Section 1
The link between inflammation and cardiovascular risk in rheumatoid arthritis
Chapter 1.1
Cardiovascular risk management in rheumatoid arthritis patients still suboptimal: the I-CaRe project

I.A.M. van den Oever
M. Heslinga
E.N. Griep
J.R.M. Griep-Wentink
R. Schotsman
W. Cambach
B.A.C. Dijkmans
Y.M. Smulders
W.F. Lems
M. Boers
A.E. Voskuyl
M.J.L. Peters
D. van Schaardenburg
M.T. Nurmohamed

Submitted
Chapter 1.1

Abstract

Objective The Dutch cardiovascular risk management (CV-RM) guideline considers rheumatoid arthritis (RA) an independent risk factor for cardiovascular disease (CVD), for which CV-RM is necessary. We performed CV risk screening in RA patients from two hospitals to examine 1) the 10-year CV risk score and 2) the (under) treatment of CV risk factors.

Methods Demographics, CV risk factors and prevalence of CVD were assessed by questionnaire. To calculate the 10-year CV risk score according to the Dutch CV-RM guideline, systolic blood pressure was measured and cholesterol levels were determined from fasting blood samples. Patients were categorized into four groups: 1) indication for treatment but not treated; 2) inadequately treated, i.e. not meeting goals (SBP ≤140 mmHg and/or LDL ≤2.5 mmol/l); 3) adequately treated; or 4) no treatment necessary.

Results A total of 720 consecutive RA patients were included, 375 from Reade and 345 from the Antonius Hospital. Mean age was 59±12 and 73% was female. Seventeen per cent of the patients had a low 10-year CV risk (<10%), 21% had an intermediate risk (10-19%), 53% a high risk (≥20%) and 9% had CVD. In total, 69% had an indication for preventive treatment (cholesterol lowering or antihypertensive drugs). Of those, 42% received inadequate treatment and 40% received no treatment at all.

Conclusion Optimal CV-RM remains a major challenge and better awareness and management are urgently needed to reduce the high risk of CVD in the RA population.
Introduction

Patients with rheumatoid arthritis (RA) have an increased risk of premature death compared with the general population, mainly because of the risk of cardiovascular disease (CVD) (1, 2). The cardiovascular (CV) risk of patients with RA is comparable to the risk of patients with type 2 diabetes mellitus (T2DM) (3, 4). In addition to CV mortality, non-fatal CVD, such as myocardial infarction (MI), cerebrovascular accidents (CVA) and heart failure (HF) are more common in RA (5).

Several determinants contribute to this increased risk, including traditional CV risk factors such as age, gender, dyslipidemia, hypertension, smoking, obesity and diabetes mellitus, however, these factors only partially explain the excess CV risk (6, 7). In addition to traditional risk factors, systemic inflammation is an important independent contributor to CV risk in RA (8, 9).

Another explanation for the increased CV risk is that in RA, (traditional) CV risk factors are under-treated, as co-morbidity in patients with a chronic disease is often undertreated (10). However, details of under-treatment in RA are sparse.

In light of the strong evidence that the CV risk in RA is in the same order of magnitude as that in T2DM, the Dutch cardiovascular risk management (CV-RM) guideline considers RA, like T2DM, an independent risk factor for CVD, for which CV-RM is necessary (11). Evidence on (pharmacological) management of traditional CV risk factors in patients with rheumatic diseases is limited, but there are no indications that the effects of statins or antihypertensives in RA would be different than in the general population (12-16); thus CV-RM should be offered to all patients meeting the criteria set for risk reduction in the general population (17). However, implementation of CV risk screening is still a challenge (18). This strategy would require that all patients with RA, like patients with T2DM and/or CVD are screened regularly (yearly), and CV risk managed accordingly. Since 2011 ‘I-CaRe: Implementation of Cardiovascular Risk Management in Rheumatoid Arthritis’ offers CV risk screening to RA patients visiting Reade, a rheumatology and rehabilitation center in Amsterdam or Antonius Hospital in Sneek, a small city in the northern rural area of the Netherlands. The goal of this project was 1) to assess the 10-year CV risk score and 2) to identify (under) treatment of CV risk factors in RA patients.
Methods

