Franciscus Rheumatoid Arhtritis and Cardiovascular Intervention Study

Published: 20-10-2010
Last updated: 15-05-2024

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Coronary artery disorders
Study type	Interventional

Summary

ID

NL-OMON34401

Source
ToetsingOnline

Brief title
FRANCIS

Condition

- Coronary artery disorders
- Synovial and bursal disorders
- Arteriosclerosis, stenosis, vascular insufficiency and necrosis

Synonym
Atherosclerosis

Research involving
Human

Sponsors and support

Primary sponsor: Sint Franciscus Gasthuis
Source(s) of monetary or material Support: Het onderzoek is grotendeels standaard patientenzorg en valt daarom dinnen het patientenzorgbudget. Het is mogelijk dat in en later

stadium voor een deel van het projekt externe subsidie wordt geworven.

Intervention

Keyword: Cardiovascular risk, Prevention, Rheumatoid Arthritis, Treatment

Outcome measures

Primary outcome

Primary outcome measure is the progression of the carotid artery intima media thickness (IMT) at 5 years follow-up.

Secondary outcome

Secondary outcome measures are the following:

1) cardiovascular mortality

2) cardiovascular events, i.e. nonfatal stroke, nonfatal myocardial infarction, coronary artery bypass grafting, percutaneous coronary intervention, revascularisation for peripheral atherosclerotic arterial disease, amputation because of ischaemia.

Study description

Background summary

Recent studies have shown without doubt, that inflammation is closely linked to atherosclerosis. Inflammatory markers such as C-reactive protein (CRP), leukocyte count and complement component 3 (C3) have been linked to coronary heart disease (CHD) as well as to hyperlipidemia, insulin resistance, the metabolic syndrome and type 2 diabetes mellitus. Elevation of these inflammatory markers is associated to activation of endothelial cells and leukocytes and/or disturbances in adipose tissue fatty acid metabolism, which in turn are closely, associated to the well-known CHD risk factors like for example dyslipidemia, hypertension and obesity and even atherosclerotic plaque progression. It has been shown that lipoproteins, triglycerides (TG), fatty acids and glucose can activate endothelial cells in part due to the production of reactive oxygen species. Elevated TG, disturbances of fatty acid metabolism

and glucose are frequently found in many disorders related to premature atherosclerosis such as the metabolic syndrome and type 2 diabetes. All of these have been shown to lead to leukocyte activation in vitro and in vivo, which is obligatory for the development of atherosclerosis. Therefore, inhibition of leukocyte activation and/or endothelial cell activation is a promising target for intervention in the struggle against atherosclerosis. Patients with RA have an increased risk for atherosclerosis and cardiovascular death. Recent studies suggest that the risk may be comparable to patients with type 2 diabetes mellitus. One of the causes of the increased risk in RA may be leukocyte activation, which is part of the disease. The generation of oxidative stress by this widespread inflammation may be one of the mechanisms. Recent studies also suggest an impaired capacity to support vascular regeneration. Inflammatory mediators such as TNF alpha and IL-6 are associated with the severity of subclinical atherosclerosis. It has been suggested that a better treatment of RA and a lower disease activity score could reduce the cardiovascular risk. Data regarding cardiovascular risk reduction with changed treatment options have been conflicting. So far there are no clinical studies available investigating the clinical outcome of patients with RA treated according current guidelines as proposed in patients with type 2 DM. It is well known that multiple risk intervention in the latter group can result in impressive risk reduction, even for cardiovascular mortality, within a short follow up period. These results have been achieved in type DM in groups of a few hundred subjects.

