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MINIMALLY INVASIVE AORTIC VALVE REPLACEMENT

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THESIS FOR DOCTORAL DEGREE (Ph.D.)

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ABSTRACT

Background
Minimally invasive aortic valve replacement (AVR) through a ministernotomy has been developed as an alternative approach to conventional full sternotomy AVR. During recent years, sutureless aortic bioprostheses were introduced with the aim to facilitate implantation, especially in minimally invasive procedures. The aim of this thesis was to evaluate minimally invasive and sutureless AVR on the aspects of clinical outcomes, cardiac function, and prosthetic valve function.

Methods and Results
Study I Early postoperative outcomes and 2-year survival after isolated AVR with the Perceval sutureless bioprosthetic valve (LivaNova, Milan, Italy) performed through ministernotomy compared with full sternotomy was investigated. Of 267 patients, 189 (70.8%) were performed through ministernotomy and 78 through full sternotomy. Aortic cross-clamp (44 minutes in both groups) and cardiopulmonary bypass time (69 vs. 74 minutes, p=0.363) did not differ between the groups after propensity score matching. Apart from slightly higher postoperative transvalvular gradients in the ministernotomy group, early postoperative outcomes did not differ. There were no differences regarding in-hospital mortality rate or 2-year survival between the groups.

Study II Early postoperative outcomes and 2-year survival after isolated AVR through ministernotomy with implantation of a sutureless bioprosthesis compared with full sternotomy with implantation of a stented bioprosthesis was studied. Of 565 patients, 182 (32%) underwent ministernotomy with a sutureless bioprosthesis and 383 full sternotomy with a stented bioprosthesis. Aortic cross-clamp (40 vs. 65 min, p<0.001) and cardiopulmonary bypass time (69 vs. 87 min, p<0.001) were shorter in the ministernotomy sutureless group after propensity score matching. Patients undergoing ministernotomy received less packed red blood cells but the risk for postoperative permanent pacemaker implantation was higher. There were no differences regarding 30-day mortality or 2-year survival between the two groups.

Study III Right ventricular function after AVR was investigated in forty patients undergoing primary isolated AVR randomized to ministernotomy or full sternotomy. Four days postoperatively, tricuspid annular plane systolic excursion had decreased in both the ministernotomy and the sternotomy group (ministernotomy: 25 vs. 16 mm, p<0.001; sternotomy: 22.5 vs. 8 mm, p<0.001) but was higher in the ministernotomy group (p<0.001). Pulsed wave tissue Doppler right ventricular velocity decreased significantly in patients who underwent sternotomy (10.5 vs. 6.5 cm/s, p<0.001) but did not decrease significantly in patients who underwent ministernotomy (11.5 cm/s vs. 10 cm/s, p=0.054). Right ventricular fractional area change was equally decreased in both groups (ministernotomy: 46 vs. 38 %, p<0.001; sternotomy: 45 vs. 37 %, p=0.003). The differences between the groups were similar 40 days postoperatively.

Study IV Hypo-attenuated leaflet thickening (HALT) and reduced leaflet motion (RLM) assessed with cardiac computed tomography were studied in 47 patients who underwent AVR and received a Perceval sutureless bioprosthetic valve. Also, the relation between HALT and RLM and the influence of anticoagulation treatment on HALT and RLM were investigated. Hypo-attenuated leaflet thickening was found in 18 (38%) patients and RLM in 13 (28%) patients. All patients with RLM had HALT. Both HALT and RLM was found in patients with ongoing anticoagulation treatment. Hypo-attenuated leaflet thickening and RLM were not associated with clinical symptoms.

Conclusions
[1] AVR with implantation of the Perceval sutureless bioprosthetic valve through a ministernotomy was a safe procedure with early postoperative outcomes and 2-year survival comparable to full sternotomy AVR. Procedural times were not prolonged in patients undergoing ministernotomy compared to patients undergoing full sternotomy. [2] AVR through a ministernotomy with implantation of a sutureless bioprosthetic valve was associated with shorter procedural times and less transfusion of packed red blood cells, but a higher risk for permanent pacemaker implantation compared with a full sternotomy with implantation of a stented bioprosthesis. [3] Right ventricular long axis function was reduced after both ministernotomy and full sternotomy aortic valve replacement, but the reduction was more pronounced in the full sternotomy group. Global right ventricular function was equally impaired after ministernotomy and full sternotomy AVR. [4] Hypo-attenuated leaflet thickening and RLM were prevalent in the Perceval sutureless bioprosthetic valve. Both HALT and RLM was found in patients with ongoing anticoagulation treatment.

LIST OF SCIENTIFIC PAPERS

I. **Dalén M**, Biancari F, Rubino AS, Santarpino G, De Praetere H, Kasama K, Juvonen T, Deste W, Pollari F, Meuris B, Fischlein T, Mignosa C, Gatti G, Pappalardo A, Sartipy U, Svenarud P.
Ministernotomy versus full sternotomy aortic valve replacement with a sutureless bioprosthesis: A multicenter study.
Ann Thorac Surg. 2015;99:524-530

II. **Dalén M**, Biancari F, Rubino AS, Santarpino G, Glaser N, De Praetere H, Kasama K, Juvonen T, Deste W, Pollari F, Meuris B, Fischlein T, Mignosa C, Gatti G, Pappalardo A, Svenarud P, Sartipy U.
Aortic valve replacement through full sternotomy with a stented bioprosthesis versus minimally invasive sternotomy with a sutureless bioprosthesis.
Eur J Cardiothorac Surg. 2016;49:220-227

III. **Dalén M**, Oliveira Da Silva C, Sartipy U, Winter R, Franco-Cereceda A, Barimani J, Bäck M, Svenarud P.
Right ventricular function after aortic valve replacement through ministernotomy versus full sternotomy: A randomized controlled trial.
Submitted

IV. **Dalén M**, Sartipy U, Cederlund K, Franco-Cereceda A, Svensson A, Themudo R, Svenarud P, Bacsovics Brolin E.
Hypo-attenuated leaflet thickening and reduced valve leaflet motion in sutureless bioprosthetic aortic valves.
Submitted

CONTENTS

LIST OF ABBREVIATIONS

AVR	Aortic valve replacement
CT	Computed tomography
FAC	Fractional area change
HALT	Hypo-attenuated leaflet thickening
RLM	Reduced leaflet motion
RV	Right ventricular
TAPSE	Tricuspid annular plane systolic excurison
TAVI	Transcatheter aortic valve implantation

INTRODUCTION

Aortic valve replacement (AVR) is the definitive treatment for severe aortic stenosis and has traditionally been performed through a median full sternotomy. Minimally invasive AVR was developed as an alternative approach to full sternotomy AVR to reduce surgical trauma while maintaining the efficacy and safety of a full sternotomy and was first described in 1993 [1]. Today, minimally invasive AVR is predominantly performed through an upper hemisternotomy, also known as a ministernotomy. Previous studies have demonstrated that ministernotomy AVR can be performed safely without risk for increased early mortality and with possible benefits in terms of shorter intensive care unit and hospital stay compared with conventional AVR [2-6].

One drawback of minimally invasive AVR is that it is associated with a reduction of surgical exposure and working space, which makes it a more technically demanding procedure compared with conventional AVR. This is reflected in prolonged aortic cross-clamp and cardiopulmonary bypass time [2, 3], which may offset the benefits of minimally invasive incisions [7-9]. Therefore, it has been hypothesized that ways to shorten procedural time may be of importance in minimally invasive AVR. During recent years sutureless aortic bioprosthetic valves have been introduced in order to facilitate implantation, especially in minimally invasive procedures, and thereby possibly shorten procedural time [10-13].

The aim of this thesis was to evaluate minimally invasive and sutureless AVR on the aspects of clinical outcomes, cardiac function, and prosthetic valve function.

BACKGROUND

Aortic stenosis

Aortic stenosis is the most prevalent cardiac valve pathology in the western world, with a prevalence of 2-7% for individuals over the age of 65 years [14, 15]. The primary etiology in adults is calcification of the valve and the incidence is increasing, which reflects an ageing of the general population. Aortic stenosis is a chronic disease, slowly progressing over a long subclinical period which varies in duration between individuals. After the onset of symptoms the expected survival is very low with a 5-year estimated survival rate within the range of 15-50% [16]. The classic symptom triad consists of effort dyspnea, angina, and syncope. Echocardiography is used to confirm the diagnosis and assess the severity of the valve disease. No medical treatment for aortic stenosis has been shown to improve outcomes. Retrospective studies have shown positive effects of statins but this has not been confirmed in randomized trials [17].

Aortic valve replacement

AVR is the definitive treatment for severe aortic stenosis and is strongly recommended in symptomatic patients with no contraindications for cardiac surgery. Decision regarding operation is largely based on presence of symptoms. Aortic valvotomy was first described in 1947 but a more effective treatment for aortic valve disease was possible after the introduction of cardiopulmonary bypass in 1954. Initially, only aortic valvotomy and decalcification was performed but a single-leaflet prosthesis was soon developed, followed by the first single-unit prosthesis, the polytetrafluoroethylene sleeve prosthesis, first implanted in 1961. The ball valve prosthesis was first reported in 1963, the pulmonary autograft for AVR first used in 1967, and sequentially other biological autograft valves were implanted. Stentless porcine aortic valves was first implanted in 1965 followed by stent-mounted porcine valves in 1967 and frame-mounted bovine pericardial valves in 1971 [18]. The first transcatheter bioprosthetic valve implantation was performed in 2002 [19].

Today operative mortality is low in patients undergoing AVR (1-3% in patients younger than 70 years) and factors associated with increased mortality include advanced age, female gender, comorbidities, symptoms of heart failure, left ventricular dysfunction, and previous cardiac surgery [16, 20]. Surgery improves symptoms and quality of life and increases survival. For older patients, long-term survival after AVR is similar to the age-matched population whereas younger patients have a lower survival compared to the age-matched population [16].

In patients undergoing AVR through a full median sternotomy (FIGURE 1), a vertical midline skin incision is made from the suprasternal notch to the xiphoid, the suprasternal ligament is cut, followed by the complete midline division of the sternum. The pericardium is fully opened in the midline. Cardiopulmonary bypass is established with central venous and arterial cannulation and catheters for cardioplegia delivery are placed in the ascending aorta and possibly in the coronary sinus. The

ascending aorta is occluded with a cross-clamp and blood or crystalloid cardioplegia is delivered into the coronary arteries antegrade through the aortic root or retrograde through the coronary sinus. The aorta is incised anteriorly above the origin of the coronary arteries and continued either transversely or caudally through the sinotubular junction. The native aortic valve is excised and the aortic annulus decalcified and sized with prosthesis-specific sizers. Sutures are most frequently placed in the aortic annulus from the ventricular side using an interrupted mattress suturing technique and the prosthesis parachuted into the aortic annulus. After prosthesis implantation, the aortotomy is closed, cardiopulmonary bypass weaned, and cannulas removed. After weaning from cardiopulmonary bypass, proper function of the prosthetic valve and presence of any paravalvular regurgitation are assessed with transesophageal echocardiography. The pericardium is left open and the sternum sutured with steel wires.

Minimally invasive aortic valve replacement

Minimally invasive heart valve surgery is defined as a valve surgery procedure not performed through a full sternotomy but with a small chest wall incision [21, 22]. Minimally invasive AVR was developed as an alternative approach to full sternotomy AVR with the aim to reduce surgical trauma, while maintaining the efficacy and safety of a median full sternotomy conventional AVR procedure [22]. Minimally invasive AVR was first described in 1993 when anterior thoracotomy was described as an incision for AVR [1]. A wide variety of incisions have been used during the years, including upper, lower, and transverse sternotomy as well as parasternal incisions. Today, minimally invasive AVR is predominantly performed through an upper hemisternotomy, also known as a ministernotomy (FIGURE 2), but the anterior thoracotomy approach is also frequently used (FIGURE 3) [23]. Previous studies of the current era of ministernotomy AVR have shown good results without risk for increased early mortality and with possible small benefits in shorter intensive care unit and hospital stay compared with conventional AVR [2-6]. Generally, the evidence is based on retrospective reports and randomized trials are lacking [4]. The few randomized trials that have been performed have likely been underpowered to demonstrate potential differences in clinical outcomes [24-27], but a meta-analysis of randomized trials demonstrated a marginally decreases in intensive care unit length of stay in patients undergoing ministernotomy [28].

However, minimally invasive AVR is associated with a reduction of surgical exposure and working space, which makes it a more technically demanding procedure than conventional AVR. This is reflected in prolonged aortic cross-clamp and cardiopulmonary bypass time [2, 3], which may offset the benefits of minimally invasive incisions [7-9].

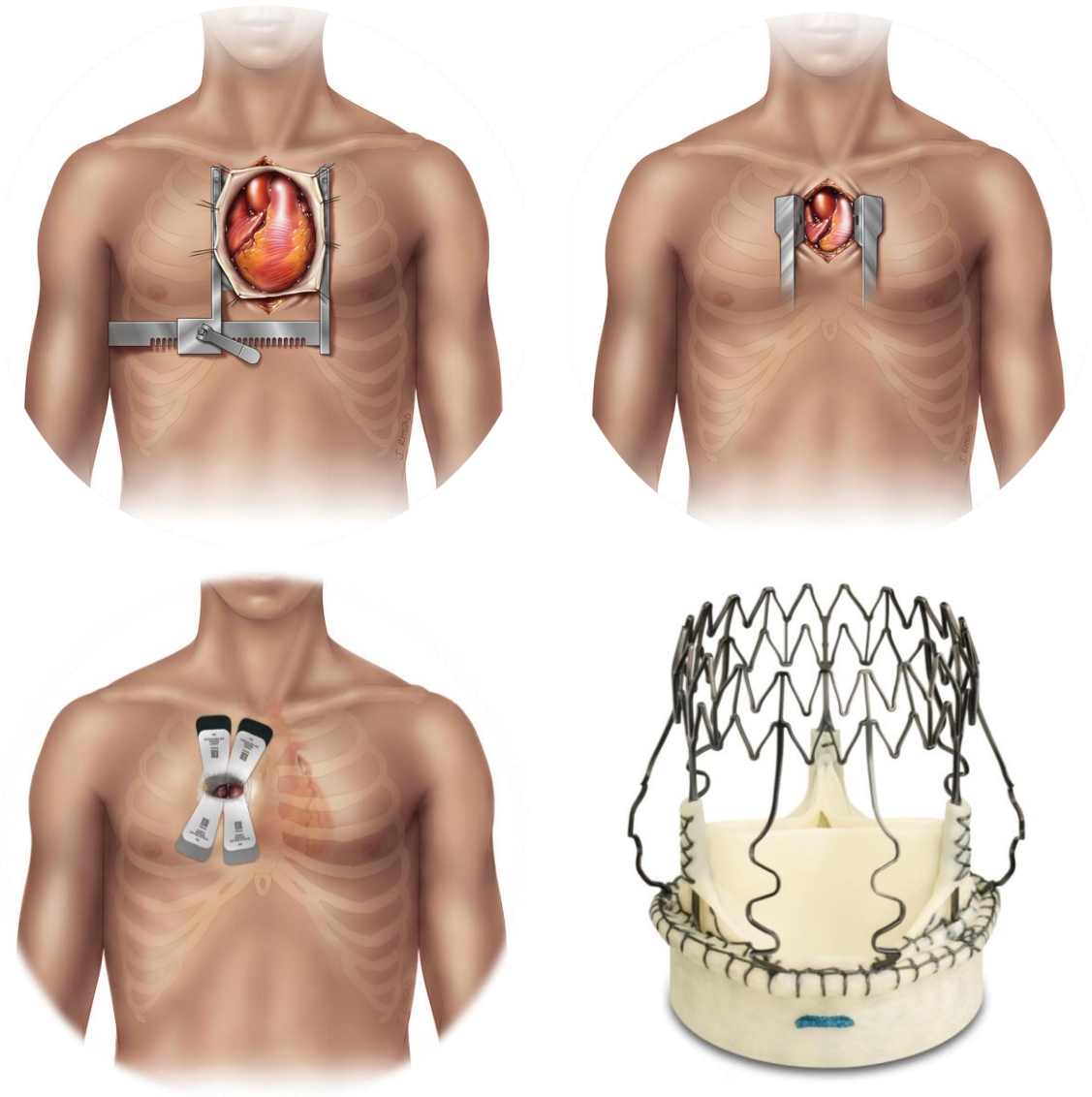

FIGURE 1-4. Incisions used for aortic valve replacement: full median sternotomy (upper left), ministernotomy (upper right), and anterior thoracotomy (lower left). The Perceval sutureless bioprosthetic valve (LivaNova, Milan, Italy; lower right). Images provided courtesy of Edwards Lifesciences, Irvine, CA, USA, and LivaNova, Milan, Italy.

