The role of detailed coronary atherosclerosis evaluation by CT in ischemic heart disease

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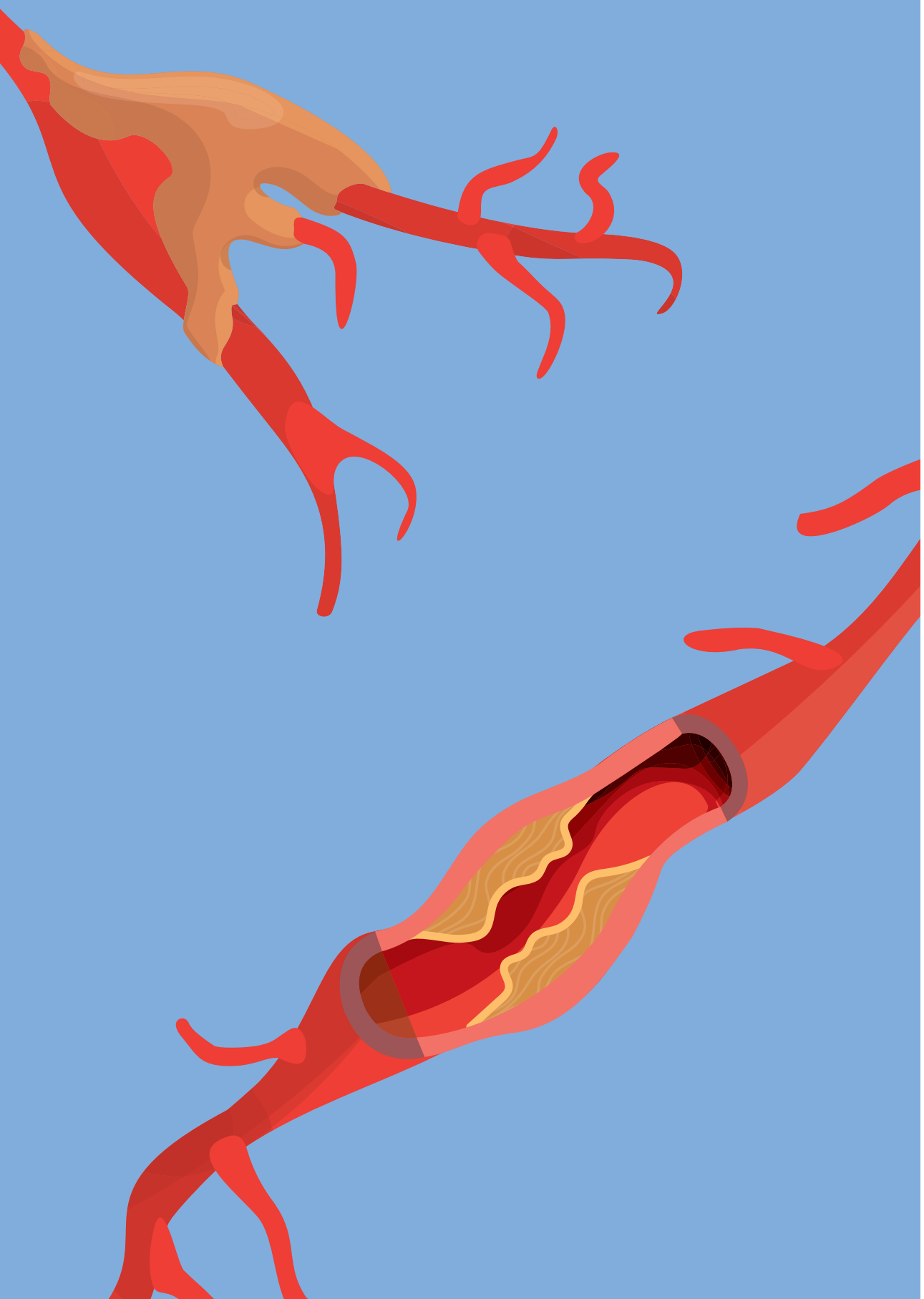

