Cardiovascular risk in rheumatoid arthritis patients, diagnosis and treatment:
a report of the FRANCIS

Deborah F. van Breukelen-van der Stoep

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Colophon

Cardiovascular Risk in Rheumatoid Arthritis Patients, Diagnosis and Treatment:
A report of the FRANCIS

Cardiovasculair risico in patiënten met reumatïode arthritis, diagnose en behandeling:
Een rapportage van de FRANCIS

Proefschrift

Ter verkrijging van de graad van doctor aan de
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Erasmus University Rotterdam

Voor mijn opa

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CHAPTER 1

General introduction and outline of the thesis
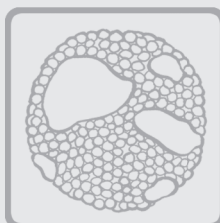
Introduction and aims of the thesis

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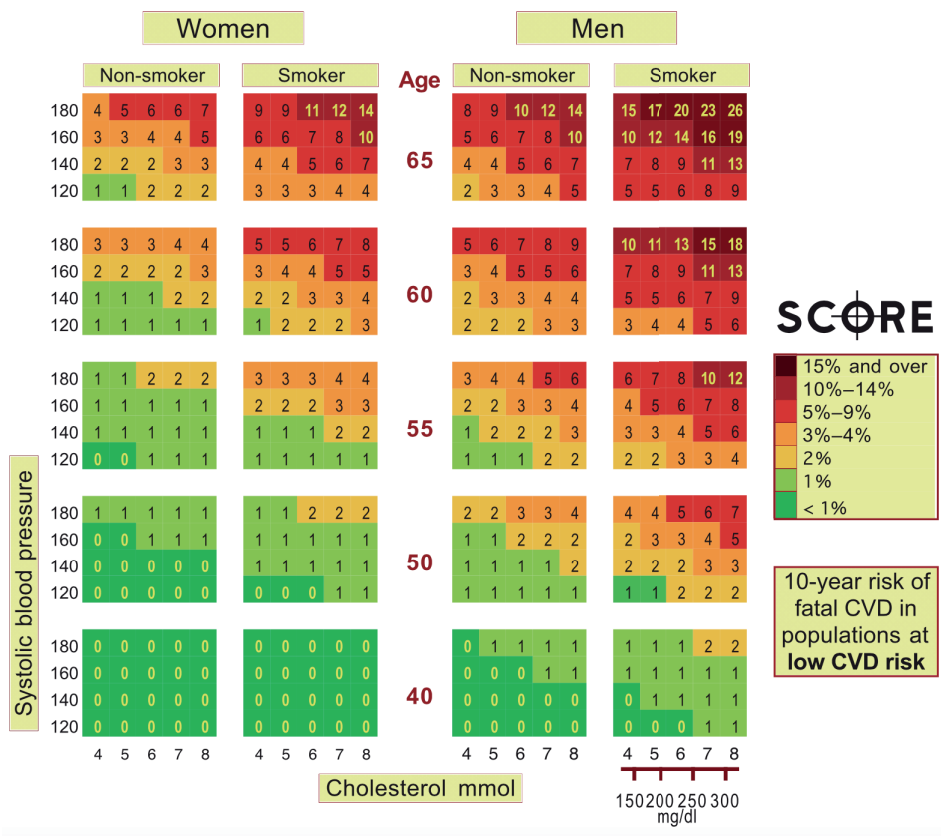
Figure 1. The unadjusted SCORE model to calculate the 10-year risk of fatal cardiovascular disease (6).

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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.

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CHAPTER 2

Cardiovascular risk in rheumatoid arthritis: How to lower the risk?

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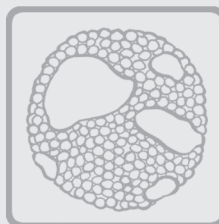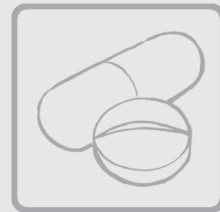
Summary

Patients with rheumatoid arthritis (RA) carry an excess risk for cardiovascular disease, which is comparable to the risk in patients with type 2 diabetes mellitus. The mechanisms involved are partly related to traditional cardiovascular risk factors, disease-associated inflammation and undertreatment of traditional cardiovascular disease (CVD) risk factors. Since atherosclerosis is an inflammatory disease, the auto-immune mediated inflammation observed in RA patients contributes to increased endothelial dysfunction, oxidative stress and activation and vascular migration of leukocytes. This concept is underscored by the CVD risk reduction that is seen by anti-inflammatory disease modifying anti-rheumatic drugs such as methotrexate and TNFα inhibitors. The evidence for underdiagnosis and undertreatment of traditional CVD risk factors in RA strengthens the potential benefit of structured CVD risk management in these patients. Current cardiovascular guidelines recommend screening and treatment of CVD risk factors in RA patients, without well defined treatment targets. At present, there is a lack of scientific evidence to establish treatment targets for CVD risk factors in RA. Therefore, expanding research regarding screening and treatment of traditional CVD risk factors in RA patients is needed.

Introduction

The evidence on the excess of cardiovascular disease (CVD) risk in rheumatoid arthritis (RA) has accumulated during the last two decades (1-3). It has been suggested that the prevalence of CVD in patients with RA is as high as in patients with type 2 diabetes mellitus (1). Interestingly, the increased CVD risk observed in RA may be independent from traditional risk factors for CVD (1, 4). These risk factors such as dyslipidemia, hypertension, smoking and obesity have been found in patients with RA in a similar frequency as in the general population (5, 6). It has been shown that these traditional risk factors contribute to the development of atherosclerosis in RA, but their presence alone can not fully explain the increased CVD risk (7, 8).

RA-specific factors, such as rheumatoid factor (RA) and/or anti-CCP positivity, joint erosions and extra-articular RA have been linked to the development of premature atherosclerosis in this condition. Since atherosclerosis is an inflammatory disease, it has been proposed that the increased inflammatory state of patients with RA explains, at least in part, the increased CVD risk (2, 4, 6, 7, 9). Furthermore, joint damage and physical inactivity are common in patients with RA and have been associated with an increased prevalence of CVD (8). In addition, RA is treated with different disease modifying drugs (DMARDs), with anti-inflammatory effects and with potential anti-antherosclerotic con-

sequences(8). To date, the exact contribution of all of these factors to the development of premature atherosclerosis in RA remains unclear. There is need for studies investigating the pathogenesis of atherosclerosis in RA and a well defined treatment protocol to lower the excess CVD risk is warranted. The purpose of this review is to provide an overview of the current evidence concerning the major determinants of excess CVD risk and the optimal CVD risk management in RA and to explore future scientific directions.

RA, inflammation and atherosclerosis

The formation of an atherosclerotic plaque takes place in different stages, which are driven by deposition and oxidation of lipids in the subendothelial space, activation of leukocytes and endothelial cells and finally thrombosis (Figure 1) (10).

All apolipoprotein (apo) B containing lipoproteins e.g. chylomicrons, chylomicron remnants, very low density lipoproteins (VLDL), intermediate density lipoproteins (IDL) and low density lipoproteins (LDL) can enter the subendothelial space via disrupted tight junctions between altered endothelial cells (11, 12). These lipoproteins can be taken up by macrophages converting them to foam cells. LDL needs to become oxidized (oxLDL) before it can induce foam cell formation, whereas chylomicrons and their remnants do not need modification (13). There is evidence that tumor necrosis factor alpha (TNFα) can directly stimulate the oxidation of LDL (14), and it has been observed that oxLDL levels are higher in patients with RA (15). Moreover, increased oxLDL concentrations have been linked to increased RA disease activity (15). The oxidation of LDL is catalysed by lipoprotein associated phospholipase A2 (Lp-PLA2) (16), but its precise contribution to the development of atherosclerosis in RA is uncertain since reduced levels of Lp-PLA2 have been observed in RA (17), whereas increased Lp-PLA2 activity has been found in association with CVD (18).

Lp(a), which is a pro-atherogenic lipoprotein that consists of an LDL-like particle and apo(a), can become oxidized and provoke an immune response similar to oxLDL. Apo(a) promotes thrombosis and inhibits fibrinolysis due to its homology with plasminogen (19, 20). An increase in Lp(a) has also been associated with inflammation, but data are inconsistent (21-23). Lp(a) is an independent risk factor for CVD (20) that may be disproportionally elevated in RA (19, 21, 22).

A key event in the development of both atherosclerosis and RA is inflammation (10, 24). Pro-inflammatory cytokines like TNFα and interleukin-6 (IL-6) are produced by the synovial tissue and play a key role in both the pathogenesis of RA and the development of atherosclerosis (25). One of the effects of TNFα is an increase in monocyte activation and cytokine release (25, 26). IL-6 causes T and B-cell proliferation and recruitment of neutrophils, all of which are involved in tissue damage in RA and development of the

atherosclerotic plaque and subsequent risk of plaque rupture (10, 25). Both, IL-6 and TNFα levels are elevated in RA (Table 1). The release of pro-inflammatory cytokines from the synovial tissue induces systemic inflammation triggering all these events (25). These circulating cytokines may also cause inflammatory changes in the adipose tissue resulting in an increased production of adipokines leading to a further enhancement of systemic inflammation (Table 1) (11, 27). Macrophages present atherogenic antigens against oxLDL or apolipoprotein (apo) B to CD4+ T cells, resulting in chemo attraction of leukocytes, T-cell proliferation and production of TNFα and interferon-γ (IFN-γ) (28, 29). These pro-inflammatory cytokines induce lipid uptake by macrophages (28, 30). In addition, macrophage activation leads to increased expression of endothelial leukocyte adhesion, resulting in higher adherence of monocytes and T-lymphocytes and secretion of pro-inflammatory cytokines such as IL1-α, IL1-β, and TNFα (31).

Specific CD4+ T cells, which are deficient for CD28, secrete high levels of pro-inflammatory cytokines and due to their capacity to infiltrate unstable atherosclerotic plaques can cause plaque rupture (32). CD4+ CD28- T cells are more often present in RA compared to healthy subjects (64% vs. 45%, P=0.02) (33). These cells also have been associated with increased extra-articular manifestations of RA and with endothelial dysfunction and subclinical atherosclerosis (34, 35). Eventually, all these processes contribute to a state of chronic inflammation and the premature development of atherosclerosis in RA (Figure 1).

RA specific alteration in high density lipoprotein function

High density lipoproteins (HDL) exert an atheroprotective effect via reverse cholesterol transport together with their anti-inflammatory, anti-oxidant and anti-thrombotic properties (36-38). Therefore, the pathofysiological association between HDL and CVD risk is complex. Several studies have shown that HDL function is impaired in RA and HDL may even express pro-inflammatory characteristics in up to 20% of RA patients (36).

Using mass spectrometry, 85 different proteins have been identified on HDL (37). Surprisingly proteomic profiling of HDL in active RA showed an increase in pro-inflammatory proteins including fibrinogen and several complement factors (C3, C9 and factor B) (39).

Interestingly, the cholesterol efflux capacity of HDL by the ATP-binding cassette transporter G1 (ABCG1), which is crucial for cholesterol efflux from hepatocytes to lipid poor HDL is impaired (40). These results were confirmed by other investigators (41). In RA higher serum levels of myeloperoxidase (MPO) correlated with a reduction in HDL cholesterol efflux capacity and this was accompanied by a reduction in the anti-oxidant function of HDL (41).

The RA-associated alterations in HDL function including its impaired cholesterol efflux capacity, a shift from anti-inflammatory to pro-inflammatory properties and a reduction in its anti-oxidant capacity may all contribute to the increased CVD (38).
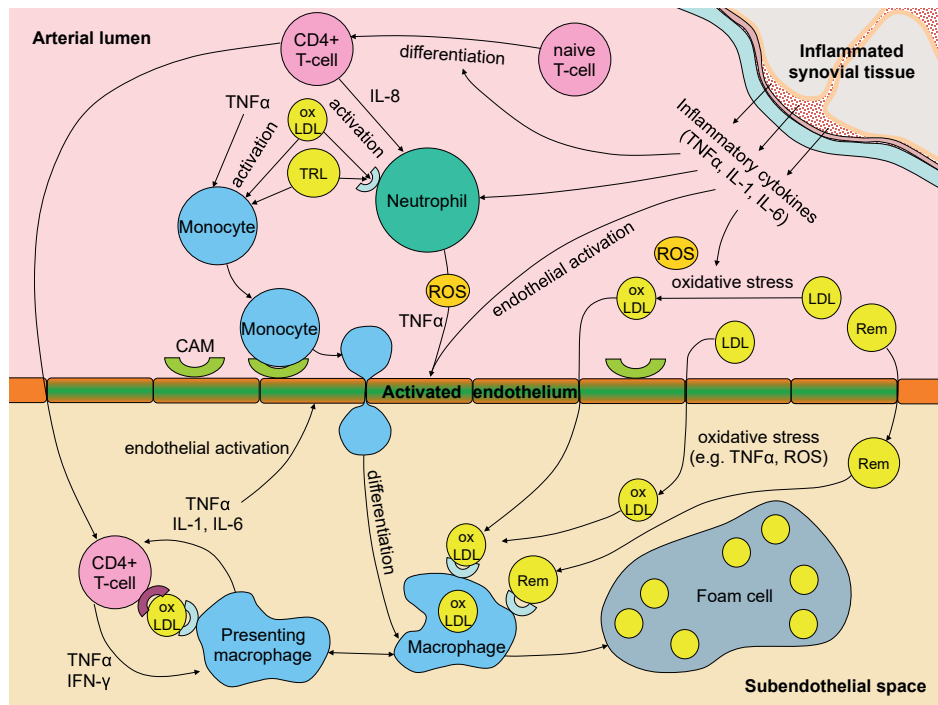
Figure 1. The inflammation-driven atherogenicity of rheumatoid arthritis (RA). Release of pro-inflammatory cytokines from the synovial tissue in RA has direct effects on systemic inflammation and the initiation of atherosclerosis. The released cytokines modulate the function of the endothelium, leukocytes and the oxidation of lipoproteins. Oxidation of low-density lipoproteins (LDL) can be initiated by TNFα and reactive oxygen species (ROS), inducing uptake by macrophages, converting them into foam cells when cholesterol influx exceeds cholesterol efflux. Native chylomicron remnants (Rem) can be taken up by macrophages without modification leading to foam cell formation. Macrophages present atherogenic antigens like ox-LDL to CD4+ T cells, which attracts additional leukocytes and leads to T cell proliferation and production of more TNFα and interferon-γ (IFN-γ). These proinflammatory cytokines, and triglyceride-rich lipoproteins (TRL), which include chylomicrons, chylomicron remnants and VLDL, activate monocytes and neutrophils, promote additional lipid uptake by macrophages and increased expression of cellular adhesion molecules (CAM) on the endothelium, which further attracts monocyte derived macrophages and T-lymphocytes and the expression of pro-inflammatory cytokines such as IL1-α, IL1-β, and anti TNFα (31). All these enhanced cascades in RA contribute to chronic inflammation and the premature development of atherosclerosis in RA.

Table 1. RA mediated changes in cellular adhesion molecules, cytokines and chemokines associated with the development of atherosclerosis

Cytokines, chemokines, adhesion molecules	Changes in RA	Atherogenic effect
CRP	25% of RA patients have CRP>10mg/L (4)	Activation of inflammatory cells (11)
TNFα	Increased with 62% (61)	Local and systemic inflammatory response (11) and increased VCAM-1 expression (146)
IL-6	Three-fold increased (61)	Local and systemic inflammatory response
E-selectin	20-43% increased (61, 147, 148)	Adherence of leukocytes to endothelium
sVCAM-1	May be increased, but data are inconsistent (61, 147-150)	Endothelial adhesion of leukocytes
sICAM-1	7-115% Increased (61, 147, 148, 150)	Endothelial adhesion of leukocytes
sTF	Almost three-fold increased (151)	Endothelial cells and leukocytes; initiates coagulation cascade
VEGF	Both an increase (149) as well as no change have been reported (61)	Endothelial permeability, pro-angiogenic
Angpt-2	Increased (149)	Upregulation of growth factors, cytokines and chemokines
MPO	33% increased (61)	Produces cytotoxic agents during respiratory burst of neutrophils

CRP = C-reactive protein; sTF = soluble tissue factor; Angpt-2 =angiopoetin-2; VEGF = vascular endothelial growth factor; TNFα = Tumour Necrosis Factor-α; ICAM-1 = intercellular adhesion molecule-1; MPO = my-eloperoxidase; IL = interleukin; CAC = coronary artery calcium score

RA and markers of subclinical atherosclerosis

Atherosclerosis is a slowly progressive disease, which remains asymptomatic for many years before clinical CVD becomes evident. The first stages of subclinical atherosclerosis include endothelial dysfunction and the formation of fatty streaks and atherosclerotic plaques, which result in increased arterial stiffness and thickening of the intima and media of the arterial wall (42). There are several surrogate markers of atherosclerosis available such as flow mediated dilatation (FMD), augmentation index (AIx), pulse wave velocity (PWV), carotid intima media thickness (cIMT), the coronary artery calcification score (CAC) and computed tomography angiography (CTA). Data on these surrogate markers of atherosclerosis in RA have been summarized in Table 2. Overall, a decrease in FMD and an increase in AIx and PWV have been reported in RA-patients, suggesting endothelial dysfunction (43-48). Inflammation during the early course of RA, which is characterised by increased CRP concentrations, has been associated with increased arterial stiffness (measured by PWV and AIx) after 15 years of follow up (49). Several studies have shown increased cIMT and formation of plaques within the carotid artery in RA patients, which was already observed early in the disease when compared to non-RA

controls (43, 44, 50). However, a small cohort study of 105 RA patients did not identify cIMT as a predictor for future cardiovascular events (51). Recently, van Sijl et al. showed no differences in cIMT between RA patients and healthy controls. They described a maladaptive outward carotid arterial remodelling, which plays an important role in plaque instability and rupture, but this is not measured using the regular cIMT technique (52).

Both, in the general population and in RA patients the presence of carotid artery plaques increase the CVD risk (51, 53). The presence of vulnerable plaques, with a thin fibrous cap, a larger lipid core and infiltration of inflammatory cells, increases the CVD risk even more. Patients with RA have more carotid plaques than the general population (54, 55) and RA patients had more vulnerable plaques when compared to controls (56).

CTA can be used to visualize soft, non-calcified plaques and the presence of stenotic arteries like the coronary and carotid arteries. Since carotid plaques are recently shown to be a predictor of poor cardiovascular survival, CTA may provide additional accuracy in CVD risk prediction in RA.

With the improvement of Computed Tomography, CAC is an established, non-invasive instrument to measure the atherosclerotic burden. CAC has a high sensitivity and negative predictive power for obstructive coronary artery disease, but the specificity of CAC is limited (57). The ability of CAC to predict future coronary events in symptomatic persons has been proven in several studies (57). The severity of coronary artery calcification has been found to be increased in RA patients compared to controls (58, 59). However, Chung et al. did not find a significant difference in CAC between early RA patients (less than 5 years after diagnosis) and healthy controls (58). These results suggest that the development of coronary calcifications may depend on the duration of RA.

In addition to functional tests, also circulating markers of endothelial function such as E-selectin, vascular and intercellular cell adhesion molecules have been proposed as markers of endothelial dysfunction (42). Increased plasma levels of these molecules have been observed in RA, but there was no correlation between several adhesion molecules and CVD risk or subclinical markers of atherosclerosis (Table 1) (60-62).

Prevalence of traditional cardiovascular risk factors in RA

Research on atherosclerosis in RA patients for the last 25 years has focussed on inflammation (31). In our opinion, traditional CVD risk factors need to be addressed in RA since the prevalence in RA may be as high as in patients with diabetes mellitus, which is known for its increased frequency of hypertension and dyslipidemia (63).

As known, smoking is one of the most important environmental risk factors for the development of CVD, but smoking is also known as a risk factor for the development of RA and accounts for approximately 25% of the risk to develop the disease (64). This

Table 2. Overview of studies comparing RA to healthy controls regarding different surrogate markers of (sub)clinical atherosclerosis.

Study	RA Patients	Controls	RA disease duration	Evaluation Method	Results
Kocabay 2012 (46)	24	19	Newly diagnosed RA	PWV	Increased PWV in RA compared to controls
Provan 2011 (49)	113	86	No specific timing	PWV/AIx	Increased PWV and AIx in RA patients with high disease activity compared to controls and RA patients in remission.
Klocke 2003 (45)	14	14	No specific timing	AIx	Increased AIx in RA
Wong 2003 (47)	53	53	No specific timing	PWA	Decreased small and large artery elasticity and increased systemic vascular resistance in RA patients compared to controls
Chatterjee-Adhikari 2012 (44)	35	35	Disease duration 1 year	FMD	FMD was lower in RA compared to controls
Veselinovic 2012 (48)	52	30	No specific timing Mean disease duration 5.7±5.2 years	FMD	Decreased FMD in RA patients compared to controls
Sodegren 2010 (43)	79 baseline, 27 in follow-up	44	Symptoms <12months at baseline, follow-up after 18 months	FMD	No significant differences at baseline or at follow-up
Veselinovic 2012 (48)	52	30	No specific timing Mean disease duration 5.7±5.2 years	cIMT	Greater cIMT in RA patients compared to controls
Van Sijl 2012 (52)	96	274	No specific timing Mean disease duration 13±10 years	cIMT	No difference in cIMT, but a difference in parameters suggesting maladaptive outward remodelling of the carotid artery
Chatterjee-Adhikari 2012 (44)	35	35	Disease duration 1 year	cIMT	Increased cIMT in RA
Sodegren 2010 (43)	79 baseline, 27 in follow-up	44	Symptoms <12 months at baseline, follow-up after 18 months	cIMT	No significant difference at baseline. Increased cIMT after 18 months of follow up in RA
Hannawi 2007 (50)	40	40	Symptoms <12 months	cIMT	Significant higher cIMT in RA
Giles 2009 (59)	195	1073	None, median disease duration 9 (IQR4-17) years	CAC	Significant higher CAC in Male RA patients but not in female patients compared to controls
Chung 2005 (58)	141	86	Disease duration <5years (early RA) or >10 years (established RA)	CAC	CAC was higher in patients with established RA when compared to controls and patients with early RA

PWV = pulse wave velocity; Aix = augmentation index; cIMT = carotid intima media thickness; IQR = inter quartile range; CAC = coronary artery calcium score

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risk for developing RA is dose dependent and even higher in anti-citrullinated peptide antibody (ACPA) positive RA patients (65-68). Smoking is therefore frequently seen in RA populations and may provide a potential bias in studies on RA and CVD. A recent meta-analysis by Sugiyama et al. showed that the prevalence of ever, current and past smokers in RA was as high as 50.6%, 26,5% and 26,3%, respectively (66).

