Summary

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This thesis aimed to give more insight in cardiovascular disease (CVD) risk and treatment and diagnosis of traditional cardiovascular risk factors in RA patients. **Chapter 2** reviews current evidence on this topic. The main objectives of this thesis were: (1) To determine the 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 hyperlipidemia, as a novel risk factor, in RA patients. The first objective is addressed in chapter 3, 5 and 7. The second objective is addressed in chapter 4 and the third objective is addressed in chapter 5.

Chapter 3 describes the presence of hypertension and hyperlipidemia in the FRANCIS cohort at baseline. As reported previously in other studies, we found a high prevalence of CVD risk factors. The assessed CVD risk depended on the model used. When using the adaptations to the SCORE model as suggested in the Dutch guideline for cardiovascular risk management (CVRM), 221,of the 327 included patients had a calculated CVD risk ≥10%. Of them 185 (84%) had a LDL-C >2.5mmol/l and were therefore eligible for treatment with lipid lowering drugs using current guidelines. Of the few patients that already used statins at inclusion (14 patients) the vast majority (12 patients; 89%) did not reach recommended treatment targets. Regarding hypertension 72 patients (32%), of the 221 with a CVD risk ≥10%, had a systolic blood pressure >140mmHg.

In **Chapter 4** patients believes on their adherence were investigated using questionnaires. Questionnaire were send to all patients included in the tight control arm with a minimum of 6 months follow up. The response rate was 82%, resulting in 111 questionnaires. The questionnaires consisted of two parts. In the first part patients were asked about adherence in general and the second part questioned adherence to specific advices. In the first part, asking about believes and adherence in general, patients stated overall to follow the advice without difficulty. 69% of the patients (n=65) stated to follow the doctors advice exactly and only 5% said to be unable to do what the doctor told them to do. Part two of the questionnaire was on adherence to specific recommendations. Most patients took their prescribed medication (83%-90%), but for lifestyle recommendations such as a diet or more exercise adherence rates varied from 68%-56%.

In **Chapter 5** the association of several CVD risk factors, both traditional and RA specific, on subclinical atherosclerosis measured by carotid intima media thickness (cIMT) was investigated. In univariate regression analysis several traditional CVD risk factors were associated with cIMT in RA patients and in controls. In RA patient also a significant association between cIMT and RA disease duration was found. The diagnosis RA itself was not associated with cIMT. In multivariable analysis the only factor, besides age, that

was associated with cIMT was systolic blood pressure in RA patients (B=0.001 [-0.000-0.002]; p=0.003) and smoking in controls (0.101[0.041-0.162]; p=0.001). The average cIMT of both groups are comparable (0.556±0.120 mm and 0.573±0.134 mm for RA and controls respectively) and within normal range. A reason for this lack of difference may be the fact that the RA patients in this study have low disease activity (median [IQR] DAS28=2.4 [IQR 1.6-3.2]).

Chapter 6 describes the first report on apolipoprotein B48 (apo B48) levels in RA patients. Apo B48 is the structural protein of chylomicrons and serum concentrations are increased in conditions associated with systemic inflammation. The median apo B48 concentration in our cohort was 8.6 mg/L [IQR 5.2-12.5mg/L] which is markedly higher than the suggested normal values for healthy controls. Furthermore patients in the highest apoB48 tertile are, compared to the lowest tertile, more often rheumatoid factor positive 75% [n=72] vs. 58% [n=62]; p=0.04) and anti-CCP positive (75% [n=62] vs. 59% [n=59]; p=0.005). Despite the high apo B48, remnant cholesterol concentrations and fasting plasma triglycerides were relatively low (0.52±0.26 mmol/l and 1.25±0.88 mmol/l respectively), which indicates that chylomicron remnant clearance may be delayed in RA.

Chapter 7 shows data after two years of follow up in the FRANCIS. Both patients in the tight control group (3.3±0.9 mmol/l vs. 2.5±0.8mmol/l; p<0.001) and in the usual care group (3.4±0.8 mmol/l vs. 3.1±0.9 mmol/l; p<0.001) had a significantly lower LDL-C, but the decrease was significantly greater (2.7 times) in the tight control group (- 0.4±0.8 mmol/l vs -1.0±1.0 mmol/l; p=0.03). Furthermore, significantly more patients reached treatment the target for LDL-C compared to usual care. Also systolic blood pressure was significantly lower in the tight control group (132±19 mmHg vs. 127±14 mmHg; p<0.004) and treatment targets were reached in 75% (n=90) of the patients. In the usual care group the decrease in blood pressure did not reach statistical significance (130±18 mmHg vs. 127±16 mmHg; p<0.078) and less patients reached treatment targets (70%; n=76). This difference in patient numbers reaching targets was not significantly different.

Overall patients in the tight control arm were more treat-to-to target resulting in significantly lower LDL-C and systolic blood pressure. Longer follow-up is necessary to evaluate the effect of this treatment difference on subclinical atherosclerosis.