Study population and design
For this prospective cross-sectional cohort study, consecutive RA patients visiting the outpatient rheumatology clinic of Reade in Amsterdam or Antonius Hospital in Sneek, were included. All patients were 18 year or older and diagnosed by a rheumatologist, according to the American College of Rheumatology criteria of 1987 for RA (19). There were no other exclusion criteria. All patients were asked to sign an informed consent before study participation and the study was approved by the local ethical committees of Slotervaart Hospital/Reade and Antonius Hospital.

CV risk screening comprised a questionnaire, physical examination, laboratory investigations and assessment of the 10-year CV risk according to the Dutch CV-RM guideline.

Patient characteristics
Information on age, gender, smoking, disease history with a special focus on CVD, CV risk factors and CV preventive medication use, including antihypertensive medication, statins, anti-diabetic medication and anticoagulants. RA related factors, disease duration, rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPAs) positivity and presence of erosive disease were collected from the medical files. Assessment of current anti-inflammatory medication included use of non-steroidal anti-inflammatory drugs (NSAIDs), disease modifying anti-rheumatic drugs (DMARDs) and corticosteroids.

Cardiovascular risk and disease definitions
CVD history was defined as a history of coronary heart disease (including angina pectoris, myocardial infarction, percutaneous coronary intervention (PCI) and coronary artery bypass surgery (CABG)), heart failure, cerebral vascular disease (including ischemic stroke (CVA), TIA and carotid endarterectomy), and peripheral arterial disease. This was asked by questionnaire but also checked afterwards in the medical files, to verify that the diagnosis was confirmed by a specialist (cardiologist, neurologist or vascular specialist). Cardiovascular risk factors included self-reported DM, self-reported hypertension and/or the use of antihypertensives, self-reported hypercholesterolemia and/or the use of statin therapy and smoking status assessed by the questionnaire or the presence of high blood pressure (systolic blood pressure (SBP) > 140 mmHg) or high cholesterol (LDL >2.5 or
TC/HDL ratio > 8) measured during the physical examination. Overweight was defined as a body mass index (BMI) ≥25 kg/m² and obesity as a BMI ≥30 kg/m².

**Physical examination**
Specially trained and experienced research nurses performed a physical examination, including blood pressure, waist and hip circumference, length and weight. Blood pressure was measured twice (left and right) in sitting position after 5 minutes of rest. Waist circumference was measured at the level of the navel, hip circumference at the level of the trochanter major of the hip bone (widest circumference). The waist-hip-ratio (WHR) ratio comprised the ratio of these two measurements. BMI was calculated from height and weight (clothed without shoes). RA was assessed by the disease activity score of 28 joints (DAS28) (20), and physical functioning by the Health Assessment Questionnaire (HAQ) (21).

**Laboratory tests**
Glucose and lipid profile, including total cholesterol (TC), triglycerides (TG), high density lipoprotein (HDL) and low density lipoprotein (LDL) were assessed in fasting blood samples using the standard techniques, and the atherogenic index (TC/HDL ratio) was calculated. All the above tests were performed the same day that blood was drawn.

**10-year cardiovascular risk calculation**
10-year CV risk was calculated with the Dutch SCORE table, that uses gender, age, smoking status, SBP and the TC/HDL-C ratio (11). To account for RA as risk factor the Dutch CV-RM guideline adds 15 years to the actual age in order to calculate 10-year CV risk. This is the same strategy as used for the risk factor DM, since a large population-based cohort study has shown that the vascular age of DM patients is 15 years higher than the vascular age of patients without DM (22) and other studies have shown that CV risk of RA patients resembles that of DM patients (3, 5, 23, 24). According to the Dutch CV-RM guideline we classified a risk < 10% as low, between 10% and 20% as intermediate and a risk ≥ 20% as high. Patients with a history of CVD were assessed separately, as secondary prevention group. In high risk patients, and in intermediate risk patients with a BMI ≥35 kg/m² antihypertensive therapy is recommended when SBP > 140 mm/Hg and/or statin therapy is recommended when LDL >2.5 mmol/l. In patients with an intermediate or low 10-year CV risk the criteria are SPB > 180 or TC/HDL-ratio > 8.
Chapter 1.1

