General introduction and outline of the thesis

Introduction and aims of the thesis

The evidence of excess cardiovascular disease (CVD) risk in rheumatoid arthritis (RA) is mounting and this risk may even be as high as in patients with type 2 diabetes mellitus (T2DM) (1-3). Initial research regarding the excess CVD risk in RA was focussed on the ongoing inflammation in RA. Since inflammation is a key factor in the development of atherosclerosis, RA-associated inflammation may contribute to the increased CVD risk. Several studies showed that elevated inflammatory parameters such as C-reactive protein and erythrocyte sedimentation rate are associated with the increased CVD risk (4, 5). More recently the traditional CVD risk factors, such as hyperlipidemia, hypertension, diabetes mellitus and smoking have gained more interest in RA. However, the exact contribution of traditional CVD risk factors in the development of CVD in RA is unclear. It is also not known if treatment of these traditional risk factors influences the course of development of CVD in RA (5).

The FRANCIS study

All the research of this thesis is based on the FRANCIS study, which is a prospective, randomized clinical trial in RA patients investigating the potential benefit of strict cardiovascular risk reduction compared to standard care. RA patients younger than 70 years of age and without clinical CVD or T2DM were eligible. CVD was defined as a prior myocardial infarction, cerebrovascular event, amputation due to peripheral artery disease, intermittent claudication, percutaneous transluminal coronary angioplasty (PTCA) or coronary artery bypass graft (CABG). T2DM was defined as fasting glucose >7.0 mmol/l. All patients at inclusion were routinely screened for traditional CVD risk factors at the Diabetes and Vascular Centre, Franciscus Gasthuis, Rotterdam, the Netherlands. After inclusion patients were either randomized to intensive treatment of traditional CVD risk factors at the Diabetes and Vascular Centre, of the Franciscus Gasthuis, with pre-specified treatment targets and recommendations on lifestyle changes or they were randomized to usual care and referred to their general practitioner for further treatment. All patients visited the outpatient clinic routinely every six months (which is similar to the appointments of the usual care group), but extra appointments were made when necessary for patients in the tight control group. Before randomization the CVD risk score according to the 2010 unadjusted SCORE risk assessment was calculated. The SCORE risk assessment estimates the 10 year risk of fatal CVD risk based on sex, age, smoking, blood pressure and the total cholesterol/HDL-cholesterol ratio (Figure 1) (6). Patients with a CVD risk score <10% were eligible for randomization (comparable to <20% in the currently used, unadjusted SCORE table that also includes non-fatal CVD (7)). Patients with a CVD risk score ≥10% were followed in a separate cohort and treated according to the tight control protocol.

The primary objective of the FRANCIS was to investigate whether a tight cardiovascular risk reduction program is effective in reducing progression of the intima media

thickness, a marker for subclinical atherosclerosis, in patients with RA compared to usual care. The follow-up was set at five years and will be completed in all participants at the end of 2017. Results discussed in this thesis are reports of baseline data, subanalyses and interim analyses.

The main objectives of this thesis

1. To determine the prevalence and impact of traditional CVD risk factors such as hypertension and hyperlipidemia on CVD risk and (subclinical) atherosclerosis in RA patients that do not have a history of CVD or diabetes mellitus.
2. To determine patients believes on adherence to their advised CVD preventive treatment.
3. To explore the presence of postprandial dyslipidemia, as a novel risk factor, in RA patients.

