EXTENDED REPORT

Results from systematic screening for cardiovascular risk in outpatients with rheumatoid arthritis in accordance with the EULAR recommendations

Jette Primdahl,1 Joan Clausen,2 Kim Hørslev-Petersen3

ABSTRACT

Aim To investigate risk factors for the development of cardiovascular disease (CVD) and estimate the risk of cardiovascular death in rheumatoid arthritis (RA) patients in accordance with EULAR recommendations.

Materials and methods Outpatients with RA ≤ 85 years of age from a Danish hospital were invited to participate. Participants’ risk of cardiovascular death was calculated according to the SCORE system, based on total cholesterol/high-density lipoprotein (HDL) ratio, smoking habits, blood pressure, age and gender. The SCORE was adjusted based on disease duration, IgM-RF/anti-c-CCP positivity and the presence of extra-articular manifestations. Factors such as history of CVD, hypertension or diabetes mellitus (DM), fasting glucose, exercise habits, body mass index (BMI) and waist circumference were explored.

Results 836 patients participated; 71.5% women; mean (SD) age 64.3 years (12.0); 152 (19.1%) were already diagnosed with CVD and 74 (9.0%) with DM. Among the 644 patients without CVD or DM, 14.3% had a fasting glucose ≥ 6.0 mmol/L. The SCORE was > 5 in 122 (20.2%). They were referred to follow-up by their GP and community advice services.

Conclusions Systematic screening revealed several risk factors that needed medical follow-up or support to initiate lifestyle changes.

INTRODUCTION

It is well documented that people with rheumatoid arthritis (RA) have excess mortality compared to the general population, partly due to an increased risk of cardiovascular events and cardiovascular death.1-3 Although people with RA have an increased number of the traditional risk factors for the development of cardiovascular disease (CVD), this does not seem to explain all excess mortality in RA compared to the general population.4 It seems likely that the inflammatory process and disease severity also increases the risk of CVD.4-8 The excess risk posed by having RA may be compared to the risk from having diabetes mellitus (DM) type II,9-11 and is influenced by other disease-related factors and the pharmacological treatment, that is, with glucocorticoids, non-steroidal anti-inflammatory drugs, methotrexate, leflunomide and cyclosporine.12 13 Male gender is associated with a greater risk of CVD.14

Longer disease duration, whether the patient is IgM-rheumatoid factor (RF) positive and/or anti-cyclic citrullinated peptide (anti-CCP) positive and the presence of certain extra-articular manifestations seem to be linked with the increased CVD risk due to RA.1 15 16 In 2010, 10 European League Against Rheumatism (EULAR) recommendations for cardiovascular risk management were published.1 Cardiovascular risk assessment in all patients with RA was recommended. Any identified risks should be managed according to local guidelines, and the patient’s risk should be scored according to the SCORE system.17 The risk SCORE should be adapted by a multiplication factor of 1.5 if the patient met two of the following three criteria: disease duration of more than 10 years, RF and/or anti-CCP positivity and the presence of certain extra-articular manifestations18 (pericarditis, pleuritis, Felty’s syndrome, polynuropathy, mononeuritis, scleritis, episcleritis, glomerulonephritis, severe skin vasculitis or vasculitis in other organs). Adequate control of disease activity is also necessary to lower the CVD risk.1

To date, only one study has been identified that reported results from the implementation of the EULAR recommendations for cardiovascular risk management in patients with RA.19 This Spanish study reported risk scores for 200 patients, but included patients with known CVD and DM, even though the SCORE system is not recommended in these patients. Furthermore, the study included rheumatic nodules in the risk assessment, whereas, in the EULAR recommendations, rheumatic nodules are not on the list of extra-articular manifestations that affect the modified SCORE.1 18 There is a need for a larger study to assess the impact of risk factors for CVD when implementing the EULAR recommendations.

OBJECTIVE

The objective was to investigate the spread of traditional risk factors for the development of CVD and the risk SCORE for cardiovascular death when implementing the EULAR recommendations for cardiovascular risk management in a Danish hospital population of outpatients with RA.
METHODS
Implementation of the EULAR recommendations
A multidisciplinary group was established at King Christian X’s Hospital for Rheumatic Diseases in Graasten, Denmark, to implement the EULAR recommendations for RA, to offer smoking cessation, low-lipid diet and RA were offered. If the patient fulfilled the above-mentioned criteria, the risk SCORE was calculated based on the number of observations available for each variable. Results are reported with mean and SD or median and IQR depending on the distribution of the data. Percentages are calculated based on the number of observations available for each variable.

