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Comparing quality of life and postoperative pain after limited access and conventional aortic valve replacement: Design and rationale of the LImited access aortic valve replacement (LIAR) trial

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ABSTRACT

Background: Surgical aortic valve replacement (SAVR) via limited access approaches ('mini-AVR') have proven to be safe alternative for the surgical treatment of aortic valve disease. However, it remains unclear whether these less invasive approaches are associated with improved quality of life and/or reduced postoperative pain when compared to conventional SAVR via full median sternotomy (FMS).

Study design: The LImited access Aortic valve Replacement (LIAR) trial is a single-center, single blind randomized controlled clinical trial comparing 2 arms of 80 patients undergoing limited access SAVR via J-shaped upper hemi-sternotomy (UHS) or conventional SAVR through FMS. In all randomized patients, the diseased native aortic valve is planned to be replaced with a rapid deployment stented bioprosthesis. Patients unwilling or unable to participate in the randomized trial will be treated conventionally via SAVR via FMS and with implantation of a sutured valve prosthesis. These patients will participate in a prospective registry.

Study methods: Primary outcome is improvement in cardiac-specific quality of life, measured by two domains of the Kansas City Cardiomyopathy Questionnaire up to one year after surgery. Secondary outcomes include, but are not limited to: generic quality of life measured with the Short Form-36, postoperative pain, perioperative (technical success rate, operating time) and postoperative outcomes (30-day and one-year mortality), complication rate and hospital length of stay.

Conclusion: The LIAR trial is designed to determine whether a limited access approach for SAVR ('mini-AVR') is associated with improved quality of life and/or reduced postoperative pain compared with conventional SAVR through FMS.

The study is registered at ClinicalTrials.gov, number NCT04012060.

1. Background and rationale

Aortic valve stenosis has a growing prevalence with the increasing age of the population. Currently, one in eight individuals over 75 years has moderate or severe aortic valve disease (Aortic valve area <1.5 cm^2, mean aortic valve gradient >20 mmHg and/or a peak velocity >3.0 m/s) [1,2]. To date, surgical aortic valve replacement (SAVR) remains the preferred treatment for aortic valve stenosis in patients with a low surgical risk (STS or logistic EuroSCORE II $<4\%$ or logistic EuroSCORE I $<10\%$) and no other specific risk factors such as frailty, severely calcified ('porcelain') aorta or sequala of radiotherapy to the chest or with an increased surgical risk as assessed by the Heart Team based on individual patient characteristics and current guidelines [2]. SAVR has traditionally been performed through full median sternotomy (FMS), combined with a sutured aortic valve prosthesis [3]. Limited access aortic valve replacement (LA-AVR or 'mini-AVR') techniques have been developed to decrease surgical trauma and hence improve outcome. These techniques gained more and more acceptance since they were first described by Cosgrove and Sabik in 1996 [4]. In particular, the mini-sternotomy (predominantly via J-shaped upper hemi-sternotomy (UHS)) and anterior right thoracotomy (ART) approaches have

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Abbreviations and acronyms

ACC	Aortic Cross Clamping
ART	Anterior Right Thoracotomy
CPB	Cardiopulmonary Bypass
FMS	Full Median Sternotomy
ICU	Intensive Care Unit
KCCQ	Kansas City Cardiomyopathy Questionnaire
LA-AVR	Limited Access Aortic Valve Replacement
LIAR	LImited access Aortic valve Replacement trial
MCS	Mental Component Summary
MEC-U	Medical Ethics Committees United
PCS	Physical Component Summary
QoL	Quality of Life
REDCap	Research Electronic Data Capture
SAVR	Surgical Aortic Valve Replacement
SD	Standard Deviation
SF-36	Short Form-36
SPSS	Statistical Package for Social Sciences
STS	The Society of Thoracic Surgeons
TOE	transesophageal echo
UHS	Upper Hemi-Sternotomy
VAS	Visual Analogue Scale

become established alternatives for conventional SAVR [5]. Technical innovations, in particular the introduction of rapid deployment or sutureless bioprostheses, facilitated the increase in mini-AVR procedures.

