Rationale and design of a prospective, randomized, controlled, multicenter study to evaluate the safety and efficacy of transcatheter heart valve replacement in female patients with severe symptomatic aortic stenosis requiring aortic valve intervention (Randomized researcH in womEn all comers wIth Aortic stenosis [RHEIA] trial)

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Background Limited data suggest that transcatheter (TAVR) as compared with surgical aortic valve replacement (SAVR) may be more effective in female than male patients. To date, most evidence is derived from subgroup analyses of large trials, and a dedicated randomized trial evaluating whether there is a difference in outcomes between these interventions in women is warranted. The RHEIA trial will compare the safety and efficacy of TAVR with SAVR in women with severe symptomatic aortic stenosis requiring aortic valve intervention, irrespective of surgical risk.

Methods/Design The RHEIA trial is a prospective, randomized, controlled study that will enroll up to 440 patients across 35 sites in Europe. Women with severe symptomatic aortic stenosis, with any but prohibitive surgical risk status, will be randomized 1:1 to undergo aortic valve intervention with either transfemoral TAVR with the SAPIEN 3 or SAPIEN 3 Ultra device or SAVR and followed up for 1 year. The objective is to determine whether TAVR is non-inferior to SAVR in this patient population and, if this is fulfilled whether TAVR is actually superior to SAVR. The primary safety/efficacy endpoint is a composite of all-cause mortality, all stroke, and re-hospitalization (for valve or procedure-related symptoms or worsening congestive heart failure) at 1 year post-procedure. Other outcomes (assessed at 30 days and/or 1 year) include all-cause mortality; bleeding, vascular, cardiac, cerebrovascular and renal complications; aortic valve prosthesis and left ventricular function; cognitive function, health status, and quality of life.

Discussion The RHEIA study has been designed to evaluate the safety and efficacy of TAVR compared with SAVR specifically in women with severe symptomatic aortic stenosis, irrespective of the level of surgical risk. The results will be the first to provide specific randomized evidence to guide treatment selection in female patients with severe symptomatic aortic stenosis.

Trial registration clinicaltrials.gov: NCT04160130 (Am Heart J 2020;228:27-35.)

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Background

Aortic stenosis affects approximately 12% of elderly people in western countries and, given the aging population, the prevalence is expected to increase in coming years, especially in women because of their increased life expectancy.[1] Interventional treatment options for patients with symptomatic severe aortic stenosis include surgical aortic valve replacement (SAVR), transcatheter aortic valve replacement (TAVR) and balloon aortic valvuloplasty.[2] SAVR has been generally favored in patients at low surgical risk, while TAVR is favored in patients at intermediate, high or prohibitive surgical risk.[2] However, there is an increasing trend, to perform TAVR in lower risk patients as evidence from randomized clinical trials up to 1-year follow-up indicates that TAVR is at least non-inferior to SAVR in patients at low surgical risk.[3,4]