Participants
All outpatients with RA 85 years of age or less connected to King Christian X’s Hospital for Rheumatic Diseases in Graasten, Denmark, were invited by a standard letter to a screening consultation.

Study design
Before the screening consultation, the patients had their fasting glucose, triglycerides, total cholesterol, high density lipoprotein (HDL) cholesterol and low density lipoprotein (LDL) cholesterol levels checked. The patient’s habits regarding smoking (smoker/non-smoker), exercise (less than five times a week/five times a week or more), alcohol (below or above the national recommendations of a maximum seven units per week for women and 14 for men) were explored. The patient’s height (cm) and weight (kg) were measured with the patient in light clothes and without shoes, and the patient’s body mass index (BMI) was calculated as weight (kg) by squared height (m²). Waist circumference (cm) was measured 2 cm above the patients’ umbilicus (midway between the lower rib margin and the iliac crest). Blood pressure was measured while the patient was sitting in a chair and after at least 5 min rest. If the patient’s blood pressure exceeded 5 mm Hg above the nationally recommended limits, a total of four measures (two on each arm) were performed and the mean of the last two measures was used. Each patient’s risk SCORE was calculated based on age, gender, smoking habits, systolic blood pressure and total cholesterol/HDL ratio. Denmark was considered to be a high-risk area for CVD in Europe when implementing the screening consultations. In accordance with the EULAR recommendations and national guidelines for the management of RA, the risk SCORE was multiplied by 1.5 if the patient fulfilled the above-mentioned criteria. To determine whether the patient had any of the specific extra-articular manifestations, the patient was asked whether a rheumatologist at any time had said that the patient had arthritis apart from in the joints, such as in the eyes, nerves, the vascular system or in other organs. The findings from the screening were discussed with the patient and advice and training in relation to identified risks were offered. Patients were referred to follow-up by the general practitioner (GP) in cases in which the modified risk SCORE was 5% or greater. Patients with blood pressure above the recommended level, total cholesterol above 8 mmol/L or fasting glucose of 6 mmol/L or greater were also referred to their GP. Patients were informed about opportunities to receive additional lifestyle change support in community health centres. Written pamphlets concerning smoking cessation, low-lipid diet and RA were offered.

Statistical analysis
STATA V.10.1 was used to perform descriptive statistical analyses. Results are reported with mean and SD or median and IQR depending on the distribution of the data. Percentages are calculated based on the number of observations available for each variable.

RESULTS
From September 2011 to November 2012, 836 patients accepted and completed a screening consultation (74.3% of the hospital RA population); 398 (71.3%) were women. Reasons to decline were due to severe disability or co-morbidities, or that it was difficult for them to attend due to transportation or work-related issues. Some patients felt that their GP already took care of the content in the screening consultation or that they did not want to discuss lifestyle issues. Approximately 10% of the patients declined to participate, but the exact number was not recorded.

Patients’ disease activity measured by the disease activity score in 28 joints (DAS28)–C reactive protein (CRP) score and physical disability measured by the health assessment questionnaire (HAQ) were not recorded in the screening consultations; however, we drew data from an outpatient visit if it was performed within 2 months before or after the screening consultation in order to characterise the population. For some of the patients the most recent follow-up fell outside the 2-month range. DAS28–CRP was thus available in only 526 patients and the HAQ in 626 patients. The demographic and disease-related data relating to the screened population are set out in table 1.

Among the screened patients, 349 (42.0%) were already diagnosed with hypertension, 152 (19.1%) with ischaemic CVD and 74 (9.0%) with DM.

The spread of the traditional risk factors for ischaemic CVD is reported in table 2 for all 836 patients.

Out of the 748 patients without previously diagnosed DM, 95 (14.3%) had an impaired fasting glucose (≥6.0 mmol/L), which means that DM cannot be excluded. A fasting glucose of 7.0 or greater indicates that the patient probably has undiagnosed DM. A total of 15 patients (2.0%) had a fasting glucose of 7.0 or greater.

Out of the 836 screened patients, 644 patients (77%) were not previously diagnosed with DM or CVD. The number of patients exceeding the recommended levels for each risk factor is shown in table 3.

Thirty-four patients reported that they had both CVD and DM. The recommended level for LDL cholesterol is 1.8 mmol/ L or less for this group and 25 (73.9%) of these patients did not meet that recommendation. Among the 349 patients with known hypertension who already received antihypertensive...
The SCORE system is not recommended for patients with CVD and/or DM as the SCORE chart will underestimate their risk. Due to a lack of blood test results in some of the 644 patients without known DM and CVD, we only managed to obtain a risk SCORE on 605 patients. In 170 (28.1%) of these patients the multiplication factor 1.5 was applied.