Transcatheter aortic valve implantation

In patients with severe symptomatic aortic stenosis deemed not suitable for cardiac surgery, transcatheter aortic valve implantation (TAVI) can be considered [29, 30]. Transcatheter aortic valve implantation is recommended for patients who are assessed as inoperable or at very high surgical risk by a heart team including a cardiac surgeon and an interventional cardiologist. Patients that are not candidates for surgical AVR benefit from TAVI compared with medical treatment [30]. For high-risk patients the decision between AVR and TAVI is individualized after discussion in the heart team, and the estimation of surgical risk includes clinical judgment and risk scoring methods. In trials comparing TAVI with AVR in patients with high surgical risk, 1-year mortality has been similar between the two treatments [29]. Thirty-day mortality is approximately 5-15% and 1-year survival 60-80%, largely determined by patient risk factors [29, 30]. Trials comparing TAVI with AVR in intermediate risk

patients are ongoing but surgical AVR is still the recommended treatment in this patient group. Paravalvular regurgitation is more frequent after TAVI than after AVR and more than mild paravalvular regurgitation has been associated with increased mortality [29, 30]. Approximately 1-2% of patients need peroperative conversion to surgical AVR owing to life-threatening complications [31] and TAVI should therefore not be performed at hospitals where cardiac surgery is not performed. Since TAVI is a relatively recently introduced therapy, long-term durability of transcatheter heart valves is not excessively studied, however, outcomes at 5 years after implantation have proven to be satisfactory [32].

The transfemoral approach is the first choice in most centers but the use of this access is dependent on the ileofemoral vascular anatomy. The procedure is performed in a catheter lab or hybrid operating room and predominantly with a fully percutaneous technique without surgical cut-down and with the use of sedation rather than general anesthesia. Other access routes used are the transapical (via a left lateral minithoracotomy), the transaortic (via a right anterior thoracotomy), and the subclavian. In the transfemoral approach, the valve delivery catheter is inserted through the right or left femoral artery. Balloon aortic valvuloplasty is usually performed before prosthesis implantation. Fluoroscopy, or at some centers transesophageal echocardiography, is used for positioning of the transcatheter heart valve. Some prosthetic valves need balloon expansion, while some are self-expandable systems.

Aortic bioprosthetic valves

Stented bioprosthetic valves

Stented bioprosthetic valves are designed to mimic the anatomy of the native aortic valve. The most frequently used are the bovine pericardial and the porcine bioprosthetic valves. The pericardial bioprosthetic valves consist of bovine pericardium constructed to form aortic valve leaflets, while porcine bioprosthetic valves consist of three porcine aortic valve leaflets. Both bioprosthetic valves are mounted on a supporting stent made of metal or a polymer.

Current European Society of Cardiology and American College of Cardiology/American Heart Association guidelines state that anticoagulation treatment with a vitamin K antagonist may be considered for the first 3 months after implantation of a bioprosthetic valve [16, 33], but there is no strong evidence supporting this statement and many centers prescribe only low-dose acetylsalicylic acid after the procedure.

Sutureless bioprosthetic valves

Sutureless aortic bioprosthetic valves have been introduced to facilitate implantation and thereby shorten procedural time, especially in minimally invasive procedures [10-13]. The concept of sutureless AVR was first introduced more than 50 years ago when a caged-ball valve with annular fixation pins was implanted in a patient with aortic regurgitation. Using current sutureless bioprosthetic valves , reduced operative time is thought to be beneficial since extended aortic cross-

clamp and cardiopulmonary bypass time have been associated with adverse postoperative outcomes [7]. The sutureless implantation enables bioprosthetic valve implantation without the need for placement and tying of sutures. Implantation is simplified compared with conventional stent-mounted bioprosthetic valves, and this has been shown to shorten cross-clamp and cardiopulmonary bypass time [34, 35]. It has been speculated that the reduction in procedure time may be of particular importance in patients with high surgical risk and patients undergoing complex procedures.

Sutureless valves are bioprostheses that are anchored in the aortic annulus without the use of sutures. Rapid deployment valves are positioned with three sutures and anchored with a balloon-inflatable stent. The terms sutureless and rapid deployment valves are sometimes used interchangeably, however they should be regarded as two different entities. Two sutureless aortic bioprosthetic valves have been introduced: the Perceval sutureless bioprosthetic valve (LivaNova, Milan, Italy; FIGURE 4) and the ATS 3f Enable valve system (Medtronic, Minneapolis, MN, USA; recently withdrawn from the market by the company). The only currently used rapid deployment valve is the Edwards Intuity (Edwards Lifesciences, Irvine, CA, USA). Although evidence regarding sutureless bioprosthetic valves is still limited to observational data this technique has been associated with good early clinical and hemodynamic outcomes comparable to implantation of conventional stent-mounted bioprosthetic valves [36]. All recommendations regarding the use of sutureless AVR is limited to expert consensus statements [37].

The simplified implantation procedure makes sutureless bioprosthetic valves a good alternative for minimally invasive AVR, where the reduction of surgical exposure and working space is associated with technical difficulties in implanting conventional stent-mounted sutured bioprosthetic valves. Few studies have reported on the outcomes in patients undergoing minimally invasive sutureless bioprosthesis implantation [38].In these reports, minimally invasive sutureless AVR have been associated with good clinical and hemodynamic outcomes with low incidence of paravalvular regurgitation and relatively short procedural time [38]. Since sutureless minimally invasive AVR have shown good outcomes and the procedure is less invasive compared with full sternotomy AVR, it has been speculated that this treatment strategy could be an alternative to TAVI in patients with high operative risk [39], however this remains to be shown in prospective trials.

Sutureless valves have several similarities to conventional stent-mounted aortic bioprosthetic valves. Both valve types are implanted surgically, either with full sternotomy or through a minimally invasive incision, with the use of cardiopulmonary bypass and cross-clamping of the aorta. The native aortic valve is excised and the aortic annulus completely decalcified. The stent-mounting of the sutureless prosthetic valves differ from the mounting of conventional stented prosthetic valves and both the Perceval and the ATS 3f Enable sutureless valve are mounted on a nitinol-frame which enables self-expansion of the device after release into the aortic annulus.

Several possible limitations with sutureless bioprosthetic valve implantation have been addressed. The implantation technique differs from implantation of a sutured bioprosthetic valve and is associated with a learning curve. Proctoring by a surgeon experienced in sutureless AVR is therefore recommended when initiating a sutureless valve program [37]. Postoperative prosthetic valve embolization is very rare but has been described. Reports have also shown an increase in postoperative conduction disorders and pacemaker implantation rate following sutureless compared with sutured AVR [11, 40]. Owing to the recent introduction of sutureless prosthetic valves, no long-term durability data exist. Furthermore, it has been questioned whether the reductions in aortic cross-clamp and cardiopulmonary bypass time in fact translate into better outcomes [41].

Right ventricular function after aortic valve replacement

Postoperative right ventricular (RV) dysfunction has been associated with adverse clinical outcomes [42]. The left ventricle has been extensively studied but the right ventricle has been the subject of fewer clinical and imaging investigations [43]. The right ventricle has a complex shape, thereby making it difficult to assess size and function and many physicians still rely on visual estimation. This is in contrast to the left ventricle which has a relatively predictable shape and for which normal values regarding size and function are well established. However, standardized methods for RV echocardiographic assessment have also been formulated [43]. The assessment is often based on tricuspid annular peak systolic excursion (TAPSE) and pulsed wave tissue Doppler velocity for the estimation of RV long axis function, and fractional area change (FAC) as a measure of global RV function. Although TAPSE and pulsed wave tissue Doppler velocity measures RV long axis function, it has been demonstrated to correlate with global RV function [43].

Previous observational studies have shown impairment of RV long axis function after cardiac surgery including AVR [44-50]. Proposed explanations have included inadequate RV myocardial protection, untreated right coronary artery disease, and postoperative mediastinal adhesions [46]. However, the time point at which RV long axis velocities begin to decline have been demonstrated to coincide with pericardial opening [46, 47], suggesting that reduction in RV long axis movement is a result of altered pericardial constraint. However, fractional shortening of the RV midcavity transverse diameter increase and RV ejection fraction assessed by 3D echocardiography remains unchanged after AVR [51], suggesting that global RV function is not compromised. These findings propose that even though RV long axis function generally correlates with global RV function [52], this may not be true for patients who have undergone cardiac surgery. Also, although severe postoperative impairment of RV function after cardiac surgery is associated with mortality [42], the clinical significance of the RV long axis function impairment seen in the majority of patients undergoing cardiac surgery is uncertain. Transcatheter aortic valve implantation has not been associated with postoperative impairment of RV function [45, 51, 53].

Prosthetic valve function

The durability of bioprosthetic valves is, in contrast to mechanical valves, limited by calcific or non-calcific tissue deterioration. Prosthetic valve function is assessed by echocardiography. The echocardiographic assessment includes evaluation of leaflet morphology and mobility, measurement of transvalvular gradients, regurgitation estimation, and evaluation of left ventricular dimension and function. Shadowing caused by the stent frame may limit transthoracic echocardiography assessment and transesophageal echocardiography is therefore recommended in order to improve visualization of leaflet morphology and mobility [54].

Bioprosthetic valve obstruction may be caused by pannus ingrowth or thrombosis. Overt thrombosis in bioprosthetic valves is rare compared with mechanical valve thrombosis. Symptomatic prosthetic valve thrombosis presents with dyspnea, fatigue or systemic embolization and transesophageal echocardiography is recommended for the assessment [55]. Initial treatment of left-sided thrombosis consist of systemic anticoagulation [56], but if unsuccessful, surgery with thrombectomy or valve replacement should be considered [16, 33, 56].

Bioprosthetic valves are subject to structural valve deterioration that increases over time and eventually leads to valve failure. Younger age, renal insufficiency, left ventricular dysfunction, and valve size are factors associated with structural valve deterioration [57-59]. Freedom from structural valve failure in bioprostheses is 70-90% at 10 years and 50-80% at 16 years [57, 58] and studies have not demonstrated a clear difference in durability of pericardial bovine compared with porcine valves [57]. Treatment of structural valve deterioration is generally valve replacement. Since redo AVR frequently carries a significant operative risk, also transcatheter valve-in-valve implantation has been used for degenerated bioprosthetic aortic valves [60].

Hypo-attenuated leaflet thickening and reduced leaflet motion

Recent TAVI series have shown a high prevalence of hypo-attenuated leaflet thickening (HALT) and reduced leaflet motion (RLM) detected with cardiac computed tomography (CT) [61-63]. The prevalence of HALT and RLM in surgically implanted bioprosthetic valves is unknown since only a limited number of surgically implanted bioprosthetic valves have been studied [62]. Patients are frequently asymptomatic and the phenomena were first reported as incidental findings in clinical trials [62]. The previous reports indicate that HALT and RLM can be detected with cardiac CT but are typically not associated with elevated aortic valve gradients on echocardiography [61-63], thereby not fulfilling the clinical definition of prosthetic valve thrombosis. Both HALT and RLM have been shown to resolve with anticoagulation treatment for 3–6 months [61-63], which has led to the interpretation that HALT and RLM indicate subclinical prosthetic valve thrombosis. The clinical consequences of HALT and RLM are still uncertain but left-sided prosthetic valve thrombosis is a risk factor for stroke [64, 65] and prosthetic valve thrombosis is associated with dysfunction and reduced prosthesis durability of the valve [56].

AIMS OF THE THESIS

The overall aim of this thesis was to evaluate minimally invasive and sutureless aortic valve replacement on the aspects of clinical outcomes, cardiac function, and prosthetic valve function.

The specific aims were:

- To analyze early postoperative outcomes and 2-year survival after aortic valve replacement with a sutureless bioprosthetic valve implanted through a ministernotomy compared with a full sternotomy (Study I)
- To analyze early postoperative outcomes and 2-year survival after aortic valve replacement through a ministernotomy with a sutureless bioprosthetic valve compared with a full sternotomy with implantation of a stented valve (Study II)
- To study right ventricular function after ministernotomy versus full sternotomy aortic valve replacement (Study III)
- To investigate the prevalence of hypo-attenuated leaflet thickening and reduced leaflet motion by cardiac computed tomography in a sutureless bioprosthetic valve (Study IV)

PATIENTS AND METHODS

Ethical considerations

All studies were approved by the regional Human Research Ethics Committee in Stockholm, Sweden. Study I and II were additionally approved by human research ethical review boards at each participating center.

Study design and population

Study I

This was a retrospective analysis of a consecutive series of patients who were operated on from June 2007 to April 2014 at 6 European centers (Belgium, Finland, Germany, Sweden, and Catania and Trieste in Italy). The inclusion criterion was severe aortic stenosis with indication for isolated AVR with use of the Perceval sutureless bioprosthetic valve. Implantation of the Perceval valve was considered feasible if the aortic annulus size was between 19 and 27 mm and the ratio between the sinotubular junction and aortic annulus diameters did not exceed 1.3. Patients undergoing any concomitant cardiac procedure were excluded.

Study II

This was a retrospective analysis of two consecutive series (ministernotomy with implantation of the Perceval sutureless bioprosthetic valve or full sternotomy with implantation of a stented sutured valve) of patients who underwent primary isolated non-emergent AVR at the same centers as in Study I. Patients who underwent AVR through a ministernotomy with implantation of the Perceval sutureless bioprosthetic valve were operated on from June 2007 to April 2014 at any of the 6 centers specified above. Patients who underwent AVR through full sternotomy with stented valve implantation were operated at Karolinska University Hospital between January 2005 and December 2010. The inclusion criterion was severe aortic stenosis with indication for primary isolated non-emergent AVR with the use of the Perceval sutureless valve or the Carpentier-Edwards Perimount stented bovine pericardial bioprosthetic valve (Edwards Lifesciences, Irvine, CA, USA). Patients who had previous cardiac surgery, active endocarditis or a concomitant cardiac procedure were excluded.

Study III

This was a single-center, open-label, randomized controlled trial. Adult patients scheduled for isolated AVR at Karolinska University Hospital between January 2014 and May 2015 were eligible. Exclusion criteria were left ventricular ejection fraction less than 45%, presence of any coexisting severe valvular disorder, previous cardiac surgery or urgent surgery. Patients were randomly assigned 1:1 to either ministernotomy or full sternotomy. The echocardiography examiner and the physician performing the follow-up were not blinded to study group assignment.

Study IV

This was a single-center prospective observational study. All patients who had undergone surgical AVR with implantation of the Perceval sutureless bioprosthetic valve at Karolinska University Hospital between October 2012 and February 2016 were eligible. The criterion to implant the Perceval sutureless bioprosthesis was aortic stenosis with indication for primary isolated non-emergent AVR. Exclusion criteria were death, severely impaired renal function (glomerular filtration rate less than 30 mL/min/1.73 m^2), and unwillingness or inability to undergo CT examination.

Surgical technique

Ministernotomy

In patients who underwent ministernotomy, a 6- to 10-cm midline skin incision was made over the upper part of the sternum. In Study I and II, a partial J-shaped ministernotomy in the third to fourth intercostal space or a V-shaped ministernotomy at the level of the second intercostal space was performed. In Study III and IV, a partial J-shaped ministernotomy to the third intercostal space was performed. In Study I and II, cardiopulmonary bypass was established with central arterial and central or peripheral venous cannulation and antegrade crystalloid or cold blood cardioplegia was used. In Study III and IV, cardiopulmonary bypass was established with central arterial and peripheral venous cannulation and antegrade crystalloid cardioplegia was used. A cranial partial pericardial incision was made anterior to the ascending aorta, not extending over the right ventricle. The pericardial incision was closed at the end of the procedure in all patients who underwent ministernotomy in Study III and IV.

Full sternotomy

In patients undergoing full sternotomy, a complete pericardial incision was made and the pericardium left open after the procedure. Cardiopulmonary bypass was established with central arterial and venous cannulation. In Study I, antegrade and/or retrograde cold blood or crystalloid cardioplegia was used. Antegrade and/or retrograde cold blood cardioplegia was used in all patients who underwent full sternotomy in Study II-IV.