There is also a complex relation between obesity, RA and CVD. In RA patients, obesity results in higher RA disease severity, increased swollen joint count and higher work disability (69, 70). Besides the negative impact on RA itself, obesity is associated with cardiovascular morbidity and mortality (71, 72). Similar associations between obesity and CVD have also been found in RA (70, 73, 74). A different effect of a low body mass index (BMI) on CVD mortality in RA has also been suggested. The incidence in CVD mortality for RA patients with a BMI below 20 kg/m^2 is increased compared to the general population (75). A possible explanation of this increased CVD risk is that a low BMI in RA patients may indicate the presence of rheumatoid cachexia. This condition reflects predominantly a loss of skeletal muscle and is, among others, mediated by an increased production of pro-inflammatory cytokines (76). Furthermore, RA patients are less active than their healthy counterparts and physical inactivity in RA has been associated with an increased arterial stiffness (77).

Several studies have shown an underdiagnosis and undertreatment of traditional CVD risk factors, such as hypercholesterolemia and hypertension in RA (78-80). Hypertension is common in RA, with a prevalence ranging from 57% to 70.5% and hypertension is frequently not optimally controlled in RA (78, 79). In these studies, 40% to 45% of RA patients with hypertension did not reach target blood pressure levels as defined in current therapeutic guidelines (i.e. a systolic blood pressure of ≤ 140mmHg and/or a diastolic blood pressure of ≤ 90mmHg) (78, 79). Panoulas et al. showed that 32% of RA patients with target organ damage (defined as described in the European guideline for management of arterial hypertension) had undiagnosed hypertension (78). RA itself can be seen as a risk factor for the development of hypertension. As described earlier, the RA associated inflammatory state may activate the endothelium, which can lead to endothelial dysfunction, inhibition of the vasodilatory function, vascular calcification and therefore increased central blood pressure (31, 45, 81).

In the inflammatory state of RA, cholesterol levels, which include HDL-C, LDL-C and total cholesterol, may be suppressed (82). However, HDL-C concentrations are more suppressed in RA than the atherogenic LDL-C, which results in a more atherogenic lipid profile (29, 82, 83). This might be the explanation why several investigators found that lower cholesterol levels were associated with increased CVD risk in RA (84, 85). Furthermore, these studies did not take into account the heterogeneity of HDL function as described earlier. Interestingly, a decrease in total cholesterol and LDL-C, but not in HDL-C, can already be observed 5 years prior to the diagnosis of RA (86). The mechanism

behind these changes, which are different from the changes during active RA disease, is not fully understood. It is believed that the inflammatory state, which is present prior to diagnosis, plays an important role (86). Serum apo B levels and the number of circulating chylomicrons are higher in RA patients when compared to age matched healthy controls (87). Knowlton et al. measured lipid profiles as well as apolipoproteins in 152 RA patients and determined the coronary artery calcification score at baseline and after 3 years of follow-up. They showed that RA patients with progression in CAC had significantly higher total cholesterol/HDL-C, higher levels of apo B and a higher number of circulating chylomicrons compared to RA patients that did not show any CAC progression (88). No differences in plasma apo A-I levels were found.

Drug related cardiovascular risk factors in RA

Non-steroidal-anti-inflammatory-drugs (NSAIDs) and oral glucocorticoids are widely prescribed in RA, which are both associated with the development of hypertension (78, 89-91). A recent meta-analysis by Trelle et al. evaluated several NSAIDs in relation to myocardial infarction, stroke, cardiovascular death. They found that cardiovascular profiles of individual NSAIDs varied considerably. Overall naproxen seemed less harmful regarding cardiovascular risk when compared to other NSAIDs (91). The exact mechanism by which NSAIDs increase the risk of a cardiovascular event is not fully understood. The degree of blocking of cyclooxigenase-2 is suggested to play an important role in the cardiovascular risk profile of an individual NSAID (92, 93).

Regarding glucocorticoïds, Aviña-Zubieta et al. recently showed an increased risk for myocardial infarction in current users (94). No significant correlation between cerebral vascular disease and the use of glucocorticoïds was found (95). The contribution of glucocorticoïds to CVD risk is believed to be dose dependent (94).

Cardiovascular risk prediction in RA

The most widely used risk scores for the prediction of CVD are the Framingham Risk Score and the SCORE model (96, 97). These risk models are based on traditional CVD risk factors in non-high risk populations, but they do not take into account the excess CVD risk observed in RA patients. Because of the mounting evidence regarding the excessive CVD risk in RA and the lack of precise management and risk stratification in RA, the European League Against Rheumatism (EULAR) published in 2010 recommendations for CVD risk management specifically for RA and other forms of inflammatory arthritis (98). EULAR recommends an annual risk assessment for all RA patients using national

guidelines. A first attempt to adapt the traditional SCORE model (97) and Framingham Risk Score (96) for RA patients was made, to correct for the underestimated CVD risk (Table 3). This modification includes a multiplication of the measured CVD risk (with the use of SCORE or the Framingham Risk Score) by a factor of 1.5 for patients with RA and two of the following three criteria: RA disease duration >10 years, the presence of rheumatoid Factor (RF) or anti-CCP and/or presence of severe extra-articular manifestations (98). However, the criterion of disease duration of >10 years is debatable because recent publications have shown that the risk for cardiovascular morbidity and mortality is already increased shortly after the diagnosis of RA, which underscores the importance of early intervention (43, 99). In addition, Finck et al. showed that the addition of RF or anti-CCP to the traditional FRS did not improve the accuracy of CVD risk prediction in RA patients (100). Despite these shortcomings, the EULAR has made a first attempt to improve CVD risk assessment in RA. In our opinion, clinical trials are necessary to establish the validity of these recommendations.

The 2011 Dutch guideline for CVD risk management also suggests to adapt the standard risk assessment tool in RA patients (101). It was advised to add 15 years to the age of RA patients when establishing their risk according to the SCORE table (Table 3). However, once again evidence for this approach is lacking. The recently developed guideline for the management of dyslipidaemias from the European Atherosclerosis Society (EAS) and European Society of Cardiology (ESC) recognises RA as a risk factor for the development of atherosclerosis but does not provide specific recommendations for CVD risk assessment in the case of RA (Table 3) (98, 102). Therefore, further research to develop an accurate risk assessment tool with treatment recommendations aimed at RA is necessary. In the mean time risk stratification might be improved by the combination of risk assessment tools with atherosclerotic imaging.

Table 3. Overview of national and international guidelines for CVD risk assessment in RA patients.

	Adaptations to current CVD risk assessment
EULAR	CVD risk* x 1,5 when 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	Age +15 years for all RA patients**
EAS guideline for dyslipidaemia	No adaptations

* According to SCORE and/or Framingham
** For assessment of CVD risk according to SCORE

Treatment of traditional cardiovascular risk factors in RA

Treatment of traditional CVD risk factors is the cornerstone of successful CVD risk reduction in the general population (102). In our opinion, awaiting further studies, this is also the case in RA. Treatment of CVD risk factors includes both, lifestyle modification and pharmaceutical interventions.

Exercise is in the general population an important behavioural strategy for CVD prevention, but also in RA patients (103). It has been shown that an individualized exercise training program, which consisted of a 6 months tailored aerobic and resistance exercise intervention, improved endothelial function in patients with RA (104). RA guidelines emphasize indeed the role of exercise and physical activity, but they do not provide clear recommendations (105). More studies are necessary to investigate the effect of exercise in reducing CVD risk in RA and to provide clear recommendations for RA patients. Dietary advice may include a traditional low-fat diet or a Mediterranean diet. The Mediterranean diet is rich in omega-3-fatty acids as opposed to predominantly omega-6-fatty acids in western diets and has been shown to reduce cardiovascular risk (106). Besides their protective role in cardiovascular disease, omega-3-fatty acids reduce inflammation in chronic inflammatory diseases such as RA (107, 108).

Pharmaceutical interventions are the next step in CVD risk prevention after improving lifestyle. A recent study showed that patients with inflammatory joint disease receiving statin therapy had a comparable decrease in cholesterol levels and CVD risk reduction as patients without inflammatory joint disease (109). This is further illustrated by De Vera et al. who showed that discontinuation of statin therapy in RA patients who already used statins was associated with increased cardiovascular mortality (HR 1.41, 95% CI 1.02-1.96) (110). Statin therapy successfully lowers LDL-C and CVD risk (Table 4), but the benefit of treatment in primary prevention depends on age and other risk factors. Uncertainty exists when to initiate lipid lowering therapy in RA patients for primary prevention. The Dutch guideline for CVD risk management 2011 recommends to treat RA patients similarly as patients with diabetes mellitus, suggesting early and intensive lipid lowering therapy with LDL-C treatment targets of 2.5 mmol/l (101). Recently, Rollefstad et al. showed that a structured approach and treatment to target is possible in patients with inflammatory joint disease since 90% of the study population (n=426) was successfully treated to lipid targets (80).

Besides their lipid lowering effect, statins also have anti-inflammatory properties (111, 112). The Jupiter trial showed that rosuvastatin significantly reduced the incidence of major cardiovascular events in apparently healthy persons without hyperlipidemia, but with elevated high-sensitivity CRP levels (112). These data suggest that the beneficial effects of statins are more than just LDL-C lowering and that the anti-inflammatory role of these drugs may also contribute to CVD risk reduction. However, others have shown that, in non-RA patients, most of the CVD risk reduction by statins can be accounted for

by the LDL-C reduction and not by these so called (anti-inflammatory) pleiotropic effects (113). In addition to the lipid lowering effect, reduction of RA disease activity on statin therapy has also been described (114). El Barbary et al. showed that atorvastatin in RA resulted in a marked reduction in RA disease activity, a more advantageous atherogenic index and improved endothelial function (115). However, the opposite has also been described. A recent study with an arthritis mouse model by Vandebriel et al. showed that treatment with atorvastatin or pravastatin accelerated arthritis onset and resulted in a higher prevalence of arthritis compared to non-statin using mice (116). These results confirm previous reported associations of statin use and the development of RA in observational studies (117). Whether these associations outweigh the beneficial effect of statins on atherosclerosis in RA is not yet clear. Prospective studies on the use of statins in RA are lacking. Therefore, we feel that routinely prescription of statin therapy to RA patients regardless their lipid profile is not justifiable. Whether the treatment target for LDL-C of 2.5mmol/L is justifiable, remains to be investigated in prospective studies.

Strict regulation of blood pressure with treatment targets of a systolic blood pressure ≤140 mmHg have been recommended in all patients including patients with RA (101), although prospective data on strict blood pressure regulation in RA patients are lacking. It is important to perform blood pressure measurements on a routine basis to properly diagnose hypertension in RA patients (118). Especially since small increases in systolic blood pressure (1-5 mmHg) have already been associated with an increased CVD risk (119). However, there are limited data available regarding the preferred antihypertensive agents in specifically RA. There is some evidence that angiotensin converting enzyme (ACE) inhibitors may be beneficial in RA. Flammer et al. showed that 8 weeks of treatment with ACE-inhibitors improved endothelial function (assessed by FMD of the brachial artery) in RA patients, together with a reduction in CD40, which is an important inflammatory mediator and member of the TNFα superfamily (Table 4) (120).

Current guidelines recommend to start pharmaceutical interventions early for traditional CVD risk factors. However, since the exact contribution of the classical CVD risk factors to the development of CVD in RA is still unclear and specific RA-related evidence for initiating CVD risk management is lacking, we feel that more evidence on the beneficial effect of early and aggressive treatment of traditional CVD risk factors is necessary before starting widespread primary prevention. Nevertheless, much improvement may already be achieved with routine blood pressure monitoring and adequate treatment of existing hypertension using general guidelines for hypertension.

Although the incidence of both arterial and venous thrombo-embolism is increased in RA (121, 122), the use of anti-platelet therapy in RA to decrease CVD risk has not been investigated. The concomitant use of NSAIDs might be a complicating factor, since some diminish the effect of aspirin, while others have significant anti-platelet effects (123). Further studies are needed to clarify the role and safety of anti-platelet therapy in RA patients.

Table 4. An overview of major studies, which investigated the relation of RA and non-RA medication on atherosclerosis in RA.

Drugs	Evidence for its association with atherosclerosis in RA (Studies in both humans and animals)	Biological mechanism
NSAIDs	Meta-analysis of human studies: higher risk of CVD. Differences between different NSAIDs (91) Animal studies not available	Not fully understood. Inhibition of COX-2 is believed to play a role (92, 93)
Hydroxychloroquine	Case-control study: Reduced cardiovascular risk (132) Animal studies not available	Improvement of dyslipidemia has been proposed.
Methotrexate	Several studies (case control, cohort): cardiovascular risk reduction (8, 132), but no reduction has also been described (135) Animal studies not available	Potentially due to its anti-inflammatory properties, but it may also be drug specific.
Anti-TNFα	Several case-control studies: cardiovascular risk reduction (130, 132) Animal studies not available	Anti-inflammatory effects Improvement of endothelial function
Rituximab	Conflicting data; small groups Human: improvement of arterial stiffness as well as no improvement has been described. However, most data suggest a decrease of atherosclerosis progression (140-142) Animal studies not available	Improvement of lipid profile and endothelial function has been suggested.
ACE-I/AT2 antagonists	Small randomized trial: cardiovascular risk reduction (120, 152) ' Animal study (153)	Improvement of endothelial function Dose dependent depression of TNFα
Statins	Randomized trial: Cardiovascular risk reduction (109) Animal study (154)	Reduction of LDL-C, which is comparable to the reduction in non-RA patients. Improvement of endothelial function. Mild anti-inflammatory effects. Anti-inflammatory effects
Fibrates	Small pilot cohort study (155) Animal studies not available	Decrease in CRP and IL-6 Decrease of TC and TG, increase of HDL-C
PUFA's	Meta-analysis in humans: a possible reduction in cardiovascular risk Animal study: preventive against atherosclerosis (156, 157)	Decrease of NSAID use. Less necrosis and collagen in the atherosclerotic plaque. Reduction of IL-10. Anti-inflammatory properties
Fishoil	Small cohort study: Reduced cardiovascular risk Animal studies not available	Several mechanisms such as increase of n-3- fatty acids and decrease of n-6-fatty acids, but also a concomitant decrease in NSAID use (158)

NSAIDs = non-steroidal anti-inflammatory drugs; COX = cyclo-oxygenase; ACE-I = angiotensin converting enzyme inhibitor; AT2 = angiotensin 2; TC = total cholesterol; TG = triglycerides; PUFA = poly-unsaturated fatty acids; IL = interleukin; TNF = tumour necrosis factor

The influence of DMARD therapy on lipid levels

Intensive DMARD therapy results in a better suppression of disease activity and therefore a suppression of the general inflammatory state. There is a complex interplay between traditional CVD risk factors and the risk caused by the inflammatory burden at the lipid level. Since DMARD therapy decreases inflammation it is not surprising that dyslipidemia may improve upon DMARD therapy. Hydroxychloroquine decreases LDL-C and total cholesterol levels (124). Long term treatment with TNFα inhibitors is significantly associated with increased HDL-C, total cholesterol and triglyceride levels and may be associated with a decreased apo B to apo A-I ratio (125-127), but there is no significant change in LDL-C and the atherogenic index (125, 126). Recently Navarro-Milán et al. showed an increase in HDL-C, LDL-C and total cholesterol shortly after treatment initiation with methotrexate alone or in combination with etanercept or hydroxychloroquine and sulphasalazine (128). Interestingly, increased HDL-C levels were only observed in RA patients who responded to DMARD therapy (93% methotrexate, 14% other DMARDs) in contrast to non-responders who did not show a beneficial effect on HDL-C levels (129). This illustrates that change in lipid levels upon DMARD therapy correlates with disease activity.

DMARD treatment and cardiovascular disease

Over the last years a growing number of studies on CVD risk reduction by different individual DMARDs has been published. Numerous studies have described a beneficial effect on CVD in RA by methotrexate (MTX) and biologicals, showing a decrease in cardiovascular morbidity and mortality (Table 4) (8, 130-132). However, the reduction in CVD by TNFα inhibitors is not as consistently seen as with studies of MTX. Improvement of subclinical and clinical atherosclerosis by DMARDs has been observed as well. Treatment with MTX, during one year, resulted in a reduction in cIMT, reflecting a reduction in atherosclerosis (133). A systematic review concerning MTX and CVD in RA showed strong evidence that the use of MTX was associated with reduced cardiovascular morbidity and mortality (134). However, a recent cohort study did not confirm this finding (135). It should be noted that all 10.156 included RA patients in this study were receiving various DMARDs. It is not clear whether lowering the CVD risk by MTX is caused by reducing RA disease activity or by a reduced inflammation in general. Therefore, it remains to be shown whether MTX will lower cardiovascular event rates in non-RA patients. The first trial addressing this question is the ongoing Cardiovascular Inflammation Reduction Trial (CIRT) (www.clinicaltrials.gov; trial number NCT01594333). Because of the important role of TNFα in the development of atherosclerosis, most studies investigated

the effects of anti-TNFα therapy in relation to CVD (136). The addition of infliximab to MTX for 12 weeks resulted in improved FMD (137). One-year treatment with anti-TNFα therapy in patients with inflammatory arthropathies including RA resulted in reduced arterial stiffness and less progression in cIMT when compared to RA patients not receiving anti-TNFα therapy (131, 138). A longitudinal cohort study reported that RA patients using anti-TNFα showed a reduction in cardiovascular events compared to RA patients using other DMARDs than anti-TNFα (HR 0.39; 95% CI 0.19-0.82) (135). A recent systematic review showed that in most studies, anti-TNFα therapy reduced the likelihood of CVD in RA (139). The balance of evidence suggests that TNF-α antagonists have a beneficial effect on cardiovascular risk (Table 4). However, larger and more robust studies are warranted to confirm recent findings. The effects of anti B-cell therapy, i.e. Rituximab, remains inconclusive (140, 141). Several studies showed improvement of endothelial function after treatment with rituximab (140, 142, 143), but others did not show (141). These contradictory results may be explained by the role of B-cells in the development of atherosclerosis since immature B-lymphocytes (B1) seem to be protective against atherosclerosis (144) and mature B-lymphocytes (B2) may aggravate atherosclerosis (145).

Conclusion

Current knowledge suggests that RA patients need to be routinely screened for CVD risk factors. RA patients will benefit from routine cardiovascular screening since there is much evidence of underdiagnosis and undertreatment of traditional CVD risk factors in RA. The first steps to improve CVD risk assessment in RA are being taken in national as well as international guidelines with the adaptation of traditional risk assessment tools such as the SCORE or Framingham risk score. Risk stratification may be further improved by carotid plaque detection with ultrasound in all RA patients. Randomized controlled trials are needed to evaluate the effects of the suggested strict cardiovascular treatment versus current practise. It would be interesting to investigate treatment of RA patients with lipid lowering drugs to the same extent as current practise in patients with diabetes mellitus of CVD. Finally, a validated CVD risk assessment tool for RA should be developed. Considering current evidence a routinely referral of RA patients to a vascular outpatient clinic for cardiovascular screening and treatment seems advisable.

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CHAPTER 3

Marked underdiagnosis and undertreatment of hypertension and hypercholesterolemia in rheumatoid arthritis

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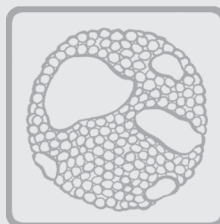
Abstract

Objective: To investigate the prevalence of underdiagnosis and undertreatment of traditional cardiovascular risk factors in RA patients.

Methods: RA patients ≤70 years of age without CVD or diabetes mellitus were included. Systolic blood pressure (sBP) and a fasting lipid profile were measured. The 10-year CVD risk was estimated using the Dutch Cardiovascular Risk Management (CVRM) guideline and EULAR modifications of the SCORE Tables.

Results: 327 Patients were included (female gender: 68%). Age (mean±SD) was 53±11 years. Median disease duration was 7 years (IQR: 2-14 years). According to the CVRM guideline, 52% patients had a CVD risk ≥20% and according to the EULAR guideline 18%. LDL-C ≥2.5mmol/l was found in >80% of the patients with a CVD risk ≥10% estimated by both the CVRM and EULAR guidelines. 32-42% of the patients with a CVD risk ≥10% had a sBP >140mmHg, depending on the risk model used. Statins were used in 6% and antihypertensives in 23-25% of whom 50-86% did not reach the recommended treatment targets.

Conclusion: Regardless of the adapted risk assessment model used, untreated hypertension and hypercholesterolemia were frequently found in RA patients with increased CVD risk. Treatment of these cardiovascular risk factors deserves more attention in RA.

Introduction

The evidence on the increased risk for cardiovascular disease (CVD) in rheumatoid arthritis (RA) has accumulated during the last two decades (1-3). It has been suggested that the prevalence of CVD in patients with RA is as high as in patients with type 2 diabetes mellitus (T2DM) (1, 4). Traditional cardiovascular risk factors, such as hypercholesterolemia and hypertension, and RA specific risk factors, such as RA disease activity, erythrocyte sedimentation rates and C-reactive protein levels may play a role in the overall CVD risk of RA patients (5-8). The importance of traditional CVD risk factors has been strengthened by recent national and international recommendations. However, because of the excess CVD risk, the traditional risk assessment algorithms (the SCORE [Systemic COronary Risk Evaluation] or Framingham Risk Score Tables) do not seem valid. Therefore, adaptations of these risk models were suggested by the European League Against Rheumatism (EULAR) in 2010 specifically aimed at CVD risk management in RA and other forms of inflammatory arthritis (9). These recommendations include a multiplication of the measured CVD risk as assessed by the SCORE or the Framingham Risk Score Tables by a factor of 1.5 for patients with RA and extra risk criteria as described in Table 1 (9). The 2011 Dutch guideline for CVD risk management (CVRM) also proposes modifications of the standard risk assessment tool for RA patients (10). The Dutch CVRM guideline recommends the addition of 15 years to the age of RA patients when establishing their risk according to the SCORE Tables (Table 1). These modifications of the original risk stratification models have a large impact on current care, since the number of patients eligible for treatment of hypertension and hypercholesterolemia may increase substantially. In this study, we evaluated the degree of underdiagnosis and undertreatment of hypertension and hypercholesterolemia in RA patients at inclusion in an open label intervention trial treating CVD risk factors (the FRANCIS study) when two different risk assessment models were applied.

