Marked underdiagnosis and undertreatment of hypertension and hypercholesterolemia in rheumatoid arthritis

D. F. van Breukelen-van der Stoep, D. van Zeben, B. Klop, G.J.M. van de Geijn, H.J.W. Janssen, N. van der Meulen, M.A. De Vries, M. Hazes, E. Birnie, M. Castro Cabezas

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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).

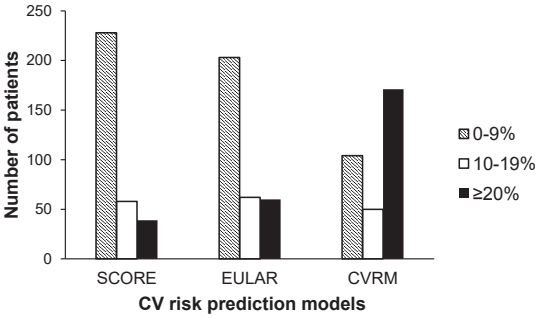

Figure 1. Ten-year cardiovascular risk stratification according to different CVD risk assessment tools. Abbreviations: SCORE = Systemic Coronary Risk Evaluation, CVRM = the Dutch guideline for Cardiovascular Risk Management, EULAR = European League Against Rheumatism.

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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