Perceval sutureless bioprosthetic valve

The Perceval sutureless valve is a bioprosthetic heart valve that received Conformité Européene mark approval in 2011 and Food and Drug Administration approval in 2016. The biologic component consists of glutaraldehyde-fixed bovine pericardium treated with homocysteic acid and the stent is made of an elastic nickel-titanium alloy covered by Carbofilm (LivaNova, Milan, Italy). The design features one proximal and one distal ring segment and nine vertical struts designed to support the valve and allow the prosthesis to anchor to the aortic root and the sinus of Valsalva. The stent supports the valve and holds it in place without the need for sutures. To aid the positioning of the prosthesis into the aortic annulus, the inflow ring has three loops through which temporary guiding sutures are

passed. After temporary deformation the valve can return to its original shape owing to the elastic alloy design.

Sutureless bioprosthetic valve implantation

The ascending aorta was incised transversally 1.5 cm above the sinotubular junction. After removal of the native valve, complete decalcification of the annulus was performed. Product-specific sizers were used to estimate annular size. Three guiding sutures were placed at the nadir of each sinus of Valsalva and passed through the corresponding loop in the inflow ring of the prosthetic valve. At back table, the valve was collapsed and loaded onto the delivery device. The valve was released at the level of the aortic annulus, followed by dilation of the inflow ring segment with a specifically designed balloon catheter at 4 atmospheres for 30 seconds. The guiding sutures were removed and the aortotomy closed. After weaning from cardiopulmonary bypass, transesophageal echocardiography was performed to confirm correct positioning of the valve and to detect any paravalvular regurgitation.

Implanted bioprosthetic valves

In Study I and IV, the Perceval sutureless valve was implanted in all patients. In Study II, the Perceval sutureless valve was implanted in patients who underwent ministernotomy and the stented Carpentier-Edwards Perimount bioprosthetic valve in patients who underwent full sternotomy. In Study III, mechanical and bioprosthetic (sutured or sutureless) aortic valves were implanted.

Peri- and postprocedural antithrombotic regime

In study IV, according to the standard antithrombotic protocol for aortic bioprosthetic valves at our center, postoperative antithrombotic treatment consisted of low-molecular-weight heparin until full mobilization and life-long treatment with acetylsalicylic acid 75 mg once daily. Patients without atrial fibrillation did not receive oral anticoagulation postoperatively. In patients preoperatively receiving long-term anticoagulation treatment, warfarin or a novel oral anticoagulant (dabigatran, apixaban or rivaroxaban) treatment was paused 3 days prior to the operation without bridging with low-molecular-weight heparin. In these patients anticoagulation therapy was re-administered at day 1 postoperatively. These patients were not treated with acetylsalicylic acid.

Data collection

Study I and II

Data on patient characteristics and operative details were retrieved retrospectively from medical records. Follow-up data were retrieved from national registries, by reviewing medical records or by contacting the patient or the treating physician.

Study III

Patient characteristics, postoperative clinical outcomes, laboratory work, and medications were retrieved from medical records by a research nurse. All data was collected prospectively.

Each patient was scanned using standard two-dimensional and pulsed and continuous wave Doppler before surgery and at postoperative day 1, 4, and 40 by one of four experienced examiners. Transthoracic examinations were conducted with the subject in the left lateral position with a Vivid E9 (GE Healthcare, Milwaukee, Wisconsin, USA). Echocardiographic images were digitally stored for offline analysis using commercially available software (EchoPAC PC version 110.0.0; GE Healthcare). Measurements were repeated four times in patients with atrial fibrillation and the average value was calculated. All examinations were analyzed in a blinded fashion by an experienced reader.

Tricuspid annular peak systolic excursion was measured in the apical 4-chamber view using M-mode echocardiography and was defined as the maximal excursion at the lateral aspect of the tricuspid valve annulus in the apical four-chamber view. Pulsed wave tissue Doppler RV velocity was measured by placing the pulsed wave sample volume at the level of the basal RV free wall. Each recorded value was the mean from four consecutive beats. Fractional area change was quantified by two-dimensional echocardiography in the apical four-chamber view by measuring the fractional change in the area inscribed by the RV endocardium at peak diastole and peak systole. Right ventricular basal and mid dimensions were quantified by two-dimensional echocardiography in the apical four-chamber view.

Standard left ventricular systolic and diastolic dimensions were measured. Left ventricular volumes were measured from the standard four and two-chamber views according to the biplane Simpson method and ejection fraction was derived.

Study IV

Clinical data were obtained by review of the medical records. Data on antithrombotic treatment was collected at the time of cardiac CT. We also collected data on symptoms of heart failure according to the New York Heart Association functional classification.

Patients were scanned using a dual source 2×64 row multidetector computed tomograph (Siemens Somatom Definition Flash; Siemens Healthcare, Forchheim, Germany) with retrospective ECG gating and individualized contrast medium administration.

Cardiac CT examinations were analyzed independently by two experienced readers. Joint readings, involving a third experienced reader, were subsequently performed to reach a consensus. For assessment of leaflet anatomy and motion, multiplanar reformatted reconstructions were used as still images from selected phases of the cardiac cycle, as well as dynamic images of the entire cardiac cycle. An examination was considered non-diagnostic if artifacts prevented reliable assessment of one or more valve leaflet (for example due to motion or image noise). During subsequent separate reading sessions, the two readers performed additional analyses of leaflet motion, with access only to three-dimensional volume-rendered images of the aortic bioprosthetic valve, blinded to findings of previous multiplanar reformatted reconstruction analyses.

Outcome measures

Study I

The primary outcome measures were all-cause in-hospital mortality and 2-year survival. Secondary outcome measures were aortic cross-clamp time, cardiopulmonary bypass time, conversion to conventional AVR, paravalvular regurgitation, transfusions of packed red blood cells, reoperation for bleeding, stroke, de novo dialysis, permanent pacemaker implantation, reoperation for prosthetic valve-related complications, intensive care unit stay, and hospital stay.

Study II

The primary outcome measures were all-cause 30-day mortality and 2-year survival. Secondary outcome measures were aortic cross-clamp time, cardiopulmonary bypass time, paravalvular regurgitation, transfusions of packed red blood cells, reoperation for paravalvular regurgitation, reoperation for bleeding, de novo dialysis, permanent pacemaker implantation, and intensive care unit stay.

Study III

Primary outcome measures were TAPSE, RV pulsed wave tissue Doppler velocity, RV FAC, and basal and mid RV transversal diameter at postoperative day 4 and 40.

Study IV

The primary outcome measures of this study were prevalence of HALT and RLM. Hypo-attenuated leaflet thickening was defined as evidence of one or more leaflet with hypo-attenuated thickening, with or without rigidity, identifiable in at least two different multiplanar reformatted reconstruction projections. Leaflet motion was based on visual assessment and was considered reduced when the entire cusp displayed reduced motion.

Statistical analysis

Data management and statistical analyses were performed using SPSS version 22.0 (IBM SPSS Inc., Chicago, IL, USA) and Stata version 13.1 (StataCorp LP, College Station, TX, USA).

Study I and II

Independent-samples *t* test and χ^2 test were used for univariate analyses in the overall cohort, and paired samples *t* test and univariate conditional logistic regression was used in the propensity score matched cohort. The Kaplan-Meier method was used to calculate cumulative survival and to construct survival curves, and the log-rank test was used to compare differences between the curves. To reduce selection bias, a propensity score was calculated for each patient by logistic regression, with ministernotomy as the dependent variable. A propensity score matched cohort was constructed by nearest-neighbor matching of 1 ministernotomy patient to 1 full sternotomy patient, without

replacement. We calculated standardized differences for variables to investigate postmatch balance. Standardized differences of less than 10% are generally considered a small and acceptable imbalance.

Study III

We calculated that a minimum of 17 patients in each group would give the study 80% power, at a significance level of 5%, to detect a between-group difference of 5 mm in TAPSE. This was calculated based on data from a previous study of change in TAPSE in patients who underwent full sternotomy AVR [53], and the estimation that a minimum of 5 mm difference in TAPSE would be clinically relevant. Patients intraoperatively converted from ministernotomy to full sternotomy were analyzed in the full sternotomy group. Continuous variables were compared using *t* test, analysis of variance or Wilcoxon signed-rank test, and categorical or binary variables were compared using Pearson's χ^2 test.

Study IV

Continuous variables were compared using the *t* test or analysis of variance, and categorical or binary variables were compared using Pearson's χ^2 test.

RESULTS

Study I

Patient characteristics

One hundred eighty-nine (70.8%) patients underwent AVR with the Perceval sutureless valve through a ministernotomy and 78 (29.2%) patients through a full sternotomy. Baseline characteristics of the study population are presented in TABLE 1. More patients in the ministernotomy group underwent elective operations, and more patients in the full sternotomy group had undergone previous cardiac surgery. European System for Cardiac Operative Risk Evaluation (EuroSCORE) II was higher in patients in the full sternotomy group (4.76 ± 4.19 vs. 3.35 ± 2.86; p=0.044). Propensity score matching resulted in 56 pairs with similar baseline characteristics. In the overall cohort, 1 patient (0.5%) in the ministernotomy group required intraoperative conversion to implantation of a conventional sutured bioprosthetic valve because of prosthesis dislodgement. There were no conversions from ministernotomy to full sternotomy.

Primary outcome measure

Operative data are presented in TABLE 2 and postoperative outcomes in TABLE 3. In the overall cohort, in-hospital mortality was 1.1% in the ministernotomy group and 2.6% in the full sternotomy group (p=0.583). The 2-year survival was 92% (95% confidence interval [CI]: 85-96%) in the ministernotomy group and 91% (95% CI: 81-96%; p=0.423; FIGURE 5) in the full sternotomy group. In the propensity-matched cohort, the overall in-hospital mortality was 1.8%. These 2 patients had both undergone full sternotomy. In the propensity-matched cohort, 2-year survival was 94% (95% CI: 76-99%) in patients who underwent ministernotomy and 91% (95% CI: 79-97%) in patients who underwent full sternotomy (p=0.463; FIGURE 6).

Secondary outcome measures

Four patients (2.1%) in the ministernotomy group and 1 patient (1.3%) in the full sternotomy group were discharged with mild paravalvular regurgitation. In the propensity-matched cohort, there were no differences in cross-clamp (44 minutes for both groups, p=0.931) or cardiopulmonary bypass time (69 minutes for ministernotomy, 74 minutes for full sternotomy, p=0.363). Postoperative peak and mean aortic valve gradients were significantly higher after ministernotomy compared with full sternotomy (28.1 vs. 23.3 mm Hg, p=0.026; and 15.2 vs. 11.7 mm Hg, p=0.011). The incidence of reoperation for major bleeding was 1.8% in the ministernotomy group and 5.4% in the full sternotomy group (p=0.341). The number of packed red blood cells transfused did not differ significantly between the two groups (1.15 vs. 1.91 units, p=0.128). Rate of permanent pacemaker implantation (11.0% vs. 3.6%, p=0.178), stroke (1.8% in both groups), intensive care unit stay (2.5 vs. 3.3 days, p=0.155), and hospital stay (12.5 vs. 13.4 days, p=0.569) were similar between the groups.

Table 1. Baseline Characteristics of Patients Who Underwent Sutureless Aortic Valve Replacement Through Ministernotomy or Full Sternotomy

Variables[a]	Overall Cohort			Propensity Score–Matched Cohort			Standardized Difference (%)
	Ministernotomy (n = 189)	Full Sternotomy (n = 78)	*p* Value	Ministernotomy (n = 56)	Full Sternotomy (n = 56)	*p* Value	
Age, y	77.4 ± 5.1	75.7 ± 5.5	0.016	76.0 ± 5.6	76.2 ± 5.0	0.840	3.7
Female gender	116 (61)	55 (71)	0.164	45 (80)	42 (75)	0.533	13
Weight, kg	74.7 ± 14.0	74.4 ± 15.2	0.874	73.6 ± 16.8	74.1 ± 14.3	0.880	3.0
Height, cm	164.2 ± 10.7	161.1 ± 7.6	0.018	160.6 ± 14.7	160.8 ± 7.4	0.950	1.1
Diabetes	46 (24)	24 (31)	0.287	17 (30)	14 (25)	0.514	12
Insulin-dependent diabetes	12 (6)	12 (15)	0.032	8 (14)	6 (11)	0.566	11
Creatinine clearance			0.162			0.198	
>85 mL/min	76 (40)	21 (27)		12 (21)	19 (34)		28
50–85 mL/min	72 (38)	34 (44)		25 (45)	22 (39)		11
<50 mL/min	41 (22)	23 (30)		19 (34)	15 (27)		16
NYHA class			0.275			0.151	
I	5 (2.6)	1 (1.3)		2 (3.6)	1 (1.8)		11
II	45 (24)	24 (31)		24 (43)	18 (32)		22
III	128 (68)	45 (58)		25 (45)	32 (57)		25
IV	11 (5.8)	8 (10.3)		5 (8.9)	5 (8.9)		0
Poor mobility	26 (14)	4 (5.1)	0.054	2 (3.6)	3 (5.3)	0.657	8.6
CCS class IV	2 (1.1)	2 (2.6)	0.583	2 (3.6)	2 (3.6)	1.0	0
Coronary artery disease	7 (3.7)	4 (5.1)	0.736	6 (11)	2 (3.6)	0.142	28
Chronic pulmonary disease	20 (11)	18 (23)	0.012	15 (27)	12 (21)	0.493	12
Extracardiac arteriopathy	28 (15)	19 (24)	0.077	10 (18)	10 (18)	1.0	0
Recent myocardial infarction	2 (1.1)	2 (2.6)	0.583	2 (3.6)	1 (1.8)	0.571	11
Left ventricular ejection fraction			0.696			1.0	
>0.50	159 (84)	63 (81)		48 (86)	48 (86)		0
0.30–0.50	29 (15)	14 (18)		7 (13)	7 (13)		0
<0.30	1 (0.5)	1 (1.3)		1 (1.8)	1 (1.8)		0
Systolic pulmonary artery pressure			0.539			0.842	
31–55 mm Hg	62 (33)	31 (40)		22 (39)	21 (38)		3.7
>55 mm Hg	21 (11)	7 (9.0)		3 (5.4)	5 (8.9)		14
Critical preoperative state	0	2 (2.6)	0.085	0	1 (1.8)	…	19
Elective procedure	187 (99)	72 (92)	0.010	54 (96)	54 (96)	1.0	0
Previous cardiac operation	7 (3.7)	23 (30)	<0.001	6 (11)	9 (16)	0.273	16
Permanent pacemaker	5 (2.6)	2 (2.6)	1.0	2 (3.6)	2 (3.6)	1.0	0
Active endocarditis	0	0	…	0	0	…	…
EuroSCORE II, %	3.35 ± 2.86	4.76 ± 4.19	0.044	3.74 ± 3.19	4.00 ± 4.17	0.662	7.2

[a] Continuous variables are reported as mean ± standard deviation, and dichotomous variables are reported as counts (%). Definition criteria for preoperative variables are according to the European System for Cardiac Operative Risk Evaluation (EuroSCORE) II.

CCS = Canadian Cardiovascular Society; NYHA = New York Heart Association.

Table 2. Operative Data of Patients Who Underwent Sutureless Aortic Valve Replacement Through Ministernotomy or Full Sternotomy

Variables[a]	Overall Cohort			Propensity Score–Matched Cohort		
	Ministernotomy (n = 189)	Full Sternotomy (n = 78)	*p* Value	Ministernotomy (n = 56)	Full Sternotomy (n = 56)	*p* Value
Crystalloid cardioplegia	31 (16)	4 (5)	0.019	16 (29)	3 (5.4)	0.007
Hypothermic circulatory arrest	0	2 (2.6)	0.085	0	1 (1.8)	…
Perceval[b] bioprosthetic valve size			0.015			0.649
Small	16 (8.5)	16 (21)		7 (12)	11 (20)	
Medium	70 (37)	30 (39)		25 (45)	20 (36)	
Large	82 (43)	29 (37)		22 (39)	22 (39)	
Extra large	21 (11)	3 (3.8)		2 (3.6)	3 (5.4)	
Aortic cross-clamp time, min	41 ± 18	43 ± 36	0.527	44 ± 23	44 ± 18	0.931
Aortic cross-clamp time <30 min	45 (24)	17 (22)	0.873	17 (30)	10 (18)	0.167
Cardiopulmonary bypass time, min	70 ± 23	70 ± 24	0.979	69 ± 23	74 ± 28	0.363
Cardiopulmonary bypass time <60 min	69 (37)	31 (40)	0.677	23 (41)	18 (32)	0.356

[a] Continuous variables are reported as mean ± standard deviation, and dichotomous variables are reported as counts (%). [b] Sorin Biomedica Cardio Srl, Salluggia, Italy.

