Novel diagnostic test to improve cardiovascular disease risk reduction in subjects with type 2 diabetes, increasing cost effectiveness and quality of life.

Published: 04-09-2014
Last updated: 23-04-2024

The aim of this study is to answer the question: *Will the addition of the lipoprotein profile to the conventional diagnostics for dyslipidemia in T2D patients, lead to a better risk classification of CVD development?*. The improved risk...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Cardiac disorders, signs and symptoms NEC
Study type	Interventional

Summary

ID

NL-OMON41247

Source
ToetsingOnline

Brief title
Improved CVD risk test in T2D.

Condition

- Cardiac disorders, signs and symptoms NEC
- Diabetic complications

Synonym
Diabetes, type 2 diabetes mellitus

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: mRace doelmatigheidsproject

Intervention

Keyword: CVD, Diagnostic, T2D, Treatment

Outcome measures

Primary outcome

The main study parameter is the number of cardiovascular events in T2D patients being treated with lipid lowering therapy based on the information of the conventional method in combination with the LP compared to the number of cardiovascular events in T2D patients treated with lipid lowering therapy based on the information of the conventional method exclusively. We will determine the percentage of patients that are being reclassified to a different risk group according to the addition of the LP to the conventional method (see protocol, scheme in §2. Objectives). We will also look at all-cause mortality in both the control and the intervention group.

Secondary outcome

Quality of life and cardiovascular disease will be assessed every 3 months (in combination with regular visits to the diabetic nurse). The questionnaires used are: the Rose questionnaire, EQ5D level 5 and we will add personal questions (about work, ethnicity, additional costs made because of the disease). At the end of the study we will make a cost-effectiveness analysis according to:- The extra costs of the LP as a diagnostic test- The reduction in costs because of reduced morbidity (for example: hospitalization)- Non-medical costs (for

example productivity loss).

Study description

Background summary

The incidence of T2D is increasing dramatically with a shift towards the younger population and an increase in morbidity and mortality. Because of aging and the expansion of obesity, the incidence of T2D is expected to increase more in the forthcoming years.
It has been estimated that 221 million people worldwide and 1 million in the Netherlands have this condition. The number of patients in the Netherlands is expected to increase with 71.000 a year. Because persons with T2D are at utmost high risk for CVD, treatment and prevention of CVD are healthcare priorities. Even when treated with statins the 10-years incidence of CVD-related events in patients with T2D remains high.
Despite statin treatment, about 70% of the T2D patients still experience a cardiovascular event (risk reduction 21% (95% CI 11-30%)), nor is the severity of the event diminished by statin treatment. CVD is still a major cause of death in The Netherlands. With the increasing incidence of T2D the number of CV-events is increasing, even when treated with statins.
The conventional CVD risk assessment, as routinely performed at clinical chemistry labs, is a.o. based on plasma levels of total cholesterol, LDL- and HDL-cholesterol and triglycerides. Studies in the US have shown that this method identifies only 50% of the subjects at risk for CVD in the general population. This figure could be improved to 84 % by analysis of all atherogenic lipoproteins with the LP method. However, it has not been examined whether improved identification of at-risk subjects results in fewer cardiovascular events.
The aim of this project is to improve individualized treatment based on information obtained from the Lipoprotein Profile (LP) as a diagnostic method and thereby to reduce the number of cardiovascular events in T2D patients as well as improve the quality of life and cost-effectiveness.
Important alterations in plasma lipoproteins characteristic for T2D are being missed by the conventional method based on plasma cholesterol and TG concentration, but is readily detected by the LP method. On top of the classical risk factors, this method provides information in a single glance on all atherogenic lipoproteins. The LP method provides more information about the size, density, concentration and density distribution of each lipoprotein. T2D patients show a different more atherogenic lipoprotein profile: for example, they show a reduction in the size of low density lipoprotein (LDL) and high density lipoprotein (HDL). Small LDL and HDL lipoproteins, high levels of plasma Lipoprotein(a) concentration and triglyceride rich lipoproteins are independent risk factors for CVD. Specially small-dense LDL seems to be