There appears to be a gender difference in outcomes after aortic valve interventions. Women have an increased risk of adverse outcomes after SAVR.[5-8] In contrast, there is evidence of improved long-term survival in women versus men after TAVR, although women experience more bleeding or vascular complications.[9-13] In the WIN TAVI registry (the first all-female TAVR registry with collection of female sex-specific baseline parameters), a total of 1019 intermediate to high-risk women with severe symptomatic aortic stenosis were enrolled. At 30-day and 1-year follow-up, the VARC-2 composite safety endpoint was 14.0% and 16.5%, respectively with a low incidence of early mortality and stroke. Prior revascularization and EuroSCORE I were independent predictors of the VARC-2 efficacy endpoint, whereas EuroSCORE I, baseline atrial fibrillation, and prior percutaneous coronary intervention were independent predictors of death or stroke at the 1-year follow-up.[14,15] Furthermore, data from meta-analyses of randomized trials comparing TAVR with SAVR for the treatment of symptomatic severe aortic stenosis reported TAVR to be associated with a survival benefit compared with SAVR in women but not men.[16,17] One of these reports found a 13% relative risk reduction in 2-year all-cause mortality in favor of TAVR compared with SAVR in the overall analysis population (hazard ratio 0.87, 95% confidence interval 0.76-0.99, $P = .038$); noteworthy, the benefit was driven by a significant reduction in mortality among women undergoing TAVR (HR 0.68, 95% CI 0.50-0.91, $P = .010$), with no difference evident in men (HR 0.99, 95% CI 0.77-1.28, $P = .952$).[16] Another meta-analysis found that TAVR was associated with reduced mortality compared with SAVR in women at both 1 (odds ratio 0.68, 95% CI 0.50-0.94) and 2 years follow-up (OR 0.74, 95% CI 0.58-0.95), whereas there was no difference among men at either time point (OR 1.09, 95% CI 0.86-1.39 and OR 1.05, 95% CI 0.85-1.30, respectively).[17] The difference in treatment effect between the sexes was significant at both 1 ($P = .02$) and 2 years ($P = .04$). Additional analysis of the data for women revealed lower rates of peri-procedural mortality, bleeding, acute kidney injury, and severe prosthesis-patient mismatch, and better left ventricular function recovery following TAVR compared with SAVR.[17] Notably, peri-procedural mortality and major bleeding were 54% and 57% lower, respectively, after TAVR compared with SAVR.

In light of the available evidence suggesting a favorable risk reduction with TAVR compared with SAVR in women, it is appropriate to conduct a prospective dedicated trial to determine the extent of a difference in outcomes between these interventions in women with severe symptomatic aortic stenosis. To this end, the RHEIA trial will compare the safety and efficacy of TAVR with SAVR in women with severe symptomatic aortic stenosis requiring aortic valve replacement, irrespective of their level of surgical risk.

Methods/design

The RHEIA trial is a prospective, randomized, controlled study that will enroll up to 440 patients across 35 sites in Europe (Austria, Finland, France, Germany, Ireland, Italy, the Netherlands, Sweden, Switzerland, United Kingdom) (Figure 1). Women with severe symptomatic aortic stenosis with indication for aortic valve intervention will be randomly assigned to undergo aortic valve intervention by either TAVR or SAVR and followed up for 1 year post-procedure. The primary objective is to determine whether TAVR is non-inferior to SAVR in this patient population and, if this is fulfilled whether TAVR is superior to SAVR.

Approval will be obtained from the responsible ethics committees/institutional review boards prior to study commencement. All patients will provide written informed consent before enrolment, and the study will be conducted in accordance with medical device-specific Good Clinical Practice and the principles of the Declaration of Helsinki. The trial is registered with clinicaltrials.gov under the number NCT04160130.

