Rationale and design of the early valve replacement in severe asymptomatic aortic stenosis trial

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ABSTRACT

Background Aortic valve replacement in asymptomatic severe aortic stenosis is controversial. The Early valve replacement in severe ASYmptomatic Aortic Stenosis (EASY-AS) trial aims to determine whether early aortic valve replacement improves clinical outcomes, quality of life and cost-effectiveness compared to a guideline recommended strategy of 'watchful waiting'.

Methods In a pragmatic international, open parallel group randomized controlled trial (NCT04204915), 2844 patients with severe aortic stenosis will be randomized 1:1 to either a strategy of early (surgical or transcatheter) aortic valve replacement or aortic valve replacement only if symptoms or impaired left ventricular function develop, or other cardiac surgery becomes nessessary. Exclusion criteria include other severe valvular disease, planned cardiac surgery, ejection fraction <50%, previous aortic valve replacement or life expectancy <2 years. The primary outcome is a composite of cardiovascular mortality or heart failure hospitalization. The primary analysis will be undertaken when 663 primary events have accrued, providing 90% power to detect a reduction in the primary endpoint from 27.7% to 21.6% (hazard ratio 0.75). Secondary endpoints include disability-free survival, days alive and out of hospital, major adverse cardiovascular events and quality of life.

Results Recruitment commenced in March 2020 and is open in the UK, Australia, New Zealand, and Serbia. Feasibility requirements were met in July 2022, and the main phase opened in October 2022, with additional international centers in set-up.

Conclusions The EASY-AS trial will establish whether a strategy of early aortic valve replacement in asymptomatic patients with severe aortic stenosis reduces cardiovascular mortality or heart failure hospitalization and improves other important outcomes. (Am Heart J 2024;275:119–127.)

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Background

Aortic stenosis is the commonest cause of severe valvular heart disease, with an estimated global prevalence of calcific aortic valve disease of approximately 13 million cases in 2017, resulting in 103,000 annual deaths.[1] The prevalence of aortic stenosis increases markedly with age and it is estimated that 2% to 3% of the population >75 years in high income countries have moderate or severe stenosis.[2] Thus, the number of individuals living with moderate to severe aortic stenosis, and the impact of this on healthcare services, is growing rapidly.[1]

Aortic stenosis progresses over decades without apparent symptoms due to compensatory mechanisms but ultimately may result in dyspnea, angina, syncope, heart failure, and occasionally sudden death without preceding symptoms. Once symptoms develop, patients have a dire prognosis without aortic valve replacement.[3,4] Conventional teaching and current guidelines recommend a policy of watchful waiting, with prompt aortic valve replacement if symptoms develop.[5,6] Current class I indications for aortic valve replacement in asymptomatic patients include those undergoing cardiac surgery for other reasons or with a left ventricular ejection fraction <50%.[5,6] While a conservative approach in asymptomatic patients with severe aortic stenosis may remain appropriate, it is being increasingly questioned.[7,8] Traditional recommendations are based on historical data in the pre-transcatheter aortic valve implantation era and when peri operative risks after cardiac surgery were much higher than observed in contemporary practice. In addition, life expectancy was generally lower. Conversely, contemporary patients with severe aortic stenosis are older with a higher burden of comorbidities. This may make them less able to tolerate the hemodynamic consequences, but also increases the risk associated with aortic valve replacement (Table 1).[8-10]

The wisdom of 'watchful waiting' has been challenged by a greater understanding of the pathophysiology of aortic stenosis and the impact that prolonged pressure overload has on the myocardium. The development of replacement myocardial fibrosis, which is present in up to 50% of asymptomatic patients with aortic stenosis[11] progresses rapidly, is irreversible and may remain an adverse prognostic marker even after aortic valve replacement.[11,12] In addition, registry data have reported benefits of early valve replacement over conservative management of patients with severe asymptomatic aortic stenosis[13,14] but these observational non-randomized data have limitations and are prone to bias.

