Summary
SUMMARY

Cardiovascular diseases (CVDs) are a large contributor to the global mortality rate. Non-invasive imaging techniques, such as computed tomography (CT) imaging, have been playing a growing role in the risk assessment, diagnosis, and prognosis of coronary artery disease (CAD). One of the main challenges in the evaluation of CAD is the establishment of the optimal workflow to evaluate the anatomical as well as the functional aspects of CAD in all phases of the ischemic cascade. Although multiple modalities offer the possibility to visualize specific phases of the ischemic cascade, CT is currently the only modality with the potential to visualize all phases of the ischemic cascade.

The research described in this thesis investigates the possibilities of CT to perform both morphological and functional evaluation of CAD. The first chapters focus on early signs of CAD such as coronary calcium and atherosclerotic plaque (Part I), followed by chapters investigating coronary flow (Part II) and myocardial perfusion (Part III), while the last chapters focus on the final stages of CAD, investigating myocardial fibrosis (Part IV). One way to enhance the performance of CT imaging and reduce evaluation times is the use of automated procedures, for example by using artificial intelligence (AI) algorithms. Chapter 2 discusses the use of AI in cardiac CT imaging and describes various applications for which an AI based algorithm is used. Several of these applications are being used throughout this thesis.

Part I

Part I of this thesis focuses on the anatomical evaluation of coronary plaque and especially on automating this process to optimize the workflow and promote clinical implementation. One of the first visualizable steps in the ischemic cascade is the development of coronary artery calcification which can be easily done using CT. Coronary artery calcium scoring (CACS) serves as a reliable tool for risk assessment and to guide follow-up testing and treatment. However, manually performed CACS is a time-consuming and labor intensive task. In Chapter 3 an AI based algorithm for CACS is described, showing excellent accuracy at reduced variability and work load. Although CACS has proven itself as an excellent risk predictor, previous studies have proposed that a combination of morphological and functional plaque characteristics, such as plaque burden and composition, can aid in the prognostication of major adverse cardiac events (MACE). Patients with non-obstructive CAD and a high-risk plaque profile based on CCTA analysis can be assigned to the most appropriate therapy and/or longitudinal follow-up for possible intensification or downgrading of therapy. Chapter 4 reports on the added value of plaque burden and composition for the prognostication of CAD patients using a fully automated system. The results of our study demonstrate...
that CCTA-derived quantitative morphological features show increased discriminatory power to predict MACE compared to clinical risk factors alone.

**Part II**

Morphological changes of the vessel wall, causing atherosclerotic plaque, can cause a stenosis in the coronary arteries and result in changes in coronary flow. It is believed that this has a direct effect on the blood flow to the myocardium. One method to evaluate these changes in coronary flow is to measure the fractional flow reserve (FFR) over these stenoses. Recently a non-invasive CT based FFR measurement has become available for on-site evaluation using an AI algorithm instead of real-time computational fluid dynamics. The AI algorithm decreases the computational time while maintaining high accuracy for determination of the functional significance of a stenosis. **Part II** focuses on the optimization of the clinical use of CT-FFR. CT-FFR allows for FFR measurement throughout the coronary tree, in contrast with invasive FFR, which is measured over a pre-specified lesion. In **Chapter 5** the effect of the measurement location of CT-FFR is evaluated in patients without CAD. Results show that distal CT-FFR measurements are subject to a non-stenosis specific drop in CT-FFR values, probably caused by overall lower HU values and steep decreases in HU values over the course of the vessel. **Chapters 6** and **7** focus on the relationship between CT-FFR and myocardial blood flow measurements derived from CT. With CT-FRR it is assumed that changes in coronary flow will ultimately lead to decreased myocardial perfusion. Although we assume that there indeed is relationship between coronary flow and myocardial perfusion, it is an indirect relationship influenced by many factors. CT myocardial perfusion imaging (MPI) offers the possibility to directly visualize and quantify the myocardial blood flow (MBF). In **Chapter 6**, it is discussed that CT-FFR and CT perfusion, although both used to evaluate the functional significance of CAD, only show a moderate correlation and are susceptible to measurement location. Combining the influence of CT-FFR measurement location and the poor correlation with CT MPI led to a higher prognostic value of CT MPI analysis compared to CT-FFR analysis (**Chapter 7**). It should be mentioned that both CT-FFR and CT MPI analysis added value to anatomical evaluation of coronary CT angiography (CCTA) images alone, once emphasizing the value of the functional evaluation of CAD. A special region of interest for CT-FFR analysis are the intermediate values (0.70-0.80), where the diagnostic accuracy decreases significantly. Values in this region also show the lowest correlation with perfusion values and might possibly be enhanced by the measurement location.

