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# Computed tomography coronary angiography : from quantification of coronary atherosclerosis to risk stratification of patients

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# Chapter 12

## Summary and conclusions

The aim of this thesis was to explore the value of coronary computed tomography angiography in clinical practice. Specifically, the thesis focuses on the feasibility of quantitative assessment of coronary atherosclerosis on CTA. Additionally, the clinical value of coronary CTA in the specific setting of high risk diabetic patients without chest pain syndrome was established.

The general introduction in **Chapter 2** of this thesis discusses the evolving role of cardiac CT in the diagnosis of patients with suspected CAD. An overview is provided of the performance of cardiac CTA and CAC score in the specific setting of patients with stable angina and patients presenting with acute chest pain at the emergency department. Furthermore, novel applications as myocardial perfusion and CT derived fractional flow reserve are discussed.

# Part 1

Part 1 of this thesis established the value of quantitative assessment of coronary atherosclerosis on coronary CTA in clinical practice.

**Chapter 3** provides an overview of the different imaging modalities for quantitative assessment of coronary atherosclerosis and progression of coronary plaque. The clinical value of progression of atherosclerosis and corresponding medical therapy is discussed.

The value of QCT to assess coronary plaque constitution is assessed in **Chapter 4-6.** For this purpose the QCT datasets were registered based on anatomical landmarks with IVUS VH as reference standard.

In **Chapter 4** the ability of QCT to assess coronary plaque composition was assessed. For this purpose 57 patients who had undergone CTA prior to IVUS VH were included. QCT was performed in all patients. CTA plaque volume was differentiated in 4 different plaque types: necrotic core, dense calcium, fibrotic and fibro-fatty tissue. The same parameters were derived from IVUS VH and compared. The performance of two different approaches for tissue characterization was evaluated. The first used fixed Hounsfield unit (HU) cut-off values to different the different components. The second used a dynamic threshold model, for which the HU threshold were adapted to the lumen HU intensity. The different plaque types on QCT were well-correlated with IVUS VH. The dynamic threshold approach performed better, compared to the fixed threshold approach, as demonstrated by more narrow limits of agreement on the Bland–Altman analyses. Based on these results it was concluded that automatic, quantitative CTA tissue characterization is feasible using a dedicated software tool.

The relation between coronary atherosclerosis on QCT as compared to IVUS VH is further explored in **Chapter 5**. A major limitation of IVUS VH is the inability of the echo signal to penetrate coronary calcium. As a result, tissue located in the acoustic shadow behind calcium is difficult to classify. Using a novel algorithm this shadow can be automatically detected and quantified. The quantified volumes were added to the total volume of calcium to compensate for the expected underestimation of calcium by IVUS VH. Indeed, by applying the novel algorithm, the agreement between IVUS VH and QCT for the assessment of coronary calcium improved.

In **Chapter 6** the ability of QCT to assess the Agatston coronary artery calcium score (CAC) was investigated. For this purpose 100 patients, 20 patients for each CAC category (i.e. 0, 1–99, 100–399, 400–999, ≥1,000), were randomly selected. The Agatston CAC score on non-contrast CT was calculated manually, while the novel algorithm was used to automatically detect and quantify Agatston CAC score in contrast CTA images. The resulting Agatston CAC scores were validated against the non-contrast images. The automatically computed CAC score showed a high correlation and intra-class correlation with non-contrast CT CAC score. Moreover, agreement within the CAC categories was good. It was concluded that fully automatic detection of Agatston CAC score on contrast CTA is feasible and showed high correlation with the non-contrast CT CAC score. This could imply a radiation dose reduction and time saving by omitting the non-contrast scan.

Previous studies have demonstrated the disagreement between significant stenosis on CTA and ischemia on SPECT MPI. Potentially, QCT can improve the correlation between stenosis severity and the presence of ischemia. Therefore, the aim of **Chapter 7** was to evaluate the association between QCT parameters of coronary artery lesions and the presence of myocardial ischemia on gated myocardial perfusion SPECT. Forty patients were included with known or suspected coronary artery disease who had undergone CTA and gated myocardial perfusion SPECT within 6 months. From the CTA datasets, vessel-based and lesion-based visual analyses were performed. Consecutively, lesion-based QCT was performed to assess plaque length, plaque burden, percentage lumen area stenosis and remodelling index. Subsequently, the presence of myocardial ischemia was assessed using the summed difference score (SDS ≥2) on gated myocardial perfusion SPECT. Myocardial ischemia was seen in 25 patients (62.5%) in 37 vascular territories. Coronary lesion length and quantitatively assessed significant stenosis were independently associated with myocardial ischemia. Both quantitative parameters had incremental value over baseline variables and traditional visual assessment of significant stenosis. It was concluded that QCT can possibly enhance assessment of CAD, which may be of potential use for identification of patients with myocardial ischemia.

To evaluate the prognostic value of the severity, location and composition of CAD combined in a CTA risk score, the study of **Chapter 8** was designed. The hypothesis was that a risk score incorporating all quantitative stenosis parameters allows for accurate risk stratification. Therefore, the purpose of this study was to determine if an automatic quantitative assessment of CAD using QCT combined into a single CTA risk score allows risk stratification of patients. In 300 patients QCT was performed to automatically detect and quantify all lesions in the coronary tree. Using QCT, the novel CTA risk score was calculated based on plaque extent, severity, composition, and location on a segment basis. During follow-up, the composite end point of all-cause mortality, revascularization, and nonfatal infarction was recorded. In 127 patients with obstructive CAD (≥50% stenosis), 27 events were recorded, all in patients with a high CTA risk score. In conclusion, the present study demonstrated that a fully automatic QCT analysis of CAD is feasible and can be applied for risk stratification of patients with suspected CAD. The novel CTA risk score incorporating location, severity, and composition of coronary lesion may improve risk stratification, but this needs to be confirmed in larger studies.

