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Research article

Rationale and design of the ELEANOR trial early aortic valve surgery versus watchful waiting strategy in severe asymptomatic aortic regurgitation, ACRONYM: ELEANOR

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ABSTRACT

Background: The optimal treatment of patients with severe symptomatic aortic regurgitation (AR) is state-of-the-art surgery. Asymptomatic patients with advanced left ventricular (LV) dilatation and/or impaired ejection fraction should undergo surgical treatment, but there is no guidelines consensus on cut-off values for this recommendation. Multimodality imaging has brought new tools for the accurate selection of asymptomatic patients at risk of early clinical deterioration, however, prospective and randomized data are pending. Cardiac magnetic resonance (CMR)-derived AR quantification along with LV remodeling assessment appears to be the most accurate tool for a selection of such patients at risk.

Trial design: The objective of our prospective and multicenter study is to determine whether patients at risk of early clinical deterioration as per CMR assessment will benefit from early surgical treatment. The study is designed as a superiority trial to demonstrate that early surgical treatment is safe and more effective than the standard treatment. A total of 217 asymptomatic patients with severe AR, but without current guidelines-based surgical indication, will be enrolled across all centers. We expect 24 % of patients identified as high clinical risk and therefore eligible for 1:1 randomization to early surgical treatment within 3 months or a watchful waiting strategy. Follow-up will be annual. We expect a complete restoration of LV size and function along with

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improved quality of life and physical performance in a short-term follow-up of 12 months. The primary endpoint will be a composite safety and efficacy with all criteria mandatory: 15 % or larger reduction of baseline CMR-derived LV end-diastolic volume index, LV ejection fraction >50 %, and no major adverse cardiovascular events. The annual follow-up will continue for a minimum of 4 years until the required number of endpoints is achieved to show a statistically significant difference in cardiovascular morbidity and mortality in early surgically treated patients.

Conclusion: The ELEANOR trial is the first multicenter randomized controlled study to compare early surgical treatment with a watchful waiting strategy in asymptomatic patients with chronic severe AR at high risk of early clinical deterioration as per CMR assessment but without guidelines-based indications for surgical treatment.

1. Introduction

Aortic regurgitation (AR) is the third most common valvular disease with a prevalence of 13.0 % in men and 8.5 % in women [1,2] with male predominance 4:1[3]. Degenerative etiology is the main cause of the disease and is markedly accelerated in patients with genetically abnormal aortic valve morphology such as bicuspid or unicuspid aortic valve [4]. Patients undergoing valve surgery for isolated AR are in the average 6th decade (57 years old) with a minority 17.2 % of female gender [3]. Therefore, in this cohort of relatively younger patients with long life expectancy, the optimal timing of surgical intervention is of major importance, considering the nature of their professions, sports activities, and the possibility of family planning in female patients.

Aortic valve surgery is indicated in all patients with severe AR who develop symptoms of heart failure, as recommended by Guidelines [5,6]. However, surgical treatment in asymptomatic patients is conditioned by an advanced left ventricular (LV) dilatation or reduced ejection fraction (LVEF) [5,6]. However, there is no consensus on the exact cut-off values of LV size and LVEF [7]. Moreover, these criteria stated in guidelines are rather insensitive to detecting patients at risk of early disease progression as previously documented [8–11]. The mortality rate in asymptomatic patients with severe AR is as high as 19 % within 6.6 years following the diagnosis [10]. Prospective and randomized data on the management of asymptomatic patients with severe AR utilizing multimodality imaging and modern techniques are lacking. This may explain why there has only been a mild shift towards earlier surgical treatment in the most recent 2021 ESC/EACTS Guidelines [5], despite a decline in perioperative adverse events in patients undergoing sole aortic valve surgery [10,12,13].

Recently introduced multimodality-imaging markers of AR quantification or LV remodeling assessed by using 3-dimensional echocardiography (ECHO) or cardiac magnetic resonance (CMR) along serum natriuretic peptide level [11,14–22], have shown high accuracy in identifying asymptomatic patients who are at risk of early clinical progression and could potentially benefit from early surgical intervention [14,17]. Specifically, the approach integrating CMR-derived AR quantification with LV remodeling assessment has shown very promising results in observational studies [14,17].

Thus, we designed a prospective and multicenter trial where asymptomatic patients with severe AR who are at high risk of early clinical deterioration as per CMR assessment, but without current guidelines-based surgical indication [5,6], will be randomized to early surgical treatment or watch-full-waiting strategy. We hypothesize that early surgical treatment in patients with low surgical risk, severe AR, and advanced LV remodeling as per CMR assessment will be a safe, and superior procedure. We hypothesize a complete restoration of LV size and function in surgically treated patients and an improvement of quality of life and physical performance in a short-term follow-up of 12 months. In the long term, we hypothesize that earlier surgery will positively impact cardiovascular morbidity and mortality and will not significantly increase the number of reoperations for aortic valve disease.