After we calculated the 10-year CV risk, we categorized patients into four groups: 1) untreated patients with an indication for treatment; 2) inadequately treated patients (i.e. not meeting treatment goals, i.e. SBP ≤140 mmHg or LDL ≤2.5 mmol/l); 3) adequately treated patients; and 4) untreated patients without an indication for treatment (i.e., no increased CV risk).

Statistical analysis

For the statistical analysis SPSS version 22.0 (SPSS IBM software, USA) was used. Patient characteristics were expressed as number and percentage, means ± standard deviation (SD), when normally distributed or median (interquartile range), when not normally distributed. Independent t-tests were used to compare variables with a normal distribution. The Pearson Chi-Square test was performed on dichotomous variables. The threshold for significance was set at p<0.05 (two-sided).
Results

Patient characteristics
From 2011 to 2015, a total of 720 consecutive RA patients underwent cardiovascular risk screening, 375 from Reade, Amsterdam and 345 from Antonius Hospital, Sneek. Patients from Sneek were more often male, older had more prevalent CVD and more frequently were on statins and anticoagulant drugs (Table 1). In contrast, patients from Amsterdam had longer RA disease duration, were more often RF and ACPA positive, and had more active and erosive disease. In Amsterdam patients biological treatment was more frequent, and glucocorticoid treatment less frequent.

Table 1. Characteristics of rheumatoid arthritis patients in Reade, Amsterdam and St. Antonius hospital, Sneek, with and without CVD

<table>
<thead>
<tr>
<th></th>
<th>All patients (n=720)</th>
<th>Amsterdam (n=375)</th>
<th>Sneek (n=345)</th>
<th>CVD (n=61)</th>
<th>no CVD (n=659)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Females</td>
<td>73</td>
<td>77</td>
<td>69*</td>
<td>59</td>
<td>74#</td>
</tr>
<tr>
<td>Age, years</td>
<td>59±12</td>
<td>58±11</td>
<td>61±12*</td>
<td>68±8.5</td>
<td>59±11.7#</td>
</tr>
<tr>
<td>Cardiovascular disease history</td>
<td>8</td>
<td>7</td>
<td>10*</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td><strong>Cardiovascular risk factors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Currently smoking</td>
<td>22</td>
<td>22</td>
<td>21</td>
<td>20</td>
<td>22</td>
</tr>
<tr>
<td>Hypercholesterolemia (self-reported)</td>
<td>33</td>
<td>38</td>
<td>28</td>
<td>54</td>
<td>32#</td>
</tr>
<tr>
<td>Hypertension (self-reported)</td>
<td>43</td>
<td>47</td>
<td>38</td>
<td>67</td>
<td>42#</td>
</tr>
<tr>
<td>Diabetes mellitus (self-reported)</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>18</td>
<td>4#</td>
</tr>
<tr>
<td><strong>Cardiovascular preventive medication use</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antihypertensives use</td>
<td>36</td>
<td>33</td>
<td>39</td>
<td>77</td>
<td>32#</td>
</tr>
<tr>
<td>Statins use</td>
<td>21</td>
<td>15</td>
<td>27*</td>
<td>66</td>
<td>17#</td>
</tr>
<tr>
<td>Anti-diabetics use</td>
<td>5</td>
<td>4</td>
<td>5</td>
<td>13</td>
<td>4#</td>
</tr>
<tr>
<td>Anticoagulants use</td>
<td>11</td>
<td>8</td>
<td>14*</td>
<td>77</td>
<td>5#</td>
</tr>
<tr>
<td><strong>Disease characteristics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease duration, years</td>
<td>7 (2-14)</td>
<td>10 (5-18)</td>
<td>4 (2-9)*</td>
<td>9 (4-16)</td>
<td>7 (2-14)</td>
</tr>
<tr>
<td>RF positive</td>
<td>61</td>
<td>67</td>
<td>55*</td>
<td>60</td>
<td>63</td>
</tr>
<tr>
<td>ACPA positive</td>
<td>61</td>
<td>64</td>
<td>58*</td>
<td>64</td>
<td>66</td>
</tr>
<tr>
<td>Erosive disease</td>
<td>46</td>
<td>53</td>
<td>39*</td>
<td>58</td>
<td>46</td>
</tr>
</tbody>
</table>
Chapter 1.1