Two randomized controlled trials have recently addressed the timing of valve replacement. The randomized comparison of early surgery versus conventional treatment in very severe aortic stenosis (RECOVERY) trial[15] reported a reduction in peri-operative and cardiovascular mortality in the early aortic valve replacement group. Similarly, the aortic valve replacement versus conservative treatment in asymptomatic severe aortic stenosis (AVATAR) trial[16] showed a reduction in all-cause mortality, acute myocardial infarction, stroke and heart failure hospitalization at 3 years in the early aortic valve replacement group. Whilst these results suggest possible benefits of early intervention, both trials were small including a combined total of only 302 highly selected and generally younger patients with little comorbidity that are not typical of the general population of patients with aortic stenosis.[9,17]

A large-scale pragmatic randomized trial that is representative of the broad contemporary population of patients with aortic stenosis is required to provide robust evidence before implementing a change in clinical practice. The Early valve replacement in severe ASYmptomatic Aortic Stenosis (EASY-AS) trial (NCT04204915) aims to provide clear evidence as to whether a strategy of early aortic valve replacement reduces clinical events, improves quality of life and is cost effective compared to a watchful waiting strategy.

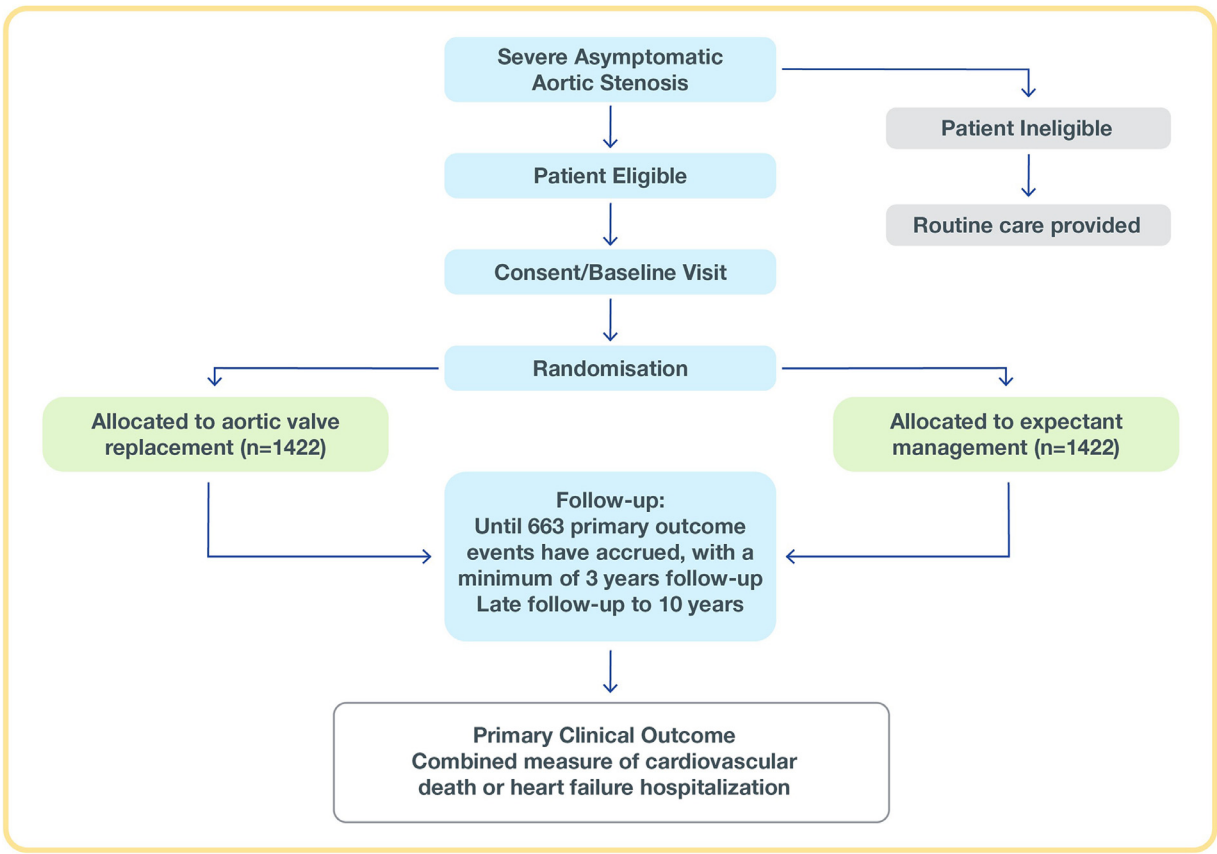
Methods

Design: The EASY-AS trial is an international, pragmatic, multicenter, prospective, parallel group, open randomized controlled strategy trial. Patients are randomly

