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DISSERTATION

**Predictors of early and late survival after surgical ventricular restoration of  
antero-apical left ventricular aneurysms**

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## I. Abbreviations

BMI	body mass index
BSA	body surface area
CABG	coronary artery bypass grafting
CBP	cardiopulmonary bypass
CMR	cardiac magnetic resonance
CI	cardiac index
CO	cardiac output
EF	ejection fraction
ESVI	end-systolic volume index
GFR	glomerular filtration rate
HR	hazard ratio
IABP	intra-aortic balloon pump
ICD	implantable cardioverter defibrillator
LA	left atrium
LAD	left anterior descending artery
LAVI	left atrial volume index
LCOS	low cardiac output syndrome
LV	left ventricle
LVA	left ventricular aneurysm
LVAD	left ventricular assist device
LVEDD	left ventricular end-diastolic diameter
LVEDP	left ventricular end-diastolic pressure
LVEDV	left ventricular end-diastolic volume
LVEDVI	left ventricular end-diastolic volume index
LVEF	left ventricular ejection fraction

LVESV	left ventricular end-systolic volume
LVESVI	left ventricular end-systolic volume index
LVSI	left ventricular sphericity index
MCS	mechanical circulatory support
MR	mitral regurgitation
MSCT	multi-slice computed tomography
MV	mitral valve
MVR	mitral valve repair
MVS	mitral valve surgery
NNT	number needed to treat
NYHA	New York Heart Association
PCI	percutaneous coronary intervention
PIRA	patent infarct-related artery
PTCA	percutaneous transluminal coronary angioplasty
SHFM	Seattle Heart Failure Model
SI	sphericity index
SVI	stroke volume index
SVR	surgical ventricular restoration
TTE	transthoracic echocardiography

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## IV. Zusammenfassung

**HINTERGRUND:** Linksventrikuläre Aneurysmen (LVA) bilden sich nach abgelaufenem Myokardinfarkt und führen zu einer Herzinsuffizienz. Die chirurgische Ventrikelrekonstruktion (LVR) ist ein Verfahren zur Behandlung der LVA.

**ZIELSETZUNG:** Ziele dieser Studie waren: (I) das Früh- und Langzeitüberleben nach LVR zu analysieren, (II) das Überleben der LVR-Patienten mit dem Überleben, das von Seattle Heart Failure Model (SHFM) für konservativ behandelte Patienten prognostiziert wurde, zu vergleichen, (III) die volumetrischen, geometrischen und funktionellen Parameter nach LVR zu vergleichen, (IV) die volumetrischen, geometrischen und funktionellen Parameter und Grenzwerte, die mit einem Ereignis-freien Überleben assoziiert sind, zu definieren, (V) die Prädiktoren der unerwünschten Ereignisse bei frühem und spätem Follow-up bei LVR-Patienten zu identifizieren (VI) die Bedeutung der multimodalen Bildgebung für operative Planung der LVR zu ermitteln.

**METHODEN:** 192 Patienten (Altersmedian 64.2 Jahre [range: 27–87], 73.4% männlich, New York Heart Failure Association (NYHA) Median-Stadium III), bei denen eine LVR durchgeführt wurde, wurden retrospektiv analysiert. Daten der Multischicht-Computertomographie und transthorakaler Echokardiografie wurden verwendet.

**RESULTATE:** (I) Die 1-, 5- und 10-Jahre-Überlebensrate waren jeweils 83.5%, 69.6% und 49%. NYHA-Funktionsklasse verbesserte sich vom mittleren Stadium 3.02 auf 1.82 in frühem Follow-up ( $p < 0.001$ ) und blieb stabil auch bei spätem Follow-up. (II) Im Vergleich zu dem prognostizierten Überleben konnte ein signifikanter Überlebensvorteil der LVR-Patienten nach 5 Jahren nachgewiesen werden (65.7% vs. 51%,  $p < 0.001$ ). (III) Die LVR führte zu einer Abnahme des linksventrikulären endsystolischen indexierten Volumens (LVESVI; 102.9 vs. 58.6 mL/m<sup>2</sup>,  $p < 0.001$ ) und zu einer Zunahme der linksventrikulären Ejektionsfraktion (32.1% vs. 39.5%,  $p < 0.001$ ). (IV) Der präoperative linksventrikuläre end-diastolische Diameter (LVEDD) über 60.5 mm und eine moderate bis hochgradige Mitralklappeninsuffizienz, sowie auch ein postoperativer LVESVI  $\geq 55$  mL/m<sup>2</sup>, waren assoziiert mit erhöhtem Risiko von unerwünschten Ereignissen. (V) Präoperative

Prädiktoren des Ereignis-freien Überlebens waren: LVEDD (hazard ratio [HR]: 1.044 [1.020–1.069],  $p < 0.001$ ), Grad der MI (HR: 1.427 [1.086–1.874],  $p = 0.011$ ), Diabetes (HR: 2.170 [1.365–3.452],  $p = 0.001$ ), und glomeruläre Filtrationsrate (HR: 0.976 [0.965–0.987],  $p < 0.001$ ). Einziger postoperativer Prädiktor des Ereignis-freien Überlebens war LVESVI (HR: 1.020 [1.011–1.028],  $p < 0.001$ ). (VI) Vernarbung in basalen Segmente des Myokards war prädiktiv für geringere Überlebensraten.

**SCHLUSSFOLGERUNG:** LVR führt zu einer Verbesserung der NYHA-Funktionsklasse und des Überlebens bei LVA-Patienten. Adäquate chirurgische Reduktion des LV-Volumens ist nötig, um gute Langzeitergebnisse zu erzielen. Die Patientenselektion und Planung der optimalen Behandlungsstrategie sollte bei Patienten mit LVA auf der Grundlage einer multimodale Bildgebung durchgeführt werden.

## V. Summary

**BACKGROUND:** Left ventricular aneurysms (LVA) develop following myocardial infarction and lead to heart failure. Surgical ventricular restoration (SVR) is an operative technique in the treatment of LVA.

**OBJECTIVES:** The aims of this study were to (I) analyze early and late survival and functional outcomes of patients undergoing SVR, (II) compare the survival in patients undergoing SVR with the survival predicted by the Seattle Heart Failure Model (SHFM) in patients treated with conservative therapy, (III) analyze the change of volumetric, geometric, and functional parameters following SVR, (IV) define the volumetric, geometric, and functional parameters and cut-offs associated with adverse event-free survival, (V) identify the predictors of adverse events at the early and late follow-up in patients undergoing SVR, (VI) determine the importance of multimodality imaging in SVR planning.

**METHODS:** 192 patients undergoing SVR (median age 64.2 years [range: 27–87], 73.4% male, median New York Heart Association [NYHA] functional class 3) were analyzed retrospectively. Multi-slice computed tomography and transthoracic echocardiography data were used.

**RESULTS:** (I) 1-, 5-, and 10-year adverse event-free survival was 83.5%, 69.6%, and 49% respectively. The NYHA class improved from a mean of 3.02 to 1.82 ( $p < 0.001$ ). (II) Compared to the prediction by the SHFM, survival benefit of SVR was seen at 5 years (65.7% vs. 51%,  $p < 0.001$ ). (III) SVR resulted in a decrease in left ventricular end-systolic volume index (LVESVI; 102.9 vs. 58.6 mL/m<sup>2</sup>,  $p < 0.001$ ) and an increase in left ventricular ejection fraction (32.1% vs. 39.5%,  $p < 0.001$ ) following surgery. (IV) A preoperative left ventricular end-diastolic diameter (LVEDD) greater than 60.5 mm and moderate or severe mitral regurgitation, as well postoperative LVESVI  $\geq 55$  mL/m<sup>2</sup>, were associated with an increased risk of adverse events. (V) Preoperative factors influencing adverse event-free survival were LVEDD (hazard ratio [HR]: 1.044 [1.020–1.069],  $p < 0.001$ ), MR grade (HR: 1.427 [1.086–1.874],  $p = 0.011$ ), diabetes (HR: 2.170 [1.365–3.452],  $p = 0.001$ ), and glomerular filtration rate (HR: 0.976 [0.965–0.987],  $p < 0.001$ ). The only postoperative predictor of adverse event-free survival was LVESVI

(HR: 1.020 [1.011–1.028],  $p < 0.001$ ). (VI) Scarification of basal segments predicted an adverse outcome.

**CONCLUSION:** SVR can be performed with good results in LVA patients, leading to a long-term improvement in NYHA class and survival. Adequate surgical volume reduction is essential to achieve good long-term results. This study supports the contention that using multimodality imaging facilitates the candidate selection and planning of the optimal treatment strategy in LVA patients.

# 1. Introduction

## 1.1. Left ventricular aneurysm

Acute myocardial infarction can lead to the development of a left ventricular aneurysm (LVA) [1]. The ischemic myocardium may become hypokinetic (poor contractility), akinetic (absent contractility), or dyskinetic (outward paradoxical bulging). While a consistent scientific definition of LVA is still missing, it is commonly understood as an akinetic or dyskinetic wall motion abnormality, resulting from a myocardial fibrosis, ischemic wall thinning, and scar calcification, and leading to a decrease in the left ventricular (LV) function. Infarction of an area exceeding 20% of the LV surface results in cardiac dyssynchrony and significant wall motion abnormalities [2]. A gradual left ventricular remodeling causes a ventricular cavity enlargement and an abnormal ventricular shape. This ventricular dilation is a compensatory mechanism for the contractility loss in infarcted areas. Low cardiac output results from a dysfunctional ventricle, in which a portion of the stroke volume is retained by the aneurysm. The dilated and fibrotic aneurysmal wall decreases diastolic filling and increases diastolic stretch, left ventricular end-diastolic and end-systolic volume (LVEDV/LVESV), and left ventricular end-diastolic pressure (LVEDP). Endocardial wall tension increases due to the larger longitudinal radius of the ventricle curvature. The oxygen consumption in remote functional subendocardial areas increases, leading to progressive ischemia. The result of this mechanism is the enlargement of the entire ventricle, not only of its aneurysmatic part. This development is paralleled by changes in neurohumoral regulation, sustaining the dilatation process [3]. Such remodeling can develop over several years before it becomes symptomatic; however, in some cases the progression is rapid. Even asymptomatic patients with mild forms of ventricle dilation have an increased risk of sudden cardiac death [4]. Overall left ventricular dysfunction and the severity of the heart failure with the resulting functional impairment are far more important predictors of survival than the presence or the extent of an aneurysm [5].

LVA formation following myocardial infarction was observed in 7.6% of cases in a study of 15,019 patients with coronary artery disease [5]. Tikiz [6] observed that the LVA formation was not significantly decreased in patients receiving thrombolytic therapy compared to patients receiving no thrombolysis. However, once reperfusion resulted in a patent infarct-related artery (PIRA), the incidence of LVA formation was

significantly reduced (7.2 vs. 18.8%). Left anterior descending artery (LAD) occlusion or stenosis and the absence of PIRA were shown to be independent determinants of LVA formation.

A classic aneurysm is described in the literature as a visible white fibrous scar of the epicardium and the endocardium [7]. The fibrotic wall is thin and collapses upon cardiac decompression during an operating procedure. A scar border between the ischemic and healthy myocardium can be clearly delineated. As suggested by M.J. Antunes and P.E. Antunes [7], this classic presentation is rarely seen in modern cardiac surgery because with the development of percutaneous transluminal coronary angioplasty (PTCA) and thrombolysis most ischemic areas tend to appear as scattered, non-homogenous non-transmural akinetic trabecular scars. Instead of a border zone, a transition zone with no clear delineation can be observed. As a result of reperfusion, the stretched and thinned ischemic area is reduced and the ventricular wall becomes thicker. This, however, does not improve the hemodynamics and the contractility, which can be worsened by even higher LV volumes and left ventricular end-diastolic pressure (LVEDP) when compared to isolated ventricular aneurysms. Remote zones suffer from increased endoventricular pressures, high oxygen demand, and a subsequent hypertrophy, causing congestive heart failure. Functional mitral regurgitation (MR) results from ventricular dilation, changes in interpapillary distance, and valvular tethering. Concomitant MR leads to an earlier onset of symptomatic heart failure, as it is responsible for a more rapid LV dilation through the stimulation of molecular and cellular abnormalities in remote functional myocardium [8]. In an experimental study, MR development was observed even before ventricular dilation, and only the shape change, reflected by an increasing sphericity index (SI), was a sign of a heart failure onset [9].

In a study of 40 patients, overall 10-year survival without operation was 90% in asymptomatic LVA patients on medication but only 46% in symptomatic patients [10]. Nonfatal complications included arrhythmias (34%), thromboembolic events (29%), recurrent myocardial infarction (22.5%), and congestive heart failure (29%).



## 1.2. Surgical ventricular restoration: an overview of operative techniques

Surgical ventricular restoration (SVR) comprises a group of different surgical procedures and methods, which underwent modifications over time.

The first surgical aneurysmectomy was performed by Ferdinand Sauerbruch [11] at the Charité Berlin in 1931 by sewing over a perforated right ventricle. Cooley [12] extended the method in the era of modern cardiac surgery by using a linear closure technique with a 2-layer horizontal mattress suture and a 2-layer vertical running suture after the resection of the ventricular aneurysm.

In the mid-eighties of the 20<sup>th</sup> century, several techniques were developed to restore a more physiological shape of the left ventricle by excluding the septal scar.

Jatene [13] developed the Cooley technique further by adding septal plication and using purse-string sutures at the proximal part of aneurysmatic septal localization. Using a Dacron patch to close the ventriculotomy, the physiological conical shape of the apex could be restored, though the relation to the septum remained unchanged.

Vincent Dor [14] introduced a technique by which the LV apex could be repositioned more laterally to the septum. During the endoventricular circular patch plasty, a purse-string suture (a so-called Fontan suture) was then placed at the border of scarred tissue and tied to restore the hemodynamically beneficial geometry of the ventricle. The remaining opening was closed using a patch from Dacron or pericardium. Dor also advocated complete revascularization with the goal of recruiting viable, hibernating myocardium. The operation had several modifications and became known as surgical ventricular restoration (SVR). By showing the effectiveness of the operation in patients with large akinetic scars, the Dor group extended the indication for SVR beyond simple isolated aneurysmectomy, thus creating one of the most important surgical techniques in the domain of heart failure surgery [15]. Importantly, no survival difference could be observed by the Di Donato et al. between patients with isolated aneurysms and heart failure patients with global akinesia of the left ventricle undergoing SVR [16].

Mickleborough [17] expanded the technique further by adding patch septoplasty using bovine pericardium in cases with excessive septal thinning and incorporating it into the linear ventriculotomy repair.

McCarthy [18] modified the endoventricular circular plasty by discarding the akinetic patch and using two or more purse-string sutures and ventricular free wall closure.

### **1.3. Effects of SVR on functional and volumetric parameters**

Following the operation, paradoxical contractile forces were reduced due to the restored LV geometry. An acute improvement in contractile state, mechanical energy efficiency, and relaxation pattern following wall stress decrease was observed [19]. The global wall motion score index improved significantly [20]. An improvement of the function of the remote non-dyskinetic myocardium was also observed [21] [22].

A normal left ventricular end-systolic volume index (LVESVI) has a range of 11–31 mL/m<sup>2</sup> for male and 8–24 mL/m<sup>2</sup> for female patients [23]. A significant LVESVI increase is seen in patients with LVA. The main goal of SVR is to achieve left ventricular reverse remodeling, which was defined by the Dor group [24] as a postoperative reduction rate of baseline LVESVI of 15% or more. Di Donato and coworkers [25] established a postoperative LVESVI of less than 60 mL/m<sup>2</sup> as a target postoperative volume associated with favorable outcomes. Analyzing a subset of high-risk patients undergoing SVR but excluded from the STICH trial, Dor et al. could observe a sustained and significant LVESVI reduction and left ventricular ejection fraction (LVEF) improvement at 1-year follow-up [26].

Concerns about possible diastolic dysfunction following volume reduction were not confirmed in the study by Castelvechio and associates [27], showing that the diastolic function in most patients undergoing SVR remained unchanged. However, in a minority of patients with a smaller preoperative LVEDV (<160 ml), worsening of the diastolic function was reported.

Menicanti et al. [28] showed the importance of MR in the setting of a dilated left ventricle with depressed function. SVR was able to improve the tenting area and interpapillary muscle distance, thus significantly reducing MR even without mitral valve repair. However, as baseline MR was associated with an increased mortality risk, the authors advocated mitral valve repair even in patients with mild MR but annular dilatation and/or severely depressed ventricular function.

### **1.4. Role of non-invasive imaging in preoperative LVA assessment**

#### **1.4.1. Transthoracic echocardiography**

Transthoracic echocardiography (TTE) is the most widely available and cost-effective imaging modality to detect LVA. It allows for the initial assessment of wall motion

abnormalities, ventricular dimensions, ejection fraction, and valvular regurgitation. However, the quality of images is dependent on the observer experience and quality of echocardiographic windows. Bellenger et al. [29] observed that TTE measurements of LVEF and ventricular volumes are biased in the presence of regional asynergy and in more spherical ventricles, which are often seen in heart failure patients. Teichholz and associates [30] suggested that geometrical assumptions in TTE rely on normal volumetric measurements and are therefore not reliable in deformed ventricles. In a study [31] of patients undergoing SVR, TTE underestimated the LVESVI by 30% when compared with left ventriculogram and scintigram, showing that LVESVI measurements using these methods are not interchangeable.