Table 3. Perioperative and Postoperative Data of Patients Who Underwent Sutureless Aortic Valve Replacement Through Ministernotomy or Full Sternotomy

	Overall Cohort			Propensity Score–Matched Cohort		
Variable[a]	Ministernotomy (n = 189)	Full Sternotomy (n = 78)	*p* Value	Ministernotomy (n = 56)	Full Sternotomy (n = 56)	*p* Value
Implantation success	187 (99)	78 (100)	1.0	55 (98)	56 (100)	…
Prosthesis repositioning	5 (3.0)	1 (1.7)	1.0	2 (3.6)	1 (1.8)	…
Intraoperative prosthesis dislodgement	1 (0.5)	0	…	1 (1.8)	0	…
Conversion to implantation of conventional stented prosthesis	1 (0.5)	0	…	0	0	…
Conversion to full sternotomy	0	0	…	…	…	…
Aortic valve gradient						
Peak gradient, mm Hg	28.2 ± 10.9	25.0 ± 12.1	0.036	28.1 ± 10.6	23.3 ± 12.0	0.026
Mean gradient, mm Hg	14.3 ± 5.9	13.1 ± 7.0	0.215	15.2 ± 6.1	11.7 ± 7.0	0.011
Paravalvular regurgitation			0.730			…
None	184 (97)	77 (99)		53 (95)	56 (100)	
Mild	4 (2.1)	1 (1.3)		2 (3.6)	0	
Moderate or severe	1 (0.5)	0		1 (1.8)	0	
Packed red blood cells, units	1.35 ± 1.71	1.99 ± 3.15	0.034	1.15 ± 1.24	1.91 ± 3.49	0.128
Stroke	4 (2.1)	2 (2.6)	1.0	1 (1.8)	1 (1.8)	1.0
De novo dialysis	2 (1.1)	4 (5.1)	0.062	0	2 (3.6)	…
Pacemaker implantation	18 (9.5)	4 (5.2)	0.329	6 (11)	2 (3.6)	0.178
Reoperation for						
Early paravalvular regurgitation	1 (0.5)	0	…	1 (1.8)	0	…
Major bleeding	8 (4.2)	4 (5.1)	0.751	1. (1.8)	3 (5.4)	0.341
Prosthesis endocarditis	0	0	…	0	0	…
Length of stay, days						
Intensive care unit	2.4 ± 2.3	3.3 ± 3.5	0.053	2.5 ± 2.8	3.3 ± 3.8	0.155
Hospital	12.2 ± 5.7	13.4 ± 10.0	0.341	12.5 ± 6.8	13.4 ± 10.9	0.569
In-hospital mortality	2 (1.1)	2 (2.6)	0.583	0	2 (3.6)	…
Prosthesis-related early mortality	0	0	…	0	0	…

[a] Continuous variables are reported as mean ± standard deviation and dichotomous variables are reported as counts (%).

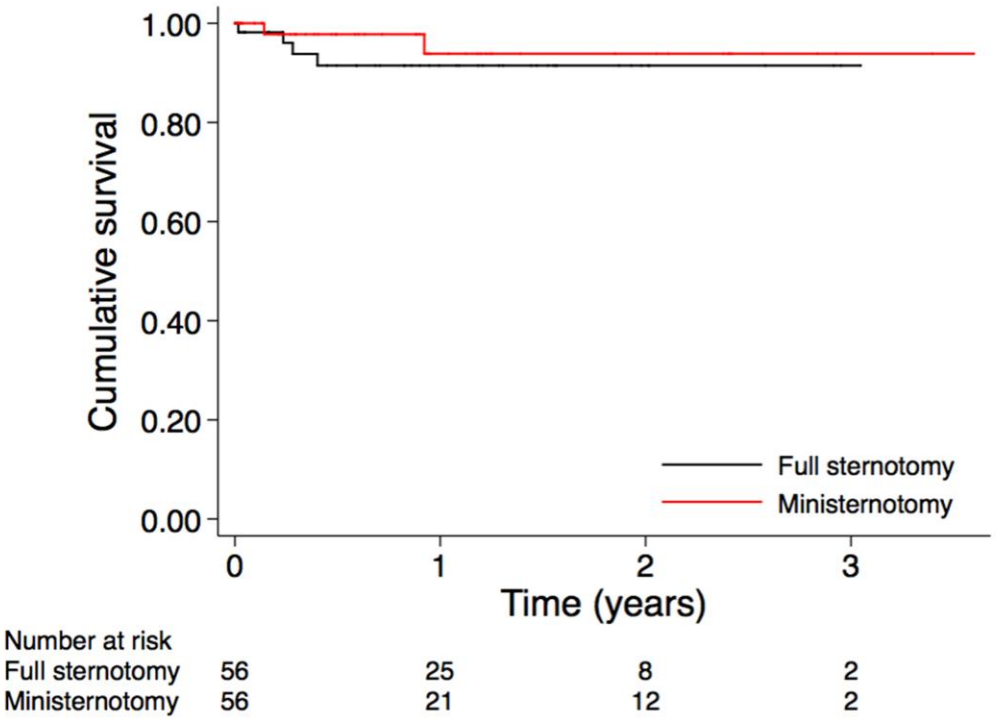

FIGURE 5. Kaplan-Meier cumulative survival in the overall cohort (n = 267) undergoing full sternotomy (black line) and ministernotomy (red line; p=0.423).

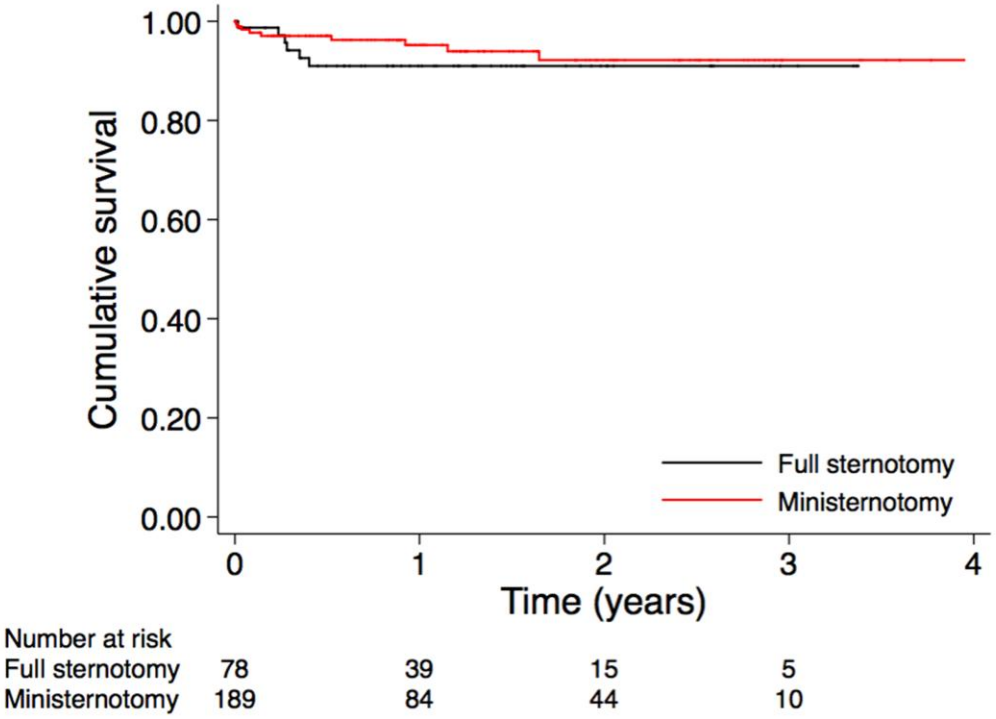

FIGURE 6. Kaplan-Meier cumulative survival in the propensity score matched cohort (n = 112) undergoing full sternotomy (black line) and ministernotomy (red line; p=0.463).

Study II

One hundred and eighty-two (32%) patients underwent AVR with the Perceval sutureless valve through a ministernotomy, and 383 (68%) patients with a stented sutured bioprosthetic valve through a full sternotomy. The baseline characteristics of the two groups are listed in TABLE 4. Logistic EuroSCORE I was higher for patients in the ministernotomy sutureless group (10.6 ± 7.5 vs. 7.7 ± 6.3%, p<0.001). Sizes of implanted bioprosthetic valves are presented in FIGURE 7. Data regarding procedural times are presented in TABLE 5. Propensity score matching resulted in 171 pairs with similar baseline characteristics (TABLE 4; FIGURE 8). In 5 (2.7%) cases, the sutureless bioprosthesis needed to be repositioned after release in the aortic annulus. One patient (0.5%) had intraoperative prosthesis dislodgement of the sutureless bioprosthetic valve, requiring conversion to implantation of a stented sutured valve. There were no conversions from ministernotomy to full sternotomy.

Primary outcome measure

Postoperative outcomes are presented in TABLE 6. In the overall cohort, 2-year survival was 92% (95% CI: 84–96%) in the ministernotomy sutureless group and 92% (95% CI: 89–95%; FIGURE 9) in the full sternotomy stented group. In the propensity matched cohort, the 30-day mortality was 1.8% in the ministernotomy sutureless group and 2.3% in the full sternotomy stented group (p=0.706). Two-year survival was 91% (95% CI: 82–96%) in the ministernotomy sutureless group, and 93% (95% CI: 88–96%) in patients who underwent full sternotomy with stented bioprosthesis (FIGURE 10).

Secondary outcome measure

No patient in the ministernotomy sutureless group and one patient (0.3%) in the full sternotomy stented group had severe postoperative paravalvular regurgitation, necessitating reoperation within the primary hospital stay. No patient in the ministernotomy group and 4 patients (1.0%) in the full sternotomy stented group were discharged with moderate paravalvular regurgitation (p=0.381). After propensity score matching, aortic cross-clamp (40 vs. 65 min, p<0.001) and cardiopulmonary bypass time (69 vs. 87 min, p<0.001) were shorter in the ministernotomy sutureless group. Patients in the ministernotomy sutureless group received fewer transfusions of packed red blood cells than patients in the full sternotomy sutureless group (1.4 vs. 2.4 units, p<0.001). The proportion of patients undergoing postoperative permanent pacemaker implantation was significantly higher in the ministernotomy sutureless group (9.9 vs. 2.9%, p=0.016).

Table 4 Baseline characteristics for patients who underwent aortic valve replacement through a ministernotomy with implantation of a sutureless bioprosthesis or through a full sternotomy with a stented bioprosthesis

	Overall cohort			Propensity score matched cohort			
	Ministernotomy sutureless 182 patients	Full sternotomy stented 383 patients	*P*-value	Ministernotomy sutureless 171 patients	Full sternotomy stented 171 patients	*P*-value	Standardized difference (%)
Age (years)	77.5 ± 5.2	73.8 ± 8.2	<0.001	77.3 ± 5.1	77.4 ± 6.1	0.923	−0.9
Female gender	112 (62)	172 (45)	<0.001	102 (60)	108 (63)	0.513	−7.2
Weight (kg)	74.5 ± 14	76.8 ± 16	0.088	74.8 ± 14	74.7 ± 15	0.945	0.7
Height (cm)	164 ± 11	160 ± 40	0.058	165 ± 11	159 ± 36	0.072	21
Body mass index (kg/m^2)	27.3 ± 4.4	26.5 ± 4.5	0.058	27.3 ± 4.4	26.7 ± 4.7	0.268	11
Diabetes mellitus	43 (24)	55 (14)	0.009	38 (22)	31 (18)	0.309	10
Insulin-dependent	11 (6.0)	21 (5.5)	0.846	10 (5.9)	7 (4.1)	0.469	8.1
Creatinine clearance			<0.001			0.823	
>85 (ml/min)	37 (20)	82 (22)		67 (40)	69 (39)		2.4
50–85 (ml/min)	67 (37)	203 (54)		66 (39)	71 (42)		−6.0
<50 (ml/min)	78 (43)	94 (25)		36 (21)	33 (19)		4.4
Coronary artery disease	3 (1.6)	22 (5.7)	0.028	3 (1.8)	3 (1.8)	1	0
Recent myocardial infarction	2 (1.1)	11 (2.9)	0.240	2 (1.2)	3 (1.8)	0.657	−4.9
Chronic pulmonary disease	20 (11.0)	27 (7.0)	0.141	15 (8.8)	15 (8.8)	1	0
Extracardiac arteriopathy	25 (13.7)	33 (8.7)	0.075	22 (13)	20 (12)	0.715	3.6
Left ventricular ejection fraction			0.064			0.884	
>50%	152 (84)	297 (79)		143 (84)	142 (83)		1.6
30–50%	29 (16)	65 (17)		28 (16)	29 (17)		−1.6
<30%	1 (0.5)	15 (4.0)		0	0	–	–
Non-elective procedure	2 (1.1)	29 (7.6)	0.002	2 (1.2)	3 (1.8)	0.657	−4.9
Logistic EuroSCORE I (%)	10.6 ± 7.5	7.7 ± 6.3	<0.001	9.8 ± 5.5	9.6 ± 6.9	0.701	3.6

Continuous variables are reported as mean ± standard deviation; dichotomous variables are reported as counts and percentages in parentheses.

Table 5 Aortic cross-clamp and cardiopulmonary bypass time for patients who underwent aortic valve replacement through a ministernotomy with implantation of a sutureless bioprosthesis or through a full sternotomy with a stented bioprosthesis

	Overall cohort			Propensity score matched cohort		
	Ministernotomy sutureless 182 patients	Full sternotomy stented 383 patients	*P*-value	Ministernotomy sutureless 171 patients	Full sternotomy stented 171 patients	*P*-value
Aortic cross-clamp time (min)	41 ± 17	65 ± 15	<0.001	40 ± 15	65 ± 15	<0.001
Aortic cross-clamp time <30 min	45 (25)	0	<0.001	43 (25)	0	<0.001
Cardiopulmonary bypass time (min)	69 ± 23	86 ± 20	<0.001	69 ± 20	87 ± 20	<0.001
Cardiopulmonary bypass time <60 min	69 (38)	19 (5.0)	<0.001	65 (38)	6 (3.5)	<0.001

Continuous variables are reported as mean ± standard deviation; dichotomous variables are reported as counts and percentages in parentheses.

Table 6 Postoperative data for patients who underwent aortic valve replacement through a ministernotomy with implantation of a sutureless bioprosthesis or through a full sternotomy with a stented bioprosthesis

	Overall cohort			Propensity score matched cohort		
	Ministernotomy sutureless 182 patients	Full sternotomy stented 383 patients	*P*-value	Ministernotomy sutureless 171 patients	Full sternotomy stented 171 patients	*P*-value
Paravalvular regurgitation			0.381			0.484
None	178 (98)	370 (97)		167 (98)	165 (96)	
Mild	4 (2.2)	9 (2.3)		4 (2.3)	4 (2.3)	
Moderate or severe	0	4 (1.0)		0	2 (1.2)	
Packed red blood cells (units)	1.4 ± 1.7	2.6 ± 4.5	<0.001	1.4 ± 1.7	2.4 ± 2.7	<0.001
Stroke	4 (2.2)	2 (0.5)	0.088	4 (2.3)	2 (1.2)	0.423
De novo dialysis	2 (1.1)	10 (2.6)	0.354	2 (1.2)	3 (1.8)	0.657
Pacemaker implantation	17 (9.3)	7 (1.8)	<0.001	17 (9.9)	5 (2.9)	0.016
Reoperation for early paravalvular regurgitation	0	1 (0.3)	1	0	0	–
Reoperation for bleeding	8 (4.4)	30 (7.8)	0.152	7 (4.1)	11 (6.4)	0.323
Intensive care unit stay (days)	2.4 ± 2.3	1.6 ± 2.8	<0.001	2.5 ± 2.3	1.9 ± 2.9	0.054
30-day mortality	3 (1.6)	8 (2.1)	1	3 (1.8)	4 (2.3)	0.706

Continuous variables are reported as mean ± standard deviation; dichotomous variables are reported as counts and percentages in parentheses.