2. Methods

2.1. Study design

The study is conducted in accordance with the Declaration of Helsinki and with ethics committee approval in all participating sites: Na Homolce Hospital Ethics Committee No 11.5.2022/19; Ethics Committee, University Hospital Hradec Králové No 202205 P08; Ethics Committee of the General University Hospital in Prague No 120/23 S-IV; Ethics Committee of Center of Cardiovascular and Transplant Surgery, Brno No 08.06.2022; Ethics Committee of the International Clinical Research Center, St. Anne's University Hospital Brno No 24.06.2022; Ethical committee OLVZ Aalst No 2022/111. All patients sign the informed consent on the enrolment. The study was registered in ClinicalTrials.gov under a unique identifier: NCT05438862 on June 21st, 2022.

The study is investigator-initiated and has a prospective, randomized, open-label design. Echocardiography data will be analyzed in the accredited CoreLab of the Cardiovascular Center in Aalst, Belgium. Cardiac magnetic resonance data will be analyzed in the accredited CoreLab based in University Hospital Hradec Králové, Czechia.

2.2. Study population

Heart Valve Teams at participating centers screen all consecutive patients referred for AR to determine their eligibility for the study. Patients with chronic asymptomatic AR grade 3 and grade 4 as per ECHO assessment who do not have a guideline-based surgical

indication are offered an opportunity to participate in the study. After signing the informed consent, patients undergo a baseline examination which consists of a clinical examination, the questionnaire (RAND 36-Item Health Survey 1.0 Questionnaire Items, Supplementary material), electrocardiography, blood analysis, a comprehensive 2D and 3D ECHO, exercise stress test, cardiopulmonary exercise test (CPET) preferably, and cardiac CMR. The study population will consist of 217 patients who meet the study inclusion and exclusion criteria listed in Table 1.

2.3. The Rationale for patients selection and randomization

The selection of eligible individuals is based on pre-defined CMR criteria using a central Corelab analysis. Patients with the CMR-derived regurgitant fraction (RF) >35 % or regurgitant volume (RV) >45 ml, and LV end-diastolic volume index (EDVI) >125 ml/m^2 will be randomized in a 1:1 ratio between early aortic valve, preferably sparing, surgery (Group A) or watchful waiting strategy (Group B) as per current guidelines. Patients, not fulfilling these CMR criteria, will enter the registry (Group C) (Fig. 1). The selection of CMR-derived RF and RV cut-off values are based on previously published prognostic data of four independent groups: Myerson et al. (RV >42 mL, RF >33 %) [14], Harris et al. (RV >50 mL, RF ≥37 %) [15], Vejpongsa et al. (RF >35 %) [16] and our data, Kockova et al. (RV >45 mL and RF >34 %) [17]. Left ventricular diameters and volumes have lower predictive accuracy, however, a combination of AR quantification parameters (cut-offs: RV > 45 mL and RF >34 %) and LV EDVI (cut-off LV EDVI >125 mL/m2) showed high accuracy in identifying patients at risk of early clinical deterioration requiring surgery during a median of 399 (IQR 209) days [17].

Randomization: The randomization process is computer-based, utilizing the covariate adaptive method to achieve a balanced distribution of both patients' groups in between participating centers, age, and gender.

2.4. Patients groups

Patients in Group An undergo aortic valve surgery within 3 months after randomization. The regular follow-up every 6 months will include a clinical examination, 2D and 3D ECHO, and blood tests. Cardiac CMR, questionnaire (Supplementary material), and CPET will be repeated 12 months after enrolment. Patients who will decline early surgical treatment might be reassigned to Group B but the total number must not exceed 6 % of the total number of enrolled patients in a particular center. The results will be statistically tested for both, intention to treat and as treated (Fig. 1).

Patients in Group B and C will be reviewed every 6 months including a clinical examination, 2D and 3D ECHO, and blood tests. A repeated cardiac CMR study, questionnaire (Supplementary material), and CPET will be performed 12 months after enrolment. Patients who develop an indication for aortic valve surgery as per current Guidelines during the watchful waiting period will undergo aortic valve surgery within 3 months after the onset of the guideline-based indication (Fig. 1).

AV – aortic valve, CMR – cardiac magnetic resonance, CPET – cardiopulmonary exercise test, ECHO - echocardiography, ESC/EACTS – European Society of Cardiology/European Association For Cardio-Thoracic surgery, EDVI – end-diastolic volume index, M – month, NT-proBNP - N-terminal pro-brain natriuretic peptide, RF – regurgitant fraction, RV – regurgitant volume.