Chapter 1

General introduction

Coronary artery disease is one of the major causes of death within the Netherlands.[1] Prediction of the presence of coronary atherosclerosis is currently based on age, cardiovascular risk factors, and cardiac symptoms. Lifestyle optimization and medical treatment of hypertension, hypercholesterolemia, and diabetes are initiated if the estimated risk is high. These strategies aim to reduce the risk of future myocardial infarction, stroke, peripheral artery disease, and other vascular events. In patients presenting with chest pain symptoms, further diagnostic testing can be performed to detect myocardial ischemia, using exercise ECG or cardiac stress tests. However, these strategies have demonstrated to be imprecise in identifying individuals that will experience cardiovascular events.[2,3] Most heart attacks occur in patients that were not considered high risk based on their clinical risk profile.[3] The majority antecedently performed stress tests are normal in patients experiencing myocardial infarction or cardiac death.[3] Also, more than half of patients do not report symptoms suggestive of myocardial ischemia during or prior to their myocardial infarction.[4] Acute coronary events result from an interplay between coronary atherosclerosis, inflammation, and plaque destabilization, which lead to vascular thrombosis under certain conditions.[5] With few exceptions, coronary atherosclerosis is required for acute coronary syndromes to occur.[6] Cardiovascular risk factors enhance the risk for the development of atherosclerosis but are not one to one correlated. Further, stress tests only detect severely stenotic coronary atherosclerosis but will not recognize the underlying atherosclerotic burden if it does not reach the threshold to cause myocardial ischemia.

Role of cardiac CT in the evaluation of coronary artery disease

Coronary computed tomography angiography (CCTA) allows direct, noninvasive visualization of the coronary artery and the presence and extent of coronary atherosclerosis. The location, extent, severity, and composition of atherosclerosis can be visually determined and provide information for the diagnosis of chest pain symptoms and for prognosis (FIGURE 1). Coronary plaque assessment by CT predicts all-cause mortality, cardiac death, or myocardial infarction.[7-9]

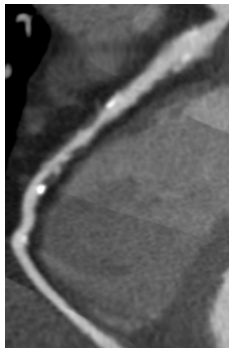

Figure 1. A right coronary artery by coronary computed tomography angiography. There is a high burden of non-calcified and mixed coronary plaques throughout the entire vessel, and a 50-70% luminal narrowing in the mid segment.

In the most simple fashion, coronary plaque is scored by the number of coronary arteries having obstructive stenosis (≥50% luminal narrowing) with special consideration of the left main or proximal left anterior descending coronary artery involvement. With each increase in vessel involvement, the atherosclerotic events risk increases.[8] Importantly, risk estimation by cardiac CT has demonstrated to be superior compared with risk estimation based on clinical variables only.[10] This means that the future risk that any individual will experience a heart attack can be more precisely estimated based on the plaque phenotype by CCTA than based on age, sex, or any present clinical risk factors. For example, extensive coronary atherosclerosis in absence of a high clinical risk profile is prognostically important and needs to be treated aggressively. Also, absence of atherosclerosis – even with present risk factors – conveys an excellent prognosis, with only 1% death, myocardial infarction or coronary revascularization at 3.5 years of follow-up.[9] The presence of extensive disease equals event rates of secondary prevention cohorts (patients that have already had any cardiovascular event) and should therefore ideally be treated equally intensive.[11]

Different components of the atherosclerotic burden provide independent prognostic value and therefore integrated clinical risk scores have been developed. The Leiden score for instance is described within this thesis and combines the full information of whole-heart coronary atherosclerosis imaging into a single score to help the physician determine the needed intensity of medical treatment. It has been consistently observed that a linear stepwise increase in risk exists with each increase in severity/extent of coronary atherosclerosis.[12] A simple measure as plaque volume has emerged as a very powerful biomarker to predict prognosis, beyond risk scoring done with clinically available factors. (Figure 2).