#### **1.4.2. Cardiac magnetic resonance**

Cardiac magnetic resonance (CMR) is currently the gold standard in ventricle measurement, calculation of ejection fraction, and characterization of cardiac tissue in patients with dilated ventricles [32]. CMR imaging does not require the use of ionized radiation, and image acquisition is not observer-dependent. However, it is still a time- and cost-intensive procedure that is not widely available in peripheral hospitals. Furthermore, some heart failure patients may not be eligible for the imaging modality because of intracorporal devices or the inability to hold breath for longer periods of time.

#### **1.4.3. Multi-slice computed tomography**

Multi-slice computed tomography (MSCT) is currently not regarded as a first-line diagnostic tool for ventricular function assessment [33]. Over the years, some technical limitations could be overcome; for example, the temporal resolution was increased to 75 ms and became heart rate independent. A constant increase in patients with intracorporal devices (such as implantable cardioverter defibrillators [ICD]) can be observed over the years, especially in the cohort of heart failure patients. MSCT is the only suitable diagnostic option in these patients as well as in unstable patients or patients unable to lie flat and hold breath for a long time. During an MSCT image acquisition, a complete morphologic dataset of the heart is recorded, which can be used for assessing the ventricle, valves, and subvalvular apparatus [34]. Coronary CT

angiography is performed in the same session without a need for higher doses of radiation or contrast [33].

While Guo et al. [35] showed in an MSCT study accurate assessment of LV volumes and functional parameters when compared to 2D TTE and nonsignificant differences with CMR findings, Delgado and coworkers [36] showed that mitral valve geometry and the anatomy of the subvalvular apparatus can be assessed with great precision using MSCT in patients with heart failure and ischemic MR.

It was also observed that contrast-enhanced viability imaging using MSCT provides accurate data for assessing the ventricular morphology and scar extension in post-infarction hearts [37].

## **1.5. Predictors of survival following SVR**

### **1.5.1. Single-center studies**

Over the years, several single-center studies were conducted to identify factors influencing survival following SVR.

In the largest single-center study to date, Menicanti et al. [38] identified moderate to severe MR, New York Heart Association (NYHA) functional class greater than II, and diastolic dysfunction as the most important predictors of survival.

White and colleagues [4] were the first to suggest that not the LVEF, commonly used to assess heart failure severity, but rather the LVESV should be used as a major predictor of survival after myocardial infarction, thus shifting the focus from functional to volumetric parameters. Di Donato et al. [39] reported preoperative NYHA class, LVEF, LVESVI, and remote asynergy area as important predictors of late mortality.

In another study by Di Donato group, LVESVI greater than 60 mL/m<sup>2</sup> after SVR was the strongest postoperative predictor of increased mortality [25]. Witkowski et al. [40] and Yamaguchi and coworkers [41] suggested that a preoperative LVESVI exceeding 100 mL/m<sup>2</sup> was associated with increased mortality at follow-up. Braun et al. [42] identified a left ventricular end-diastolic diameter (LVEDD) greater than 65 mm as an independent predictor of failed reverse remodeling following restrictive mitral annuloplasty in ischemic mitral regurgitation. Pocar and associates [43] considered the baseline MR degree and sphericity index as predictors of recurrent heart failure and

left ventricular re-remodeling. Bax et al. [44] suggested that, in the setting of an extensive ventricle remodeling with high end-systolic volumes, an adverse outcome is likely to occur even after a successful revascularization of viable myocardium.

A single-center study by Sartipy et al. [45] identified age, diabetes, and MR grade III–IV as significant predictors of late mortality, thus abandoning the importance of volumetric parameters. In a larger single-center study, Mickleborough and colleagues [46] found baseline ejection fraction (EF) <20%, congestive heart failure, preoperative ventricular tachycardia, and hypertension to be major predictors of the need for transplantation or repeated hospitalization for congestive heart failure.

Regarding the perioperative mortality, Chen et al. [47] suggested that the operative technique had no influence on the outcome; however, low cardiac output syndrome (LCOS) and extended operation time were associated with an early adverse outcome. Komeda and associates [48] observed that age over 60 years, LVEF under 20%, and NYHA class IV were independent predictors of 30-day mortality.

### **1.5.2. Multicenter studies**

The importance of LVESVI as a prognostic marker was further confirmed by the GUSTO I Trial [49], in which mortality rates of 33% at 1-year follow-up were observed in patients developing an LVESVI greater than 60 mL/m<sup>2</sup> early into reperfusion.

The RESTORE (Reconstructive Endoventricular Surgery returning Torsion Original Radius Elliptical Shape to the Left Ventricle) group created a multicenter registry of 1,918 patients undergoing SVR at some of the world's leading centers of expertise following a myocardial infarction and ventricular dilation. The main aim of the study was to analyze early and late survival following SVR. The RESTORE group found that patients undergoing SVR showed a significant increase in LVEF, decrease in systolic volumes, sustained improvement in NYHA class, and good mid-term survival with 70% at 5 years [50]. The study identified mitral valve repair as predictor of early mortality, while an EF lower than 30%, baseline LVESVI greater than 80 mL/m<sup>2</sup>, advanced NYHA class, and age greater than 75 years were significant risk factors of late mortality.

No survival benefit could be observed in another study by the RESTORE group in patients with a residual LVESVI >90 mL/m<sup>2</sup> or in whom an overall LVESVI reduction of 15% could not be achieved [31].

### **1.5.3. Randomized control trials**

To date, the STICH trial remains the only randomized control trial in the domain of SVR. The trial, including the problematic nature of its design and subsequent findings, is discussed in Chapter 1.6.

### **1.5.4. Meta analyses**

Analyzing a Society of Thoracic Surgeons (STS) database comprising data from 141 US hospitals for a combined endpoint of mortality and major morbidity, Hernandez et al. [51] concluded that age, female sex, elevated creatinine, insulin-dependent diabetes, myocardial infarction within 1 week prior to the operation, history of congestive heart failure, three-vessel coronary disease, severe mitral insufficiency, and emergency operation were predictive of an adverse outcome in SVR patients.

In the largest pooled meta-analysis to date (62 studies), Klein and coworkers [52] identified linear repair, concomitant mitral valve surgery, and the omission of surgical revascularization as the strongest predictors of an adverse outcome. No clinical or hemodynamic parameters, including LVEF or ventricle volumes, were predictive of the outcome after SVR.

## **1.6. STICH trial and its role in SVR research**

The Surgical Treatment for Ischemic Heart Failure (STICH) trial is an international multicenter prospective randomized trial on advanced ischemic cardiomyopathy, conducted with the aim to test 2 primary hypotheses: (1) coronary artery bypass grafting (CABG) with medical therapy improves long-term survival compared with medical therapy alone, and (2) in patients with anterior LV dysfunction, SVR plus CABG improves survival compared with CABG alone. Between 2002 and 2006, 2,136 patients were enrolled in the study in 127 centers worldwide; first findings were presented in 2009. As prospective randomized surgical trials are difficult to conduct, the medical community hoped for a clear statement on the effectiveness of revascularization as a possible single treatment in ischemic cardiomyopathy and the added benefit of SVR in patients with anterior wall motion abnormalities. The results suggested that adding SVR to CABG significantly reduced left ventricular volume but was not associated with a greater improvement of functional status or adverse event-free survival [53].

However, the findings of the trial were subject to extensive criticism from the worldwide surgical community. The average recruitment rate was 2 patients per site per year, with half of the patients being recruited in 13 centers. The mean baseline LVESVI was 83.8 mL/m<sup>2</sup>, which was criticized as rather low and thus differed from other SVR studies [54]. The initial definition of a successful SVR in study protocol was "an average LVESVI decrease of 30% as assessed on the 4-month post-operative CMR measurement" [55]. However, only a mean LVESVI reduction of 19% and a mean postoperative LVESVI of 67 mL/m<sup>2</sup> could be achieved in the CABG+SVR treatment arm and a 6% LVESVI reduction (from 82 to 77 mL/m<sup>2</sup>) in the CABG treatment arm at 4 months of follow-up [56]. It remains unclear whether this was due to the lack of experience in this kind of operations or because the initial volumes were not large enough to enable a greater volume reduction. In most surgical studies in recent years, the average volume reduction was around 40% or greater ([38], [25], [31]). In the STICH trial, the volumes were assessed 4 months after surgery; most surgical studies, however, use data from the immediate postoperative period. It is therefore not clear whether large postoperative ventricular volumes in the STICH result from the late postoperative remodeling or are caused by the initial ineffectiveness of the procedure. Echocardiography was used as the main imaging tool in 33% of patients, though it is known to systematically underestimate volumes of dysfunctional ventricles [31]. Moreover, only 33% of patients had pre- and postoperative volumetric studies [56], making a comparison with other SVR studies difficult. Only 49% of the STICH patients were in NYHA classes III or IV [53], suggesting that the population was significantly healthier compared to that of other studies.

## **2. Study design**

### **2.1. Study aims**

Based on the data collected at the German Heart Center Berlin (DHZB), predictors of early- and long-term survival after surgical ventricular restoration of antero-apical left ventricular aneurysms were analyzed.

The specific study aims were to

1. Analyze early and late survival and functional outcomes of patients undergoing SVR based on clinical, echocardiographic, and MSCT data.
2. Compare the survival in patients undergoing SVR with the survival predicted by the Seattle Heart Failure Model in patients treated with conservative therapy.
3. Analyze the change in volumetric, geometric, and functional parameters following SVR.
4. Define volumetric, geometric, and functional parameters and cut-offs in MSCT and TTE associated with adverse event-free survival.
5. Identify predictors of adverse events (all-cause mortality, left ventricular assist device implantation, and heart transplantation) at the early and late follow-up in patients undergoing SVR.
6. Determine the importance of multimodality imaging (TTE and MSCT) in SVR planning and follow-up.
7. Analyze the impact of concomitant coronary artery bypass grafting (CABG) and mitral valve surgery (MVS) in patients undergoing SVR.

### **2.2. Study population**

The data of 204 consecutive patients who underwent SVR at the German Heart Center Berlin (DHZB) from November 2005 until December 2015 were analyzed. All patients had an LV aneurysm and symptoms of heart failure, resulting from an ischemic event. Cases of acute ischemia were excluded. Twelve patients who underwent SVR due to ventricular aneurysms of the posterior wall were excluded from the analysis. 192 patients were included in the final analysis. Follow-up data was provided by the Department of Clinical Studies of the DHZB.



### 2.3. Clinical characteristics

The median age of the population was 64.2 years (range: 27–87). 141 patients were male (73.4%) and 51 were female (26.6%). 182 patients (94.8%) were in preoperative NYHA class III–IV. 106 patients (55.2%) had three-vessel disease. The median preoperative LVEF as assessed on TTE was 30% (range: 11–70). The median follow-up time was 6.1 years (range: 1 day–13.5 years). The preoperative characteristics are presented in Table 1.

**Table 1.** Baseline patient characteristics

Characteristics	Number
Median age (range), years	64.2 (27.0–87.0)
Gender, n (%)	Male:141 (73.4) Female: 51 (26.6)
Diabetes mellitus, n (%)	59 (30.7)
Hypertension, n (%)	130 (67.7)
Hypercholesterolemia, n (%)	133 (69.3)
Peripheral vascular disease, n (%)	19 (9.9)
History of renal failure, n (%)	30 (15.6)
History of atrial fibrillation, n (%)	22 (11.5)
Previous cardiac surgery, n (%)	9 (4.7)
Coronary lesions:	
No documented lesion	9 (4.7)
Single-vessel, n (%)	37 (19.3)
Two-vessel, n (%)	40 (20.8)
Three-vessel, n (%)	06 (55.2)
NYHA class II, n (%)	10 (5.2)
NYHA class III, n (%)	169 (88.0)
NYHA class IV, n (%)	13 (6.8)
Median LVEF (TTE), % (range)	30 (11–70)
LVEF>40% (TTE), n (%)	15 (7.8)
LVEF 20–40% (TTE), n (%)	152 (79.2)
LVEF<20% (TTE), n (%)	25 (13.0)
NYHA – New York Heart Association, LVEF – left ventricular ejection fraction	

## **2.4. Operative technique**

Surgery was performed through median sternotomy. Extracorporeal circulation was established with a single two-stage cavo-atrial cannula in the right atrium or selective cannulation of the superior and inferior vena cava in the case of concomitant mitral valve surgery and ascending aorta cannulation; standard myocardial protection was performed with warm-blood cardioplegia. CABG was performed where possible, aiming at complete revascularization. CABG was not performed in cases in which the LAD was completely occluded or in which the vessel was previously recanalized by drug-eluting stents. The ventricle was then opened by a linear incision lateral to the LAD, and visual inspection of the ventricle was performed to remove possible thrombus. The scarred border zone of the aneurysm was then palpated. The most common SVR techniques at the DHZB are the modified Dor technique (without patch) and the classical Dor procedure utilizing a patch. The non-patch technique was performed in 91.1% of cases, while a patch was used in 8.9%. A patch plasty was performed, if required, to preserve a normal residual left ventricular volume. During the non-patch procedure, two to three purse-string sutures reinforced with mattress sutures were placed through the border zone in the scarred tissue, creating a small tissue neck. The ventriculotomy was then closed with a Blalock suture. In the Dor procedure, the aneurysmatic border zone was sutured over a Dacron circular patch after placing the Fontan [57] suture and covered by the remaining aneurysm wall. No ventricular sizing device was used; the reduction volume was determined by preoperative CT and intraoperative findings. Concomitant mitral valve repair using the no-ring modified Paneth–Hetzer posterior annulus shortening technique with an autologous pericardial strip sewn continuously [58] was performed in patients with severe to moderate mitral regurgitation; in cases in which valve reconstruction was not possible, valve replacement with a biological valve was performed.

## **2.5. Data acquisition**

### **2.5.1. Data acquisition and analysis**

To assess the localization and the extent of the aneurysm, patients were preoperatively evaluated by MSCT and TTE. Routine measurements of functional parameters, heart chamber volumes, and valve assessment were performed. The surgeons used the diagnostic data to choose the best operative strategy. The same imaging modalities

were used during the early postoperative period to assess the effectiveness of the procedure before discharge. The preoperative functional status regarding dyspnea and heart failure was graded according to the NYHA classification pre- and postoperatively as well as at each contact with the clinic.

Pre- and postoperative imaging and clinical data were analyzed retrospectively to identify predictors of early and late adverse event-free survival.

The follow-up data were provided by the Department of Clinical Studies, German Heart Center Berlin (DHZB). The NYHA classification was determined from medical records of the latest follow-up.

The survival status was verified through the National Death Index.

The study was performed according to the principles of the Declaration of Helsinki and approved by the Ethics Committee of Charité – Universitätsmedizin Berlin (EA2/177/20).

### **2.5.2. MSCT measurements**

155 patients received a preoperative MSCT scan and 122 patients had pre- and postoperative MSCT studies. All MSCT studies were assessed by a single expert investigator. The dataset was reconstructed with a slice thickness of 0.75 mm and reconstruction increment of 0.4 mm, starting with early systole at the beginning of the cardiac cycle and ending with late diastole in 10% steps of the cardiac cycle. Standard industrial software (syngo Circulation, Siemens AG) was used to assess the functional and volumetric parameters. End diastole, end systole, and endocardial borders were identified by the software and checked manually by the investigator.

The following variables were measured to assess the functional and morphological parameters of the left ventricle:

- End-diastolic and end-systolic volume, indexed by body surface area (BSA) (mL/m<sup>2</sup>),.
- Left atrial appendage volume indexed by BSA (mL/m<sup>2</sup>),.
- Long axis length in 4-chamber view, measured as the distance between the apex and the mitral annulus plane (mm).
- Short axis in 4-chamber view, measured as the septal-lateral dimensions at the midlevel of the long axis (mm).

- Sphericity index, calculated as short-axis/long-axis ratio in diastole and systole.
- Left ventricular end-diastolic and end-systolic diameter (mm).
- Scar localization in a 17-segments model and scar property (akinesia, dyskinesia).
- Cardiac index (L/min/m<sup>2</sup>).
- Left ventricular ejection fraction, calculated as the difference of left ventricular end-systolic volume (LVESV) and LVEDV divided by LVEDV.

### **2.5.3. TTE measurements**

All patients underwent a preoperative and postoperative 2-D echocardiography study.

The following variables, which are commonly applied in the assessment of the ventricular function, were used:

- Left ventricular end-diastolic diameter (mm).
- Left ventricular ejection fraction, using the biplane Simpson technique in 2D echocardiography.
- Mitral regurgitation grade, using 2D echocardiography. Regurgitation was graded as trace (grade 0.5), mild (grade I in European nomenclature, which is used in this study), moderate (grade II), or severe (grade III) from color-flow Doppler acquisitions.