**Part III**

CT has been the last imaging modality adopting the MPI technology and the optimal image and analysis protocol remains unclear. **Part III** is dedicated to the optimization of the CT MPI technology. **Chapter 8** gives an overview of the CT MPI techniques,
possible image protocols, and analysis methodologies as well as an overview of all recent studies performed with CT MPI. From this chapter follows that a wide variety of protocols are being used resulting in a wide variety of MBF ranges and thresholds values. The studies on CT MPI discussed in this chapter, show that CT MPI derived MBF values are significantly lower than MBF values derived using other modalities such as positron emission tomography (PET) and MRI. CT MPI is limited in its number of acquisition taken over time to calculate MBF, more so than other modalities such as MRI, because of the radiation dose given for each acquisition. In Chapter 9, the influence of temporal sampling rates is discussed, concluding that the limited temporal sampling rate in current protocol results in an underestimation of MBF. Another cause of varying MBF values is the lack of research done on the optimal tracer kinetic model to calculate MBF. There are multiple models available to calculate MBF, however, most models are validated using other modalities and CT specific information is lacking. In Chapter 10, multiple models are tested and compared on CT MPI data to standardize the CT MPI analysis. It shows that although the different models greatly influence the absolute MBF values, the accuracy of the detection of ischemia is similar among models. This implicates that different models can be used but that thresholds to determine whether MBF is abnormal should be model specific. A point of discussion, involving all MPI modalities, is the adequacy of inducing stress, which is needed to perform MPI examinations. In Chapter 11, a relatively new stressor agent regadenoson, is investigated, comparing CT MPI with Single Photon Emission CT (SPECT) MPI. Regadenoson, as concluded in this study, is safe to use in CAD patients with similar accuracy to SPECT MPI, giving limited side effects and might be especially beneficial in patients with pulmonary comorbidities.

Part IV

Part IV brings us to the final stage of the ischemic cascade. When blood flow to the myocardium is impaired for extensive periods of time, the myocardial tissue will suffer from structural changes and permanently impaired perfusion resulting in myocardial infarction. Infarction causes the irreversible replacement of viable myocardial tissue with fibrotic tissue, ultimately impairing cardiac function. With the introduction of dual energy CT (DECT), using two different energy beams simultaneously, tissue characterization became a possibility with CT. By making use of the two different energy spectra iodine quantification can be performed accurately and can thereby give information about the myocardial blood flow. In Chapter 12, the use of iodine quantification was investigated with DECT to detect ischemic and infarcted myocardium. By quantifying the myocardial iodine concentration in rest and stress, DECT is able to distinguish between healthy and diseased myocardium. In Chapter 13, CT derived extracellular volume (ECV) measurements are used to evaluate the amount of fibrotic tissue throughout the myocardium, either caused by myocardial infarction
or by cardiomyopathies. Magnetic resonance imaging (MRI) is the current standard to measure ECV. However, recent studies have shown that CT is also able to accurately measure ECV using a single energy approach. CT can be a great modality to measure ECV, especially in patients with metal assist devices, making MRI less suitable. In Chapter 13, the use of a DECT approach is evaluated compared to a single energy approach and offers the advantages of evaluating scans at different kV levels and the possibility to reduce both beam hardening and metal artifacts. The results show that DECT has great potential for the calculation of ECV using only one image acquisition at reduced radiation dose compared to single energy acquisitions.

Part V
In the final chapter (Chapter 14), the main findings presented in the previous chapters are discussed and it is debated whether CT can be used clinically for the visualization of the entire ischemic cascade. Although CT shows great potential for the evaluation of CAD, the clinical workflow and combination of techniques to be used is yet to be optimized. Automating processes, for example with the use of AI, can enhance the clinical implementation and help the field of cardiac radiology deal with the increased demand for cardiac imaging.