A Randomised Controlled Trial of Early valve replacement in severe ASYmptomatic Aortic Stenosis

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

Summary

ID

NL-OMON57134

Source
ToetsingOnline

Brief title
EASY-AS

Condition

- Cardiac valve disorders

Synonym
Aortic Stenosis, narrowing of the aortic valve

Research involving
Human

Sponsors and support

Primary sponsor: University of Leicester
Source(s) of monetary or material Support: British Heart Foundation (UK);Australian Government Medical Research Future Fund (Australia) and Heart Foundation (New Zealand)

Intervention

Keyword: * Asymptomatic Aortic Stenosis, * clinical outcomes and cost-effectiveness, * early AVR/TAVI, * Strategy of expectant management

Outcome measures

Primary outcome

A combined measure of CV death and HHF, measured in days from randomisation until end of trial (minimum 3 years).

The primary analysis will be undertaken when 663 events have accrued, which is estimated to be after a median of 5 years follow-up assuming 2844 patients are recruited over 4 years.

Secondary outcome

• Disability-free survival (WHODAS)

• Number of days alive and out of hospital

• Number of major adverse events including: death (cardiovascular, including sudden cardiac death, and non-cardiovascular), hospitalisation for heart failure, myocardial infarction, stroke

• Additional outcomes of special interest: infective endocarditis and major bleeding, resuscitated cardiac arrest, hospitalisation with new onset atrial fibrillation, syncope, revascularization (CABG/PCI), cardiac device implantation (permanent pacemaker or implantable cardioverter defibrillator)

• Quality of life measured by the EQ-5D-5L questionnaire

Study description

Background summary

AS affects approximately 5% of individuals >65 years old, with ~3% of people >75 years having moderate to severe disease. The prevalence of AS is rising rapidly due to an aging population and is projected to double in the next two decades. Increasingly, clinicians face the dilemma of how to best manage this growing population of mainly elderly patients; many of whom are asymptomatic but have been identified as having severe AS, often as an incidental finding. Reduced aortic valve opening progresses over decades without any apparent symptoms because the heart compensates for the AS. Ultimately, compensatory mechanisms fail resulting in angina, syncope or heart failure. If these symptomatic patients with severe AS remain untreated, they have a dire prognosis. In this situation the only effective treatment is AVR, either surgically or using TAVI. Conversely, conventional teaching and clinical practice in cardiology has been that, in the absence of symptoms, the prognosis is usually excellent and, except in a few very specific circumstances, conservative management and regular review (expectant management) is recommended. This advice is reflected in current international guidelines but is based largely on historical precedent. Approximately 50% of patients with severe AS are asymptomatic at the time of diagnosis and the management of this growing population is among the most contentious issues in modern cardiology. Existing data have evident limitations, and it is impossible to be certain whether early AVR improves prognosis or results in worse outcomes. However, there is an increasing trend for clinicians to refer patients for early AVR(28). There is a widespread consensus that randomized trials comparing conventional expectant management to early AVR are required. Prior to EASY-AS commencing there were no randomized controlled trials to address the relative benefits of early AVR versus expectant management in patients with severe asymptomatic AS.

Study objective

The primary hypothesis is that early AVR or TAVI in asymptomatic patients with severe AS will result in a reduction in the composite primary outcome of cardiovascular (CV) death and hospitalisation for heart failure (HHF) when compared to the conventional approach of expectant management.
The key secondary hypotheses are that early intervention results in:
• Improved disability free survival
• Improved quality of life
• Reduced total mortality, CV mortality and HHF
• Increased days alive and out of hospital
• A more cost-effective strategy than expectant management

Study design

This is a major pragmatic multi-centre prospective parallel group open randomised controlled study. The study will be conducted in the UK, Australia and New Zealand, funding is being sought in several countries to expand

recruitment internationally. Each country will be responsible for its own sponsorship of the study. There will be an agreed master protocol to be approved by each countries respective ethics and regulatory bodies.
The proposed study is in two phases: the vanguard and main phase. Therefore, the study will run an internal pilot to prove recruitment of the relevant number of participants during the initial two years.

Agreed Stop-go criteria:
The funder in the UK (BHF) has stipulated that a vanguard phase is undertaken to prove that randomisation is feasible and 200 patients should be recruited during the first 16 months of recruitment. The following criteria have been agreed with the BHF in the UK:
Go: >= 90% of target (180) recruited by 21 months
Discuss options with BHF: 60-90% of target (120-179)
Stop: < 60% of target (<120).
A second criterion in the BHF award was that additional funding for the study should be obtained in another country outside the UK and this was achieved in 2019 with a Medical Research Future Fund (MRFF) award in Australia.

Aims of the study
The over-arching aim of the study is to determine whether early AVR results in better clinical outcomes and cost-effectiveness than a strategy of expectant management in asymptomatic patients with severe AS.

Intervention

The study will compare two clinical strategies: either early AVR (surgical or TAVI) or initial expectant management (with prompt AVR recommended if symptoms of AS develop).

Study burden and risks

E2. What is the burden of the research (and any prior inspection) for the test subjects? - follow-up:
The total duration of the study for the individual subject is 24 months for the Netherlands, 60 months for the other countries.

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

1. Age >18 years
2. Patient has severe asymptomatic AS, in line with current international guidelines, defined as either:
a) Peak velocity >=4m/s OR mean pressure gradient >=40mmHg WITH aortic valve area <=1.0cm2 OR <=0.6cm2/m2 body surface area
OR
b) Peak velocity >=4m/s OR mean pressure gradient >=40mmHg WITH aortic valve area >1.0 - <=1.2cm2 OR >0.6 - <=0.7cm2/m2 body surface area AND high sex specific calcium score*
OR
c) Peak Velocity >=3.5m/s - 3.9m/s AND mean pressure gradient <40 mmHg WITH aortic valve area <=1.0cm2 OR <=0.6cm2/m2 body surface area AND high sex specific calcium score*
*Sex specific high calcium scores (Agatston units): >1200 females; >2000 males
3. The responsible clinician feels that either ongoing surveillance or early AVR are appropriate.
4. Regarded by the treating cardiologist to be suitable for AVR (surgical or TAVI) with an acceptable risk
5. Willing to provide informed consent and be randomised to early AVR or expectant management

6. An ability to understand one of the written languages that the study has provided written and visual materials in, or the availability of a translator to explain the study documentation

Exclusion criteria

1. Symptoms related to AS
2. Additional severe valvular heart disease
3. Other cardiac surgery planned pre-randomisation (eg CABG)
4. Left ventricular systolic dysfunction (LVEF <50%)
5. Pregnancy
6. Co-morbid condition that, in the opinion of the treating cardiologist, limits life expectancy to <2 years
7. Patient has previously undergone AVR or TAVI with restenosis

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:	Pending
Start date (anticipated):	01-06-2024
Enrollment:	30
Type:	Anticipated

Medical products/devices used

Registration:	No

Ethics review

Approved WMO Date:	26-11-2024
Application type:	First submission
Review commission:	RTPO, Regionale Toetsingscie Patientgebonden Onderzoek (Leeuwarden)

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	NL86593.099.24