Despite improvements in diagnostic and treatment strategies, coronary artery disease (CAD) remains the leading cause of death in the Western world. The accurate detection of CAD is therefore an important and challenging task. Nowadays, invasive coronary angiography (ICA) is considered the gold standard for the diagnosis of obstructive CAD. However, due to its invasive nature, the use of ICA as an initial diagnostic test is not recommended by guidelines and less invasive means of establishing a diagnosis should be exhausted. Cardiologists have at their disposal a large armamentarium of noninvasive tests, including coronary computed tomography angiography (CCTA) for the visualization of coronary anatomy, single photon emission computed tomography (SPECT) and positron emission tomography (PET) for the assessment of myocardial perfusion and absolute myocardial blood flow, respectively. In this thesis, clinical studies evaluating the relationship between coronary atherosclerosis and its functional aspects are described. In addition, this thesis elaborates on the diagnostic accuracy of non-invasive cardiac imaging when compared to invasive standards.

Chapter 1

Chapter 1 is a general introduction into the field of cardiac computed tomography (CT) and positron emission tomography (PET) imaging. In this review the advantages and disadvantages of each modality are discussed. Coronary computed tomography angiography (CCTA) has a high sensitivity, but is hampered by a moderate specificity. Approximately half of the obstructive deemed lesions on CCTA (i.e., ≥ 50%) are actually flow limiting. The most important reason for this discrepancy is the occurrence of blooming-artifacts. A distinct advantage of CT based angiography over invasive coronary angiography is that CCTA goes beyond lumenography by the direct visualization of coronary plaques and not indirectly by their luminal encroachment. As such, CCTA provides a wealth of information pertaining the extent and severity of coronary artery disease, plaque composition, and plaque characteristics that is prognostically important. Cardiac PET on the other hand is a purely functional technique assessing the hemodynamic significance of coronary lesions. There is a variety of PET perfusion tracers available and each tracer has its own strengths and limitations. For the purpose of quantification of myocardial blood flow, oxygen-15-labeled water is an ideal tracer. It has in addition a low radiation dose and it allows performing baseline and stress perfusion imaging within one scan session due to its short half-life. On the other hand, its short half-life necessitate an on-site cyclotron for the production of the tracer. The majority of previously published studies pertaining the diagnostic performance of cardiac PET have been hampered by the lack of a proper reference standard. In fact, all studies except for two have utilized invasive coronary angiography (ICA) as a reference standard instead of fractional flow reserve (FFR). As such, the earlier published diagnostic values of cardiac PET should be interpreted with caution. The combination of CCTA with single-photon emission computed tomography (SPECT) or PET to configure
Appendices

A hybrid approach proves to have an incremental diagnostic value compared to stand-alone imaging, which is mainly driven by the reduced rate of false-positive CCTA findings. It is expected that in the near future a hybrid device is no longer a prerequisite for hybrid imaging. Latest efforts have been directed toward deriving physiological information from CT technology directly. As such, stand-alone CT may become a “hybrid” tool in its own right. In addition, FFR-CT appears to be a promising technique, deriving non-invasive FFR values from conventional CCTA images and as such combining anatomical and physiological data providing a comprehensive evaluation of coronary artery disease (CAD).

Chapter 2

In this chapter we investigated the predictive value of various risk scores in female patients admitted with chest pain at the outpatient clinic. We found a large variability in prediction of significant CAD using different pre-test probability risk scores. The New Score and the extended Diamond & Forrester (better performance than the conventional Diamond and Forrester score) model were significant predictors of obstructive CAD on CCTA in women (area under the curve [AUC] 0.67, p < 0.01; AUC 0.61, p = 0.04, respectively), whereas the Duke Clinical Score performed best in male patients (AUC 0.72, p < 0.001). In addition, gestational diabetes mellitus (GDM) and estrogen status were independent predictors of obstructive CAD when adjusted for the pre-test probability scores. As such, the addition of GDM and estrogen status to the extended Diamond & Forrester model, the New Score already accounts for female specific risk factors, resulted in a significant net reclassification index (p = 0.04), hence improving predictive accuracy. Therefore, a female-specific risk score incorporating female risk factors for CAD is warranted in order to improve clinical decision-making. Until then, the current results show that it is preferable to use the New Score for calculation of pre-test probability in women for the prediction of CAD.

