Early mitral valve repair versus watchful waiting in asymptomatic patients with severe organic mitral regurgitation; a multicenter, randomised trial.

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To compare early mitral valve repair versus watchful waiting.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Cardiac valve disorders
Study type	Interventional

Summary

ID

NL-OMON41282

Source
ToetsingOnline

Brief title
Dutch AMR

Condition

- Cardiac valve disorders

Synonym
leaking heart valve, mitral valve regurgitation

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht
Source(s) of monetary or material Support: ICIN (KNAW)

Intervention

Keyword: Asymptomatic mitral regurgitation, DutchAMR, Early surgery, Watchful waiting

Outcome measures

Primary outcome

Primary outcome will be calculated as *time to first event*. The primary

outcome measures the composite endpoint of:

- cardiovascular mortality;

- congestive heart failure*;

- non-fatal cardiovascular events requiring hospitalization, defined as:

stroke/cerebrovascular accident (CVA), atrial fibrillation* (permanent or

requiring hospitalization) and/or reoperation after elective MV surgery.

* the occurrence of:

- congestive heart failure or atrial fibrillation in the watchful waiting arm

resulting in a class I or

class IIa indication for elective MV surgery; and

- post-operative congestive heart failure or atrial fibrillation or reoperation

within 30 days after elective MV surgery (likely to be related to MV surgery

and not directly life threatening)

will not be considered as an endpoint.

Death is cardiovascular mortality, unless you can prove there is another cause

for death.

Congestive heart failure is the clinical diagnosis of heart failure and/or requiring diuretics medication. According to the World Health Organisation (WHO) definition, we explain stroke by "rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting 24 hours or longer or leading to death, with no apparent cause other than of vascular origin". Permanent atrial fibrillation (AF) is defined as AF present for >24 hours.

Secondary outcome

- 'Key secondary outcome' inlcudes the separate components of the composite primary endpoint:
cardiovascular mortality, congestive heart failure and hospitalization for nonfatal cardiovascular events. divided in the endpoints:
stroke/cerebrovascular accident (CVA), AF (permanent or requiring hospitalization) and reoperation after elective MV repair.
A detailed description of the components *cardiovascular mortality*, *congestive heart failure* and hospitalization for nonfatal cardiovascular events* is given in the definition of the primary outcome.

- 'Explorative secondary outcome' measures the outcome of the separate components:
incidence of all-cause mortality, incidence of myocardial infarction, incidence of pacemaker implantation, incidence of transient ischemic attack (TIA), incidence of pulmonary embolism, total direct and indirect costs, cost-effectiveness, health-related quality of life, echocardiographic and

cardiac magnetic resonance (CMR) parameters, exercise test parameters, paroxysmal atrial fibrillation (AF present for <24 hours) and BNP levels. Myocardial infarction is defined as angina pectoris together with a rise in biomarkers (troponin) and ECG changes. For the definition of TIA symptoms need to be determined by a neurologist and established on imaging.

Additionally, complication rates in the surgery group (e.g. re-operation for bleeding, pneumonia, residual or recurrent mitral valve regurgitation) and rate of surgery in the watchful waiting group will be determined.

Study description

Background summary

Severe asymptomatic organic mitral valve (MV) regurgitation with preserved left ventricular (LV) function is a challenging clinical entity as data on the recommended treatment strategy for these patients are scarce and conflicting, which is reflected in current guidelines. European guidelines advocate a more conservative strategy i.e. watchful waiting, with yearly echocardiography, whilst American guidelines are more in favour of early surgery to reconstruct the MV, i.e. MV repair (in contrast to mitral valve replacement) in order to prevent future LV dysfunction and complaints.
A number of non-randomised trials show a favourable outcome of early surgery. At the other hand, non-randomised trials describe also that a conservative strategy (i.e. watchful waiting) can be safely accomplished and has proven to be eventually associated with good perioperative and postoperative outcome when careful follow-up is being carried out.
Non-randomised trials inherently have a number of drawbacks; therefore a randomised trial comparing the two treatment strategies is highly needed.

Study objective

To compare early mitral valve repair versus watchful waiting.

Study design

Multicenter prospective randomised trial.

Patients who provide informed consent will be randomly assigned to either: 1) watchful waiting; 2) early MV repair.
At baseline, like in routine clinical assessment, an echocardiography, holter registration, exercise test and routine laboratory testing (e.g. BNP) will be performed. Furthermore patients will undergo CMR and fill in a QOL questionnaire. Echocardiographic and CMR core-lab reading is planned to assess (1) severity of MR and (2) left ventricular function.
Follow-up in both groups will be 5 years at least and according to clinical practice, as recommended by the ESC guidelines. Apart from clinical practice by the own treating cardiologist (standard care), at 1 year (+/- 3 weeks), 3 years (+/- 3 weeks) and 5 years (+/- 3 weeks) study related visits will take place in one of the study centers, including an echocardiography, holter registration exercise test, routine laboratory testing (BNP) and QOL forms. After 5 years (+/- 3 weeks) echocardiography and CMR are repeated, including core-lab reading.
Every 6 months (+/- 3 weeks) a telephone consultation with the patient will take place. Furthermore, a QOL form is sent to the patient 5x during follow-up. Additional patient*s information from referring centres will be collected by the researcher if necessary.