Table 1. Benefits and risks of early valve replacement in asymptomatic severe aortic stenosis Modified from reference (8)

Favours early aortic valve replacement	Against early aortic valve replacement
• May prevent irreversible myocardial damage secondary to excessive afterload, which may improve long-term outcomes. • Potentially reduces the risk of sudden death without preceding symptoms. • Reduces the risk of other complications, which can occur if new onset symptoms are reported or identified too late during conservative care. • Asymptomatic patients have lower operative risk than symptomatic patients.	• The risk of death with conservative treatment is low in asymptomatic patients. • Close follow-up can identify patients who develop indications for aortic valve replacement before irreversible complications arise. • Avoids or delays the risks of peri-procedural morbidity and mortality. • Avoids or delays the long-term complications of aortic valve replacement such as anticoagulation, endocarditis, need for reoperation, thrombosis etc.

Figure 1. Overview of EASY-AS trial.



assigned 1:1 to a strategy of early aortic valve replacement or watchful waiting. An overview of the trial is shown in Figure 1 and a schedule of study procedures in the supplementary section appendix 1.

Setting: The trial is currently recruiting in 90 secondary and tertiary care cardiology centers in the UK, Australia, New Zealand and Serbia. It is expanding to recruit in additional sites in these countries, as well as opening in several other countries.

Patient Population: Patients with severe aortic stenosis (Table 2) who do not have symptoms attributable to their valve disease. Symptoms will be assessed by the responsible clinical team, according to local practice. Exclusions have been kept to a minimum (Table 2). Eligibility criteria number 2 has also been expressed in visual form (Figure 2).

Funding: The EASY-AS trial is supported by grants from the British Heart Foundation (CS/18/7/33714), the Australian Government Medical Research Future Fund (Ref: 1170844) and the New Zealand Heart Foundation (Grant No. 1823) and is supported by the National Institute for Health Research and Social Care Clinical Research Network in the UK.

The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents.

Screening, baseline assesment, and data collection

Patients attending cardiology clinics and echocardiography databases are screened for eligibility, which is confirmed by a clinician and based on an echocardiogram within the previous 6 months. Exercise testing is encouraged where feasible and particularly if there is any uncertainty regarding symptom status.

Written informed consent or electronic consent (using the Research Electronic Data Capture consent module: https://www.project-redcap.org/) is obtained. Consent to obtain trial related information from relatives or friends is also recorded, in case patients cannot be contacted or lose capacity during follow-up.

Baseline assessment: Age, sex, ethnicity, cardiovascular risk factors, comorbidities, functional status, operative risk, height, weight, blood pressure, New York Heart Association functional classification are collected, and a 12-lead electrocardiogram is performed. Echocardiographic measures of aortic stenosis severity, ejection frac-

Table 2.

Inclusion Criteria*

1. Age >18 years
2. Patient has severe asymptomatic aortic stenosis in line with current international guidelines, defined as:
   a) Peak velocity ≥4 m/s **OR** mean pressure gradient ≥40 mmHg **WITH** aortic valve area ≤1.0 cm^2 **OR** ≤0.6 cm^2/m^2 body surface area
   OR
   b) Peak velocity ≥4 m/s **OR** mean pressure gradient ≥40 mmHg **WITH** aortic valve area ≤1.2 cm^2 **OR** ≤0.7 cm^2/m^2 body surface area **AND** high sex-specific calcium score†
   OR
   c) Peak velocity ≥3.5 to 3.9 m/s **AND** mean pressure gradient <40 mmHg **WITH** aortic valve area ≤1.0 cm^2 **OR** ≤0.6 cm^2/m^2 body surface area **AND** high sex-specific calcium score†
3. The responsible clinician feels that *either* ongoing surveillance *or* early aortic valve replacement are appropriate.
4. Regarded by the treating cardiologist to be suitable for aortic valve replacement (surgical or transcatheter aortic valve implantation) with an acceptable risk.
5. Willing to provide informed consent and be randomized to early aortic valve replacement 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*

7. Symptoms related to aortic stenosis.
8. Additional severe valvular heart disease.
9. Other cardiac surgery planned prior to randomization.
10. Left ventricular systolic dysfunction (LVEF <50%).
11. Pregnancy.
12. Co-morbid condition that, in the opinion of the treating cardiologist, limits life expectancy to <2 years.
13. Previous aortic valve replacement or transcatheter aortic valve implantation with restenosis.