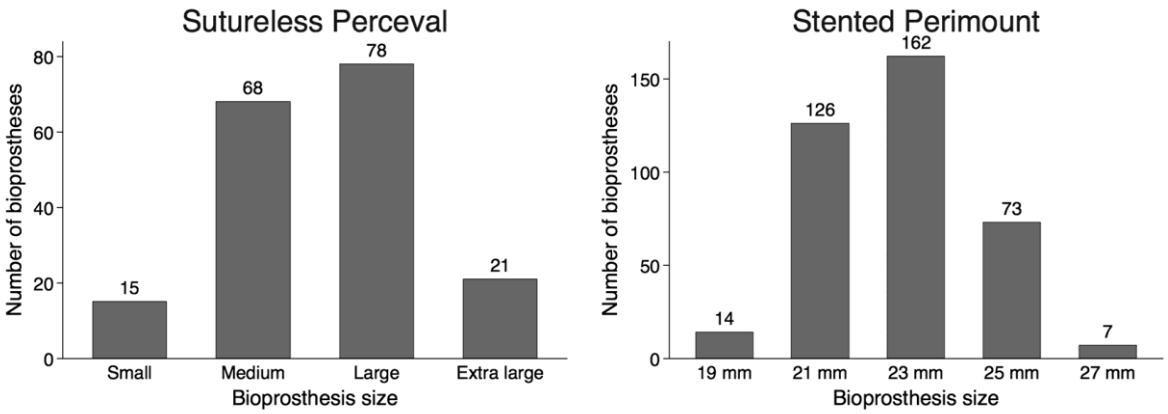

FIGURE 7. Sizes of implanted bioprosthetic valves.

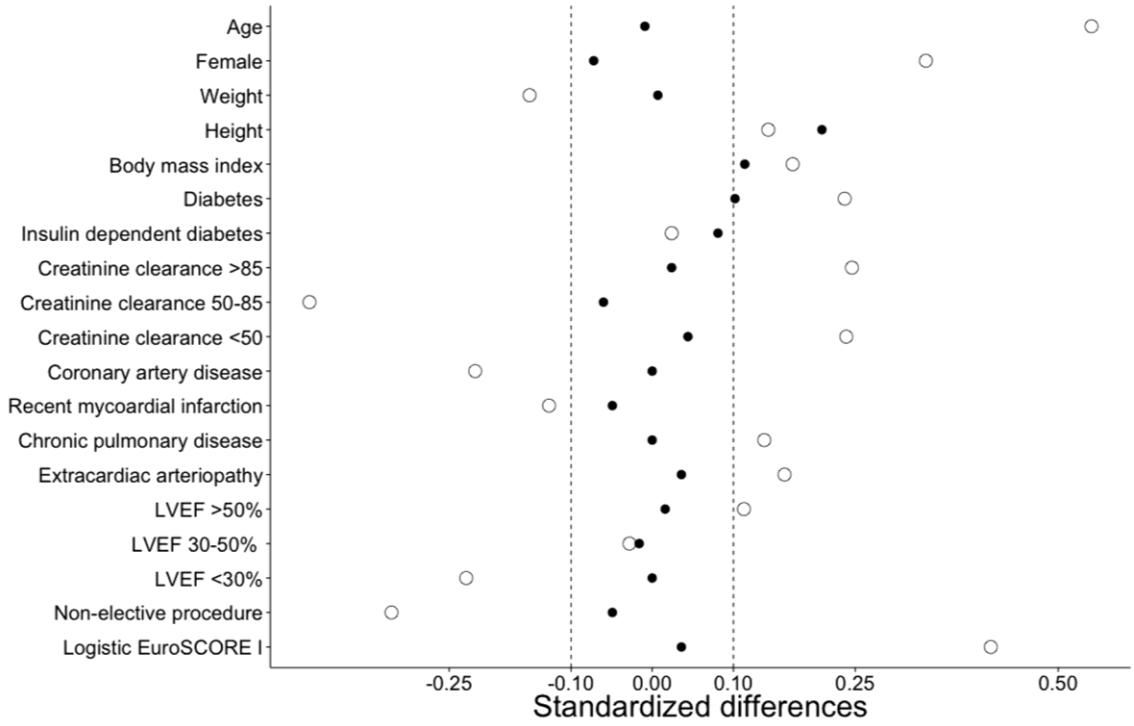

FIGURE 8. Standardized differences for variables in the overall population (hollow circles) and in the propensity score matched cohort (dots).

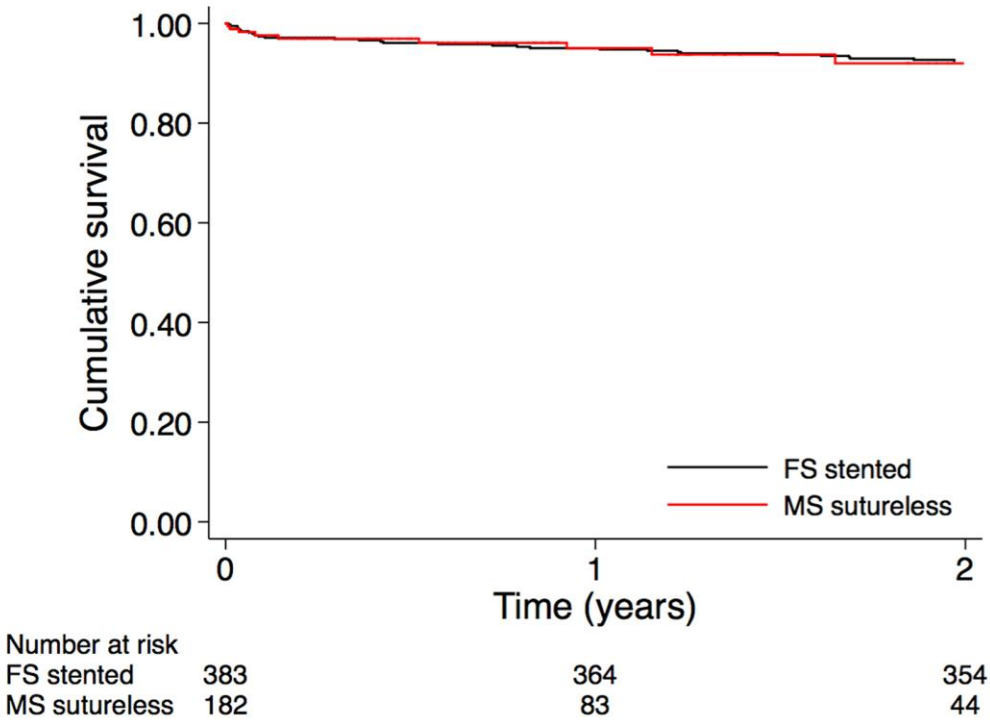

FIGURE 9. Kaplan–Meier cumulative survival in the overall cohort (n = 565, p=0.669). FS: full sternotomy; MS: ministernotomy.

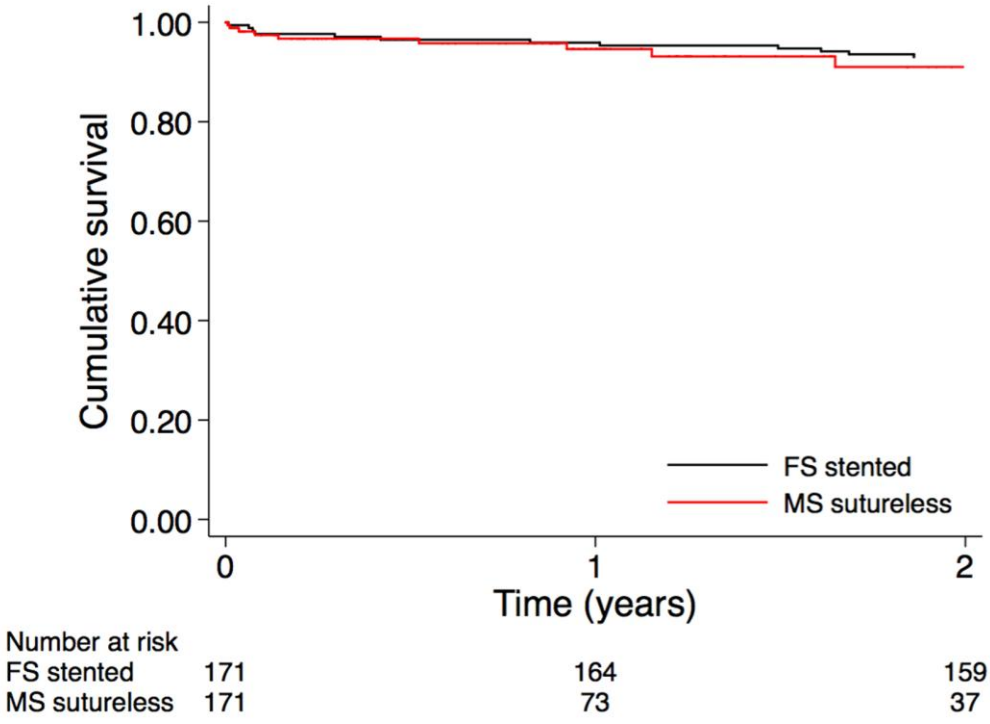

FIGURE 10. Kaplan–Meier cumulative survival in the propensity score matched cohort (n = 342, p=0.895). FS: full sternotomy; MS: ministernotomy.

Study III

A total of 40 patients underwent randomization. Twenty patients were randomized to ministernotomy and 20 patients to full sternotomy AVR. One patient randomized to ministernotomy was intraoperatively converted to full sternotomy and was analyzed in the full sternotomy group. The baseline characteristics of the patients were similar between the two groups (TABLE 7). Operative data are presented in TABLE 8. There were no differences regarding clinical postoperative outcomes between the two groups (TABLE 9).

Primary outcome measure

Echocardiographic data are presented in TABLE 10 and FIGURE 11. Four days postoperatively, TAPSE and pulsed wave tissue Doppler RV velocity were significantly higher in the ministernotomy compared with the sternotomy group (TAPSE: 16 [quartile 1: 11, quartile 3: 18] mm vs. 8 [7, 12] mm, p<0.001; pulsed wave tissue Doppler RV velocity: 10 [9, 11] cm/s vs. 6.5 [5, 8] cm/s, p<0.001). Fractional area change and RV dimensions did not differ between the two groups (FAC: 38 [34, 44] % vs. 37 [25, 39.5] %, p=0.29; basal RV diameter: 34 [31, 36] mm vs. 32 [29, 35] mm, p=0.36; mid RV diameter: 26 [22, 28] mm vs. 22.5 [19, 26] mm, p=0.20). The differences between the two groups were similar at echocardiography assessment 40 days postoperatively.

Four days postoperatively, TAPSE had decreased in both the ministernotomy and the sternotomy group (ministernotomy: 25 [21, 28] mm vs. 16 [11, 18] mm, p<0.001; sternotomy: 22.5 [22, 22.5] mm vs. 8 [7, 12] mm, p<0.001). Also FAC decreased in both groups (ministernotomy: 46 [39, 51] % vs. 38 [34, 44] %, p<0.001; sternotomy: 45 [40, 49] % vs. 37 [25, 39.5] %, p=0.003). Pulsed wave tissue Doppler RV velocity decreased significantly in patients who underwent sternotomy: 10.5 [10, 12] cm/s vs. 6.5 [5, 8] cm/s, p<0.001) but did not decrease significantly in patients who underwent ministernotomy (11.5 [11, 12] cm/s vs. 10 [9, 11] cm/s, p=0.054). Right ventricular dimensions were unchanged at four days postoperatively compared with preoperatively for both groups. The results within the groups at day 4 compared with preoperatively were similar at echocardiography assessment 40 days postoperatively.

Table 7. Baseline characteristics

	Total population	Sternotomy	Ministernotomy	p-value
N (%)	40 (100%)	21 (52.5%)	19 (47.5%)	
Age, years, mean (SD)	68.6 (8.5)	70 (7.9)	67 (9.0)	0.27
Female	15 (38%)	8 (38%)	7 (37%)	0.93
Body mass index, kg/cm^2, mean (SD)	27.8 (4.6)	28.2 (4.9)	27.5 (4.2)	0.62
Aortic stenosis	40 (100%)	21 (100%)	19 (100%)	
Aortic regurgitation				0.51
None	25 (62%)	14 (67%)	11 (58%)	
Mild	11 (28%)	6 (29%)	5 (26%)	
Moderate	4 (10%)	1 (5%)	3 (16%)	
Severe	0	0	0	
Hypertension	27 (68%)	14 (67%)	13 (68%)	0.91
Stroke	1 (2%)	1 (5%)	0	0.34
Liver dysfunction	0	0	0	-
Prior myocardial infarction	0	0	0	-
Prior percutaneous coronary intervention	1 (2%)	0	1 (5%)	0.29
Diabetes mellitus	10 (25%)	6 (29%)	4 (21%)	0.58
Insulin-dependant	6 (15%)	2 (10%)	4 (21%)	0.31
Atrial fibrillation	1 (2%)	1 (5%)	0	0.34
Current smoker	3 (8%)	3 (14%)	0	0.095
Chronic pulmonary disease	3 (8%)	1 (5%)	2 (11%)	0.49
Extracardiac arteriopathy	1 (2%)	1 (5%)	0	0.34
Poor mobility	0	0	0	-
Prior cardiac surgery	0	0	0	-
Active endocarditis	0	0	0	-
Critical preoperative state	0	0	0	-
Unstable angina	0	0	0	-
Recent myocardial infarction	0	0	0	-
Emergent operation	0	0	0	-
Thoracic aortic surgery	0	0	0	-
CCS angina class IV	0	0	0	-
New York Heart Association class				0.63
I	8 (20%)	5 (24%)	3 (16%)	
II	18 (45%)	8 (38%)	10 (53%)	
III	14 (35%)	8 (38%)	6 (32%)	
IV	0	0	0	
EuroSCORE II, mean (SD)	1.35 (0.79)	1.44 (0.90	1.26 (0.65)	0.49
Pacemaker	0	0	0	-

Data are n (%) unless otherwise noted. CCS = Canadian Cardiovascular Society, EuroSCORE II = European System for Cardiac Operative Risk Evaluation Score II.

Table 8. Operative data

	Total population	Sternotomy	Ministernotomy	p-value
N (%)	40 (100%)	21 (52.5%)	19 (47.5%)	
Crystalloid cardioplegia	20 (50%)	1 (5%)	19 (100%)	<0.001
Aortic cross-clamp time, minutes, mean (SD)	76 (24)	69 (20)	83 (27)	0.076
Cardiopulmonary bypass time, minutes, mean (SD)	99 (34)	86 (26)	113 (36)	0.009
Operation time, minutes, mean (SD)	180 (58)	164 (40)	197 (70)	0.073
Prosthesis type				0.85
Mechanical	10 (25%)	5 (24%)	5 (26%)	
Biological	30 (75%)	16 (76%)	14 (74%)	
Sutureless bioprosthesis	7 (17%)	0	7 (37%)	<0.001
Peroperative bleeding, ml, median (Q1, Q3)	475 (300, 775)	400 (300, 750)	600 (380, 825)	0.45
Intra-aortic balloon pump	0	0	0	-
Extracorporeal membrane oxygenation	0	0	0	-

Data are n (%) unless otherwise noted. Q = quartile.

Table 9. Postoperative data

	Total population	Sternotomy	Ministernotomy	p-value
N (%)	40 (100%)	21 (52.5%)	19 (47.5%)	
Intraoperative conversion to sternotomy	1 (2%)	1 (5%)	0	0.34
Postoperative dialysis	1 (2%)	1 (5%)	0	0.34
De novo pacemaker	3 (8%)	2 (10%)	1 (5%)	0.61
Peroperative myocardial infarction	0	0	0	-
Reoperation for paravalvular regurgitation	0	0	0	-
Stroke	0	0	0	-
Reoperation due to bleeding	1 (2%)	1 (5%)	1 (5%)	0.94
Pericardiocentesis within 30 days	1 (2%)	1 (5%)	1 (5%)	0.94
Reoperation due to deep sternal wound infection	1 (2%)	1 (5%)	0	0.34
Respiratory insufficiency	1 (2%)	1 (5%)	0	0.34
Pneumonia	1 (2%)	0	1 (5%)	0.29
Invasive ventilation, hours, median (Q1, Q2)	2 (1, 3)	2 (1, 3)	2 (1, 3)	0.94
Intensive care unit stay, days, mean (SD)	1.4 (1.0)	1.6 (1.3)	1.1 (0.3)	0.11
In-hospital stay, days, mean (SD)	6.1 (3.1)	6.5 (4.1)	5.7 (1.2)	0.46
New-onset atrial fibrillation	13 (32%)	6 (29%)	7 (37%)	0.58
Transient ischemic attack	0	0	1 (5%)	0.29
Intra-aortic balloon pump	0	0	0	-
Extracorporeal membrane oxygenation	0	0	0	-
Postoperative bleeding, ml, mean (SD)	350 (240)	350 (180)	360 (300)	0.89
Packed red blood cells within 7 days, units, mean (SD)	1.0 (1.5)	0.9 (1.5)	1.2 (1.6)	0.61
30-day mortality	2 (5%)	2 (10%)	0	0.17

Data are n (%) unless otherwise noted. Q = quartile.