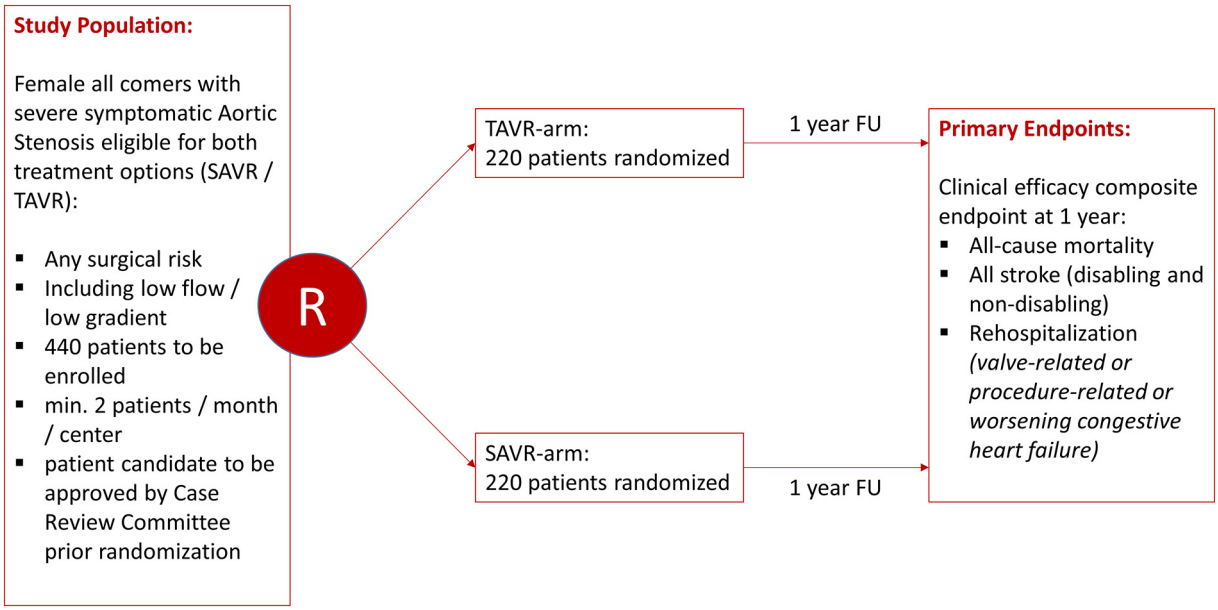
Patients

Women aged ≥18 years with symptomatic severe aortic stenosis, who are operable and with any surgical risk status, and who meet all the inclusion criteria and none of the exclusion criteria presented in Table I, will be eligible for participation in the study. Potential candidates will be screened by site investigators for operative risk and eligibility criteria, after which each case will be reviewed by a Case Review Board to confirm their suitability for enrolment.

Procedures and data collection

Patients whose eligibility is confirmed will be randomized 1:1 to undergo treatment by either transfemoral TAVR or conventional SAVR. Randomization will be performed centrally by an electronic system. Valve implant procedures will occur within 14 days of

Figure 1



Trial Design.

randomization. TAVR will be performed by transfemoral access using the SAPIEN 3 (model 9600TFX) or SAPIEN 3 Ultra (model 9750TFX) transcatheter heart valve and associated delivery systems, in accordance with the relevant Instructions for Use for device sizing, preparation and recommended implant procedure. SAVR will be performed using a commercially available surgical valve and associated components, in accordance with the standard of care at the institution. The protocol also includes new generation sutureless or rapid deployment valve and does not exclude surgical annulus enlargement. Prior to the start of the study, investigators will undergo guided review of the Instructions for Use of the devices, to ensure correct device usage. Study sites will be provided with uniform guidance on anticoagulation/antithrombotic regimens.

All patients who receive a SAPIEN 3 or SAPIEN 3 Ultra transcatheter heart valve or undergo SAVR will continue in the study throughout 1-year post-procedure (including patients who are randomized to TAVR but are subsequently converted to SAVR).

Data will be collected prospectively according to the schedule presented in Table II. Assessments will include medical history, physical examinations, electrocardiograms, echocardiograms, laboratory tests, neurological assessments, medications, adverse events, and quality-of-life questionnaires. Echocardiograms will be performed according to a standardized protocol and images will be analyzed by a central echocardiography core laboratory. Data will be entered onto electronic case report forms by study site and central laboratory personnel, and checked for completeness and accuracy by automated systems and by on-site monitoring.

An independent clinical events committee, which will include cardiologists and cardiothoracic surgeons experienced in the field of aortic stenosis, will adjudicate endpoint events (unblinded) and assess serious adverse events and device/procedure relatedness. An independent Data Safety Monitoring Board, which will include at least one cardiothoracic surgeon experienced in aortic stenosis, will monitor all adverse events.

Outcome measures

The primary endpoint is a composite clinical safety/efficacy endpoint, comprising all-cause mortality, stroke (disabling and non-disabling), and re-hospitalization (for valve or procedure-related symptoms or worsening congestive heart failure) at 1 year post-procedure. Definitions are as to VARC-2.

