Summary and Conclusion

Over the past decade, multidetector computed tomography technology has developed rapidly, allowing high-resolution non-invasive imaging of the heart. Since the introduction of this technique, acquisition time, detector number, and spatial and temporal resolution have improved with each new scanner generation, resulting in excellent image quality and diagnostic accuracy in the detection of coronary artery disease (CAD). Previous 4-, 16- and 64-row computed tomography coronary angiography (CTA) systems used a helical scanning technique with retrospective ECG gating. More recent developments in CTA technology have focused on the reduction of patient radiation dose, using dose modulation and prospective ECG triggering. With the introduction of 320-row CTA, image acquisition of the entire heart in a single heart beat has become possible for the first time. This technique uses a volumetric imaging approach, thus significantly reducing the time of image acquisition, breath-hold time, radiation and contrast doses. As a result, the use of 320-row CTA represents an important step forward in CTA technology.

Chapter 1, the introduction of this dissertation, provides a general overview of cardiac applications of multidetector computed tomography. Recent technical developments using CTA, visualization of the coronary arteries, diagnostic performance in the evaluation of CAD, several non-coronary applications, and consequences for clinical management are evaluated. At the end of the chapter an outline of the dissertation is presented. The dissertation constitutes two parts. The first part deals with the diagnostic performance of 320-row CTA in the evaluation of patients with known or suspected CAD, and the second part describes the prognostic value of CTA and its role in clinical management of patients with suspected CAD.
PART I

The first part of the dissertation focuses on the diagnostic performance of 320-row CTA in the evaluation of CAD and left ventricular function. In Chapter 2, the diagnostic performance of 320-row CTA in 64 patients with known or suspected CAD is assessed. Sensitivity, specificity, and positive and negative predictive values to detect significant coronary stenosis on a patient basis were 100%, 88%, 92% and 100%, respectively. Moreover, sensitivity, specificity, and positive and negative predictive values to detect ≥70% luminal narrowing on a patient basis were 94%, 95%, 88% and 98%, respectively. As a result, the study showed that 320-row CTA allows for accurate, non-invasive assessment of significant CAD. In Chapter 3 the diagnostic performance of CTA in 100 patients is evaluated for the detection of two endpoints: significant stenosis (using invasive coronary angiography as reference) and atherosclerosis (using intravascular ultrasound as the standard of reference). The sensitivity, specificity, and positive and negative predictive values for the assessment of significant stenosis were 100%, 85%, 81%, and 100%, respectively, while the sensitivity, specificity, and positive and negative predictive values for the detection of atherosclerosis were each 100%. Accordingly, the diagnostic performance of CTA to detect atherosclerosis was superior to the detection of significant stenosis.

Also, in patients after revascularization, early detection and treatment of in-stent restenosis or coronary artery bypass graft failure is of great clinical importance. Chapter 4 provides an overview of several anatomic and functional imaging techniques to evaluate patients after revascularization. Next, in Chapter 5, the diagnostic accuracy of 320-row CTA to evaluate significant in-stent restenosis is described in 53 patients with a total of 89 stents. Invasive coronary angiography served as the standard of reference. After the exclusion of 7 stents (8%) due to non-diagnostic CTA stent image quality, sensitivity, specificity, and positive and negative predictive values were 92%, 91%, 65% and 98%, respectively, on a stent basis. However, stents with a large diameter and thin struts allowed better in-stent visualization than stents with a small diameter or thick struts. These findings show that non-invasive assessment of in-stent restenosis using CTA is possible in carefully selected patients. Subsequently, in Chapter 6, the diagnostic performance of 320-row CTA in the evaluation of 40 patients with prior CABG is discussed. On a vessel-based analysis, the sensitivity, specificity, and positive and negative predictive values in the evaluation of significant graft stenosis were 96%, 92%, 83% and 98%, respectively, while the diagnostic accuracy for the assessment of recipient and non-grafted vessels was 89% and 80%, respectively. Thus, in selected patients, 320-row CTA also allows for the accurate assessment of patients with a history of CABG. Nevertheless, the assessment of small coronary branches and heavily calcified vessels remained challenging using this
Summary and Conclusion