In comparison to SAVR via FMS, the main advantage of mini-AVR is reduced surgical trauma, which in turn can lead to reduced postoperative pain and blood loss. Mini-AVR was found to be associated with reduced length of intensive care unit (ICU) stay, shorter hospital stay and improved cosmetic outcome [6–12] in some studies. Although, more recently the results of a randomized trial (Mini-Stern trial) demonstrated conflicting outcome, stating that mini-AVR actually prolonged postoperative length of stay [13]. Additionally, mini-AVR was found to be less cost-efficient. Other papers found comparable perioperative and postoperative results comparing conventional SAVR and mini-AVR in both short term (up to 30 days) and intermediate term (up to one year) follow-up [6,14]. Mini-AVR combined with a conventional sutured valve prolonged both cardiopulmonary bypass (CPB) and aortic cross clamping (ACC) times due to limited exposure and increased technical complexity [11]. While mini-AVR is associated with a significant reduction in blood loss, this did not lead to a reduction in the rate of postoperative blood transfusion [15]. Interestingly, despite being associated with increased CPB and ACC times, Merk et al. [16] demonstrated that mini-AVR was associated with an improvement in long-term survival compared to conventional SAVR.

The use of sutureless and/or rapid deployment valve prostheses facilitate limited-access approaches and compensate partially for the reduced exposure and increase in technical difficulty. They are associated with a reduction in both ACC and CPB times [17,18], potentially reducing postoperative morbidity and mortality. Additionally, there is evidence suggesting mini-AVR is associated with improved postoperative health status and quality of life (QoL) [6], possibly explained by less postoperative pain [3,19]. However, in the majority of studies investigating the impact of mini-AVR on health status and QoL, conventional sutured aortic valve prostheses were used with the aforementioned increase in CPB and ACC times, potentially mitigating the beneficial effect of the limited access approach. The empirical basis for the advantages in pain and QoL after mini-AVR seems limited as the conducted studies were mostly retrospective cohort studies, employing small sample sizes. Actually, only two published papers assessed QoL [6, 13]. Therefore, there is a need for well powered randomized clinical trials examining QoL and postoperative pain [20] after mini-AVR compared to SAVR.

The primary goal of the LImited Access aortic valve Replacement (LIAR) Trial is to assess and compare the effectiveness in terms of QoL and postoperative pain between LA-AVR through J-shaped UHS and conventional SAVR through FMS, both utilizing rapid deployment stented bioprosthesis, in patients suffering from symptomatic and/or severe aortic valve stenosis, up to one year postoperatively.

The primary hypothesis is that a limited access approach for the treatment of an aortic valve stenosis combined with the use of a rapid deployment aortic valve prosthesis improves cardiac specific QoL and is associated with equal surgical outcomes when compared to conventional SAVR.

2. Study design

The LIAR Trial is a single-center, single blind, randomized controlled clinical trial comparing isolated SAVR by using a J-shaped UHS for the implantation of a rapid deployment stented aortic valve prosthesis (Edwards Intuity Elite Valve System®, Edwards Lifesciences Corporation), with the implantation of a rapid deployment stented aortic valve prosthesis through FMS. Patients who are unable or unwilling to participate in the randomized trial for any reason but who will undergo an isolated SAVR in our center will be monitored, if they consent, in a prospective registry. The prospective registry is part of the LIAR-trial and will be conducted simultaneously. The LIAR-trial will be executed in the St. Antonius Hospital. This is the largest cardiothoracic surgery department of the Netherlands. Over 2000 open heart operations are performed on a yearly basis, of which approximately 200 isolated aortic valve replacements. The study is registered at ClinicalTrials.gov, number NCT04012060.

3. Patient selection

The Heart Team, consisting of an (intervention-)cardiologist and a cardiothoracic surgeon, will determine whether a patient has an indication for an isolated aortic valve intervention and whether SAVR is recommended. Patients are considered eligible for SAVR if they suffer from severe and/or symptomatic aortic valve stenosis as defined by the guidelines of the European Society of Cardiology, the European Association for Cardio-Thoracic Surgery and the American College of Cardiology and the American Heart Association [2,21] as an aortic valve area of $\leq$1.0 square centimeters and a mean aortic valve gradient of $\geq$40 mm of mercury and/or a peak velocity of at least 4.0 m per second, and prefer implantation of a biological aortic valve prosthesis.

Patients will be excluded from the trial if they i) are unable or unwilling to give written informed consent; ii) are unable to answer the questionnaires due to cognitive or language barriers; iii) are undergoing concomitant cardiac surgery; iv) are undergoing a reoperation; v) are unable to undergo a limited access approach; vi) are undergoing an emergency operation; vii) had a recent myocardial infarction (<90 days); and/or viii) had a recent stroke or transient ischemic attack (<6 months). For a complete overview see Appendix S1.

