Arrhythmia Risk Stratification in a Clinical Patient Cohort and Correlation with Genotype and Environmental Modulators

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1) To electrophysiologially characterise a selected, large cohort of patients prone to malignant ventricular arrhythmias (ICD recipients)2) To exactly quantitate outcome by total mortality as well as malignant arrhythmia risk through number of...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Cardiac arrhythmias
Study type	Observational invasive

Summary

ID

NL-OMON37942

Source
ToetsingOnline

Brief title
EU-Trig Treat Study

Condition

- Cardiac arrhythmias
- Cardiac and vascular disorders congenital

Synonym
arrhythmia risk stratification

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: Europese Unie Seventh Framework Programme

Intervention

Keyword: electrocardiography, genotype, implantable defibrillator, programmed cardiac electrostimulation

Outcome measures

Primary outcome

1. target genes/cardiac: SCN5A, SCN1B, PLN, HRC, HSP20, NCX, CSQ, HAX-1, JCN,

RyR, Dystrophin, Troponin, KCNQ1, KCNH2, ANK2, DRB1 (19 genes).

Metabolic/diabetes: INS + INS receptor (two genes). Metabolic/obesity: MC4R

(one gene). Analysis of new unknown genes is possible.

2. digital resting ECG

3. signal averaging ECG

4. T-wave-alternans-test

5. electrophysiological study

6. 24h ECG

Secondary outcome

NA

Study description

Background summary

Numerous noninvasive ECG derived methodologies have been proposed to risk stratify patients for ventricular arrhythmias, and sudden cardiac death. Some of them, like T-wave alternans and signal averaging are commercially available,

others, like beat-to-beat variability
of repolarisation, are clinically still in their testing or developmental phase. Both T-wave alternans and BVR are repolarisation dependent biomarkers that have been associated with disturbed intracellular calcium handling. Where BVR can be determined at resting or slow heart rates, the use of micro-voltage T wave alternans has been limited to heart rates above 110 beats/min. Still a common aetiology (disturbed intracellular calcium handling) may exist, because experimentally the frequency dependency of BVR shows increasing values at the two extremes of the heart rate spectrum. In this clinical study, a direct link between these various risk markers of repolarisation pathophysiology will be assessed.

Study objective

1) To electrophysiologially characterise a selected, large cohort of patients prone to malignant ventricular arrhythmias (ICD recipients)
2) To exactly quantitate outcome by total mortality as well as malignant arrhythmia risk through number of adequate ICD shocks and pacing induced ventricular tachyarrhythmias at electrophysiological testing
3) To reassess the predictive value of all typical noninvasive risk stratification techniques in a specific population deemed at high risk of arrhythmias, with or without a history of myocardial infarction - with particular emphasis to temporal dispersion of repolarisation, including T-wave alternans and BVR
4) To establish a link between phenotype, clinical risk assessment and genotype for selected candidate genes involved in the pathophysiology of ventricular arrhythmias
5) To establish a link between arrhythmia risk and environmental factors such as obesity and diabetes
6) To establish a direct link between various risk markers of repolarisation pathophysiology - T wave alternans, T wave morphology and beat-to-beat variability of repolarisation (BVR)

Study design

The study is designed as an observational study involving genetic testing and noninvasive and invasive diagnostics. No therapeutic intervention or randomisation is performed. No medicinal products, medical devices or drugs are evaluated.

Study burden and risks

1. blood sampling - Possible individual benefits for he individual study participant (benefits): none. - Possible risks fort he individual study participant (risks): not study-related, because blood sample is taken at same time as clinical routine blood sample is taken. In general, occasionally