In Chapter 7, the diagnostic accuracy of 320-row CTA in the identification of significant stenosis in 106 patients presenting with acute chest pain was explored. In total, 16 patients (15%) were immediately discharged after normal CTA and 90 patients (85%) underwent clinically referred invasive coronary angiography. Sensitivity, specificity, and positive and negative predictive values to detect significant CAD on CTA were 100%, 87%, 93%, and 100%, respectively. In addition, the relation to outcome during follow-up (mean: 13.7 months) was examined. Accordingly, it was shown that normal or non-significant CAD on CTA predicted a low rate of adverse cardiovascular events (defined as cardiac death, non-fatal myocardial infarction, and unstable angina requiring revascularization) and a favorable outcome.

Although volumetric imaging using 320-row CTA may be performed in a single heart beat in patients with low and stable heart rate, image acquisition may also be performed during multiple heart beats in patients with a high or irregular heart rate at the cost of increased ionizing radiation exposure. Chapter 8a serves as an introduction to Chapter 8 and describes the importance of heart rate reduction prior to CTA to improve image quality and reduce patient radiation exposure. Accordingly, heart rate lowering medication, such as beta-blocking agents, is routinely administered prior to investigation. However, contraindications to beta-blocking agents are frequently present. Therefore, in Chapter 8, the use, contraindications, and efficacy of pre-scan beta-blocking agents regarding heart reduction and CTA image quality are investigated. Compared to patients with optimal heart rate control, patients receiving no or suboptimal beta-blocking agents in the presence of contraindications had significantly fewer examinations of good image quality (40% vs. 74%, p<0.001). Thus, alternative approaches to control heart rate prior to CTA would be beneficial. Although it is important to note that image acquisition during multiple heart beats increases radiation burden, advantages of multi-segment (multi heart beat) reconstructions include improved temporal resolution and CTA image quality. In Chapter 9 the value of motion ratio and displacement to evaluate the influence of coronary artery motion on multi-segment reconstruction images using 320-row CTA is discussed. Motion ratio was proposed to be a better index than displacement to evaluate the influence of coronary motion on multi-segment reconstruction image quality. However, multiple heart beat imaging should be carefully weighed against the increase in radiation dose, and single heart beat image acquisition at low heart rates should be strived for. In Chapter 10 the accuracy of 320-row CTA in the assessment of global left ventricular function is assessed as compared with 2-dimensional echocardiography as the reference standard. In 114 patients who were clinically referred for CTA, good correlation was demonstrated between CTA and 2-dimensional echocardiography for the assessment of left ventricular ejection fraction ($r^2 = 0.87; p < 0.001$). Left ventricular ejection fraction was only slightly overestimated with CTA ($0.9 \pm 3.6\%; p < 0.05$).
Accordingly, accurate assessment of left ventricular function and volumes is feasible with single heart beat 320-row CTA.

PART II

The second part of the dissertation focuses on the prognostic value of CTA and its role in clinical management of patients with suspected CAD. At present, invasive coronary angiography is considered to be the standard of reference for the evaluation of CAD. However, due to its invasive nature, this procedure is associated with a small but non-negligible risk of complications. Accordingly, a non-invasive method to identify patients who would benefit from subsequent invasive coronary angiography and percutaneous coronary intervention would be beneficial. In Chapter 11, the potential role of CTA as a gatekeeper prior to invasive coronary angiography is considered. Particularly in patients with an intermediate pre-test likelihood of obstructive CAD, CTA could potentially exclude patients without obstructive stenosis, and thus avoid unnecessary invasive coronary angiography procedures. Therefore, in Chapter 12 the rate of subsequent invasive coronary angiography and revascularization in relation to CTA results is investigated in 637 patients with chest pain. During a follow-up period of one year, in patients with significant CAD on CTA subsequent invasive coronary angiography rate was significantly higher (76%) than in patients with normal CTA results (5.7%, p<0.001). Similarly, in patients with significant CAD on CTA, revascularization rate was 47% as compared to no revascularizations in patients with a normal CTA results (p<0.001). Indeed, CTA results were identified as the strongest independent predictors of invasive coronary angiography and revascularization. It is therefore concluded that CTA has the potential to serve as a gatekeeper for invasive coronary angiography to identify patients who are most likely to benefit from revascularization and exclude patients who can safely avoid invasive coronary angiography.