<table>
<thead>
<tr>
<th>Anti-inflammatory medication use</th>
<th>All patients</th>
<th>Amsterdam</th>
<th>Sneek</th>
<th>CVD</th>
<th>no CVD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NSAID use</strong></td>
<td>36</td>
<td>36</td>
<td>37</td>
<td>21</td>
<td>38</td>
</tr>
<tr>
<td><strong>Methotrexate use</strong></td>
<td>68</td>
<td>70</td>
<td>65</td>
<td>73</td>
<td>68</td>
</tr>
<tr>
<td><strong>Other DMARD use</strong></td>
<td>24</td>
<td>20</td>
<td>28*</td>
<td>18</td>
<td>25</td>
</tr>
<tr>
<td><strong>Biological use</strong></td>
<td>36</td>
<td>59</td>
<td>12*</td>
<td>45</td>
<td>36</td>
</tr>
<tr>
<td><strong>Corticosteroid use</strong></td>
<td>24</td>
<td>18</td>
<td>30*</td>
<td>33</td>
<td>24</td>
</tr>
</tbody>
</table>

| Physical examination            |             |           |       |     |       |
| **Systolic blood pressure, mm/Hg** | 138±19     | 135±18    | 140±19* | 141±19 | 137±19 |
| **Waist Hip Ratio**             | 0.91±0.09   | 0.91±0.09 | 0.91±0.09 | 0.93±0.07 | 0.91±0.09# |
| **Body Mass Index, kg/m2**      | 26.8±4.9    | 26.7±5.1  | 26.9±4.6 | 27.1±4.6 | 26.8±4.9 |
| **Disease activity score of 28 joints** | 2.44±1.15  | 2.65±1.22 | 2.20±1.02* | 2.72±1.18 | 2.41±1.15 |

| Laboratory tests                |             |           |       |     |       |
| **Lipid profile**               |             |           |       |     |       |
| **Total cholesterol, mmol/l**   | 5.3±1.0     | 5.5±1.0   | 5.1±1.1* | 4.7±1.0 | 5.4±1.0# |
| **Triglycerides, mmol/L**       | 1.4±0.7     | 1.4±0.8   | 1.3±0.7* | 1.5±1.0 | 1.3±0.7 |
| **LDL-cholesterol, mmol/l**     | 3.1±0.9     | 3.2±0.9   | 3.0±0.9* | 2.5±0.8 | 3.2±0.9# |
| **HDL-cholesterol, mmol/l**     | 1.6±0.5     | 1.6±0.5   | 1.6±0.4  | 1.5±0.4 | 1.6±0.5# |
| **Total cholesterol/HDL-ratio** | 3.6±1.2     | 3.7±1.3   | 3.4±1.1* | 3.4±1.1 | 3.6±1.2 |
| **Fasting glucose, mmol/l**     | 5.5±1.5     | 5.6±1.7   | 5.5±1.2  | 6.0±1.9 | 5.5±1.4# |

Results are presented as mean and standard deviation (SD), median and interquartile range (IQR) or percentage (%)
*p<0.05 between Amsterdam and Sneek
#p<0.05 between patients with cardiovascular disease (CVD) and patients without cardiovascular disease (no CVD)
ACPA=Anti-citrullinated protein antibodies, DMARD= Disease Modifying Anti-Rheumatic Drugs, HDL=High-density lipoprotein, LDL=Low-density lipoprotein, NSAID=Non-steroidal Anti-Inflammatory drugs, RF=Rheumatoid factor.