Additional combined safety/efficacy endpoints include: death or stroke (disabling and non-disabling) at 30 days and 1 year; death or disabling stroke at 30 days and 1 year; and death or disabling stroke or rehospitalization at 1 year.

Single safety/efficacy endpoints that will assessed at both 30 days and 1 year include mortality (all cause and cardiovascular); stroke (disabling and non-disabling); rehospitalization (valve-related or procedure-related or worsening congestive heart failure); new-onset atrial fibrillation; major vascular complications; bleeding

Table I. Eligibility criteria for the RHEIA trial

Inclusion criteria

- Female patients with severe symptomatic aortic stenosis requiring aortic valve replacement
- Severe aortic stenosis as follows:
  - High gradient severe AS (Class I Indication for AVR): peak aortic jet velocity ≥ 4.0 m/s or mean gradient ≥40 mmHg with AVA ≤1.0 cm^2 or AVA index ≤0.6 cm^2/m^2, OR
  - Low gradient severe AS (Class I/IIa indication of AVR): peak aortic jet velocity< 4.0 m/s and mean gradient <40 mmHg and AVA ≤1.0 cm^2 and AVA index ≤0.6 cm^2/m^2, with confirmation of severe AS by a mean gradient ≥40 mmHg on dobutamine stress echocardiography and/or aortic valve calcium score ≥ 1200 AU on non-contrast CT
- NYHA Functional Class ≥ II, OR exercise test that demonstrates a limited exercise capacity, abnormal BP response, or arrhythmia
- Age ≥ 18 years
- Provided written informed consent

Exclusion criteria

- Patient is not a candidate for both surgical and transcatheter aortic valve intervention
- Native aortic annulus size unsuitable for sizes 20, 23, 26, or 29 mm transcatheter heart valve based on 3D imaging analysis
- Iliofemoral vessel characteristics precluding safe placement of the introducer sheath
- Evidence of an acute myocardial infarction ≤30 days before randomization
- Aortic valve is unicuspid, bicuspid, or is non-calcified
- Severe aortic regurgitation
- Any concomitant valve disease that requires an intervention
- Pre-existing mechanical or bioprosthetic valve in any position
- Complex coronary artery disease
  - Unprotected left main coronary artery stenosis
  - Syntax score >32 (in the absence of prior revascularization)
  - Heart Team assessment that optimal revascularization cannot be performed.
- Symptomatic carotid or vertebral artery disease or successful treatment of carotid stenosis within 30 days of randomization
- Leukopenia, anemia, thrombocytopenia, history of bleeding diathesis, coagulopathy, or hypercoagulable states
- Hemodynamic or respiratory instability requiring inotropic support, mechanical ventilation or mechanical heart assistance within 30 days of randomization
- Hypertrophic cardiomyopathy with obstruction
- Ventricular dysfunction with left ventricular ejection fraction <30%
- Cardiac imaging evidence of intra-cardiac mass, thrombus or vegetation
- Inability to tolerate, or condition precluding, anti-thrombotic/anticoagulation therapy during or after the valve implant procedure
- Stroke or transient ischemic attack within 90 days of randomization
- Renal insufficiency (eGFR <30 ml/min per the Cockcroft-Gault formula) and/or renal replacement therapy
- Active bacterial endocarditis within 180 days of randomization
- Severe lung disease or currently on home oxygen
- Severe pulmonary hypertension (PA systolic pressure ≥2/3 systemic pressure)
- History of cirrhosis or any active liver disease
- Significant abdominal or thoracic aortic disease that would preclude safe passage of the delivery system or cannulation and aortotomy for surgical AVR
- Hostile chest or conditions or complications from prior surgery that preclude safe reoperation
- Patient refuses blood products
- Body mass index >50 kg/m^2
- Estimated life expectancy <24 months
- Absolute contraindications or allergy to iodinated contrast
- Immobility that would prevent completion of study procedures
- Currently participating in an investigational drug or another device study
- Pregnancy or lactation