Study objective

The primary aim of this study is to investigate if a tight multiple cardiovascular risk reduction program is effective in reducing progression of Intima media thickness progression (subclinical atherosclerosis) in patients with RA compared to usual care.
The secondary aims are:
(1) to investigate if a tight multiple cardiovascular risk reduction program is effective in reducing the number of cardiovascular events (clinical atherosclerosis) in patients with RA compared to usual care.
(2) To investigate if there is any difference in reducing progression of clinical and subclinical atherosclerosis between the tight control group and the parallel cohort of RA patients with a cardiovascular risk >10% at baseline. Cardiovascular risk is determined by using the score model (72)
(3) To investigate if cell-bound apoB (e.g. apoB bound to leukocytes and erythrocytes) can be used
as marker of risk in these patients;
(4) To evaluate if apoB is a modifiable marker in RA;
(5) To investigate the relationship between leukocyte activation, skin AGEs and atherosclerosis.

Primary endpoint:

Primary outcome measure is the progression of the carotid artery intima media thickness (IMT) at 5 years follow-up.

Secondary endpoints:
Secondary outcome measures are the following:
1) cardiovascular mortality
2) cardiovascular events, i.e. nonfatal stroke, nonfatal myocardial infarction, coronary artery bypass grafting, percutaneous coronary intervention, revascularisation for peripheral atherosclerotic arterial disease, amputation because of ischaemia.

Study design

The study is designed as a randomized, open, parallel clinical trial and a prospective cohort. RA patients with a cardiovascular mortality risk >10% at study entry are, after proper assessment of inclusion and exclusion criteria, included in the prospective cohort, and monitored and treated according to the tight multiple cardiovascular risk reduction program. RA patients with a cardiovascular mortality risk <10% at study entry, eligible for study participation, are randomly (1:1) assigned either of two strategies: (1) conventional therapy for multiple risk factors (*usual care*) or (2) the tight multiple cardiovascular risk reduction program, i.e. intensive multifactorial intervention involving strict treatment goals. Patients receiving usual care will be treated by there general practitioner for cardiovascular risk factors and patients receiving tight control will be treated according to a well defined program. The rheumatoid arthritis will be treated by patients own rheumatology. Treatment goals is a disease activity score <2,6 measured by the DAS 28. Written informed consent will be obtained from each subject.

Participants are recruited at the outpatient clinic of the Departments of Rheumatology and Internal Medicine, Sint Franciscus Gasthuis, Rotterdam.
At study entry before randomization, subjects will be asked for their medical history, medication use and family history. Furthermore, they are physically examined and undergo conventional anthropometric determinations; weight, length, BMI, waist, waist-hip ratio and blood pressure. A rheumatoid arthritis disease activity score will be recorded once a year using the DAS28.
Primary outcome measure is increase in Intima media thickness (IMT). Secondary outcome measures are measures of cardiovascular disease activity at the both on clinical and laboratory level. Patients in de tight control are offered three individual outpatient consultations annually at which blood is sampled.
Patients in the usual care group will be offered a consulation once a year.
Intima media thickness (IMT) is measured once a year . In order to be informed about patient adherence to therapy, patients are asked to fill out a questionnaire regarding adherence once a year. The follow-up period will be 5 years.

Intervention

Patients with a cardiovascular risk <10% will be randomized into two groups. A usual care group and a tight control group. The tight control group will be followed 3 times a year (or more often when necessary because of treatment) in the outpatient clinic for vascular medicine and treated according to the treatment algorithm described below.. Patients in the usual care group will be followed once a year in the outpatient clinic. Cardiovascular risk factors will be determined, but treatment will be left to the general practitioner.
Treatment target levels in the tight multiple cardiovascular risk reduction program (see below and attachment 1).
Treatment goals for blood pressure, cholesterol and triglyceride levels are determined using the current NIV guidelines for cardiovascular risk management.
- Blood pressure: In the intensive therapy group systolic blood pressure <130 and diastolic blood pressure <85.
- HbA1c: Metformin therapy will be initialized when HbA1c is > 6.4%. When Hba1c is above 7.0% sitagliptine is added. When HbA1c stays above 7.0% treatment may be altered as seen fit. To minimize the burden for patients participating HbA1c is chosen as parameter for glucose tolerance and diabetes. Target levels for HbA1c are not well defined. A HbA1c level of > 6,5% is considered diabetes, HbA1c Levels of Metformin therapy will be initialized when HbA1c is > 6.4%. When Hba1c is above 7.0% sitagliptine is added. When HbA1c stays above 7.0% treatment may be altered as seen fit. To minimize the burden for patients participating HbA1c is chosen as parameter for glucose tolerance and diabetes. Target levels for HbA1c are not well defined. A HbA1c level of > 6,5% is considered diabetes, HbA1c Levels of 5,7-6,5% are considered pre diabetes. For diabetes the advised HbA1c level is 7.0%. It is well known that metformin may reduce the risk to develop diabetes/ further glucose intolerance.
- HDL-C: In male patients > 1mmol/l, in female patients >1,2 mmol/l.
- LDL-C: <3,0 mmol/L
- TG: <2.2 mmol/l
-apoB: 0.9 g/l (76).