Subsequently, the prognostic value of CTA-derived left ventricular function analysis and its incremental prognostic value over the detection of significant stenosis using CTA is evaluated in Chapter 13. In 728 patients with known or suspected CAD, follow-up was performed for the occurrence of events (all-cause mortality, non-fatal myocardial infarction, and unstable angina pectoris requiring hospitalization). During follow-up an event occurred in 6.2% of patients. Left ventricular ejection fraction and left ventricular end systolic volume cutoff values were identified as independent predictors of events with an incremental prognostic value over clinical risk factors and anatomic assessment of CAD using CTA. As a result, left ventricular function analysis provides incremental prognostic information beyond anatomic assessment of CAD using CTA. Finally, the use of CTA for
the purpose of risk stratification in patients with type 2 diabetes mellitus is explored in Chapter 14. In 202 diabetic patients, the presence of the ‘hypertriglycerideremic waist’ phenotype (defined as the combined presence of increased waist circumference and elevated plasma triglyceride levels) was shown to translate into a deteriorated blood lipid profile and more extensive CAD on CTA as compared to diabetic patients without this phenotype. Therefore, the hypertriglycerideremic waist phenotype translated into an increased likelihood of CAD on CTA in patients with type 2 diabetes mellitus and may accordingly serve as a practical clinical marker to improve risk stratification in this patient population.

CONCLUSION

The primary objective of this dissertation is to determine the diagnostic performance of 320-row CTA for cardiac applications, particularly in the assessment of significant coronary stenosis in patients with known or suspected CAD. It was shown that 320-row CTA allows accurate, non-invasive assessment of significant CAD and global left ventricular function in patients with suspected CAD, as well as in patients with a history of revascularization. Importantly, all diagnostic accuracy studies demonstrated that 320-row CTA has a particularly high negative predictive value, approaching 100%, which makes this modality particularly suitable for the exclusion of CAD. Notably, while CTA image quality and radiation dose are inversely related to heart rate, heart rate lowering medication, such as beta-blocking agents, are routinely administered prior to examination. Unfortunately, contraindications to beta-blocking agents are frequently present, indicating the need for alternative approaches for heart rate control prior to CTA investigation.

In the second part of the dissertation, the prognostic value of CTA and its role in clinical management of patients with suspected CAD were investigated. First, the potential of CTA to serve as a gatekeeper prior to CTA was explored. In patients with chest pain, CTA results were identified as strong and independent determinants of subsequent invasive coronary angiography and revascularization. As a result, CTA has the potential to serve as a gatekeeper for invasive coronary angiography in patients with a low-to-intermediate pre-test likelihood of obstructive CAD. Subsequently, it was shown that the assessment of left ventricular function analysis on CTA may further enhance risk stratification beyond the assessment of degree of stenosis. Finally, in patients with type 2 diabetes mellitus, the combined presence of increased waist circumference and elevated plasma triglyceride levels (the ‘hypertriglycerideremic waist’ phenotype) was shown to translate into an increased likelihood of CAD on CTA and may therefore serve as a practical clinical biomarker to improve risk stratification. Although CTA is increasingly used in
the evaluation of patients with suspected coronary artery disease, future randomized controlled trials in large patient populations are warranted.