2.5. Study hypothesis

1. We hypothesize that early surgical treatment in patients with low surgical risk and severe AR as per CMR assessment will be a superior, safe procedure with a low incidence of early and late periprocedural complications.
2. We hypothesize that early surgical treatment will lead to early LV reverse remodeling leading to the complete normalization of LV structure and function.
3. We hypothesize that early surgical treatment will lead to early improvement in quality of life and exercise performance in the majority of patients.
4. We hypothesize that early surgical treatment will be associated with lower long-term mortality and morbidity.

2.6. Study outcomes

The primary outcome is the composite of safety and efficacy endpoint at 12 months post-randomization (all 3 criteria must be fulfilled):

Table 1
Inclusion and exclusion criteria.

Inclusion Criteria	Exclusion Criteria
Chronic asymptomatic AR grades 3 and grade 4	Age <18 years
Surgery not indicated when enrolled	Creatinine Clearance <30 mL/min
Left ventricular ejection fraction >50 %	Absolute contraindication of CMR examination
Concomitant valve disease less than moderate	Pregnancy
Absence of complex congenital heart disease	Permanent atrial fibrillation

AR – aortic regurgitation, CMR – cardiac magnetic resonance.

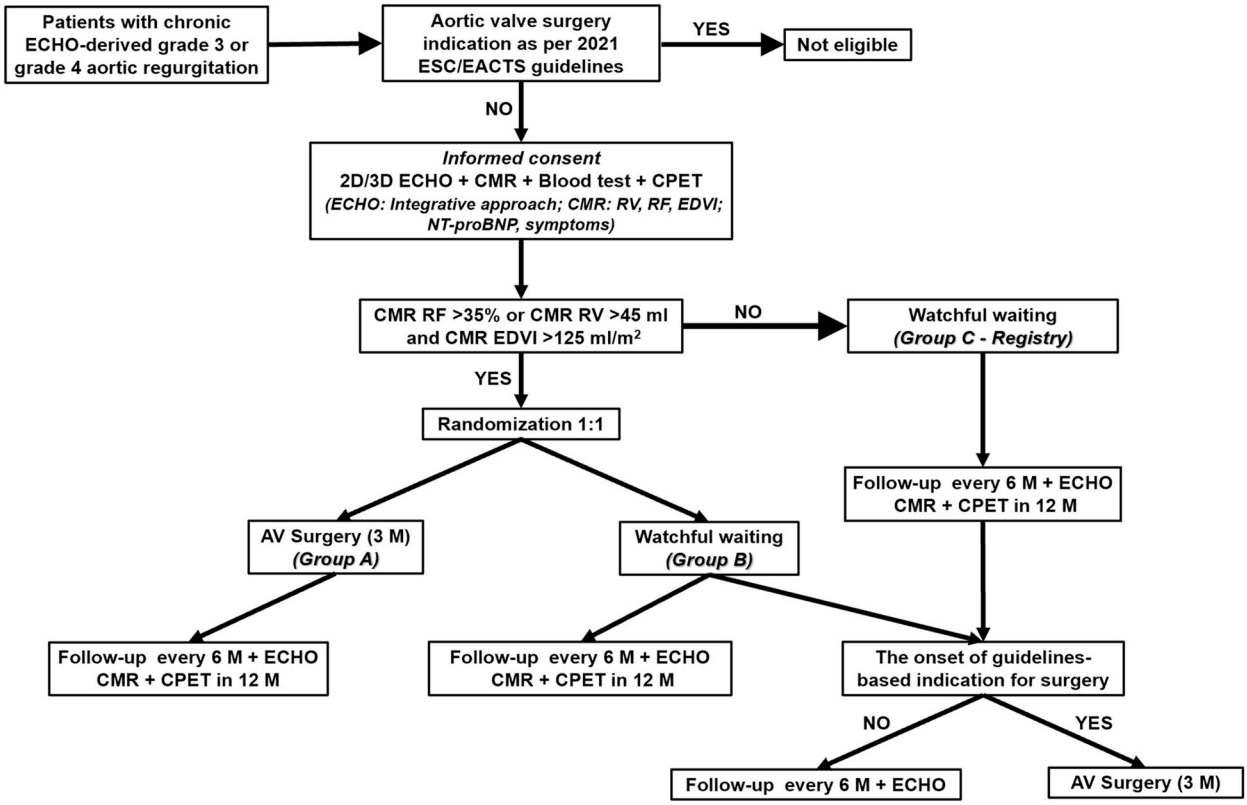

Fig. 1. Study flow chart.

