DISCUSSION AND SUMMARY

In this thesis several areas of cardiovascular disease in AS were investigated. With new imaging techniques we investigated the effect of inflammation on cardiac fibrosis and vascular stiffness. Furthermore, the effect of anti-inflammatory treatment on diastolic left ventricular function and lipid profile was studied. We also present the new EULAR cardiovascular risk management guidelines emphasizing the importance of suppressing inflammation and optimal cardiovascular risk management.

Cardiac involvement in Ankylosing Spondylitis

In our systematic review (of the limited data available) we saw that several echocardiography studies show an increased prevalence of diastolic left ventricular dysfunction in patients with AS compared to control groups (Chapter 1). In Chapter 2 and 3 we explored these possible causes with cardiovascular magnetic resonance imaging (CMR), currently the gold standard to visualize cardiac tissue. We performed an explorative study in AS patients without a history of cardiac disease that had advanced diastolic left ventricular dysfunction (grade II) established with echocardiography. Among the included patients, 20% showed signs of focal fibrosis on CMR. Furthermore, quantitative measurements of the myocardial tissue with myocardial extracellular volume showed a relationship with inflammation. These findings suggest an effect of AS disease activity or inflammation on myocardial tissue, likely contributing to, or even causing, diastolic left ventricular dysfunction. In the same patient group, we saw that overall pulse wave velocity, as a measure of vascular stiffness, was increased in AS patients compared to controls (Chapter 3). This is important, as aortic stiffness is an independent predictor of vascular morbidity and mortality in the general population. Henceforth, vascular stiffness may lead to hypertension and increased systolic load, resulting in impaired systolic and diastolic left ventricular function.

With inflammation presumed as the main cause of diastolic left ventricular dysfunction in AS, we investigated the effects of decreasing the inflammatory load with TNF-α blocking treatment on diastolic left ventricular function (Chapter 4). We found an improvement of diastolic left ventricular dysfunction during treatment with TNF-α blockers in several patients. This might be an additional argument to administer these drugs in an early stage or proceed
with the treatment for longer periods of time in order to decrease the cumulative inflammatory burden over the years. When looking at the general patient population with diastolic heart failure it is tempting to speculate that anti-inflammatory medication might be a novel therapeutic option for patients with diastolic heart failure, warranting further and adequate trial investigation. Investigating TNF-α blocking therapy in heart failure of diastolic origin patients is important as no therapy has been proven successful thus far.

**Cardiovascular disease and risk management in rheumatic diseases**

Prevention strategies are important to decrease cardiovascular morbidity, and ultimately, mortality. Cardiovascular risk management has been widely adopted in the Netherlands. The Dutch Cardiovascular Guidelines notably mentions Rheumatoid Arthritis, another inflammatory joint disease, as a condition for which cardiovascular risk management is necessary, and advises to add 15 years to all Rheumatoid Arthritis patients when calculating the cardiovascular risk. For AS however, it is unknown whether or not a multiplication factor should be used when calculating cardiovascular risk, as the precise magnitude of the cardiovascular burden in AS is still not clearly identified. However, we do know that the overall cardiovascular risk in AS is increased and therefore proper cardiovascular risk management is of the upmost importance in these patients.

Unfortunately, cardiovascular risk management appears to be difficult to implement in daily clinical practice, as we demonstrated in a study where 254 AS patients were included (Chapter 6). We found that in three-quarters of AS patients who should receive cardiovascular risk reductive treatment, treatment goals were not achieved. These observations illustrate the importance of better awareness for cardiovascular risk management in AS, and the need for more practical guidelines to be used in daily practice. One of the most accessible and modifiable parameters of cardiovascular risk management is the lipid profile, which was investigated in Chapter 7.

This study showed that the lipid profile in patients with AS is altered compared to the general population, with lower total cholesterol levels in patients with high inflammation. Instead of high cholesterol levels, normally associated with increased cardiovascular risk, low total cholesterol in inflammatory disease is associated with increased cardiovascular risk. In our study, anti-inflammatory treatment with TNF-α blockers decreased inflammation and
normalized these lipid levels. These altered cholesterol levels in AS patients need to be considered when initiating cardiovascular risk management, as in patients with active disease having with high inflammatory markers, cholesterol levels may be incorrectly interpreted as being normal during high disease activity. We advise to use the total cholesterol-high density cholesterol ratio for cardiovascular risk management as it was the most stable lipid parameter during treatment.