AS, aortic stenosis; AVA, aortic valve area; AVR, aortic valve replacement; CT, computed tomography; NYHA, New York heart Association; RHEIA, Randomized researcH in womEn all comers with Aortic stenosis.

complications (life-threatening, disabling, or major); myocardial infarction; new permanent pacemaker implantation resulting from new or worsened conduction disturbances; New York Heart Association class; hemodynamic valve performance evaluation by echocardiography for aortic valve stenosis and aortic valve regurgitation (paravalvular and central); cognitive function (mini-Mental State Examination, National Institutes of Health Stroke Scale, modified Ranking Scale); frailty assessment; health status as evaluated by quality-of-life questionnaires (Kansas City Cardiomyopathy Questionnaire, SF-12 = 12-item Short Form survey). Other safety/efficacy endpoints include: length of index hospitalization; moderate and/or severe prosthesis-patient mismatch at 30 days; acute kidney injury stage II/III (AKIN classification) at 30 days; and renal replacement therapy at 1 year.

Sample size

Event rate estimates for the primary endpoint were based on data from the PARTNER 3 study.[18] The sample size estimation assumes an event rate for the composite primary endpoint of 16% in the SAVR arm and 8% in the TAVR arm. Using a one-sided alpha = 0.05 and a specified non-inferiority margin of 6.0%, a sample size of 132 patients with 1-year data would provide 80% power to fulfill non-inferiority (Figure 2). A sample size of 402 patients would provide 70% power (two-sided alpha 0.05) or 80% for a one-sided slpha of 0.05) to fulfill superiority. Because the feasibility assumptions are uncertain in an all-comer (i.e. including low to intermediate surgical risk) population and patients dropping out, an actual sample size of 440 has been chosen.

Statistical analysis

The primary population for endpoint analysis will be the As Treated population (patients in whom the index procedure is begun, whether or not the procedure is completed). The As-Treated population was chosen as patients dying before the intervention, with protocol violations and withdrawing their consent would not make sense. Cross-overs are not expected in this context, as TAVR is not an option for patients with initiated surgery. SAVR in patients undergoing TAVR is considered a potential solution for procedural complications. All results are also reported for the Intent to Treat Population (all randomized patients). Echocardiogram data will be analyzed in the Valve Implant population (the subset of the As Treated population who receive and retain the intended valve during the index procedure). Sensitivity analyses will be performed using the Intent to Treat population (all randomized patients). Time-dependent variables will be analyzed using the Kaplan-Meier algorithm, with the log-rank statistic used for group comparisons.

The primary composite clinical endpoint will be evaluated in a non-inferiority analysis with a non-

Table II. Schedule of assessments for the RHEIA trial

Procedure	Screening	Post procedure	Discharge[a]	30 days	6 months	12 months
Clinical Assessments						
Medical History	X					
CCS Angina; SYNTAX Score	X					
NYHA Classification	X	X	X	X		X
Risk Scores	X					
Mini-Mental State Examination-2	X			X		X
NIHSS[b]; Modified Rankin Scale[b]	X	X	X	X	X	X
Frailty Index[c]	X			X		X
Non-Invasive Tests						
Pulmonary function test	X[e]					
Electrocardiogram	X	X	X	X		X
Echocardiogram (TTE)	X[d]	X		X		X
Invasive Procedures						
3D Cardiac imaging (CT, TEE, or cardiac MRI)[f]; CT angiography; Cardiac catheterization	X					
Quality-of-Life						
KCCQ and SF-12	X			X		X

CT, computed tomography; KCCQ, Kansas City Cardiomyopathy Questionnaire; MRI, magnetic resonance imaging; NIHSS, National Institutes of Health Stroke Scale; NYHA, New York Heart Association; RHEIA, Randomized researcH in womEn all comers wIth Aortic stenosis; SF-12, 12-item Short Form survey; TEE, transesophageal echocardiogram; TTE, transthoracic echocardiogram.
a For patients discharged <48 hours after exiting the catheter laboratory/operation room, it is not required to repeat tests collected during the post-procedure period that are also required for the discharge visit.
b Patients diagnosed with stroke after the procedure should undergo a follow-up modified Rankin Scale assessment 90 days after the diagnosis. NIHSS not performed at 6 month.
c Frailty Index includes activities of daily living (ADLs), 5-meter walk test (5MWT), grip strength, and albumin level.
d Qualifying echocardiogram must have been performed <90 days prior to randomization.
e Only for patients with a history of lung disease.
f Qualifying imaging must have been performed within 1 year of randomization.

