HCMR - Novel Predictors of Outcome in Hypertrophic Cardiomyopathy.

Published: 10-09-2014
Last updated: 19-04-2025

Primary:To understand the relationship between novel risk markers (based on the following) and clinical outcome. Secondary:Developing a score from the predictive model that can be used to assess risk given a patient*s combination of risk factors.

Ethical review	Approved WMO
Status	Completed
Health condition type	Myocardial disorders
Study type	Observational invasive

Summary

ID

NL-OMON41965

Source
ToetsingOnline

Brief title
HCMR (2222/0003)

Condition

- Myocardial disorders

Synonym
enlargement of the heart, thickness of heart muscle

Research involving
Human

Sponsors and support

Primary sponsor: University of Oxford
Source(s) of monetary or material Support: Ministerie van OC&W,Department of Health and Human Services;National Institutes of Health

Intervention

Keyword: Hypertrophic cardiomyopathy, Predictor model, Risk factors

Outcome measures

Primary outcome

Primary outcomes

Using exploratory data mining methods to identify demographic, clinical, and novel cardiac magnetic resonance imaging, genetic and biomarker variables associated with the outcomes.

Risk Markers

1. CMR to measure cardiac volumes, mass, function and fibrosis

2. Genotyping

3. Serum biomarkers of fibrosis

4. Clinical risk factors

Clinical outcome

Primary

1. The composite of cardiac death due to sudden cardiac death (SCD) and congestive heart failure (CHF)

2. Aborted SCD including appropriate intracardiac defibrillator (ICD) firing

3. Need for heart transplantation

Secondary

1. All-cause mortality

2. Ventricular tachyarrhythmias

3. Hospitalisation for heart failure

4. Atrial fibrillation

5. Stroke

Secondary outcome

Secondary outcomes

Using the demographic, clinical, imaging, biomarker and genetic measures, plus

any interactions, identified in the tree analysis, Cox proportional hazards

regression will be used to develop a predictive model.

Study description

Background summary

While the majority of patients with hypertrophic cardiomyopathy (HCM) remain asymptomatic, the prognosis is poor in a subset of affected individuals who present with Sudden Cardiac Death (SCD) or progress to heart failure (HF). Current clinical methods to assess risk of these adverse events and to target therapy are limited. The currently accepted risk predictors for SCD as indication for primary prevention with implantable cardioverter defibrillators (ICD) include: (1) family history of HCM-related SCD, (2) unexplained recent syncope, (3) massive left ventricular hypertrophy (LVH) (thickness >=30 mm), (4) multiple bursts of non-sustained ventricular tachycardia on ambulatory electrocardiography and (5) hypotensive or attenuated blood pressure response to exercise.1 However, these risk factors are incomplete as sudden death events still occur in clinically identified patients with 0 or 1 risk factor, currently considered low risk.2 ICD placement for primary prevention based on these 5 risk factors was associated with appropriate therapy rates of 17% over 5 years and rates of inappropriate shocks and complications of 27% and 20%, respectively.2 Thus, improvement is needed over and above current clinical risk stratification in order to reduce morbidity and lifetime costs of treatment. In addition, currently used risk factors do not reflect key underlying pathophysiologic processes such as myocardial fibrosis. Fibrosis and replacement scarring due to small vessel ischemia are prominent features of HCM and are implicated in promoting HF (due to diastolic dysfunction or LV remodelling and systolic dysfunction) and creating risk for SCD. Therefore, this study will identify potential targets for therapeutic intervention using existing or novel drug therapy, leading to new approaches for altering the

underlying abnormal substrate responsible for SCD and HF. Accordingly, a recent NIH working group report on research in HCM3 specifically recommended a prospective natural history study to enable identification of such risk markers.

Study objective

Primary:
To understand the relationship between novel risk markers (based on the following) and clinical outcome.

Secondary:
Developing a score from the predictive model that can be used to assess risk given a patient*s combination of risk factors.