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

Material and Methods

Study design

Cross-sectional study in RA patients investigating the prevalence and treatment of hypercholesterolemia and hypertension. Differences between the performance of different risk assessment models were explored.

Data collection

The data for this study were part of the FRANCIS (Franciscus Rheumatoid Arthritis and Cardiovascular Intervention Study) study. The FRANCIS study is an open label randomized clinical trial in which RA patients younger than 70 years old and without current CVD or T2DM were either randomized to intensive treatment with pre-specified targets and recommendations on lifestyle changes or were referred to their general practitioner for treatment of these risk factors (Dutch Trial Register NTR3873; ABR no. NL32669101.10). All the data presented here are baseline data, which were collected at study entry before randomization.

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 cardiovascular risk factors at the Diabetes and Vascular Center, Sint Franciscus Gasthuis, Rotterdam, the Netherlands.

The Institutional Review Board of the Sint Franciscus Gasthuis in Rotterdam and the regional independent medical ethics committee, Maasstad Hospital, Rotterdam, approved the study. The study was conducted according to the Declaration of Helsinki. All participants gave written informed consent. The FRANCIS study is registered in the Dutch Trial Register (NTR3873).

Definition of hypertension and hypercholesterolemia

Hypertension was defined as a systolic blood pressure of >140mmHg and/or the use of antihypertensive drugs. Hypercholesterolemia was defined a LDL-C >2.5mmol/l and/or the use of lipid lowering drugs.

Underdiagnosis was defined as a systolic blood pressure or LDL-C above the above mentioned targets in patients with a CVD risk ≥10%. Undertreatment was established when a specific patient was already treated for hypertension and/or hypercholesterolemia without reaching the treatment targets.

Cardiovascular risk assessment

The 10-year cardiovascular risk was assessed using the SCORE Tables following the modified 2010 EULAR recommendations and the 2011 Dutch CVRM guideline (Table 1) (9, 10).

Rheumatoid arthritis disease activity

Rheumatoid arthritis disease activity was assessed using the Disease Activity Score with 28 joints counted (DAS28). This score included swollen joint count (28), tender joint count (28), VAS score (scale 0-100) indicating pain and discomfort due to RA, and the level of C-reactive protein (CRP).

Laboratory measurements

A standardized set of measurements was performed in each subject. Blood samples were drawn after an overnight fast. Laboratory parameters were determined at the Department of Clinical Chemistry, Sint Franciscus Gasthuis, Rotterdam, the Netherlands. Renal and liver function tests as well as glucose, CRP, total cholesterol, HDL-C and triglycerides (TG) were measured using Synchrom LX or DxC analyzers (Beckman Coulter, Anaheim CA, USA). LDL-C was calculated using the Friedewald formula if TG were below 4.00 mmol/l. Apolipoprotein (apo) AI and apo B were determined by rate nephelometry using IMMAGE with commercially available kits (Beckman Coulter).

Statistics

Data are given as mean ± standard deviation (SD) in the text and Tables unless stated otherwise. Differences between risk assessment models were determined using the paired t-test. P-values below 0.05 (two sided) were considered statistically significant. All statistical analyses were performed using PASW statistics version 18.0 (IBM SPSS Statistics, New York, United States).

Results

General Characteristics

Of the 332 patients who were referred to the outpatient clinic, 5 were excluded because of previously undiagnosed T2DM. 223 Of the 327 included RA patients were female (68%). The mean age was 53 ± 11 years and the median RA disease duration was 7 years (IQR 2-14 years). The median DAS28CRP was 2.1 (IQR 1.6-3.0). Disease remission (DAS-28CRP <2.6) was achieved in 187 patients (57.3%), 41 (12.5%) had low disease activity (DAS28CRP 2.6-3.1), 66 (20.2%) moderate disease activity (DAS28CRP 3.1-5.1) and 27 (8.3%) had high disease activity (DAS28CRP >5.1). DAS28CRP data were missing in six patients at inclusion. The general characteristics are shown in Table 2.

Table 2. General characteristics and fasting laboratory measurements.

	N= 327 Mean ± SD
Female (n,%)	223 (68%)
Age (yrs)	53 ± 11
Body mass index (kg/m^2)	26.5 ± 4.5
Waist circumference (cm)	94 ± 14
Current smoker (n,%)	60 (19%)
Systolic blood pressure (mmHg)	132 ± 19
Diastolic blood pressure (mmHg)	79 ± 10
Total cholesterol (mmol/l)	5.4 ± 1.1
LDL-C (mmol/l)	3.4 ± 0.9
HDL-C (mmol/l)	1.47 ± 0.41
Triglycerides (mmol/l) median (IQR)	1.05 (0.73-1.51)
Apolipoprotein AI (g/L)	1.69 ± 0.37
Apolipoprotein B (g/L)	1.00 ± 0.26
Fasting glucose (mmol/L)	5.46 ± 0.56
HbA1C (mmol/mol)	35 ± 4.4
RA disease duration (yrs) median (IQR)	7 (2-14)
Rheumafactor positive (n,%)	198 (60%)
Anti CCP positive (n,%)*	181 (66%)
Erosive disease (n,%)**	126 (44%)
DAS28CRP median (IQR)	2.1 (1.6-3.0)
Statin use (n,%)	15 (4.6%)
Anti-hypertensive use (n,%)	56 (17.1%)

* Anti-CCP levels were available in 274 patients
** Status of erosive disease was available in 284 patients

Cardiovascular risk assessment

The mean CVD risk according to the SCORE model was 8%. According to the standard SCORE model 228 patients (70%) had a CVD risk of 0-9%, 58 patients (18%) had a CVD risk of 10-19% and 39 (12%) had a CVD risk of ≥20%. According to the EULAR guidelines the mean CVD risk increased to 11%. The number of patients with a CVD risk of 0-9% decreased to 203 (61%), 62 patients (20%) had a CVD risk of 10-19% and 60 patients (18%) had a CVD risk of ≥20%. According to the Dutch CVRM guideline, the mean CVD risk increased to 21%. The number of patients with a CVD risk of 0-9% decreased to 104 (32%), 50 patients (16%) had a CVD risk of 10-19% and the number of patients with a CVD risk of ≥20% increased to 171 patients (52%) (Figure 1). The estimated CVD risk by the three models was significantly different (P<0.001).
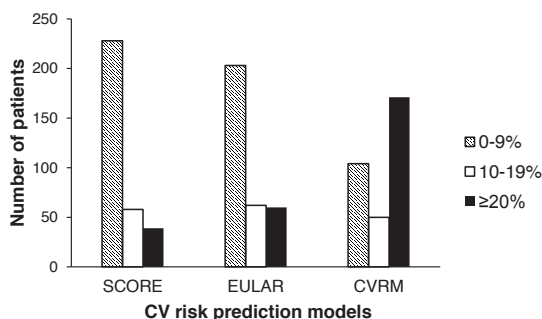
Figure 1. Ten-year cardiovascular risk stratification according to different CVD risk assessment tools. Abbreviations: SCORE = Systemic Coronary Risk Evaluation, CVRM = the Dutch guideline for Cardiovascular Risk Management, EULAR = European League Against Rheumatism.

Underdiagnosis and undertreatment of hypertension and hypercholesterolemia

When using the Dutch CVRM recommendations, 221 patients had a CVD risk score ≥10% and therefore, had an indication for treatment of their cardiovascular risk. Of those 221 patients, 72 (32%) had a systolic blood pressure >140 mmHg and 185 (84%) had anLDL-C >2.5 mmol/l. Considering all patients with a CVD risk of ≥10%, only 51 patients (23%) were treated with antihypertensives of whom 28 (50%) still had a systolic blood pressure >140mmHg. When analyzing the 14 patients already treated with statins, 12 (86%) did not reach the treatment target (Table 3).

With respect to the 171 patients with a CVD risk of ≥20%, 9 (5%) and 43 (25%) patients were treated with antihypertensives and/or statins, respectively (Table 3). Despite treatment, 24 (56%) out of the 43 patients treated with antihypertensives still had a systolic blood pressure >140 mmHg. In addition, six patients (67%) out of the nine patients treated with statins still had hypercholesterolemia in the highest CVD risk group.

When applying the EULAR guideline for CVD risk assessment, 122 (38%) patients had a CVD risk of ≥10%. Fifty-one of those patients (42%) had a systolic blood pressure >140mmHg and 102 (84%) had an LDL-C >2.5 mmol/l. 31 Patients (25%) used antihypertensives and of those, 18 (58%) did not reach the treatment target (Table 3). Only seven out of those 122 patients used statins and six (86%) did not reach the target. Considering the 60 patients with a CVD risk ≥20% according to the EULAR guideline, only 1 (2%) used a statin but without reaching the treatment target. Antihypertensives were prescribed to 14 patients (23%) and 7 (50%) still had a systolic blood pressure of >140mmHg. There was no significant correlation between systolic blood pressure and CRP (Pearson's r=0.052; p=0.353) although there was a trend with ESR (r=0.106; p=0.056). A statistical significant correlation between systolic blood pressure and DAS28 levels was found (r=0.128; p=0.027).

Table 3. Risk factors and medication use in different CVD risk categories according to the CVRM and EULAR guidelines.

	Estimated CVD risk according to CVRM guideline		Estimated CVD risk according to EULAR guideline	
	10-19% (n=50)	≥20% (n=171)	10-19% (n=62)	≥20% (n=60)
LDL-C >2.5 mmol/l (n,%)	37 (74%)	148 (87%)	53 (86%)	49 (88%)
sBP >140mmHg (n,%)	7 (14%)	65 (38%)	25 (40%)	26 (43%)
Statin use (n,%)	5 (10%)	9 (5%)	6 (10%)	1 (2%)
Anti-hypertensive use (n,%)	8 (16%)	43 (25%)	17 (27%)	14 (23%)

Abbreviations: sBP = systolic blood pressure, CVRM = Cardiovascular Risk Management, EULAR = European League Against Rheumatism

Discussion

This study shows that traditional cardiovascular risk factors such as hypertension and hypercholesterolemia are highly prevalent in RA patients following current guidelines, indicating significant underdiagnosis. Furthermore, the majority of RA patients already treated for hypertension and hypercholesterolemia did not reach the advised treatment targets for systolic blood pressure and/or LDL-C. These results are in line with previous studies reporting undertreatment of hypertension and hyperlipidemia in RA patients (11, 12). Some experts may argue that the cardiovascular risk in RA is so high that these patients may be eligible for preventive measures at an earlier stage. An option could be to define targets for risk factors in these patients and apply a treat-to-target approach, independently from the risk calculated by the above mentioned algorithms. However, at this stage there are no clinical trials to support such an approach. Furthermore, it is not currently known to what extent traditional CVD risk factors in the general population are directly applicable to RA patients. We therefore chose to apply here the SCORE risk Tables and the Dutch Risk Score algorithm for RA patients to calculate the overall risk.

The number of patient with hypercholesterolemia in our study is markedly higher than previously reported and this may be the result of application of the current CVRM guideline. The consequence of this guideline, is that the number of patients eligible for treatment increases. Moreover, the treatment target for LDL-C is lower than in previous recommendations. This situation is similar to primary prevention in the general population where undertreatment of 50% of the investigated patients has been reported (12, 13). Even in the case of secondary prevention large numbers of patients do not reach treatment targets for blood pressure and lipid levels (14, 15).

Although the ongoing inflammation is directly related to arterial wall stiffness and endothelial dysfunction (6), the role of inflammation on blood pressure is still under debate. In this study, we found a statistical significant association between DAS28

and systolic blood pressure, however the low correlation coefficient implies that this influence is probably not clinically significant. We did not find a significant association between other markers of inflammation (ESR, CRP) and systolic blood pressure. This is in line with data reported by Manavathongchai et al. (16).

The exact contribution of traditional CVD risk factors in the development of CVD in RA remains unclear since their presence alone does not seem to fully explain the excess CVD risk in these patients (5, 17). However, currently there is no reason to believe that the traditional CVD risk factors would not be associated to CVD risk in RA, similarly to the general population (5, 7). In order to minimize underdiagnosis and undertreatment it is important to identify the patients at risk. At present RA specific CVD risk assessment tools are not available and the existing algorithms for the general population may not be valid in RA. The differences in CVD risk in both suggested models for RA patients (CVRM and EULAR) underscore the level of uncertainty when predicting the CVD risk of an individual RA patient. Also, the scientific basis for the suggested adaptations of the CVRM and EULAR guidelines is limited. Inclusion of the factor "RA disease duration of >10 years" as recommended in the EULAR guideline (9), is debatable because the risk for cardiovascular morbidity and mortality is already increased shortly after the diagnosis of RA, which underscores the importance of early detection and intervention in relation to CVD risk factors (18, 19). Recent studies showed that the EULAR adaptations do not offer a better risk prediction in RA compared to the original SCORE system (20). The addition of 15 years of age in the Dutch guideline for cardiovascular risk management is based on data in T2DM patients and it is unclear whether this can be extrapolated to RA patients (21). To date no studies have validated the predictive value of the adaptations according to the CVRM guideline. The modifications of the existing SCORE (22) and Framingham (23) risk assessment by the EULAR and Dutch CVRM guidelines do not, therefore offer a real solution and there is need for an RA specific risk assessment tool (24). A recent study by Arts et al. investigated the predictive value of different adaptations to the original SCORE risk model. The authors added RA specific risk factors to the algorithm (i.e. DAS28, CRP, swollen joint count, Health Assessment Questionnaire (HAQ)) and found that these changes did not show sufficient improvement in risk prediction of future CVD to serve as an appropriate alternative to the original SCORE model (25).

Although many questions regarding the best risk assessment model remain, it is important that both, patients and physicians are aware of the increased CVD risk associated with RA and that known CVD risk factors are being treated. More routine screening and more strict adherence to treatment targets are necessary in RA patients, especially since statin treatment has shown to improve lipid levels (27,28) and treatment with ACE-inhibitors improves vascular function in RA patients (26-28). However, it must be noted that these studies used surrogate endpoints. Randomized clinical trials showing improved survival in RA by treating cardiovascular risk factors are still lacking. We

believe that in the meantime, strict cardiovascular control in RA is warranted due to the well established elevated cardiovascular risk. Additionally, since inflammation plays a key role in the development of atherosclerosis (29), a tight control of RA disease activity may also be very important in order to lower the CVD risk.

A risk assessment tool helps to identify patients at risk and offers guidance to physicians. In view of the limited value in RA patients of the original SCORE model and the modified EULAR model, the modified CVRM model may be an alternative. We have shown that the modification according to the CVRM guideline results in a markedly higher CVD risk compared to the original SCORE and the EULAR modifications. Whether this high increase in risk is valid remains to be seen. The CVRM modification (adding 15 years to the age of the patient) is easily applicable and may facilitate the use in daily practice. For general practitioners, information necessary to apply the EULAR recommendation (i.e. rheumatoid factor of anti-CCP positivity, disease duration and extra-articular disease) is not always available. Since patients with RA not always visit their general practitioner regularly, rheumatologists also have a responsibility to identify patients at risk. In order to unify risk assessment it is desirable that both general practitioners and rheumatologists use the same risk model. As stated above, the modified score according to the CVRM guideline may be helpful. When applying the modified SCORE model, patients with a CVD risk ≥20% should be advised treatment. This can be carried out either by the patient's general practitioner, in which case increased awareness of the increased CVD risk in RA amongst general practitioners is necessary alternatively, screening and treatment could take place in a specialized vascular outpatient clinic. In our study, the majority of RA patients who were already treated for hypertension and/or hypercholesterolemia did not reach the recommended treatment targets. Therefore, treatment and follow-up need to be intensified. In patients with a CVD risk of 10%-19% according to the modified SCORE, treatment with lipid lowering drugs and/or antihypertensives should be weighed individually. Lifestyle interventions such as regular exercise, weight loss and smoking cessation should always be given.

In conclusion, hypertension and hypercholesterolemia are not being identified optimally and, when identified, not adequately treated. Although the validity of the adapted risk score systems in RA is debatable, it remains important to screen for and to treat cardiovascular risk factors. The CVRM may at this point be the best and most practical risk assessment tool. The FRANCIS study will reveal whether it is effective to screen and treat RA patients following a tight control regimen for traditional CVD risk factors. Awaiting these results as well as an RA specific risk assessment tool, physicians need to be more aware of screening and treatment of CVD risk factors in RA patients.

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CHAPTER 4

Adherence to cardiovascular prevention strategies in patients with rheumatoid arthritis

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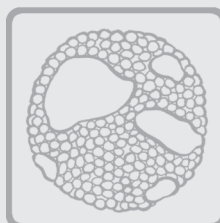
Abstract

Objective: Patients with rheumatoid arthritis (RA) have a high cardiovascular disease (CVD) risk. Recent national and international guidelines suggest strict treatment of CVD risk factors in RA. The aim of this study is to evaluate the self-reported adherence to cardiovascular prevention strategies in patients with RA.

Methods: RA patients visiting an outpatient clinic for strict CVD risk management received a validated questionnaire in order to evaluate adherence to cardiovascular prevention strategies. Strict treatment targets were defined and lifestyle recommendations were given following a pre-specified protocol. CVD risk was assessed using the SCORE algorithm.

Results: In total, 111 questionnaires were returned (response rate of 82%). A high 10-year CVD risk (≥20%) was present in 53%, but only 3% thought they had an increased CVD risk. 53% Reported to "follow the doctors' suggestions exactly" and 75% reported to find it "easy to follow the suggestions". From the 69% of patients who were prescribed lipid and/or blood pressure lowering drugs, 90% reported to take all prescribed tablets. The advice to follow a diet was given to 42% of whom 68% said to follow the advised diet. Physical exercise was advised to 67% of whom 62% said to perform specific physical exercise on 3 days or more per week. The adherence to lifestyle recommendations was not significantly different across CVD risk groups.

Conclusion: RA patients tend to underestimate their CVD risk. The self-reported adherence of RA patients to CVD risk management was high concerning pharmaceutical interventions and moderate in the case of lifestyle interventions.

Introduction

Patients with rheumatoid arthritis (RA) have an increased cardiovascular disease (CVD) risk. The exact mechanism behind this increased risk is still unclear. Since atherosclerosis is an inflammatory disease, the increased inflammatory state of RA patients may explain, at least in part, the increased CVD risk (1-4). Several studies showed that traditional CVD risk factors behave differently in RA patients compared to the general population, nevertheless it is a common believe that they remain important in the development of atherosclerosis in RA patients (4).

There is evidence of underdiagnosis and undertreatment of traditional CVD risk factors in RA patients both in primary prevention (5-7) and in secondary prevention (8). Recent cardiovascular risk management guidelines included specific adaptations for RA patients for the calculation of their CVD risk (9, 10). For instance, the Dutch cardiovascular risk management (CVRM) guideline states that 15 years should be added to the age of RA patients, when assessing the CVD risk according to the score algorithm (10). Awareness of this increased risk among physicians is growing and with that, the screening for and treatment of cardiovascular risk factors in RA patients.

Adherence to cardiovascular prevention regimens is generally low (45-66%), especially in the case of primary prevention (11). This lack of adherence to recommendations results in an increased risk of CVD due to suboptimal treatment (12-14). In order to be able to assess the effect of primary cardiovascular prevention it is necessary be informed on the adherence to given recommendations and treatments. The adherence to cardiovascular prevention strategies in RA patients has not yet been investigated. Therefore, the aim of this study was to investigate CVD risk awareness and adherence to lifestyle and pharmaceutical interventions for primary cardiovascular prevention in RA patients.

Materials and methods

Subjects

RA patients visiting the Diabetes and Vascular Medicine outpatient clinic, St. Franciscus Hospital, Rotterdam, the Netherlands, who participated in the FRANCIS study (Franciscus Rheumatoid Arthritis aNd Cardiovascular Intervention Study) (the Dutch trial register number NTR3873) received a questionnaire in order to evaluate adherence to primary cardiovascular prevention strategies.

The FRANCIS study is an open label randomised intervention trial. RA patients up to 70 years old and without type 2 diabetes mellitus or cardiovascular were eligible to participate. The age limit of 70 was chosen in order to achieve a more favourable cardiovascular condition at inclusion and to increase the probability for a long-term follow up. CVD was

defined as a previous myocardial infarction, PTCA or CABG, cerebrovascular accident or transient ischemic attack, severe intermittent claudication and/or amputation due to arterial vascular disease. Patients were recruited by their rheumatologist and referred to the outpatient clinic for Diabetes and Vascular Medicine. Since this study was initiated before the publication of the Dutch CVRM, that suggests an adaptation of the SCORE risk assessment for RA patients, at inclusion the unadjusted risk assessment was used. Patients with a cardiovascular risk score of <20% were randomized 1:1 into two groups; usual care versus tight control. Patients with a risk score >20% received tight control according to the protocol and were followed in a separate cohort. All included patients visited the outpatient clinic every six months. At each visit standard laboratory tests and physical examination were performed. Patients allocated to the usual care arm were referred to their general practitioner for treatment of cardiovascular risk factors (i.e. high blood pressure, dyslipidaemia, diabetes, obesity) with detailed information. Patients allocated to the tight control arm or the high risk cohort were treated according to a structured CVD risk management program offered by a multidisciplinary team comprising a vascular specialist, a dietician and specialized nurses for vascular and RA care. Lifestyle recommendations and pharmaceutical therapy to reduce CVD risk were initiated according to a strict pre-specified protocol. Furthermore, smoking habit was addressed repeatedly and patients were offered a visit to the outpatient clinic for smoking cessation.

In total 706 patients were eligible for participation in the FRANCIS trial, of whom 324 consented to participation. Of them 316 patients had a CVD <20% and were randomized; the remaining 8 patients entered the high CVD risk group. All patients who had been included in the tight control arm or the high-risk cohort and who had been followed for at least 6 months received a questionnaire concerning adherence to the given interventions. Patients were reminded once by telephone in case of non-response.

