Cardiovascular disease remains to be one of the leading causes of death in Western society. In acute myocardial infarction (AMI), lack of oxygen due to an occlusion of one of the coronary arteries causes damage to the myocardium, with subsequent loss of cardiac function. With the emergence of percutaneous coronary interventions (PCI), early mortality rates for myocardial infarction have decreased in the last decades. However, the loss of cardiac function has led to an increase in the number of patients suffering from congestive heart failure. In order to develop new treatment strategies to mitigate the development of heart failure after myocardial infarction, it is necessary to recognize patients with extensive myocardial damage at risk for developing heart failure.

Cardiovascular Magnetic resonance imaging (CMR) is a non-invasive technique that allows for accurate depiction of cardiac morphology, function, perfusion and tissue composition. Advantage of CMR over other diagnostic tools are the high spatial resolution (in comparison to echocardiography) and the use of radio waves instead of ionizing radiation (as compared to computed tomography or SPECT). A decrease in myocardial perfusion after PCI is associated with a decreased recovery of myocardial function and an increased chance of developing congestive heart failure. Current theories attribute the decrease in myocardial perfusion to obstruction of the myocardial capillaries due to atherosclerotic and/or thrombotic debris originating from the coronary occlusion. This phenomenon is known as microvascular obstruction (MVO) or microvascular injury (MVI). A different phenomenon which can be detected with CMR is the presence of intramyocardial haemorrhage (IMH), a finding associated with a further decrease in myocardial recovery and increased chance of developing heart failure.

Novel CMR techniques have been evaluated in their usefulness for measuring the extent and severity of myocardial damage after acute myocardial infarction. The composition of the tissue determines the characteristics of the signal that the tissue disperses. Two of these properties are the T1 and T2* relaxation time, two signal properties that increase or decrease with changes in tissue composition. In chapter 2, we assessed how local T1 and T2* values of the myocardium change after a PCI treated myocardial infarction and whether the presence of MVI changes these values. A few days after myocardial infarction, T1 and T2* values were increased in the infarcted myocardial areas. However, if MVI was present, T1 and T2* values significantly decreased in the infarcted area, with T1 values approaching normal values. This shows that T1 and T2* values need to be interpreted carefully when MVI is present.

In chapter 3, we investigated the tissue composition of areas with MVI. This was done by using a porcine model of myocardial infarction, in which a myocardial infarction was induced by occluding the LAD coronary with a balloon catheter for 75 minutes and by treating the animals with similar medication as patients. After 1 week, CMR imaging was performed, directly followed by histological examination of the myocardium. Examination showed that areas of MVI, defined as contrast-devoid areas within the myocardium,
contain extensive necrosis with extravasation of erythrocytes, and complete destruction of the vasculature. In the surrounding infarcted area, containing contrast enhancement on LGE-CMR images, necrosis was seen, but with intact microvessels containing microthrombi. Additionally, measurement of areas of MVI and IMH showed a near complete overlap, suggesting that MVI and IMH are one and the same phenomenon, characterized by intramyocardial haemorrhage and destruction of microvessels. This strongly suggests that when IMH is visible on T2 or T2* weighted images, the area of haemorrhage is large enough to exert paramagnetic effects to be detected on the images, making it likely that the poor prognosis of patients with IMH is more likely due to the severity of the haemorrhage and the extent of the infarction, and less due to the presence of IMH alone. The new insight that MVO/MVI may not be caused by microvascular ‘obstruction’ alone allows for further research in strategies aiming to preserve the microvasculature to attenuate damage.

Chapter 4 assessed whether the composition of the infarcted tissue as visualized by late gadolinium enhanced cardiovascular magnetic resonance imaging (LGE-CMR) can predict the occurrence of ventricular tachycardia (VT) on 24-hour Holter monitoring 1 month after the AMI. The infarcted area was divided into an infarct core and a surrounding penumbra based on the measured signal intensity. It was shown that larger proportions of penumbra in the total infarcted area were associated with an increased risk of developing VTs, supporting the theory that infarct heterogeneity may facilitate VT development in the infarcted tissue.

In chapter 5, we investigated whether intracoronary cell therapy after a PCI treated AMI augments the recovery of myocardial perfusion in the infarcted area. The HEBE study is a multicentre trial in which 200 patients with large first acute myocardial infarction treated with PCI, were randomized to either intracoronary infusion of bone marrow mononuclear cells (BMMCs) (n=69), peripheral blood mononuclear cells (PBMCs) (n=66) or standard therapy (n=65). At baseline and after 4 months of follow-up, we performed cardiac MR imaging consisting of cine imaging, rest first-pass perfusion and late gadolinium enhancement (LGE). In 152 patients perfusion data were available. Myocardial perfusion was measured semi-quantitatively by measuring signal intensity-time curves and calculating the relative upslope (% signal intensity change) for the myocardial infarct core, the adjacent border zone and remote, unaffected myocardium. At baseline, perfusion differed between the core, the border and remote myocardium. These regional differences persisted after 4 months. No difference in perfusion recovery was found for any treatment group in any of the regions. Therefore, no effect of cell therapy could be found on the recovery of resting perfusion after AMI.

In chapter 6, we evaluated the long-term effects of cell therapy on left ventricle volume and function, and the occurrence of adverse clinical events, including death, myocardial reinfarction and hospitalisation for heart failure. At baseline, after 4 months and after
In chapter 7, we investigated the association between inflammatory characteristics of monocytes and myocardial injury and functional outcome in patients after AMI. Using flow cytometry, we measured the levels of two subtypes of monocytes, i.e. ‘classical’ (CD14++CD62L+) and ‘nonclassical’ (CD14+CD62L−) monocytes. Analyses were performed on peripheral blood samples of 58 patients with STEMI at a median of 5 days (4-6 days) after PCI and compared to CMR examination performed in the same period. At baseline, patients with high levels of classical monocytes had impaired left ventricular ejection fraction, larger infarct size and microvascular obstruction was more often present. At follow-up, high levels of classical monocytes were negatively associated with regional systolic LV function independent of the transmural extent of myocardial infarction. This shows an association between a proinflammatory monocyte response, characterized by high levels of classical monocytes, more severe myocardial injury directly after infarction and worse functional outcome.

Chapter 8 describes an investigation as a substudy of the HEBE trial, in which we investigated whether intracoronary cell therapy alters the prevalence of ventricular arrhythmias after 1 month or the rate of severe arrhythmogenic events (SAE) in the first year. In 164 patients of the trial we measured function and infarct size with cardiac MR imaging. Holter registration was performed after 1 month from which the number of triplets (3 successive PVCs) and ventricular tachycardias (VT, >4 successive PVCs) was assessed. Thirty-three patients (20%) showed triplets and/or VTs, with similar distribution amongst the groups. SAE occurred in 2 patients in the PBMC group and 1 patient in the control group, suggesting that intracoronary cell therapy is not associated with an increase in ventricular arrhythmias or SAE in the first year of follow-up.