**Prevalence of cardiovascular disease**

A history of CVD was present in 61 (8%) patients, with a slightly higher prevalence in Sneek compared to Amsterdam (10% vs 7%). The following conditions were present: coronary heart disease (n = 29, heart failure (n = 4) cerebrovascular disease (n = 29) and peripheral arterial disease (n = 6). Of the men, 13% had a history of CVD versus 7% of women. Patients with a history of CVD were significantly older, more often diagnosed with diabetes, hypertension and hypercholesterolemia and more often used anti-diabetic drugs,
antihypertensives, statins and anticoagulants, but less often NSAIDs compared to patients without CVD. They also had a higher WHR, lower TC, lower HDL, lower LDL and higher fasting glucose levels versus patients without CVD (table 1).

10-year CV risk assessment
The presence of high blood pressure and high cholesterol as measured during the CV risk screening as well as the mean 10-year cardiovascular risk score are shown in table 2.

Table 2 Cardiovascular risk score of rheumatoid arthritis patients in Reade, Amsterdam and St. Antonius hospital, Sneek

<table>
<thead>
<tr>
<th></th>
<th>All patients (n=720)</th>
<th>Amsterdam (n=375)</th>
<th>Sneek (n=345)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10-year cardiovascular risk score</td>
<td>22±13</td>
<td>21±12</td>
<td>23±13</td>
</tr>
<tr>
<td>Systolic bloodpressure &gt;140 mm/Hg</td>
<td>40</td>
<td>36</td>
<td>45*</td>
</tr>
<tr>
<td>Systolic bloodpressure &gt;180 mm/Hg</td>
<td>3</td>
<td>1</td>
<td>4*</td>
</tr>
<tr>
<td>LDL &gt; 2.5 mmol/l</td>
<td>73</td>
<td>79</td>
<td>68*</td>
</tr>
<tr>
<td>Total cholesterol/HDL-ratio ≥ 8</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Total cholesterol ≥ 6.5 mmol/l</td>
<td>12</td>
<td>15</td>
<td>9*</td>
</tr>
</tbody>
</table>

Results are presented as mean and standard deviation (SD) or percentage (%). *p<0.05 between Amsterdam and Sneek. LDL= Low-density lipoprotein, HDL=High-density lipoprotein.

A total of 125 (17%) patients had a low 10-year CV risk, 153 (21%) patients had an intermediate CV risk and 381 (53%) patients had a high risk of CVD (figure 1).
Cardiovascular risk preventive treatment

In total, 500 patients (69%) had an indication to receive antihypertensives, statins or both (figure 2). Of those, 199 (40%) did not receive treatment at all and 212 (42%) were inadequately treated, the other 18% was adequately treated. 419 patients had an indication for statin treatment but 270 patients (64%) did not use statins despite having an indication, and 149 received treatment; 50% of them reached a LDL<2.5. 378 patients had an indication for antihypertensive treatment; 123 patients (33%) did not receive this, 255 used antihypertensives; 50% of them reached a SBP<140mm/Hg. In figure 3 the numbers and percentages are specified per CV risk group.
Figure 2 Percentages of rheumatoid arthritis patients receiving (adequate) cardiovascular risk preventive treatment

- Treatment indication, not treated
- Treatment goal not reached
- Adequately treated
- No treatment (indication)
Figure 3 Cardiovascular preventive treatment per risk group

- **Low 10-year CV risk**
  - CVD
  - High 10-year CV risk: 6%
  - Medium 10-year CV risk: 37%
  - Low 10-year CV risk: 94%