Questionnaires

The questionnaire used in this study (Appendix) was a combination of the Medical Outcome Study Measures of Patient Adherence (MOS) (15) and a previous version of the current disease specific Summary of Diabetes Self Care Activities (SDSCA) questionnaire (16). Both original questionnaires were validated English questionnaires and our version was translated into Dutch through back translation by a native English speaker.

In the MOS questionnaire patients were given 5 general statements on adherence and they were provided with 6 answer categories ranging from none of the time to all of the time.

In the SDSCA questionnaire adherence to specific advices a patient may have received were asked. Answer categories regarding diet and exercise varied between percentages (0%, 25%, 50%, 75%, 100%) and number of days per week (1-7 days). For medication intake there are 4 answer categories ranging from "all of them" to "none of them". This

differs from the current version of the SDSCA questionnaire where all questions are changed in order to uniform all answer categories into the total number of days per week. In addition, we removed questions on glucose monitoring and foot care since we considered them irrelevant to this RA patient group since the presence of diabetes mellitus was an exclusion criterion. Questions regarding oral glucose lowering drugs and insulin were replaced by medication in general and RA medication.

Furthermore, a non-validated question about cardiovascular risk awareness was added. (i.e. How high do you think your risk of getting a myocardial infarction is? "High", "not more than average", "low", "almost zero").

Laboratory measurements

A standardized set of measurements was performed in each subject. Blood samples were drawn after an overnight fast. Laboratory parameters were determined at the Department of Clinical Chemistry, Sint Franciscus Gasthuis, Rotterdam, the Netherlands. Glucose, C-reactive protein, total cholesterol, HDL-C and triglycerides (TG) were measured using LX-20 or DxC analysers (Beckman Coulter, Anaheim CA, USA). LDL-C was calculated using the Friedewald formula if TG were below 4.00 mmol/l. The erythrocyte sedimentation rate was measured using an Alifax Test-1TH analyser (Beckman Coulter, Anaheim CA, USA)

Disease activity

Rheumatoid arthritis Disease Activity Score (DAS28) was calculated with erythrocyte sedimentation rate and the following 3 variables: swollen joint count (28), tender joint count (28) and VAS (scale 0-100).

Statistical analysis

In order to compare adherence to general statements in different groups based on their CVD risk, sumscores per patient were calculated. In total 5 general statements were given. Each statement had 6 answer categories ranging from 'none of the time' to 'all of the time'. The answer 'all of the time' was given 0 points and the statement 'none of the time' 5 points. Negative phrased statements were scored in reverse. A higher sumscore indicates poorer adherence. A patient's sumscore was the total number of points allotted according to their answers of these five statements. Sumscores were only calculated if 4 or more statements were answered.

The actual CVD risk was calculated using the adjusted SCORE algorithm, following the recommendation of the 2011 CVRM guideline (9). This results in a higher CVD risk compared to the calculated risk using the unadjusted SCORE algorithm as we used at inclusion. Therefore some patients have a CVD risk of >20% who were initially included with a lower CVD risk.

Data are given as mean ± standard deviation (SD) unless stated otherwise. Differences between groups were determined using the unpaired Student's t-test, Chi-square test or ANOVA, where appropriate. In the case of skewed variables (DAS28, TG), non-parametric tests (Mann Whitney U test or Kruskal-Wallis test) were performed. All statistical analyses were carried out using PASW statistics version 18.0 (IBM SPSS Statistics, New York, United States). P-values below 0.05 (two sided) were considered statistically significant.

Results

General characteristics

Questionnaires were sent between June 2012 and November 2012. At that time 136 patients with a minimum follow-up time of 6 months had been randomized in the tight control arm or enrolled in the high-risk cohort. In total, 111 (82%) returned a completed questionnaire. Respondents' general characteristics are shown in Table 1. A high 10-year CVD risk (≥ 20%) (according to the SCORE model with adaptations according to the Dutch CVRM guideline) was found in 60 patients (53%), but only 3 patients (3%) reported to think they had an increased cardiovascular risk. Most patients (n=93; 85%) were Dutch, highly educated (college/university: n=74; 69%) and had a relationship (n=82; 75%). Subjects with a high CVD risk were more often male, had a higher waist circumference, blood pressure, LDL-C, TG and glucose. Furthermore patients with a high CVD risk were more often rheumatoid factor and anti-CCP positive (Table 1).

General adherence statements

In the first part of the questionnaire patients were invited to answer 5 statements addressing patient's general view on the given recommendations (Figure 1). The majority of the patients (n=74; 75%) stated to have "none of the time" or "a little of the time" a "hard time following the doctors' suggestions" (Figure 1A). In total, 65 patients (69%) reported to "follow the doctors' suggestions exactly" ("most of the time" to "always") (Figure 1B) and only 4 patients (5%) were unable "to do what was necessary to follow the doctors' treatment plans" ("most of the time" to "always") (Figure 1C). The majority (71 patients; 75%) reported to find it easy to "follow their doctors' suggestions exactly" ("most of the time" to "always") (Figure 1D). Generally, over the past 4 weeks, 67 patients (72%) were "able to do what the doctor told them to do" ("most of the time" to "always") (Figure 1E). The medium sumscore was 5 (IQR 3-7) in the group with a CVD risk <10% and 10-19%. The group with a CVD risk ≥20% had a median sumscore of 4 (IQR 1-8), which was significantly lower than the other groups (p=0.03).

Table 1. General Characteristics.

	Total (n=111)	CVR <10% (n=31)	CVR 10-20% (n=20)	CVR ≥20% (n=60)	p-value
Female (n,%)	86 (78%)	31 (100%)	16 (80%)	39 (65%)	0.001
Age (yrs)	54 ± 11	40 ± 7	54 ± 6***	62 ± 6***,##	<0.001
Smoking (n,%)	15 (14%)	3 (10%)	2 (10%)	10 (17%)	0.56
Height (cm)	170 ± 9	170 ± 10	173 ± 9	169 ± 9	0.29
Weight (kg)	76.7 ± 14.5	73.2 ± 13.7	78.6 ± 14.9	77.9 ± 14.6	0.27
Waist (cm)	94 ± 12	89 ± 13	95 ± 14	97 ± 11**	0.02
BMI (kg/m^2)	26.5 ± 4.4	25.4 ± 4.0	26.3 ± 4.8	27.0± 4.4	0.21
BPs (mmHg)	135 ± 21	118 ± 12	129 ± 20*	145 ± 19***,##	<0.001
TC (mmol/l)	5.4 ± 1.1	5.0 ± 1.1	5.0 ± 1.0	5.8 ± 1.1**,##	0.001
LDL-C (mmol/l)	3.3 ± 1.0	3.0 ± 0.8	3.0 ± 0.9	3.6 ± 1.0**,#	0.003
HDL-C (mmol/l)	1.53 ± 0.44	1.55 ± 0.40	1.50 ± 0.41	1.53 ± 0.47	0.91
TG (mmol/l) median (IQR)	0.97 (0.73-1.49)	0.86 (0.63-1.14)	0.87 (0.72-1.46)	1.10 (0.83-1.77)	0.036
Glucose (mmol/l)	5.5 ± 0.4	5.1 ± 0.5	5.5 ± 0.4*	5.6 ± 0.6***	<0.001
HbA1c (mmol/mol)	34.8 ± 4.8	32.7 ± 4.4	35.6 ± 3.1*	35.7 ± 5.1**	0.01
Anti-CCP + (n,%)	63 (57%)	12 (39%)	10 (50%)	41 (69%)	0.003
RF + (n,%)	64 (58%)	13 (42%)	11 (55%)	40 (67%)	0.02
Erosions (n,%)	49 (44%)	11 (36%)	11 (55%)	27 (45%)	0.61
DAS28 Median (IQR)	2.4 (1.6-3.4)	1.8 (1.1-2.6)	2.7 (2.1-4.0)	2.5 (1.7-3.0)	0.047

* P<0.05 vs. CVR <10%, ** P<0.01 vs. CVR <10%, ***P<0.001 vs. CVR <10%
# P<0.05 vs. CVR <20%, ## P<0.01 vs. CVR <20%, ###P<0.001 vs. CVR <20%

Adherence to specific recommendations

In the second part, questions regarding specific recommendations given by the doctor were asked. In the case of given recommendations, several questions followed addressing their adherence (Figure 2). All patients used RA medication and most of them (n=83; 82%) said to take most to all of the prescribed tablets. Of the 77 patients that were prescribed antihypertensives and/or lipid lowering drugs 70 (90%) stated to take most to all of the prescribed tablets. The advice to follow a diet was given to 46 patients (42%) and 30 of them (68%) said to follow the recommended diet ("usually" to "always"). Of the patients that were advised to follow a diet 35 patients (76%) said to use fibre rich meals (75-100% of the meals), 37 patients (80%) used low fat meals (75-100% of the meals) and 43 patients (94%) used low carbohydrate meals (75-100% of the meals).

Physical exercise was advised to 72 patients (67%) and of them 38 (56%) said to follow the advice. In total 42 (62%) said to perform specific physical exercise on 3 days or more per week.

Figure 2 shows the adherence to recommendations across risk categories. Overall, there was no significant difference between the CVD risk groups. Patients with a CVD

A I had a hard time doing what the doctor suggested I do…

B I followed my doctors suggestions exactly

C I was unable to do what was necessary to follow my doctor's treatment plans…

D I found it easy to do the things my doctor suggested I do…

E Generally speaking, how often during the past 4 weeks were you able to do what the doctor told you?

□ All of the time
▨ Most of the time
▨ A good bit of the time
▨ Some of the time
▨ A little of the time
■ None of the time

Figure 1. Patients reports on general adherence statements. In the MOS questionnaire patients were given 5 general statements on adherence and they were provided with 6 answer categories ranging from all of the time to none of the time.

risk of 10-19% reported a higher adherence to dietary advice compared to patients with higher and lower CVD risks: n=9 (100%) versus n=17 (71%) and n=4 (36%), respectively: p=0.018). Their cardiovascular medication use was also reported to be higher compared to patients with a lower and higher cardiovascular risk n=13 (100%) versus n=9 (82%) and n=42 (89%) respectively; p<0.001).
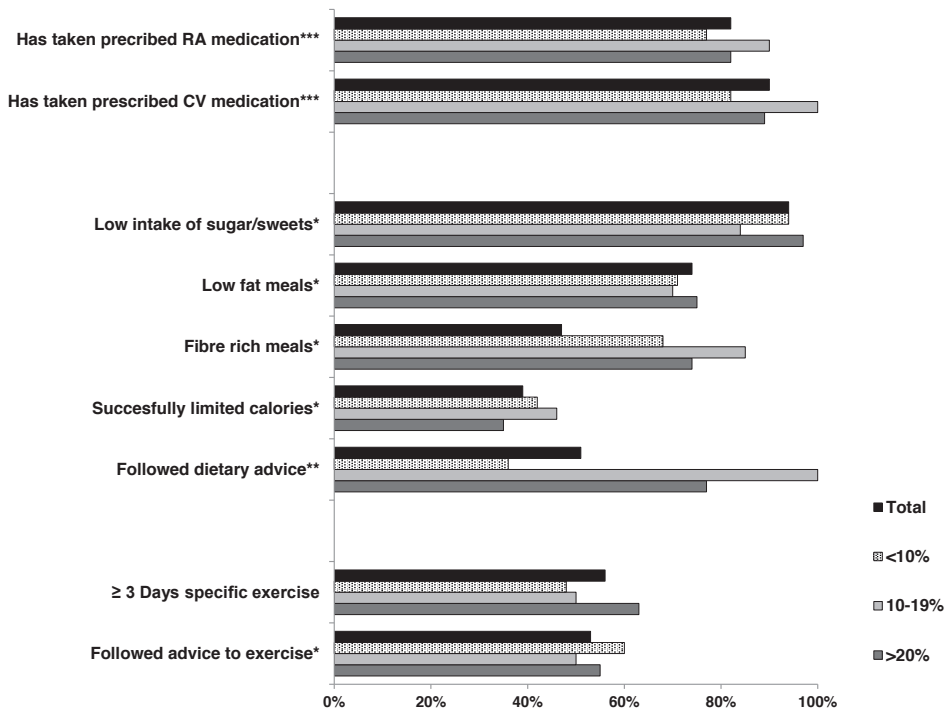
Figure 2. Patient reported adherence to given recommendations provided for the respective CVD risk groups. In The SDSCA questionnaire adherence to specific advices a patient may have received were asked. * 75%-100% of the time, **usually to always, *** most of them to all of them

Discussion

This is the first study addressing the self-reported adherence to cardiovascular risk strategies in RA patients.

All patients consented to participation in the FRANCIS study, an intervention trial on CVD risk management in RA patients. In view of the wide trial inclusion criteria we adopted, selective participation appeared minimal. However, patient's willingness of unwillingness to participate, may have resulted in higher adherence rates than is to be expected in the general unselected RA population. This selection may also be the reason why the proportion of smokers was relatively low and even lower than previously reported in the Dutch RA population (17). Despite the fact that the patient information leaflet of the FRANCIS study contained detailed information on the increased CVD risk in RA, all but three patients stated to have an average or below average risk to develop a myocardial infarction, indicating low CVD risk awareness.

The exact influence of treatment of traditional CVD risk factors in RA patients on their CVD risk is unclear, especially concerning lifestyle (1). With respect to exercise, an

individualized training program in RA has been shown to improve endothelial function (18). Furthermore, inactivity in RA has also been associated with increased arterial stiffness (19). However, the effect on real life CVD risk is unknown. Regarding cardiovascular preventive medication in RA, several studies have shown a favourable effect. Statin treatment effectively improves lipid levels in RA patients (5, 20) and anti-hypertensive treatment with ACE-I and angiotensin II antagonists effectively lower blood pressure and improves endothelial function in RA (21-23). The response to calcium channel and beta-blockers is decreased in inflammatory conditions, therefore the effect of these antihypertensives may be attenuated in RA. Clinical data, regarding this attenuated effect, however are lacking. The on-going FRANCIS study intends to answer the question what the effect of tight treatment of traditional CVD risk factors RA is on CVD risk and subclinical atherosclerosis.

The impression of the first part of the questionnaire, addressing adherence to given CVD recommendations in general, was favourable since patients stated to have a high adherence and not to have difficulties following given advices. There was a significant difference in sumscores between the risk groups, however we feel that this difference is not clinically significant. With sumscores ranging between 0 and 25, median scores of 5 and 4 indicate relatively good self-reported adherence. The second part of the questionnaire, assessing adherence to specific advices, however showed more variable adherences, depending on the advice questioned. Medication intake adherence for both RA specific and CVD preventive medication and for RA specific medication was high (82% and 90% respectively). These results are in line with previous studies on self-reported adherence to RA medication (24-26). To date, data on the adherence to primary CV preventive drugs in RA is absent. Despite the fact that overall adherence to secondary prevention is higher than adherence to primary preventive strategies, a recent report on adherence to secondary prevention in RA showed adherence rates of 80% (8). Previous reports on primary CV prevention in DM have shown adherence rates of 77%-80% (27, 28). The methods to measure adherence differs in different studies making direct comparisons difficult. The use of questionnaires may also lead to an overestimation of adherence rates. Garber et al found that questionnaires for the estimation of adherence to medication, show a moderate to high concordance with objective measurements of adherence (29). We did not establish adherence to specific medication, but measured general adherence to all CVD preventive medication, which included mainly antihypertensives and statins, and adherence to all RA specific medication. We have to admit that this way to measure adherence may be inaccurate since several studies showed that adherence strongly depended on the type of drug (8, 25, 30). Factors related to adherence may be patient related (coping, physical health) or related to specific drug related side effects (25). The overall low RA disease activity indicates a high medication adherence, which is in line with the results of the questionnaire.

The adherence to lifestyle interventions such as exercise and diet was lower than adherence to medication and ranged between 49% and 94%. One of the factors for low physical exercise in RA may be related to the RA disease activity and/or joint deformity. Although overall disease activity was low, specific information on patient reported impairment to exercise was not available. Surprisingly, a higher cardiovascular risk did not result in higher adherence. A possible explanation for this could be that most RA patients believed to have an average or below average CVD risk regardless their actual CVD risk.

In order to optimize treatment of CVD risk factors in RA it is necessary to increase patient awareness of this increased risk and to identify factors that are correlated with poorer adherence. The next step would be to optimize adherence. Ways to increase awareness may include an active role of general practitioners in screening and treatment, patient-related educational interventions with behavioural support, internet and mobile technologies regarding the CVD risk in RA and/or an active role for specialized nurses in rheumatology to inform patients.

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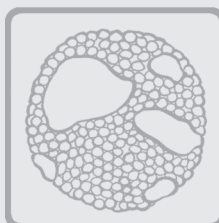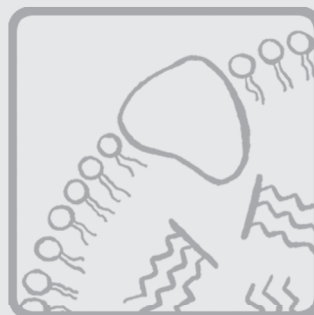
CHAPTER 5

Association of cardiovascular risk factors with carotid intima media thickness in patients with rheumatoid arthritis with low disease activity compared to controls: A cross-sectional study

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Abstract

Objectives: Rheumatoid arthritis (RA) has been identified as an independent cardiovascular risk factor. The importance of risk factors such as hypertension and hyperlipidemia in the generation of atherosclerosis in RA patients is unclear. This study analyzed clinical parameters associated with carotid intima media thickness (cIMT) in patients with RA.

Methods: Subjects with RA and healthy controls without RA, both without known cardiovascular disease, were included. Participants underwent a standard physical examination and laboratory measurements including a lipid profile. cIMT was measured semi-automatically by ultrasound.

Results: In total 243 RA patients and 117 controls were included. The median RA disease duration was 7 years (IQR 2-14 years). The median DAS28 was 2.4 (IQR 1.6-3.2) and 114 (50.4%) of the RA patients were in remission. The presence of RA and cIMT were not associated (univariate analysis). Multivariable regression analysis showed that cIMT in RA patients was associated with age (B=0.006, p<0.001) and systolic blood pressure (B=0.003, p=0.003). In controls, cIMT was associated with age (B=0.006, p0.001) and smoking (B=0.097, p=0.001).

Conclusion: cIMT values were similar between RA patients and controls. Hypertension was strongly associated with cIMT in RA patients. After adjustment, no association between cIMT and specific RA disease characteristics were found in this well treated RA cohort.

Introduction

Rheumatoid Arthritis (RA) is a chronic systemic inflammatory disease of unknown etiology, affecting ~1% of the adult general population (1, 2). Patients with RA have a higher all cause mortality risk than the general population and the leading cause of death is cardiovascular disease (CVD) (3-5). The evidence of the excess cardiovascular risk in rheumatoid arthritis (RA) has been well described (3, 5-9) and the presence of RA can be considered an independent risk factor for CVD (7, 10). The prevalence of CVD in patients with RA is as high as in patients with type 2 diabetes mellitus (7, 11). Since inflammation is a key event in the development of atherosclerosis (12-14) it has been proposed that the increased inflammatory state of patients with RA explains, at least in part, the increased cardiovascular risk (8, 10, 15-17). Several RA specific risk factors such as disease activity, inflammatory markers and anti-CCP have been associated with an increased carotid intima media thickness (cIMT) and CVD risk. A recent study by Barbarroja et al. showed that anti-CCP antibodies act as direct inductors of the pro-oxidative status and the inflammatory and atherogenic profile of lymphocytes, monocytes and neutrophils in RA (18). In line with this report, Vázquez et al. showed an association between anti-CCP levels and CRP levels with an increased cIMT and CVD risk (19). Moreover, traditional risk factors such as hypertension, hyperlipidemia, smoking and overweight are also highly prevalent among RA patients (20, 21), and several studies have shown a significant underdiagnosis and undertreatment of these traditional risk factors in RA (22, 23).

The cIMT measured by ultrasound is a surrogate marker of atherosclerosis and the most widely used non-invasive imaging method to assess atherosclerosis and CVD risk. A higher cIMT reflects a (pre-) atherogenic condition and is predictive for future cardiovascular events (24, 25). Several studies have shown an increased cIMT in RA patients, even early in the course of the disease (26-30). Traditional risk factors may also play a role besides the inflammatory state in RA. Unfortunately, the association between traditional risk factors and cIMT in RA patients is still unclear (31). Increasing evidence suggests that a cumulative number of traditional CVD risk factors contributes to the higher CVD risk in RA (32). The aim of this study was to investigate which factors are associated to cIMT in RA patients in comparison to controls.

Materials and Methods

Study design and subjects

A cross-sectional study was carried out in patients with RA and controls to determine the differences in the relationship between cIMT and clinical factors. The study was carried out between July 2009 and February 2013 at the Diabetes and Vascular Centre

and the outpatient clinic of Rheumatology of the Sint Franciscus Gasthuis, Rotterdam, the Netherlands. All patients with RA in this report were participants in the FRANCIS study, an open label randomized clinical trial to investigate the effectiveness of strict treatment of cardiovascular risk factors in RA (The Dutch Trialregister, NTR3873; ABR no. NL32669.101.10). RA patients attending the outpatient clinic from the Department of Rheumatology were asked to participate in the FRANCIS study. Inclusion criteria were the presence of RA and an age ≤70 years. Exclusion criteria were the presence of diabetes mellitus (DM) or CVD. CVD was defined as a documented history of myocardial infarction, cerebrovascular event, amputation due to peripheral artery disease, intermittent claudication, or a prior percutaneus transluminal coronary angioplasty (PTCA) or coronary artery bypass graft (CABG). In addition, kidney disease defined as an MDRD <30 ml/min was an exclusion criterium. Only patients with a CVD risk <10% according to the 2009 version of the SCORE model were randomized. Patients aged over 65 years were classified as 65 years old in order to be able to use the SCORE model. Patients with a CVD risk ≥10% were followed in a separate cohort ("high risk cohort"). For the current analysis, baseline data from both randomized patients and patients in the high risk cohort were used. The RA patients were treated by their own rheumatologists according to a treat-to-target principle, aiming for disease remission (DAS28<2.6). RA was defined by the ACR '87 criteria (33). Unmatched control subjects were non-RA patients followed in a separate observational study (ABR no. NL29910.101.09) from our department. They were recruited from the outpatient clinic of the Diabetes and Vascular Center of the Sint Franciscus Gasthuis in Rotterdam and underwent measurements identical to the RA patients of the FRANCIS study (34). Exclusion criteria for the control group were also the presence of DM, CVD and/or kidney disease. All controls fulfilling the age limit of ≤70 years were included in this analysis. In addition, RA patients and controls who used statins and/or anti-hypertensives were excluded. Controls with a CRP >10 mg/L were excluded from the analysis. Anthropometric characteristics i.e. height, weight, waist circumference and blood pressure were obtained as well as a detailed medical history and the use of medication. All subjects provided written informed consent. The studies were approved by the independent Regional Medical Ethical Committee Rotterdam of the Maasstad Hospital, the Netherlands.