Chapter 3

In chapter 3 the incremental diagnostic value of epicardial adipose tissue (EAT) volume measured on a non-contrast CT was assessed for detecting functionally relevant CAD as indicated by FFR. In this study we found a poor correlation between the coronary atherosclerotic burden as reflected by the coronary artery calcium (CAC) score and EAT volume, which is in contradiction with previous studies. In addition, no difference was seen in EAT volume with regard to the hemodynamic significance of epicardial stenosis as indicated by FFR. Furthermore, the addition of EAT volume to the CAC score did not improve the diagnostic value of the CAC score. Nevertheless, adding EAT volume to traditional risk factors significantly improved diagnostic performance for the detection of hemodynamic significant CAD.
Chapter 4

The diagnostic performance of the transient attenuation gradient for diagnosis of myocardial ischemia has been described in chapter 4. Cardiac CT has evolved as a powerful tool for the non-invasive evaluation of coronary anatomy. CCTA is characterized by a high sensitivity and negative predictive value allowing the exclusion of obstructive CAD with near to absolute certainty. However, by its nature CT is unable to discern the hemodynamic significance of coronary stenosis. Nevertheless, CT parameters such as the transient attenuation gradient have been explored to determine the functional relevance of CAD. In contrast to previous studies, the prospective study by Stuijfzand et al revealed that the attenuation gradient of contrast across an epicardial stenosis has no additional diagnostic value for assessing the functional relevance of CAD when compared against a background of fractional flow reserve. Germane to this, correcting for the physiological decline in contrast gradient using the aortic gradient revealed no benefit and did not improve the accuracy of this functional parameter above degree of stenosis alone.

Chapter 5

This review in chapter 5 discusses the current clinical applications of cardiac CT. Over the past decade, CCTA has consistently demonstrated an excellent sensitivity for the detection and exclusion of coronary atherosclerosis in patients with stable or acute chest pain symptoms. Large prospective registries have repeatedly demonstrated the prognostic significance of the presence, extent, or absence of CAD by CCTA. In response to initial concerns, technical advances have permitted a dramatic reduction in patient radiation exposure with preserved image quality. For many patients, the radiation dose of CCTA is less than half of that with conventional myocardial perfusion imaging while providing significantly more anatomic information. Furthermore, CCTA’s excellent spatial resolution is increasingly being used for noninvasive assessment of coronary plaque, including the detection of higher-risk vulnerable plaque and association between plaque characteristics and ischemia. Finally, new promising techniques that incorporate physiology with anatomy, such as CT-based fractional flow reserve (FFR-CT) and CT perfusion (CTP), are allowing for the noninvasive hemodynamic assessment of coronary stenoses and improvements in the specificity of CCTA findings. Such advances augur a coming transition when CCTA will be a first-line test for the detection, exclusion, and even management of CAD in many patients.

Chapter 6

Computed tomography has evolved into a powerful diagnostic tool, and it is impossible to imagine current clinical practice without CT imaging. The review in chapter 6 discusses the novel advances in CT technology including dual-energy CT, spectral CT, and CT-based molecular imaging. By harnessing the advances in technology, cardiac CT has advanced beyond
the mere evaluation of coronary stenosis to an imaging tool that permits accurate plaque characterization, assessment of myocardial perfusion, and even probing of molecular processes that are involved in coronary atherosclerosis. Novel innovations in CT contrast agents and pre-clinical spectral CT devices have paved the way for CT-based molecular imaging.

Chapter 7

Cardiac CT has evolved beyond anatomical imaging. Recent advances in CT technology have allowed for myocardial CT perfusion imaging. As such, CT may become a true one-stop-shop imaging tool in its own right. The review in chapter 7 discusses static and dynamic CT perfusion imaging for the evaluation of hemodynamic significant coronary artery disease.

Chapter 8

The review in chapter 8 discusses a new novel method that applies computational fluid dynamics to derive FFR from traditional CCTA images (FFRct), obviating the need of additional imaging, modifications of CT acquisition protocols or administration of medications. Notably, prospective multicenter studies demonstrated FFRct to exhibit high diagnostic accuracy for identification of flow-limiting CAD.

