Predictors Of heart failure after ST elevation Myocardial Infarction

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Primary objective:The main aim of the current study is to identify novel pathophysiological pathways associated with the development of post-MI HF using genome-wide data and innovative bioinformatics approaches. Specific aims1) Identifying and...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Heart failures
Study type	Observational non invasive

Summary

ID

NL-OMON34692

Source
ToetsingOnline

Brief title
Heart failure after an acute myocardial infarction/POST-MI

Condition

- Heart failures

Synonym
cardiac decompensation, Heart failure

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Bioinformatics, Genetics, Heart failure, Myocardial infarction

Outcome measures

Primary outcome

Time till first hospitalization for heart failure or heart failure related

mortality.

Secondary outcome

- Reinfarction

- Stent thrombosis

- Cardiac mortality

- All-cause mortality

- Combination of all endpoints

Study description

Background summary

Heart failure (HF) is a phenotypically heterogeneous disease with multiple possible etiologic factors such as coronary artery disease (CAD) with or without myocardial infarction (MI), hypertension, valve dysfunction or viral infection. An ischemic etiology such as CAD and MI underlie the development of HF in about 70% of all cases. In a community-based sample from the US, a 19.2% incidence of HF was observed 30 days post-MI and in a cohort of elderly, 64% developed HF in the first year after their first MI. Post-MI HF has a detrimental effect on prognosis. In a study of >15,000 patients with an acute MI, 23% developed HF during index hospitalization after thrombolytic therapy and more importantly patients who developed HF had a higher mortality rate at 30-days (18.9% vs. 3.1%) and 1 year (25.2% vs. 5.3%).

Despite the identification of several risk factors for post-MI HF (e.g. infarct size, age, diabetes, renal dysfunction), interindividual variability exists, with some patients experiencing significant left ventricular dilation despite the absence of risk factors and some patients classified as high risk do not. A

substantial part of this variability is thought to be genetically based and state of the art genetic research has the potential to lead to a more fundamental understanding of underlying pathophysiological mechanisms related to post-MI HF and identify new treatment targets and diagnostic biomarkers. However, genetic causes of HF have only been identified in rare causes of non-ischemic HF with monogenic inheritance. So far, only one genome-wide association study (GWAS) has been reported in unrelated individuals with HF[5]. This GWAS studied 73 subjects with HF from 1345 Framingham Heart Study participants using a 100k gene chip and did not report any significant associations. The lack of success in this study may be explained by 1) the inclusion of a heterogeneous group of HF patients and 2) the focus on main effects of single loci using strict statistical thresholds for significance which considers only one single nucleotide polymorphism (SNP) at a time and thereby ignoring the genomic and environmental context of each SNP. This single locus-based analysis may be appropriate in diseases caused by a single gene, but are not applicable to the analysis of complex diseases. A large number of risk alleles presumably with an odds ratio less than 1.3 are not detected by current single-locus GWAS analysis methods due to the use of a conservative correction for multiple tests using Bonferroni or the false discovery rate. Novel alternative analysis approaches to GWAS data that focus on the combined effects of many loci, each making a small contribution to overall disease susceptibility, may provide a solution for aforementioned statistical limitations. Associated SNPs may be selected based on prior expert knowledge and only those SNPs that are significantly enriched in particular biological groups (e.g. biochemical pathways, gene function) will be selected for replication. This bioinformatics approach will allow us to select SNPs with more liberal p-values than the traditional statistical analyses. In addition, it is likely that loci will contribute to complex diseases such as HF only through their interaction with other genes and environmental factors, while main effects of the individual loci may be small or absent.

In the present proposal, two different state of the art bioinformatics approaches to analyze genome-wide data will be utilized that each addresses the complexity of HF. First, the Exploratory Visual Analysis (EVA) database will be used and software to organize loci by biochemical pathway and gene function to capture those genetic effects that might be missed using traditional statistical methods. Second, the multifactor-dimensionality reduction (MDR) to detect those genetic effects that are dependent on other loci will be utilized. This analysis will be guided by prior knowledge on protein-protein interaction information to reduce the computational complexity.

To assist physicians in identifying those patients who are at high risk for post-MI HF, a clinical prediction model will be developed. Next to observed genetic factors, demographic data, cardiovascular risk factor status, medication use, laboratory measurements and angiographic data will be included in the prediction model.

Study objective

Primary objective:
The main aim of the current study is to identify novel pathophysiological pathways associated with the development of post-MI HF using genome-wide data and innovative bioinformatics approaches.

Specific aims
1) Identifying and validating novel pathophysiological pathways by detecting patterns of SNP associations in biochemical systems and gene-function-groups using genome-wide data.
2) Prioritizing genes by extracting prior biological knowledge from protein-protein databases to decrease the computational burden of the interaction analyses.
3) Detecting gene-gene and gene-environment interactions using a model-free, non-parametric data mining method.

Secondary objectives:
- A clinical prediction tool will be developed to predict patients at high risk for developing postinfarct heart failure.
- Potential diagnostic biomarkers identified by the primary objective will be measured and related to incidence of heart failure.
- The association between SNP*s and secondary endpoints such as reinfarction, stent thrombosis or mortality will be investigated. Potential diagnostic biomarkers for the secondary endpoints will be measured and related to the incidence of the specific secondary endpoint.

Study design

The study is a multi-center, prospective, longitudinal, observational study. A nested case-control study will be performed when 800 cases with HF are included. For each incident case of HF, we will select a control free of post-MI HF matched on age at time of the MI, gender, size of the MI using peak CK (in 1000 U/dL increments), and duration of follow-up.

Study burden and risks

This is an observational study. Participants will not be exposed to any risks associated with participation to the current study. Participants will not have any advantages or disadvantages by participating in the current study. Extra blood will be drawn to measure DNA and newly identified biomarkers. Next to standard clinical care, no additional venapunction is necessary.

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

- Patients admitted with an acute myocardial infarction and candidates for primary PCI. A diagnosis of acute myocardial infarction is defined by chest pain suggestive for myocardial ischemia for at least 30 minutes with a time from onset of symptoms of less than 12 hours before hospital admission and an ECG with ST segment elevation of more than 0.1mV in 2 or more leads.
- Minimum age 18 years.
- Verbal followed by written informed consent.

Exclusion criteria

- Presence of other serious medical conditions with a life expectancy of less than 6 months.

- Unwilling to sign informed consent.
- Previous myocardial infarction.
- Previous revascularization procedure.

Study design

Design

Study type: Observational non invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	01-01-2011
Enrollment:	2400
Type:	Actual

Ethics review

Approved WMO

Date:	23-06-2010
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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: 26126
Source: NTR
Title:

In other registers

Register	ID
CCMO	NL29888.042.10
OMON	NL-OMON26126