Rheumatoid arthritis disease activity

Rheumatoid arthritis disease activity was assessed by using the Disease Activity Score with 28 joints counted (DAS28). This score included swollen joint count (28), tender joint count (28), VAS (0-100 scale) indicating pain/discomfort due to RA, and the erythrocyte sedimentation rate (ESR). We also calculated disease activity with C-reactive protein (CRP) instead of ESR (DAS28CRP),

Laboratory measurements

A standardized set of measurements was performed in each subject. Laboratory parameters were determined at the Department of Clinical Chemistry, Sint Franciscus Gasthuis, according to standard procedures. Renal and liver function tests as well as glucose, CRP, total cholesterol, HDL-C and triglycerides (TG) were measured using Synchron LX-20 and DxC analyzers (Beckman Coulter, Anaheim CA, USA) (34, 35). LDL-C was calculated using the Friedewald formula if TG were below 4.60 mmol/l. Apolipoprotein (apo) AI and apo B were determined in serum by rate nephelometry using IMMAGE with commercially available kits (Beckman Coulter, Anaheim CA, USA) (31,32). In the case of RA patients, blood samples were obtained following the strict protocol of the FRANCIS study. Samples from control subjects were drawn with less strict criteria.

Intima media thickness of the carotid arteries

Carotid ultrasound scans were carried out using the ART-LAB (Esaote, Italy) by trained and experienced sonographers as described earlier (34, 35). Ultrasound scans were performed with the patients lying in a supine position with the head resting comfortably and the neck slightly hyperextended and rotated in the opposite direction of the probe. The ultrasound images were obtained of the distal 1 cm of the far wall of each common carotid artery (CCA) using B-mode ultrasound producing two echogenic lines. These lines represent the combined thickness of the intima and media layers of the arterial wall. Each CCA was imaged in three different projections: CCA right side 90-120-150 and CCA left side 210-240-270 degrees. The segments were measured semi-automated in triplicate. In some patients cIMT measurements were only partly available due to technical difficulties. In these cases, the mean cIMT was only calculated if at least measurements at two different angles per side were available.

Statistics

Data are given as mean ± standard deviation (SD) unless stated otherwise. Differences between groups were determined using the unpaired Student's t-test or Chi-square test, where appropriate. In case of skewed variables (DAS28(-CRP) and TG), the Mann-Whitney U test was used for comparisons between groups. For statistical analysis, cIMT was defined as the mean of the six individual measurements. Multivariable linear regression analysis was used to identify factors associated with cIMT in RA patients and controls. Covariables entered into the regression analysis were: age, sex, systolic blood pressure, waist circumference, smoking habit, glucose, apo AI, apo B, total cholesterol, HDL-C, LDL-C, TG, glucose, creatinin and CRP. For RA patients, the presence of rheumatoid factor and anti-CCP, erosive disease, disease duration, DAS28CRP, DAS28 and the use of methotrexate and biologicals were added to the model. Covariables showing a P<0.10 in the univariate analysis were entered in the multivariable analysis. In order to

create comparable models for RA patients and controls, a separate analysis with and without RA disease duration was performed for RA patients. In the case that two or more related parameters were highly correlated (multicollinearity), only one was selected for the multivariable analysis. As a result, waist circumference was selected instead of BMI; systolic blood pressure was selected instead of diastolic blood pressure; and LDL-C was chosen above apo B or TG. Significant co-variables were investigated for interaction. The multivariable analysis included age, sex, smoking, waist circumference, systolic blood pressure and LDL-C. The association between glucose and cIMT was analyzed separately because it was unknown which of the control subjects had their blood samples taken after an overnight fast. All statistical analyses were performed using PASW statistics version 18.0 (IBM SPSS Statistics, New York, United States). P-values below 0.05 (two sided) were considered statistically significant.

Results

General Characteristics

243 RA patients and 117 controls were included. General characteristics of RA patients and controls are shown in Table 1. Both groups were comparable regarding age, gender, lipid profile, waist circumference, and cIMT. There were more current smokers among RA patients compared to controls. RA patients had a significantly higher body mass index (BMI) and systolic blood pressure (Table 1).

The median RA disease duration for RA patients was 7 years (IQR 2-14 years). In total, 107 patients (44.0%) used NSAIDS, 186 (76.5%) RA patients used methotrexate and 96 (39.5%) used an anti-TNFα or other biological agent. Of the 96 patients with a biological agent, 25 (26%) used no methotrexate and 71 (74%) used a combination of methotrexate and a biological.

The median DAS28 was 2.4 (IQR 1.6-3.2). In total, 114 (50.4%) of the RA patients had a DAS28 <2.6 implying disease remission, 48 (21.2%) had low disease activity (DAS28 2.6-3.1), 47 (20.7%) had moderate disease activity (DAS28 3.1-5.1) and 17 (7.5%) had high disease activity (DAS28 ≥ 5.1). When applying DAS28CRP, the results were similar: the median DAS28CRP was 2.2 (IQR 1.6-2.9), 113 (58.8%) had disease remission, 39 (17.3%) had low disease activity, 40 (17.7%) had moderate disease activity and 14 (6.2%) had high disease activity. cIMT did not differ between RA groups based on their disease activity (data not shown).

Univariate analysis

To identify the covariables associated with cIMT, univariate regression analysis was carried out in RA patients, controls and the combined patient and control group (Table 2).

Table 1. General Characteristics. Data presented as mean ± standard deviation or n (%) unless stated otherwise.

	RA-patients (n = 243)	Controls (n = 117)	P-value
Male	79 (32.5%)	46 (39.3%)	0.204
Age (yrs)	51.8±11.6	50.0±12.1	0.186
Current smoker (n,%)	54 (22.2%)	16 (13.7%)	0.051
Weight (kg)	76.3±14.4	75.3±14.5	0.520
BMI (kg/m^2)	26.1±4.3	24.9±3.7	0.006
Systolic blood pressure (mmHg)	129±18	124±13	0.004
Waist circumference (cm)	93±14	90±12	0.054
Total cholesterol (mmol/l)	5.4±1.1	5.6±1.2	0.147
LDL-C (mmol/l)	3.4±1.0	3.5±1.0	0.372
HDL-C (mmol/l)	1.54±0.51	1.55±0.43	0.894
TG (mmol/l)*	1.03 (0.72-1.42)	1.12 (0.74-1.61)	0.182
Apo AI (g/l)	1.71±0.36	1.65±0.32	0.099
Apo B (g/l)	1.00±0.26	1.04±0.30	0.192
Glucose (mmol/l)	5.4±0.5	5.2±0.9	0.002
C-reactive protein (mg/l)*	2.00 (1.00-5.00)	1.00 (1.00-2.75)	<0.001
cIMT (mm)	0.556±0.120	0.573±0.134	0.220
Rheumatoid Factor positivity (n,%)	150 (61.7%)**	NA	
Anti-CCP positivity (n,%)	142 (58.4%)***	NA	

BMI = body mass index TG = triglycerides; Apo = apolipoprotein; cIMT = carotid intima media thickness; NA = not available
* Data presented as median (interquartile range), difference between groups tested with the Mann-Whitney U test. ** data available in 235 patients. *** data available in 204 patients.

In all groups age, systolic blood pressure, LDL-C and apo B showed a significant association with cIMT. Furthermore, in controls, current smoking was significantly associated with cIMT. In RA patients male gender, BMI, waist circumference, TG, glucose and disease duration were significantly associated with cIMT. The correlation coefficient between RA disease duration and age was 0.262. A trend towards a positive association between anti-CCP positivity and cIMT was observed (B=0.033(-0.044-0.070); p=0.078) (Table 2). When these univariate analyses were performed only in RA patients not using biologicals, the associations between cIMT and anti-CCP positivity, disease duration, glucose and TG were no longer statistically significant (data not shown). Other parameters showed similar associations as in the total RA group.

Multivariable analysis

Multivariable regression analysis with identified covariables associated with cIMT, was performed in RA patients, controls and in both groups combined (Table 3). In controls

Table 2. Univariate regression analysis identifying covariables associated with cIMT.

Variable	Controls (n=117)		RA patients (n=243)		Total population (n=360)	
	B (95% CI)	p-value	B (95% CI)	p-value	B (95% CI)	p-value
Age (yrs)	0.006 (0.004-0.007)	<0.001	0.006 (0.005-0.007)	<0.001	0.006 (0.005-0.007)	<0.001
Male sex	0.021 (-0.029-0.071)	0,243	0.050 (0.018-0.082)	0.002	0.041 (0.014-0.068)	0.003
Smoking	0.097 (0.028-0.166)	0.006	0.016 (-0.021-0.053)	0.403	0.034 (0.001-0.067)	0.044
BMI (kg/m^2)	0.005 (-0.002-0.012)	0.139	0.005 (0.001-0.008)	0.010	0.004 (0.001-0.007)	0.006
Waist (cm)	0.002 (0.000-0.004)	0.101	0.002 (0.001-0.003)	<0.001	0.002 (0.001-0.003)	<0.001
BPs (mmHg)	0.002 (0.001-0.004)	0.009	0.003 (0.002-0.004)	<0.001	0.003 (0.002-0.003)	<0.001
BPd (mmHg)	0.000 (-0.003-0.003)	0.963	0.004 (0.002-0.005)	<0.001	0.003 (0.001-0.004)	<0.001
LDL-C (mmol/l)	0.043 (0.019-0.066)	<0.001	0.034 (0.020-0.049)	<0.001	0.037 (0.025-0.050)	<0.001
HDL-C (mmol/l)	-0.010 (-0.066-0.047)	0.740	-0.010 (-0.040-0.020)	0.511	-0.010 (-0.037-0.017)	0.476
Apo AI (g/l)	0.013 (-0.065-0.091)	0.750	-0.016 (-0.059-0.027)	0.473	-0.010 (-0.048-0.028)	0.610
Apo B (g/l)	0.114 (0.034-0.194)	0.005	0,131 (0.075-0.187)	<0.001	0.126 (0.081-0.172)	<0.001
TG (mmol/l)*	0.013 (-0.020-0.045)	0.441	0.026 (0.003-0.049)	0.026	0.022 (0.003-0.040)	0.022
Glucose (mmol/l)*	0.009 (-0.019-0.036)	0.536	0.044 (0.016-0.072)	0.002	0.021 (0.001-0.040)	0.029
CRP (mg/dl)	-0.000 (-0.014-0.014)	0.964	0.001 (-0.001-0.003)	0.504	0.000 (-0.002-0.002)	0.731
Creatinin (umol/l)	0.001 (-0.001-0.003)	0.549	0.002 (0.001-0.003)	0.002	0.001 (0.001-0.003)	0.002
Absence of RA	-	-	-	-	0.017 (-0.010-0.045)	0.220
Anti-CCP	-	-	0.033 (-0.004 -0.070)	0.078		
Rheumatoid factor	-	-	0.020 (-0.013-0.053)	0.231		
Erosive Disease	-	-	0.020 (-0.011-0.051)	0.212		
DAS28	-	-	0.005 (-0.009-0.019)	0.494		
DAS28CRP	-	-	-0.001 (-0.017-0.015)	0.902		
Disease duration	-	-	0.002 (0.001-0.004)	0.012		
Methotrexate	-	-	0.001 (-0.036-0.037)	0.976		
Biological agents	-	-	-0.07 (-0.039-0.024)	0.651		

RA = Rheumatoid arthritis, BPs = systolic blood pressure, BPd = diastolic blood pressure, TG = triglycerides, DAS28 = RA disease activity score 28 joints

cIMT was significantly associated with age and current smoking and in RA patients with age and systolic blood pressure. These results remained unchanged after including glucose in the analysis. In RA patients, additional multivariable analyses including RA disease duration alone and combined with anti-CCP were performed (Table 4). The addition of RA disease activity and anti-CCP positivity, alone or combined, did not improve the predictive power of the original multivariable model (Table 4). Multivariable analysis in only those RA patients not using biological therapy showed comparable results.

Table 3. Multivariable regression analysis with identified covariables associated with cIMT.

Variable	Controls (n=117) R^2=0.321		RA patients (n=243) R^2=0.391		Total population (n=360) R^2=0.347	
	B (95% CI)	p-value	B (95% CI)	p-value	B (95% CI)	p-value
Age (yrs)	0.005 (0.003-0.007)	<0.001	0.005 (0.004-0.006)	<0.001	0.005 (0.004-0.006)	<0.001
Male sex	0.010 (-0.037-0.056)	0.678	0.013 (-0.014-0.040)	0.336	0.015 (-0.008-0.038)	0.201
Smoking	0.101 (0.041-0.162)	0.001	0.019 (-0.011-0.049)	0.207	0.034 (0.007-0.061)	0.014
Waist (cm)	0.002 (0.000-0.004)	0.127	0.001 (0.000-0.002)	0.142	0.001 (0.000-0.002)	0.106
BPs (mmHg)	0.001 (-0.001-0.002)	0.488	0.001 (0.000-0.002)	0.003	0.001 (0.000-0.002)	0.012
LDL-C (mmol/l)	0.009 (-0.016-0.034)	0.467	0.007 (-0.006-0.020)	0.270	0.009 (-0.003-0.020)	0.143
Apo B (g/l)		**		**		**

RA = Rheumatoid arthritis, BPs = systolic blood pressure, Apo = apolipoprotein
** When using apoB instead of LDL similar results were found.

Table 4. Multivariable regression analysis including RA disease characteristics.

Variable	RA patients (n=243) R^2=0.39		RA patients (n=243) R^2=0.40	
	B (95% CI)	p-value	B (95% CI)	p-value
Age (yrs)	0.005 (0.004-0.006)	<0.001	0.005 (0.004-0.007)	<0.001
Male sex	0.005 (-0.016-0.039)	0.409	0.005 (-0.026-0.035)	0.786
Smoking	0.019 (-0.011-0.049)	0.212	0.020 (-0.02-0.053)	0.220
Waist (cm)	0.001 (0.000-0.002)	0.156	0.001 (0.000-0.002)	0.216
BPs (mmHg)	0.001 (0.000-0.002)	0.002	0.001 (0.000-0.000)	0.005
LDL-C (mmol/l)	0.007 (0.006-0.020)	0.282	0.007 (-0.008-0.021)	0.365
RA disease duration (yrs)	0.000 (-0.002-0.001)	0.579	0.000 (-0.002-0.002)	0.792
Anti-CCP	-	-	0.007 (-0.024-0.037)	0.661

RA = Rheumatoid Arthritis, BPs = systolic blood pressure

Discussion

Surprisingly, cIMT in RA patients was similar to the cIMT of control subjects without RA, which is in contrast to other studies, showing increased cIMT in RA patients even early in the course of the disease (29, 30, 32, 36-38). It is even more surprising since in our study RA patients had a higher BMI, systolic blood pressure, glucose and CRP and, a larger percentage of RA patients smoked compared to controls.

A post hoc sample size calculation showed that our sample sizes of 243 RA-patients and 117 control patients are not sufficiently large to support the presence of a significant difference in mean cIMT between the groups with 80% power. However, considering that the difference in mean cIMT we found (0.017) cannot be considered clinically

meaningful, one would need to include (at least) 270 RA and control patients (at an equivalence margin of 0.05; or 68 patients at an equivalence margin of 0.10) to support that a difference in cIMT is absent. In summary, our sample sizes are sufficiently large to support that a clinically meaningful difference in cIMT in our study is absent, with 90% power.

One of the reasons for this difference with other studies may be the relatively low disease activity in our RA patients. A higher RA disease activity results in an increased cardiovascular risk. The RA disease activity in our study was low with a total of 70% of RA patients in clinical remission or with low disease activity, which may have had a beneficial effect on cIMT. When we compared cIMT in RA patients with disease remission or low disease activity with cIMT in RA patient with moderate or high disease activity, no differences in cIMT were found. This may be due in part to the small proportion of patients with moderate to high disease activity. Our outpatient clinic of Rheumatology is a large outpatient clinic that consists of a large and representative sample of RA patients in the Netherlands. At the outpatient clinic, a structured tight control regimen of RA disease activity is carried out reflecting the present situation in the Netherlands. Therefore, we believe that the sample of RA patients in this study is representative for the general Dutch RA population, although the results may not apply to RA patients with higher average disease activity. A meta- analysis by Ambrosino et al. reported outcomes of 59 studies on cIMT in RA compared to controls (30). Not all studies included information on disease activity, but the mean DAS28 of those studies reporting disease activity ranged from 2.6 to 6.2, which is higher than our reported median DAS28 of 2.4. Of those 59 studies, 51 reported an increased cIMT in RA patients compared to controls (30). Only 2 studies reported DAS28 levels <3.0 showing conflicting results concerning differences in cIMT in RA compared to controls (39, 40). The same meta-analysis by Ambrosino et al. showed that a higher inflammatory status (DAS28, CRP, ESR) was associated with an increased cIMT (30).

Besides disease activity, several RA specific risk factors, such as the presence of rheumatoid factor, anti-CCP and erosive disease, are considered risk factors for atherosclerosis. They are all surrogate markers for the inflammatory burden since the presence of rheumatoid factor and/or anti-CCP often results in a higher disease activity. Also erosive disease occurs mostly in patients with long periods of uncontrolled disease activity. In our cohort with generally a low disease activity, rheumatoid factor and anti-CCP positivity were not associated with cIMT in the multivariable model. These results are in line with several other studies that could not demonstrate an association between these parameters and cIMT (37, 39). A limitation of our study was that only qualitative data on rheumatoid factor and anti-CCP were available, since these characteristics were not re-tested at the time of inclusion. Recently, an *in vitro* study showed a positive correlation between the level of anti-CCPs and overexpression of thrombotic, inflammatory and

pro-oxidative markers in leukocytes (18). We did find a crude (univariate) association between disease duration and cIMT, but this association was no longer significant in the multivariable model. This is in line with a recent publication by Arts et al. who found that the risk of CVD in RA patients was not increased after 10 years of disease duration when compared to the first 10 years (40). Data on the association between cIMT and RA disease duration are conflicting since several other studies reported a positive association between cIMT and RA disease duration (37, 41, 42).

Traditional cardiovascular risk factors such as smoking, overweight, hyperlipidemia and hypertension are highly prevalent in RA patients and can be easily treated by lifestyle and pharmacological interventions. Nevertheless, underdiagnosis and undertreatment of these risk factors in RA patients have been described (22, 23, 43). An association between cIMT and blood pressure both in the general population and in RA patients has been described previously (17, 27, 44-46). In the present paper, regression analyses underline the association of systolic blood pressure on cIMT in RA patients. These data underscore the importance of adequate blood pressure regulation in RA.

No association between cIMT and lipid levels was found. Hyperlipidemia was strongly associated to cIMT in the univariate analysis, but it was no longer significant in the multivariable analysis after adjustment for other covariables. In contrast to the association found between smoking and cIMT in controls, no association between smoking and cIMT in RA patients was found. This is in line with earlier results reported by Gonzalez et al., who found a weaker association between smoking and CVD risk in RA patients than in non-RA patients (47).

In conclusion, in this RA cohort with relatively low disease activity, cIMT was not increased compared to controls and cIMT was not associated with RA disease characteristics. Hypertension was strongly associated with cIMT in RA patients. In light of these results and based on findings from other studies, treatment of hypertension and other traditional CVD risk factors in RA seems warranted to reduce cardiovascular risk in RA.

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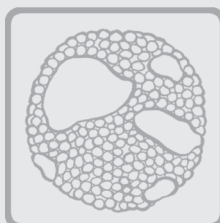
CHAPTER 6

Increased fasting apolipoprotein B48 in rheumatoid arthritis: A report of the FRANCIS study

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Abstract

Background and aims: Serum concentrations of apolipoprotein (apo) B48, the structural protein of chylomicrons, are increased in conditions associated with systemic inflammation. As such, apo B48 may help to identify patients at increased cardiovascular risk. The objective of this study was to evaluate apo B48 levels in relation to other cardiovascular risk factors in patients with rheumatoid arthritis (RA).

Methods: We performed a prospective cohort study with RA patients without clinical cardiovascular disease or diabetes mellitus. Blood samples were collected after an overnight fast and a complete lipid profile, including total serum apo B and apo B48 (ELISA), was measured.

Results: 328 Patients were included. The mean age was 53±11 years and 224 patients (68%) were female. Remnant cholesterol (remnant-C) concentration was 0.52±0.26 mmol/L and fasting plasma triglycerides 1.25±0.88 mmol/L Median plasma apo B48 was 8.6 [IQR 5.2-12.5]. Serum apo B48 correlated positively with triglycerides (r=0.651; p<0.001, remnant-C (r=0.479; p<0.001 and LDL-C (r=0.123; p=0.03). Patients in the highest apo B48 tertile were, 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).

Conclusion: RA patients have a high level of apo B48, despite low plasma triglycerides and remnant-C, which indicates that chylomicron remnant clearance may be delayed in RA, especially in rheumatoid factor or anti-CCP positive subjects.

Introduction

The evidence on the increased cardiovascular disease (CVD) risk associated to rheumatoid arthritis (RA) has accumulated during the last two decades. The prevalence of CVD in patients with RA is as high as in patients with type 2 diabetes mellitus (T2DM) (1, 2). Traditional cardiovascular risk factors, such as hyperlipidemia and hypertension, as well as RA specific risk factors, such as RA disease activity, erythrocyte sedimentation rate and C-reactive protein (CRP) levels contribute to the total CVD risk of RA patients (3-6).