### **2.6. Statistical analysis**

A composite endpoint consisting of all-cause mortality, left ventricular assist device implantation, and heart transplantation was used as a major subject of this study, because end-stage heart failure can be regarded as a pre-terminal state resulting in death if therapeutic measures are not taken. When referring to this composite endpoint, the term “adverse event–free survival” is used. 30-day mortality was included in all-cause mortality. Time was defined as time to an adverse event (all-cause death, assist device implantation, or heart transplantation) and time to last follow-up for surviving patients. Patients lost to the follow-up were censored at the time of the last contact. Patient groups were compared using the t-test or Mann-Whitney-U test for continuous variables and the chi-square test for categorical variables. Continuous data were expressed as mean  $\pm$  standard deviation or median with ranges. Categorical variables were described as frequencies and percentages. All statistical tests were 2-

sided; significance was defined as  $p$ -level at 0.05.

Actual survival curves were calculated using the Kaplan-Meier method, and a pairwise log-rank test was used to compare survival between the different groups. A Cox proportional hazards model was used to select predictors of adverse event-free survival by estimating hazard ratios (HRs) and 95% confidence intervals (CIs). The proportional hazard assumption was evaluated using the statistical package `cox.zph` in the R statistical environment, designed to test the correlation between the Schoenfeld residuals and survival time. The significance of clinical (age, sex, NYHA functional class, BSA, additional comorbidities), CT-morphological (SI, LVESVI, LVEF, aneurysm localization, MR) and echocardiographic (EF, LVEDD, MR) baseline parameters and additional surgical procedures (CABG, valve surgery) as prognostic markers for endpoints (all-cause mortality, time to assist, time to heart transplantation) was tested univariately using a Cox proportional hazards model. All variables were tested for correlation. The variables with a probability value ( $p$ ) of less than 0.05 at univariate analysis were examined in the multivariate stepwise backward logistic regression analysis with manual addition or removal of the variables. The variables were added one by one, and their significance in the model was checked with every addition.  $R^2$  was used to assess the improvement in likelihood between the fitted model and a model without the added predictor variable. Different predictor models were compared using the Akaike's Information Criterion (AIC). Once the most adequate statistical model could be established, it was checked by manually adding all previously excluded variables one by one. The model in which all variables were statistically significant and clinically feasible served as a final model.

Cut-off points predicting major adverse events were calculated using the receiver operating characteristic (ROC) method by selecting values with a most favorable sensitivity and specificity.

Cluster analysis of scar segmentation was performed using the nearest neighbor algorithm.

The data were analyzed with the SPSS 23 (SPSS Chicago, IL, USA) and R version 3.3.1 software (The R Foundation for Statistical Computing, Vienna, Austria).

The Seattle Heart Failure Model app for Mac OS X (University of Washington, USA) was used to calculate the survival probability of patients on conservative therapy. For lack of two laboratory parameters (total cholesterol and uric acid) in all patients, the same high normal values (240 mg/dL for total cholesterol and 6 mg/dL for uric acid)

were applied in all calculations. Thus, systematic bias of the results at the same level in all calculated scores was created.

8 patients were lost to follow up (4.1%) due to migration (n=6, foreign patients) or unknown reasons (n=2).

### 3. Results

#### 3.1. Procedural data

##### 3.1.1. Procedural characteristics and outcome

A non-patch repair was performed in 91.1% of cases (n=175) and myocardial revascularization in 77.6% of cases (n=149). 18.8% of patients (n=36) required a concomitant mitral valve surgery. The operative data are summarized in Table 2.

**Table 2.** Operative data.

Operative data	Number (% or range)
Concomitant CABG, n (%)	149 (77.6)
No. of grafts performed, median (range)	2 (0–5)
Concomitant mitral valve surgery, n (%)	36 (18.8)
Patch repair, n (%)	17 (8.9)
Non-patch repair (Fontan stitch), n (%)	175 (91.1)
Cardiopulmonary bypass (CBP) time, median (range), minutes	131 (0–693)
Cross-clamp time, median (range), minutes	78 (0–203)
Emergency surgery, n (%)	9 (4.4)

There was no difference in survival between patients who underwent SVR with patch implantation (n=17, 70.6% 5-year survival) and patients who underwent linear repair (n=175, 69.4% 5-year survival,  $p=0.269$ ). Pre- and postoperative characteristics were similar in both groups, though a greater percentage of LVESVI reduction could be achieved in the group of patients receiving repair with a patch than in the linear repair group (-54.7% vs. -40.4%,  $p=0.029$ ).

### 3.1.2. Procedural complications

No patient suffered a postoperative myocardial infarction, and there was one postoperative stroke event. The perioperative complications are summarized in Table 3.

**Table 3.** Postoperative complications following SVR.

Complications	Number (%)
Myocardial infarction, n (%)	0 (0.0)
Stroke, n (%)	1 (0.5)
Sepsis, n (%)	7 (3.6)
Renal failure, n (%)	5 (2.6)
In-hospital mortality, n (%)	13 (6.7)

### 3.2. In-hospital mortality

In-hospital mortality was identical with 30-day mortality (all adverse outcomes during this period occurred before discharge from the hospital) and affected 13 patients (6.7%). Of these 13 patients, 1 was operated in the emergency setting and 9 (69.2%) received a primary intra-aortic balloon pump (IABP). 4 of the 13 patients (30.7%) dying in the first 30 days required mechanical circulatory support (MCS) after the operation. The following devices were implanted: extracorporeal membrane oxygenation (ECMO) in one case, Levitronix® right ventricle assist device in one case, Impella® heart pump in one case, and BIVAD Excor® Berlin Heart in one case. In one case, a Berlin Heart Incor® left ventricle assist device was implanted 1 day after the operation. The patient survived the 30-day period and died after 214 days on Berlin Heart Incor®.

Death causes were low cardiac output in 6 patients, septic shock and multi-organ failure in 4 patients, stroke in one patient, ventricular tachycardia in one patient, and electromechanical dissociation in one patient. All of them had combined surgery (5: SVR and CABG; 4: SVR, CABG and MV surgery; 2: SVR, CABG and aortic valve replacement; 1: SVR, CABG, MV surgery and tricuspid valve reconstruction; 1: SVR, CABG, aortic valve replacement and tricuspid valve reconstruction).



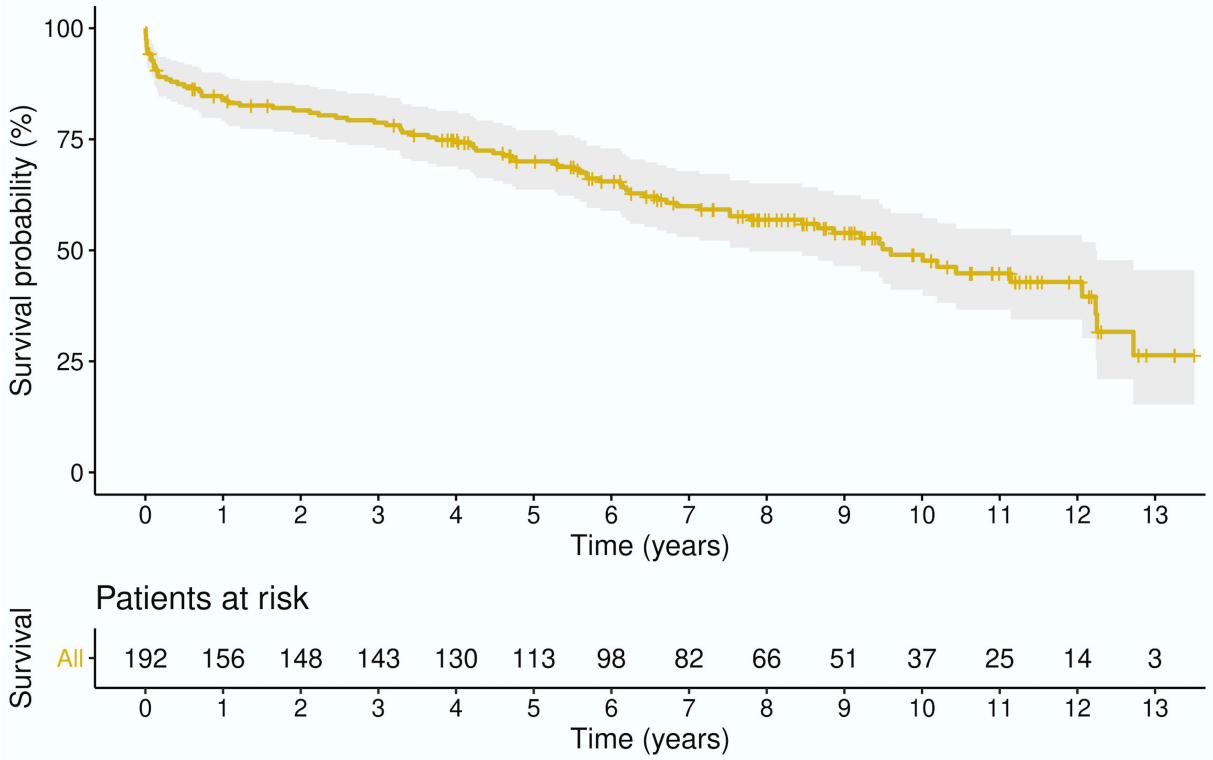
**3.3. Short-, mid-, and long-term outcomes following SVR**

1-, 5-, and 10-year survival free of adverse events was 83.5%, 69.6%, and 49% respectively (Figure 1).

89 endpoints were observed during the observation time (46.4% of the population), with 76 deaths (39.8%), 11 LVAD implantations (5.7%), and 2 heart transplantations (1%).

The mean time was 3.8 years to LVAD, 2.6 years to heart transplantation, and 4.1 years to all-cause mortality.

**Figure 1.** Survival for composite endpoint of all-cause mortality, left ventricular assist device implantation, and heart transplantation.



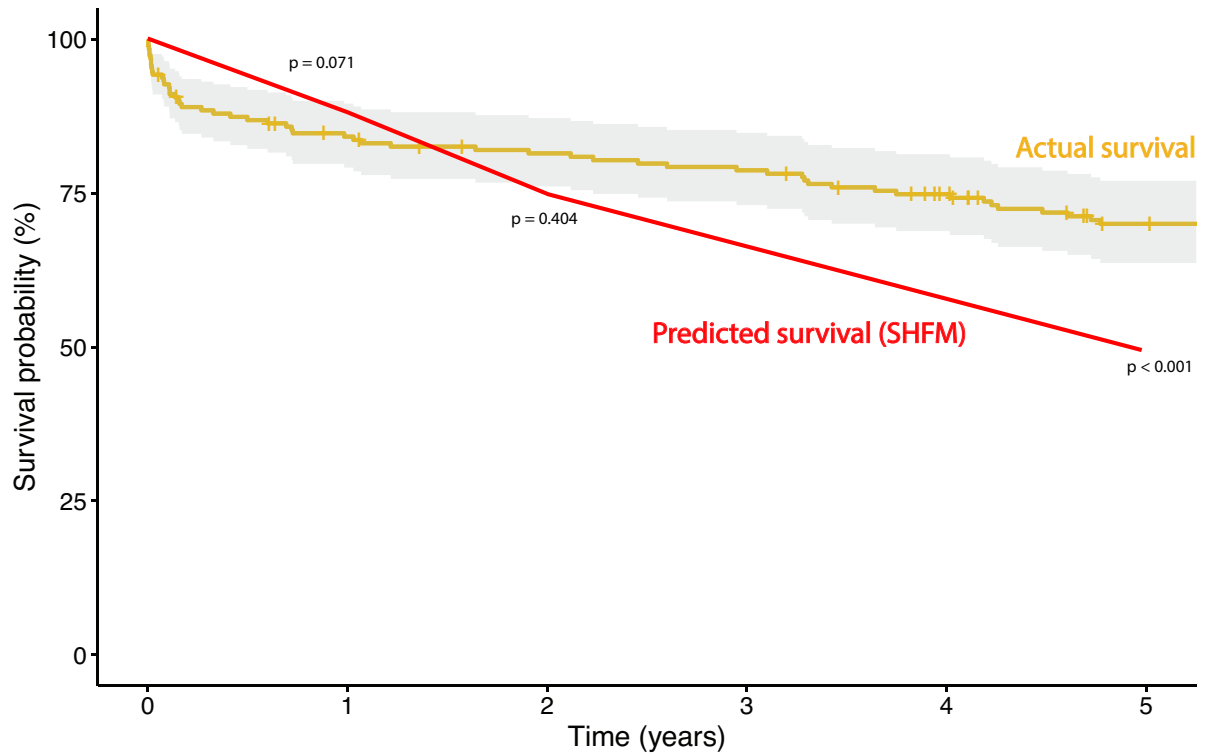
### 3.4. Comparison of survival in patients undergoing SVR with survival predicted by the Seattle Heart Failure Model

Due to the retrospective nature of this study, no comparison with a control group was possible. However, using the Seattle Heart Failure Model (SHFM) as a virtual control, it was possible to calculate the predicted survival in patients treated with conservative therapy. SHFM was derived in a cohort of 1,125 patients and is commonly used in the therapy of heart failure patients to predict their survival rate based on clinical parameters, LVEF, laboratory parameters, and current medication measured during the baseline assessment [59]. Furthermore, it serves to predict the survival benefit through the optimization of pharmacotherapy or device implantation.

Predicted survival was calculated for each patient in our cohort. Baseline measurements and characteristics recorded on the presentation of the patient in our center before the operation were used. All patients in our cohort were lacking total cholesterol and uric acid measurements in laboratory tests. To be able to calculate the SHFM survival rates, high normal values (240 mg/dL for total cholesterol and 6 mg/dL for uric acid) were imputed in each patient. By doing so, systematic bias was instated for all patients, making all predicted survival rates comparably biased.

When comparing the actual survival of patients undergoing SVR to survival predicted by the SHFM, we found no difference at 1 year (82.4% vs. 87.3%,  $p=0.071$ ) and 2 years (79.1% vs. 76.7%,  $p=0.404$ ). However, at 5 years the actual survival in patients undergoing SVR was significantly better than the survival predicted by the SHFM in patients treated with conservative therapy (65.7% vs. 51%,  $p<0.001$ ) (Figure 2).

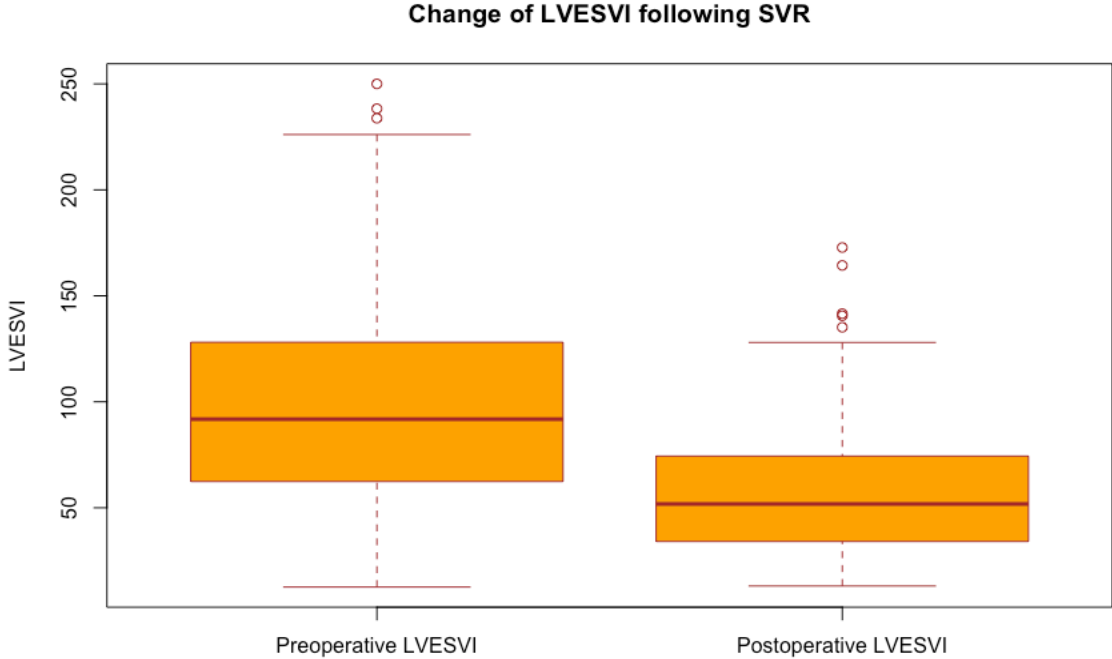
**Figure 2.** Comparison of survival rates in patients undergoing SVR (yellow line) and survival rates predicted by the Seattle Heart Failure Model in patients treated with conservative therapy (red line).



