General Introduction and Outline of the Thesis

GENERAL INTRODUCTION

Coronary artery disease

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

Usual care of stable angina

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

Cardiac CT

Cardiac CT has emerged as an alternative modality for investigation of suspected CAD. It has been increasingly used over the past years, and rapid technological developments have led to improvement of spatial and temporal resolution. With the introduction of 64-slice CT scanners high diagnostic accuracy has been achieved and the reliability to detect and particularly to exclude significant CAD against ICA has been confirmed in numerous studies(13, 14).

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

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

Aims

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

OUTLINE OF THE THESIS

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

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

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

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

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