1) Reverse LV remodeling (CMR-derived EDVI decrease >15 % compared to baseline)
2) LV ejection fraction >50 %
3) Absence of major adverse cardiovascular events (MACE) (cardiovascular mortality, stroke, myocardial infarction, heart failure, infective endocarditis, a new guidelines-based indication of aortic surgery).

Table 2 shows a summary of the study endpoints.

2.7. Diagnostic procedures

2.7.1. Echocardiography

Standardized ECHO protocol necessitates the acquisition of parasternal and apical views using a high-end echocardiograph, preferably Vivid (GE Healthcare, Horten, Norway) at baseline and in 12 months follow-up in all patients in each participating center. The ultrasound system must be equipped with 2D and 4-dimensional active-matrix volume phased array probes. Three R–R intervals will be stored for each loop. Apical 2- and 4- 4-Chamber and long-axis views and 3D datasets will be acquired with recordings optimized for frame rate, depth, sector size, gain, number of heartbeats, and breath-hold). All acquired images will be fully anonymized and stored under a patient's unique study number. The dataset will be analyzed offline using commercially available software

Table 2
Study endpoints.

Primary composite endpoint	Secondary endpoints
Safety and efficacy at 12 months (all criteria are mandatory) 1) 15 % baseline CMR-derived LVEDVI reduction 2) Left ventricular ejection fraction >50 % 3) No MACE recorded	10 % quality of life questionnaire improvement 10 % maximal oxygen consumption improvement NT-proBNP <112 ng/L In hospital and 30 days mortality Time to cardiovascular death Time to first heart failure hospitalization Major bleeding

CMR – cardiac magnetic resonance, EDVI – end-diastolic volume index, MACE – major adverse cardiovascular events, NT-proBNP - N-terminal pro-brain natriuretic peptide.

(EchoPac, TOMTEC-Arena). The endocardial border of the LV will be manually contoured to assess 2D LV volumes and LVEF using the biplane disk summation method. To perform a 3D LV assessment, the semi-automatic contouring method will be utilized. The 2D and 3D LV longitudinal strains will be measured using semi-automatic contouring with manual correction. Additionally, whenever possible, the 3D vena contracta area will be measured in 3D reconstruction after the reduction of color flow gain to measure the vena contracta area by tracing the high-velocity core, the last of which remains after gain reduction.

2.7.2. Cardiac magnetic resonance

CMR will be performed at baseline and 12 months follow-up in each participating center according to the study protocol. Protocol scan includes images such as pilots, T1 and T2 weighted images, cine images (2-, 4-, 3-Chamber and short-axis images covering the entire end-diastolic ventricular length), late gadolinium enhancement, and T1 mapping images (preferentially Modified Look-Locker sequence). Cine images will be acquired using steady-state, a free precession sequence with retrospective ECG gating and standard sequence parameters (slice thickness of 6.0–8.0 mm without gap). The extent of myocardial edema will be evaluated using a standard short tau inversion recovery sequence with fat suppression in short-axis planes. The single breath-hold ECG-triggered phase-sensitive inversion recovery gradient echo sequence will be used to assess the presence of late gadolinium enhancement in 2-, 4-Chamber, and short-axis planes covering the ventricular length at 10–15 min after contrast agent administration. The contrast agent used will be gadobutrol 1.0 mmol/mL (Gadovist, Bayer) at a dose of 0.15 mL/kg.

The flow sequence – strictly perpendicular to the blood flow, the breath-hold through-plane phase-contrast velocity mapping sequence with retrospective ECG gaiting will be acquired (slice thickness 6 mm) with careful velocity settings at four levels: sino-tubular junction and 5 mm above the aortic annulus (planning during diastole), leaflets tips level (planning in systole) and flow in the descending aorta in the axial plane at the level of the pulmonary trunk. The images will be fully anonymized and stored under a patient's unique study number. **The C*MR Image analysis*** will be performed in the CoreLab fully blinded utilizing a software Segment (Medviso, Sweden). The flow within the aortic root will be calculated semiautomatically with manual corrections and background velocity offset errors post-processing corrections. Left and right ventricular volumes and ejection fraction will be calculated from short-axis slices covering the entire ventricular volumes corrected with 2-, 4-, 3- Chamber and right ventricular outflow tract images for the exact valvular position. The endocardial border will be contoured semi-automatically.