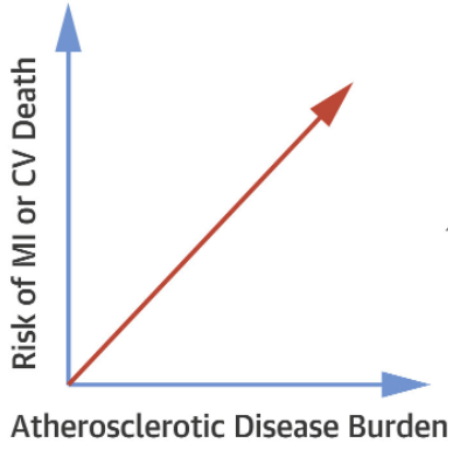

Figure 2. Linear relationship between atherosclerotic plaque burden and risk. The figure describes the linear increase in risk for myocardial infarction or cardiovascular death for each increment in plaque burden. MI, myocardial infarction; CV, cardiovascular

The unique capability of CCTA is to detect non-obstructive coronary artery disease, which generally does not relate with cardiac symptoms or positive stress tests. Non-obstructive plaque is the earliest presentation of the disease and conveys increased cardiovascular risk compared with a normal CCTA / absence of disease.[13,14] CCTA can identify patients at an early stage to provide the opportunity to intervene early. Although the associated risk of non-obstructive plaque is lower than that of obstructive plaques, non-obstructive stenosis is more prevalent. The larger the number of (non-obstructive) plaques, the larger the likelihood that one will destabilize, form thrombosis, and cause myocardial infarction.[12] In recent observations of stable patients undergoing CCTA, myocardial infarction occurred in patients with at maximum non-obstructive stenosis on their prior CT scan in approximately 50%.[15-17]

Whole-heart, detailed, coronary atherosclerotic plaque evaluation has become possible the recent years by (semi-) automated software packages.[15] This allowed quantification of a plaque phenotype of special prognostic importance: high risk, or vulnerable plaque. On CT, high risk plaques consist of a large necrotic core, show positive remodeling and contain small, spotty calcifications.[18] These plaques resemble the histopathological equivalent of thin cap fibroatheroma which consists of a large inflamed necrotic core with a very thin (<65 um) fibrous cap.[19] Thin cap fibroatheromas are considered to be precursors of acute coronary syndromes. In CT, high risk plaque within the coronary tree is independently associated with acute coronary syndrome.[15,20] However, prompt revascularization of high risk plaques is likely not needed, because the vast majority will stabilize over time by increase the content of calcium and decrease in size of the necrotic core.[21] Whether revascularization of high risk plaque improves prognosis is currently unknown and has not been shown beneficial in trials. The stabilization rate of high risk plaques by medical therapy is topic of ongoing research, and is also described within this thesis. Figure 3 shows a comparison of detailed quantification of coronary calcium and shows the histological comparisons of these plaques.

In patients with anginal chest pain symptoms, the pursue is to identify atherosclerotic plaques that cause reduced downstream blood flow eventually causing myocardial ischemia. Fractional flow reserve (FFR) has emerged as an important invasively measured surrogate of myocardial ischemia, and lesions with abnormal FFR have been considered revascularization candidates.[22,23] Detailed atherosclerotic assessment by CCTA has shown to correlate with myocardial ischemia or FFR.[24] Stenosis severity, overall plaque burden, low-attenuation plaque, high risk plaque, are some of these features. Ongoing research discusses the accuracy of a comprehensive collection of plaque features to identify ischemic coronary arteries.[25]