haematoma, extreme rare infection or injury of nerves).
2. digital resting ECG - Benefits: analysis of heart rhythm, PQ time, QRS complex (e. g. bundle-branch blocks), repolarisation incl. QT time. - Risks: wrong ECG due to reverse polarity (no risk for patient, but for exactness of study data).
3. signal averaging ECG - - Benefits: no specific benefit for individual patient. - Risks: wrong ECG due to reverse polarity (no risk for patient, but for exactness of study data).
4. T-wave-alternans-test - Benefits: 1. additional diagnostic tests may be recommended (e. g. in case of myocardial ischaemia). 2. adjust patients medication - Risks: rare allergic reaction on electrodes. The risk of occurring of a dangerous arrhythmia is the same like activity of daily life, e. g. climbing stairs and lower than clinical routine stress ECG because of much more effort for the patient.
5a. In case of invasive electrophysiological study (new ICD implant patients) - Benefits: 1. improve programming of the ICD device to avoid unnecessary ICD therapy, 2. adjust patients medication - Risks: Sustained and continuous heart rhythm disturbances from the heart chamber such as VT and VF are dangerous and life threatening or potentially life threatening. In contrast, heart rhythm disturbances from the atria are never dangerous, albeit annoying. Any of the induced heart rhythm disturbances can be terminated by the doctor, if necessary immediately. For this purpose there is fast and painless overstimulation as well as electric shocks in short narcosis. There is no risk that an arrhythmia cannot be terminated. The risk of haematoma at the puncture site is about 1%, nerve irritation and serious damage of blood vessels by the catheter is extremely rare. Thrombosis, embolism, damage to the heart with pericardial effusion and tamponade have been described but are extremely rare. All other complications together are estimated to occur with less than 0.5 %, each complication alone is extremely rare. Heart rhythm disturbances may be induced by mechanical manipulation of the heart by the catheter during placement, and usually end spontaneously. An additional risk due to the additional measurements of the EUTrigTreat Study can be ruled out.
5b. In case of non-invasive electrophysiological study (chronic ICD patients) - Benefits: 1. improve programming of the ICD device to avoid unnecessary ICD therapy, 2. adjust patients medication. - Risks: Sustained and continuous heart rhythm disturbances from the heart chamber such as VT and VF are dangerous and life threatening or potentially life threatening. In contrast, heart rhythm disturbances from the atria are never dangerous, albeit annoying. Any of the induced heart rhythm disturbances can be terminated by the doctor, if necessary immediately. For this purpose there is fast and painless overstimulation as well as electric shocks in short narcosis. There is no risk that an arrhythmia cannot be terminated.
6. 24h ECG - Benefits: monitoring for atrial fibrillation, ventricular arrhythmias so important modification of patient medication can be performed (e. g. starting anticoagulation to prevent stroke in patients with new detected atrial fibrillation) - Risks: rare allergic reaction on electrodes, wrong ECG due to reverse polarity or lowbattery (no risk for patient, but for exactness

of study data).

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

- Clinical indication (primary and secondary prevention of SCD) for ICD implantation/ICD exchange or chronically implanted ICD
- Age > 18 years
- Written informed consent
- Negative pregnancy test in women of childbearing potential
- No participation in other clinical trials within one month before and after enrolment into the study;- Cardiac resynchronisation therapy (CRT) devices are excluded from the study (for their special effects in reversal of repolarisation remodeling) for at least 6 months after implantation, thereafter single- and dual-chamber devices are still to be preferred. Single and

dual-chamber device exhange patients recruited to the invasive studies must not have RV pacing > 20% of the time.
- Up to 60% of all patients with coronary artery disease, with or without a history of myocardial infarction (occurrence of STEMI, NSTEMI and highest CKmax will be recorded). This will be monitored by Dr. Eva Müller from the clinical IFS institute in G*ttingen.
- Up to 350 patients with non-ischemic cardiomyopathies (180 dilated cardiomyopathy [DCM], 70 hypertrophic cardiomyopathy [HCM] / hypertrophic obstructive cardiomyopathy [HOCM], 20 arrhythmogenic right ventricular cardiomyopathy [ARVC], channelopathies (30 Brugada syndrome, 20 long QT syndrome, 10 catecholaminergic polymorphic ventricular tachycardia [CPVT]) or idiopathic VT/VF (n=20) with any LV ejection fraction. This will be monitored by Dr. Eva Müller from the clinical IFS institute in G*ttingen.

Exclusion criteria

- Unstable cardiac disease such as decompensated heart failure (NYHA class IV) or acute coronary syndrome or symptomatic arrhythmias
- Percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) surgery less than 3 months ago
- ICDs unable to deliver programmed ventricular stimulation via programmer (in the chronic ICD group)
- Permanent atrial fibrillation if more than 20% of all patients at a given time during the study are enrolled, this condition will be flagged by the study manager Dr. Eva Müller from the clinical IFS institute in G*ttingen which also runs the secure clinical database.

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	30-06-2011
Enrollment:	100
Type:	Actual

Ethics review

Approved WMO Date:	24-12-2010
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	22-07-2011
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	25-04-2012
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

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	NL33059.041.10