*In mid-2022, the eligibility criteria were updated by amendment. Options b) and c) were added to eligibility criterion number 2 to reflect changes in clinical practice and contemporary guidelines. Exclusion criterion number 13 was added for clarity regarding the patient population, where previously implied.
†Sex-specific high calcium scores (Agatston units): >1200 females; >2000 males.

Figure 2. Inclusion criteria number 2 expressed in tabular form.

Criteria	Hemodynamic Parameter				Valve Area Parameter				Calcium Score
A, B or C	Peak Jet Velocity (m/s)		Mean Pressure Gradient (mmHg)		Aortic Valve Area (cm^2)		Indexed Aortic Valve Area (cm^2/m^2)		High sex-specific score
A	≥ 4.0	or	≥ 40	and	≤ 1.0	or	≤ 0.6		
B	≥ 4.0	or	≥ 40	and	> 1.0 - ≤ 1.2	or	> 0.6 - ≤ 0.7	and	Required*
C	≥ 3.5 – 3.9	and	< 40	and	≤ 1.0	or	≤ 0.6	and	Required*

tion, and left ventricular wall thickness are recorded, along with diastolic function indices and pulmonary artery pressure, if available.

Additional to routine clinical data, the Edmonton Frail Scale, World Health Organization Disability Assessment Schedule 2.0 (WHODAS), European Quality of Life-5 Dimensions scale (EQ-5D-5L) and health economic questionnaires are completed.

Randomization: Participants are enrolled using the validated web-based, computer-generated randomization system, Sealed Envelope, https://www.sealedenvelope.com/access/, which ensures allocation concealment prior to randomization. Randomization incorporates minimization[18] for age (<75, ≥75), sex, peak aortic velocity (≥3.5 to <4.5, ≥4.5 to ≤6.0), and known ischemic heart disease and is stratified by country.

Intervention (group A): Early aortic valve replacement. The aim is to perform aortic valve replacement within 3 months of randomization. The method of valve replacement (surgical aortic valve replacement or transcatheter aortic valve implantation), choice of valve prosthesis (mechanical or bioprosthetic) and the need for concomitant surgery (e.g., aortic root replacement or bypass grafting) will be at the discretion of the clinical care team in consultation with the patient. Participants will undergo further investigations, such as invasive coronary angiography or computerized tomography, as per local clinical practice.

Comparator (group B): Expectant management. Participants in this arm will continue under routine clinical follow up and be referred for valve intervention if symptoms develop or when deemed appropriate by the responsible clinician as per the current clinical guidelines. Echocardiography is recommended at 6 monthly intervals.

Participants allocated to group A who do not receive valve replacement as planned and those randomized to group B who undergo aortic valve replacement whilst remaining asymptomatic will be regarded as having crossed over. However, participants in group B who undergo aortic valve replacement after developing symptoms or any other class I indication will not be considered as crossovers as this is the expected management pathway.

Follow-up: Participants will be reviewed for clinical outcomes at regular time points and to obtain safety data. The initial 1,134 participants will also complete questionnaires, ensuring an adequate sample size to assess disability free survival (see below). Long-term clinical outcomes (Table 3) for up to 10 years post randomization will be assessed by national electronic health records, where available, and used as the primary source as previously validated.[19] In Australia, during the active follow-up phase (up to 3 years), events will be self-reported or obtained through medical record review and will be adjudicated by two independent investigators, blinded to treatment allocation using standard criteria.[20] Where the primary reviewers have discordant outcomes, a third independent clinician will review. Following the active follow-up phase, administrative data will be used as a source of follow-up data in Australia, as in other countries.

Outcomes: The primary endpoint is a composite of cardiovascular death or heart failure hospitalization, measured in days from randomization until end of trial (minimum 3 years). Key secondary endpoints include disability-free survival (defined as survival and freedom from persistent or permanent disability, classified as a score >25% persisting for at least 6 months on repeat testing, using the WHODAS), quality of life, cost-effectiveness, individual components of the primary endpoint and other clinical outcomes of special interest (Table 3). Definitions of end points are provided in the supplementary material appendix 2.