Postprandial hyperlipidemia with accumulation of remnants has gained interest in the literature because of recent reports showing that non-fasting triglycerides are independent predictors of the risk of atherosclerosis (7, 8). Postprandial hyperlipidemia is often present in patients with a high CVD risk, such as patients with established coronary artery disease (CAD), T2DM (9, 10), the metabolic syndrome (11, 12), obesity (13) and familial combined hyperlipidemia (FCH) (14). Moreover, postprandial hyperlipidemia is closely associated to the generation of atherosclerosis (15-17). Postprandial chylomicrons and their remnants are able to induce leukocyte activation and can be internalized by macrophages without the need for prior modification, causing foam cell formation (18) and therefore, initiate atherosclerosis (19).

Postprandial hyperlipidemia is usually the consequence of hepatic very low-density lipoprotein (VLDL) overproduction and delayed clearance of chylomicrons and VLDL with their respective remnants since they share the same metabolic pathway (11, 14, 20, 21). In T2DM, intestinal overproduction of chylomicrons has been demonstrated, which also contributes to the postprandial hyperlipidemia typical of this disorder (22). Overall, these metabolic processes lead to elevated concentrations of chylomicrons and VLDL, and their respective remnants, collectively known as triglyceride-rich lipoproteins (TRLs). All these atherogenic lipoproteins contain apolipoprotein (apo) B as structural protein. In humans, two forms of apo B exist: apo B100, which is found on hepatically derived lipoproteins, and apo B48, which is present on the intestinally derived chylomicrons and their remnants (23). Therefore, plasma apo B48 levels represent the exact number of circulating chylomicrons and chylomicron remnants.

Apo B48 levels are closely associated to postprandial lipoprotein metabolism, even in the fasting state, and elevated levels of fasting apo B48 reflect postprandial hyperlipidemia (24). Moreover, fasting apo B48 is positively associated with several cardiovascular risk factors, including plasma triglycerides, remnant-cholesterol (remnant-C), body mass index (BMI) and carotid intima-media thickness (cIMT), a surrogate marker for subclinical atherosclerosis, and it correlates negatively with high-density lipoprotein cholesterol (HDL-C) (25, 26).

To date, no data on apo B48 or postprandial lipemia in RA are available. The chronic inflammatory state in RA may be associated to impaired chylomicron (remnant) me-

tabolism, which in turn may contribute to the increased risk of CVD in these patients. Therefore, we aimed to evaluate apo B48 levels in RA in relation to other cardiovascular risk factors.

Materials and methods

Participants

RA patients in this study were participants in the FRANCIS (Franciscus Rheumatoid Arthritis and Cardiovascular Intervention Study) trial. The FRANCIS study is an open label randomized clinical trial in which RA patients younger than 70 years old and without current CVD or T2DM are routinely screened for traditional CVD risk factors and, based on randomization, strictly treated for traditional CVD risk factors, at the Diabetes and Vascular Center of the Franciscus Gasthuis, Rotterdam, the Netherlands (27, 28). 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. The data for this study are the baseline measurements in the FRANCIS study (registered at trialregister.nl, number NTR3873).

Approval was given by the Institutional review board of the Franciscus Gasthuis and the regional independent medical ethical committee at the Maasstad Hospital in Rotterdam. All participants gave written informed consent.

Data collection

The medical history, anthropometric measures and the use of medication were recorded.

RA disease activity was assessed by using the Disease Activity Score with 28 joints counted (DAS28). This score included swollen joint count (28), tender joint count (28), VAS (0-100 scale) indicating pain/discomfort due to RA, and the erythrocyte sedimentation rate (ESR).

The estimated cardiovascular risk was assessed using the SCORE tables, and included suggested adaptations according to EULAR 2015 recommendations. The EULAR recommendation implies a multiplication of the CVD risk by 1.5 for all RA patients (29).

Blood samples were taken after an overnight fast of at least 12 hours and included a complete lipid profile with both total plasma apo B and apo B48.

Analytical Methods

Basic parameters for renal and liver function as well as glucose, total cholesterol, HDL-C and triglycerides were determined using a Synchron LX-20 or DxC analyzers (Beckman Coulter, Brea CA, USA) according to standard procedures in our laboratory for clinical

chemistry. LDL-C values were calculated using the Friedewald formula. Remnant-C was calculated by subtracting LDL-C and HDL-C from the total cholesterol. Apo AI and apo B were determined by rate nephelometry using an IMMAGE analyzer (Beckman Coulter, Brea CA, USA). The ESR was measured using an Alifax Test 1 analyzer (Alifax, Padova, Italy).

Apo B48 serum levels were quantified as previously reported (30), using a commercially available ELISA (Shibayagi Co., Ltd. Japan), consisting of a Sandwich type ELISA with absorbance dichromatic reading at 450 nm/ 620 nm (reference for plate correction) wavelength (31). All samples were assayed in three runs. Since no commercial quality controls are available for apo B48, a local internal quality control was pooled according to WHO recommendations, stored at - 80 ºC, and formerly assayed by duplicate on each plate in parallel to samples. Calculated Variation Coefficients (VC) were 5.7% (intra-assay), 11.0% (inter-assay) and 12.4% (total).

Statistics

Data are given as mean ± standard deviation (SD) unless stated otherwise. Correlation analysis was performed using a Pearson's correlation. For comparison of patients with relatively high and low apo B48 levels, tertiles were created. Analyses were performed between the lowest and the highest tertile. Analyses were performed using the Students t-test or chi-square test where applicable. For skewed variables (DAS28, C-reactive protein, triglycerides) the Mann-Whitney U test was used. All statistical analyses were carried out using PASW statistics version 18.0 (IBM SPSS Statistics, New York, United States). P-values below 0.05 (two sided) were considered statistically significant.

Results

General characteristics

In total, 328 subjects with RA were included. The general characteristics are shown in Table 1. Most patients were female (n=224; 68%) and their age was 53 ± 11 years. The median RA disease duration was 7 [IQR 2-14] years. The median DAS28 was low, indicating low RA disease activity or remission. Most RA patients (73%; n=243) used methotrexate and 39% (n=127) received biological therapy. Daily prednisone in varying dosage was used in 12% (n=40). A CVD risk of <10% was found in 57% (n=188), 23% (n=77) had a CVD risk of 10-19% and 18% (n=60) had a CVD risk ≥20%. In six patients CVD risk could not be calculated due to missing data.

Table 1. General characteristics of study participants (n=328). Data are given as mean ± SD, number (%) or as median [Interquartile Range].

	RA (n=328)
Male (n,%)	104 (32%)
Age (yrs)	53 ± 11
BMI (kg/m^2)	26.5 ± 4.5
Current Smoker	60 (18%)
Systolic BP (mmHg)	132 ± 19
Diastolic BP (mmHg)	79 ± 10
Glucose (mmol/L)	5.5 ± 0.6
Total cholesterol (mmol/L)	5.4 ± 1.1
LDL-C (mmol/L)	3.4 ± 0.9
HDL-C (mmol/L)	1.48 ± 0.41
Triglycerides (mmol/L)	1.05 [0.73-1.51]
Apo AI (g/L)	1.69 ± 0.40
Apo B (g/L)	1.00 ± 0.26
Apo B48 (mg/L) (median [IQR])	8.6 [5.2-12.5]
Remnant-C (mmol/L)	0.52 ± 0.26
Medication use	
Lipid lowering drug (n,%)	15 (5%)
Antihypertensive drugs (n,%)	56 (17%)
RA disease activity (DAS28) (median [IQR])	2.30 [1.60-3.24]

CAD = coronary artery disease; BP = blood pressure; Remnant-C = total cholesterol -(LDL-C) – (HDL-C).
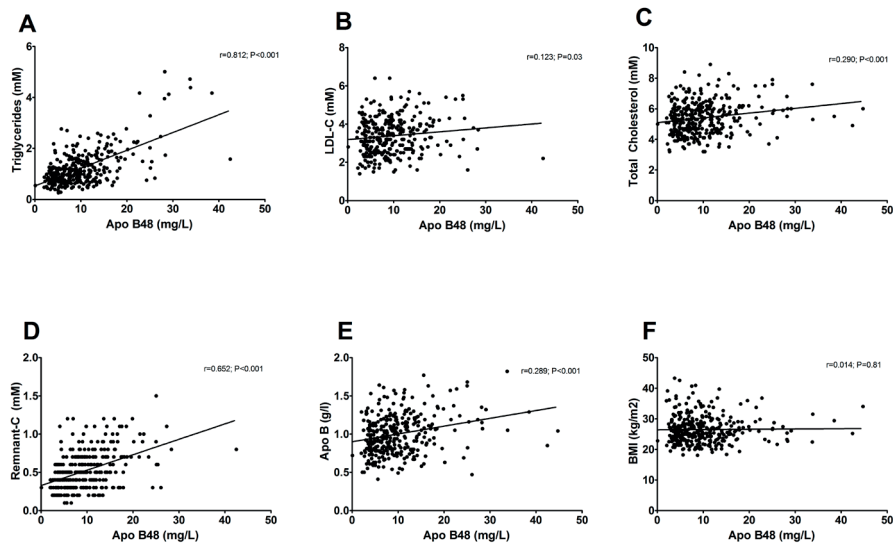
Correlation studies

Remnant cholesterol (remnant-C) concentration was 0.52±0.26 mmol/L and fasting plasma triglycerides 1.25±0.88 mmol/L. The median apo B48 was 8.6 [IQR 5.2-12.5] mg/L. Apo B48 correlated positively with triglycerides (r=0.651; P<0.001), remnant-C (r=0.479; P<0.001), total cholesterol (r=0.196; P< 0.001), LDL-C (r=0.123; p=0.03) and total serum apo B (r=0.261; p<0.001) (Figure 1). A negative correlation was found between apo B48 and HDL-C (r=-0.208; P<0.001). A positive trend was observed between apo B48 and glucose (r=0.106; p=0.06), and between apo B48 and systolic blood pressure (r=0.095; p=0.09). No significant correlation was found between apo B48 and BMI (r=0.014; p=0.81), waist circumference (r=0.067; p=0.23) or DAS28 (r=-0.03; p=0.58).

General characteristics based on apoB48 tertiles

Tertiles based on apo B48 levels showed that patients in the highest tertile were more often male (43% [n=46] vs. 28% [n=31]; p=0.03), were older (55±9 vs. 53±12 years; p=0.018) and more often anti-CCP positive (75% [n=62] vs. 59% [n=59]; p=0.005) and rheumatoid factor positive (75% [n=72] vs. 58% [n=62]; p=0.04) compared to the lowest

tertile. Triglycerides were higher in the highest tertile compared to the lowest tertile (median 1.49 [IQR 0.93-2.01] mmol/L vs. median 0.83 [IQR 0.65-1.09] mmol/L; p <0.001). The median [IQR] apo B48 was 4.4 [3.7-5.2] mg/L in the lowest tertile and 14.6 [12.4-18.5] mg/L in the highest tertile.

No differences were found in total cholesterol, LDL-C, HDL-C, DAS28, C-reactive protein, RA disease duration, the presence of erosive disease, DMARD use, statin use or prednisone use (data not shown).

Figure 1. Correlations of apolipoprotein (apo) B48 with triglycerides (A), LDL-C (B), total cholesterol (C), remnant-cholesterol (D), apo B (E) and body mass index (F).

Discussion

This is the first study to explore apo B48 levels in RA patients, showing elevated plasma concentrations, with a median apo B48 of 8.6 [5.2-12.5] mg/L, compared to previous studies in healthy controls. Alipour et al. found apo B48 levels of 5.7±0.6 mg/L in healthy individuals and Masuda et al. found apo B48 levels of 3.9 ± 2.4 mg/L in non-CAD patients without overt coronary stenosis (26, 32). In another study, Masuda et al. investigated apo B48 levels in different subgroups of healthy controls. They concluded that apo B48 levels of 5.7 mg/L should be regarded as the upper limit of normal apo B48 levels in normolipidemic healthy controls (33). Interestingly, the highest apo B48 tertile in our RA group showed threefold increased levels compared to this suggested reference value. Although the triglyceride concentrations were higher in this tertile, those levels

were still within normal limits. Patients in the highest apo B48 tertile were significantly more often anti-CCP and rheumatoid factor positive. Anti-CCP and rheumatoid factor are associated with a more progressive disease course of the RA and thus with more inflammation. Patients in the highest tertile did not show a higher C-reactive protein, DAS28 of RA disease duration and they had not more often erosive disease. Therefore, the exaggerated apo B48 levels in this subgroup remain unexplained.

Apo B48, remnant-C and triglycerides are all markers of postprandial lipemia and represent different components of the lipoprotein fractions. Apo B48 reflects the number of circulating chylomicrons and their respective remnants, while remnant-C and plasma triglycerides reflect the lipid content within the chylomicrons and remnants, including VLDL and its remnants. Interestingly, apo B48 was increased in RA while triglycerides and remnant-C were within normal range, reflecting a high number of circulating, relatively small and probably cholesterol-depleted remnants. Therefore, in RA the lipolysis of chylomicrons may be normal, while the hepatic catabolism of chylomicron remnants may be impaired. Alternatively, the intestinal production of chylomicrons may be increased, similar to the situation in T2DM (22). Further investigation of the metabolism of triglyceride-rich lipoproteins and the role of postprandial hyperlipidemia on the excess CVD risk in RA patient is necessary. It would be interesting to know whether there is an association between apo B48 and levels of auto-antibodies. These data were unavailable in this study.

In conclusion, apo B48 levels in RA patients are high, despite low triglycerides and remnant-C, which indicates that chylomicron remnant clearance may be delayed in RA. The current data suggest an association between apo B48 levels with rheumatoid factor or anti-CCP positivity in RA.

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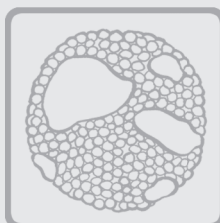
CHAPTER 7

Effect of a tight control treatment protocol for traditional cardiovascular risk factors in rheumatoid arthritis patients: 2-year data of the FRANCIS

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Abstract

Introduction: RA patients are characterized by an increased cardiovascular disease (CVD) risk in which traditional CVD risk factors and RA specific risk factors may play a role. In this study we investigated the effect of a tight control regimen on CVD risk factors after two years of follow-up.

Material and Methods: RA patients ≤70 years of age without CVD and diabetes mellitus were randomized between strict treatment of CVD risk factors or usual care.

Results: In total 239 patients were included (109 patients in the usual care group and 121 in the tight control group). The majority of the patients was female (n=151; 63%) and mean age was 54±11 years. After two years of follow-up total cholesterol, LDL-C, and apolipoprotein B levels were significantly lower in the tight control group compared to usual care. There was a trend towards lower triglycerides (p=0.05) and higher HDL-C (p=0.07) in the tight control group after 2 years. The LDL-C decrease was greater in the tight control group compared to the usual care group (-0.99±0.99 vs -0.37±0.76 mmol/l; p=0.03). Systolic blood pressure significantly decreased in the tight control group, but was blood pressure at 2-year follow up was not significantly different between the groups.

Conclusion: Tight control treatment of traditional CVD risk factors in RA was most effective in targeting lipid levels after two years compared to usual care.

Trial Registration: The Dutch Trial Register, www.trialregister.nl, NTR3873.

Introduction

The evidence on the increased risk for cardiovascular disease (CVD) in rheumatoid arthritis (RA) has accumulated during the last two decades (1-3). It has been suggested that the prevalence of CVD in patients with RA is as high as in patients with type 2 diabetes mellitus (T2DM) (1, 4). The exact cause of this increased CVD risk is unclear. Since atherosclerosis is an inflammatory process (5) the on-going inflammation in RA may play a role. It is thought that tight control of RA disease activity may help to decrease the CVD risk in RA (6, 7). Despite the fact that their exact role is unclear, traditional CVD risk factors such as hypercholesterolemia and hypertension should not be overlooked (8-10). Several studies showed that the prevalence of hypertension and hyperlipidemia in RA patients is comparable to the general population. Furthermore, there is evidence of underdiagnosis and undertreatment of traditional CVD risk factors in RA (11, 12). The importance of these risk factors has been strengthened by recent national and international recommendations proposing the need for a CVD risk estimation specifically for RA patients using an adapted version of the traditional SCORE risk assessment model (13, 14). These modifications of the original risk stratification models may have a large impact on current care, since the number of patients eligible for risk assessment, treatment and follow-up will increase substantially. Several studies showed positive effects of treatment with lipid lowering drugs and/or anti-hypertensive drugs on respectively lipid levels and blood pressure (15-19). To date, however, the effect of a tight treatment regimen for these CVD risk factors on the development of clinical and subclinical atherosclerosis has not been investigated. The FRANCIS study was designed to evaluate the effects of a predefined tight treatment protocol including all traditional CVD risk factors on subclinical atherosclerosis in RA comparing the effects to control patients who were referred to their general practitioner for treatment. In this interim analysis, we show the results of tight treatment of the CVD risk factors versus usual care after 2 years of follow-up.

Material and Methods

Study design and patients

The FRANCIS (Franciscus Rheumatoid Arthritis and Cardiovascular Intervention Study) is an open label, randomized clinical trial in RA patients investigating the effects of a strict treatment protocol for traditional CVD risk factors like hyperlipidemia, hypertension, smoking, overweight and diabetes mellitus (Dutch Trial Register, www.trialregister.nl, NTR3873). RA patients younger than 70 years of age and without clinical CVD or T2DM were either randomized to intensive treatment of traditional CVD risk factors with pre-

specified treatment targets and recommendations on lifestyle changes or they were referred to their general practitioner for treatment. Before randomization the CVD risk score according to the 2010 unadjusted SCORE risk assessment was calculated (20). Patients with a CVD risk score <10% were eligible for randomization (comparable to <20% in the current, unadjusted SCORE table). Patients with a CVD risk score ≥10% (9/326) all were treated according to the tight control protocol and were separately followed. Clinical 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.

The Institutional Review Board of the Franciscus Gasthuis in Rotterdam and the TWOR regional independent medical ethics committee, Maasstad Hospital, Rotterdam, approved the study. The study was conducted according to the Declaration of Helsinki. All participants gave written informed consent.

Treatment targets according to the tight control protocol

The flow chart for the tight control treatment regimen is shown in Figure 1. The start of anti-hypertensive drugs and or alteration of current anti-hypertensive treatment was initiated when a patients blood pressure was >140/85mmHg. The presence of hypertension was confirmed by taking a mean blood pressure of 5 measurements within 15 minutes or, if necessary an ambulant 24-hours ambulant blood pressure measurement. First choice of antihypertensive drug was an ACE inhibitor (perindopril), followed by the addition of a thiazide diuretic (indapamide) and eventually a beta and/or alpha blocker and/or calcium-antagonist when blood pressure persisted >140/85 mmHg.

Treatment with simvastatin in combination with dietary and lifestyle advices was initiated when LDL-C was >3.0 mmol/l, apolipoprotein (apo) B >0.9 g/L or triglycerides (TG) >2.20 mmol/l. Bezafibrate combined with dietary and lifestyle advices were initiated in case of isolated hypertriglyceridemia (TG >2.20 mmol/l). Dietary and lifestyle advices were given in the case of low HDL-C levels (≤1.20 mmol//l for females and ≤1.00 mmol/l for males) and/or a body mass index (BMI) >25kg/m^2.

In the case of smoking, cessation was advised and a referral to the outpatient clinic for smoking cessation was offered. In the case of HbA1c levels >6.4% (48 mmol/mol) indicating the development of diabetes mellitus, patients were treated with metformin.

Patients in the tight control group 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 due to medical/treatment related problems.
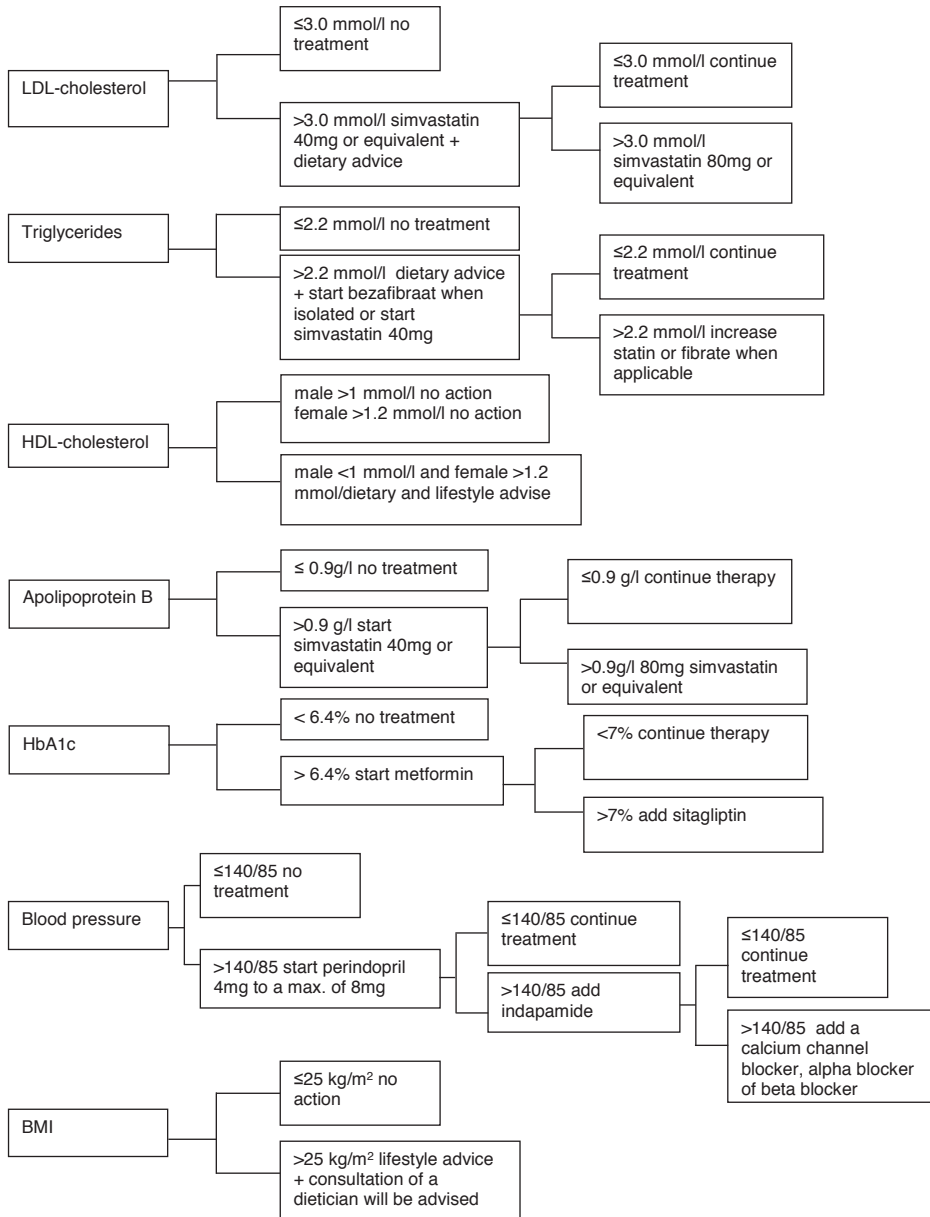
Figure 1. Flow chart tight control.

