# General discussion

## Introduction

Over the last years the evidence on the increased cardiovascular disease (CVD) risk in rheumatoid arthritis (RA) has accumulated. The main question is how to lower this risk. Several RA specific risk factors such as disease activity, inflammatory markers and anti-CCP have been associated with increased carotid intima media thickness (cIMT) and CVD. These risk factors however do not fully explain the CVD risk and traditional CVD risk factors such as hypertension and hyperlipidemia should not be overlooked. To date it remains unclear what the exact influence of individual, RA specific, or traditional CVD risk factors is on the actual risk. In order to improve risk assessment, taking into account the evidence on the increased CVD risk in RA, several adaptations to the SCORE risk assessment model are made (Table 1).

**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:<br>*- > 10 years RA disease duration*<br>*- RF and/or anti-CCP positivity*<br>*- 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

**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

## Main findings

*Objective 1*: **The impact of traditional CVD risk factors in RA patients**

This aim was threefold: First, to assess what the prevalence of hypertension and hyperlipidemia is in RA patients with no prior history of CVD or diabetes mellitus. Second, to

determine which factors, RA specific or traditional CVD risk factors, are associated with subclinical atherosclerosis measured by carotid intima media thickness (cIMT) and to investigate which factors are associated with cIMT in RA compared with controls. Third, to investigate the effect of a tight, protocol based treatment of traditional CVD risk factors on (subclinical) atherosclerosis.

**Prevalence of hypertension and hyperlipidemia in RA**

Atherosclerosis is an inflammatory disease (1) and therefore, the inflammatory burden in RA patient is believed to play a role in the development of an excess CVD risk. However, traditional CVD risk factors should not be overlooked. Even in the case of secondary prevention, where the need for tight treatment regarding CVD risk factors is commonly known and accepted, a large number of patients remained above treatment target for hypertension and hyperlipidemia (2). In primary prevention in the general population an undertreatment of 50% of the patients has been reported (3, 4). The attention for primary prevention may even be lower in patients with a chronic disease that needs a continuous therapy and evaluation, such as RA. Several studies show that there is underdiagnosis of traditional CVD risk factors in RA (4, 5). Our results, as described in **Chapter 3**, are in line with these reports, but the prevalence of hyperlipidemia is markedly higher. Of the 327 included patients, 221 patients had a calculated CVD risk ≥10%. Of them 185 (84%) had a LDL-C >2.5 mmol/l and were therefore eligible for treatment with lipid lowering drugs using current guidelines. Regarding hypertension 72 patients (32%), of the 221 with a CVD risk ≥10%, had a systolic blood pressure >140mmHg. Besides the fact that screening for risk factors might occur less in these patients, as explained above, another reason for the underdiagnosis may be the unawareness of the current guidelines. When adapting the SCORE risk assessment according to EULAR recommendations (6) and even more when following CVRM guidelines (7), the CVD risk rises markedly which leads to a larger number of patients eligible for treatment.

**Association of cardiovascular risk factors with carotid intima media thickness**

In order to better understand the exact role of traditional and RA specific CVD risk factors we studied, in **Chapter 5**, the association of those CVD risk factors with subclinical atherosclerosis measured by carotid intima media thickness. In multivariable analysis the only factor besides age, which 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 (B=0.101 [0.041-0.162]; p=0.001). It is surprising that the average cIMT of both groups were 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 had low disease activity (median [IQR] DAS28=2.4 [IQR 1.6-3.2]). This reported DAS28 is lower than in previous studies investigating on cIMT in RA (8). In order to draw

more accurate conclusions on the role of RA disease activity on cIMT, an average DAS28 over time is necessary to estimate the inflammatory burden.

**Effect of a tight control treatment protocol for traditional cardiovascular risk factors in rheumatoid arthritis patients**

Regarding cardiovascular preventive medication in RA, there are some studies showing a favourable effect. Statin treatment effectively improves lipid levels in RA patients (9, 10) and anti-hypertensive treatment with ACE-I and angiotensin II antagonists effectively lower blood pressure and improves endothelial function in RA (11-13). **Chapter 7** described the results of a randomized clinical trial investigating traditional CVD risk factor treatment following a strict treatment protocol versus usual care after two years of follow-up. There was a significant decrease in blood pressure in the tight control group (132±19 mmHg vs. 127±14 mmHg; p<0.004), but not in the usual care group (130±18 mmHg vs. 127±16 mmHg; p<0.078). However, the systolic blood pressure was comparable between both groups after 2 years. LDL-C levels were significantly lower in the tight control group and the decrease was 2.7 times greater compared to the usual care group (-0.99±099 mmol/l vs -0.37±0.76 mmol/l; p=0.03). Treatment targets in the tight control group were reached in 75% (90 patients) for systolic blood pressure and in 72% (87 patients) for LDL-C. To know the effects on subclinical atherosclerosis a longer follow-up period is needed.