strongly atherogenic. The LP thereby provides information on a number of additional independent risk factors for CVD. The consequence of the conventional cholesterol measurement is that the patients will be treated according to only the concentration of the lipoproteins regardless of the distribution of the different lipoproteins. Patients with a more atherogenic LP can take advantage of an aggressive cholesterol lowering treatment (high dosage of statins or a combination of lipid lowering medication). Treatment options can then be tailored to reduce the risk of the individual patient (based on the cholesterol lowering treatment guidelines) and goes beyond the assumption of *one size fits all*.
These dyslipidemias (small dense lipoproteins, high plasma Lipoprotein(a) and triglyceride rich lipoproteins) are being missed by the conventional plasma lipids measurement, but can be identified by the LP method. This method provides information at a single glance on all atherogenic lipoproteins in the plasma of the patient, especially about the size, density, concentration and heterogeneity of the different lipoproteins. The LP method thereby provides information on additional independent risk factors for CVD. Treatment for risk reduction can be tailored for the individual patients (within the treatment guidelines).
In this study the standard method (control group), which is treated according to the standard clincal chemistry measurements (plasma cholesterol, plasma triglyceride, LDL-C and HDL-C) will be compared to the intervention group (treated according to the concentration of lipoproteins and an additional LP).

This study uses a multicenter, prospective, randomized approach. 1500 T2D subjects will be randomized in 2 groups:
- Control group: treatment according to the results of the conventional clinical chemistry lipid measurements,
- Intervention group: treatment according to the results of the conventional lipid measurement and the LP).

The number of cardiovascular events will be monitored in a 6-year follow-up period. The differences in distribution of the patients among the risk groups (ver low, low, medium and high risk), after adding the LP compared to the conventional method alone, in terms of percentages after reclassification. Changes in quality of life will be monitored by regular questionnaires and the immediate costs of treatment and diagnostics and non-medical costs will be assessed.
By adding the LP to the standard diagnostic method of cholesterol measurement, we expect a better identification and classification of dyslipidemia in type 2 Diabetes patients. The novel LP method is therefore expected to lead to more individualized treatment strategies and consequently to additional CVD-risk reduction and increase in quality of life and cost effectiveness.
T2D patients are already at high risk for CVD. Besides changes in classical risk factors assessed by conventional methods, they show typical changes in atherogenic lipoproteins such as reduction in the size of low density- and high density lipoproteins (LDL and HDL) that are recognized as independent CVD risk

factors. Small-sized, dense LDL appears to be strongly atherogenic. This dyslipidemia is missed by the conventional lipid analyses, but can be identified with the LP method. As a consequence, patients with elevated levels of small-sized LDL are presently not being treated differently from patients with normal sized LDL. Such patients may benefit from more aggressive treatment provided by increased doses of statins or combination with additional drugs.

In the first part of this study, we will assess if improvement of treatment strategy based on individual lipoprotein profiles leads to a reduction in the CVD-related events in Dutch subjects with T2D in comparison with the individualized treatment based on the conventional method as commonly performed in the clinical chemistry laboratories.
We expect that diagnostic use of the LP method will further improve CVD risk reduction by 15 % (from 30% to 35%).The typical T2D-lipoprotein profile is largely due to an increased mobilization of fatty acids from adipose tissue, which negatively affect peripheral insulin action and the functioning of the insulin-producing pancreas beta-cells. Thus aggressive treatment of the dyslipidemia may also beneficially affect the hyperglycaemic condition.
At present, the LP method is applied to patients visiting our cardiovascular genetics clinic, who cannot be classified to a particular lipid disorder, when diagnostics is based on conventional lipid analyses alone. This makes it hard to design appropriate prevention- and treatment strategies for these patients, and to decide upon the necessity for further family screening. Our preliminary analyses of patients with lipid disorders of unknown origin have shown that the LP method provides insight into the nature of the dyslipidemia, helps to design more personalized treatment strategies and is a suitable means to follow treatment efficacy.

Implementation of the *LP* method for a detailed analysis of plasma lipoproteins will provide more insight into factors contributing to the CVD risk that are being missed by the conventional plasma lipid analyses. This will lead to a better identification of subjects at risk, a better risk assessment, a more personalized treatment and increased insight into the efficacy of treatments.
Although increasing the costs for diagnosis, use of the LP method is expected to result in a reduction of the costs for CVD-related morbidity, hospitalization and the non-medical costs (patient time costs, productivity loss), and consequently, the overall costs.
Furthermore, this project has the potential to provide evidence based guidelines for better, more personalized, treatment (including prevention of overtreatment) and improved cost effectiveness in patients with T2D, and possibly improved quality of life.