If a patient has a blood pressure above targets, on two consecutive consultations treatment will be started or intensified. The antihypertensive drug of first choice is an ACE inhibitor due to the cardiovascular protective effect, The first step is an ACE-inhibitor, perindopril 4mg. Second step perindopril 8mg. When blood pressure stays above the target with therapy, indapamide 1,25 will be added, Epitizide is chosen as second drug because of the known combination with perindopril (Coversyl plus®) If the target values are not reached a calcium channel blocker, a beta-blocker or an alfa blocker will be added. This choice is up to the treating physician/research physician.
If a patient has a total cholesterol or LDL cholesterol above target, dietary measures will be taken, as well as the consultation of a dietitian and simvastatine 40mg will be started. When there are contra indications or side effects for simvastatin an equivalent will be chosen (first choice is

atorvastatin 20mg, second choice is fluvastatin 40mg). If targets are not met on next consultation simvastatin 80mg (or equivalent) will be prescribed. When targets are not met with maximum statin therapy ezetimibe may be added when seen fit. Fibrates are only given in cases of isolated hypertrigliceridemia with levels above target or are added to a statin treatment if the non fasting serum triglyceride concentration is above 2,2 mmol/L on two consecutive meetings under optimal statin treatment. When HbA1c levels are above targets, the first choice treatment will be metformin 2x500mg. When HbA1C stays above 7% despite a maximum dosage of metformin (i.e. 3x1000mg), sitagliptine 100mg once a day will be started. If targets are not achieved, the treatment may be altered as seen fit by the physician. The start of a statin, fibrate and/ antidiabetic medication will always be accompanied by lifestyle and dietary advice and the advice to go to a dietician. Steroid induced hyperglycemia will be treated by the general practitioner in case of usual care randomization (as currently done in daily clinical practice). Patients in the tight control group will be followed and treated as stated above. Participants that smoke will be advised to stop. Participants in the tight control group and participants with a cardiovascular mortality risk >10% will be offered a consultation at the smoking cessation outpatient clinic.
As stated before, it is well known that a tight, multiple cardiovascular risk intervention in type 2 diabetes mellitus can result in impressive risk reduction, even for cardiovascular mortality, within a short follow up period. Since there will be no use of experimental medication or treatments, both treatment strategies will be relatively safe. Adverse events that can be expected are well documented. The general risk for patients participating will not exceed the risk for patients in daily clinical practice.

Study burden and risks

Since the majority of the interventions done in this trial is part of routine clinical practice, the nature of the burden will be primarily time investment. Medications used are routinely used medications. blood test will be combined with test done by the rheumatologist because of follow up. Test such as AGE, IMT are without risk and take only a couple of minutes.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Rheumatoid arhrtitis for at least 5 years
40-70 years old

Exclusion criteria

Diabetes mellitus
a prior cardiovascular event

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial

Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	01-02-2011
Enrollment:	316
Type:	Actual

Ethics review

Approved WMO

Date:	20-10-2010
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

ID: 23703
Source: NTR
Title:

In other registers

Register	ID
CCMO	NL32669.101.10
OMON	NL-OMON23703

Study results

Date completed:	06-12-2018
Actual enrolment:	327