2.7.3. Exercise stress test

All patients will undergo an exercise stress test – preferably CPET - at baseline and a 12-month follow-up in each participating center. Patients without cardiac chest pain, pathological shortness of breath, fatigue, ischemic electrocardiographic changes, ventricular tachycardia, or abnormally slow blood pressure rise during the stress test, will be considered eligible for the study. The follow-up CPET will be used to measure the changes in exercise performance. CPET will be performed on a bicycle ergometer (Ergoselect, Ergoline, Germany) with gas exchange measured using properly serviced and calibrated breath-by-breath metabolic cart specific for each center - MetaLyzer 3B (Cortex, Germany), Quark CPET (Cosmed, Italy) or PowerCube (Ganshorn, Germany). The maximal incremental ramp protocol will be applied with the final visit setting equal to the initial visit. The test will be terminated upon the patient's exhaustion, limiting symptoms, or significant abnormal reaction. Metabolic maximum will be defined as the patient's rate of perceived exhaustion $\geq$18 and respiratory exchange ratio $>$1.12 not using the target heart rate for frequent beta-blocker use. Respiratory data will be processed by mid-5 of 7 filtering for trends and 30s non-outlier average for maximum.

2.7.4. Laboratory analysis

Fasting blood samples will be obtained during each visit and serum levels of Hemoglobin, C-reactive protein, Hemoglobin A1c, Creatinine, Glucose, and N-terminal pro-brain natriuretic peptide will be measured. Creatinine clearance will be calculated using the Cockcroft-Gault equation. One sample of frozen plasma will be stored for future analyses.

2.7.5. Aortic valve surgery

Aortic valve surgery will be performed in each participating center by an experienced surgeon who is a member of the study team. Commercially available prosthetic valves, either mechanical or xenografts, have a significant risk of valve-related complications (bleeding, thromboembolic, etc.) and the risk of premature degenerations in xenografts [23]. The lifetime risk of these complications is higher in younger patients and is translated into suboptimal survival compared to age and sex-matched general population [24]. Aortic valve-sparing surgery and aortic valve repair are well-established surgical techniques in patients with tricuspid and bicuspid regurgitant aortic valves. These procedures significantly reduce the risk of valve-related complications and restore optimal survival [25]. Therefore, aortic valve-sparing procedures and aortic valve repair should be the procedures of choice, in patients randomized for early surgical treatment, whenever it is technically feasible. In patients, in whom the aortic valve is not repairable, the choice of the valve substitute is based on the patient's preferences. The Ross procedure will represent an attractive alternative to standard aortic valve replacement exceptionally in centers with deep experience. This is supported by published data showing a good quality of life and excellent long-term survival after the Ross procedure [26].

2.7.6. Sample size and statistical considerations

Power calculation: We plan to enroll a total of 217 patients across all centers within the first 36 months of the project. Power calculation was based on assumptions derived from our pilot study [17]. We presume that the CMR-derived inclusion criteria for randomization will be fulfilled in 24 % of included patients. The cardiac CMR-derived LV EDVI as a baseline was 116 ml/m2 with a standard deviation of 30 ml/m2 and an estimated reduction of LV by 20 %, i.e. 92.8 ml/m2. Alpha was set at 0.05 and required power

at standard 80 %. An online calculator (https://clincalc.com/stats/samplesize.aspx) was used to define the required sample size.

The study will be designed as a time to composite safety and efficacy outcomes in a short-term 12-month analysis. An adaptive design will be employed for long-term follow-up analysis with the possibility of increasing the study size or duration based on interim unblinded analysis. The long-term follow-up will be annual, including clinical, echocardiography, and laboratory examination. The interim unblinded analysis will be conducted annually to monitor major adverse cardiovascular events, which are defined as a composite of nonfatal stroke, nonfatal myocardial infarction, cardiovascular death, major bleeding, heart failure hospitalization, and infective endocarditis.

2.7.7. Study organization

Steering Committee: Data and safety monitoring committee: A steering committee guides the protocol preparation, ensures that the study is conducted by the study protocol, and supervises the interpretation of the results.

Data and safety monitoring board: The Independent Data and Safety Monitoring Board will review and evaluate the accumulated study data 20 and 30 months after study initiation. They will check for participant safety, the course, and the effectiveness of the study. When appropriate they might make recommendations in terms of study continuation and/or modification or premature termination.

Adverse events recording: All adverse events obtained through the subjects' interviews, physical examinations laboratory analysis, or any other means will be recorded using an electronic case report form. The investigator will be obliged to record all adverse events from randomization until the final visit, regardless of whether they occurred in connection with the study or not. If the event is resolved during the study, the end date will be recorded in the case report form. Adverse events will be ongoing at the final visit and will be followed up for an adequately long time to be able to evaluate patients' safety.