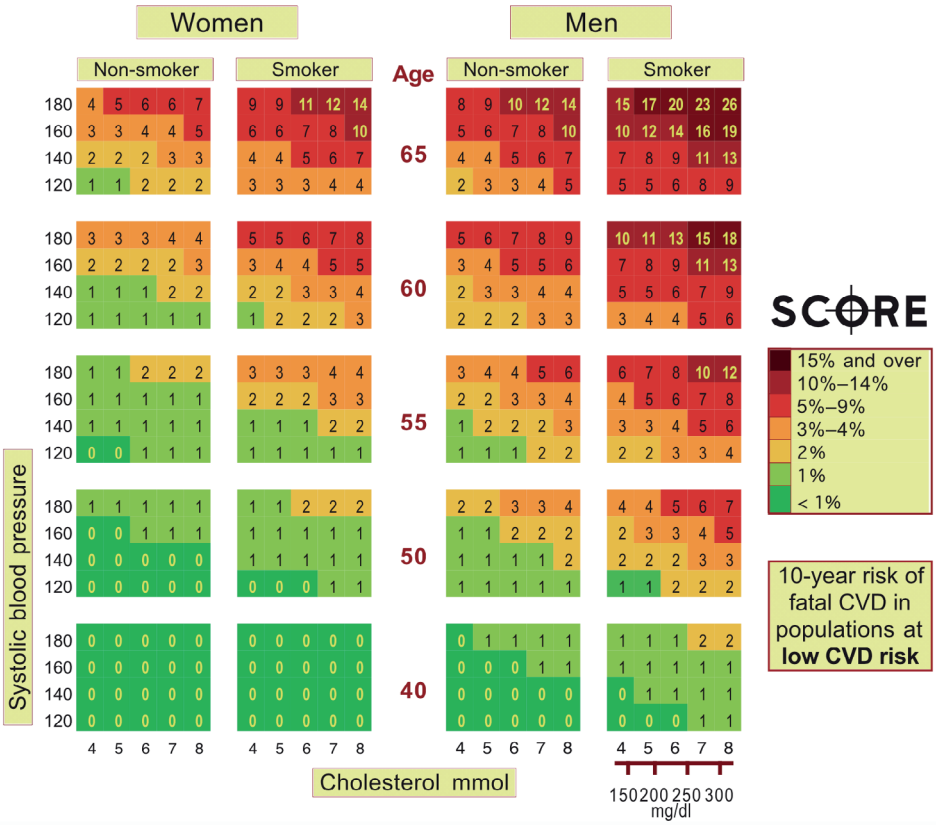

Figure 1. The unadjusted SCORE model to calculate the 10-year risk of fatal cardiovascular disease (6).

Outline of the thesis

The main focus of this thesis is on the role of traditional CVD risk factors on CVD in RA; their prevalence, their association with subclinical atherosclerosis and whether a tight treatment protocol on CVD risk factors results in improved treatment of traditional CVD risk factors. The current evidence concerning RA and CVD is reviewed in **Chapter 2**. In **Chapter 3** we investigated the prevalence of traditional CVD risk factors in the FRANCIS population, using the SCORE model and two suggested modified SCORE models by the European league against rheumatism (EULAR) and the Dutch guideline for CVD risk management (7, 8). These modifications of the SCORE model are shown in Table 1.

The aim was to investigate the prevalence of underdiagnosis and undertreatment of hypertension and hyperlipidemia in RA.

In the general population, the cornerstone of CVD risk reduction is lifestyle recommendations like following a healthy diet, cessation of smoking and performing daily exercise. We know that patients adherence to lifestyle recommendations and drug therapy for preventive measures is generally low (9). One of the explanations may be that patients perspectives regarding CVD risk may be different compared to doctors perspectives. In order to evaluate the perspective of the FRANCIS patients regarding strategies for CVD risk reduction and their adherence, all patients in the tight control arm received a questionnaire to address this matter. The results of this study are described in **Chapter 4**.

Atherosclerosis is a slowly progressive disease, which remains asymptomatic for many years before clinical CVD becomes evident. CVD presents as angina pectoris, myocardial infarction, a stroke or as intermittent claudication, but the atherosclerotic process is already on-going for years before clinical symptoms occur. A commonly used measurement for the detection of subclinical atherosclerosis is the measurement of the carotid intima media thickness (cIMT). A recent meta-analysis by Wang et al. showed that the cIMT is increased in RA compared to healthy controls. Furthermore, in RA there is an increased progression rate of cIMT described compared to controls (10). In **Chapter 5** we

Table 1. National and international guidelines for CVD risk assessment in RA patients.