The aim of the study **in Chapter 9** was to evaluate the feasibility of QCT for the assessment of coronary atherosclerosis changes over time on serial CTA in patients with stable chest pain. For this study 53 patients clinically referred for the evaluation of chest pain who underwent a coronary CTA at the Rijnland Hospital. After a minimum of 2 years CTA was repeated to evaluate changes in coronary atherosclerosis over time. For accurate and reproducible assessment of CAD changes, all CTAs were quantitatively analysed using QCT. All parameters of dimension and composition of CAD were compared between patients to assess possible regression and progression of CAD. It was demonstrated that 32(60%) showed regression of coronary total atheroma volume whereas 21(40%) showed progression of coronary atheroma. Patients with progression of coronary atheroma had progression of all four plaque types. However, patients with regression demonstrated a regression of all plaque components except for dense calcium, for which progression was observed. This study demonstrated that the assessment of changes in CAD with QCT is feasible. Potentially QCT could be applied to assess the efficacy of anti-atherosclerotic therapy.

# Part 2

Part 2 of this thesis discusses the value of CTA in high risk diabetic patients without chest pain syndrome.

**Chapter 10** primarily evaluated changes in myocardial ischemia on SPECT myocardial perfusion imaging after 2 years in a cohort of high-risk patients with diabetes

without cardiac symptoms or known CAD. Secondly, this chapter assessed the value of baseline CTA-derived coronary atherosclerosis parameters to predict changes in myocardial ischemia. The population consisted of 100 high-risk patients with diabetes without cardiac symptoms referred for cardiovascular risk stratification. All patients underwent CAC scoring, CTA, and SPECT MPI. After 2 years of follow-up, SPECT MPI was repeated to evaluate potential progression of ischemia. The rate of progression of ischemia in high-risk patients with diabetes without cardiac symptoms is limited. Few patients presented with new ischemia, whereas some patients showed resolution of ischemia. Atherosclerosis parameters on CTA were not predictive of new-onset ischemia or progression of ischemia.

**Chapter 11** aims to investigate the long term prognostic value of coronary CTA in a large population of high risk diabetic patients without chest pain syndrome. 525 diabetic patients without chest pain syndrome were prospectively included to undergo coronary artery calcium (CAC)-scoring followed by coronary CTA. During follow-up the composite endpoint of all-cause mortality, non-fatal myocardial infarction and late revascularization (>90 days) was registered. After median follow-up of 5.0(IQR 2.7-6.5) years the composite endpoint occurred in 65(14%) patients. Coronary CTA demonstrated a high prevalence of CAD (85%), mostly non-obstructive CAD (51%). Furthermore, patients with a normal CTA had an excellent prognosis (event-rate 3%). An incremental increase in event-rate was observed with increasing CAC-risk category or coronary stenosis severity. Finally, obstructive (50-70%) or severe CAD (>70%) was independently predictive of events It was concluded that coronary CTA provided prognostic value in high risk diabetic patients without chest pain syndrome. Most importantly, the prognosis of patients with a normal CTA was excellent.

# Conclusions

The objective of this dissertation was to establish the value of QCT to further enhance the clinical applicability and accuracy of coronary CTA. The automatic characterization of coronary atherosclerosis with QCT is feasible and correlates well with IVUS VH. However, further work is needed to provide quantification of coronary stents and coronary blood flow. In the near future, the parameters of dimension and composition of coronary atherosclerosis will likely gain more clinical interest. It appears that coronary CTA can provide more clinically relevant information than the mere presence of coronary atherosclerosis or obstructive stenosis. Therefore, a novel CTA risk score was created incorporating detailed information on the location, severity and composition of atherosclerosis as assessed with QCT. This CTA risk score allows

accurate risk stratification of patients with suspected CAD. The work on this CTA risk score is continued to further validate the CTA risk score in external patient cohorts.

In this thesis the feasibility of QCT to assess changes over time in coronary atherosclerosis on CTA was explored. For clinical practice, disease progression (or regression) is an important variable which could be used to evaluate the efficacy of drugs, but also provide a more detailed insight in the natural history of coronary atherosclerosis on CTA.

A drawback of coronary CTA is the fact that the hemodynamic significance of a lesion cannot be evaluated. In this thesis it was demonstrated that QCT provided better correlation with the presence of myocardial ischemia on SPECT MPI as compared to current visual assessment of coronary CTA.

With regards to the specific setting of high risk diabetic patients without chest pain syndrome several conclusion can be derived from this thesis. First, if treated with optimal medical therapy, very few patients present with progression of myocardial ischemia. Second, the prognosis of these patients is good; the overall long-term event-rate is limited. Especially diabetic patients without CAD on coronary CTA have an excellent prognosis. Even though the prognostic value of CTA was demonstrated in this thesis, it is unclear if screening using cardiac imaging influences the outcome of these patients. Additionally, cardiac CTA or CAC-score could help tailor medical therapy in this challenging patient population.