Cardiovascular risk assessment

The 10-year cardiovascular risk was assessed using the SCORE tables following the 2011 Dutch CVRM guideline (13, 14).

Rheumatoid arthritis disease activity

Rheumatoid arthritis disease activity was assessed using the Disease Activity Score with 28 joints counted (DAS28). This score included swollen joint count (28), tender joint count (28), VAS score (scale 0-100) indicating pain and discomfort due to RA, and the level of C-reactive protein (CRP).

Laboratory measurements

A standardized set of measurements was performed in each subject. Blood samples were drawn after an overnight fast. Laboratory parameters were determined at the Department of Clinical Chemistry, Franciscus Gasthuis, Rotterdam, the Netherlands. Renal and liver function tests as well as glucose, CRP, total cholesterol, HDL-C and TG were measured using Synchrom LX or DxC analyzers (Beckman Coulter, Anaheim CA, USA). LDL-C was calculated using the Friedewald formula if TG were below 4.00 mmol/l. Apo AI and apo B were determined by rate nephelometry using IMMAGE with commercially available kits (Beckman Coulter). The erythrocyte sedimentation rate (ESR) was measured using an Alifax Test 1 analyzer (Alifax, Padova, Italy).

Statistics

Data are given as mean ± standard deviation (SD) unless stated otherwise. Differences between groups were determined using the unpaired Student's t-test or Chi-square test, where appropriate. In case of skewed variables (DAS28(-ESR), C-reactive protein and TG), the Mann-Whitney U test was used for comparisons between groups and the Wilcoxon signed ranks test for comparisons within groups. All statistical analyses were performed using PASW statistics version 18.0 (IBM SPSS Statistics, New York, United States). Primary endpoint of the FRANCIS study is progression of cIMT after five years of follow-up. Since the study is still in progress, for the present analysis we aimed to investigate levels of CVD risk factors after two years of follow-up and the number of patients that reached treatment targets.

Results

General Characteristics

Table 1 shows the general characteristics of all included patients at baseline per group. In total 317 patients were randomized, 157 to usual care and 160 to tight control. Nine patients were included in the high-risk cohort. Two-year follow up data were available in 239 patients, 109 (69.4%) patients in the usual care group and 121 (75.6%) in the tight control group. In the tight control, group 3 patients died within the first two years of follow-up (probably not CVD related) and 27 patients ended study participation for

Table 1. General characteristics at baseline.

	Usual Care (n=157)	Tight control (n=160)	p-value
Male gender (n,%)	59 (38%)	36 (23%)	0.05
Age (yrs)	52±12	54±11	0.059
Body mass index (kg/m^2)	26±5	26±4	0.78
Waist circumference (cm)	94±14	93±12	0.77
Smoking (n,%)	32 (20)	29 (18)	0.67
Systolic blood pressure (mmHg)	131±18	131±19	0.89
Total cholesterol (mmol/l)	5.4±1.0	5.4±1.0	0.90
LDL-C (mmol/l)	3.4±0.9	3.3±1.0	0.67
HDL-C (mmol/l)	1.46±0.41	1.52±0.41	0.18
Triglycerides (mmol/l) median (IQR)	1.11 (0.71-1.56)	0.98 (0.73-1.42)	0.52
Apolipoprotein AI (g/L)	1.67±0.37	1.70±0.37	0.91
Apolipoprotein B (g/L)	1.00±0.26	0.99±0.25	0.90
Fasting glucose (mmol/l)	5.4±0.6	5.5±0.6	0.63
HbA1C (mmol/mol)	35±4	35±4	0.52
C-reactive protein (mg/dl) median (IQR)	2.0 (1.0-6.0)	3.0 (1.0-6.0)	0.94
DAS28ESR median (IQR)	2.4 (1.7-3.4)	2.5 (1.6-3.2)	0.69

other reasons. In the usual care group 31 patients were lost to follow-up. No patients died in the usual care group. Nine patients in the tight control group and 17 patients in the usual care group were excluded for this analysis due to missing data (i.e. a missing visit at two year follow-up).

The majority of the patients was female (n=222; 70%). Most patients (n= 268; 82%) were Dutch and currently in a relationship/marriage (n= 258 (79%)) and highly educated (college/university) (n=219; 69%). Participants in the tight control group were more often female compared to participants in the usual care group. There were no differences in other parameters between the groups at baseline. Baseline characteristics in the 239 patients that also had data at 2 years follow-up were comparable the baseline study population (Table 2) and show a significant difference in gender (i.e. more female patients in the tight control group) but no differences in other parameters.

In Table 3 medication use at baseline is shown for the patients included in the 2-year analysis. There were no differences in the use of medication at baseline between the usual care and the tight control group. In both groups, very few patients used statins at baseline (4% and 6% for usual care and tight control, respectively).

Tight control versus usual care at 2-year follow-up

LDL-C decreased in the tight control group (3.3±0.9 mmol/l to 2.5±0.8 mmol/l; p<0.001) and in the usual care group (3.4±0.8 mmol/l to 3.1±0.9 mmol/l; p<0.001). The mean de-

Table 2. Data at 2 years follow-up.

	Usual Care Baseline (n=107)	Tight control Baseline (n=121)	p-value between groups at baseline	Usual care 2yr FU (n=107)	Tight control 2yr FU (n=121)	p-value between groups at 2 year FU
Male gender (n, %)	47 (43%)	33 (27%)	0.01	-	-	-
Age (yrs)	53±11	55±10	0.1	-	-	-
Body mass index (kg/m^2)	26±4	26±4	0.39	26±5	27±5*	0.18
Waist circumference (cm)	93±13	94±12	0.51	92±13	92±13*	0.97
Smoking (n,%)	21 (19%)	17 (14%)	0.30	21 (19%)	17 (14%)	0.30
Systolic blood pressure (mmHg)	131±18	132±19	0.48	127±16	127±14*	0.98
Total cholesterol (mmol/l)	5.5±1.0	5.4±1.1	0.49	5.3±0.9	4.5±0.9*	<0.001
LDL-C (mmol/l)	3.4±0.9	3.3±1.0	0.42	3.1±0.8*	2.5±0.8*	<0.001
HDL-C (mmol/l)	1.46±0.38	1.51±0.39	0.33	1.54±0.39*	1.63±0.48*	0.07
Triglycerides (mmol/l)	1.12 (0.76-1.67)	0.98 (0.75-1.45)	0.36	1.38 (0.92-1.97)*	1.16 (0.85-1.64)*	0.05
Apolipoportein AI (g/L)	1.67±0.33	1.68±0.36	0.88	1.58±0.25*	1.62±0.29	0.29
Apolipoprotein B (g/L)	1.01±0.28	0.99±0.26	0.49	1.08±0.26*	0.93±0.25*	<0.001
Fasting glucose (mmol/l)	5.4±0.6	5.5±0.5	0.45	-	-	-
Non-fasting glucose (mmol/l)	-	-	-	5.7±1.0	5.7±1.1	0.78
HbA1C (mmol/mol)	35±4	35±4	0.84	37±5*	37±5*	0.39
C-reactive protein (mg/dl)	2.0 (1.0-5.5)	3.0 (1.0-6.0)	0.75	2.0 (1.0-5.0)	2.0 (1.0-6.0)	0.85
DAS28ESR median (IQR)	2.3 (1.7-3.3)	2.3 (1.6-3.0)	0.51	2.2 (1.7-2.7)	2.3 (1.6-3.1)	0.37

* significantly different compared to baseline within group.

crease in LDL-C was 2.7 times greater in the tight control group when compared to the usual care group (-0.99±0.99 mmol/l vs -0.37±0.76 mmol/l; p=0.03). After two years of follow-up, total cholesterol, LDL-C and apo B levels were significantly lower in the tight control group compared to usual care. There was a trend towards lower TG (p=0.05) and higher HDL-C (p=0.07) in the tight control group after 2 years. In total 72% (n=87) of the patients in the tight control group had an LDL-C <3.0 mmol/l after two years compared to 38% (n=41) in the usual care group (p<0.001).

The systolic blood pressure significantly decreased in the tight control group (132±19 mmHg to 127±14 mmHg; p<0.004) but not in the usual care group (130±18 mmHg to 127±16 mmHg; p=0.078). However, the systolic blood pressure was comparable between both groups after 2 years. Systolic blood pressure treatment targets were reached in 75% (n=90) of the patients in the tight control group versus 70% (n=76) in the usual care group (p=0.46). Diastolic blood pressure treatment targets were reached in 73% (n=88) of the patients in the tight control group versus 70% (n=76) in the usual care group (p=0.66). In the tight control group BMI was significantly higher after 2 years compared to baseline and waist circumference was significantly lower (Table 2). No differences were found in other traditional CVD risk factor after strict treatment or usual care (Table 2).

In total, 8 patients (9%) in the usual care group started with statin treatment and 41 patients (41%) in the tight control group (p<0.001). New anti-hypertensive drugs were initiated in 5 patients (5%) in the usual care group and 11 patients (9%) in the tight

Table 3. Medication use at baseline.

	Usual Care (n=109)	Tight control (n=121)	p-value
Lipid lowering drugs (n,%)	4 (4%)	7 (6%)	0.54
Anti-hypertensive drugs (n,%)	19 (17%)	26 (21%)	0.51
Use of 1 anti-hypertensive drug	4 (4%)	11 (9%)	0.11
Use of 2 anti-hypertensive drugs	13 (12%)	8 (7%)	0.25
Use of 3 anti-hypertensive drugs	2 (2%)	7 (6%)	0.18
NSAIDs (n,%)	41 (38%)	51 (42%)	0.49
Prednisone (n,%)	17 (16%)	13 (11%)	0.33
Methotrexate (n,%)	85 (78%)	85 (70%)	0.28
Hydroxchloroquine (n,%)	26 (24%)	26 (21%)	0.75
Sulphasalazine (n,%)	6 (6%)	3 (2%)	0.32
Anti-TNF (n,%)	39 (36%)	50 (41%)	0.34
Other biological (n,%)	4 (4%)	4 (3%)	>0.99
Use of >1 DMARD, excl. biologicals and steroids (n,%)	23 (21%)	20 (17%)	0.50
Use of >1 DMARD, excl. steroids incl. biologicals (n,%)	51 (47%)	54 (45%)	0.89

control group. Glucose lowering drugs were initiated in 1 patient of the tight control group. The number of smokers remained the same in two years time in both groups, despite active referral to the smoking cessation outpatient clinic of patients in the tight control group.

Discussion

In this interim analysis we showed that treatment according to a tight treatment protocol for traditional CVD risk factors resulted in more frequent use of lipid lowering drugs and a greater decrease in LDL-C with a trend to improved TG and HDL-C levels, when compared to usual care. The number of patients that reached LDL-C treatment targets was significantly greater in the tight control group compared to usual care. Also blood pressure was significantly lower after two years in the tight control group, but not in the usual care group. The number of patients that reached treatment target for LDL-C and systolic blood pressure was approximately three quarters of the patients. This means that in 25% of the cases patients were not treated to target. The reason for this may be patient-related, i.e. non-adherence or unwillingness to take the prescribed/ recommended treatment, or doctor-related, i.e. not treating as strictly as the protocol describes for various reasons. Currently data on the reasons for not following the protocol are unavailable. We know that adherence to primary, and even secondary prevention in the general population is also poor (21, 22). In our study all participants willingly participated in this randomized controlled trial regarding CVD risk management, which may lead to relatively more adherent patients to be included compared to the general population. A previous report on adherence to prescribed CV medication reported high adherence rates of 90%, this is however self-reported (21). For other CVD risk parameters such as, smoking habits and body mass index no differences after two years of follow-up were found in either group. It is generally known that adherence to recommended lifestyle changes are generally low, which may be the reason for this lack of improvement. We have shown previously that adherence to lifestyle recommendations in patients in the tight control arm varies between 56% and 68% (23). It is nevertheless surprising to see that the number of smokers stayed exactly the same, despite active referral to the outpatient clinic for smoking cessation. The number of patients using lipid lowering drugs and anti-hypertensive drugs increased in both the tight control and the usual care group. This may be due to the increased awareness of participating patients or their general practitioners. All general practitioners received a letter from the outpatient clinic of vascular medicine containing anthropometric and laboratory measurements of their patients including a brief explanation of the study and recommended treatment targets. But still, in the usual care group only few patients (n=8; 9%) were prescribed

lipid lowering drugs. Maybe the necessity of treating hypertension is perceived to be more important than the treatment of dyslipidemia by physicians, or patients, or there are differences in side-effects of the medications.

In conclusion, this study shows that a tight control treatment at the outpatient clinic resulted in a better overall lipid profile and a higher number of patients on statins and more patients reaching treatment targets regarding CVD risk reduction.

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CHAPTER 8

General discussion
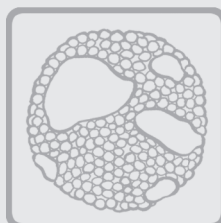
Introduction

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:
	- *> 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

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 under-diagnosis 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 (sub-clinical) 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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CHAPTER 9

Summary
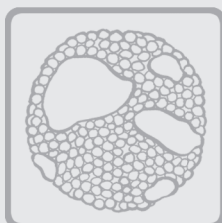
Summary

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

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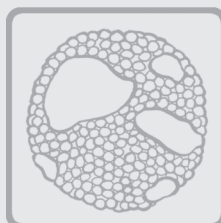
Overall patients in the tight control arm were more treat-to-to target resulting in significantly lower LDL-C and systolic blood pressure. Longer follow-up is necessary to evaluate the effect of this treatment difference on subclinical atherosclerosis.

CHAPTER 10

Nederlandse samenvatting

Introductie

Reumatoïde artritis (RA) is een auto-immuun ziekte waardoor er ontstekingen in meerdere gewrichten (artritis) kunnen ontstaan. Het is gebleken dat patiënten met RA een verhoogd risico hebben op hart- en vaatziekten wat inhoudt dat deze patiënten vaker dan normaal een myocardinfarct (hartinfarct), een beroerte of perifeer vaatlijden (etalage-benen) ontwikkelen. Nu het verhoogde cardiovasculaire (CV) risico in RA meermalen is aangetoond, is het belangrijk om de factoren die dit risico in RA patiënten bepalen in kaart te brengen. De ontwikkeling van hart- en vaatziekten begint o.a. met atherosclerose (aderverkalking), waardoor de slagaders dichtslibben. De ontwikkeling van atherosclerose is deels een inflammatoir (ontstekings) proces, waardoor het voor de hand ligt te denken dat de chronische ontsteking die bij RA patiënten aanwezig is de veroorzaker van het verhoogde CV risico is. Toch kunnen we hiermee niet volledig het verhoogde CV risico verklaren. De zogenoemde traditionele CV risicofactoren zoals hypertensie (hoge bloeddruk), hypercholesterolemie (verhoogd cholesterol), diabetes mellitus (suikerziekte), overgewicht en roken, zijn ook bij RA patiënten aanwezig. Deze risicofactoren lijken zich niet hetzelfde te gedragen als in de algemene populatie. Ondergewicht, zich uitend in een body mass index (BMI) van $<20kg/m^2$, is in RA patiënten bijvoorbeeld, in tegenstelling tot de algemene populatie, geassocieerd met een verhoogde CV mortaliteit. Over de jaren heen is er een betere en striktere behandeling voor de reumatische gewrichtsontstekingen ontwikkeld wat leidt tot minder inflammatie. Dit zou theoretisch kunnen leiden tot een vermindering van het CV risico. Tot op heden is dit echter nog niet aangetoond.

Het is niet bekend wat de lange termijn effecten zijn van een strikte, geprotocolleerde behandeling van de traditionele CV risicofactoren op de uiteindelijke ontwikkeling van hart- en vaatziekten bij patiënten met RA. Zolang de risicofactoren niet goed in kaart gebracht zijn, is het lastig een adequaat CV risico predictiemodel te ontwikkelen voor patiënten met RA. Tot op heden wordt voor RA geadviseerd om bestaande CV risico predictiemodellen (SCORE of Framingham) te gebruiken en deze aan te passen voor RA. Hiervoor bestaan meerdere voorstellen, bijvoorbeeld door het berekende risico met 1.5 te vermenigvuldigen of door 15 levensjaren bovenop de werkelijke leeftijd van de patiënt te tellen. Ondanks dat iedereen zich realiseert dat dit geen nauwkeurige inschatting van het risico geeft, is er tot op heden geen betere manier gevonden.

In **Hoofdstuk 2** wordt het reeds bestaande bewijs en laatste inzichten rondom het verhoogd CV risico in RA besproken. In het verdere proefschrift worden de prevalentie van traditionele cardiovasculaire risicofactoren, de behandeling van deze factoren en het effect op atherosclerose in RA beschreven. Al deze bevindingen zijn gebaseerd op de FRANCIS studie, een studie die speciaal hiervoor is opgezet door de afdelingen Reumatologie en Vasculaire Geneeskunde binnen het Franciscus Gasthuis.

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Globale doelen van het proefschrift:

1. Bepalen wat de impact van traditionele CV risicofactoren zoals hypertensie en hypercholesterolemie is op het CV risico en atherosclerose bij RA patiënten, die niet bekend zijn met hart- en vaatziekten of met diabetes.
2. Bepalen wat patiënten zelf denken over hun therapietrouw ten aanzien van gegeven adviezen om hun CV risico te verminderen.
3. Onderzoeken of er bij RA patiënten sprake is van een postprandiale hyperlipidemie (een sterke verhoging van vetzuren na een maaltijd), een mogelijke, nog onbekende risicofactor in RA.

Onderbehandeling van hypertensie en hypercholesterolemie in RA

In **Hoofdstuk 3** wordt de aanwezigheid van traditionele CV risicofactoren beschreven. Zoals reeds eerder gepubliceerd was, vonden wij ook een hoge prevalentie (vóórkomen) van traditionele CV risicofactoren. De exacte prevalentie hangt af van de gehanteerde afkapwaarden, namelijk wat een acceptabele bloeddruk of LDL-cholesterolwaarde is en die hangt weer af van de à priori kans op de ontwikkeling van hart- en vaatziekten. Zo is het advies om naar een LDL-cholesterol van ≤2.5 mmol/l te streven bij patiënten met een CV risico van >10% binnen 10 jaar. Als het risico lager is, is behandeling niet noodzakelijk en is er dus in strikte zin geen sprake van hypercholesterolemie. Wij vonden dat er bij 84% van die patiënten (n=172) sprake was van een LDL-cholesterol >2.5 mmol/L. Wanneer we keken naar de bloeddruk had 32% van de patiënten (n=72) met een CV risico ≥10% een systolische bloeddruk boven de gestelde grens van 140mmHg. De oorzaken voor deze hoge aantallen is tweeërlei. Veel patiënten met hypertensie en/ of hypercholesterolemie worden niet herkend en daardoor niet behandeld. Wanneer RA patiënten wel behandeld worden, bleken zij in de meerderheid van de gevallen niet de streefwaardes zoals in richtlijnen zijn vastgelegd te halen, wat duidt op onderbehandeling. Deze feiten vragen om een betere screening en behandeling van traditionele CV risicofactoren bij RA patiënten. Door het gebruik van een CV risico predictiemodel is het gemakkelijker te bepalen welke patiënten wel en welke patiënten niet in aanmerking komen voor verdere medicamenteuze therapie. Omdat, zoals hierboven beschreven, een goed werkend CV risico predictiemodel specifiek voor RA patiënten nog niet voor handen is, moet er gebruik worden gemaakt van de voorgestelde aanpassingen van bestaande modellen.

Therapietrouw ten aanzien van cardiovasculaire preventie in RA

Wanneer we patiënten meer medicatie voorschrijven en leefstijladviezen geven is het altijd de vraag of deze adviezen opgevolgd worden en wat patiënten hiervan vinden. In **Hoofdstuk 4** werd de visie van RA patiënten ten aanzien van de gegeven adviezen om hun CV risico te verminderen onderzocht door middel van een vragenlijstonderzoek. Alle RA patiënten uit de strikte CV risico reductiegroep binnen de FRANCIS studie kregen een vragenlijst. Deze vragenlijst bestond uit een eerste deel, met algemene vragen ten aanzien van het opvolgen van de gegeven adviezen, en een tweede deel waarin elk advies apart werd ondervraagd. Hieruit bleek dat patiënten het, in het algemeen, niet lastig vonden om de gegeven adviezen op te volgen. In totaal gaf 75% van de ondervraagden aan het gemakkelijk te vinden wat de dokter hen aanraadde. Wanneer specifiek werd ingegaan op de afzonderlijke adviezen bleken er echter grote verschillen afhankelijk van het gegeven advies. Het advies een speciaal dieet te volgen werd door 68% gevolgd, echter het advies om aan meer lichaamsbeweging te doen werd slechts in 56% van de RA patiënten opgevolgd. Medicamenteuze therapie leek goed te worden nagevolgd. De overgrote meerderheid (90%) gaf aan de tabletten die voorgeschreven werden ook in te nemen. Opvallend was dat RA patiënten hun CV risico veel lager inschatten dan het daadwerkelijk berekende CV risico. Mogelijk dat dit verschil van inzicht ook bijdraagt aan de relatief lage therapietrouw wat betreft leefstijladviezen.