inferiority margin of 6%. The rate was considered clinically meaningful based on the recent PARTNER 3 and Evolut LR data, which also used a 6% on-inferiority margin.[18,19] The test will be performed as a one-sided test at alpha = 0.05. Non-inferiority will be declared if the upper 95% confidence limit for the difference in event rate between the groups (TAVR – SAVR) is below 0.06. If the primary endpoint passes the non-inferiority test, an analysis for superiority will be performed.

Summary statistics will be produced, including means, standard deviations, medians and quartiles for continuous variables, and counts and percentages for categorical variables. Confidence limits will be computed. Group comparisons will be performed using t-tests or analysis of variance (and where appropriate the Wilcoxon rank-sum test) for continuous variables and Fisher's exact test for categorical variables. Time-dependent variables will be analyzed using the Kaplan-Meier algorithm, with the log-rank statistic used for group comparisons. Adverse events will be tabulated for 30 days, 6 months and 1 year, including event counts, patients with events and Kaplan-Meier event rates at specific time-points, and groups will be compared using the log-rank test. Unless specified otherwise, confidence limits and hypothesis tests will be two-sided, using alpha = 0.05. Analyses will be conducted using SAS version 9.3 or later (SAS Institute, Cary, North Carolina, USA).

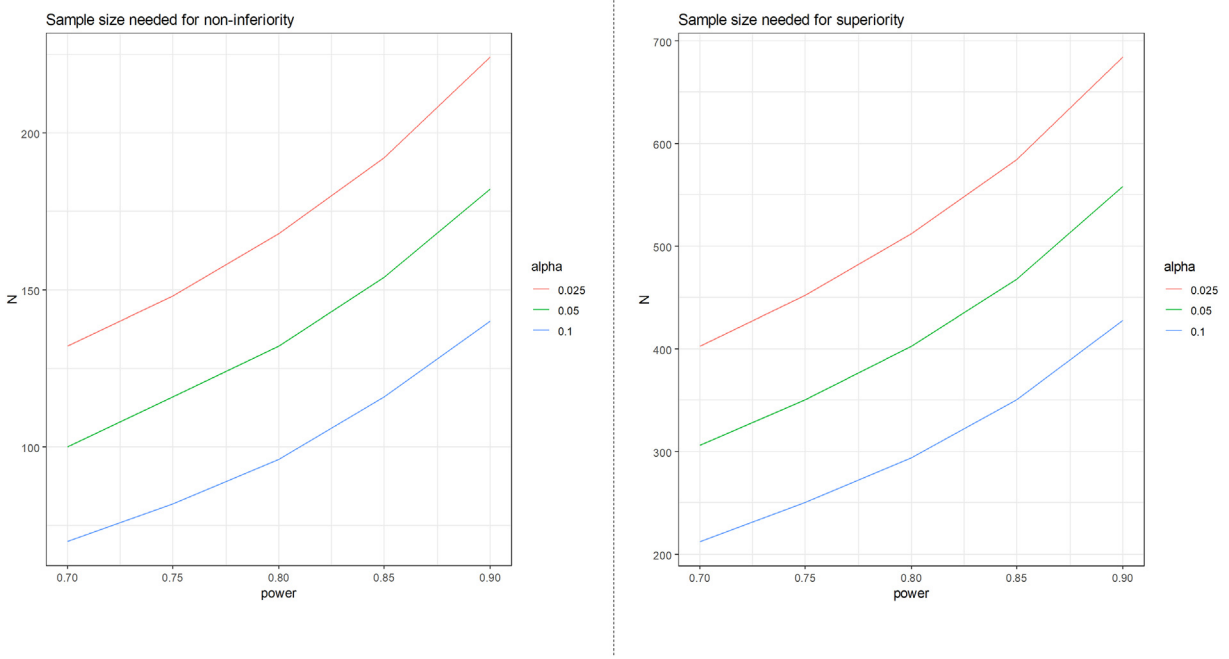
Discussion

The RHEIA study has been designed to evaluate the safety and efficacy of TAVR compared with SAVR specifically in women with severe symptomatic aortic stenosis, irrespective of their level of surgical risk.

Justification for the study

There is evidence of a sex-related difference in outcomes after SAVR[5-8] as well as after TAVR.[9-13] In the WIN TAVI registry the VARC-2 composite safety endpoint was 16.5% at 1 year with a low incidence of early mortality and stroke.[14] Data from meta-analyses suggest improved survival in women versus men after TAVR.[9-13] Moreover, data from two meta-analyses have indicated that TAVR may provide a survival benefit compared with SAVR in women, whereas similar outcomes have been observed with either intervention among men.[16,17] To date, most data are derived from subgroup analyses of large trials, and randomized trials comparing outcomes after TAVR or SAVR specifically in women are lacking. Moreover, most trials involved patients at intermediate to high surgical risk, whereas there is increasing evidence that TAVR may also be suitable for low-risk patients.[3,4] Recent randomized trials in low-surgical risk populations, i.e. PARTNER 3 and EVOLUT Low Risk, demonstrated non-inferiority or superiority of TAVR vs. SAVR,[18,19] but women were under-represented in these trials.