Table 10. Echocardiographic parameters

	Preoperatively			Day 4			Day 40		
	Sternotomy	Ministernotomy	p-value	Sternotomy	Ministernotomy	p-value	Sternotomy	Ministernotomy	p-value
Right ventricular parameters									
TAPSE, mm	22.5 (22, 25.5)	25 (21, 28)	0.54	8 (7, 12)	16 (11, 18)	<0.001	11 (9, 12)	14 (12, 17)	0.002
RV pulsed wave tissue Doppler velocity, cm/s	10.5 (10, 12)	11.5 (11, 12)	0.34	6.5 (5, 8)	10 (9, 11)	<0.001	7 (6, 8)	9 (8, 11)	<0.001
RV FAC, %	45 (40, 49)	46 (39, 51)	0.79	37 (25, 39.5)	38 (34, 44)	0.29	38.5 (36.5, 42)	43.5 (38, 45.5)	0.061
RV basal diameter, mm	34 (29.5, 36)	33 (30, 35)	0.77	32 (29, 35)	34 (31, 36)	0.36	33 (31, 35)	33 (31, 35)	0.82
RV mid diameter, mm	24.5 (21.5, 26.5)	24 (21, 27)	0.92	22.5 (19, 26)	26 (22, 28)	0.20	23.5 (21, 26)	23 (21, 28)	0.92
Left ventricular parameters									
Interventricular septum, mm	13 (12, 14.5)	13 (11, 14)	0.31	13 (12, 15)	12 (11, 14)	0.038	11 (10, 13)	11 (10, 12)	0.92
LVEDD, mm	44 (41.5, 48)	47 (41, 51)	0.28	44 (39, 49)	45 (42, 48)	0.47	43.5 (38, 45)	46.5 (42, 50)	0.10
LV posterior wall, mm	12 (10, 13)	11 (10, 11)	0.049	11 (10, 13)	11 (10, 11)	0.24	10 (9, 11)	10 (9, 10)	0.60
LVEF, %	62.5 (60, 67.5)	61 (57, 64)	0.16	65 (58.5, 68.5)	61 (57, 65)	0.19	60 (57, 64)	62 (56, 65)	0.88
LVEDV, ml	89 (72, 104)	100 (87, 117)	0.13	68 (58, 79)	92 (76, 99)	0.002	75 (66, 92)	102.5 (87.5, 120)	0.004
LVESV, ml	33 (25, 42)	38 (31, 47)	0.085	25 (18, 31)	35 (28, 43)	0.020	32 (25, 37)	39.5 (31, 54)	0.013

Data are median (quartile 1, quartile 3). LVEDD = left ventricular end-diastolic diameter, LV = left ventricular, LVEF = left ventricular ejection fraction, LVEDV = left ventricular end-diastolic volume, LVESV = left ventricular end-systolic volume, RV = right ventricular, FAC = fractional area change, TAPSE = tricuspid annular peak systolic excursion.

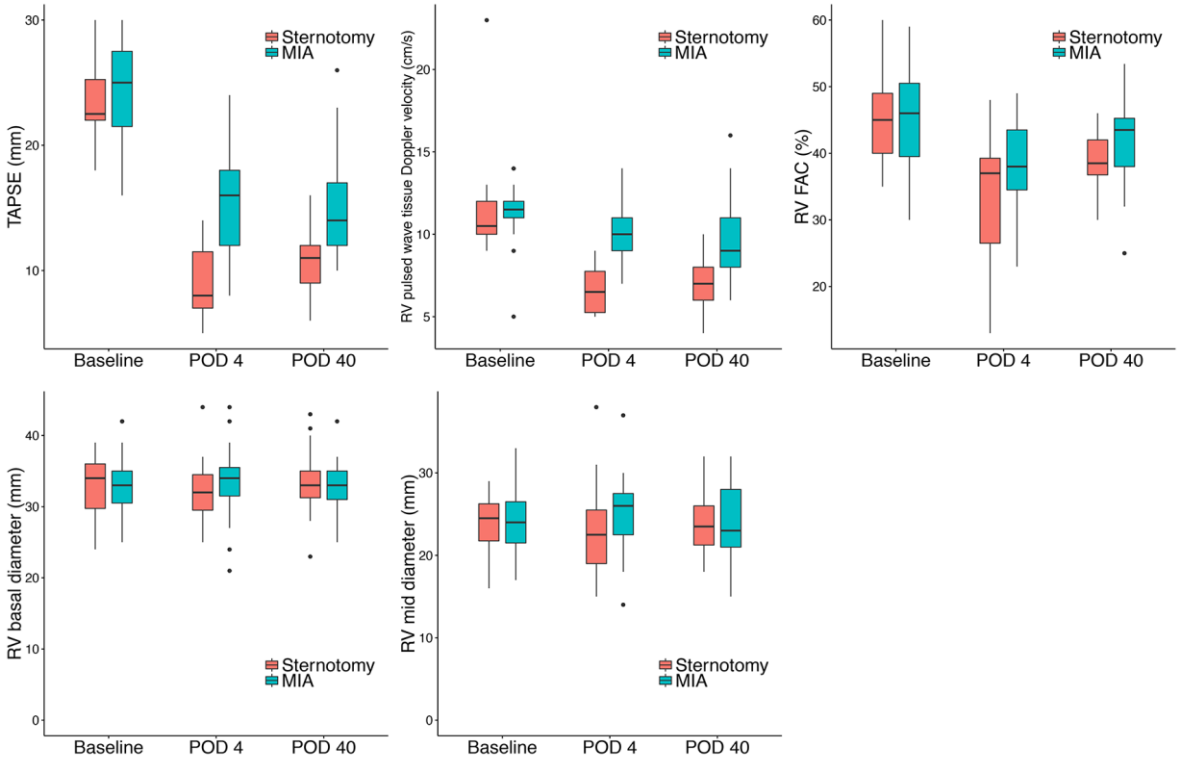

FIGURE 11. Tricuspid annular peak systolic excursion, right ventricular pulsed wave tissue Doppler velocity, right ventricular fractional area change, and right ventricular basal and mid diameter at baseline and at postoperative (POD) day 4 and 40 in patients who underwent sternotomy or minimally invasive (MIA) aortic valve replacement.

Study IV

The flow chart is presented in FIGURE 12. Cardiac CT was performed in 47 patients. All cardiac CT examinations were diagnostic regarding the evaluation of HALT. One examination was non-diagnostic regarding the assessment of valve leaflet motion due to motion artifacts. Patient characteristics at the time of surgery are shown in TABLE 11. Cardiac CT was performed at a median of 491 days (range 36–1,247 days, quartile 1: 287, quartile 3: 933 days) postoperatively.

Primary outcome measure

Hypo-attenuated leaflet thickening was found in 18 (38%) patients, of which 10 (56%) had one affected leaflet, six (33%) had two affected leaflets, and two (11%) had HALT of all three leaflets. HALT was equally frequent in all cusps. The mean HALT was 3 mm (range 1–5 mm; FIGURE 13). Reduced leaflet motion was found in 13 (28%) patients, of which 11 patients had one leaflet with reduced motion and two patients had two leaflets with reduced motion. Reduced leaflet motion was found in three right aortic valve cusps, five left cusps, and seven non-coronary cusps (FIGURE 14-15). Reduced leaflet motion was seen in 13 of 18 (72%) patients with HALT.

Other outcomes

There was no difference in the interval between AVR and CT examination among patients with or without HALT (420 [289, 750] days vs. 547 [287, 989] days; p=0.65). There was no difference regarding prosthetic valve opening area measured with cardiac CT in patients with normal and reduced leaflet motion. All patients with RLM had evidence of HALT of at least one leaflet and there was a significant association between RLM and the presence of HALT (p<0.001). There was no difference in the interval between AVR and CT examination among patients with normal or reduced leaflet motion (583 [364, 1045] vs. 331 [272, 492] days; p=0.095).

None of the patient or procedural characteristics were significantly associated with HALT. Patients with RLM were younger than patients with normal leaflet motion (69.8 ± 5.4 vs. 76.5 ± 4.3 years, p<0.001). Implanted prosthesis size and prosthetic valve opening area in relation to HALT and leaflet motion are presented in TABLE 12.

All patients treated with warfarin or a novel oral anticoagulant had been taking the medication for at least 5 months without interruption. There was no significant association between antithrombotic treatment at the time of cardiac CT and HALT or RLM (TABLE 13, FIGURE 16-17). Both HALT and RLM were found in patients treated with acetylsalicylic acid, warfarin or a novel oral anticoagulant.

Clinical outcomes are shown in TABLE 14. Three (6%) patients had a perioperative stroke, and one (2%) transient ischemic attack occurred during follow-up. Two of the four patients with a cerebrovascular thromboembolic event had HALT and RLM and two had neither HALT nor RLM at CT examination. There were no other differences in clinical outcomes between the groups.

Table 11. Patient and procedural characteristics

Baseline and procedural characteristics in relation to HALT and leaflet motion.

	Total population	No HALT	HALT	p-value	Normal leaflet motion	RLM	p-value
N (%)	47 (100%)	29 (61.7%)	18 (38.3%)		33 (71.7%)	13 (28.3%)	
Age, years, mean (SD)	74.5 (5.4)	75.6 (3.9)	72.8 (7.1)	0.082	76.5 (4.3)	69.8 (5.4)	<0.001
Female sex	36 (77%)	22 (76%)	14 (78%)	0.88	26 (79%)	9 (69%)	0.49
Body mass index, kg/m^2, mean (SD)	27.70 (4.96)	27.5 (3.9)	28.1 (6.5)	0.69	27.1 (3.9)	29.4 (7.0)	0.16
Ministernotomy	40 (85%)	23 (79%)	17 (94%)	0.35	26 (79%)	13 (100%)	0.20
Prosthesis size				0.41			0.40
Small	4 (9%)	4 (14%)	0 (0%)		4 (12%)	0 (0%)	
Medium	18 (38%)	11 (38%)	7 (39%)		14 (42%)	4 (31%)	
Large	20 (43%)	11 (38%)	9 (50%)		12 (36%)	7 (54%)	
Extra large	5 (11%)	3 (10%)	2 (11%)		3 (9%)	2 (15%)	
Left ventricular ejection fraction				0.85			0.84
>50%	44 (94%)	27 (93%)	17 (94%)		31 (94%)	12 (92%)	
30–50%	3 (6%)	2 (7%)	1 (6%)		2 (6%)	1 (8%)	
<30%	0	0	0		0	0	
Estimated glomerular filtration rate				0.56			0.27
>60 mL·min^{-1}·1.73 m^{-2}	32 (68%)	21 (72%)	11 (61%)		23 (70%)	8 (62%)	
45–60 mL·min^{-1}·1.73 m^{-2}	10 (21%)	6 (21%)	4 (22%)		8 (24%)	2 (15%)	
30–45 mL·min^{-1}·1.73 m^{-2}	4 (9%)	2 (7%)	2 (11%)		2 (6%)	2 (15%)	
15–30 mL·min^{-1}·1.73 m^{-2}	1 (2%)	0 (0%)	1 (6%)		0 (0%)	1 (8%)	
Diabetes mellitus	10 (21%)	4 (14%)	6 (33%)	0.11	5 (15%)	5 (38%)	0.084
Insulin-dependent diabetes mellitus	3 (6%)	1 (3%)	2 (11%)	0.30	1 (3%)	2 (15%)	0.13
Hypertension	34 (72%)	21 (72%)	13 (72%)	0.99	25 (76%)	9 (69%)	0.65
Stroke	0	0	0	-	0	0	-
Transient ischemic attack	6 (13%)	4 (14%)	2 (11%)	0.79	4 (12%)	2 (15%)	0.77
Chronic lung disease	4 (9%)	4 (14%)	0 (0%)	0.099	3 (9%)	0 (0%)	0.26
Hemodialysis	0	0	0	-	0	0	-
Neurologic dysfunction	0	0	0	-	0	0	-
Critical preoperative state	1 (2%)	1 (3%)	0 (0%)	0.43	1 (3%)	0 (0%)	0.53
Active cancer	0	0	0	-	0	0	-
History of cancer	5 (11%)	4 (14%)	1 (6%)	0.37	5 (15%)	0 (0%)	0.14
Peripheral artery disease	0	0	0	-	0	0	-
Coronary artery disease	0	0	0	-	0	0	-
Previous myocardial infarction	1 (2%)	0 (0%)	1 (6%)	0.20	0 (0%)	1 (8%)	0.11
Atrial fibrillation	6 (13%)	5 (17%)	1 (6%)	0.24	5 (15%)	0 (0%)	0.14
New York Heart Association class				0.42			0.91
I	3 (6%)	2 (7%)	1 (6%)		2 (6%)	1 (8%)	
II	23 (49%)	12 (41%)	11 (61%)		16 (48%)	7 (54%)	
III	21 (45%)	15 (52%)	6 (33%)		15 (45%)	5 (38%)	
IV	0	0	0		0	0	
Previous cardiac surgery	1 (2%)	1 (3%)	0 (0%)	0.43	1 (3%)	0 (0%)	0.53
Pacemaker	0	0	0	-	0	0	-
EuroSCORE II, mean (SD)	2.01 (1.07)	2.08 (1.17)	1.91 (0.92)	0.62	2.09 (1.13)	1.82 (0.97)	0.45
Days between operation and CT, median (Q1, Q3)	491 (287, 933)	547 (287, 989)	420 (289, 50)	0.65	583 (364, 1045)	331 (272, 492)	0.095

Data are n (%) unless otherwise noted. CT = computed tomography; EuroSCORE II = European System for Cardiac Operative Risk Evaluation Score II; HALT = hypo-attenuated leaflet thickening; Q = quartile; RLM = reduced valve leaflet motion; SD = standard deviation.

Table 12. Prosthesis size

Implanted prosthesis size and prosthetic valve opening area in relation to HALT and leaflet motion.

	Total population	No HALT	HALT	p-value	Normal leaflet motion	RLM	p-value
N (%)	47	33 (71.7%)	13 (28.3%)		29 (61.7%)	18 (38.3%)	
Prosthesis size							
Small	4 (9%) 2.04 (0.66)	4 (100%) 2.04 (0.66)	0	-	4 (100%) 2.04 (0.66)	0	-
Medium	18 (38%) 1.85 (0.37)	11 (61%) 1.95 (0.35)	7 (39%) 1.69 (0.36)	0.15	14 (78%) 1.93 (0.36)	4 (22%) 1.56 (0.25)	0.068
Large	20 (43%) 2.27 (0.34)	11 (55%) 2.48 (0.28)	9 (45%) 2.04 (0.24)	0.002	12 (63%) 2.37 (0.36)	7 (37%) 2.10 (0.23)	0.093
Extra large	5 (11%) 2.37 (0.51)	3 (60%) 2.13 (0.52)	2 (40%) 2.73 (0.32)	0.25	3 (60%) 2.13 (0.52)	2 (40%) 2.73 (0.32)	0.25

Data are n (%) and mean aortic valve area (standard deviation) in cm^2. HALT = hypo-attenuated leaflet thickening; RLM = reduced valve leaflet motion.

Table 13. Antithrombotic treatment at the time of computed tomography

Anticoagulant and platelet inhibition treatment at the time of cardiac computed tomography in relation to HALT and leaflet motion.