- **Medium 10-year CV risk**
  - CVD
  - High 10-year CV risk: 3%
  - Medium 10-year CV risk: 22%
  - Low 10-year CV risk: 67%

- **High 10-year CV risk**
  - CVD
  - High 10-year CV risk: 3%
  - Treatment indication, not treated: 4%
  - Treatment goal not reached: 44%
  - Adequately treated: 49%
Discussion
The results of this study confirm both a high prevalence of CVD risk and a very low prevalence of (adequate) preventive treatment in RA patients, not only in the patients with a high CV risk (primary prevention), but also in the patients who already experienced CVD (secondary prevention). Our finding that in total 80% of the RA patients are inadequately treated for CV risk is equal to that of another recently published Dutch study (25). However, that cohort was established in 2006 and thus at a time RA was not considered an independent CV risk factor yet. It is therefore worrisome that CV-RM implementation has not improved since then. There are several factors that might explain this lack of improvement.

First, the current CV-RM guideline was published very shortly before the present study actually started, this could be an explanation why CV-RM has not been implemented in all RA patients yet. Second, a potential weakness of the current Dutch CV-RM guideline is the addition of 15 years to account for the additive CV risk that comes with RA. This addition is not based on level A evidence, and this might hamper implementation, especially in young persons, knowing that they have to start a lifetime treatment. Moreover, RA patients often use many drugs to control the RA disease activity and are perhaps reluctant to take additional drugs, particularly those that do not treat actual symptoms. Also, potential side effects, as muscle and joint pain by statin use, could limit the uptake in RA patients since they often already have muscle or joint pain due to active disease.

Strengths of this study include the size of the study population and the fact that it is a two-center study, including patients from rural and urban areas, making it a diverse RA population.

A limitation of this study is that we could not take into account some secondary CV risk factors, such as family history of CVD, physical activity and kidney function. These factors are, like BMI, considered as CV risk increasing factors which can function as additional reason to give CV risk prevention treatment. Therefore, the lack of this information could have underestimated our results. Unfortunately, we were also not able to assess the reasons why RA patients were not treated (adequately). This is a future implementation project that will be initiated shortly. Another study that we are currently undertaking is to investigate if yearly CV risk screening initiated by the rheumatologist improves CV-RM implementation. Two strategies will be tested; one strategy is to send high CV risk patients to their general practitioner to implement and control CV-RM; the second strategy is to send RA patients with a high CV risk to an internal specialist who implements CV-RM in the context of a specially set up CV-RM clinic.
Thus far no intervention trials with statins or antihypertensives and CV disease prevention in RA have been published. However, data from epidemiological studies and post-hoc subgroup analyses of large, secondary cardiovascular prevention trials show that the effects of statins on cholesterol levels in RA patients appear to be at least equivalent to the effects of statins in the general population (15, 26, 27). Other studies have shown beneficial effects of angiotensin-converting enzyme (ACE) inhibitors on CV risk in RA (12). Moreover, the effects of cardio-protective agents might even be more pronounced in RA, as the pleiotropic effects of statins, ACE inhibitors and angiotensin blockers include anti-inflammatory properties (14, 28-32). In the future, randomized controlled intervention trials are necessary to assess the actual effect of statins, ACE-inhibitors and other lifestyle intervention strategies on CV risk in RA.

In conclusion, our results indicate that effective strategies for adequate CV-RM are urgently needed to reduce CV risk in the RA population.
Acknowledgements
We want to express our gratitude to B. Maat and W. Hoogland for their input to the protocol as patients and members of the Dutch society for patients with rheumatic diseases.
Also many thanks to the rheumatology nurses of Reade, Amsterdam and Antonius Hospital, Sneek for gathering the data and S. Temminghoff and D. Jonker for administration and data-entry.

Funding
This study was partly funded by the Dutch Society for Rheumatology, Nuts Ohra fonds, Pfizer and Abbvie.
References


Cardiovascular risk management in RA: the I-CaRe project