Figure 2



Sample size considerations.

The RHEIA study seeks to fill this knowledge gap, by evaluating whether there is a difference in clinical outcomes between TAVR and SAVR in a randomized trial involving women only, and by including patients with any level of surgical risk. The study will use SAPIEN 3 valves for TAVR procedures. The PARTNER I, II, and III trials demonstrated the efficacy and safety of TAVR performed using SAPIEN heart valves in patients at high, intermediate and low surgical risk, respectively.[18,20,21] With respect to gender differences, late mortality was reduced in women compared with men in PARTNER I,[22] but no sex-specific differences in survival were seen in PARTNER II.[23] There was also no significant sex-specific difference in the primary endpoint in PARTNER III (a composite of death, stroke or re-hospitalization at 1 year), although the rate difference was greater in women (endpoint rates: TAVR 8.1% versus SAVR 18.5%; difference −10.4%, 95% CI −18.3 to −2.5) than in men (8.7% versus 13.8%; difference− 5.1%, 95% CI −9.9 to −0.3).[18]

Study design and organization

The RHEIA study is a prospective, multicenter, randomized, controlled trial. It is designed to determine whether TAVR is non-inferior, or potentially superior, compared to SAVR, with respect to safety and efficacy in the treatment of women with severe symptomatic aortic stenosis. Data will be collected from a range of hospitals in Europe. The multinational nature of the study increases the applicability of the study findings to clinical practice across Europe. The study sites and investigators have been selected to ensure that the personnel and their institutions are suitably qualified, experienced and equipped to undertake the planned interventions. The trial management structure has been designed to provide disciplined oversight of trial activities. Patient eligibility will be confirmed by a Case Review Board, echocardiograms will be analyzed by a central imaging laboratory, and endpoint events will be adjudicated by a non-blinded clinical events committee. A Data Safety Monitoring Board will review adverse events and maintain oversight of safety.