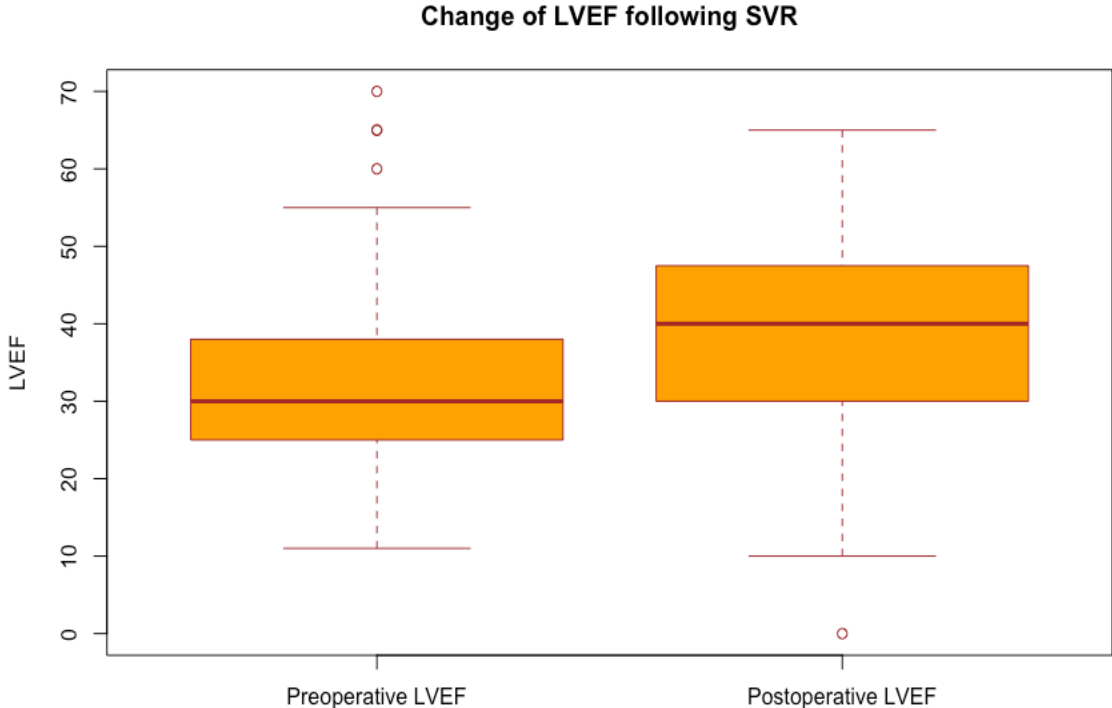
### 3.5. Change in LV volumetric and functional parameters following SVR

Postoperative MSCT scans conducted before discharge demonstrated a significant change in all functional and volumetric parameters in all patients, disregarding a later outcome. The mean left ventricular end-diastolic volume index (LVEDVI) decreased from  $149.3 \pm 52.6$  mL/m<sup>2</sup> to  $96.7 \pm 35.2$  mL/m<sup>2</sup> ( $p < 0.001$ ) and LVESVI from  $102.9 \pm 50.6$  mL/m<sup>2</sup> to  $58.6 \pm 33.4$  mL/m<sup>2</sup> ( $p < 0.001$ ) (Figure 3). The diastolic sphericity index increased from  $0.39 \pm 0.10$  to  $0.51 \pm 0.17$  ( $p < 0.001$ ) and the systolic sphericity index from  $0.30 \pm 0.10$  to  $0.35 \pm 0.16$  ( $p < 0.001$ ). The indexed stroke volume initially decreased from  $45.8 \pm 11.0$  mL/m<sup>2</sup> to  $37.4 \pm 9.8$  mL/m<sup>2</sup> ( $p < 0.001$ ). The mean left ventricular ejection fraction increased from  $31.8 \pm 10.5\%$  to  $39.3 \pm 10.8\%$  ( $p < 0.001$ ) (Figure 4) on TTE and from  $34.0 \pm 12.3\%$  to  $43.3 \pm 13.9\%$  ( $p < 0.001$ ) on MSCT scans. The cardiac index increased from  $3.07 \pm 0.75$  to  $3.28 \pm 0.71$  ( $p = 0.005$ ).

**Figure 3.** Mean LVESVI change following SVR (MSCT measurements at discharge).



**Figure 4.** Mean LVEF change following SVR (MSCT measurements at discharge).



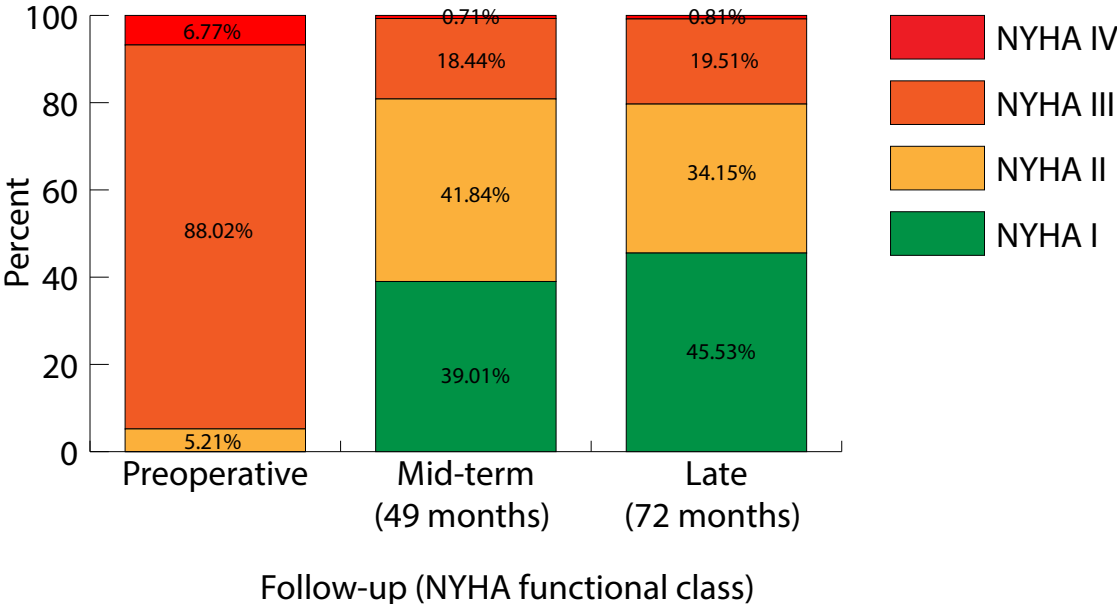
The mean postoperative LVESVI was 58.8 mL/m<sup>2</sup> (range: 13.1–172.8), suggesting that a target volume considered beneficial in current studies (e.g., LVESVI<60 mL/m<sup>2</sup>) [25] was reached in most cases. A postoperative LVESVI reduction to less than 55 mL/m<sup>2</sup>

(target volume with beneficial outcome identified in our population, Chapter 3.12.3) was achieved in 68 patients (54% of patients with postoperative MSCT studies).

### 3.6. Clinical functional outcome at mid- and long-term follow-up

The preoperative median NYHA functional class was III, with 88% of patients being in NYHA class III and 6.8% in class IV. At mid-term follow-up (mean time to follow-up: 49 months) after the operation, 80.9% were in NYHA class I or II and the median NYHA class was II, indicating a significant improvement ( $p<0.001$ ). At the late follow-up (mean time to follow-up: 72 months), 79.6% of patients were in NYHA class I or II and the median NYHA class was II, suggesting that the significant postoperative improvement was preserved ( $p<0.001$ ). The NYHA functional class change is presented in Figure 5.

**Figure 5.** NYHA functional class before operation, at mid-, and at long-term follow-up in patients undergoing SVR.



### 3.7. Volumetric and functional differences between patient subgroups stratified by outcome

Significant differences could be observed between the group of patients with a good outcome (e.g., who were alive and not needing a mechanical assist device or heart transplantation at the time of the follow-up) and patients suffering from an adverse event (Table 4).

Patients with an adverse outcome were significantly older (65.6 vs. 61.4 years,  $p=0.011$ ) and in a higher preoperative NYHA functional class (3.07 vs. 2.96,  $p=0.019$ ) than patients alive at the time of the follow-up. Their LVESVI was greater before (110.8 vs. 90.8 mL/m<sup>2</sup>,  $p=0.011$ ) and after the operation (74 vs. 49.2 mL/m<sup>2</sup>,  $p<0.001$ ). The percentage reduction of the LVESVI achieved during the operation was lower (36.1 vs. 45%,  $p=0.015$ ). The postoperative LVEF differed significantly between the two groups (36.2 vs. 42%,  $p<0.001$ ), while there was no difference regarding the preoperative LVEF (30.4 vs. 33.2%,  $p=0.074$ ). The LVEDD was larger before (62.3 vs. 57.9 mm,  $p=0.002$ ) and after (56.8 vs. 53.7 mm,  $p=0.017$ ) the operation in the group with poorer outcome. The left atrial volume index (LAVI) was significantly increased before (64.4 vs. 57.9 ml/m<sup>2</sup>,  $p=0.033$ ) and after (55.2 vs. 47.4 ml/m<sup>2</sup>,  $p=0.023$ ) the operation. The systolic SI was higher pre- (0.32 vs. 0.28,  $p=0.010$ ) and postoperatively (0.40 vs. 0.32,  $p=0.010$ ). MR was significantly greater before (1.25 vs. 0.85,  $p=0.001$ ) and after (0.44 vs. 0.26,  $p=0.006$ ) the operation. Perfusion time (151.8 vs. 128.6 min,  $p=0.039$ ), preoperative stroke volume index (SVI; 42 vs. 47.8 mL/m<sup>2</sup>,  $p=0.002$ ), and cardiac index (2.9 vs. 3.2 l/m<sup>2</sup> BSA,  $p=0.016$ ) differed significantly between the patients who suffered an adverse event and those with adverse event-free survival. The volumetric, geometric, and functional parameters of both groups are summarized in Table 4.

**Table 4.** Volumetric, geometric, and functional parameters before and after SVR in event-free surviving patients and patients with adverse events. MSCT measurements, unless otherwise indicated. Mean and standard deviation reported.

<b>Characteristics</b>	<b>Adverse event</b>	<b>No adverse event</b>	<b>p-value</b>
LVEDVI postoperative, mL/m <sup>2</sup>	117.3 ± 49.1	89.9 ± 26.3	<b>&lt;0.001</b>
LVESVI preoperative, mL/m <sup>2</sup>	113.7 ± 56.7	93.2 ± 44.2	<b>0.014</b>
LVESVI postoperative, mL/m <sup>2</sup>	80.0 ± 46.1	51.9 ± 24.4	<b>&lt;0.001</b>
LVESVI intraoperative reduction, %	-32.2 ± -18.8	-43.6 ± -21.8	<b>0.01</b>
LAVI syst. preoperative, mL/m <sup>2</sup>	69.0 ± 22.4	56.9 ± 16.2	<b>&lt;0.001</b>
LAVI syst. postoperative, mL/m <sup>2</sup>	62.0 ± 22.6	46.7 ± 15.6	<b>&lt;0.001</b>
LVSI syst. preoperative	0.33 ± 0.11	0.29 ± 0.9	<b>0.021</b>
LVSI syst. postoperative	0.42 ± 0.21	0.33 ± 0.14	<b>0.01</b>
SVI preoperative, mL/m <sup>2</sup>	41.0 ± 12.2	47.1 ± 10.7	<b>0.002</b>
LVEDD preoperative (TTE), mm	62.6 ± 11.6	58.6 ± 8.6	<b>0.006</b>
LVEDD postoperative (TTE), mm	57.0 ± 10.3	53.9 ± 7.8	<b>0.016</b>
LVEF preoperative (TTE), %	29.6 ± 12.1	36.3 ± 11.4	<b>0.001</b>
LVEF postoperative (TTE), %	36.3 ± 14.4	45.3 ± 13.1	<b>0.002</b>
LVEDVI - left ventricular end-diastolic volume index, LVESVI – left ventricular end-systolic volume index, LAVI – left atrial volume index, LVSI – left ventricular sphericity index, SVI – stroke volume index, LVEDD – left ventricular end-diastolic diameter, LVEF – left ventricular ejection fraction			

### 3.8. Volumetric and functional differences between patient subgroups stratified by mitral regurgitation grade

During the preoperative echocardiographic assessment, 31.3% of patients had no or trace MR. 50.6% of patients had mild MR, while 35 patients (18.2%) had moderate to severe MR. The subgroup of patients with moderate to severe MR is compared with patients with a lower MR grade in Table 5.

**Table 5.** Pre- and postoperative volumetric, geometric, and functional parameters of patients with baseline MR grade  $\geq 2$  compared to patients with no or mild MR. MSCT measurements, unless otherwise indicated. Mean and standard deviation reported.

Characteristics	MR grade $\geq 2$	No MR or MR grade $< 2$	p-value
LVEDVI postoperative, mL/m <sup>2</sup>	116.2 $\pm$ 49.3	93.2 $\pm$ 31.4	<b>0.01</b>
LVESVI postoperative, mL/m <sup>2</sup>	80.5 $\pm$ 46.6	55.0 $\pm$ 28.8	<b>0.002</b>
LVESVI intraoperative reduction, %	-30.9 $\pm$ -21.3	-43.4 $\pm$ -19.3	<b>0.011</b>
LAVI syst. preoperative, mL/m <sup>2</sup>	76.4 $\pm$ 23.7	57.4 $\pm$ 16.4	<b>&lt;0.001</b>
LAVI syst. postoperative, mL/m <sup>2</sup>	62.1 $\pm$ 25.7	48.4 $\pm$ 16.5	<b>0.003</b>
LVSI syst. preoperative	0.34 $\pm$ 0.10	0.29 $\pm$ 0.09	<b>0.015</b>
LVSI diast. preoperative	0.44 $\pm$ 0.12	0.39 $\pm$ 0.09	<b>0.027</b>
CI postoperative	2.9 $\pm$ 0.6	3.2 $\pm$ 0.7	<b>0.048</b>
LVEDD preoperative (TTE), mm	65.2 $\pm$ 11.9	58.9 $\pm$ 9.0	<b>&lt;0.001</b>
LVEDD postoperative (TTE), mm	58.2 $\pm$ 9.5	54.2 $\pm$ 8.6	<b>0.014</b>
LVEF preoperative (TTE), %	27.3 $\pm$ 10.3	33.3 $\pm$ 10.3	<b>0.002</b>
MR grade postoperative (TTE)	0.31 $\pm$ 0.50	0.35 $\pm$ 0.43	0.656
LVEDVI - left ventricular end-diastolic volume index, LVESVI – left ventricular end-systolic volume index, LAVI – left atrial volume index, LVSI – left ventricular sphericity index, CI – cardiac index, LVEDD – left ventricular end-diastolic diameter, LVEF – left ventricular ejection fraction, MR – mitral regurgitation			



### **3.9. Predictors of 30-day mortality**

Multivariate logistic regression was used to determine factors predictive of a 30-day mortality. Operative perfusion time (OR 1.033, CI 1.017–1.055,  $p < 0.001$ ) was the most significant predictor. A perfusion time longer than 160 minutes was associated with an adverse outcome (sensitivity 0.769, specificity 0.777, AUC=0.881).

Predicting 30-day mortality using MSCT-morphological data was difficult because only few patients suffering an adverse outcome in the early postoperative phase had MSCT scans. Of the 13 patients who did not survive the first 30 days after the operation, only one had pre- and postoperative MSCT imaging. 9 had only preoperative MSCT imaging, while 3 patients had neither pre- nor postoperative assessment with MSCT. No parameters measured by MSCT were predictive of 30-day mortality in multivariate analysis.

### **3.10. Univariate analysis of predictors of adverse events**

All clinical, operative, and postoperative variables as well as all functional and volumetric characteristics estimated before and after the operation were first analyzed univariately by means of the Cox proportional hazards regression to establish a possible association with an adverse outcome. The variables significant at the level of  $p = 0.05$  were then analyzed multivariately, applying the method described in Chapter 2.6. All variables are summarized in Tables 6, 7, 8 and 9.

**Table 6.** Univariate analysis of baseline clinical characteristics predictive of all-cause mortality, ventricular assist implantation, and heart transplantation for the overall patient population.

Characteristics	Hazard ratio (CI)	p-value
Age	1.031 (1.011;1.051)	<b>0.002</b>
Age over 64 years	1.486 (0.990;2.230)	0.056
Sex:		
- male	0.870 (0.562;1.347)	0.533
- female	1.139 (0.736;1.761)	0.559
BMI	1.030 (0.983;1.078)	0.217
BSA	1.721 (0.656;4.512)	0.270
Diabetes	2.021 (1.336;3.057)	<b>0.001</b>
Arterial hypertension	1.900 (1.180;3.061)	<b>0.008</b>
Hyperlipoproteinemia	1.043 (0.677;1.607)	0.850
Peripheral artery disease	2.365 (1.358;4.117)	<b>0.002</b>
Renal failure preoperative	2.582 (1.610;4.143)	<b>&lt;0.001</b>
Atrial fibrillation preoperative	2.338 (1.357;4.026)	<b>0.002</b>
NYHA class II preoperative	0.426 (0.105;1.736)	0.234
NYHA class III preoperative	1.097 (0.583;2.065)	0.773
NYHA class IV preoperative	1.316 (0.655;2.644)	0.440
NYHA class I postoperative	0.560 (0.237;1.324)	0.187
NYHA class II postoperative	1.224 (0.529;2.831)	0.637
NYHA class III postoperative	1.752 (0.687;4.470)	0.241
Coronary artery disease	0.990 (0.799;1.227)	0.929
PCI preoperative	1.182 (0.744;1.879)	0.479
ICD preoperative	1.445 (0.853;2.447)	0.171
Prior cardiac surgery	2.079 (0.905;4.777)	0.085
Prior aortic valve replacement	1.139 (0.278;4.671)	0.857
Prior CABG	3.245 (1.405;7.493)	<b>0.006</b>
Prior MVS	0.641 (0.088;4.649)	0.660
BMI – body mass index, BSA – body surface area, NYHA – New York Heart Association, PCI – percutaneous coronary intervention, ICD – implantable cardioverter defibrillator, CABG – coronary artery bypass grafting, MVS – mitral valve surgery		

**Table 7.** Univariate analysis of intraoperative procedures and postoperative complications predictive of all-cause mortality, ventricular assist implantation, and heart transplantation for the overall patient population.