As shown, inflammation in AS affects the myocardium, the vascular system and the lipid profile. Over the years, it has become evident that AS patients also have an increased risk for conduction disorders. Possible is that inflammatory activity leads to damage of the conduction system. From this viewpoint, one may also expect a higher prevalence of conduction disorders in other inflammatory arthritis. Contrary to our expectations, we did not find an increased prevalence of conduction disorders in inflammatory arthritis patients (Chapter 5). It suggests that there is a limited, or even no effect of inflammation on the conduction system. This indicates that other mechanisms, such as a more local fibrosis of the conduction system, possibly HLA-B27 related, might be responsible. With a higher prevalence of conduction disorders in AS, we advocate to use regular electrocardiographic screening in AS patients. Furthermore continuous investigation is required to determine whether there is a specific AS phenotype that is at risk for conduction disorders.

Preventing cardiovascular complications is important when trying to decrease cardiovascular morbidity and mortality. Our final chapter, Chapter 8, concerns the updated EULAR guidelines on cardiovascular risk management in inflammatory diseases, including AS. Cardiovascular screening was advised every five years for patients with AS, and should be implemented according to existing local guidelines. The main objective is to controlling the disease activity in order to decrease cardiovascular risk in AS.

**Future research**

The whole cardiovascular system is affected in AS. However, only through ongoing research and their results can additional information be obtained on the exact prevalence of cardiovascular complications and specific cardiac manifestations such as aortic valve dysfunction and conduction disorders. Once this information is attained, screening and
prevention strategies can be developed, and treatment initiated. For this reason we started the CArdiac Disease in Ankylosing Spondylitis (CARDAS) study in 2012, an ongoing study to investigate the prevalence of cardiac manifestations with echocardiography and electrocardiography in AS patients older than 50 years. Preliminary data of the first 169 included AS patients indicate that the heart is affected in the majority of older AS patients, with over 45% having diastolic left ventricular dysfunction and 12% having aortic insufficiency which is almost double compared to literature studies of the general population. Overall, 70% of the included AS patients had at least one cardiac abnormality. All these patients were asymptomatic which meant that they should be categorized according to the prevalence of asymptomatic cardiac abnormalities in general population before we can recommend routine echocardiographic screening in AS patients. Currently, matched healthy controls are included in the CARDAS study for this goal.

Only when the precise prevalence of AS-related cardiac abnormalities such as aortic valve dysfunction has been clarified, screening and treatment strategies can be developed. Firstly, treatment of AS disease activity should be optimized as treatment of disease is the most important way to decrease cardiovascular risk. Secondly, prevention strategies need to be implemented and possibly the commencement of screening programs. Consequently, general and specific cardiovascular risk management guidelines should be continuously updated. To ensure proper initiation of cardiovascular risk management, studies need to be performed to take into account the pros and cons of cardiovascular risk management. Furthermore, studies on anti-inflammatory treatment with TNF-α blockers in AS, along with other rheumatic or inflammatory diseases, should be performed to determine possible positive effect of this treatment on diastolic left ventricular dysfunction.

Several major research topics need to be addressed in the near future:

- The risk of ischemic events in AS needs to be evaluated and correctly classified in accordance with Rheumatoid Arthritis and Diabetes Mellitus in order to adjust cardiovascular risk management for AS. Therefore, setting up or combining large international datasets is recommended. When the cardiovascular risk for AS patients has been properly identified, then is it possible to create a cardiovascular risk screening tool specifically tailored for the AS patient. AS can be implemented properly
in existing cardiovascular risk screening tool, possibly by use of a multiplication factor for the calculation of cardiovascular risk.

- Imaging studies of the heart in AS should be performed in order to evaluate the scope of cardiac manifestations in AS patients. If an increased prevalence of cardiac manifestations in AS is confirmed, regular echocardiography screening of all AS patients should be considered. Risk factors of developing AS related cardiac manifestations should be evaluated, in order to classify the AS patient with the highest risk of AS cardiac manifestations, by doing so reducing the burden of echocardiography screening.

- Clinical trials should be initiated to compare the effects of various anti-inflammatory treatment on the cardiac function. This requires cooperation among specialists in the areas of cardiology and rheumatology. Proper medical treatment could lead to a decrease in congestive heart failure in patients with rheumatic diseases. Simultaneously, these trials may lead to new insights in the pathogenesis of congestive heart failure. Of special interest will be the effects of anti-inflammatory treatment on patients with heart failure with preserved ejection fraction, as trials with TNF-α blockers in patent heart failure with reduced ejection fraction have failed.

**Conclusion**

It is clear that the cardiovascular burden in AS patients is nowadays still high, despite the more effective anti-rheumatic treatment. Proper initiation and optimization of cardiovascular risk management according to guidelines is therefore very important. But whether or not this leads to reduction of cardiovascular morbidity and mortality in AS, remains to be established. Given the increased prevalence of diastolic left ventricular dysfunction, aortic valve insufficiency and conduction disorders it remains to be established whether or not incorporating routine electrocardiography and echocardiography leads to a further decrease of the cardiovascular risk in our patients.