Based on the European recommendations, a SCORE less than 5% is considered to be low to moderate risk, 5–10% is high risk and 10% or greater is very high risk for cardiovascular death within 10 years. The risk SCORE are reported in table 4. When Denmark was considered to be a high-risk country, 20.2% of the patients without previously diagnosed CVD or DM had a high or very high risk (≥5%) for cardiovascular death within 10 years. Due to a reduced number of cardiovascular deaths, Denmark is now considered to be a low-risk area according to new recommendations from the European and Danish Societies of Cardiology. The number of patients with a SCORE of 5% or greater thus decreases to 16.2%. The corresponding number for female patients is 11.4%, decreasing to 6.9% and for male patients 45.3%, decreasing to 42.6% when using the low-risk score charts.

### DISCUSSION

By implementing systematic screening for cardiovascular risk factors in nursing consultations, the patient, the outpatient department and the patient’s GP attained an overview of the patient’s individual risk profile. This arrangement also allowed us to explore the patient’s motivation for lifestyle changes and offer relevant health promotional training relating to the patient’s everyday life, and offer written information (brochures) and support to initiate desired lifestyle changes in primary care.

Initiation or adjustment of lipid-lowering or anti-hypertensive medication or follow-up on lifestyle issues in general would require extra follow-up visits, and we considered that the work involved would lie outside the rheumatologists’ core competences. We therefore chose to refer these patients to their GPs. The screened patients seem representative of the more than 16 000 Danish RA patients registered in the DANBIO registry (73% women and 73% RF positive). The patients seen at King Christian X’s Hospital for Rheumatic Disease represent more than 90% of known patients with RA in the uptake area for the hospital.

We found that 14.3% of the patients without known DM had an impaired fasting glucose (≥6.0 mmol/L), meaning that DM cannot be excluded. Two per cent had a fasting glucose of 7 mmol/L or greater, which is considered in Denmark to be the threshold for diagnosing DM. The percentages with elevated fasting glucose above 6 and 7 mmol/L were even higher in the subgroup with known CVD (27.2% and 10.3%, respectively). In a Danish study from 2003, the prevalence of impaired fasting glucose varied between 4.7% and 17.8%, depending on age and gender. The prevalence of DM is increasing and increases with increasing age, BMI, lack of physical activity and male gender.

CVD was already known in 19.1% of the patients and 42% were diagnosed with hypertension, compared to 9.3% with CVD and 32% with hypertension in a European sample. Although 42% of our sample was already treated with antihypertensive drugs, only 54.2% of these patients had a systolic blood pressure below 140 mm Hg at the time of the consultation. The prevalence of a well-treated systolic blood pressure is a little higher in the Danish general population (63.1%).

Unfortunately, 63.8% in the group who were already known to have CVD had elevated blood pressure and, among medication, only 189 (54.2%) had a systolic blood pressure below 140 mm Hg.

The SCORE system is not recommended for patients with known CVD and DM as the SCORE chart will underestimate their risk. Due to a lack of blood test results in some of the 644 patients without known DM and CVD, we only managed to obtain a risk SCORE on 605 patients. In 170 (28.1%) of these patients the multiplication factor 1.5 was applied.

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Unfortunately, 63.8% in the group who were already known to have CVD had elevated blood pressure and, among medication, only 189 (54.2%) had a systolic blood pressure below 140 mm Hg.

The SCORE system is not recommended for patients with known CVD and DM as the SCORE chart will underestimate their risk. Due to a lack of blood test results in some of the 644 patients without known DM and CVD, we only managed to obtain a risk SCORE on 605 patients. In 170 (28.1%) of these patients the multiplication factor 1.5 was applied.
### Table 3  
The number of patients exceeding the recommended levels reported for patients with no known DM or CVD and for the subgroups of patients with known CVD or DM displayed separately