<b>Characteristics</b>	<b>Hazard ratio (CI)</b>	<b>p-value</b>
Cross-clamp time	1.007 (1.001;1.013)	<b>0.028</b>
CBP time	1.007 (1.004;1.010)	<b>&lt;0.001</b>
Mitral valve repair	1.617 (0.995;2.627)	0.052
Mitral valve replacement	0.855 (0.119;6.141)	0.876
Aortic valve replacement	1.591 (0.826;3.067)	0.165
Tricuspid valve repair	5.255 (2.112;13.074)	<b>&lt;0.001</b>
Maze procedure	1.467 (0.538;4.001)	0.454
Aneurysmectomy only	1.014 (0.634;1.623)	0.953
Aneurysmectomy and concomitant CABG	0.960 (0.604;1.526)	0.863
SVR with linear repair	1.176 (0.636;2.176)	0.606
SVR with patch	0.863 (0.452;1.544)	0.567
Thrombectomy	1.015 (0.592;1.739)	0.958
Number of CABG bypasses	0.952 (0.825;1.099)	0.503
Primary IABP implantation	2.714 (1.734;4.247)	<b>&lt;0.001</b>
Primary LVAD implantation	10.884 (4.888;24.232)	<b>&lt;0.001</b>
Emergency surgery	2.726 (1.187;6.260)	<b>0.018</b>
Rethoracotomy	1.675 (0.864;3.247)	0.126
Reoperation	1.471 (0.680;3.185)	0.327
Atrial fibrillation postoperative	1.725 (1.145;2.598)	<b>0.009</b>
Stroke postoperative	5.053 (0.692;36.890)	0.075
Sepsis postoperative	4.680 (2.148;10.194)	<b>&lt;0.001</b>
Renal failure postoperative	1.610 (0.504;5.138)	0.421
CBP – cardiopulmonary bypass, SVR – surgical ventricular restoration, CABG – coronary artery bypass grafting, IABP – intra-aortic balloon pump, LVAD – left ventricular assist device		

**Table 8.** Univariate analysis of pre- and postoperative imaging characteristics predictive of all-cause mortality, ventricular assist implantation, and heart transplantation for the overall patient population. MSCT measurements.

<b>Characteristics</b>	<b>Hazard Ratio (CI)</b>	<b>p-value</b>
LVSI diast. preoperative	6.148 (0.654;57.73)	0.112
LVSI diast. postoperative	11.966 (2.398;59.711)	<b>0.012</b>
LVSI syst. preoperative	20.84 (2.569;169.032)	<b>0.004</b>
LVSI syst. postoperative	21.725 (4.236;111.414)	<b>&lt;0.001</b>
LVEDV preoperative, ml	1.002 (1.000;1.004)	<b>0.048</b>
LVEDV postoperative, ml	1.008 (1.005;1.012)	<b>&lt;0.001</b>
LVESV preoperative, ml	1.003 (1.001;1.005)	<b>0.008</b>
LVESV postoperative, ml	1.010 (1.006;1.014)	<b>&lt;0.001</b>
SV preoperative, ml	0.988 (0.978;0.998)	<b>0.022</b>
SV postoperative, ml	1.002 (0.988;1.016)	0.812
LVEF preoperative, %	0.965 (0.943;0.986)	<b>0.002</b>
LVEF postoperative, %	0.961 (0.941;0.982)	<b>&lt;0.001</b>
LVEDVI preoperative, mL/m <sup>2</sup>	1.003 (0.999;1.007)	0.182
LVEDVI postoperative, mL/m <sup>2</sup>	1.019 (1.011;1.027)	<b>&lt;0.001</b>
LVESVI preoperative, mL/m <sup>2</sup>	1.005 (1.001;1.009)	<b>0.026</b>
LVESVI postoperative, mL/m <sup>2</sup>	1.020 (1.011;1.028)	<b>&lt;0.001</b>
LVESVI postoperative exceeding 55 mL/m <sup>2</sup>	2.859 (1.569;5.208)	<b>0.001</b>
LVESVI intraoperative reduction, %	1.023 (1.009;1.037)	<b>0.001</b>
SVI preoperative	0.967 (0.946;0.988)	<b>0.002</b>
SVI postoperative	1.006 (0.976;1.037)	0.705
CO preoperative, l/min	0.885 (0.763;1.027)	0.107
CO postoperative, l/min	0.989 (0.815;1.200)	0.913
CI preoperative	0.660 (0.477;0.913)	<b>0.012</b>
CI postoperative	0.743 (0.472;1.168)	0.198
LAV syst. preoperative, ml	1.012 (1.005;1.018)	<b>&lt;0.001</b>
LAV syst. postoperative, ml	1.016 (1.008;1.0284)	<b>&lt;0.001</b>
LAVI syst. preoperative, mL/m <sup>2</sup>	1.019 (1.007;1.031)	<b>0.002</b>
LAVI syst. postoperative, mL/m <sup>2</sup>	1.026 (1.011;1.041)	<b>0.001</b>
LVSI – left ventricular sphericity index, LVEDV - left ventricular end-diastolic volume, LVESV – left ventricular end-systolic volume, SV – stroke volume, LVEF – left ventricular ejection fraction, LVEDVI - left ventricular end-diastolic volume index, LVESVI – left ventricular end-systolic volume index, SVI – stroke volume index, CO – cardiac output, CI – cardiac index, LAV – left atrial volume, LAVI – left atrial volume index		

**Table 9.** Univariate analysis of pre- and postoperative imaging characteristics predictive of all-cause mortality, ventricular assist implantation, and heart transplantation for the overall patient population. TTE measurements.

Characteristics	Hazard Ratio (CI)	p-value
LVEF preoperative (TTE), %	0.981 (0.961;1.002)	0.082
LVEF postoperative (TTE), %	0.932 (0.911;0.955)	<b>&lt;0.001</b>
LVEDD preoperative (TTE), mm	1.021 (1.009;1.053)	<b>0.005</b>
LVEDD>60.5 mm preoperative (TTE)	1.621 (1.082;2.428)	<b>0.019</b>
LVEDD postoperative (TTE), mm	1.038 (1.014;1.062)	<b>0.002</b>
MR preoperative (TTE)	1.597 (0.999;2.552)	<b>0.050</b>
No MR preoperative (TTE)	0.630 (0.397;1.001)	<b>0.050</b>
MR grade I preoperative (TTE)	1.032 (0.691;1.540)	0.879
MR grade II preoperative (TTE)	1.372 (0.801;2.351)	0.251
MR grade III preoperative (TTE)	2.565 (1.239;5.312)	<b>0.011</b>
No MR postoperative (TTE)	0.692 (0.454;1.057)	0.088
MR grade I postoperative (TTE)	1.388 (0.907;2.125)	0.131
LVEF – left ventricular ejection fraction, LVEDD – left ventricular end-diastolic diameter, MR – mitral regurgitation.		

### 3.11. Multivariate analysis of predictors of adverse events

#### 3.11.1. Preoperative predictors of adverse event-free survival

Four preoperative parameters could be identified as independent predictors of an adverse outcome following a surgical ventricular restoration. These were preoperative LVEDD as measured with TTE (HR: 1.044 [1.020–1.069],  $p<0.001$ ), preoperative MR grade (HR: 1.427 [1.086–1.874],  $p=0.014$ ), diabetes (HR: 2.170 [1.365–3.452],  $p=0.001$ ), and glomerular filtration rate (GFR; HR: 0.976 [0.965–0.987],  $p<0.001$ ).

### 3.11.2. Survival difference in patients stratified by preoperative glomerular filtration rate

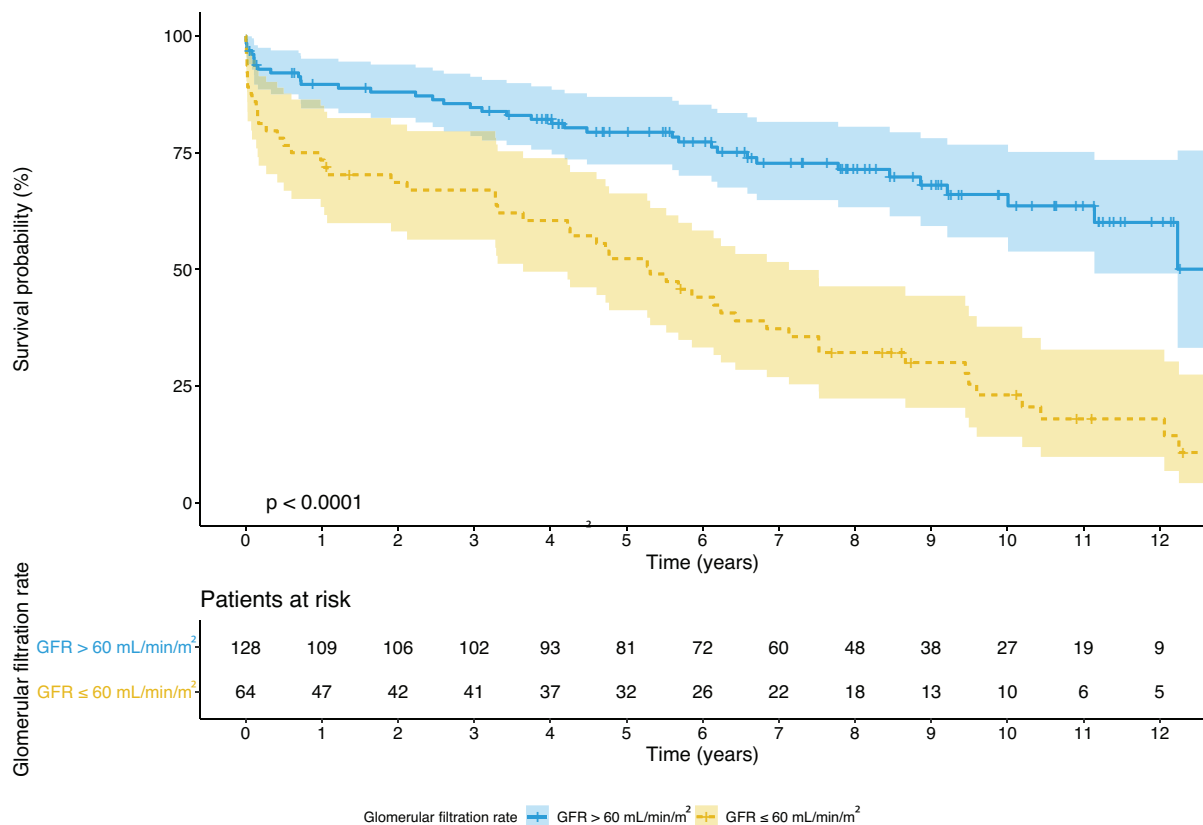
The CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation was used to calculate GFR in individual patients:

$$\text{GFR} = 141 * \min(\text{Scr}/\kappa, 1)^\alpha * \max(\text{Scr}/\kappa, 1)^{-1.209} * 0.993^{\text{Age}} * 1.018 \text{ [if female]}$$

GFR < 60 mL/min per 1.73 m<sup>2</sup> was used for stratification, a cut-off commonly used in nephrology for renal failure [60].

The findings are presented in Figure 6.

**Figure 6.** Kaplan-Maier curve for composite endpoint of all-cause mortality, left ventricular assist device implantation, and heart transplantation, stratified by glomerular filtration rate.

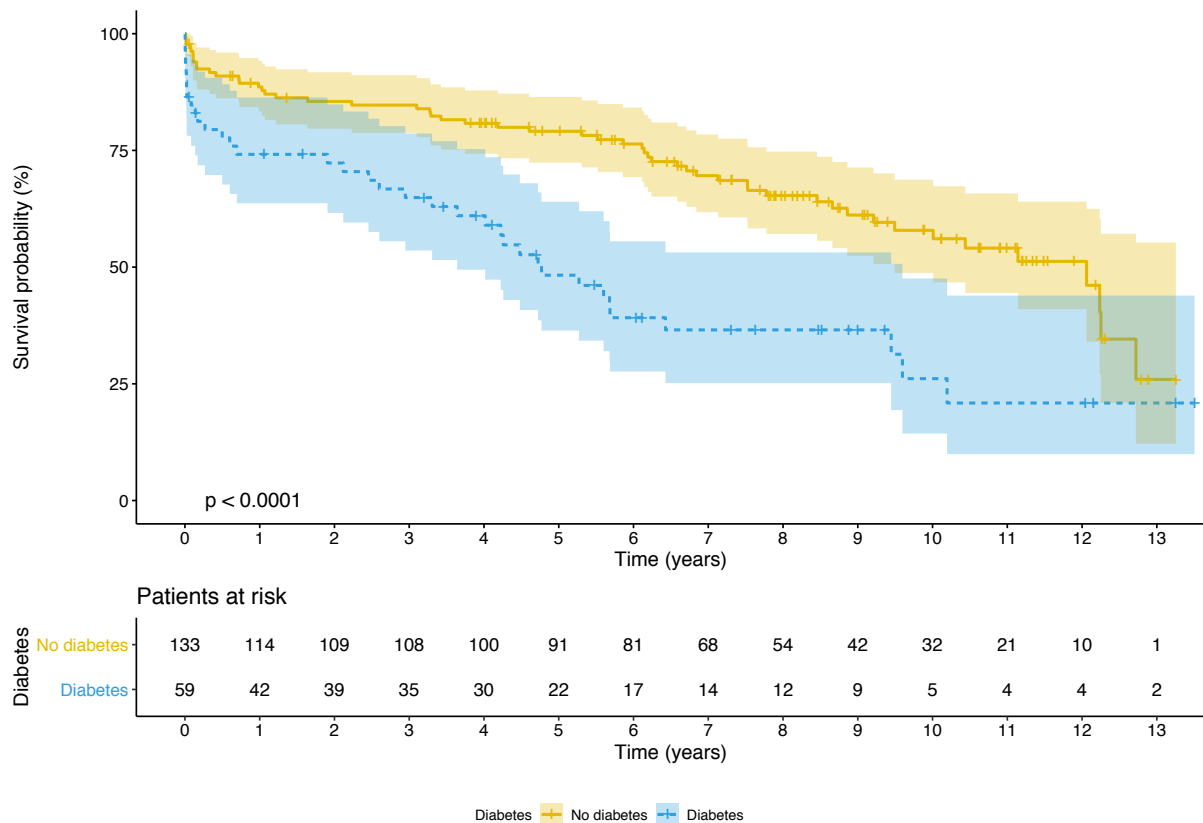


### 3.11.3. Survival difference in patients stratified by diabetes

The diagnosis diabetes was retrieved from referral reports; both types (I and II) were included.

The findings are presented in Figure 7.

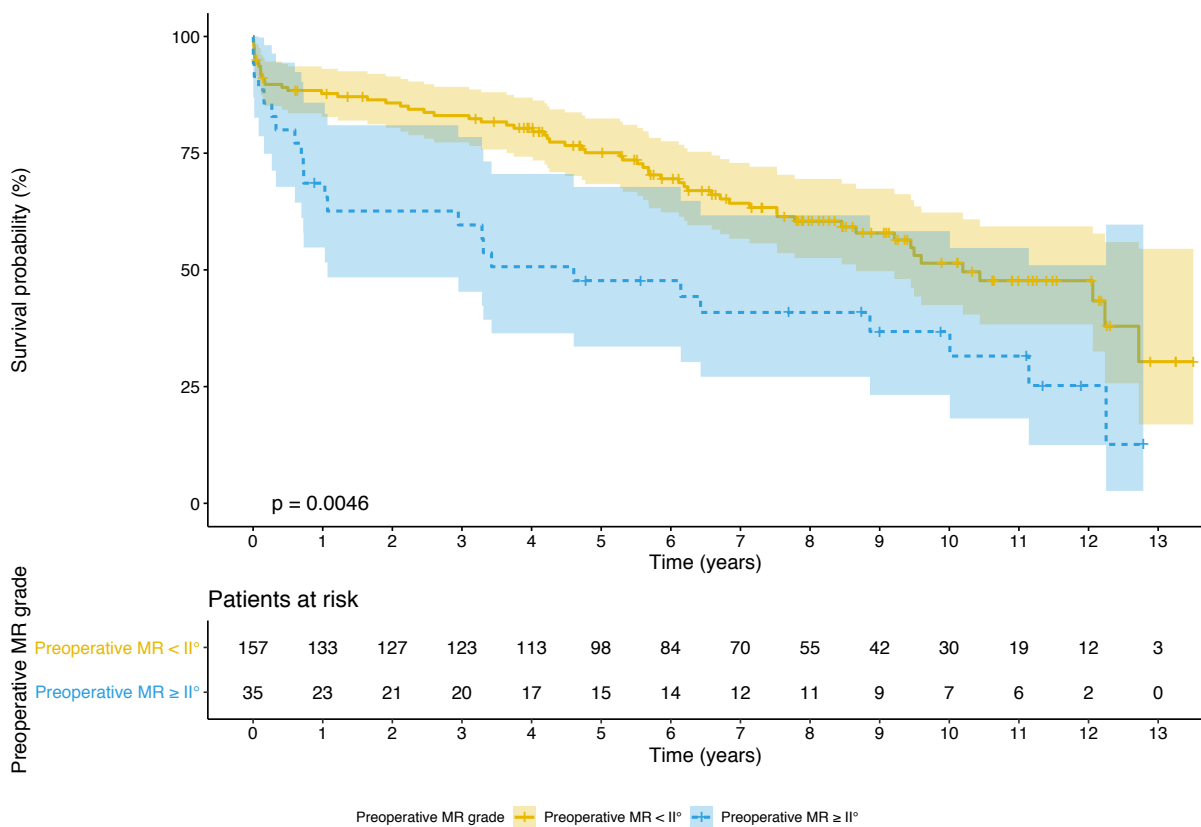
**Figure 7.** Kaplan-Maier curve for composite endpoint of all-cause mortality, left ventricular assist device implantation, and heart transplantation, stratified by diabetes.