	Adaptations to CVD risk assessment according to SCORE
EULAR guideline (2010)	CVD risk* x 1.5 if at least two of following characteristics are present:
	- > 10 years RA disease duration
	- RF and/or anti-CCP positivity
	- severe extra articular disease
Dutch guideline for CVD risk management (2011)	Age +15 years for all RA patients**

* According to SCORE and/or Framingham

** For assessment of CVD risk according to SCORE

investigated the association of several traditional and RA-specific CVD risk factors with cIMT and compared these results with healthy controls.

Since traditional and RA-specific CVD risk factors cannot fully explain the excess CVD risk in RA search for novel CVD risk factors in RA is warranted. In **Chapter 6** we therefore investigated apolipoprotein B48 levels, the structural protein of chylomicrons and a marker of postprandial lipemia, in RA patients. Postprandial lipemia is of exceptional interest since it is linked to both inflammation and the traditional risk factor hyperlipidemia.

Besides searching for new and RA specific CVD risk factors it is important to investigate the effect of treatment of traditional CVD risk factors. There is no reason to believe that treatment of traditional CVD risk factors is of less importance than they are in the general population, but it is unknown whether they should be treated with extra attention and intensity in RA like in diabetes mellitus or patients with known CVD. **Chapter 7** describes the results of strict CVD risk reduction versus standard care in RA after two years of follow-up, which is an interim analysis of the original planned follow-up of 5 years.

Finally, the results of the performed studies will be discussed and reflected upon in **Chapter 8**. Recommendations will be made for clinical practice and the remaining uncertainties, which need future explorations, will be described.

References

1. van Halm VP, Peters MJ, Voskuyl AE, et al. Rheumatoid arthritis versus diabetes as a risk factor for cardiovascular disease: a cross-sectional study, the CARRE Investigation. Ann Rheum Dis 2009;68:1395-400.
2. Avina-Zubieta JA, Choi HK, Sadatsafavi M, Etminan M, Esdaile JM, Lacaille D. Risk of cardiovascular mortality in patients with rheumatoid arthritis: a meta-analysis of observational studies. Arthritis Rheum 2008;59:1690-7.
3. Steen KS, Lems WF, Visman IM, et al. High incidence of cardiovascular events in patients with rheumatoid arthritis. Ann Rheum Dis 2009;68:1509-10.
4. Graf J, Scherzer R, Grunfeld C, Imboden J. Levels of C-reactive protein associated with high and very high cardiovascular risk are prevalent in patients with rheumatoid arthritis. PLoS One 2009;4:e6242.
5. del Rincon I, Freeman GL, Haas RW, O'Leary DH, Escalante A. Relative contribution of cardiovascular risk factors and rheumatoid arthritis clinical manifestations to atherosclerosis. Arthritis Rheum 2005;52:3413-23.
6. Conroy RM, Pyorala K, Fitzgerald AP, et al. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. Eur Heart J 2003;24:987-1003.
7. Wiersma T, Smulders YM, Stehouwer CD, Konings KT, Lanphen J. [Summary of the multidisciplinary guideline on cardiovascular risk management (revision 2011)]. Ned Tijdschr Geneeskd 2012;156:A5104.
8. Peters MJ, Symmons DP, McCarey D, et al. EULAR evidence-based recommendations for cardiovascular risk management in patients with rheumatoid arthritis and other forms of inflammatory arthritis. Ann Rheum Dis 2010;69:325-31.
9. Naderi SH, Bestwick JP, Wald DS. Adherence to drugs that prevent cardiovascular disease: meta-analysis on 376,162 patients. Am J Med 2012;125:882-7 e1.
10. Sodergren A, Karp K, Boman K, et al. Atherosclerosis in early rheumatoid arthritis: very early endothelial activation and rapid progression of intima media thickness. Arthritis Res Ther 2010;12:R158.