The same TAVR systems (SAPIEN 3 or SAPIEN 3 Ultra, with the Commander Delivery System) will be used at all centers participating in the trial, and transfemoral delivery will be undertaken in all patients. Uniform guidance on peri-procedural anticoagulation/antithrombotic therapy will be provided to all centers; there are currently no validated guidelines for this specific study population and the guidance has been based on a survey of the literature, with recommendations provided for the risk categories used in the PARTNER 2 and 3 trials.[18,19]

The primary composite clinical safety/efficacy endpoint will be tested for non-inferiority of TAVR versus SAVR, and if non-inferiority is demonstrated, will then be evaluated for superiority. In addition, several composite endpoints, individual safety and efficacy endpoints will be analyzed; this may provide evidence about possible mechanisms/reasons underlying any difference identified for the primary endpoint. Another is transcatheter vs surgical valve function in female patients with small aortic annuli. There is some primary evidence that transcatheter valves may have some advantages in terms of lower residual gradients and higher effective orifice area in the early postoperative phase.[24] The clinical significance of these findings have not been demonstrated so far.

The interventionalists cannot be blinded because of the inherent differences between the two interventions being studied. However, potential bias will be minimized in several ways. Consecutive enrolment and central randomization of patients will minimize selection bias. Endpoint events will be adjudicated by an independent Clinical Event Committee, which will reduce assessment bias. Publication of the study design and protocol details before analysis of the study results will help prevent reporting bias.

Conclusions

The RHEIA study is a prospective, multicenter, randomized, controlled trial that will include women with symptomatic severe aortic stenosis and will be performed in Europe. Based on a randomized comparison, it will evaluate whether there are differences in outcomes between TAVR and SAVR among women with symptomatic severe aortic stenosis requiring aortic valve replacement, irrespective of their surgical risk. The results of this study may contribute to optimize the therapeutic management of severe aortic stenosis in women.

Declarations

Ethics approval and consent to participate

Approval from the relevant ethics committees/institutional review boards for all study sites will be obtained prior to implementation of the protocol. All patients will be required to provide signed informed consent.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

Competing interests

The authors represent the steering committee of the RHEIA study and are as such reimbursed for their efforts by the sponsor (travels and expenses). HE, NB, BP, FN, MVN, AC, PP, PB, ND and DT have received research funding and/or lecture fees and/or consultancy honoraria from Edwards Lifesciences, the funder of the study. PP runs the Echo CoreLab of the study and his laboratory receives separate funding for these. PB gets reimbursed for his consultancy on RHEIA.

SW has received research and educational grants to the institution from Amgen, Abbott, Bayer, BMS, Biotronik, Boston Scientific, CSL Behring, Edwards Lifesciences, Medtronic, Polares and Sinomed.

JJB has declared departmental research grants from Abbott, Bayer, Biotronik, Boston Scientific, Edwards Lifesciences, GE Healthcare, Medtronic; speaker fees from Abbott, Edwards Lifesciences, Medtronic.

LS and JK are employees of the funder Edwards Lifesciences.

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Authors' contributions

The study protocol was developed by the author group. It was drafted by PB, initially revised by HE, LS, JK, and DT and then critically discussed and amended by the group of authors. The final version of the protocol was taken as a basis for the manuscript development for which PB provided an initial draft. This was critically revised by all authors and finally approved for submission.

Acknowledgements

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Appendix A. Appendix

A.1. Steering Committee

Didier Tchetche (Toulouse, France)—Principal Investigator, Helene Eltchaninoff (Rouen, France)—Principal Investigator, Mariuca Vasa-Nicotera (Frankfurt, Germany), Fabian Nietlispach (Zürich, Switzerland), Bernard Prendergast (London, UK), Jeroen Bax (Leiden, Netherlands), Philippe Pibarot (Quebec, Canada), Alaide Chieffo (Milano, Italy), Stephan Windecker (Bern,

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A.2. Data Safety Monitoring Board

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A.3. Clinical Events Committee

Rick Steeds (Birmingham, UK), David Messika-Zeitoun (Ottawa, Canada).

A.4. Study Logistics and Support

Christine Schubert, Sabine Pauli, Sigrid Pottkämper, Astrid Schwarz, Michael Sigmund (all Germering, Germany), Claudia Lüske (Cloppenburg, Germany), Claudia Zemmrich (Berlin, Germany).

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