3.1. Recruitment and consent

All patients identified by the Heart Team and fulfilling the inclusion criteria will be recruited at the outpatient clinic. For those patients willing to participate in the trial, written informed consent will be obtained, after which patients will be scheduled for surgery. Patients

identified as not eligible for participation in the randomized trial will be recruited at the outpatient clinic to participate in the prospective registry.

4. Randomization and treatment

Patients will be randomized 1:1, 80 patients per arm. Allocation concealment is achieved as follows:

1. An independent clinical epidemiologist will construct a randomization model which randomizes patients in blocks, with different sizes ranging from four to twenty, so that the randomization outcome is difficult to anticipate.
2. Randomization is performed via a secure web application for managing online databases called REDCap (Research Electronic Data Capture) [22].
3. Randomization will take place after the patient has been scheduled for operation and, more importantly, after the baseline visit and completion of the QoL questionnaires. The randomized allocation of the surgical technique will be revealed to the surgeons one day prior to surgery. Both surgical interventions will be performed by three surgeons who are trained/experienced in both the conventional and limited access technique.
4. Whereas it is impossible to blind surgeons, the patients and nurses at the general ward will be blinded until four days after surgery, when the bandage is removed from the sternum.

4.1. Mini-AVR

A partial or limited J-shaped UHS to the right 3rd or 4th intercostal space through a 6–8 cm vertical midline skin incision will be performed for surgical access depending on the relative location of the aortic valve to the sternum [3]. Arterial cannulation will be in the distal ascending aorta or proximal aortic arch. Venous cannulation will either be trough the right atrial appendage using a 2-stage venous cannula or through the common femoral vein using a long cannula (positioned over a guidewire under transesophageal echo guidance (TOE)) into the superior vena cava. A left ventricular vent is positioned through the right upper pulmonary vein, through the mitral valve, into the left ventricle. Alternatively, a 13Fr. angulated canula inserted through the main pulmonary artery can be used for venting. After placement of the aortic cross clamp, approximately 800–1200 ml cold crystalloid cardioplegia (St. Thomas II solution) is administered through a root needle. At the discretion of the surgeon, the 500–600 ml cardioplegia is repeated administered directly in the coronary ostia after 30–40min. of cross clamping time or when electrical activity of the heart is observed.

After removal of the leaflet of the diseased aortic valve and standard annular decalcification, an Intuity Elite rapid deployment stented aortic bioprosthesis will be implanted using 3 guiding-sutures. The guiding sutures are tied after correct deployment of the valve in the annulus. When the correct size of the valve prosthesis is not available (>27 mm) or when the rapid deployment prosthesis is deemed unsuitable, a conventional sutured valve will be implanted at the surgeon's discretion.

After weaning the patient from extracorporeal circulation, TOE will be used to assess function of the valve prosthesis, presence of paravalvular leakage and global and regional left and right ventricular function. Standard epicardial pacing wires will be placed at a 'bare' muscular part of the free-wall of the right ventricle. A single intrapericardial chest drain is placed. When hemostasis is considered sufficient, the sternum is stabilized with 3–4 steel wires and then closed in layers in routine fashion using absorbable sutures. The patient will be transferred to the ICU or recovery room after surgery.

4.2. Conventional SAVR

All patients randomized to the control group will undergo an isolated SAVR through FMS, which approximately leads to an 18–20 cm midline vertical skin incision [7]. Arterial cannulation will be at the distal ascending aorta. Venous cannulation will be through the right atrial appendage using a 2-stage venous cannula. The rest of the procedure is identical to the mini-AVR, with the exception of the number of chest drains (2–4) and steel wires (6–10). The anesthetic protocol is similar for all patients.

Patients participating in the prospective registry will undergo an isolated SAVR through FMS. The choice of valve to be implanted is at the surgeon's discretion. The choice for either a mechanical or biological valve will be decided in consultation with the patient.

4.3. Data collection and follow-up

Up to thirty days prior to surgery (baseline assessment) the Kansas City Cardiomyopathy Questionnaire (KCCQ) and the Short Form-36 (SF-36) will be administered to all patients face-to-face or by telephone, by reading the questions and response options out loud.

Postoperative pain scores will be obtained by a physician of the research team on day one (with the operation being on day zero) until day seven, or until discharge (in case postoperative length of stay is shorter than seven days). The use of analgesic drugs will be monitored during hospital stay and at follow-up by the same physician. Postoperatively, the same (oral) analgesics will be prescribed to all patients on the nursing ward: OxyContin (two times daily), Oxynorm (up to six times daily) and paracetamol (up to four times daily). This is part of our postoperative protocol, which is the same for every patient. After four days we stop prescribing the morphine and continue to prescribe the paracetamol. Patients are discharged home with only paracetamol up to four times a day.