Intervention

Intervention will be early MV repair compared to a watchful waiting strategy.

Study burden and risks

All patients will be treated according to current ESC guidelines. As a result, the increased peri-procedural risk of surgery will be weighed against known outcome. Participation in this study implicates that patients will be randomised to either early prophylactic surgery (early MV repair) or will be treated conservatively (watchful waiting) and if necessary undergo facilitated surgery. Most important, patients that are allocated to the surgery group are inherently exposed to the surgical risk of MV repair (operative 30-day mortality ranging from 0 to 2.8%). The heart team will exclude patients that have higher expected surgical risks in advance, so before randomisation. Potentially, the conservative group is exposed to deterioration of the left ventricular function possibly related to medical treatment and/or hospitalization and the possibility of a less repairable valve and/or higher risk of surgery, while waiting to fulfil the guidelines criteria for surgery. At present, no data are available in literature that indicate these risks.
Follow-up of the patient cohort is similar to routine daily practice. Next to routine clinical practice, extra follow-up visits are planned in view of the trial at the study centre at baseline, 12 months (+/- 3 weeks), 36 months (+/- 3 weeks) and 60 months (+/- 3 weeks), including echocardiography,

holter-monitoring, exercise testing, core lab reading and completing a questionnaires including quality of life form (QOL). Rare but serious complications in exercise testing are reported in one out of ten thousand patients, which can be easily stratified in advance based on resting ECG, medical history and risk factors. Additional diagnostic testing includes blood examination (BNP) which requires a venous puncture and a CMR with contrast at baseline and at 5 years (+/- 3 weeks). CMR provides no other side effects, although it is contra-indicated in patients with metallic implants and claustrophobic or pregnant patients. Metallic implants, claustrophobia, pregnancy and moderate to severe kidney disease are no exclusion criteria for study participation.
Gadolinium administration can lead to mild, mostly self-limiting, reactions in <1%. Nevertheless, in patients with moderate to severe kidney disease (estimated glomerular filtration rate (eGFR) less than 30 mL/min) contrast administration has been rarely associated with the syndrome of nephrogenic systemic fibrosis. It is recommended that gadolinium-based imaging be avoided in such patients. Therefore we will exclude patients with moderate to severe kidney disease from study participation.
In case of venous puncture there will be a very small risk of excessive bleeding, fainting, dizziness, hematoma and infection.
Regardless low risks associated with exercise testing, CMR (including contrast administration) and venous puncture, no extra burden, risk or benefit is associated with the study participations compared to non-participating patients. It can be concluded that the risk assessment for the patients included in the Dutch AMR trial can be considered to be a moderate risk.

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

- 18-75 years.
- Asymptomatic patients. *Asymptomatic* is defined as absence of subjective limitations of exercise capacity or complaints expressed by the patient and confirmed by the treating cardiologist.
- Severe organic mitral valve regurgitation. *Severe organic mitral valve regurgitation* is defined as non-ischemic mitral valve regurgitation with an organic cause (intrinsic valve lesion) as determined by echocardiographic core-lab reading based on the criteria for definition of severe mitral regurgitation as issued by the ESC guidelines. For practical reasons, referring cardiologists can use a ESC guidelines based index that was validated in our core-lab (Jansen et al, Practical echocardiographic semi-quantitative scoring system to determine severity of mitral regurgitation. Abstract presentation at ESC EUROECHO Congress 2011 and annual spring congress 2012 Netherlands Society of Cardiology).
- Preserved left ventricular function, *Preserved left ventricular function* is defined as left ventricular ejection fraction >60% and left ventricular end-systolic dimension <45 mm.
- The likelihood of MV repair should be more than 90% determined by the local heart team with a cardiologist and cardiothoracic surgeon.

Exclusion criteria

- Pulmonary hypertension (>50 mmHg at rest).
- Atrial fibrillation, either on 12-lead ECG or holter-monitoring.
- Physical inability as determined by the heart team to undergo surgery.
- Other life-threatening morbidity.
- Higher expected surgical risks in advanve, according to the dedicated heart team.
- Patients with moderate to severe kidney disease (estimated glomerular filtration rate (eGFR) less than 30 mL/min).
- Flail leaflet together with a left ventricular end systolic diameter (LVESD) >=40 mm

Study design

Design

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

Primary purpose: Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	13-05-2013
Enrollment:	250
Type:	Actual

Ethics review

Approved WMO Date:	22-01-2013
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	24-09-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	04-03-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	04-09-2015
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	NL39851.041.12