*Objective 2*: **Patients believes on adherence**

Although many doctors like to believe their patients follow all the given advice, we know that adherence to treatment recommendations varies according to the given advice and the result achieved for the patients. In the case of primary prevention adherence rates of 44-66% have been described (14). Now that the excess CVD risk in RA has been accepted, it is important to investigate how to lower the risk. As stated above, besides a tight control treatment for RA, primary prevention by screening and treating traditional CVD risk factors is important. Since a large part of the success of primary prevention programs is based on patients adherence, we wanted to investigate the believes of the FRANCIS patients regarding their given advices. We chose to do this by using validated questionnaires (15, 16). The result of this questionnaire is discussed in **Chapter 4**. Self-reported adherence by a questionnaire may overestimate actual adherence, but in contrast to more objective measurements like counting pills, questionnaires give a good insight in patients believes. In general, patients state to be able to follow the given advices: 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. When taking a closer look by asking about adherence to specific recommendations, the percentage of adherent patients varied. Most patients took their prescribed medication (83-90%), but

for lifestyle recommendations such as a diet or more exercise adherence rates varied from 56-86%. Besides the fact that these data are self-reported adherence rates, also the fact that all patients were willingly participating in a trial to lower CVD risk may result in higher adherence rates. Despite of these reasons for overestimation, adherence to lifestyle interventions are moderate.

*Objective 3*: **Postprandial hyperlipidemia in RA**

Postprandial hyperlipidemia is associated with the generation of atherosclerosis (17-19). Apolipoprotein (apo) B48 is the structural protein of intestinally derived chylomicrons (20) and therefore, a marker for postprandial hyperlipidemia. More specifically apo B48 represents the exact number of circulating chylomicrons and chylomicron remnants. Based on several reports, the suggested upper limit of normal apo B48 levels is 5.7 mg/L in healthy controls (21). Our study is the first to report on apo B48 levels in RA patients. The median apo B found in our cohort was 8.6 mg/L [IQR 5.2012.5], which is markedly higher than the suggested upper limit in healthy controls. Moreover when creating tertiles based on apo B48 levels, the highest tertile showed apo B48 levels three times as high as reported in healthy controls. Also patients in this highest tertile were significantly more often anti-CCP and rheumatoid factor positive compared to the lowest tertile.

## Methodological considerations

### The FRANCIS as a randomized controlled trial

The main strength of the FRANCIS study is that the impact of a pre-defined tight control regimen regarding lifestyle and drug treatment is compared to usual care (treatment as suggested by a patients own general practitioner), in an open label randomized control trial (RCT). A RCT is considered the optimal study design when two (or more) alternative interventions are compared in terms of effectiveness, because potential covariables and confounders are equally distributed among the alternative treatment strategies under consideration. Consequently, as a principle, the potential impact of these covariables and confounders on the outcome measures is reduced to random error, and the effect size, or systematic difference between alternatives, can be measured validly. Despite randomization, valid outcome measurement may be threatened by (1) incorrect randomization procedure, (2) selective drop-out of patients (after randomization), and (3) invalid outcome assessment. The randomization procedure was simple and did not leave any room for incorrectness. Envelopes with randomization numbers and outcome were numbered. When a patients was randomized the first envelop available (i.e. the envelop with the lowest number) was taken. Furthermore, only a few physicians, who were all familiar with the study, were responsible for randomization. Selection bias may

occur as a result of selective drop out as stated second, in the first two years of FRANCIS there appears not to be a selective drop out. The number of patients that dropped out in both groups was similar after two years as described in **Chapter 7** and there were no significant differences between data at baseline when comparing all randomized patients to the patients that were still available after 2 years of follow-up. The third point mentioned is information bias. There are several levels in which information bias may play a role. First of all the FRANCIS is an open label study automatically implying information bias. A double blind approach however is not possible in this setting. Furthermore, the outcome of the FRANCIS depends on the usual care provided by general practitioners. This treatment may strongly depend on the individual general practitioner. Over the last years guidelines for primary prevention in RA patients have become more strict and strive after lower treatment targets compared to the FRANCIS protocol. This may minimize the effect measured in the FRANCIS study. In addition, general practitioners received a letter stating the participation in the study, the rationale for the study and the presence of CVD risk factors if applicable. This may have lead to increased awareness of the general practitioner as well, which may lead to better treatment and screening. The data reported in **Chapter 7** however indicate that patients in usual care were overall not treated according to current guidelines. Data on the believes of general practitioners on the screening for and treatment of traditional CVD risk factors in RA are unavailable.