Study objective

The aim of this study is to answer the question: *Will the addition of the lipoprotein profile to the conventional diagnostics for dyslipidemia in T2D

patients, lead to a better risk classification of CVD development?*. The improved risk classification can lead to improvement of the individualized treatment of these patients, leading to a decrease of CVD related events.

Our data will show whether improved personalized treatment as a result of the additional novel method for atherogenic lipoprotein analyses, the *LP* to the conventional diagnostic method, for CVD-risk estimation, in T2D subjects leads to:

1. A reduction of CVD-risk in T2D subjects;
a) We expect that a certain percentage of the T2D patients will be reclassified in a different riskscore among the 4 groups (Very Low, Low, Medium or high); according to the results of the LP.
b) This improved risk classification may lead to better treatment strategies and to
c) reduced CVD risk in these patients)
2. Improved health-related quality of life;
3. An increased cost effectiveness.

The LP analyses will be performed and optimized in the laboratory of Vascular Medicine (Bd-279), and in case of positive outcome will be further optimized and implemented in collaboration with the department of Clinical Chemistry.

Study design

For this multicenter randomized intervention trial we will include 1500 T2D patients. These patients will be asked to participate to this 6-year follow up intervention study. The patients will provide 3 blood tubes (during a regular blood withdrawal) at baseline (2 SST a 9ml and 1 small EDTA a 4ml) and 2 blood tubes (SST a 9ml) during a regular blood withdrawal at the end of the study (after 6 year of the inclusion). These 1500 patients will be divided into 2 groups of 750. The control group of 750 patients will have the normal clinical chemistry measurements of the lipoproteins. The intervention group of 750 patients will have a combination of the clinical chemistry measurement of the lipids and the LP method.

The outcome of the LP analysis will be evaluated by a treatment team (Dr. Roeters van Lennep (Internal Medicine doctor specialized in lipidology), Dr. H.W.O. Roeters van Lennep (Cardiologist), Drs. S. Bos (physician researcher) and Drs. R. Yahya (physician researcher)). This team will give individualized treatment advices to the outpatient clinic specialist regarding the treatment of the patients in the intervention group, based on the combination of results of the conventional lipid measuring method and the LP method. These treatment advices will follow out of the flowchart (version 2). The treatment group will choose for example: low to moderate statin dose. This advice will be given to the specialist in the outpatient clinic. The specialist will choose the specific cholesterol lowering drug based on the *Statin equivalent dosages

scheme* (see also protocol §3.0 Study Design), taking into account the possible drug intolerance of the individual patient.
Plasma of all patients (control + intervention group) will be stored after the inclusion, to offer the possibility to perform retrospective LP analysis in the control group.
The next time the patient visits the outpatient clinic for the regular control of diabetes, the physician will discuss the results of the test (by the control group, the physician will discuss the results of the clinical chemistry measurement of the lipids, and by the intervention group the physician will discuss the results of the clinical chemistry measurement of the lipids and the LP).

Patients in both groups will receive a personalized treatment advice within the EAS guidelines:
- Control group: the patients in this group will receive their treatment advice from their own physician based on the results of the clinical chemistry measurement of cholesterol
- Intervention group: the patients in this group will receive their treatment advice from their own physician (who will be advised by the treatment team of this project) (see above), based on the results of the clinical chemistry measurement of cholesterol in combination with the results of the LP method.

The patients will be followed for a period of 3 years. In this 3-year follow-up study, the incidence of CVD will be the endpoint of the study.