Chapter 9

In this chapter the role of cardiac CT for the differentiation between ischemic and non-ischemic cardiomyopathy is discussed. Cardiac CT provides a wealth of comprehensive information on coronary atherosclerosis, myocardial perfusion, lesion-specific ischemia, myocardial structure, cardiac function and geometry of both the left and right ventricle that will allow the cardiologist to determine the etiology of the cardiomyopathy with unequalled high diagnostic accuracy in patients without a previous cardiac history.

Chapter 10

In this chapter we investigated the feasibility and diagnostic utility of detecting myocardial ischemia via iodine-based material decomposition and monochromatic dual-energy computed tomography (DECT) imaging, while employing SPECT as a reference standard. We found monochromatic DECT myocardial perfusion imaging at 40 keV to possess similar accuracy for the detection of myocardial ischemia as compared with material decomposition methods using an iodine/muscle basis pair. The findings highlight the importance of monochromatic CT imaging for the assessment of myocardial perfusion and may be a useful adjunct for CCTA in the clinical setting.
Chapter 11

A review article on dual-energy CT imaging, which focuses on the different dual-energy CT methods utilized by the major CT system manufacturers. In addition, the review describes in detail the advantages and disadvantages of each system with regard to cardiac imaging.

Chapter 12

In this chapter we investigated the normal limits of myocardial blood flow and assessed the impact of age, gender, and CAD risk factors on myocardial blood flow by using [15O]H2O PET in a large clinical cohort of patients (n = 128) without obstructive coronary artery disease. We found normal hyperemic myocardial blood flow (MBF) to vary considerably from 1.5 to approximately 8.0 mL min⁻¹ g⁻¹, whereas coronary flow reserve ranged from 1.2 to 9.0. Interestingly, females had significantly higher hyperemic perfusion values (3.78 ± 1.27 mL min⁻¹ g⁻¹) in comparison to their male counterparts (2.90 ± 0.85 mL min⁻¹ g⁻¹). In addition, age and body mass index were found to negatively impact hyperemic MBF. As such, gender, age, and body mass index substantially influence reference values and should be corrected for when interpreting hyperemic myocardial blood flow values.

Chapter 13

Chapter 13 describes a study conducted to explore the quantitative relationship between CAC and coronary vasodilator response in patients who were being evaluated for CAD by hybrid 15O-water PET/CT. In patients with an intermediate pre-test of CAD and with multiple CAD risk factors there is a statistically significant inverse correlation between hyperaemic myocardial blood flow, coronary flow reserve (CFR), and the extent of coronary calcifications as reflected by the CAC score. However, the strength of this association attenuated after adjusting for age, gender, body mass index (BMI), and conventional risk factors. In addition, in contradiction to previous studies there was no relation between the extent of coronary calcifications and the longitudinal base to apex gradient. In conclusion, these results suggest that the CAC score adds little incremental value regarding hyperaemic MBF and CFR over established CAD risk factors. Therefore, it seems that coronary calcifications and vasodilator reactivity reflect different aspects of coronary atherosclerosis.

Chapter 14

Chapter 14 describes the results of a retrospective study investigating whether CAC and / or carotid intima-media thickness (C-IMT) are of value in predicting coronary microvascular disease (CMVD) as reflected by an increase in minimal coronary vascular resistance (CVR). The results indicate that both CAC and C-IMT are related to augmented minimal
CVR. However, after adjusting for traditional risk factors, the relation between coronary calcifications and minimal was no longer apparent. Only age, gender, BMI, and C-IMT were identified to be independently associated with minimal CVR. This finding may be partially explained by the notion that CAC and C-IMT probably reflect different stages of the atherosclerotic process. Early alterations in C-IMT, as a reflection of pre-clinical atherosclerosis, likely precede the process of detectable coronary calcification as measured by CT.

Chapter 15

This chapter discusses the association between diabetes and epicardial adipose tissue in patients who underwent cardiac hybrid PET-CT imaging. Coronary artery calcium and the epicardial adipose tissue volumes were comparable between those with and without diabetes. A pooled analysis showed a positive association of EAT volume with hyperemic coronary vascular resistance, while EAT volume showed a positive correlation only in patients without diabetes. In conclusion, these results suggest a role for EAT in myocardial microvascular dysfunction; however, once diabetes has developed, other factors might be more dominant in contributing to impaired myocardial microvascular dysfunction.