### 3.11.4. Survival difference in patients stratified by preoperative MR

MR grade was retrieved from the latest preoperative TTE or intraoperative TEE if no TTE was available. The findings are presented in Figure 8.

**Figure 8.** Kaplan-Maier curve for composite endpoint of all-cause mortality, left ventricular assist device implantation, and heart transplantation, stratified by preoperative MR grade.



### 3.11.5. Cut-off for left ventricular end-diastolic diameter associated with adverse events

Cut-offs were calculated using the receiver operating curves (ROC) method. A preoperative LV end-diastolic diameter greater than 60.5 mm, as measured on TTE (sensitivity 0.562, specificity 0.641, AUC=0.619), was associated with an increased adverse postoperative outcome.

In the group of patients with an LVEDD exceeding 60.5 mm, a postoperative LVESVI lower than 55 could be achieved only in 34.9% of cases ( $p < 0.001$ ). The mortality in



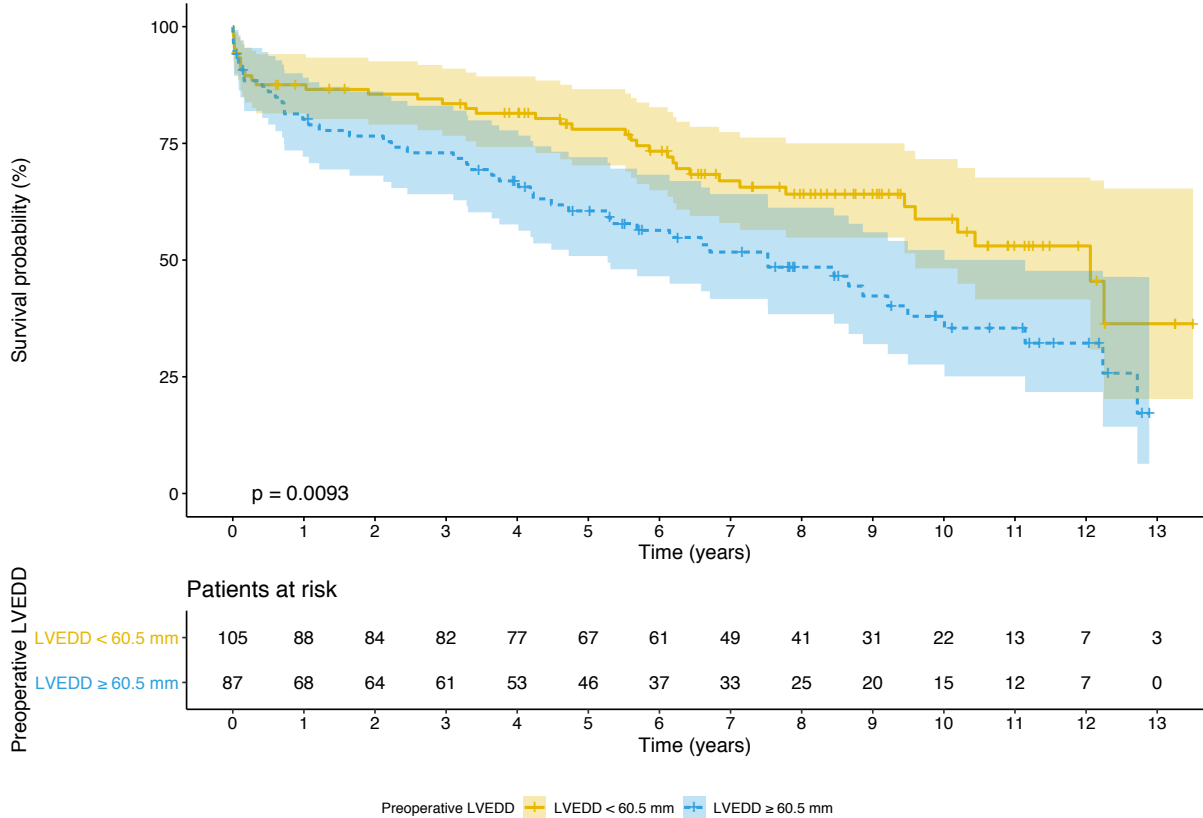
this group was increased, resulting in a 5-year survival rate of 59.2% compared to 77.8% in patients with a preoperative LVEDD lower than 60.5 mm ( $p=0.008$ ).

**3.11.6. Survival difference in patients stratified by preoperative LVEDD**

LVEDD was retrieved from the latest preoperative TTE. Stratification was based on the cut-off identified in this study—60.5 mm (see Chapter 3.11.5).

The findings are presented in Figure 9.

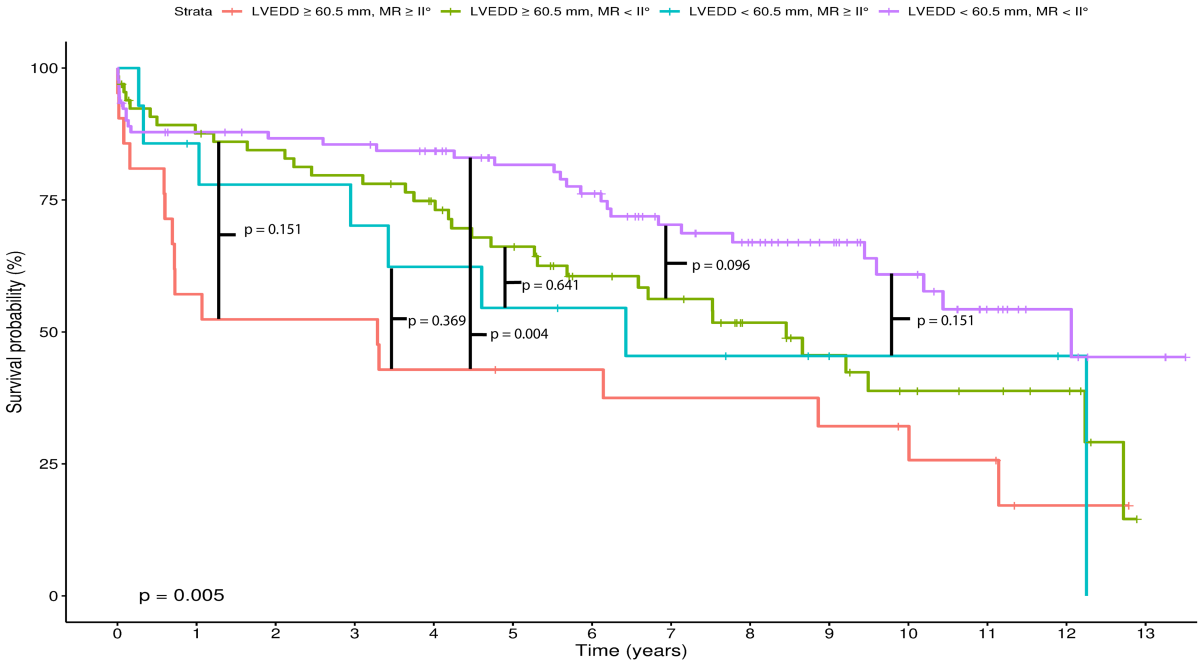
**Figure 9.** Kaplan-Maier curve for composite endpoint of all-cause mortality, left ventricular assist device implantation, and heart transplantation, stratified by preoperative LVEDD.



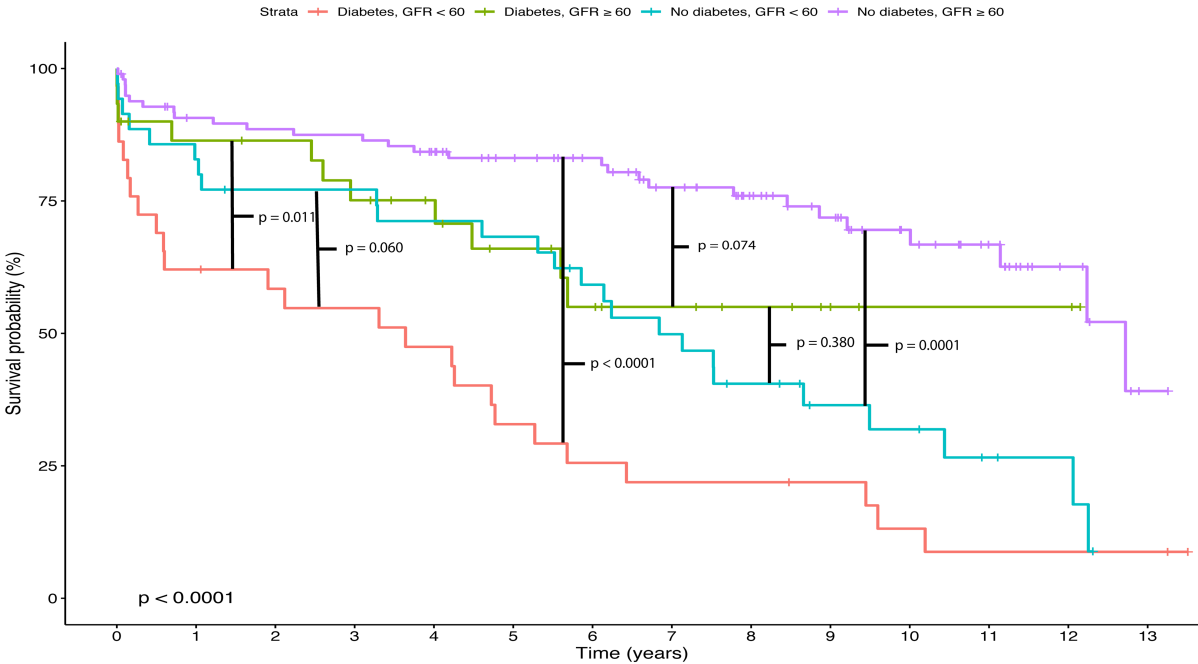
**3.11.7. Survival probability in patients with competing risk factors**

Plots were created to assess the survival probability in patients with multiple functional (Figure 10) and clinical risks factors (Figure 11). Cut-offs of variables identified in a multivariate Cox proportional hazards regression were used to create subgroups to allow for survival analysis.

**Figure 10.** Survival probability in patients stratified by preoperative LVEDD and MR grade. Log-rank test performed to compare all survival curves. Global  $p$ -value indicated.



**Figure 11.** Survival probability in patients stratified by diabetes and GFR. Log-rank test performed to compare all survival curves. Global  $p$ -value indicated.



### **3.11.8. Survival nomogram**

A survival nomogram (Figure A, Appendix) was created on the basis of the preoperative predictors established in this study. The nomogram can be used to predict adverse event-free survival in patients undergoing SVR by assessing competing risk factors and calculating a score. This score may then be used to calculate the relative chances of survival at specific time points. The validation of this nomogram is planned as part of a future project.

### **3.12. Volumetric cut-offs in predicting an adverse outcome**

#### **3.12.1. Preoperative LVESVI**

Though preoperative LVESVI did not prove to be an independent predictor of mortality in multivariate regression (Chapter 3.11.1), the ROC method was used to identify a baseline LVESVI cut-off (92 mL/m<sup>2</sup>, sensitivity 0.563, specificity 0.558, AUC=0.601) associated with adverse events. However, no survival difference could be shown in patients stratified by this cut-off, with 65.5% survival at 5 years in patients with LVESVI>92 mL/m<sup>2</sup> vs. 75.3% survival in patients with a lower LVESVI ( $p=0.092$ ). In patients with a preoperative LVESVI>92 mL/m<sup>2</sup> (49.7%), a postoperative LVESVI reduction of <55 mL/m<sup>2</sup> could be achieved only in 29.2% of cases ( $p<0.001$ ). In patients with a preoperative LVESVI>92 mL/m<sup>2</sup> and undergoing concomitant MVS ( $n=22$ ), elevated mortality could be observed, with most adverse events occurring in the first year after the surgery and a 1-year survival of 59.1%. In this group of patients, a sufficient LVESVI reduction (e.g., LVESVI<55 mL/m<sup>2</sup> identified in this study [Chapter 3.12.3]) could be achieved only in 2 of 17 patients receiving postoperative MSCT scan (11.7%,  $p<0.001$ ). A significant reduction of mitral regurgitation could still be observed in postoperative TTE, with only one patient having moderate MR after valve surgery.

#### **3.12.2. Intraoperative LVESVI reduction**

The mean postoperative LVESVI reduction when compared to the preoperative volume was 41.5%±20% in all patients. A significant difference in mortality could be observed in patients in whom the mean reduction exceeded the 42% threshold (sensitivity 0.592, specificity 0.587, AUC=0.639). In group 1 (LVESVI reduction more than 42%) the

survival was 96.8% at 1 year, 91.8% at 3 years, and 84.8% at 5 years. In group 2 (LVESVI reduction less than 42%) the survival was 76.2% at 1 year, 70.7% at 3 years, and 60% at 5 years. The log-rank test showed a significant statistical difference ( $p=0.002$ ) in outcomes between the two groups.

It should be noted that the mean reduction was  $57.4\% \pm 10.1\%$  in group 1 and only  $24.2\% \pm 12.3\%$  in group 2. This may be partially explained by a larger preoperative LVESVI in group 1 (mean  $111 \pm 49.1$ ) compared to group 2 (mean  $95.2 \pm 51.5$ ), which, however, was not significantly different ( $p=0.085$ ). However, the postoperative LVESVI in group 2 was exceedingly greater than the one deemed beneficial (mean  $71.9 \pm 37.5$ ), while the LVESVI in group 1 was below the cut-off point of  $55 \text{ mL/m}^2$  identified in this study (mean  $47.3 \pm 25.1$ ,  $p < 0.001$ ) (Chapter 3.12.3).

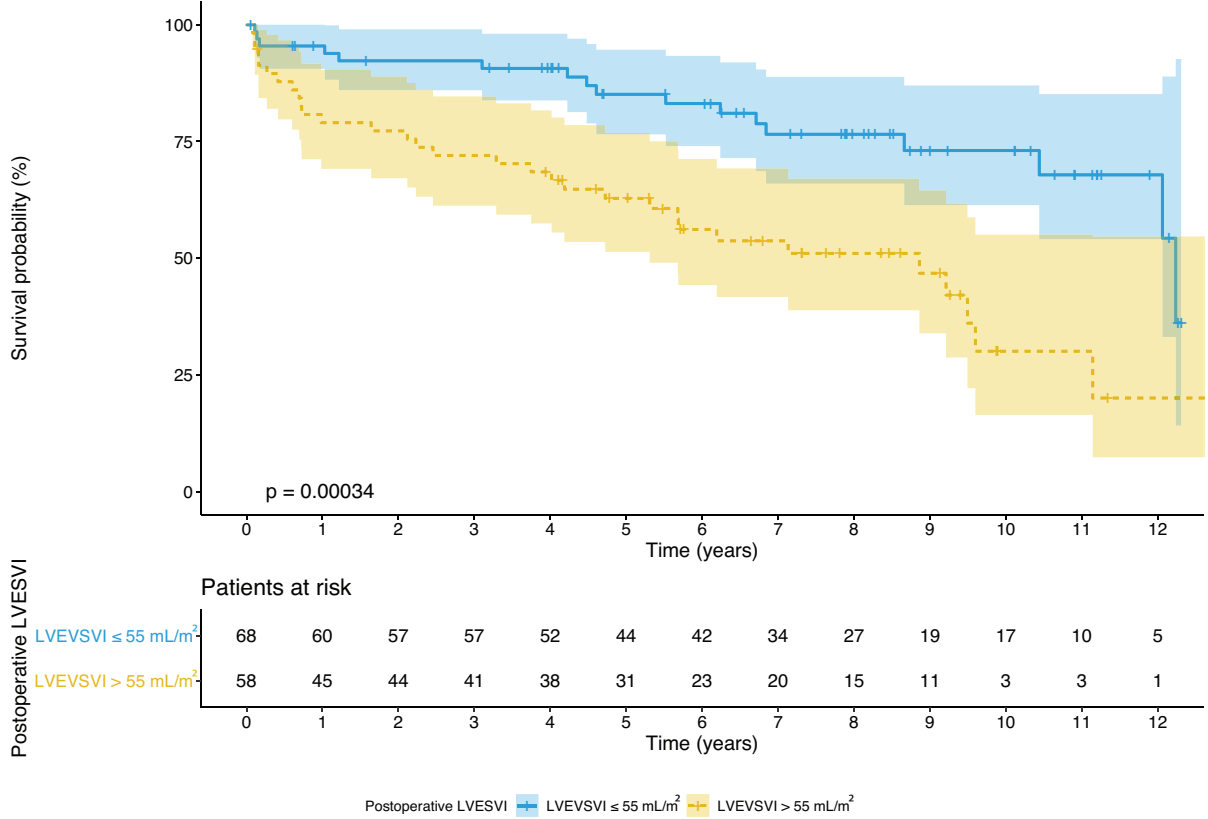
Preoperative LVESVI ( $p=0.041$ ) and moderate or severe MR ( $p=0.033$ ) were identified in multivariate logistic regression as independent predictors of a postoperative LVESVI reduction of less than 42%.