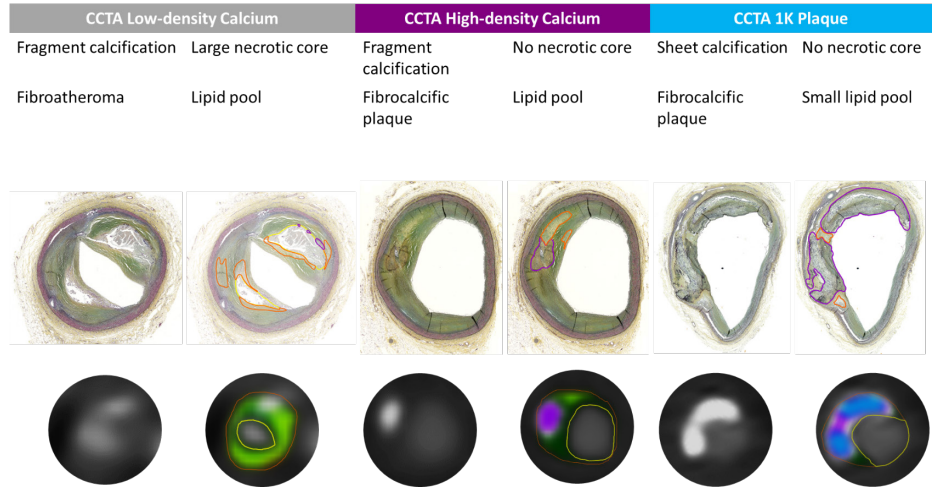

Figure 3. Comparison of calcium between histopathology and CCTA. The left panel represents low-density calcium by CCTA (plaque with 350 to 700 Hounsfield Units [HU], as shown as white-gray color). The surrounding non-calcified plaque reduces the attenuation of the smaller calcified spot. Histopathological comparison shows a fibroatheroma with small fragments of calcification (purple line) surrounded by lipid pool (orange line) and necrotic cores (yellow line). The middle panel represents high-density calcium by CCTA (plaque with 701-1000 HU, as shown as purple color). Histopathology shows a fibrocalcific plaque with a larger calcification (purple line) and small spots of lipid pool (orange line). The right panel represents 1K plaque by CCTA (plaque with >1000 HU). Histopathology shows a fibrocalcific plaque with large sheets of calcification (purple line) with almost no lipid pool (orange line). The figure shows a trend of higher calcium attenuation by CT with increasing size of histopathological calcium sheets.

Clinical implications of myocardial perfusion and adipose tissue quantification by cardiac CT

Stress myocardial perfusion imaging aims to detect the presence and extent of myocardial ischemia and is usually done using nuclear imaging, cardiac magnetic resonance or stress echocardiography. Recent improvements in CT technology have allowed myocardial enhancement imaging to detect ischemia as well. This is a novel application not clinically used on a routine basis, but diagnostic accuracy studies of CT myocardial perfusion imaging have been promising.[26] An advantage is combined imaging with CCTA and subsequent CT perfusion when anatomical stenosis is detected of intermediate severity. Clinical effectiveness and safety of this strategy is largely unknown and this thesis describes our experiences with this technique.

Cardiac CT enables quantification of the epicardial adipose tissue, and endocrinologically active organ that exerts beneficial and harmful effects on the adjacent myocardium.[27] Ongoing research is evaluation its effects on the presence and severity of atrial fibrillation.

Outline of the thesis

Part 1 of the thesis describes an introduction of role of cardiac CT in the evaluation of coronary artery disease. In **Chapter 2** coronary plaque information (stenosis severity, plaque location, and composition) from the entire coronary tree is combined by means of machine learning to assess the accuracy to predict future myocardial infarctions and death. **Chapter 3** describes the development and validation of the Leiden CCTA risk score for purposes of risk stratification and compares its prognostic accuracy with clinical indices and scores based on standard reads of CCTA scans. **Chapter 4** shows four clinical cases where high risk plaques are illustrated by detailed atherosclerotic assessment and subsequent clinical course is followed. **Chapter 5** presents a comprehensive review of the literature how CCTA should be applied in risk stratification for ischemic events and how CCTA performs compared with other currently used strategies. **Chapter 6** evaluates the association of dyspnea as a presenting symptom with the exent of coronary artery disease and associated cardiovascular prognosis. **Chapter 7** evaluates whether very dense coronary calcium is associated with a reduced risk for future acute coronary syndromes. In **Chapter 8** plaque progression on serial CT is measured, and subsequently a threshold of important plaque progression is defined based on its prognostic value for major adverse cardiovascular events. **Chapter 9** presents the ability of serial CCTA is investigated changes in plaque phenotype over time. Specifically, the change in plaque composition according to statin use is evaluated. **Part 2** describes the clinical implications of CT myocardial perfusion imaging and quantification of adipose tissue. **Chapter 10** investigated the clinical value of a combined protocol of CCTA followed by CT myocardial perfusion when significant stenosis is observed. Patients were followed over time and rates of events, invasive angiography and revascularization procedures were determined. Finally, **Chapter 11** describes the value of left atrial adipose tissue quantification to distinguish patients with sinus rhythm from atrial fibrillation.

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