CVD is defined as the occurrence of Major adverse cardiac event (MACE), including non-fatal myocardial infarction, not fatal stroke or death from cardiovascular causes. Also coronary revascularization, hospitalization for congestive heart failure and unstable angina pectoris and peripheral artery disease will be included in the definition of CVD. Microalbuminuria (albumin-to-creatinine ratio 2.5-25 mg/mmol for men and 3.5-35 mg/mmol for women, in any urine sample) is also part of the composite endpoint as it is a very strong indicator of CVD risk in T2D patients. The albumin-to-creatinine ratio is being measured during the regular visits at the outpatient clinic for type 2 diabetes control.
We will also assess all-cause mortality, we hereby will divide the death cause in percentages of the all cause mortality in to different groups according to the cause of death, such as death from CVD, and other causes.
The patients that suffer from one of the specified events will be included in the composite endpoint. Because the endpoints can vary in *weight*, (for example: death from cardiovascular causes vs urine microalbumin-to-creatinin ratio) we will look at the effects of the intervention on the specific endpoints separately additional to the effect of the intervention on the total composite endpoint. We will do that in order of *weight* or clinical importance of the different endpoints.
The patients will also be asked to fill in questionnaires every 3 months (every time the patient has an appointment with the diabetic nurse). These are needed

to obtain more insight into improvement of quality of life, cost-effectiveness and the development of cardiovascular disease. We established an *events committee* to control if the documented events meet the CVD events definition in this study. This committee consists of: Prof. Dr. J. Roos (Cardiologist, Erasmus MC) and Anho Liem (Cardiologist, Sint Franciscus Gasthuis). The events will be documented in a separate database by the coordinating investigator (with explanation about the type of the event: for example an inferior myocardial infarction). This database will be finished after 6 years of follow-up and will be controlled by the events committee. This committee will decide if the documented events meet the CVD events definition in this study.

Time schedule:
Year 1: Start: august/september 2014; Organization of the study (first 6 months). First visit of ~520 patients. (intermin analysis at 4 months focused on logistics).
Year 2: Examination of ~1020 patients.
Year 4:Follow-up after 3 years, analyses of clinical endpoints (power not enough)
Year 7: Follow-up after 6 years
Year 7 and 8: Analyses of all data and reporting, publication of papers. In this year also the protocol for implementation of the LP method will be established.

Intervention

The intervention group will be subjected to measurements of the lipids by the standard clinical chemistry and additionally by the LP method. The control group will obtain only the clinical chemistry measurements of cholesterol (like in the outpatient clinic).

The LP is analyzed after ultracentrifugation which leads to separating the different lipoproteins based on their density and collected in 45 fractions. After that the LP is provided by measuring cholesterol and triglycerides in the fractions. The results of the LP will be shown in 3 figures:
- Cholesterol profile
- Triglyceride profile
- Cholesterol/Triglyceride ratio profile.
Based on the analysis of these 3 profiles in addition to the conventional measurements the treatment team will choose the individualized treatment for the patients in the intervention group according to the flowchart, within the EAS guidelines.

EAS treatment guidelines:
- Primary prevention is defined as all T2D patients who don*t belong in the secondary prevention group.
- Secondary prevention is defined as T2D with 1 of the following:
• CVD

• CKD (chronic kidney disease)
• > 40 years old + > 1 CVD risk factor or markers of target organ damage

Statin doses with <40% LDL reduction will be considered as low/moderate doses.
Statin doses with > 40% LDL reduction will be considered as high doses.

Treatment strategy of the control group (EAS guidelines), see flowchart version 2:

- Primary prevention: LDL-C > 2.5 mmol/L: treat with statin (the highest (tolerated) dose to reach the target level of LDL-C< 2.5 mmol/L)*
- Secondary prevention: LDL-C > 1.8 mmol/L: treat with statin (the highest (tolerated) dose to reach the target level of LDL-C< 1.8 mmol/L)*
*If target level is not achieved with highest tolerable statin dose, a combination of statin + cholesterol absorption inhibitor/bile acid binding resins/nicotinic acid can be used.
- TG >2,3 mmol/L / HDL-C <0,88 mmol/L / Lp(a) > 0,5 g/L: can be treated with fibrate/nicotinic acid or combination of fibrate/nicotinic acid with statin.**
**When a statin-fibrates combination therapy is used, fenofibrate will be the first option (lower myopathy incidence when fenofibrate is used compared to other fibrates).

