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 prespecified 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

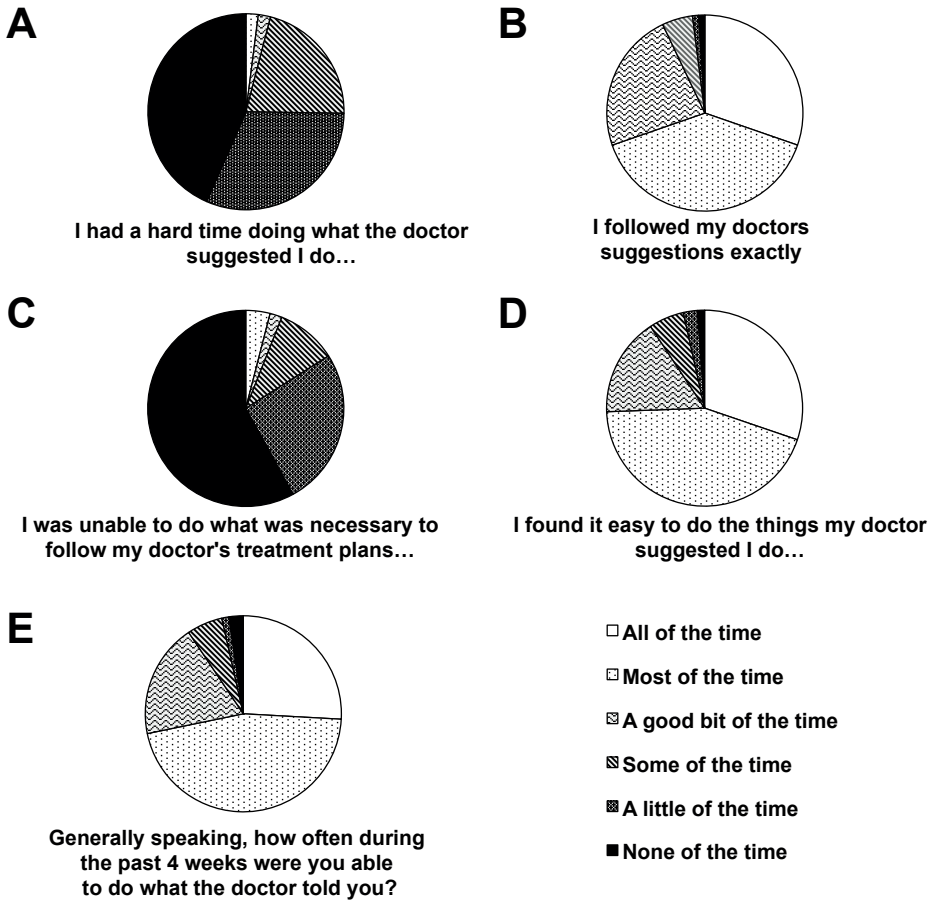

Figure 1. Patients reports on general adherence statements. In the MOS questionnaire patients were given 5 general statements on adherence and they were provided with 6 answer categories ranging from all of the time to none of the time.

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).

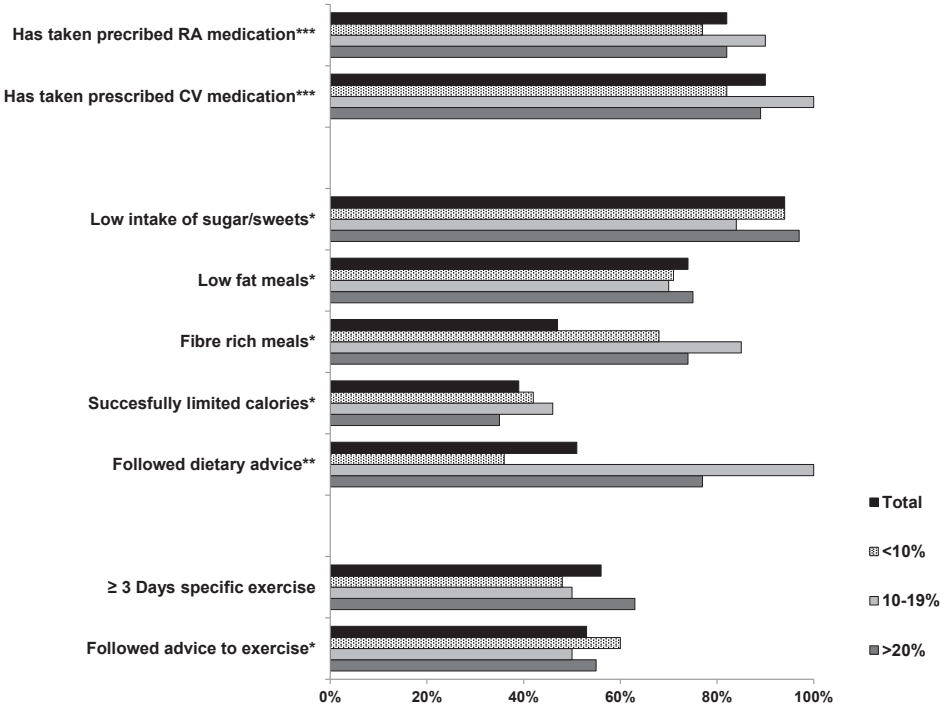

Figure 2. Patient reported adherence to given recommendations provided for the respective CVD risk groups. In The SDSCA questionnaire adherence to specific advices a patient may have received were asked. * 75%-100% of the time, **usually to always, *** most of them to all of them

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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