Chapter 16

EAT volume is associated with left ventricular mass (LVM) independently of BMI and might therefore be a better predictor of cardiovascular risk than BMI. However, EAT provides no incremental information on coronary microvascular function beyond traditional risk factors and LVM. Finally, an increased coronary microvascular resistance is only associated with LVM in obese subjects.

Chapter 17

In this chapter we have investigated the feasibility of cardiac $[^{15}\text{O}]$H$_2$O PET imaging to distinguish subendocardial from subepicardial perfusion in the myocardium of normal dimensions. A total of 66 patients, without a previous cardiac history, were included in this study. Hyperaemic transmural perfusion gradient is significantly lower in ischaemic myocardium ($0.97 \pm 0.16$ vs. $0.88 \pm 0.18$, $p < 0.01$) as defined by a FFR $\leq 0.80$. As such, this technique can potentially be employed to study subendocardial perfusion impairment in more detail. However, the diagnostic accuracy of subendocardial hyperaemic perfusion (83%) and transmural perfusion gradient ([TPG], 59%) appears to be limited compared with quantitative transmural hyperemic MBF (85%) for the detection of myocardial ischemia as defined by FFR.
Chapter 18

In chapter 18 we provided the results of the CutWater study. This prospective multicenter study is, to the best of our knowledge, the first to determine cut-offs for MBF as assessed with $[^{15}\text{O}]\text{H}_2\text{O}$ PET using ICA in conjunction with FFR as reference standard. In the current analysis involving 330 patients, the ideal cut-off for absolute stress perfusion was 2.3 mL∙min$^{-1}$∙g$^{-1}$ and 2.5 for the perfusion reserve for diagnosis of ischemia as defined by a FFR $\leq$ 0.80. Another observation of this study was the significantly higher accuracy of hyperemic MBF compared with that of myocardial flow reserve (MFR) for the detection of flow limiting stenosis. Dependency of MFR on both baseline and hyperemic MBF likely contributes to this observation, since a reduction in MFR is not necessarily caused by diminished stress perfusion. Whilst flow reserve has been shown to be of incremental value for prognosis, it seems that hyperemic MBF outperforms MFR in the non-invasive diagnosis of functionally relevant CAD ($p < 0.001$). This finding paves the way for stress-only protocols, obviating the need of resting perfusion imaging with concomitant reduction in radiation dose and scan acquisition time. Finally, the performance of $[^{15}\text{O}]\text{H}_2\text{O}$ PET derived quantitative hyperemic perfusion shows promise as an accurate discerner of the physiological importance of coronary stenosis. Indeed, hyperemic MBF as a perfusion parameter yielded a sensitivity and specificity of 89% and 84%, respectively, when compared against a background of fractional flow reserve.

Chapter 19

Chapter 19 describes a study that was conducted to evaluate the diagnostic accuracy of quantitative hybrid $[^{15}\text{O}]\text{H}_2\text{O}$ PET/CCTA imaging for the detection of CAD as defined by ICA/FFR. The PET perfusion results indicate that hyperemic MBF is superior to MFR and yields a diagnostic accuracy of 80%. Furthermore, the combination of CCTA and $[^{15}\text{O}]\text{H}_2\text{O}$ PET configuring a hybrid protocol improved diagnostic accuracy significantly from 61% (CCTA) and 80% (PET) to 85%, respectively. This increase was primarily mediated through a reduction in the number of false-positive CCTA scans as reflected by an improvement in both specificity and PPV. Hyperemic MBF as a functional parameter has been shown promising in clinical practice, however there is lack of uniformity regarding the optimal threshold for ischemia detection. In this study, the optimal cut-off was defined to be 1.85 mL∙min$^{-1}$∙g$^{-1}$ for hyperemic MBF using mixed ICA/FFR standards. Of note, hyperemic MBF as measured with PET reflects the net impact of epicardial stenoses and microvascular resistance. We found age, gender and BMI to impact myocardial blood flow, even in the absence of significant coronary stenosis. The conductance capacity of the microvasculature is known to be affected by CAD risk factors and disturbances in coronary microvascular resistance are recognized as the functional counterpart of coronary atherosclerosis. As such, (e.g. age and gender) may improve diagnostic accuracy, although further studies are correction of MBF threshold values for specific patient subgroups obviously warranted to test this hypothesis.
Appendices