	Total population	No HALT	HALT	p-value	Normal leaflet motion	RLM	p-value
N (%)	47 (100%)	29 (61.7%)	18 (38.3%)		33 (71.7%)	13 (28.3%)	
Anticoagulation treatment at the time of computed tomography							
Warfarin	8 (17%)	4 (14%)	4 (22%)	0.45	6 (18%)	2 (15%)	0.82
Any novel oral anticoagulant	9 (19%)	8 (28%)	1 (6%)	0.062	7 (21%)	1 (8%)	0.28
Warfarin or any NOAC	17 (36%)	12 (41%)	5 (28%)	0.35	13 (39%)	3 (23%)	0.30
Rivaroxaban	2 (4%)	2 (7%)	0 (0%)	0.25	2 (6%)	0 (0%)	0.36
Apixaban	7 (15%)	6 (21%)	1 (6%)	0.16	5 (15%)	1 (8%)	0.50
Dabigatran	0	0	0	-	0	0	-
Platelet inhibition treatment at the time of computed tomography							
Dual antiplatelet therapy	0	0	0	-	0	0	-
Acetylsalicylic acid	28 (60%)	15 (52%)	13 (72%)	0.16	19 (58%)	9 (69%)	0.47

Data are n (%) unless otherwise noted. HALT = hypo-attenuated leaflet thickening; NOAC = novel oral anticoagulant; RLM = reduced valve leaflet motion.

Table 14. Clinical outcomes

Clinical outcomes in relation to HALT and leaflet motion.

	Total population	No HALT	HALT	p-value	Normal leaflet motion	RLM	p-value
N (%)	47 (100%)	29 (61.7%)	18 (38.3%)		33 (71.7%)	13 (28.3%)	
Paravalvular leakage grade at discharge				0.25			0.36
None	45 (96%)	27 (93%)	18 (100%)		31 (94%)	13 (100%)	
Mild	2 (4%)	2 (7%)	0 (0%)		2 (6%)	0 (0%)	
Moderate	0	0	0		0	0	
Severe	0	0	0		0	0	
Reoperation due to paravalvular leakage	0	0	0	-	0	0	-
Device embolization perioperatively	0	0	0	-	0	0	-
Conversion to sternotomy	0	0	0	-	0	0	-
Transaortic pressure gradient at discharge							
Maximum, mmHg, mean (SD)	28.9 (10.7)	27.3 (7.3)	31.7 (14.7)	0.20	28.2 (9.5)	31.3 (13.8)	0.40
Mean, mmHg, mean (SD)	15.1 (5.3)	14.5 (4.1)	16.2 (6.9)	0.32	15.2 (5.3)	15.5 (5.6)	0.84
New-onset atrial fibrillation	22 (47%)	15 (52%)	7 (39%)	0.39	16 (48%)	6 (46%)	0.89
Atrial fibrillation before discharge	28 (60%)	20 (69%)	8 (44%)	0.096	21 (64%)	6 (46%)	0.28
Atrial fibrillation after discharge	13 (28%)	11 (38%)	2 (11%)	0.046	11 (33%)	1 (8%)	0.075
De novo pacemaker	6 (13%)	2 (7%)	4 (22%)	0.13	3 (9%)	3 (23%)	0.20
Stroke postoperatively excluding perioperatively	0	0	0	-	0	0	-
Stroke perioperatively	3 (6%)	1 (3%)	2 (11%)	0.30	1 (3%)	2 (15%)	0.13
Transient ischemic attack	1 (2%)	1 (3%)	0 (0%)	0.43	1 (3%)	0 (0%)	0.53

Data are n (%) unless otherwise noted. HALT = hypo-attenuated leaflet thickening; RLM = reduced valve leaflet motion; SD = standard deviation.

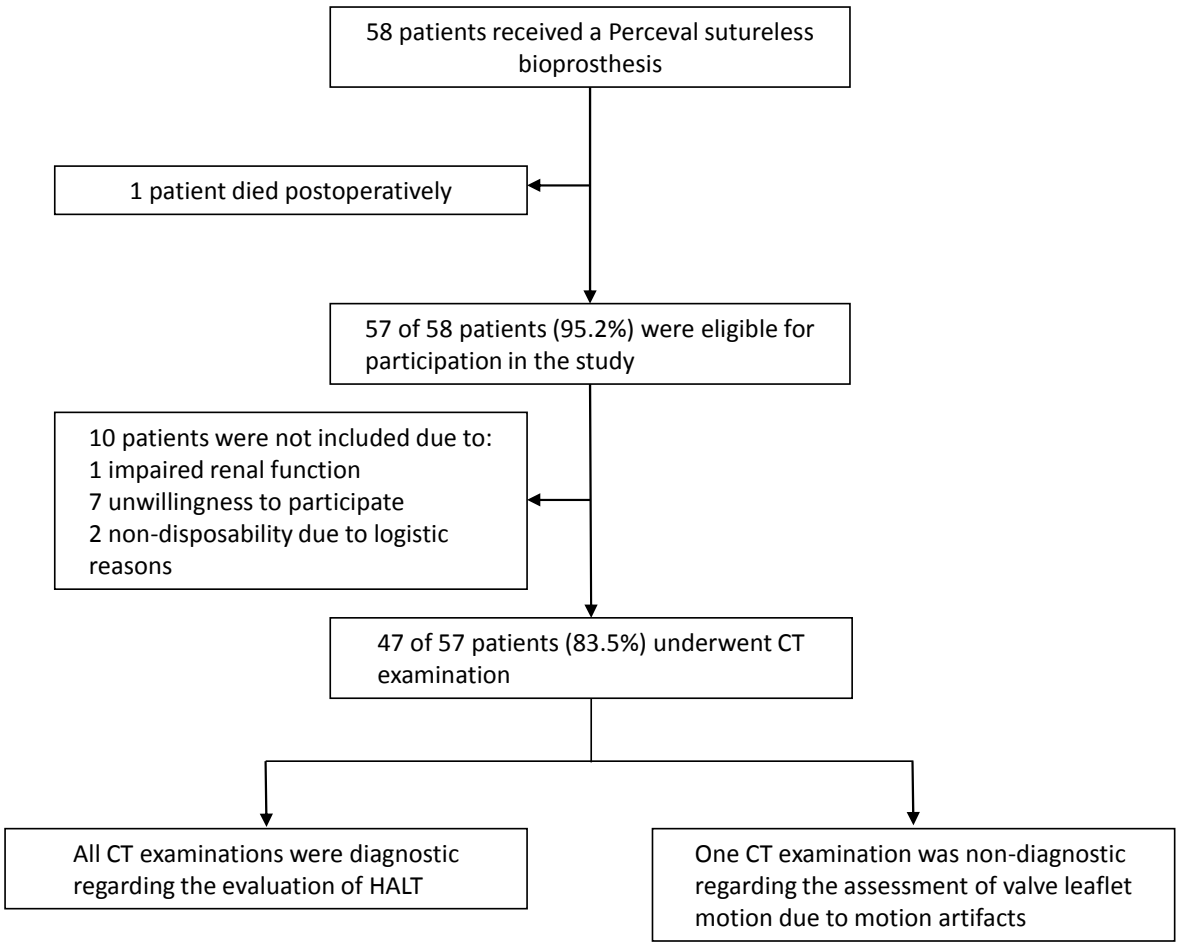

FIGURE 12. Study flow chart. CT = computed tomography.

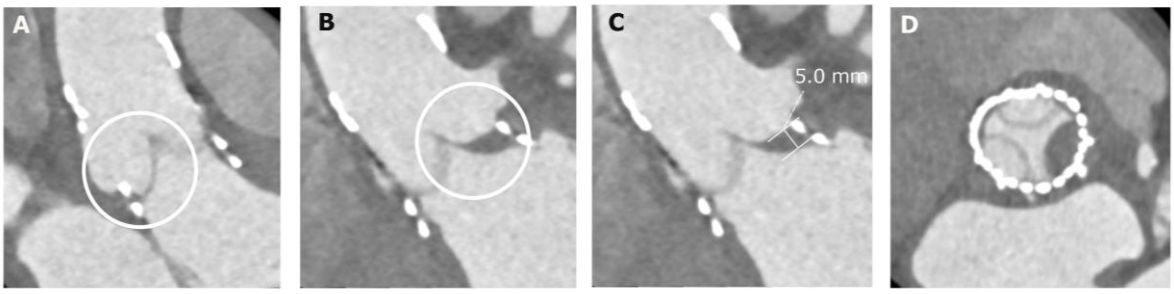

FIGURE 13. Cardiac computed tomography multiplanar reformatted reconstructions of a Perceval sutureless bioprosthetic valve in mid-diastole. The non-coronary cusp (*panel A*) was normal, with no signs of hypo-attenuated leaflet thickening. The left cusp (*panel B*) was markedly thickened with hypo-attenuated leaflet thickening. The maximum leaflet thickness was 5 mm (*panel C*). The three-valve leaflets are shown simultaneously; two of them normal and the left cusp with hypo-attenuated leaflet thickening (*panel D*).

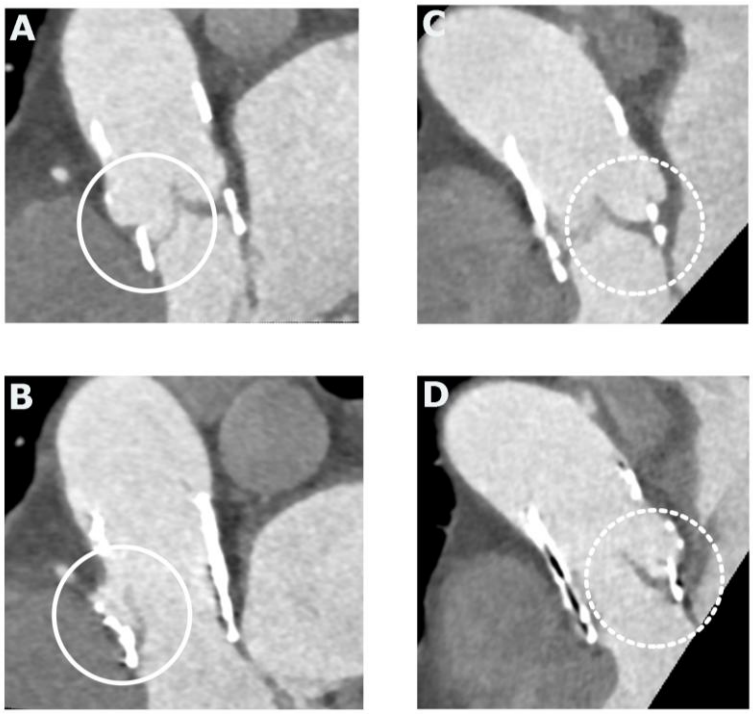

FIGURE 14. Multiplanar reformatted reconstructions for evaluation of leaflet motion in a Perceval sutureless bioprosthetic valve. Top panels show images in diastole and bottom panels show images of maximum leaflet opening in systole. Images to the left show the normal right cusp (white circle) in diastole (*panel A*) and fully open in systole (*panel B*). Images to the right show the non-coronary cusp (dashed circle) of the same patient in diastole (*panel C*) and with reduced leaflet opening in systole (*panel D*). Hypo-attenuated leaflet thickening of the non-coronary cusp was also present.

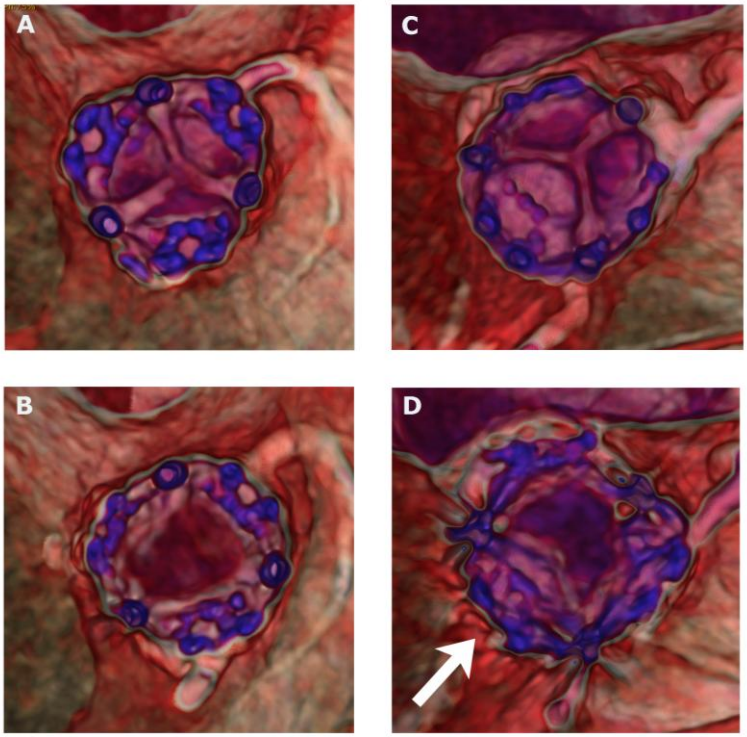

FIGURE 15. Three-dimensional volume-rendered en face images of the Perceval sutureless bioprosthetic valve. Top panels show images in diastole and bottom panels show images in systole. Images to the left show a normal bioprosthesis in diastole (*panel A*) and in systole (*panel B*). To the right, a bioprosthesis with reduced motion of the right cusp (white arrow) is shown in diastole (*panel C*) and in systole (*panel D*).

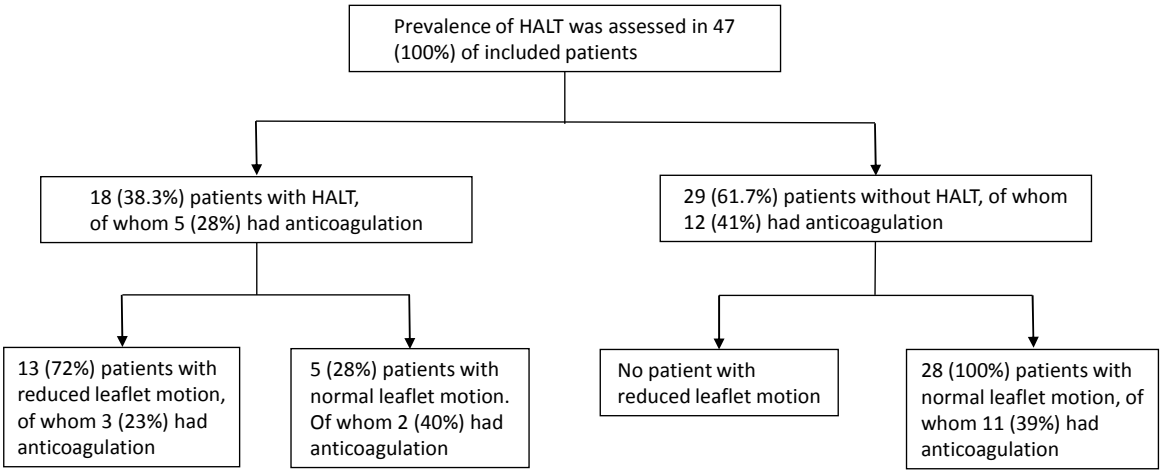

FIGURE 16. Prevalence of hypo-attenuated leaflet thickening in relation to anticoagulation treatment (warfarin or any novel oral anticoagulant) and reduced leaflet motion. HALT = hypo-attenuated leaflet thickening.

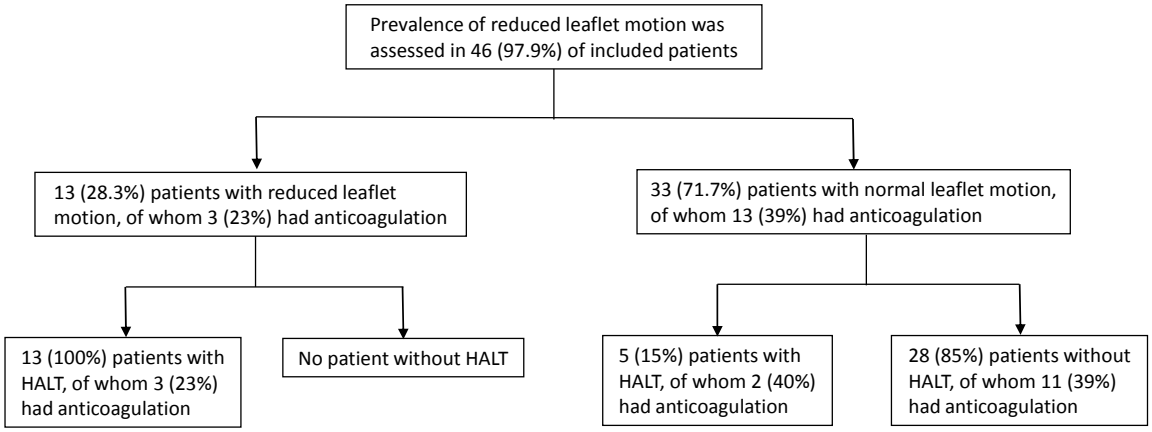

FIGURE 17. Prevalence of reduced leaflet motion in relation to anticoagulation treatment (warfarin or any novel oral anticoagulant) and hypo-attenuated leaflet thickening. HALT = hypo-attenuated leaflet thickening.