<table>
<thead>
<tr>
<th>Variable</th>
<th>No DM or CVD</th>
<th>Known CVD</th>
<th>Known DM</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=605</td>
<td>n=152</td>
<td>n=74</td>
</tr>
<tr>
<td>Women</td>
<td>448 (69.6%)</td>
<td>644</td>
<td>26 (17.1%)</td>
</tr>
<tr>
<td>Current smokers (0/1)</td>
<td>158 (24.5%)</td>
<td>644</td>
<td>19 (12.9%)</td>
</tr>
<tr>
<td>Normal BP (SBP &lt;140)</td>
<td>411 (64.2%)</td>
<td>640</td>
<td>97 (63.8%)</td>
</tr>
<tr>
<td>Diabetes patients (SBP &lt;130)</td>
<td>158 (24.5%)</td>
<td>644</td>
<td>26 (17.1%)</td>
</tr>
<tr>
<td>Light HT (SBP 140–159)</td>
<td>168 (26.3%)</td>
<td>644</td>
<td>38 (25.0%)</td>
</tr>
<tr>
<td>Moderate HT (SBP 160–179)</td>
<td>48 (7.5%)</td>
<td>644</td>
<td>12 (7.9%)</td>
</tr>
<tr>
<td>Severe HT (SBP ≥180)</td>
<td>13 (2.0%)</td>
<td>644</td>
<td>5 (3.3%)</td>
</tr>
<tr>
<td>Total cholesterol ≥5.0 mMol/L</td>
<td>397 (65.6%)</td>
<td>605</td>
<td>98 (64.5%)</td>
</tr>
<tr>
<td>Diabetes or CVD ≥4.5 mM/L</td>
<td>12 (1.8%)</td>
<td>559</td>
<td>88 (64.9%)</td>
</tr>
<tr>
<td>LDL-cholesterol ≥3.0 mMol/L</td>
<td>326 (55.4%)</td>
<td>588</td>
<td>128 (84.2%)</td>
</tr>
<tr>
<td>Diabetes or CVD ≥1.8 mM/L</td>
<td>605</td>
<td>19 (12.1%)</td>
<td>157</td>
</tr>
<tr>
<td>HDL-cholesterol</td>
<td>70 (11.6%)</td>
<td>602</td>
<td>4 (2.6%)</td>
</tr>
<tr>
<td>Triglycerides &gt;1.7 mM/L</td>
<td>71 (12.7%)</td>
<td>559</td>
<td>37 (27.2%)</td>
</tr>
<tr>
<td>Diabetes or CVD &gt;2.0 mM/L</td>
<td>10 (1.8%)</td>
<td>559</td>
<td>14 (10.3%)</td>
</tr>
<tr>
<td>F-glucose ≥6.0 mmol/L</td>
<td>409 (63.8%)</td>
<td>641</td>
<td>96 (63.2%)</td>
</tr>
<tr>
<td>F-glucose ≥7.0 mmol/L</td>
<td>163 (25.4%)</td>
<td>641</td>
<td>42 (27.6%)</td>
</tr>
<tr>
<td>Overweight (BMI &gt;25)</td>
<td>409 (63.8%)</td>
<td>641</td>
<td>96 (63.2%)</td>
</tr>
<tr>
<td>Obese (BMI &gt;30)</td>
<td>163 (25.4%)</td>
<td>641</td>
<td>42 (27.6%)</td>
</tr>
<tr>
<td>High waist circumference</td>
<td>643</td>
<td>4 (0.6%)</td>
<td>2 (0.8%)</td>
</tr>
<tr>
<td>Women (&gt;80 cm)</td>
<td>297 (63.3%)</td>
<td>469</td>
<td>66 (66.7%)</td>
</tr>
<tr>
<td>Men (&gt;94 cm)</td>
<td>111 (63.8%)</td>
<td>174</td>
<td>36 (67.9%)</td>
</tr>
<tr>
<td>Exercise &lt;5 times a week</td>
<td>418 (64.9%)</td>
<td>644</td>
<td>48 (31.6%)</td>
</tr>
</tbody>
</table>

Percentages are calculated based on the number of observations for each variable in each subgroup. 
BMI, body mass index calculated as weight (kg)/squared height (m²); CVD, cardiovascular disease; F, fasting; HDL, high-density lipoprotein; HT, hypertension; LDL, low-density lipoprotein, SBP, systolic blood pressure in mm Hg.

### Table 4  
High-risk modified SCORE based on Denmark considered being a high-risk area and the extra RA risk for the 644 patients without DM and CVD, the European low risk area SCORE reports the risk SCORE in the period since Denmark has been considered to be a low-risk area (since May 2012)