Due to the nature of the intervention, blinding of the participants and the study team is not possible. Use of objective and clearly defined outcomes ascertained using health system administrative data in the UK and New Zealand and independent end point adjudication in Australia will minimize bias.

Coenrolment in other trials: Coenrolment with the EVOLVED trial (Early Valve Replacement Guided by Biomarkers of Left Ventricular Decompensation in Asymptomatic Patients with Severe Aortic Stenosis, NCT03094143) was encouraged at participating sites. Eligible EVOLVED participants essentially represent a subgroup of participants with evidence of myocardial fibrosis on cardiac magnetic resonance and were randomized using the EASY-AS trial processes, with allocation accepted by the EVOLVED trial. The EVOLVED trial completed recruitment in October 2022, having enrolled 273 patients, of which 54 were coenrolled in the EASY-AS trial.

Optional Substudies: These include a biomarker substudy where plasma taken at the baseline visit is stored for future analyses to aid better risk stratification, subject to additional funding; and a qualitative experience substudy at selected sites where patient attitudes to recruitment, randomization and acceptability of the interventions will be explored to inform future policy on aortic valve replacement.

Statistical considerations

Sample Size: We estimate that the three-year event rate for cardiovascular death or heart failure hospitalization will be 17.7% for those managed conservatively.[14] Assuming a 6.29% event rate per year, the proportion of individuals free from cardiovascular death or heart failure hospitalization at 3 years follow-up is estimated as 82.3%. As the effect of early aortic valve replacement on the primary outcome is expected to be non-linear, the power calculation is based on analysis with restricted mean sur-

Table 3. EASY-AS trial outcomes

Primary outcome	A combined measure of cardiovascular death or heart failure hospitalization, measured in days from randomization (time to first event) until end of trial (minimum 3 years).
Secondary outcomes	1. Death (cardiovascular death, including sudden cardiac death, and noncardiovascular death). 2. Heart failure hospitalization. 3. Disability-free survival (12-item WHODAS 2.0 questionnaire). 4. Number of days alive and out of hospital. 5. Myocardial infarction. 6. Stroke. 7. Quality of life measured by the EQ-5D-5L questionnaire. 8. Health care resource use and cost effectiveness.
Outcomes of special interest	Infective endocarditis, major bleeding, resuscitated cardiac arrest, hospitalization with new onset atrial fibrillation, syncope, revascularization (coronary artery bypass surgery or percutaneous coronary intervention), cardiac device implantation (permanent pacemaker or implantable cardioverter defibrillator)

vival time with the sample size based on the number of events accruing.[21,22] To increase mean survival time by 2 months in group A v B, a sample size of 2,700 (accruing 663 primary events) will provide 90% power (2 sided α=0.05) to detect an absolute risk reduction of 4.4% to 13.3% (event free survival rate 86.7% vs 82.3%). This equates to a hazard ratio of 0.75, in the primary endpoint at a median of five years, assuming recruitment over 4 years and allowing for a 5% cross-over rate. Additionally, allowing for a further 5% loss because of noncardiovascular deaths, the final estimated sample size is 2,844. For the key secondary outcome of disability-free survival, to detect an increase from 65% at median three years in participants managed expectantly to 75% in participants who undergo early aortic valve replacement requires 1134 patients to achieve >90% power (two sided α=0.05).

Statistical Analyses: Descriptive characteristics at baseline will be presented by treatment arm. Prespecified analyses will include the primary and secondary outcomes assessed by sex and age ≥75 or <75 years. All analyses will be undertaken using the principles of modified intention-to-treat, using a complete case approach. Where substantial levels of missing data occur, analyses using imputation for missing outcome measures will be undertaken as a sensitivity analysis.

The primary outcome will be measured from randomization until event or last known event-free observation during the follow-up period. A point estimate of the difference in the restricted mean survival time, 95% confidence interval and 2-sided *P*-value will be presented. A *P*-value < .05 will be regarded as statistically significant. The primary analysis will be adjusted for the minimization factors used at randomization. Secondary outcomes will be analysed using appropriate methodology; time to event using restricted mean survival analysis, binary outcomes using logistic regression, continuous outcomes using linear regression or where not normally distributed using appropriate non-parametric methods. Cost-effectiveness analyses will be undertaken using standard methodologies.[23]

Quality of life and cost-effectiveness analyses

For quality of life a health profile will be generated by visit and by treatment. Summary statistics will be derived for the five EQ-5D dimensions and the EQ visual analogue scale score.

