis on transmural myocardial blood flow. Circulation. 1982;65(5):928-35.
24. George RT, Arbab-Zadeh A, Miller JM, Kitagawa K, Chang HJ, Bluemke DA, et al. Adenosine stress 64- and 256-row detector computed tomography angiography and perfusion imaging: a pilot study evaluating the transmural extent of perfusion abnormalities to predict atherosclerosis causing myocardial ischemia. Circ Cardiovasc Imaging. 2009;2(3):174-82.
25. Yang DH, Kim YH, Roh JH, Kang JW, Han D, Jung J, et al. Stress Myocardial Perfusion CT in Patients Suspected of Having Coronary Artery Disease: Visual and Quantitative Analysis-Validation by Using Fractional Flow Reserve. Radiology. 2015;276(3):715-23.
26. Bettencourt N, Ferreira ND, Leite D, Carvalho M, Ferreira Wda S, Schuster A, et al. CAD detection in patients with intermediate-high pre-test probability: low-dose CT delayed enhancement detects ischemic myocardial scar with moderate accuracy but does not improve performance of a stress-rest CT perfusion protocol. JACC Cardiovasc Imaging. 2013;6(10):1062-71.
27. Jorgensen ME, Andersson C, Norgaard BL, Abdulla J, Shreibati JB, Torp-Pedersen C, et al. Functional Testing or Coronary Computed Tomography Angiography in Patients With Stable Coronary Artery Disease. J Am Coll Cardiol. 2017;69(14):1761-70.
28. Douglas PS, Hoffmann U, Patel MR, Mark DB, Al-Khalidi HR, Cavanaugh B, et al. Outcomes of Anatomical versus Functional Testing for Coronary Artery Disease. N Engl J Med. 2015;372:1291-300.
29. Goldstein JA, Chinnaiyan KM, Abidov A, Achenbach S, Berman DS, Hayes SW, et al. The CT-STAT (Coronary Computed Tomographic Angiography for Systematic Triage of Acute Chest Pain Patients to Treatment) trial. J Am Coll Cardiol. 2011;58(14):1414-22.

30. Hoffmann U, Truong QA, Schoenfeld DA, Chou ET, Woodard PK, Nagurney JT, et al. Coronary CT angiography versus standard evaluation in acute chest pain. N Engl J Med. 2012;367(4):299-308.
31. Litt HI, Gatsonis C, Snyder B, Singh H, Miller CD, Entrikin DW, et al. CT angiography for safe discharge of patients with possible acute coronary syndromes. N Engl J Med. 2012;366(15):1393-403.
32. Cury RC, Feuchtner GM, Batlle JC, Pena CS, Janowitz W, Katzen BT, et al. Triage of patients presenting with chest pain to the emergency department: implementation of coronary CT angiography in a large urban health care system. AJR Am J Roentgenol. 2013;200(1):57-65.
33. Truong QA, Hayden D, Woodard PK, Kirby R, Chou ET, Nagurney JT, et al. Sex differences in the effectiveness of early coronary computed tomographic angiography compared with standard emergency department evaluation for acute chest pain: the rule-out myocardial infarction with Computer-Assisted Tomography (ROMICAT)-II Trial. Circulation. 2013;127(25):2494-502.
34. Magid DJ, Wang Y, Herrin J, McNamara RL, Bradley EH, Curtis JP, et al. Relationship between time of day, day of week, timeliness of reperfusion, and in-hospital mortality for patients with acute ST-segment elevation myocardial infarction. JAMA. 2005;294(7):803-12.
35. Jneid H, Fonarow GC, Cannon CP, Palacios IF, Kilic T, Moukarbel GV, et al. Impact of time of presentation on the care and outcomes of acute myocardial infarction. Circulation. 2008;117(19):2502-9.