<table>
<thead>
<tr>
<th>Variable</th>
<th>All</th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=605</td>
<td>n=448</td>
<td>n=157</td>
</tr>
<tr>
<td>European high-risk area RA modified SCORE</td>
<td>2 (1, 4)</td>
<td>2 (1, 3)</td>
<td>4 (3, 7)</td>
</tr>
<tr>
<td>Risk SCORE</td>
<td>483 (79.8%)</td>
<td>397 (86.6%)</td>
<td>86 (54.8%)</td>
</tr>
<tr>
<td>Low/moderate risk</td>
<td>101 (16.7%)</td>
<td>48 (10.7%)</td>
<td>53 (33.8%)</td>
</tr>
<tr>
<td>High risk</td>
<td>21 (3.5%)</td>
<td>3 (0.7%)</td>
<td>18 (11.5%)</td>
</tr>
<tr>
<td>European low-risk area SCORE</td>
<td>529 (87.4%)</td>
<td>426 (95.1%)</td>
<td>103 (65.6%)</td>
</tr>
<tr>
<td>Low/moderate risk</td>
<td>67 (11.1%)</td>
<td>21 (4.7%)</td>
<td>46 (29.3%)</td>
</tr>
<tr>
<td>High risk</td>
<td>9 (1.5%)</td>
<td>1 (0.2%)</td>
<td>8 (5.1%)</td>
</tr>
<tr>
<td>European low-risk area RA modified SCORE</td>
<td>2 (1, 4)</td>
<td>1.5 (1, 3)</td>
<td>4 (2, 6)</td>
</tr>
<tr>
<td>Risk SCORE</td>
<td>567 (83.8%)</td>
<td>417 (93.1%)</td>
<td>90 (57.3%)</td>
</tr>
<tr>
<td>Low/moderate risk</td>
<td>77 (12.7%)</td>
<td>30 (6.7%)</td>
<td>47 (29.9%)</td>
</tr>
<tr>
<td>High risk</td>
<td>21 (3.5%)</td>
<td>4 (0.2%)</td>
<td>20 (12.7%)</td>
</tr>
</tbody>
</table>

Median and (IQR). The number of patients without known DM and CVD are reported for low/moderate risk (<5%), high risk (5 ≤ high risk <10%) and very high risk (≥10%) and the percentages of the population without DM and CVD that we obtained a risk score for and stratified by gender. For gender-specific numbers, the percentages are calculated as the share of the female or male population with no known DM and CVD when we have obtained a risk score. 
CVD, cardiovascular disease; DM, diabetes mellitus; RA, rheumatoid arthritis.
In young people the SCORE will be low, regardless of smoking habits, cholesterol and blood pressure levels and thus the chart may underestimate their risk.\(^\text{37}\) In the new European guidelines for prevention of CVD,\(^\text{14}\) it is recommended that young people with a low risk should be scored by a relative risk chart. Furthermore, the SCORE chart only includes age groups up to 65–70 years,\(^\text{17}\) and thus will probably underestimate the risk for older patients.

One of the strengths of our study is the large number of patients and the systematic documentation in a national registry. Furthermore, most of the hospital population had been invited for a cardiovascular risk assessment during the first 15 months.

The study also had some limitations. Unfortunately, we are not able to report the exact number of patients who declined to participate and compare them to the group who participated to assess potential bias. We did not verify the patients’ self-reported version of whether they had extra-articular manifestations of their RA and comorbidities in registry data or in the patients’ clinical journals. This may have caused an underestimation of the modified risk scores. Also, we did not include information on whether patients had a family history of CVD, if patients were undergoing lipid-lowering treatment or whether they had severe kidney disease.

The results from this study can help other hospitals plan the resources needed for a systematic approach to screening. As we have reported the SCORE for both high and low-risk countries, other European countries can compare their risk SCORES to the ones reported in this study.

Our results indicate gender differences in lipid status and there are substantial gender differences in the distribution of the risk SCORE. The other risk factors should be further explored for age and gender differences. Future studies need to explore the patients’ experiences of screening consultations and reasons to decline participation, and whether the SCORE system provides a realistic estimation of the patients’ actual risk of cardiovascular death. This study provides a solid background for a prospective follow-up study to determine whether the patients actually visit their GP as recommended and whether changes in risk and development of CVD occur over time.

CONCLUSIONS
Systematic screening revealed several risk factors that required medical follow-up or support to initiate lifestyle changes in order to reduce patients’ risk of CVD and cardiovascular death. Cardiovascular risk management in patients with already known DM or CVD needs to be improved. When using the charts for high-risk countries, more than 20% of our patients have an increased risk of cardiovascular death in 10 years. When using the charts for low-risk countries, the number decreases to 16%.

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Contributors JP: Study design, data acquisition, data analysis, manuscript drafting; JC: Study design, data acquisition and critical comments to manuscript drafting; KHP: Study design and critical comments to manuscript drafting.

Competing interests None.

Ethics approval As this was an observational study in which screening consultations were implemented as an integral part of clinical practice at the hospital, ethical approval was not obtained and the patients were not asked for written consent to participate. The patients could decline to participate at any time
without influencing their follow-up at the hospital in general. We did not invite patients considered have dementia or those over 85 years of age, as we considered it unethical to discuss lifestyle with this group of patients.

Provenance and peer review Not commissioned; externally peer reviewed.

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