Multicenter Automatic Defibrillator Implantation Trial with Subcutaneous Implantable Cardioverter Defibrillator (S-ICD)

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Ethical review	Approved WMO
Status	Will not start
Health condition type	Cardiac arrhythmias
Study type	Interventional

Summary

ID

NL-OMON45670

Source
ToetsingOnline

Brief title
MADIT S-ICD

Condition

- Cardiac arrhythmias
- Glucose metabolism disorders (incl diabetes mellitus)

Synonym
diabetes, Heart attack, reduced heart function

Research involving
Human

Sponsors and support

Primary sponsor: Boston Scientific
Source(s) of monetary or material Support: Boston Scientific

Intervention

Keyword: Post-MI diabetic patients, Subcutaneous Implantable Cardioverter Defibrillator (S-ICD)

Outcome measures

Primary outcome

The primary endpoint is all-cause mortality.

The primary objective is to test the hypothesis that post-MI diabetic patients

with relatively preserved ejection fraction of 36-50% will have a survival

benefit from a subcutaneous implantable cardioverter defibrillator (S-ICD).

Secondary outcome

The secondary objective of the study is to evaluate the effects of the S-ICD on

all-cause mortality in various subgroups and on sudden cardiac death.

Study description

Background summary

Implantable cardioverter defibrillators (ICD) and more recently the subcutaneous ICD (S-ICD) have been shown to be effective in preventing sudden cardiac death in high-risk cardiac patients. The MADIT II trial previously demonstrated a significant reduction in all-cause mortality with an ICD implantation compared to optimal medical therapy (hazard ratio 0.69; 95% CI 0.51 to 0.93; two-sided P=0.016) in high-risk cardiac patients with prior myocardial infarction and severely impaired left ventricular ejection fraction (LVEF * 30%).

However, patients with severely impaired LVEF represent only a minority of

patients at risk for sudden cardiac death (SCD). Other cohorts at high risk for SCD who could potentially benefit from an ICD include patients following a coronary event, especially those with other clinical risk factors, such as age or diabetes mellitus (DM).

Diabetes mellitus has been shown to be associated with increased risk for SCD following a myocardial infarction, independent of the infarct size and LVEF, but is not currently used in the indication for ICD implantation. Data from a substudy of the VALIANT trial, which enrolled 11,000 subjects (3, 095 diabetics), indicate that diabetes was associated with a 37% higher risk of all-cause mortality, independent of LVEF, (adjusted hazard ratio of 1.37, 95% CI 1.25-1.51) compared to non-diabetics. The mortality risk in diabetic patients with LVEF >39% was similar to the mortality risk in non-diabetic patients with LVEF in the 30% range. This observation was further supported by another large clinical study, the Candesartan in Heart Failure * Assessment of Reduction in Mortality and Morbidity (CHARM) program, and by smaller single and multicenter studies. The large multi-center study assessing 3276 post infarction patients from Germany and Finland showed that the incidence of SCD was significantly higher in diabetic versus non-diabetic patients with an LVEF >35% (HR 3.8 (95% CI 2.4-5.8; p<0.001), and the incidence of SCD in diabetic patients with LVEF >35% was similar to the incidence in non-diabetic patients with an LVEF * 35% (4.1% vs 4.9%, respectively).

These data indicate that post-MI diabetic patients have a significant risk for SCD even with a relatively preserved LVEF, and present a population with a significant unmet need that could potentially be addressed with an expanded ICD indication. This may have an important global health impact and clinical implications. Diabetes is currently one of the most prevalent, major health issues in the United States and throughout the world. It is estimated that DM affects nearly 29 million people in the United States alone and claims more than 250,000 lives annually, with higher mortality risk in those older than 60 years of age; furthermore, the prevalence of diabetes is expected to increase dramatically in the US and worldwide in the near future.

Therefore, the MADIT S-ICD study was designed to prospectively test the hypothesis that post-MI diabetic patients with a relatively preserved left ventricular ejection fraction (LVEF 36-50%) will demonstrate a lower rate of all-cause mortality with an S-ICD than in those who do not receive an S-ICD.
The S-ICD was chosen for this study design due to device system characteristics that could potentially provide advantages in diabetic patients who may otherwise be at a higher risk for device-related infections.
The EMBLEM S-ICD System is intended to provide defibrillation therapy for the treatment of life-threatening ventricular tachyarrhythmias in patients who do not have symptomatic bradycardia, incessant ventricular tachycardia, or spontaneous, frequently recurring ventricular tachycardia that is reliably terminated with anti-tachycardia pacing.

Study objective

The primary objective is to test the hypothesis that post-MI diabetic patients with relatively preserved ejection fraction of 36-50% will have a survival benefit from a subcutaneous implantable cardioverter defibrillator (S-ICD).

Study design

Prospective, multicenter, international, randomized, controlled trial.

Intervention

Approximately 2/3 of study participants (about 1200 out of 1800) will receive the S-ICD and 1/3 of study participants (about 600 of 1800) will continue their current medical care without an S-ICD.

Participants assigned to the group receiving an S-ICD will undergo a medical procedure to implant the S-ICD system.

Study burden and risks

If a patient is randomized to receive an S-ICD system, the following risks will apply to his/her participation. If the patient is not randomized to the S-ICD system he/she will not be exposed to these risks.

