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

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

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Abstract

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

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

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

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

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

Introduction

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

Material and Methods

Study design and patients

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

specified treatment targets and recommendations on lifestyle changes or they were referred to their general practitioner for treatment. Before randomization the CVD risk score according to the 2010 unadjusted SCORE risk assessment was calculated (20). Patients with a CVD risk score <10% were eligible for randomization (comparable to <20% in the current, unadjusted SCORE table). Patients with a CVD risk score ≥10% (9/326) all were treated according to the tight control protocol and were separately followed. Clinical CVD was defined as a prior myocardial infarction, cerebrovascular event, amputation due to peripheral artery disease, intermittent claudication, percutaneous transluminal coronary angioplasty (PTCA) or coronary artery bypass graft (CABG). T2DM was defined as fasting glucose >7.0 mmol/l. All patients at inclusion were routinely screened for traditional CVD risk factors at the Diabetes and Vascular Centre, Franciscus Gasthuis, Rotterdam, the Netherlands.

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

Treatment targets according to the tight control protocol

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

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

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

Patients in the tight control group visited the outpatient clinic routinely every six months (which is similar to the appointments of the usual care group), but extra appointments were made when necessary due to medical/treatment related problems.

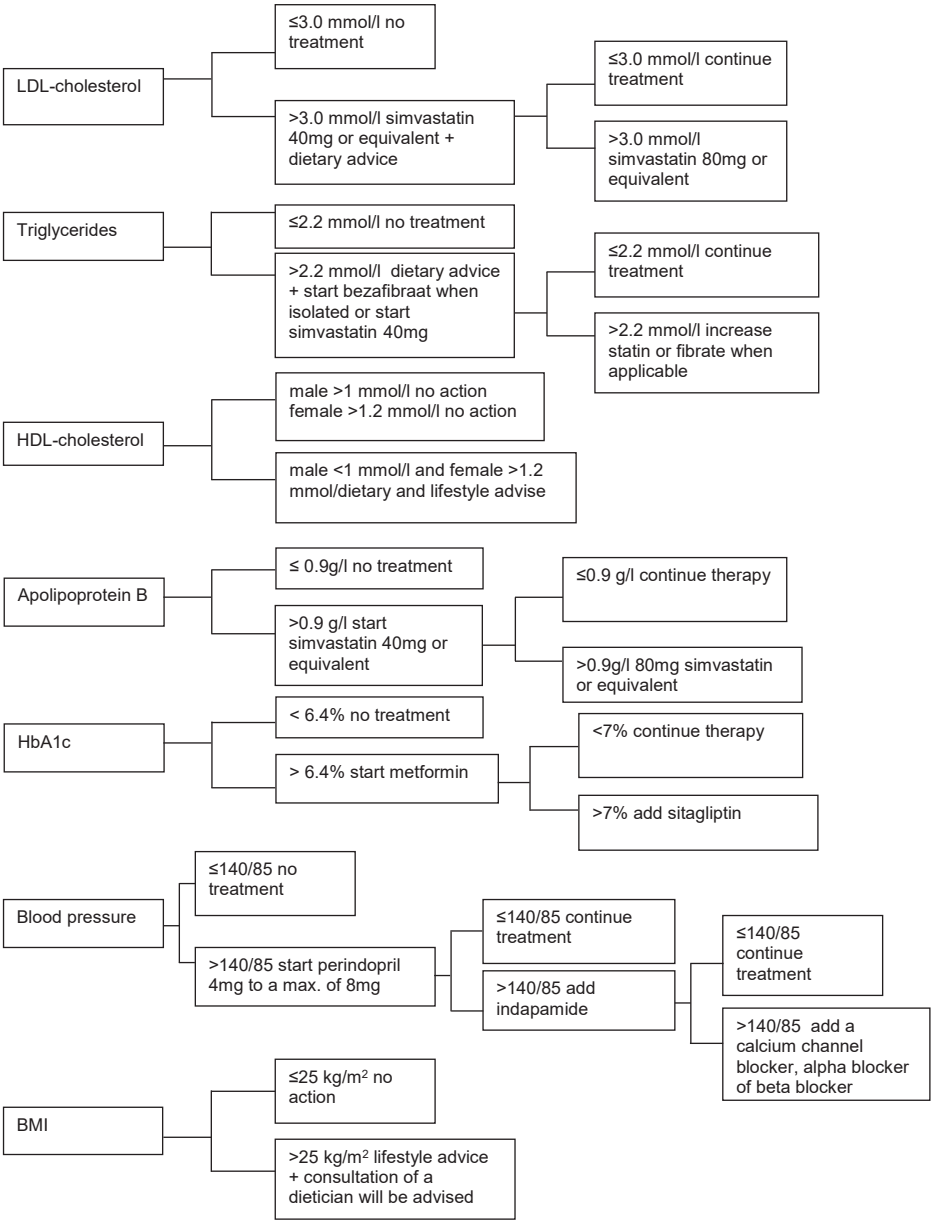

Figure 1. Flow chart tight control.

Cardiovascular risk assessment

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

Rheumatoid arthritis disease activity

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

Laboratory measurements

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

Statistics

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

Results

General Characteristics

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

Table 1. General characteristics at baseline.

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

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

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

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

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

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

Table 2. Data at 2 years follow-up.

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

* significantly different compared to baseline within group.

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

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

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

Table 3. Medication use at baseline.

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

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

Discussion

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

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

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

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