Study design

This is an international, multi-centre, observational, prospective study of patientsinvolving sites in the UK, Italy , Netherlands and Germany with clinically diagnosed HCM, studied at baseline with will be invited to attend one study visit followed by a yearly telephone call. At this visit there will be collection of demographic data, clinical risk factors, CMR imaging for novel markers from CMR, genotyping, and serum biomarkers of collagen turnover and myocardial injury, enrolled. Enrolment will take place over a 2-year period and follow-up by annual telephonefollowed for 3-5 years (mean of 4 years), by annual telephonefollowed for at least 10 with annual telephone follow-up.

Study burden and risks

Risks
1. Blood Draw and IV Placement:
The risk of IV line placement and blood draw are of bruising, bleeding, and local infection. A vagal reaction and fainting due to either procedure is quite rare (<1%).
2. CMR:
CMR is a safe and non-invasive technique with no known risk when appropriately supervised. It does not involve ionising radiation (X-rays). Potential participants with ferromagnetic objects in their bodies or with implanted devices which can be damaged by the CMR magnet will be excluded. All participants entering the scanner room are screened for such objects. The site is fully equipped for resuscitation (including defibrillation) in the unlikely event of a medical emergency during scanning.
While most people do not experience discomfort in a MRI environment, the enclosed space of the scanner can potentially feel uncomfortable, especially for more elderly participants. Discomfort from lying still for a long period of time will be minimised with comfortable padding and positioning. People with a

history of severe claustrophobia would be excluded from participation in the study. Participants will be given a chance to see the scanner before the study starts. All participants would be introduced carefully to the scanner and allowed to leave at any stage, should they wish to do so. Once in the scanner, participants would be able to indicate immediately if they wish the scanning to cease by squeezing a bulb placed in their hands, or by requesting it verbally. As the MRI scanner is noisy, participants can be provided with ear plugs and/or headphones to reduce noise and aid communication between them and the investigators.
3. Gadolinium:
Gadolinium contrast is widely used for clinical indications in CMR and is safe. Occasionally it may cause a mild headache, rash and very rarely (< 1 in 1000) a more severe allergic reaction. These side effects are reversible upon stopping the infusion. However, in people with reduced kidney function, it can lead to a rare condition, nephrogenic systemic fibrosis (NSF); hence, as per departmental guidelines based on Food and Drug Administration guidelines, all research participants with estimated glomerular filtration rate (eGFR) <30ml/min (stage 3-5 renal disease) should not be given gadolinium. For this study, all potential participants with eGFR <30ml/min will not be recruited. If there is no laboratory blood result for creatinine within the last 30 days or investigators make a clinical judgement that a new creatinine result is needed, a pre*scan blood test to check their kidney function will be performed. No gadolinium will be given before this result is available. The SISICF explains this to participants.

Benefits:
For the participants, this study would require their time and would not directly provide any benefit to the participants themselves.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

• Male or Female, aged 18-65
• Established diagnosis of HCM defined as unexplained LVH defined as any segment >= 15mm thick
• Signed informed consent
• Able (in the investigator's opinion) and willing to comply with all study requirements

Exclusion criteria

• Uncontrolled hypertension as judged by the investigator
• Uncontrolled atrial fibrillation at time of enrollment
• Angiographically documented >50% coronary stenosis
• Prior septal myectomy or alcohol septal ablation
• Prior myocardial infarction
• Incessant ventricular arrhythmias
• Diabetes with end organ damage
• Stage IV/V chronic kidney disease (eGFR <30ml/min)
• Inability to tolerate MRI scanning (severe claustrophobia, inability to lie flat)
• Contraindications to CMR imaging (implantable devices or other metal implants, cranial aneurysm clips, metallic ocular foreign bodies, hypersensitivity to gadolinium)
• Female participant who is pregnant or lactating
• Malignancy or other serious medical condition expected to limit lifespan <5 years
• Any other significant disease or disorder which, in the opinion of the investigator, might influence the participant*s ability to participate in the study.

• Involvement in other studies thought to compromise resulting study data or the health of the participant
• Prior inclusion in the study of 5 members of the same immediate family.
• Inability to give informed consent

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	30-12-2014
Enrollment:	140
Type:	Actual

Ethics review

Approved WMO Date:	10-09-2014
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	30-01-2015
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	04-05-2015
Application type:	Amendment

Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	18-03-2025
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

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
ClinicalTrials.gov	NCT01915615
CCMO	NL50098.056.14