### **3.12.3. Postoperative volumetric parameters as predictors of adverse event-free survival**

In a group of 124 patients in which pre- and postoperative MSCT scans were carried out, the only postoperative predictor of an adverse outcome in a multivariate Cox proportional hazards analysis was LVESVI (HR: 1.020 [1.011–1.028],  $p < 0.001$ ).

A postoperative LVESVI greater than  $55 \text{ mL/m}^2$  (sensitivity 0.653, specificity 0.662, AUC=0.681) was associated with an adverse outcome. This finding was in accordance with the cut-offs indicated in the current SVR literature [25]. Kaplan-Meier curves (Figure 12) showed significant differences ( $p < 0.001$ ) in survival between the two groups. 1-year survival was 95.3%, 3-year 92%, and 5-year 84.6% in the group in which a postoperative  $\text{LVESVI} \leq 55 \text{ mL/m}^2$  could be achieved vs. 78.6%, 71.5%, and 62.1%, respectively, in the group in which the postoperative LVESVI was greater.

**Figure 12.** Kaplan-Maier curve for composite endpoint of all-cause mortality, left ventricular assist device implantation, and heart transplantation, stratified by postoperative LVESVI.



For every 10 mL/m<sup>2</sup> increase in postoperative LVESVI, the probability to suffer from an adverse event increased by 20%.

In Table 10 pre- and postoperative volumetric parameters of patients with a postoperative LVESVI > 55 mL/m<sup>2</sup> are compared with those of patients with a lower LVESVI.

**Table 10.** Volumetric and geometric parameters of patients with postoperative LVESVI >55 mL/m<sup>2</sup> compared to those of patients with lower LVESVI. Only significant variables are presented, indexed variables are preferred if available. MSCT measurements, unless otherwise indicated. Mean and standard deviation reported.

Characteristics	LVESVI > 55 mL/m <sup>2</sup>	LVESVI ≤ 55 mL/m <sup>2</sup>	p-value
LVESVI preoperative, mL/m <sup>2</sup>	137.2 ± 48.5	74.6 ± 31.2	<0.001
LVESVI postoperative, mL/m <sup>2</sup>	86.4 ± 28.3	35.3 ± 12.5	<0.001
LVEDVI preoperative, mL/m <sup>2</sup>	183.4 ± 49.4	120.2 ± 34.9	<0.001
LVEDVI postoperative, mL/m <sup>2</sup>	124.6 ± 31.4	72.9 ± 15.6	<0.001
LVESVI intraoperative reduction, %	-33.2 ± -18.9	-48.4 ± -18.3	<0.001
LAVI syst. preoperative, mL/m <sup>2</sup>	66.6 ± 19.4	55.1 ± 18.4	0.001
LAVI syst. postoperative, mL/m <sup>2</sup>	55.5 ± 20.0	46.2 ± 16.5	0.005
LVSI syst. preoperative	0.35 ± 0.10	0.26 ± 0.08	<0.001
LVSI syst. postoperative	0.44 ± 0.15	0.26 ± 0.11	<0.001
LVSI diast. preoperative	0.44 ± 0.10	0.36 ± 0.08	<0.001
LVSI diast. postoperative	0.59 ± 0.17	0.45 ± 0.14	<0.001
LVEDD preoperative (TTE), mm	61.1 ± 8.7	56.4 ± 7.5	<0.001
LVEDD postoperative (TTE), mm	60.7 ± 9.7	52.6 ± 7.2	<0.001
LVEF preoperative (TTE), %	26.9 ± 9.3	35.1 ± 9.2	<0.001
LVEF postoperative (TTE), %	33.6 ± 9.0	44.0 ± 8.1	<0.001
MR grade (TTE)	1.164 ± 0.8	0.88 ± 0.63	0.038
LVESVI – left ventricular end-systolic volume index, LVEDVI - left ventricular end-diastolic volume index, LAVI – left atrial volume index, LVSI – left ventricular sphericity index, LVEDD – left ventricular end-diastolic diameter, LVEF – left ventricular ejection fraction, MR – mitral regurgitation			

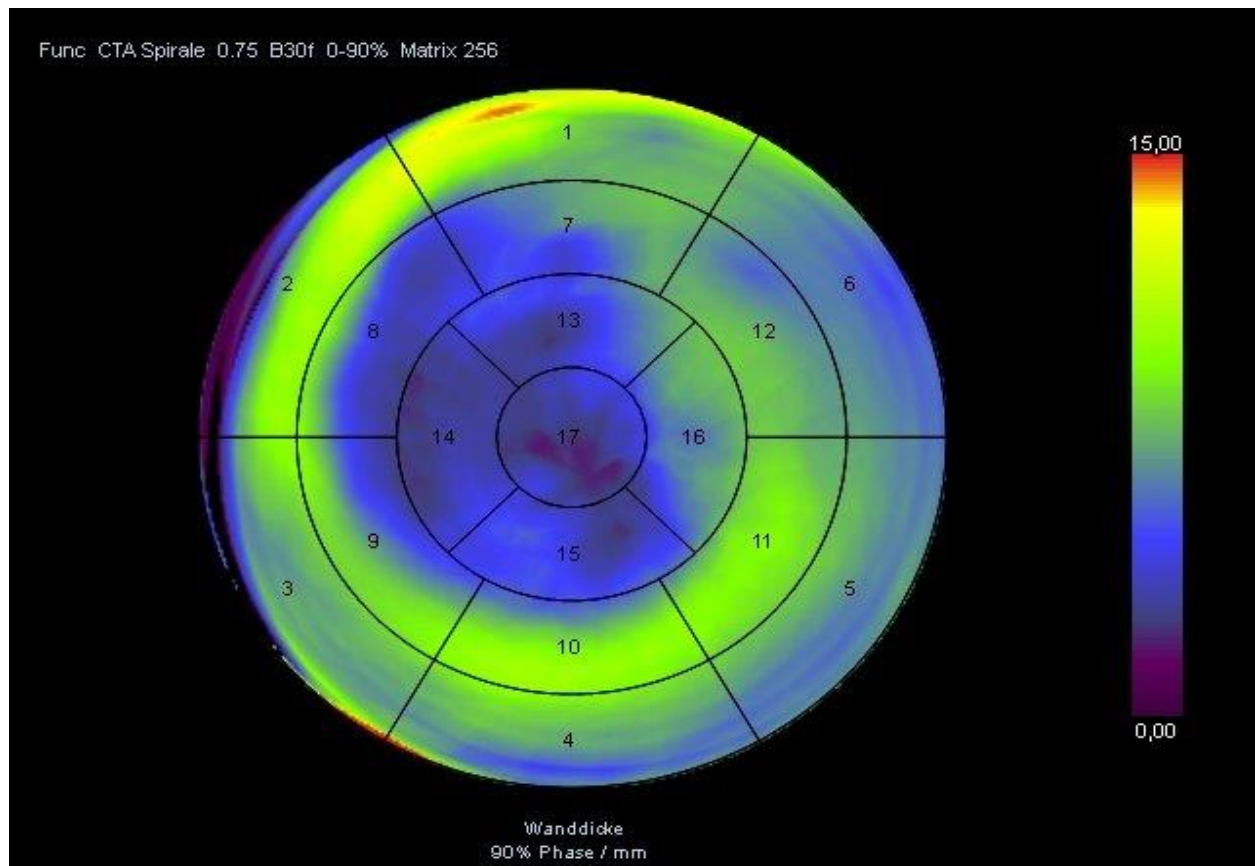
In multivariate logistic regression, the preoperative LVESVI ( $p < 0.001$ ) and percentage reduction of LVESVI reduction rate ( $p < 0.001$ ) could be established as independent predictors of a postoperative LVESVI greater than 55 mL/m<sup>2</sup>. A preoperative LVESVI exceeding 100 mL/m<sup>2</sup> (sensitivity 0.804, specificity 0.838, AUC=0.863) and a surgical reduction of the preoperative LVESVI of less than 42% (sensitivity 0.643, specificity 0.647, AUC=0.713) were associated with a higher probability of a postoperative LVESVI exceeding 55 mL/m<sup>2</sup>.

### 3.13. LV scar segmentation

#### 3.13.1. Morphological analysis of LV scar segmentation

To assess the extension of left ventricular aneurysms, MSCT datasets were analyzed and a 17-segment bull's eye model (Figure 13), commonly used in echocardiographic studies, was applied. Each aneurysm involved a certain number of dyskinetic segments. The scar localization was described using standard nomenclature, which is common in cardiac imaging studies.

**Figure 13.** Clinical case with antero-septal LV aneurysm with myocardial segmentation according to nomenclature used in cardiac imaging.



Segments: 1) basal anterior, 2) basal anteroseptal, 3) basal inferoseptal, 4) basal inferior, 5) basal inferolateral, 6) basal anterolateral, 7) mid anterior, 8) mid anteroseptal, 9) mid inferoseptal, 10) mid inferior, 11) mid inferolateral, 12) mid anterolateral, 13) apical anterior, 14) apical septal, 15) apical inferior, 16) apical lateral, 17) apex. Nomenclature after Cerqueira et al. [61]

Scarification at baseline in the basal anterior (segment 1,  $p < 0.001$ , HR 2.708 [1.564–4.687]) or mid inferoseptal (segment 9,  $p = 0.026$ , HR 1.939 [1.120–3.359]) localization was associated with an increased risk of adverse events. The assessment of healthy myocardium, in which no scarification occurred, was performed to establish segments that could have a protective function in LVA patients. No such segments could be identified.

Patients were then divided into morphological subgroups according to their LVA localization and extension. Those were antero-apical, antero-apical and another localization, antero-apical and septal, antero-apical and septal with another localization. Antero-apical localization, defined as involvement of segments 7, 8, 13, 14, 15, and 17, was associated with a lower risk of an adverse event (HR 0.601, CI 0.385–0.939,  $p = 0.022$ ). 5-year survival was 79.4% in this group ( $n = 80$ ) compared to 63.5% in the rest of the patients ( $n = 109$ ,  $p = 0.024$ ). Patients in this antero-apical group were characterized by a lower baseline LVESVI (83.1 mL/m<sup>2</sup>) than the patients with other scar localizations (116.8 mL/m<sup>2</sup>,  $p < 0.001$ ). The postoperative LVESVI was significantly lower as well (44.4 mL/m<sup>2</sup> vs. 73.7 mL/m<sup>2</sup>,  $p < 0.001$ ). A greater LVESVI reduction could be achieved in this group (-46.2% vs. -36.6%,  $p = 0.007$ ).

### **3.13.2. Cluster analysis of LV scar segmentation**

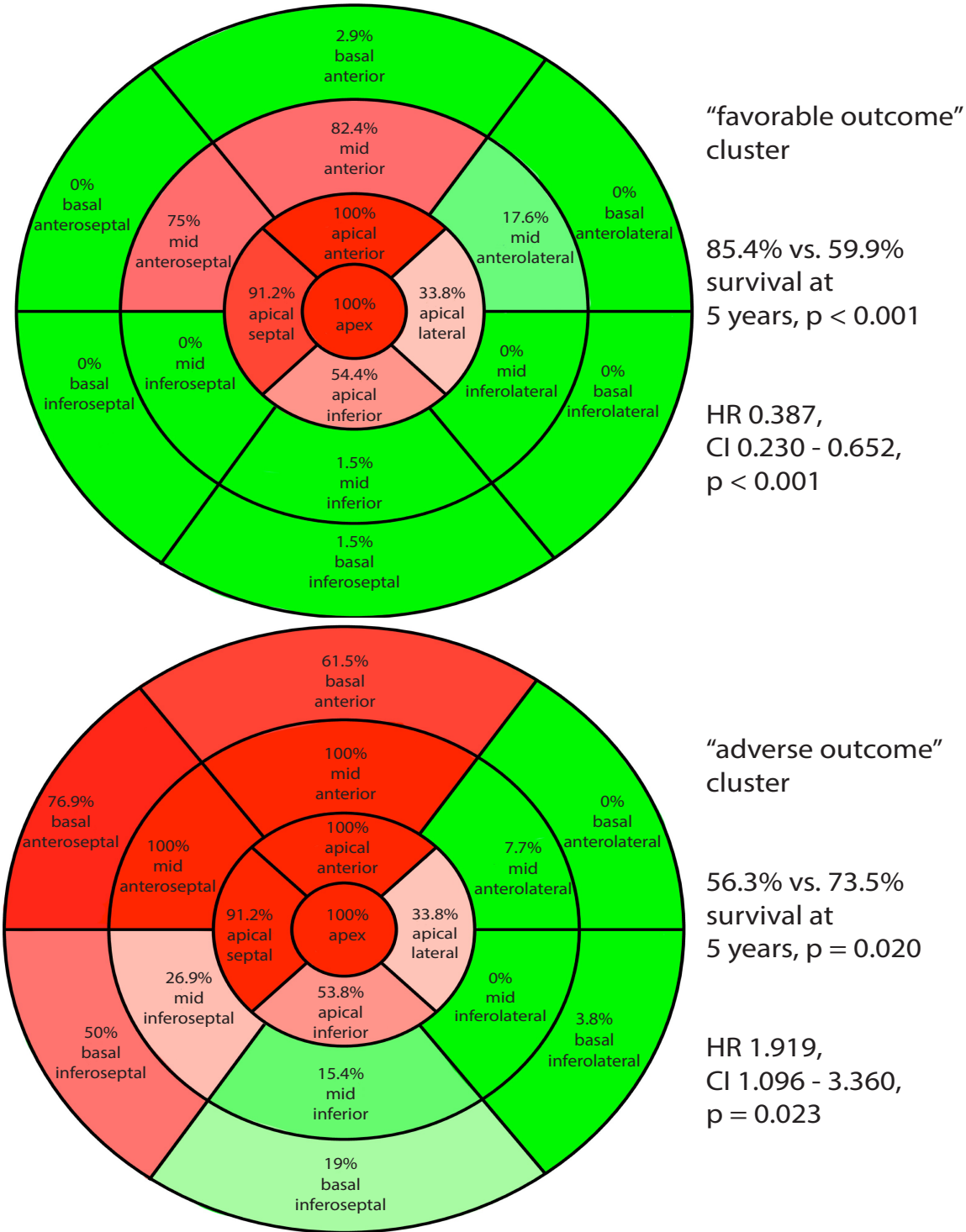
A cluster analysis was performed to establish patterns of scar segmentation by identifying the most common combinations of scars. The defined clusters were then tested for their influence on survival. Overall, 5 clusters could be identified. Patients assigned to cluster 1 (“favorable outcome” cluster) due to their scar segmentation ( $n = 68$ , 43.3% of patients with preoperative MSCT) were characterized by a better survival than patients in the other clusters (85.4% vs. 59.9% at 5 years,  $p < 0.001$ ). In the univariate Cox proportional hazards analysis, this cluster showed a significant protective importance (HR 0.387, CI 0.230–0.652,  $p < 0.001$ ). In patients assigned to cluster 4 (“adverse outcome” cluster) ( $n = 26$ , 16.6%) lower survival rates were observed (56.3% vs. 73.5% at 5 years,  $p = 0.020$ ). The univariate analysis showed a significant association with adverse events (HR 1.919, CI 1.096–3.360,  $p = 0.023$ ). None of the clusters was significant in the multivariate analysis.

The frequency of scar localization in the 17 heart segments is compared in Figure 14 for the “favorable outcome” and the “adverse outcome” cluster. Based on the difference in survival rates and the significant predictive value of both clusters, it can be



postulated that the additional involvement of basal segments is associated with a greater risk of an adverse outcome.

**Figure 14.** Frequency of scar localization in patients assigned to the “favorable outcome”-cluster and in patients assigned to the “adverse outcome” cluster based on preoperative MSCT imaging.