2.7.8. Data collection and protection

Patients' data are anonymized according to General Data Protection Regulation and databased in a common electronic database (RedCap 12.5.12, Vanderbilt University, Nashville, U.S.) for all participating centers. It requires a unique identification code for a patient and a center. Under no circumstances will the patient data such as name, address, or other contact details be collected. The electronic database is built and managed by a professional mathematician.

The protection of personal data is ensured by Act No. 101/2000 on the protection of personal data, as amended, and with Council directive 95/46/EC of the European Parliament. Generally, the principle of identifying the ownership of the data record is respected by clearly assigning the user's login to the created record. System users are only allowed access after entering a valid username and password. Key user management features include the user rights system. This feature minimizes the possibility of data misuse in the case of an unguarded computer. Data sources will be handled by the Cyber Security Act 181/2014 Coll.

3. Discussion

This is the first randomized, investigator-driven, prospective surgical trial to our knowledge in patients with severe asymptomatic AR. The lack of respected guidelines consensus on clear cut-off criteria to trigger aortic valve surgery [7] may lead to either too early or, conversely, too late intervention, with all its consequences. Taking into account recent scientific papers and our previous work, we have designed a study using new imaging indices with proven prognostic value to identify asymptomatic patients with severe AR at risk of early disease progression. The decision to use preferentially cardiac CMR for patient selection is based on recent publications showing the superiority of CMR over ECHO for AR quantification [27]. Moreover, CMR is recognized as a gold standard for the assessment of ventricular size, function, and myocardial structure. Over half of the patients with severe AR have bicuspid aortic valves, which are often associated with an eccentric regurgitant jet or multiple jets [15,17] making the ECHO quantification challenging. A significant disagreement to differentiate moderate from severe AR between the ECHO integrated approach and CMR has been documented [14,15,17,27]. Based on current publications, the most accurate prognostic markers are CMR-derived RV and RF followed by CMR-derived LV volumes [14–17]. Nevertheless, 2D ECHO remains an irreplaceable imaging method for AR detection, assessment of valve morphology and the etiology of regurgitation, patient follow-up, perioperative guidance, or in case of contra-indications for CMR [28]. Modern 2D global longitudinal strain and novel 3D ECHO techniques such as 3D vena contracta area [17,29] have shown a prognostic value, but their use is limited to highly specialized centers. In the final analysis, we will evaluate the prognostic significance of individual imaging markers.

The current study will use a combination of imaging markers of AR severity, i.e., CMR RV or CMR RF, and LV remodeling,i.e., CMR LVEDVI, with the strongest prognostic value for patient selection. The cut-off values of these parameters are set up relatively high to assure that the selected patients will have advanced AR with a high probability of developing a guideline indication within one year, for details see the previous paragraph on The Rationale for patient selection and Randomization.

Only surgical centers of excellence for aortic valve surgery with access to high-quality cardiac CMRs will be invited to participate in the study. When amenable, valve-sparing surgery will be preferred. The Ross procedure might be an alternative for aortic valve replacement in the younger population, but only for centers with high experience with this particular surgical technique.

We assume, that the surgical risk of included patients will be low because of younger age and infrequent comorbidities. Furthermore, we assume that, within 8–10 months of surgery, the LV size and function will recover completely. This is a desired benefit of early surgery which might be followed by better quality of life, and lower cardiac morbidity and mortality compared to late intervention. A certain increase of redo surgery in patients' life span must be taken into account but may be tempered by the required state-of-the-art surgery and also by an ever-expanding spectrum of percutaneous structural interventions.

4. Conclusions

The main purpose of our study is to investigate if an implementation of new CMR-derived parameters can facilitate the decision on the timing of surgical intervention in asymptomatic patients with chronic severe AR. The priority is to make the study safe. So, all included patients will have advanced disease with a high risk of early clinical progression but not yet fulfilling the guidelines indication for aortic valve surgery. A thorough analysis of the prognostic value of modern 2D and 3D echocardiography markers is part of the project.

CRediT authorship contribution statement

Radka Kočková: Writing – original draft, Validation, Supervision, Project administration, Methodology, Investigation, Conceptualization. **Jan Vojáček:** Validation, Methodology, Conceptualization. **Helena Bedáňová:** Methodology. **Petr Fila:** Methodology. **Ivo Skalský:** Methodology. **Daniela Žáková:** Methodology. **Michal Klán:** Methodology. **Barbora Míková:** Methodology. **Karel Mědílek:** Methodology. **Martin Tuna:** Methodology. **Monika Fialová:** Methodology. **Radka Dvořáková:** Methodology. **Zuzana Hlubocká:** Methodology. **Roman Panovský:** Methodology. **Kryštof Slabý:** Methodology. **Elayne Kelen de Oliveira:** Methodology. **Filip Casselman:** Methodology. **Martin Pěnička:** Writing – review & editing, Writing – original draft, Methodology, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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The author Elayne Kelen de Oliveira is currently attending the Cardiopath PhD program.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e29470.