DISCUSSION

Study I and II

Mortality

In previous studies, early mortality after ministernotomy AVR has been comparable to mortality after full sternotomy AVR [2-4]. Conversion to full sternotomy is rare but associated with increased mortality [3]. Our findings are in line with these previous reports with similar 30-day mortality between patients undergoing ministernotomy sutureless AVR and full sternotomy AVR with implantation of a sutureless or a stented sutured bioprosthetic valve. Two-year survival was comparable between patients who underwent ministernotomy sutureless AVR and full sternotomy AVR with implantation of a sutureless or a stented sutured valve. These results support that ministernotomy AVR can be performed safely without increased early mortality risk.

Length of stay

Meta-analyses have demonstrated that minimally invasive AVR may be associated with small benefits in terms of shorter intensive care unit and hospital stay compared with conventional AVR [2-4]. One meta-analysis demonstrated that intensive care unit stay was approximately 0.6 days less and hospital stay 1.3 days less in minimally invasive compared with full sternotomy AVR [4]. However, there is a heterogeneity across studies for length of stay [4] and this outcome is likely to be influenced by physician preferences since studies have not been blinded regarding type of incision. When the Perceval sutureless valve was compared with conventional sutured bioprosthetic valves, intensive care unit and hospital stay was shorter in the sutureless group (intensive care unit stay 2.0 vs. 2.8 days, hospital stay 10.9 vs. 12 days) [34]. Our results did not support these previous findings since we did not find that ministernotomy or sutureless AVR was associated with reduced intensive care unit or hospital length of stay.

Paravalvular regurgitation and transvalvular gradients

Owing to the less invasiveness of minimally invasive sutureless AVR compared with full sternotomy AVR, minimally invasive sutureless AVR has been proposed as an alternative to TAVI in patients with high surgical risk. Transcatheter heart valves are implanted using oversizing of the prosthetic valve in the aortic annulus and malsizing, suboptimal placement or stent frame underexpansion can lead to paravalvular regurgitation [66]. Paravalvular regurgitation is more common after TAVI compared with surgical AVR, and more than mild paravalvular regurgitation is associated with increased morbidity and mortality after TAVI [66]. Our results demonstrate a low prevalence of paravalvular regurgitation after ministernotomy and sutureless AVR. This composes a possible advantage of this procedure compared with TAVI in high-risk patients. In contrast to TAVI, minimally invasive AVR allows removal of the diseased native valve as well as complete decalcification of the aortic annulus and this may be the reason for the low prevalence of paravalvular

regurgitation. In the initial experience of Perceval sutureless valve implantation, complete decalcification was not deemed necessary, however, this was associated with a higher prevalence of paravalvular regurgitation and complete decalcification is therefore now recommended [22].

In Study I, after propensity matching, the only difference between patients undergoing ministernotomy and full sternotomy sutureless AVR was postoperative transvalvular gradients. There was a slight increase in transvalvular gradients in patients undergoing ministernotomy AVR. However, ministernotomy AVR was not associated with a higher prevalence of paravalvular regurgitation and it is therefore unlikely that the higher transvalvular gradients should indicate suboptimal valve placement due to limited surgical exposure in the ministernotomy group. Bioprosthetic valve size and body size were similar between the two groups and could therefore not explain the small differences in postoperative transvalvular gradients.

Transfusions

Some studies have demonstrated reduced blood loss in patients undergoing ministernotomy compared with full sternotomy AVR [3, 4]. Also sutureless valve implantation has been associated with a lower transfusion rate of packed red blood cells [34]. This is in line with our results, since we found that patients undergoing ministernotomy sutureless AVR received less transfusion of packed red blood cells compared with patients undergoing full sternotomy with implantation of a stented bioprosthetic valve. The reduction in perioperative blood loss may be related to the less invasiveness of ministernotomy AVR, however, another possibility that must be considered is that minimally invasive procedures are normally performed by more experienced surgeons.

Postoperative pacemaker implantation

Implantation of a sutureless valve through a ministernotomy was associated with a higher risk for postoperative permanent pacemaker implantation compared with implantation of a conventional sutured bioprosthetic valve through a full sternotomy. Since we did not have information regarding indication for postoperative pacemaker implantation, it is unclear whether the increased risk in the ministernotomy sutureless group should be attributed to the prosthesis itself or to possibly different policies regarding indications for pacemaker implantation between participating centers. Other studies have shown that new-onset complete atrioventricular block and other conduction disorders are frequent after sutureless AVR [40, 67] but the incidence is lowered if the aortic annulus is completely decalcified [40].

Cross-clamp and cardiopulmonary bypass duration

Studies have consistently demonstrated that minimally invasive AVR is associated with prolonged aortic cross-clamp and cardiopulmonary bypass time compared with full sternotomy AVR [2, 3]. It has been hypothesized that longer aortic cross-clamp and cardiopulmonary bypass time may reduce the benefits of minimally invasive AVR, since prolonged aortic cross-clamp and cardiopulmonary bypass time has been associated with increased morbidity and mortality [68, 69]. However, it is hard

to demonstrate that prolonged procedure time *per se* is associated with increased risk since it may just be a marker for increased procedure complexity and peroperative complications.

Sutureless aortic bioprosthetic valves were designed to facilitate implantation and thereby reduce operative and ischemic time. Previous studies show that implantation of the Perceval sutureless valve is associated with reduced aortic cross-clamp and cardiopulmonary bypass time compared with implantation of conventional stented bioprosthetic valves [35]. It has been proposed that the shorter procedure time achieved with sutureless valves may be the reason for a lower rate of transfusion of packed red blood cells and shorter length of stay [34]. We found that ministernotomy and full sternotomy implantation of the Perceval sutureless bioprosthetic valve was associated with comparable aortic cross-clamp and cardiopulmonary bypass time. Ministernotomy sutureless AVR was associated with shorter aortic cross-clamp and cardiopulmonary bypass time than full sternotomy implantation of a sutured bioprosthetic valve. Hence, sutureless valve implantation reduces procedural duration in minimally invasive AVR, excluding this drawback of minimally invasive AVR.

Clinical implications

Our results demonstrate that ministernotomy sutureless AVR can be performed safely without increased risk for early mortality. Ministernotomy sutureless AVR may be associated with similar postoperative outcomes as full sternotomy AVR with implantation of a stented sutured bioprosthetic valve but the risk for postoperative permanent pacemaker implantation is increased after sutureless AVR. Cross-clamp and cardiopulmonary bypass time is reduced by using sutureless bioprosthetic valves and this may be of importance in minimally invasive AVR for which prolonged ischemic and operative time has been acknowledged as a limitation.

Study III

Right ventricular long axis function after minimally invasive aortic valve replacement

Previous observational studies have shown impairment of RV long axis function after cardiac surgery [44-50]. In contrast to our findings, a small study that investigated the effect of different cardiac operations on RV long axis velocities demonstrated no significant impairment of RV long axis function after ministernotomy AVR with partial opening of the pericardium [47]. However, the impairment of RV long axis function we found after ministernotomy AVR may have been too small to detect in a smaller patient cohort than the one studied in Study III.

Right ventricular long axis velocities begin to decline at pericardial opening during cardiac surgery [46, 47], suggesting that reduction in RV long axis movement is a result of altered pericardial constraint. Two possible explanations for this have been discussed; either the pericardium may be important for allowing the RV long axis to function at full efficiency or the pattern of RV contraction may be dependent on the pericardial constraint and without it the pattern may change [47]. Our results indicate that RV long axis function is impaired also after ministernotomy AVR, although to a lesser

degree than after full sternotomy AVR, thus suggesting that partial opening of the pericardium anterior to the ascending aorta is associated with partial impairment of RV long axis function.

Impaired right ventricular function or geometric alteration

Right ventricular long axis function is not impaired after TAVI [45, 51, 53], and it has been hypothesized that TAVI may be superior to surgical AVR in terms of RV function preservation [51, 53, 70, 71]. In a study where 20 patients underwent full sternotomy AVR and 20 patients underwent transfemoral TAVI, TAPSE was reduced but fractional shortening of the RV midcavity transverse diameter increased after full sternotomy AVR [51]. Right ventricular ejection fraction assessed by 3-dimensional echocardiography was unchanged after AVR, suggesting that global RV function was not compromised. This is in line with a previous study in which RV ejection fraction assessed by magnetic resonance imaging did not change after full sternotomy AVR [72]. These findings suggest that even though RV long axis function generally correlates with global RV function [73], this may not be true for patients who have undergone cardiac surgery with opening of the pericardium.

The design of this study do not permit conclusions about whether the reduction in RV long axis function after full sternotomy and ministernotomy AVR was due to globally reduced RV function or RV geometric alteration. We found that FAC, an echocardiographic parameter commonly used to assess global RV function, was equally impaired in both groups postoperatively. However, similar to other measures of RV function, FAC has not been studied in patients who have undergone cardiac surgery.

Clinical implications

Our results demonstrate the change in commonly used echocardiographically derived parameters of RV long axis and global function following ministernotomy and full sternotomy AVR, information that may be useful for physicians involved in the postoperative care of these patients. Although severe postoperative impairment of RV function after cardiac surgery is associated with mortality [42], the clinical significance of the impairment of RV long axis function seen in the majority of patients undergoing cardiac surgery is uncertain. Our results do not permit speculations about whether the less reduced RV long axis function in patients who underwent ministernotomy may translate into better clinical outcomes or whether patients with preoperative RV dysfunction may benefit from ministernotomy AVR.

Study IV

Prevalence of hypo-attenuated leaflet thickening and reduced leaflet motion

Hypo-attenuated leaflet thickening and RLM have been demonstrated in practically all studied aortic bioprosthetic valve types, including a small number of surgically implanted bioprostheses, but the reported prevalence of HALT and RLM has varied considerably. There are several differences between the previous reported series that might explain the variability, for example prosthetic valve

type, duration between valve implantation and CT, and different cardiac CT techniques. The prevalence of HALT in the Perceval sutureless bioprosthetic valve was high (38%) compared with previous TAVI studies (4–10%) [61-63, 74] and the prevalence of RLM (28%) was higher than reported in two registries of transcatheter and surgical valve implantations (13%), but slightly lower than the prevalence found in a clinical TAVI trial (40%) [62].

Differences between Study IV and previous reports regarding the prevalence of HALT and RLM may be related to the different prosthesis designs and to the fact that cardiac CT was generally performed late in our study (median 491 days after AVR) compared with previous reports. In some studies, cardiac CT was performed within the first week after valve implantation [61] and in other studies cardiac CT was performed later [62, 63, 74]. It is still unknown how the prevalence of HALT and RLM varies after valve implantation, but a high prevalence has been found early as well as late after the procedure. The highest risk for symptomatic bioprosthetic valve thrombosis is within 3 months after implantation [75]. Another explanation to the high prevalence of HALT and RLM found in the Perceval sutureless valve may be the high diagnostic quality of the cardiac CT scans with no non-diagnostic examinations.

Owing to the small number of patients studied, it is not possible to conclude whether there is a difference in the prevalence of HALT and RLM between different percutaneously or surgically implanted prosthesis types. Given the very scarce data on HALT and RLM in surgically implanted valves and the lack of no direct comparisons, it is not possible to conclude whether these phenomena are more prevalent in the Perceval sutureless valve than in other surgically implanted bioprosthetic valves. Implantation of the Perceval sutureless valve has been associated with satisfactory hemodynamic performance without any overall increase in transvalvular gradients over time, as well as low incidence of postoperative adverse events such as stroke, structural valve degeneration and clinically apparent valve thrombosis [10, 11]. However, maximum follow-up is currently limited to 5 years with very few patients followed for more than 2 years postoperatively, which prohibits definitive conclusions regarding clinical outcomes and structural valve degeneration.

Anticoagulation therapy

Thrombosis has been considered to be the likely cause of HALT and RLM in transcatheter valves, owing to CT characteristics and that the findings have resolved with anticoagulation treatment [62, 74]. The Perceval sutureless valve has several features in common with transcatheter valves, for example the metal stent design that may cause blood trauma and thereby induce a hypercoagulable state [61, 76]. It has also been speculated that the leaflet material of transcatheter and surgical bioprostheses may to some degree be pro-coagulant [61]. Our results did not show an association between anticoagulation therapy at the time of CT and HALT or RLM but the number of patients included in Study IV may be too small to detect such an association. However, both HALT and RLM were noted in patients receiving anticoagulation therapy, indicating that anticoagulation therapy do not completely protect against these phenomena. This is consistent with previous reports [74].

Guidelines for the possible treatment of HALT and RLM are currently lacking. The risk-benefit profile of anticoagulation treatment for HALT and RLM remains uncertain since HALT and RLM have not been associated with adverse clinical events and anticoagulation therapy carries a risk for major bleeding complications [77].

Clinical implications

Hypo-attenuated leaflet thickening and RLM were frequent findings in the Perceval sutureless bioprosthetic valve. As well as for transcatheter valves, the potential clinical consequences of HALT and RLM in the Perceval sutureless valve are uncertain. The study was not designed to investigate a potential association between these imaging findings and adverse events. Previous reports have not demonstrated an association between HALT or RLM and adverse events such as symptoms of heart failure, increased transvalvular gradients, or cerebrovascular embolic events [61-63].

Limitations

Study I and II

The findings in Study I and II may have been influenced by selection bias. In the overall cohorts of both Study I and II, the groups were not balanced regarding several potentially confounding factors such as age, comorbidities, procedure urgency, and preoperative risk score evaluation (EuroSCORE I and II). Although we attempted to adjust for differences between the treatment groups with propensity matching analyses, a number of risk factors with importance for the decision of surgical approach might have been left unrecognized.

Owing to the retrospective data collection and multicenter design of Study I and II, treatment strategies may have differed between participating centers and therefore data regarding outcome measures such as hospital stay should be interpreted with caution.

In Study II, data on patients operated with a full sternotomy and implantation of a stent-mounted sutured prosthetic valve were collected from a single-center (Karolinska University Hospital) series. This differed from the ministernotomy sutureless cohort which consisted of patients operated on at several different centers. Also, the two treatment groups were not operated during the same time period. Since full sternotomy implantation of a sutured bioprosthetic valve is the conventionally used implantation strategy for AVR, with very similar short- and long-term results between different European centers, we believe that the results of a single institution can be generalized to serve as a European standard that new surgical techniques can be compared to. However, this methodology could have led to important, but not acknowledged, differences between the treatment groups.

Study III

The two treatment groups differed in regard of type of cardioplegia used and implanted prosthetic valve types. The assessment of RV function cannot be regarded as comprehensive since we did not include certain echocardiographic parameters of RV function such as three-dimensional ejection

fraction or fractional shortening of the RV transverse diameter. The study was designed to demonstrate how frequently used echocardiographic parameters of RV long axis and global function change following ministernotomy and full sternotomy AVR. Hence, it was not designed to investigate potential differences in clinical outcomes associated with these changes. Postoperative day 1 echocardiography was included in the initial study plan; however, these examinations were omitted owing to insufficient transmission quality.

Study IV

The study may not have been adequately powered to detect differences related to anticoagulation treatment. No echocardiographic assessment was performed at the time of cardiac CT and the time interval between AVR and CT examination varied considerably since patients were not included in the study at the time of surgery.

CONCLUSIONS

1. Aortic valve replacement with implantation of a sutureless bioprosthetic valve through a ministernotomy was a safe procedure with early postoperative outcomes and 2-year survival comparable to full sternotomy aortic valve replacement. Procedural time was not prolonged in patients undergoing ministernotomy compared to patients undergoing full sternotomy sutureless aortic valve replacement.
2. Aortic valve replacement through a ministernotomy with implantation of a sutureless bioprosthetic valve was associated with shorter procedural time and less transfusion of packed red blood cells but a higher risk for permanent pacemaker implantation compared with a full sternotomy with implantation of a stented sutured valve.
3. Right ventricular long axis function was reduced after both ministernotomy and full sternotomy aortic valve replacement, but the reduction was more pronounced in the full sternotomy group. Global right ventricular function was equally impaired after ministernotomy and full sternotomy aortic valve replacement.
4. Hypo-attenuated leaflet thickening and reduced leaflet motion were frequent findings in the Perceval sutureless bioprosthetic valve. Both hypo-attenuated leaflet thickening and reduced leaflet motion was found in patients with ongoing anticoagulation treatment.

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