Factoren van invloed op subklinische atherosclerose in RA

In **Hoofdstuk 5** werden de baseline data van de FRANCIS studie samengevoegd met data van controle patiënten uit een observationele studie binnen dezelfde afdeling Vasculaire geneeskunde. Deze controle patiënten waren ook patiënten zonder hart- en vaatziekten of diabetes mellitus, maar in tegenstelling tot de RA patiënten van de FRANCIS hadden de controle patiënten geen RA. De mate van subklinische atherosclerose, dat wil zeggen de aanwezigheid van atherosclerose zonder dat het al tot klachten lijdt, werd gemeten met behulp van echografie. Hiermee werd dan de dikte van de intima en de media (onderdelen van de vaatwand) van de carotiden (halsslagaders) gemeten, wat wordt uitgedrukt als de intima media dikte (IMT). Vergeleken werd tussen RA en controle patiënten welke factoren geassocieerd waren met de IMT. In tegenstelling tot wat verschillende malen in de literatuur is gepubliceerd, vonden wij geen verschil in IMT tussen de RA patiënten en de controle patiënten. De gemiddelde IMT van de RA patiënten was 0.556±0.120mm, wat beschouwd mag worden als een normale IMT. Vervolgens hebben wij door middel van regressie analyse onderzocht welke parameters bijdroegen aan de hoogte van de IMT. Dit bleek voor beide groepen verschillend. Bij de

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controlegroep was roken geassocieerd met IMT, terwijl dit bij RA patiënten niet zo was. Voor de systolische bloeddruk (de bovendruk) was dit andersom. Deze was bij RA patiënten geassocieerd met de IMT en bij controle patiënten niet. Wat wel bij beide groepen duidelijk naar voren kwam was dat de leeftijd de belangrijkste voorspeller bleek bij de ontwikkeling van subklinische atherosclerose. Hiermee lijken zowel de bloeddruk als de leeftijd een sterke bijdrage te leveren aan de ontwikkeling van hart- en vaatziekten binnen RA.

Verhoogd aantal circulerende chylomicronen in RA

Omdat tot op heden de exacte spelers in het veld van hart- en vaatziekten bij RA patiënten nog niet geheel bekend is, beschreven wij in **Hoofdstuk 6** een potentiële CV risicofactor, namelijk apolipoproteïne (apo) B48. Iedere keer als we eten worden cholesterol en vetzuren vanuit de darm afgegeven via de lymfe aan het bloed middels water (of in bloed) oplosbare partikels genaamd chylomicronen. Iedere afzonderlijke chylomicron heeft precies één apo B48 als structuureiwit. Door apo B48 in het bloed te meten kan een indruk verkregen worden van de hoeveelheid circulerende chylomicronen. Het bijzondere van chylomicronen is dat zij een ontstekingsreactie in de bloedbaan veroorzaken iedere keer wanneer wij eten, maar andersom kunnen chylomicronen bij inflammatie ook weer vaker verhoogd zijn. Chylomicronen induceren atherosclerose via directe afgifte van cholesterol in de vaatwand in combinatie met het induceren van een lokale ontstekingsreactie. Tot op heden was niet bekend of het metabolisme van chylomicronen gestoord was in RA als mogelijke verklaring voor het verhoogde CV risico.

We hebben het apo B48 gemeten in de nuchtere toestand bij alle RA patiënten die deelnamen aan de FRANCIS studie. Wij vonden dat apo B48 in RA patiënten sterk verhoogd was, hoger dan eerder gerapporteerde waardes bij gezonde vrijwilligers of patiënten die reeds bekend waren met hart- en vaatziekten. Dit was extra bijzonder aangezien de triglyceriden (vetzuren) welke getransporteerd worden door chylomicronen, juist niet verhoogd waren in RA patiënten. Dit betekent dat er in RA patiënten relatief veel chylomicronen, maar met een geringe hoeveelheid triglyceriden en dus kleinere diameter, circuleren in de bloedbaan. Mogelijk dat dit zou kunnen passen bij een vertraagde opruiming van de chylomicronen, terwijl de verwerking van de triglyceriden in de postprandiale staat wel goede doorgang vindt. RA patiënten die positief waren voor reumafactoren (reumafactor en anti-CCP) bleken ook een hoger apo B48 te hebben. Het verhoogd aantal circulerende chylomicronen in RA kan dus een extra verklaring zijn voor het verhoogde CV risico in RA.

Effect van strikte primaire CV preventie na 2 jaar

We weten nu dat het CV risico verhoogd is bij RA patiënten en dat hypercholesterolemie en hypertensie hiervoor belangrijke factoren zijn. Wat de effecten zijn van een gestructureerde, strenge behandelwijze van de traditionele CV risicofactoren op het uiteindelijke risico op hart- en vaatziekten en het effect op subklinische atherosclerose is onduidelijk. Het primaire doel van de FRANCIS studie is om deze vraag te beantwoorden. In **Hoofdstuk 7** worden de resultaten van strikte CV preventieve maatregelen versus standaard behandeling na twee jaar follow-up gepresenteerd. In beide groepen bleek dat het LDL-cholesterol na twee jaar significant lager was dan bij start van de studie. De daling was echter 2.7 keer groter voor de strikt behandelde groep. Voor bloeddruk bleek er alleen een significante daling te zijn in de strikt behandelde groep en niet in de standaard groep. Verder werd duidelijk dat de RA patiënten in de strikte groep duidelijk meer cholesterolverlagende medicatie kregen voorgeschreven (41 patiënten vs. 8 patiënten in de standaard groep). Voor bloeddrukverlagende medicatie was dit minder duidelijk.

Conclusie

Na 2 jaar FRANCIS onderzoek is gebleken dat traditionele CV risicofactoren zoals hypertensie en hypercholesterolemie veel voorkomen bij RA patiënten en (meer) aandacht verdienen. 2 jaar geprotocolleerde strikte CV leidde tot een grotere bloeddrukverlaging en verlaging van het cholesterol. Een belangrijke nieuwe vraag is opgekomen, namelijk waarom het chylomicronen metabolisme in RA gestoord is en wat het belang hiervan is. Tot slot moeten we als arts nooit vergeten dat ook de patiënt zijn eigen gevoel en overtuigingen heeft. Dit resulteert niet altijd in het gewenste gedrag vanuit de arts bezien. De perceptie van de patiënt moet daarom nooit uit het oog verloren worden.
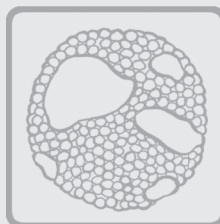
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APPENDIX

List of publications

About the author

Dankwoord

PhD Portfolio

List of publications

Publications (in this thesis)

·   van Breukelen-van der Stoep DF, Klop B, van Zeben D, Hazes JM, Castro Cabezas M. **Cardiovascular risk in rheumatoid arthritis: how to lower the risk.** Atherosclerosis 2013;231:163-72

·   van Breukelen-van der Stoep DF, Zijlmans J, van Zeben D, Klop B, van de Geijn GJM, van der Meulen N, Hazes JMW, Birnie E, Castro Cabezas M. **Adherence to cardiovascular prevention strategies in patients with rheumatoid arthritis.** Scand J Rheum 2015;14:1-6

·   van Breukelen-van der Stoep DF, van Zeben D, Klop B, van de Geijn GJ, Janssen HJ, Hazes MJ, Birnie E, van der Meulen N, de Vries MA, Castro Cabezas M. **Associaton of cardiovascular risk factors with carotid intima media thickness in patients with rheumatoid arthritis with low disease activity compared to controls: A cross-sectional study.** PLoS One 2015;10:e0140844

·   van Breukelen-van der Stoep DF, van Zeben D, Klop B, van de Geijn GJM, Janssen HJW, van der Meulen N, de Vries MA, Hazes JMW, Birnie E, Casto Cabezas M. **Marked underdiagnosis and undertreatment of hypertension and hypercholesterolemia in rheumatoid arthritis.** Rheumatology 2016;55:1210-6

Publications (other)

·   van der Stoep DF, Van Paassen H. **Eosinofiele fasciitis, een case report.** NTvR 2007/4.

·   van der Stoep DF, Braunstahl GJ, van Zeben J, Wouters J. **Sarcoidosis during anti-tumor necrosis factor-alpha therapy, no relapse after rechallenge.** J Rheumatol 2009;36:2847-8

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About the author

Deborah Francisca van Breukelen-van der Stoep was born on October 26th 1980 in Dordrecht, The Netherlands. After graduating athenaeum in 1999 at the Willem van Oranje in Oud-Beijerland she started Biomedical Sciences at the University of Antwerp during 1 year (propedeuse obtained). In 2000 she started her medical studies at the University of Antwerp. After receiving her medical degree in 2006 she worked for 3 months as a resident at the Department of Rheumatology in Ziekenhuisgroep Twente in Enschede. In November 2006 she started her residency in Internal Medicine at the Sint Franciscus Gasthuis under the supervision of A.P. Rietveld. In the third year of that residency, the idea of a promotion developed. In 2010 she started as a rheumatology fellow at the Erasmus Medical Center Rotterdam under supervision of Prof. dr. J.M.W. Hazes. That year the protocol for the FRANCIS was written and judged by the medical ethics committee. In 2011 she continued her fellowship at the Sint Franciscus Gasthuis Rotterdam under supervision of dr. M. Huisman. In January of that year the FRANCIS trial started (under direct supervision of dr. M. Castro Cabezas and dr. D. van Zeben). In 2013 she completed her rheumatology training and started as a rheumatologist at Hospital Gelderse Vallei in Ede.

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Dankwoord

Als promovenda ben ik slechts de bevoorrechte vertegenwoordiger van een groot team dat samen de werklast en verantwoordelijkheid heeft gedragen. Ik vind het dan ook best moeilijk om in slechts een paar worden mijn oprechte dank uit te spreken aan iedereen die dit mogelijk heeft gemaakt. Ik doe graag een poging.

Allereerst wil ik alle patiënten bedanken die deelgenomen hebben (en nog steeds deelnemen) aan de studie. Zonder jullie was er niks te onderzoeken geweest!

Daarnaast alle mensen die een directe of indirect bijdrage hebben geleverd aan dit boekje. Mijn promotor Professor Hazes. Beste Mieke, toen ik mijn plannen voor een promotie in het Franciscus besprak, was je direct enthousiast. Ook al lag het onderwerp ver buiten de bestaande onderzoekslijnen van het Erasmus MC. Je hebt me alle ruimte gegeven om mijn eigen pad te ontwikkelen, waarbij je me het vertrouwen hebt gegeven dat het zou lukken. Op de momenten dat we elkaar spraken over een artikel wist je altijd feilloos de zwakke plekken te benoemen en verbeteringen voor te stellen. Nooit was je, ondanks je drukke agenda, te beroerd om richting het Franciscus te fietsen om daar te vergaderen, zodat Manuel, Jendé en ik niet naar het Erasmus MC hoefden te komen. Bedankt voor al je steun en vertrouwen.

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Lieve Boudewijn, jij bent mijn (letterlijk en figuurlijk) grote wetenschapsmaatje. Wat was het heerlijk om even samen te kunnen overleggen over praktische zaken van het

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onderzoek, ervaringen uit te wisselen, tegenslagen te verwerken, samen te ploeteren aan weer een revisie enz. enz. enz. Zonder jou zou de wetenschap voor mij niet hetzelfde zijn geweest. Wat ooit begon als 'samen optrekken als mede promovendi' is inmiddels uitgegroeid tot een mooie vriendschap. De afstand Rotterdam-Rhenen blijkt helemaal niet zo groot. En ik denk met veel plezier terug aan onze gezamenlijke racefietstochten, of het bezoek aan het Kröller-Möller museum. Ik hoop dat er nog meer gaan volgen. De wetenschap gaat ongetwijfeld nog veel van je zien. En de kunstwereld ook. Ik kan je niet genoeg bedanken voor alles wat je voor me gedaan hebt. Dankjewel.

Lieve Noëlle, wat zou de FRANCIS zijn zonder jou. Jij was toch wel de draaiende motor achter al dit onderzoek. Onvermoeibaar, nou ja, meestal onvermoeibaar, draaide je poli's en belde je mensen eindeloos om ze over te halen weer naar de poli te komen als ze niet verschenen waren. Alle data heb je ingevoerd. En dat was geen gemakkelijke klus. Zeker niet omdat er onderweg nog wel eens wat veranderde, waardoor je stukken weer opnieuw kon doen. Ik ben blij met alles wat je gedaan hebt, jij bent het fundament van dit onderzoek. Al het andere had niet gekund als we niet zo'n stevig fundament hadden. Dankjewel!

Beste Gert-Jan, jouw taak binnen de FRANCIS begon als coördineren van het verrichtte laboratoriumonderzoek en het invriezen van spijtsamples. Maar al snel groeide dit uit naar veel meer. Je volgde een cursus om met de database te kunnen werken en dacht mee over verdere ontwikkelingen en de toekomst van de FRANCIS. Ik heb veel profijt gehad van jouw nauwgezetheid. Alle ontwikkelingen hou je netjes bij in mappen, keurig gearchiveerd. Dankzij jou konden we altijd de draad weer op het goede punt oppakken als we na een poosje weer verder wilde met een bepaald onderdeel. Ook hield jij een oogje in het zeil op de dagen dat ik er niet was. Dankjewel voor al je hulp en betrokkenheid, het was gezellig om de maandagen met jou op het lab door te brengen.

Beste René, vaak heb ik me afgevraagd wanneer je er genoeg van zou krijgen. Ik bleef je maar bestoken met nieuwe vragen en verzoeken tot aanpassing van de database. Gelukkig ben je nooit afgehaakt en hebben we het er aardig van afgebracht samen. En dat komt vooral door jouw vindingrijkheid en enthousiasme om steeds de database weer zo aan te passen dat we verder konden. Het was een leerzaam traject voor ons beiden en voor mij was het de gezelligheid met jou die alle frustratie over de 'niet meewerkende' database weer snel liet verdwijnen. Op maandagen kwam je regelmatig even een praatje maken. Wat ik me ook herinner is je lach, die ik heel regelmatig al van een eind hoorde. Je bracht altijd gezelligheid mee en ik vond het fijn met je samen te werken.

Ook wil ik de klinisch chemici, in het bijzonder Hans Janssen en Tjin Njo, bedanken voor hun hulp bij het mogelijk maken van deze studie.

Beste Marijke, als opvolger van Boudewijn ging jij de 'FRANCIS straatjes' draaien. En al snel had je de dingen goed georganiseerd, werden brieven naar huisartsen gestuurd en

mede hierdoor vonden patiënten de rust en regelmaat die maakte dat ze met de studie door wilde gaan. Bedankt voor de fijne samenwerking en veel succes met de opleiding.

Beste Evelien, Mathilde, Chantal, Sonja en Jessica. Jullie ook bedankt voor het zien van al die patiënten en het op orde houden van alle gegevens. Dank dat jullie tijd en zin hebben gevonden om dit project zo goed op de rit te houden.

Beste Erwin, de man in de coulissen van menig onderzoek in het Franciscus. Ik heb altijd plezier beleeft aan onze overleg momenten en heb veel van je geleerd. Wat ik vooral zo bijzonder aan jou vind, is dat jij goed in staat bent om de klinische praktijk en de statistiek met elkaar te verbinden. Ik denk dat de bochten waarin we ons hebben moeten wringen om de database en SPSS te laten doen wat we wilden bij jou voor enkele grijze haren hebben gezorgd. Toch zijn we er bijna altijd uitgekomen. Dankjewel voor alles, overleggen met jou was niet alleen leerzaam, maar ook altijd leuk en gezellig. Ik mis het nu al!

Lieve Margriet, Saskia, Wai Kwan, Jacques, Femke en Lindy-Anne, bedankt voor jullie steun en de inclusie van al die patiënten.

Beste dokter van der Loos, beste Theo en lieve Chiara, dank voor jullie hulp bij het zien van de patiënten op de vasculaire poli. Jullie hebben er voor gezorgd dat de patiëntenzorg altijd gewoon door heeft kunnen lopen in periodes dat ik de poli niet kon draaien door verplichtingen voor de opleiding reumatologie of zwangerschapsverlof.

Beste poli assistentes van de poli reumatologie en interne geneeskunde ook jullie bedankt voor het opnemen van alle administratie rond de FRANCIS.

Beste Ga-Lai, jij verdient ook een plekje in dit dankwoord. Al een tijd wist ik dat ik graag een originele kaft wilde voor mijn boekje. Het moest terugslaan op het onderwerp en bij voorkeur symbolisch. Ik vroeg Boudewijn of hij eens mee wilde denken, en tot mijn grote verbazing vond ik een paar dagen later een mail in mijn inbox met enkele schitterende eerste schetsen van jou. Bedankt voor je enthousiasme en het spontane aanbod om dit onderzoek in een passend jasje te steken.

Beste dokter Rietveld, beste Arie. De wekelijkse FEAR besprekingen en de druk op de befaamde lege dia, maakte mij snel duidelijk dat geen onderzoek doen geen optie was. Na een aantal kleine case reports en case series leek het mij zinvoller mijn tijd in een meerjarenplan te steken en er zo mogelijks nog een boekje en een titel aan over te houden ook. Ik begon te denken, gooide een balletje op bij Manuel en Jendé en een promotietraject werd geboren. Of het zover was gekomen zonder jouw duwtje in de rug weet ik eerlijk niet.

Lieve Jan, Maarten en Ellen, het was bij de start in Ede best even zoeken naar een evenwicht. Enerzijds wennen aan een nieuwe baan, een nieuwe omgeving en een nieuwe mentaliteit. Anderzijds mijn promotieonderzoek afronden en voldoende contact houden met het hele team in Rotterdam. Maar het is gelukt, mede dankzij jullie flexibiliteit. Dank jullie wel voor al de ruimte die ik heb gekregen om mijn werk af te

maken, vooral tijdens de laatste fase van dit traject. Nu het boekje klaar is, ontstaat er weer wat rust.

Lieve Hester, Hester en Francisca, al 23 jaar een hechte vriendenclub. Wat is het heerlijk om zulke fijne vriendinnen te hebben. En wat zijn we allemaal druk. Met wat moeite vinden we elkaar toch regelmatig en doen we op die momenten ons best om even te onthaasten. Wat we ook doen, het is altijd gezellig. Ik hoop op nog vele jaren vriendschap en nog heel veel mooie AMAM uitjes!

Lieve Pa en Ma, Arnold, Miranda en Maurice. Jullie hebben vaak geprobeerd te begrijpen waar ik nou mee bezig was. Nou, dit is het dan. Al die jaren ging het om dit boekje. Jullie kennen de inhoud dan niet zo, jullie zijn wel ervaringsdeskundige voor wat betreft datgene dat het doorlopen van een promotietraject met een mens kan doen. Regelmatig maakte ik jullie deelgenoot van frustratie, teleurstelling, blijdschap, stress, het enthousiasme, gewonnen prijzen, inspirerende congressen en contacten met nieuwe mensen. Het was een heel traject. Goed dat het nu klaar is, dan is er weer ruimte voor andere dingen.

Mijn allerliefste Jef, wat ben je toch een heerlijk ventje. Niks kan zo snel al mijn zorgen naar de achtergrond verplaatsen als een knuffel van jou. Of gewoon kijken naar hoe je ligt te slapen. Mijn promotietraject is aan je voorbij gegaan, daar ben je nog veel te klein voor. Maar wat leuk dat je oud genoeg bent om bij de verdediging te zijn. Ik prijs me elke dag gelukkig met je.

Lieve Joost, het boekje is af. Laten we het vieren!

PhD Portfolio

PhD Portfolio

Name PhD student: D.F. van Breukelen	PhD period: 2010-2016
Erasmus MC Department: Rheumatology	Promotor: J.M.W. Hazes
	Supervisors: M. Castro Cabezas, D. van Zeben

	Year	ECTS
General courses		
- BROK cours on medical ethics in research ('Basiscursus Regelgeving Klinisch Onderzoek')	2012	1
- Didactic skills (including 20h teaching), Universiteit Antwerpen	2003-2006	15
Specific courses (e.g. Research school, Medical Training)		
- Erasmus Summer programme statistics and methodology	2011	4
Scientific Presentations		
Oral presentations		
- Research meeting Erasmus MC/journal club	2010-2012	5
- Presentation regional scientific rheumatology meeting	2010	
- Presentation rheumatologists FRANCISCUS	2011	
- Presentation rheumatologists FRANCISCUS	2012	
- Oral presentation annual scientific meeting Internal Medicine (Internistendagen)	2013	
- Oral presentation scientific meeting FRANCISCUS	2013	
- Oral presentation annual scientific meeting Internal Medicine (Internistendagen)	2014	
- Oral presentation scientific meeting FRANCISCUS	2014	
Posters		
- Poster presentation scientific meeting FRANCISCUS	2012	
- Poster presentation ISA Sydney	2012	
- Poster presentation scientific meeting FRANCISCUS (2x)	2013	
- Poster presentation EULAR (2x)	2013	
- Poster presentation EULAR	2014	
- Poster presentation EAS	2014	
- Poster presentation ACR	2015	
(Inter)national conferences		
- Najaarsdagen NVR, Annual meeting	2010	1
- Annual meeting ACR, Atlanta	2010	1
- Najaarsdagen NVR, Annual meeting, Papendal	2012	1
- Internistendagen, Maastricht	2013	1
- EULAR Madrid	2013	1
- Najaarsdagen NVR, Annual meeting, Papendal	2013	1
- Oslo Centre of Excellence Meeting	2013	1

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	Year	ECTS
- EULAR Paris	2014	1
- Najaarsdagen NVR, Annual meeting, Papendal	2014	1
- Annual meeting EULAR, Rome	2015	1
- Annual meeting ACR, San Francisco	2015	1
Teaching		
- Radiology unit Erasmus MC	2010	0.1
- Rheumatology outpatient clinic employees Erasmus MC	2010	0.3
- Bed-side teaching General practitioners Erasmus MC	2010	0.2
- Lboratory employees Franciscus Gasthuis	2010	0.1
- Supervision of medical students, Franciscus Gasthuis	2006-2013	0.5
- Medical students Gelderse Vallei	2013	0.1
- Residents internal medicine Gelderse Vallei	2015	0.2
- Laboratory employees Franciscus Gasthuis	2015	0.2
Lecturing		
- General practitioners Gelderse Vallei region	2014	0.2
- Jubilee fellowship rheumatology in Rotterdam	2014	0.2
- General practitioners Gelderse Vallei region	2016	0.5
Other		
- Invited Reviewer for Arthritis Research and Therapy	2015	0.2
Total		40.1