Telephone contact will be made during follow-up at one month (+/− one week), three months (±30 days), six months (±30 days) and twelve months (±60 days). At these moments the SF-36 and KCCQ will be administered and information regarding any adverse events will be collected. All follow-up assessments will be conducted by the same research physician.

In the prospective registry the QoL questionnaires and all clinical data from the patients will be collected and analyzed the exact same way as the data from patients included in the randomized trial. The patients participating in the prospective registry will be compared to the trial patients to gain insight in possible selection bias and generalizability of the results.

A flowchart is given in appendix S2.

5. Outcome measures

5.1. Primary outcome

The primary outcome is cardiac-specific QoL, measured by the physical limitations and symptoms domains from the KCCQ. The KCCQ consists of 23 items that are combined to form five domains: physical limitations, symptoms, self-efficacy, social interference and quality of life [23]. All items refer to the past two weeks. Subscale scores are linearly transformed and range from 0 to 100, higher scores indicating a more favorable outcome.

5.2. Secondary outcomes

The secondary QoL outcomes are:

1) the remaining domains of the KCCQ, *2)* generic QoL assessed with the Physical Component Summary (PCS) and the Mental Component Summary (MCS) of the SF-36. The SF-36 consists of eight domains: physical functioning, role physical functioning, role emotional

functioning, bodily pain, vitality, mental health, role social functioning and general health [24]. These domains can be combined into the PCS and MCS. Response options vary per set of items and are linearly transformed to scores that range from 0 to 100 with higher scores indicating better QoL. All items refer to the past four weeks and *3)* postoperative pain, assessed with a visual analogue scale (VAS). The instrument we use to determine the VAS is a straight line from left to right and ranges from 0 (no pain) to 10 (worst imaginable pain) [25]. A physician of the research team will ask the patients to put a mark on the line, on the exact spot that indicates how much pain they experience. The distance measured from 0 to the patient's mark on the line is the VAS score. The percentage of patients with a VAS >3 will be calculated. This represents the cutoff for moderate pain and the need for administration of additional oral analgesic medication in our center [26]. All questionnaire scores will be calculated using the scoring algorithms published by the developers [23–25,27]. All secondary QoL outcomes will be analyzed exploratory.

Secondary, clinical outcomes include: *1)* perioperative results, measured by ACC time (minutes), CPB time (minutes), operating time (minutes) and technical success rate defined as a limited access approach without conversion and implantation of a rapid deployment bioprosthesis and *2)* 30-day mortality and one year mortality rate, complication rate, hospital length of stay (nights spent in the hospital postoperatively), length of ICU stay (hours), hemodynamic outcomes, reoperation, readmission rate and the use of analgesic drugs during admission and at follow-up. A more detailed overview is given in Appendix S3.

5.3. Sample size calculation

The minimal clinically important difference for the KCCQ is five points, assuming a standard deviation (SD) of 11 points based on previous literature [28]. To be able to detect a 5-point difference between the intervention and control group in physical limitations and symptoms assessed with the KCCQ with a two-sided 5% significance and a power of 80% (Alpha 5% and Beta 20%), at least 76 patients per group are required.

5.4. Statistical analysis

Baseline characteristics and patients' questionnaire scores at baseline, will be compared between the two randomized groups using independent samples Student t tests for continuous variables and chi-square tests for categorical variables.

5.5. Statistical analysis

The differences between the intervention and control group in mean scores on the primary outcomes, i.e. symptoms and physical limitations domains (KCCQ), will be investigated using general linear models with the baseline score and other baseline characteristics included as covariates. Additionally, differences in mean scores on the KCCQ and the PCS and MCS between the intervention and control groups over time (one, three, six and twelve months after surgery) will be investigated using linear mixed model regression analyses with baseline scores and baseline characteristics included as covariates. We will compare the proportion of patients with a VAS score >3 between the intervention and control group over time using generalized estimating equations.

All perioperative outcomes will be measured in minutes and presented as the mean ± SD (continuous data), except for technical success rate, which is measured in percentages (categorical data). The same applies to the postoperative outcomes. The mortality rate, complication rate, reoperation rate and readmission rate will also be presented in percentages (categorical data), while ICU stay and hospital length of stay will be presented as median ± SD and hemodynamic outcomes will be presented as the mean ± SD (continuous data). All categorical peri- and postoperative outcomes will be analyzed using the Chi-square test, while all continuous peri- and postoperative outcomes will be analyzed using the independent samples Student t-test or Mann Whitney *U* test, depending on their distribution.