References

[1] J.P. Singh, J.C. Evans, D. Levy, et al., Prevalence and clinical determinants of mitral, tricuspid, and aortic regurgitation (the Framingham Heart Study), Am. J. Cardiol. 83 (6) (1999) 897–902, https://doi.org/10.1016/S0002-9149(98)01064-9.

[2] B. Iung, A prospective survey of patients with valvular heart disease in Europe: the Euro heart Survey on valvular heart disease, Eur. Heart J. 24 (13) (2003) 1231–1243, https://doi.org/10.1016/S0195-668X(03)00201-X.

[3] B. Iung, V. Delgado, R. Rosenhek, et al., Contemporary presentation and management of valvular heart disease the EURObservational research programme valvular heart disease II survey, Circulation 140 (14) (2019) 1156–1169, https://doi.org/10.1161/CIRCULATIONAHA.119.041080.

[4] W.K.F. Kong, J.J. Bax, H.I. Michelena, V. Delgado, Sex differences in bicuspid aortic valve disease, Prog. Cardiovasc. Dis. 63 (4) (2020) 452–456, https://doi.org/10.1016/j.pcad.2020.06.004.

[5] A. Vahanian, F. Beyersdorf, F. Praz, et al., 2021 ESC/EACTS Guidelines for the management of valvular heart disease, Eur. Heart J. 43 (7) (2022) 561–632, https://doi.org/10.1093/eurheartj/ehab395.

[6] Writing Committee Members, C.M. Otto, R.A. Nishimura, et al., ACC/AHA guideline for the management of patients with valvular heart disease: a report of the American college of Cardiology/American heart association joint committee on clinical practice guidelines, J. Am. Coll. Cardiol. 77 (4) (2020) e25–e197, https://doi.org/10.1016/j.jacc.2020.11.018, 2021.

[7] V. Galusko, G. Thornton, C. Jozsa, et al., Aortic regurgitation management: a systematic review of clinical practice guidelines and recommendations, Eur Heart J - QCCO 8 (2) (2022) 113–126, https://doi.org/10.1093/ehjqcco/qcac001.

[8] L.T. Yang, H.I. Michelena, C.G. Scott, et al., Outcomes in chronic hemodynamically significant aortic regurgitation and limitations of current guidelines, J. Am. Coll. Cardiol. 73 (14) (2019) 1741–1752, https://doi.org/10.1016/j.jacc.2019.01.024.

[9] C. de Meester, B.L. Gerber, D. Vancraeynest, et al., Do guideline-based indications result in an outcome penalty for patients with severe aortic regurgitation? JACC Cardiovasc Imaging 12 (11 Pt 1) (2019) 2126–2138, https://doi.org/10.1016/j.jcmg.2018.11.022.

[10] A. Mentias, K. Feng, A. Alashi, et al., Long-term outcomes in patients with aortic regurgitation and preserved left ventricular ejection fraction, J. Am. Coll. Cardiol. 68 (20) (2016) 2144–2153, https://doi.org/10.1016/j.jacc.2016.08.045.

[11] M. Malahfji, A. Senapati, B. Tayal, et al., Myocardial scar and mortality in chronic aortic regurgitation, J. Am. Heart Assoc. 9 (23) (2020) e018731, https://doi.org/10.1161/JAHA.120.018731.

[12] M.Y. Desai, Aortic regurgitation: are we operating too late? Ann. Cardiothorac. Surg. 8 (3) (2019) 39092–39392, https://doi.org/10.3978/16600.

[13] K.S. Dujardin, M. Enriquez-Sarano, H.V. Schaff, K.R. Bailey, J.B. Seward, A.J. Tajik, Mortality and morbidity of aortic regurgitation in clinical practice. A long-term follow-up study, Circulation 99 (14) (1999) 1851–1857.

[14] S.G. Myerson, J. d'Arcy, R. Mohiaddin, et al., Aortic regurgitation quantification using cardiovascular magnetic resonance: association with clinical outcome, Circulation 126 (12) (2012) 1452–1460, https://doi.org/10.1161/CIRCULATIONAHA.111.083600.