A cost-effectiveness analysis will be primarily based on a health economics questionnaire completed by participants at baseline, 6, 12, 24, and 36 months. Additional information may be derived from administrative datasets. Due to differences in healthcare systems, separate analyses will be undertaken in each participating country. Analyses will compare mean differences in costs and health outcomes between the two study arms.

Trial oversight and governance

The EASY-AS trial is sponsored by the University of Leicester in the UK and Serbia, the University of Western Australia in Australia, and Auckland City Hospital in New Zealand.

Ethical Considerations: The trial was approved in each country and will be conducted in accordance with the principles of Good Clinical Practice. The trial received a favorable ethical opinion in the UK on 27/11/2019 (19/WA/0325), in Australia on 17/03/2020 (RGS3776), in New Zealand on the 26/06/2020 (New Zealand Health and Disability Ethics Committee (20/CEN/31) and in Serbia on 22/12/2022 (2265-1/3) and 28/12/2022 (1177/11). Appropriate ethical approval status will be obtained from other countries which join the trial.

Trial coordination: The trial is coordinated by the University of Leicester Clinical Trials Unit and a trial management group which meets monthly to discuss recruitment, issues arising and possible amendments for consideration by the Trial Steering Committee. The Data Safety and Monitoring Committee also meets 6-monthly. A list of members of the oversight committees is provided in the supplementary material appendix 3.

Patient and Public Involvement and Engagement: The trial was developed with extensive input from members of patient and public involvement and engagement groups in the UK and Australia, including the British

Heart Foundation Patient Advisory Group. Recommendations were implemented into the final trial design such as the inclusion of patient reported outcome measures, as well as the development of participant facing documentation. There is ongoing input to trial oversight, with three patient representatives on the Trial Steering Committee.

Trial progress: The first participant was randomized on 10th March 2020 shortly before all non-COVID-19 research was suspended temporarily. The trial has since successfully completed its vanguard phase (recruitment of 180 participants in the UK) and is now recruiting in 4 countries as part of the main phase. As of the date of submission, there have been 700 participants randomized into the trial.

Discussion

The appropriate timing of aortic valve replacement in patients with severe, asymptomatic aortic stenosis remains controversial. The conventional guideline recommended approach of watchful waiting is being increasingly questioned. Until recently, there has been an absence of randomized data. However, two recent trials, RECOVERY[15] and AVATAR,[16] have shown a benefit of early aortic valve replacement compared to watchful waiting. Both trials were small, randomizing 145 participants with 12 primary outcome events and 157 participants with 39 primary events respectively, and therefore do not provide robust evidence to change clinical practice and guidelines.[24] Additionally, both trials recruited highly selected populations. The RECOVERY trial randomized patients with very severe aortic stenosis with an upper age limit of 80 years and prior cardiac surgery being an exclusion. The average age of participants was 64 years with 64% of patients having a bicuspid valve.[15] Participants randomized into AVATAR required a negative mandatory exercise test, and initially invasive coronary angiography, which is not routinely undertaken in asymptomatic patients. Many common comorbidities were trial exclusions, including coronary artery disease and chronic obstructive pulmonary disease. Patients with a high 30-day perioperative risk (≥8%) were also excluded and these factors resulted in a relatively young average age of 67 years.[16] Larger, more representative trials are therefore required.

The EASY-AS trial aims to be inclusive and representative. There is no additional testing required above standard care and the exclusion criteria have been kept to a minimum. Recruiting clinicians must be comfortable that equipoise exists for early aortic valve replacement or watchful waiting and patients have to be willing to be randomized to either arm.

To be eligible, patients cannot have symptoms related to aortic stenosis, other severe valvular heart disease, or other cardiac surgery planned at the time of randomization. Exercise testing has not been mandated to assess symptoms, although this is encouraged. This liberal approach reflects the fact that exercise test symptoms are non-specific, occur in many individuals without cardiac disease and do not predict spontaneous symptoms in the short-term.[25] Additionally, there are no randomized data demonstrating the benefits of exercise testing in the management of patients with severe aortic stenosis.