If a patient takes part in this study, he/she will be subject to risks shared by patients outside of this study who receive the same S-ICD system that is used in this study. There may also be additional risks or side effects which are unknown at this time.

Possible Risks and Side Effects of Taking Part in this Study:
Acceleration/induction of atrial or ventricular arrhythmia
Adverse reaction to induction testing
Allergic/adverse reaction to system or medication
Bleeding
Conductor fracture
Cyst formation
Death
Delayed therapy delivery
Discomfort or prolonged healing of incision
Electrode deformation and/or breakage
Electrode insulation failure
Erosion/extrusion
Failure to deliver therapy
Fever
Hematoma/seroma

Hemothorax
Improper electrode connection to the device
Inability to communicate with the device
Inability to defibrillate or pace
Inappropriate post shock pacing
Inappropriate shock delivery
Infection
Keloid formation
Migration or dislodgement
Muscle/nerve stimulation
Nerve damage
Pneumothorax
Post-shock/post-pace discomfort
Premature battery depletion
Random component failures
Stroke
Subcutaneous emphysema
Surgical revision or replacement of the system
Syncope
Tissue redness, irritation, numbness or necrosis
If any adverse events occur, invasive corrective action and/or S-ICD System modification or removal may be required.
Patients who receive an S-ICD System may develop psychological disorders that include, but are not limited to, the following:
o Depression/anxiety
o Fear of device malfunction
o Fear of shocks
o Phantom shocks

Contacts

Public
Boston Scientific

Lambroekstraat (Green Square) 5D
Diegem 1831
NL
Scientific
Boston Scientific

Lambroekstraat (Green Square) 5D
Diegem 1831
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

* Age * 65 years on date of consent
* Diabetes mellitus treated with oral hypoglycemic agents, non-insulin injectable and/or insulin for the past 3calendar months or longer prior to consent date
* LV ejection fraction (LVEF) of 36-50% documented by imaging (preferably by MRI or echocardiographic methods), within 12 calendar months before consent date and at least 3 calendar months after most recent MI, PCI or CABG
* One or more clinically documented, enzyme-positive myocardial infarctions, more than 3 calendar months prior to consent date*.
o If enzyme information and clinical documentation is not available, there must be a clear evidence of prior silent myocardial infarction identified as either new pathologic Q waves on ECG or imaging documentation of an infarcted area (left ventricular angiography/ nuclear scan/ MRI)*
* MI qualification based on the Universal Definition of MI1
* Qualifying 12-lead ECG within 6 calendar months before consent date and at least 3 calendar months after most recent MI, PCI or CABG
* The qualifying ECG can be sinus rhythm or atrial fibrillation (patients with persistent or permanent atrial fibrillation should have a controlled ventricular response <100 bpm on consent date)
*QRS duration on the qualifying ECG >90 msec
* Passing S-ICD Screening ECG performed per applicable user*s manual on or after the consent date that identifies one or more qualifying S-ICD sensing vectors

Exclusion criteria

* Ejection fraction >50% or <36% within 12 calendar months prior to consent date and at least 3 calendar months after the most recent MI, PCI or CABG
* Existing guideline based indication for an ICD, pacemaker, CRT, or CRT-D therapy

* Existing or previously implanted ICD, CRT, CRT-D, or pacemaker device system
* Active infection at the time of consent
* Contraindication for S-ICD implantation according to the S-ICD pulse generator (PG) User*s Manual
* Hemodialysis and/or peritoneal dialysis at the time of enrollment
* New York Heart Association Class IV in the past 3 calendar months prior to or at the time of consent date
* Coronary artery bypass graft surgery or percutaneous coronary intervention (balloon and/or stent angioplasty) within 3 calendar months prior to the consent date
* Enzyme-positive myocardial infarction or silent myocardial infarction diagnosed within 3 calendar months prior to the consent date
* Unstable angina with need for outpatient treatment or hospitalization (change/addition of anti-anginal medication and/or coronary revascularization), within 3 calendar months prior to the consent date
* Angiographic evidence of coronary disease in a patient that is a candidate for coronary revascularization and is likely to undergo CABG or PCI in the next 3 calendar months
* High risk for arterial embolism (e.g. presence of mobile left ventricular
* thrombus)
* Hemodynamically significant congenital heart disease, aortic valvular heart disease, or amyloid heart disease
* Baseline body mass index > 45 kg/m2
* On a heart transplant list or likely to undergo heart transplant within one calendar year
* Presence of any other disease, other than the subject*s cardiac disease, that in the opinion of the investigator is likely to significantly reduce the patient*s likelihood of survival for the duration of the trial (e.g. cancer, liver failure).
* Unwillingness or inability to cooperate with the protocol
* Resides at such a distance from the enrolling site so travel to follow-up visits would be unusually difficult
* Reversible causes of heart disease (e.g. viral myocarditis or tachycardia induced cardiomyopathy)
* Participation in other clinical trials (observational registries are allowed with approval from the CDC)
* Does not anticipate residing in the vicinity of the enrolling site for the duration of the trial
* Unwillingness to sign the consent for participation

Study design

Design

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

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

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	90
Type:	Anticipated

Medical products/devices used

Generic name:	EMBLEM S-ICD System
Registration:	Yes - CE intended use

Ethics review

Approved WMO

Date:	31-08-2017
Application type:	First submission
Review commission:	METC Amsterdam UMC

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	NL59539.018.16