Treatment strategy of the intervention group will be according to the following protocol (within the EAS guidelines) see flowchart version 2 :

Primary prevention:
LDL< 2.5 mmol/L+ small/large LDL ratio>1: low to moderate dosages of statins.*
LDL>2.5 mmol/L + small/large LDL ratio<1: low to moderate statin dose.*
LDL>2.5 mmol/L + small/large ratio>1: high statin dose.*
LDL>2.5 mmol/L + small/large ratio>2: a combination of highest tolerable dose of statin + cholesterol absorption inhibitor/bile acid binding resins/nicotinic acid can be used.*

Secondary prevention:
LDL<1,8 mmol/l+ small/large LDL ratio>1: low to moderate statin dose*
LDL>1,8 mmol/L + small/large LDL ratio<1: low to moderate statin dose*
LDL>1,8 mmol/L + small/large ratio>1: high statin dose.*
LDL>1,8 mmol/L + small/large ratio>2: a combination of highest tolerable dose of statin + cholesterol absorption inhibitor/bile acid binding resins/nicotinic acid can be used.*

*If target level is not achieved with highest tolerable statin dose, a combination of statin + cholesterol absorption inhibitor/bile acid binding resins/nicotinic acid can be used.

- TG >2,3 mmol/L / HDL-C <0,88 mmol/L / Lp(a) > 0,5 g/L: can be treated with fibrate/nicotinic acid or combination of fibrate/nicotinic acid with statin**

**When a statin-fibrates combination therapy is used, fenofibrate will be the first option (lower myopathy incidence when fenofibrate is used compared to other fibrates).

The outcome of the LP analysis will be accompanied by advice of a treatment team (see protocol § 3. Study design).
In case of statin intolerance (in both the control and the intervention group) the following lipid lowering medication can be used: bile acid binding resins/nicotinic acid/ cholesterol absorption inhibitor (with or without bile acid binding resins/nicotinic acid).
If the target level is not reached (in both the control and the intervention group) the following medication can be used: combination of statin with cholesterol absorption inhibitor/bile acid binding resins/nicotinic acid.

Study burden and risks

The risk of developing CVD by T2D patients is still high even after treatment with lipid-lowering therapy. The risk might be reduced further if the new diagnostic method *Lipoprotein Profile* will improve risk assessment leading to a better individualized treatment of T2D subjects and subsequently to an increase in quality of life and cost-effectiveness.

Contacts

Public
Erasmus MC, Universitair Medisch Centrum Rotterdam

's-Gravendijkwal 230
Rotterdam 3015 CE
NL
Scientific
Erasmus MC, Universitair Medisch Centrum Rotterdam

's-Gravendijkwal 230
Rotterdam 3015 CE
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:;- T2D patients with a glycated haemoglobin HbA1c level of >58 mmol/mole (or >7,5%).
T2D definition: T2D is the most common type of diabetes. In this condition, plasma glucose levels cannot be kept within the normal range. T2D is being developed due to a gradual decrease of insulin production by beta cells in the pancreas and/or due to a decrease of insulin sensitivity (insulin resistance). Causing a reduction in glucose uptake from the bloodstream. That can lead to continuously high glucose levels (hypertriglyceridemia). The diagnosis of T2D can be made according to fasting glucose levels >7.0 mmol/L. The golden standard is the Oral Glucose Tolerance Test (OGTT) where the glucose levels are being measured 2 hours after the ingestion of a glucose-load and have to be >11.1 mmol/L to makeobtain the diagnosis.;- Age > 18 years

Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:;- (potential) pregnancy (pregnancy / wishing to get pregnant / might be pregnant due for example loss of good anticonception).
In all these cases the women will be excluded from the study. The reason therefore is that the effect of cholesterol lowering treatment on the unborn infant has not been tested before, and therefore can potentially be harmful to the unborn infant. Women in the productive age will be asked about the possibility of pregnancy and the anticonception used, before they can be included in this study. (This procedure does not differ from usual care).

- Incapacitated subjects.
- Patients who allready partcipated in an another ongoing intervention study

Study design

Design

Study type: Interventional

Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Diagnostic

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	31-10-2014
Enrollment:	1500
Type:	Actual

Ethics review

Approved WMO Date:	04-09-2014
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	23-10-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

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

No registrations found.

In other registers

Register	ID
CCMO	NL42635.078.13