[15] A.W. Harris, E.V. Krieger, M. Kim, et al., Cardiac magnetic resonance imaging versus transthoracic echocardiography for prediction of outcomes in chronic aortic or mitral regurgitation, Am. J. Cardiol. 119 (7) (2017) 1074–1081, https://doi.org/10.1016/j.amjcard.2016.12.017.
[16] P. Vejpongsa, J. Xu, M.A. Quinones, D.J. Shah, W.A. Zoghbi, Differences in cardiac remodeling in left-sided valvular regurgitation, JACC (J. Am. Coll. Cardiol.): Cardiovascular Imaging 15 (10) (2022) 1730–1741, https://doi.org/10.1016/j.jcmg.2022.05.006.
[17] R. Kočková, H. Línková, Z. Hlubocká, et al., Multiparametric strategy to predict early disease decompensation in asymptomatic severe aortic regurgitation, Circ Cardiovasc Imaging 15 (12) (2022) e014901, https://doi.org/10.1161/CIRCIMAGING.122.014901.
[18] A. Alashi, T. Khullar, A. Mentias, et al., Long-term outcomes after aortic valve surgery in patients with asymptomatic chronic aortic regurgitation and preserved LVEF: impact of baseline and follow-up global longitudinal strain, JACC Cardiovasc Imaging 13 (1 Pt 1) (2020) 12–21, https://doi.org/10.1016/j.jcmg.2018.12.021.
[19] A.A. Kammerlander, M. Wiesinger, F. Duca, et al., Diagnostic and prognostic utility of cardiac magnetic resonance imaging in aortic regurgitation, JACC Cardiovasc Imaging 12 (8 Pt 1) (2019) 1474–1483, https://doi.org/10.1016/j.jcmg.2018.08.036.
[20] M. Weber, M. Hausen, R. Arnold, et al., Diagnostic and prognostic value of N-terminal pro B-type natriuretic peptide (NT-proBNP) in patients with chronic aortic regurgitation, Int. J. Cardiol. 127 (3) (2008) 321–327, https://doi.org/10.1016/j.ijcard.2007.07.174.
[21] R. Pizarro, O.O. Bazzino, P.F. Oberti, et al., Prospective validation of the prognostic usefulness of B-type natriuretic peptide in asymptomatic patients with chronic severe aortic regurgitation, J. Am. Coll. Cardiol. 58 (16) (2011) 1705–1714, https://doi.org/10.1016/j.jacc.2011.07.016.
[22] A. Senapati, M. Malahfji, D. Debs, et al., Regional replacement and diffuse interstitial fibrosis in aortic regurgitation, JACC (J. Am. Coll. Cardiol.): Cardiovascular Imaging 14 (11) (2021) 2170–2182, https://doi.org/10.1016/j.jcmg.2021.04.028.
[23] K. Hammermeister, G.K. Sethi, W.G. Henderson, F.L. Grover, C. Oprian, S.H. Rahimtoola, Outcomes 15 years after valve replacement with a mechanical versus a bioprosthetic valve: final report of the Veterans Affairs randomized trial, J. Am. Coll. Cardiol. 36 (4) (2000) 1152–1158, https://doi.org/10.1016/s0735-1097(00)00834-2.
[24] N. Glaser, M. Persson, V. Jackson, M.J. Holzmann, A. Franco-Cereceda, U. Sartipy, Loss in life expectancy after surgical aortic valve replacement: SWEDEHEART study, J. Am. Coll. Cardiol. 74 (1) (2019) 26–33, https://doi.org/10.1016/j.jacc.2019.04.053.
[25] B. Arabkhani, A. Mookhoek, Centa I. Di, et al., Reported outcome after valve-sparing aortic root replacement for aortic root aneurysm: a systematic review and meta-analysis, Ann. Thorac. Surg. 100 (3) (2015) 1126–1131, https://doi.org/10.1016/j.athoracsur.2015.05.093.
[26] J. Gofus, P. Fila, S. Drabkova, et al., Ross procedure provides survival benefit over mechanical valve in adults: a propensity-matched nationwide analysis, Eur. J. Cardio. Thorac. Surg. 61 (6) (2022) 1357–1365, https://doi.org/10.1093/ejcts/ezac013.
[27] R.P. Steeds, S.G. Myerson, Imaging assessment of mitral and aortic regurgitation: current state of the art, Heart 106 (22) (2020) 1769–1776, https://doi.org/10.1136/heartjnl-2019-316216.
[28] P. Lancellotti, C. Tribouilloy, A. Hagendorff, et al., Recommendations for the echocardiographic assessment of native valvular regurgitation: an executive summary from the European Association of Cardiovascular Imaging, Eur Heart J - Cardiovascular Imaging 14 (7) (2013) 611–644, https://doi.org/10.1093/ehjci/jet105.
[29] R. Kockova, H. Linkova, Z. Hlubocka, et al., New imaging markers of clinical outcome in asymptomatic patients with severe aortic regurgitation, J. Clin. Med. 8 (10) (2019), https://doi.org/10.3390/jcm8101654.