Chapter 20

In chapter 20 the impact of cardiac hybrid $^{15}$O-water PET/CCTA imaging on downstream referral for invasive coronary angiography and revascularization rate was assessed in a retrospective study involving 375 patients. The study demonstrates that cardiac hybrid $^{15}$O-water PET/CCTA imaging provides additional information and influences clinical decision-making, leading to an apparent more judicious treatment strategy with regard to referral for ICA and revascularization procedures. The yield of CAD by ICA after hybrid PET/CCTA imaging was 59% in patients with an equivocal CT study and abnormal MPI, and 69% in whom hybrid PET/CCTA identified obstructive stenosis and abnormal perfusion, which is favourably compared with the relatively low yield of 38% reported in a large clinical cohort (Patel et al N Engl J Med, 2010). Pursuant to these findings, a revascularization rate per angiogram of 59% was seen in patients with an equivocal CT and abnormal myocardial perfusion imaging (MPI), compared with no revascularizations in those with normal PET perfusion imaging. In addition, the revascularization rate per invasive coronary angiogram was 65% and 26% in patients who displayed obstructive CAD on CCTA in combination with abnormal and normal MPI, respectively. All in all, these findings suggest that the hybrid evaluation of CAD facilitates clinical decision-making, particularly when compared with the revascularization rate of 38% per invasive angiogram, which has been reported in a large European registry study. In conclusion, the combination of MPI and assessment of coronary anatomy by hybrid $^{15}$O-water PET/CCTA imaging impacts referral for ICA and downstream revascularization. Particularly, in the presence of an equivocal or abnormal CCTA, MPI acts as an arbiter to guide a judicious referral to the catheterization laboratory and revascularization strategy.

Chapter 21

In this meta-analysis cardiac imaging methods were compared directly to FFR. Only studies performing FFR in at least 75% of coronary vessels for the diagnosis of ischaemic CAD were included. Twenty-three articles reporting on 3788 patients and 5323 vessels were identified. On a per-patient basis, the sensitivity of CCTA (90%, 95% CI: 86-93), FFRCT (90%, 95% CI: 85-93), and magnetic resonance imaging (MRI) 90%, 95% CI: 75-97) were higher than for SPECT (70%, 95% CI: 59-80), stress echocardiography (77%, 95% CI: 61-88), and ICA (69%, 95% CI: 65-75). The highest and lowest per-patient specificity was observed for MRI (94%, 95% CI: 79-99) and for CCTA (39%, 95% CI: 34-44), respectively. Similar specificities were noted for SPECT (78%, 95% CI: 68-87), stress echocardiography (75%, 95% CI: 63-85), FFRCT (71%, 95% CI: 65-75%), and ICA (67%, 95% CI: 63-71). Cardiac MRI had the highest performance for diagnosis of hemodynamically significant CAD. Both CCTA and FFR$^\text{CT}$ yielded high diagnosis sensitivity, with low specificity for CCTA. Diagnostic performance for SPECT, stress echocardiography, and ICA was generally poorer.
Chapter 22

In chapter 22 diagnostic performance of contemporary CCTA, SPECT, and PET was assessed in a prospective study including 208 patients without a previous cardiac history. This study possesses an array of unique design features: (1) CCTA, SPECT and PET were compared prospectively in a true head-to-head fashion; (2) invasive FFR of all coronary arteries, irrespective of the imaging findings, was used as the reference standard; (3) latest-generation techniques — such as CT based attenuation-correction in SPECT perfusion imaging — were used; and (4) all scans were analyzed by core lab experts blinded to other imaging and clinical data. The study revealed PET to exhibit the highest accuracy (85%) for diagnosis of myocardial ischemia. In addition, SPECT has a poor sensitivity of 57%, which is balanced by a high specificity of 94%. CCTA has a high negative predictive value, but a moderate positive predictive value (PPV). Furthermore, a combined anatomical and functional assessment (i.e. hybrid SPECT/CCTA and PET/CCTA) does not add incremental diagnostic value and guides clinical decision-making in an unsalutary fashion by improving specificity at a cost of sensitivity.