Given the rapidly evolving evidence for medium-term outcomes with transcatheter aortic valve implantation,[26] and the anticipated older, comorbid population being recruited, both surgical aortic valve replacement and transcatheter aortic valve implantation are acceptable interventions. The decision as to which is appropriate is made locally, in discussion with the patient. Likewise, the type of valve and the need for other concomitant procedures are all made on an individual patient basis.

Our primary outcome is a composite of cardiovascular death or heart failure hospitalization. This reflects important and objective events that are direct consequences of severe aortic stenosis. We anticipate an increase in early events related to peri-procedural complications, which it is hypothesized will be offset by a reduction in long-term events with early aortic valve replacement. The trial is powered to see a 25% hazard reduction and ~ 4% absolute reduction in events at a median of 3 years following randomization. Whilst subjective, we believe that effect sizes smaller than this would make it hard to justify early intervention. Power calculations for the trial were based on conservative estimates due to a lack of established randomized data at the time of protocol development. We expect the differences in clinical outcomes to increase with time and where possible, participants will undergo long term follow-up. EASY-AS also has a major focus on patient-reported outcomes, as emphasized by our patient groups who indicated that quality rather than duration of life was most important to many patients. Measures of quality of life will also allow robust cost-effectiveness analyses.

Other large comparable, studies currently in progress include the EARLY-TAVR (NCT03042104) EVOLVED (NCT03094143) and DANAVR (NCT03972644) trials. Whilst these trials are also examining the optimal timing of aortic valve replacement in patients with severe asymptomatic aortic stenosis, each has a slightly different design and focus. EASY-AS is the most generalizable, reflecting usual clinical practice. These differences are depicted in Table 4.

In summary, the EASY-AS trial is a large, pragmatic, international, multicenter, randomized controlled trial comparing early aortic valve replacement to watchful waiting in patients with severe asymptomatic aortic stenosis. Along with complementary studies in this area, EASY-AS will provide robust and much-needed evidence to address a longstanding area of uncertainty in cardio-

Table 4. Other large-scale aortic valve replacement versus expectant management trials in patients with severe asymptomatic aortic stenosis

Trial Acronym	ClinicalTrials.gov registration	Definition of severe AS	Other key inclusion criteria[1]	Other key exclusion criteria	Method of AVR	Primary outcome	Sample size	Duration of follow-up	Status
EARLY-TAVR	NCT03042104	1) AVA ≤1 cm^2 or ≤0.6 cm^2/m^2 and 2) Vmax ≥4 m/s and/or mean PG ≥40 mmHg	≥65 years, STS score ≤10% (30-day mortality)	LVEF <50%, Technically unsuitable for transcatheter AVR, Positive exercise test (selective)	Transcatheter AVR	All-cause death, stroke and unplanned CV hospitalization	901 patients[2]	Minimum 2 years	In follow-up
EVOLVED	NCT03094143	1) Vmax ≥4 m/s or 2) Vmax ≥3.5 m/s with AVA <0.6 cm^2/m^2	≥18 years, Mid-wall LV fibrosis on cardiac MRI scan	LVEF <50%, eGFR <30 mL/min/1.73 m^2, contraindication to cardiac MRI scanning	Surgical or transcatheter AVR	All-cause death and unplanned AS related hospitalization	273 patients[2]	Average 2.75 years	In follow-up
DANAVR	NCT03972644	1) AVA ≤1 cm^2 and 2) Vmax ≥3.5 m/s and 3) Deemed severe by Heart Team	18 to 85 years, Signs of increased LV filling pressure or reduced LV longitudinal strain	LVEF <50%, Vmax >5 m/s, eGFR <30 mL/min/1.73 m^2	Surgical or transcatheter AVR	All cause death	1,700 patients	Approximately 5 years	Recruiting

[1] Selected criteria, see ClinicalTrials.gov for full details. In general, all trials exclude patients with any symptoms attributable to aortic stenosis, other significant valvular disease, other indications for cardiac surgery or significantly reduced life expectancy

[2] Completed recruitment.

Modified from reference 24.

vascular medicine, guide clinicians and patients and inform clinical practice and guidelines.

Patient and public involvement

Patients and/or the public were involved in the design of the trial. Refer to the Methods section for further details.

Declaration of competing interest

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ahj.2024.05.013.

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