**External validity**

The external validity of the FRANCIS depends on the inclusion and exclusion criteria. All patient with RA and without CVD younger than 70 years of age were able to participate. The only exclusion criterion was a chronic kidney disease (MDRD <30 ml/min). These criteria make the result widely applicable. However, the CVD risk of RA patients overall may be underestimated since patients with CVD were excluded. There are several specific characteristics in this cohort that limit the external validity. First of all most patients were Caucasian and highly educated. Secondly, patients in this cohort also followed a tight controlled treatment regimen regarding the RA disease activity, as is part of the standard care in the outpatient clinic of rheumatology. Since the ongoing inflammation as a result of RA disease activity may play a role in the CVD risk, our data is only generable to patients in countries that have possibilities for high RA disease control.

**Other considerations**

**Chapter 4** describes the results of a questionnaire. This may lead to information bias because this self-reported adherence may have overestimated actual adherence. The reason to use this method of measurement was primarily to investigate patients believes rather than the most accurate measurement of adherence itself. Furthermore, the cross-sectional design of the study makes it impossible to comment on adherence over

time. Adherence tends to decline over years and it would therefore be interesting to know how the self-reported adherence changes over time.

**Chapter 5** also has a cross-sectional study design. The reported associations therefore, do not give insight on the effect of individual risk factors on the development of (subclinical) atherosclerosis. A longitudinal analysis at this point is not possible/informative due to the short follow-up period, but may be interesting in the future.

## New insights

The new insights acquired from this thesis are

- Hypertension and hyperlipidemia are highly prevalent in RA
- Hypertension is associated with cIMT in RA patients
- Patients believe they follow the recommendations regarding CVD risk management well. The exact self-reported adherence varies between the different recommendations provided by physicians.
- RA patients have very high apo B48 levels and patients with the highest apo B48 levels are more often rheumatoid factor positive and/or anti-CCP positive.
- A tight treatment protocol regarding traditional CVD risk factors results in a significantly lower LDL-C compared to standard care.

## Recommendations for clinical practice

There have been numerous reports on the excess CVD risk in RA and to date more and more rheumatologists are aware of this increased risk. In daily practice however screening and treatment of this excess risk is not common practice. This may be partly because the exact role of known risk factors and the influence of currently unknown risk factors is subject of ongoing investigation. However, given the evidence that traditional CVD risk factors are highly prevalent, associated with subclinical atherosclerosis and improve in a tight control regimen, a routine screening and structured treatment is warranted.

## Recommendations for future research

The follow-up period of two years, described in this thesis, is too short to draw conclusions on the effect of tight control of traditional CVD risk factors in RA on the development of subclinical atherosclerosis. This is even more the case when investigating the effect on clinical atherosclerosis (i.e. cardiovascular disease/events/mortality). A longer

follow-up period is necessary and planned. The FRANCIS study will continue until all included subjects have completed their 5 years of follow-up. In addition, it is likely that the FRANCIS study will be expanded for another 5 years of follow-up. This future research will give better understanding of the role and treatment of traditional CVD risk factor on the excess CVD risk in RA.

As described in detail in **Chapter 3** and more briefly in other parts of this thesis, there is need for an accurate risk assessment tool in RA patients. Current risk assessment profiles such as SCORE and Framingham are not accurate in RA patients. In order to better assess the risk several adaptations to these models have been suggested. However, this still does not take into account the RA specific risk factors such as CRP levels or the presence of auto-antibodies. Recently Arts et al. investigated the performance of the SCORE risk model after recalibration and adaptation with additional RA–specific CVD risk factors. This did not lead to major improvements in the accuracy of CVD risk prediction in RA. They also added RA specific CVD risk factors to the model, which resulted only in a modest improvement in discriminatory ability in comparison with the traditional SCORE (22). The lack of accurate risk assessment together with the uncertainty of the role of individual risk factors on CVD risk makes it difficult to implement a structured treatment advice in clinical practice. Therefore, further research in order to result in better risk assessment is necessary.

A remarkable and very interesting finding in the FRANCIS study is the high apo B48 levels in RA. There is currently is no explanation why apo B48 levels are so high, despite low remnant cholesterol levels in RA, which would be interesting to explore in the future. Since the use of currently known traditional and RA specific CVD risk factors has not resulted in better CVD risk assessment, novel, currently unknown CVD risk factors needs to be investigated. Apo B48 as a marker of postprandial hyperlipidemia may be such a novel marker in RA, which may improve CVD risk calculation in RA.

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