Our primary analysis will be according to intention to treat. In the intention to treat analysis all patients are included and they are analyzed in the group to which they were randomly assigned. Additionally, we will conduct a per protocol analysis. In the per protocol analysis we will include all patients who actually receive the intervention they were randomly assigned to. In both analyses we will correct and account for cross overs and for patients who are lost to follow-up.

5.6. Registry group analysis

In addition to the trial we will collect data from all patients participating in the prospective registry. Baseline characteristics, in terms of QoL and medical history, of the registry group will be compared to the baseline characteristics of the trial patients using general linear models for continuous variables and chi-square tests for categorical variables. Postoperative QoL and clinical data will be analyzed the same way as the data from the trial patients.

Statistical analysis will be performed using the Statistical Package for Social Sciences, version 24.0 or higher (SPSS, Chicago, Illinois, USA). All p-values will be two-tailed and a p-value <0.05 will be considered statistically significant.

5.7. Strength and limitations of the study

The LIAR-Trial focusses on cardiac related and generic QoL and postoperative pain after mini-AVR. Limited access strategies for SAVR might result in a better quality of life and less pain than full sternotomy strategies. There is controversy on the effect of mini-AVR on QoL as today, to the best of our knowledge; only two previous studies have investigated the impact of mini-AVR on QoL. This is surprising because QoL and pain are of great importance to the majority of patients undergoing an any surgical procedure. Another strength of this study is the randomized design, comparing mini-AVR via UHS with conventional SAVR through FMS, the current surgical golden standard for the treatment of severe and/or symptomatic aortic valve stenosis. As a consequence, any effect on QoL has to be the result of the intervention. Adding a prospective registry will give insight in the generalization of the results of the trial and the presence of possible selection bias. This is a single center study, therefor a relatively homogeneous group of patients is referred to and screened for surgery in our center. Because of the single center design, all procedures (screening and surgery) are relatively homogeneous. This will potentially limit the external validity. For example, the results may not be reproducible by surgeons in other centers. Blinding the patients and nurses on the ward for four days ads strength to this study, leading to less biased patient assessments. Surgical skill interfering with the results is not to be expected, since the three surgeons are experienced in performing both surgical techniques and are beyond their learning curve with implanting the Intuity Elite rapid deployment valve prosthesis. The outcome measures are validated questionnaires, which are taken directly from the patients by the same research physician, either face to face or through telephone interview. Since the assessor of the questionnaires is not blinded, unconscious bias might potentially be introduced. Furthermore, we are aware that the aforementioned technique may lead to socially desired answers. This shouldn't interfere with the results however, since this approach is used in both randomized groups and also in the registry patients. Moreover, it is a time-consuming and careful approach producing complete responses to the questionnaires.

6. Conclusions

While mini-AVR is increasingly performed as an alternative for

SAVR, there is conflicting evidence regarding any superior outcomes and well powered randomized, prospective studies on patient reported outcome measures are lacking. The LIAR trial will give better insight into cardiac-specific postoperative physical functioning, generic physical QoL and postoperative pain after mini-AVR. Furthermore it will determine whether a limited access approach for SAVR results in an improved quality of life and less postoperative pain when compared to conventional SAVR through FMS. The results of this trial will aid in well informed decision making regarding SAVR.

Medical Ethics Committee approval

The study protocol of the LIAR-Trial is reviewed and approved by the Medical Research Ethics Committees United (MEC-U), the Ethics Committee of the St. Antonius Hospital in Nieuwegein.

Safety monitoring board

The Medical Ethics Committee waived the need for a safety monitoring board. However, every serious adverse event will be reported to the Medical Ethics Committee. They are able to halt the study at any point in time if they feel patient's health and safety are jeopardized.

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Author declaration

1) We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.
2) We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us.
3) We confirm that neither the entire paper nor any of its content has been submitted, published, or accepted by another journal. The paper will not be submitted elsewhere if accepted for publication in the Journal.
4) We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property.
5) We confirm that any aspect of the work covered in this manuscript that has involved either experimental animals or human patients has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.
6) We understand that the Corresponding Author is the sole contact for the Editorial process (including Editorial Manager and direct communications with the office). He/she is responsible for communicating with the other authors about progress, submissions of revisions and final approval of proofs.

Declaration of competing interest

Patrick Klein is consultant to Edwards Lifesciences and proctor for the EDWARDS INTUITY ELITE valve system.

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None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.conctc.2021.100700.

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