### 3.14. Impact of coronary revascularization during SVR

There was no statistically significant difference ( $p=0.952$ ) in survival between patients with either single-, two- or three- vessel disease and patients with no documented CAD (ischemic event resulting mostly from thromboembolism). At 5 years the survival was 55.6% in patients with no documented CAD ( $n=9$ ), 71.9% in patients with single-vessel CAD ( $n=37$ ), 76.6% in patients with two-vessel CAD ( $n=40$ ), and 68.3% in patients with three-vessel CAD ( $n=106$ ). There was no survival difference between patients receiving at least one bypass ( $n=149$ ) or none ( $n=43$ ,  $p=0.558$ ). The survival at 5 years was 72.7% in the CABG group and 61% in patients receiving no revascularization. Revascularization was not performed when total occlusion of the target coronary artery was present, when transient ischemia resulted from a thromboembolic event, and when coronary vessels were patent on recent coronary angiography. CABG was also not performed in patients who underwent percutaneous coronary intervention (PCI) and in whom the stent showed no evidence of stenosis. Of special interest was the group with chronic total occlusion of the vessel ( $n=15$ ), in which surprisingly no survival difference could be observed when compared with other patients (72.7% vs. 69.8% at 5 years,  $p=0.830$ ). There was no significant difference in preoperative NYHA functional class (3.1 vs. 3,  $p=0.171$ ), LVESVI (124 vs. 97.6 mL/m<sup>2</sup>,  $p=0.066$ ), LVEF (29.6 vs. 32.2%,  $p=0.364$ ), and LVEDD (61.2 vs. 59.8 mm,  $p=0.590$ ) when compared to other patients (with or without CAD). Postoperative NYHA functional class improvement, LVESVI and LVEDD percentage reduction, and LVEF increase were similar in both groups.

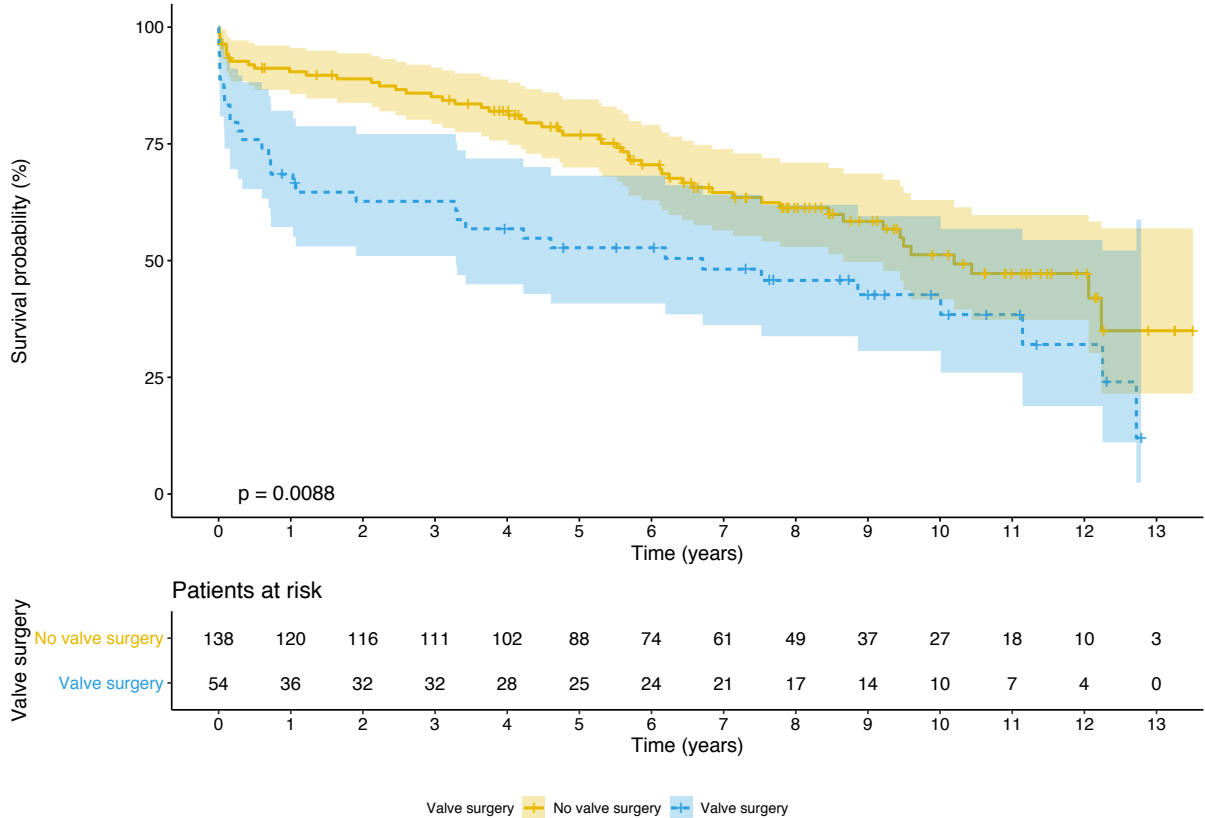
### 3.15. Impact of concomitant valve surgery during SVR

Overall, 54 patients (28.1%) underwent concomitant valve surgery. 33 mitral valve reconstructions (17.2%), 3 mitral valve replacements (1.8%), 17 aortic valve replacements (8.9%), and 5 tricuspid valve reconstructions (2.6%) were performed. Patients undergoing concomitant valve surgery had reduced survival compared to those in whom no valve surgery was performed (52.8% vs. 76.4% at 5 years,  $p=0.009$ ) (Figure 15).

In the univariate analysis, valve surgery (including mitral surgery, aortic valve replacement, and tricuspid valve reconstruction) was an independent predictor of adverse events ( $p=0.010$ , HR=1.767 [1.148–2.721]), while isolated mitral valve surgery

had no impact on the adverse events ( $p=0.063$ , HR=1.583 [0.975–2.569]). Both types of surgery were not significant in the multivariate risk analysis.

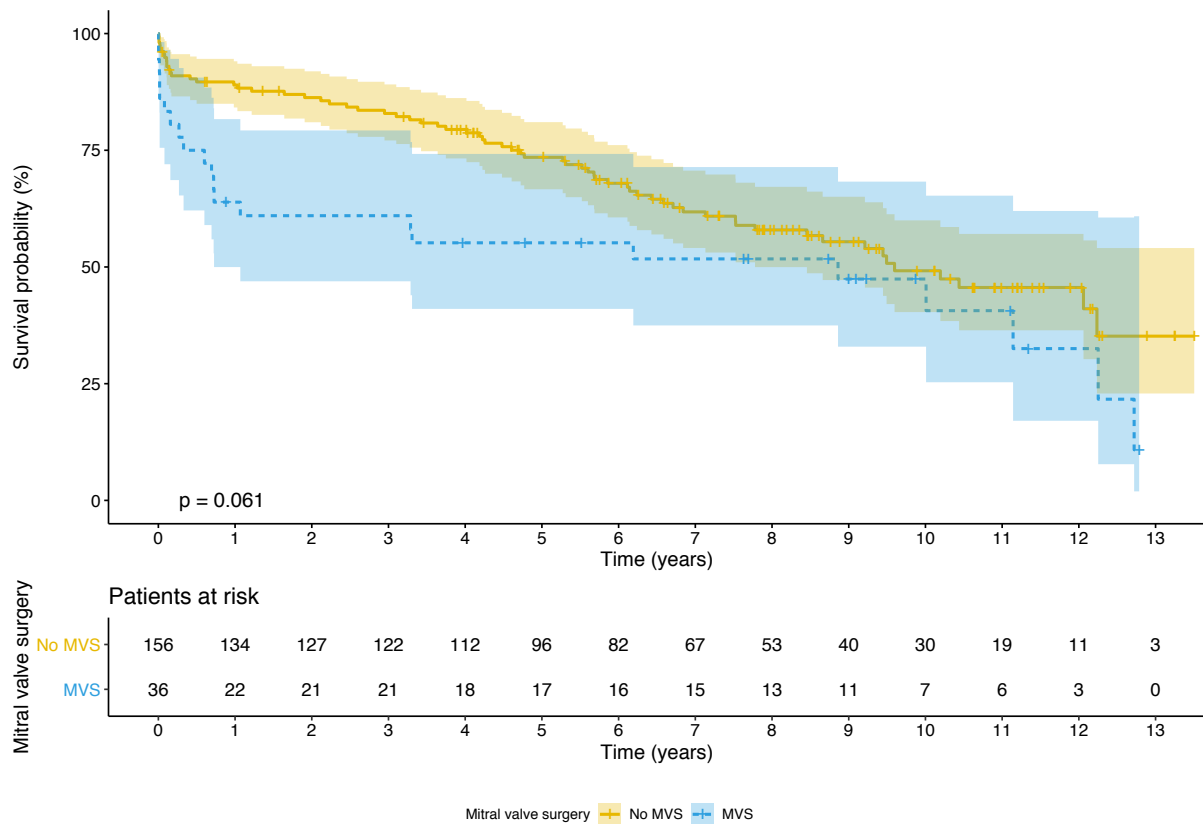
**Figure 15.** Kaplan-Maier curve for composite endpoint of all-cause mortality, left ventricular assist device implantation, and heart transplantation, stratified by concomitant valve surgery.



### 3.16. Impact of concomitant mitral valve surgery

MVS was associated with an increased rate of adverse events despite the lack of statistical significance (55.2 vs. 73.5% at 5 years,  $p=0.065$ ). Most adverse events occurred in the first year (63.9% survival at 1 year, 61% at 2 and 3 years) (Figure 16).

**Figure 16.** Kaplan-Maier curve for composite endpoint of all-cause mortality, left ventricular assist device implantation, and heart transplantation, stratified by concomitant mitral valve surgery.



In the subgroup of patients with moderate to severe MR, 24 MVR procedures were performed (68.5% of the patients with moderate to severe MR), and MV replacement was carried out in 3 cases. In the complete population, 33 MVR procedures and 3 MV replacements were performed, suggesting that MVS was performed in 9 patients with mild MR on preoperative TTE. The decision to perform MVS was based on intraoperative findings and transesophageal echocardiography. Of the 36 patients receiving MVS, 26 had no MR on postoperative TTE, 5 had trace MR, 4 mild MR, and one moderate MR after SVR. Notably, MVS required extended clamp (72 min vs. 108 min) and perfusion (124 min vs. 203 min) time (both  $p < 0.001$ ).

Patients receiving MVS had an increased risk profile before and after the operation, which might explain the increased rate of adverse events. Their MR grade was higher (2.15 vs. 0.78,  $p < 0.001$ ), EF lower (27.6 vs. 33.0%,  $p = 0.006$ ), and LVEDD greater (65.3 vs. 58.6 mm,  $p < 0.001$ ) when compared to the patients not receiving MVS. Baseline LVESVI was not significantly greater in comparison to the other group

(112.8 vs. 96.6 mL/m<sup>2</sup>,  $p=0.102$ ). During the operation only a 33.4% LVESVI reduction could be achieved when compared to 43.3% in the “no MVS” group ( $p=0.036$ ). Following SVR, a significant MR reduction could be achieved in both groups (postoperative MR grade 0.236 in the MVS group vs. 0.372 in the “no MVS” group,  $p=0.101$ ). However, after the operation LVEF was still lower (36 vs. 40.2%,  $p=0.034$ ), LVEDD greater (59.5 vs. 54.1 mm,  $p=0.001$ ), and LVESVI significantly greater (83 vs. 53.7 mL/m<sup>2</sup>,  $p<0.001$ ) than in the “no MVS” group.

A preoperative LVESVI exceeding 100 mL/m<sup>2</sup>, which is identified in our study to be a cut-off for a successful LVESVI reduction to <55 mL/m<sup>2</sup>, did not influence survival in patients undergoing concomitant MVS. 5-year survival was 50% in these patients ( $n=18$ ) and 60.6% in patients with lower baseline LVESVI ( $n=13$ ,  $p=0.324$ ). In MVS patients in whom a postoperative LVESVI<55 mL/m<sup>2</sup> could be achieved ( $n=6$ ), no mortality could be observed during the whole observational period. All these patients were characterized by a baseline LVESVI<100 mL/m<sup>2</sup>. The mortality in patients in whom the postoperative LVESVI exceeded 55 mL/m<sup>2</sup> ( $n=16$ ) was significantly higher with 50% at 5 years ( $p=0.030$ ).

### **3.17. Decrease in functional mitral regurgitation following SVR**

8 patients did not receive any kind of MVS despite preoperative moderate to severe MR. It was a group of patients with volumetric (LVESVI [103 vs. 96.3,  $p=0.744$ ]), functional (LVEF [34.6 vs. 33,  $p=0.671$ ], CI [3.1 vs. 3,  $p=0.799$ ]) and clinical (NYHA [2.8 vs. 2.9,  $p=0.324$ ], coronary artery disease [1.7 vs. 2.2,  $p=0.118$ ]) characteristics very similar to the patients with mild to no MR. The only significant difference was the MR grade (2.0 vs. 0.71,  $p<0.001$ ). After the SVR, MR was significantly reduced in both groups (0.375 vs. 0.372,  $p=0.983$ ). Of 8 patients not receiving MVS, 5 patients had no MR and 3 had mild MR, reflecting the functional genesis of the MR. The postoperative morphological and functional parameters were satisfactory and not statistically different in both groups.

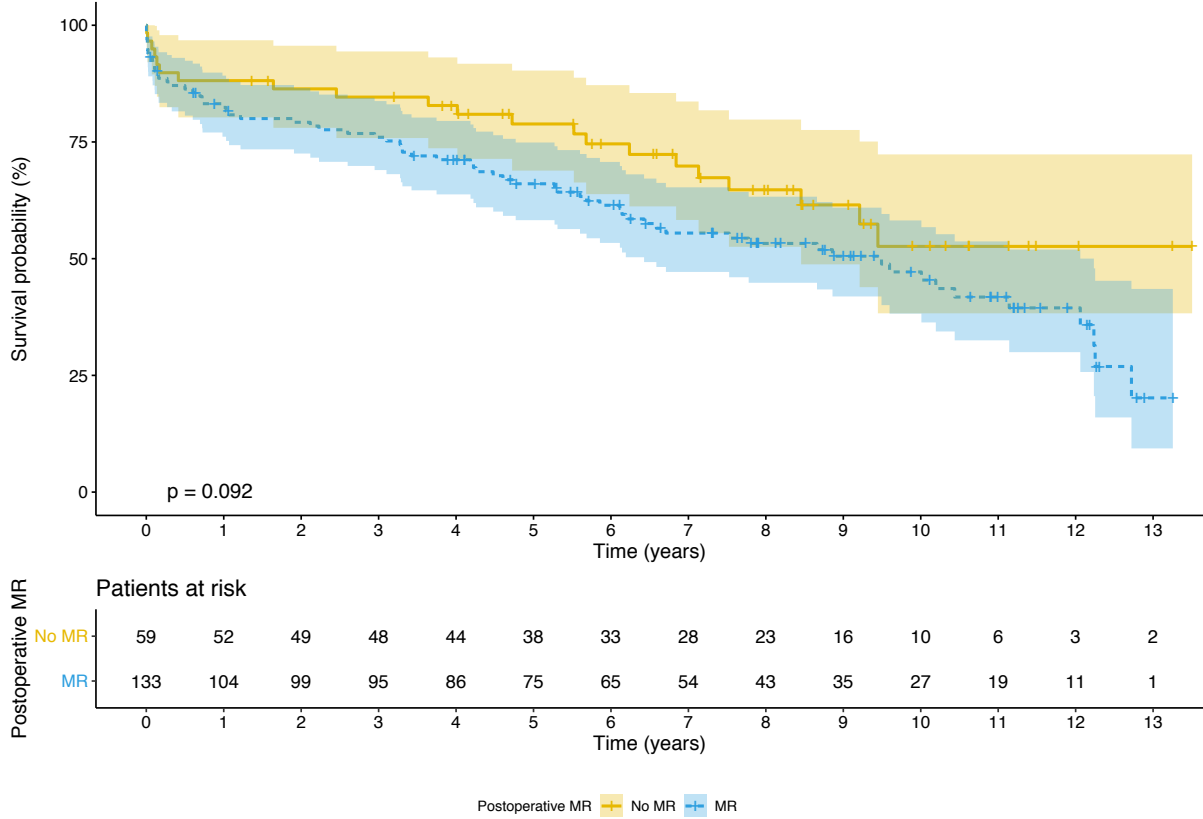
No significant difference ( $p=0.101$ ) in mean postoperative MR could be found between patients receiving MVS (0.236) and patients without MVS (0.372).

In patients in whom no MVS was performed, MR decreased significantly (0.37 vs. 0.78,  $p<0.001$ ) when compared to the preoperative MR grade, indicating the functional

nature of the MR. Following SVR, only 44 patients (28.2%) in this group had mild MR, with the rest of the patients having no (54.5%) or trace (17.3%) MR.

No statistically significant survival difference could be observed between patients with no or trace MR following SVR and patients with mild MR (70.7% vs. 66.6% at 5 years,  $p=0.096$ ) (Figure 17). There were no cases of postoperative MR higher than grade I in patients not receiving concomitant MVS; one patient undergoing concomitant MVR had postoperative MR grade II. 47 patients (24.4%) had no pre- or postoperative MR.

**Figure 17.** Kaplan-Maier curve for composite endpoint of all-cause mortality, left ventricular assist device implantation, and heart transplantation, stratified by absence or presence of postoperative mild MR.



## 4. Discussion

This study is based on our single-center experience with 204 consecutive patients who underwent SVR from November 2005 until December 2015, when the modified non-patch Dor technique was introduced and MSCT was used as a routine in preoperative imaging assessment. While the discussion on the patient selection became more complex with the STICH trial results, this study clearly demonstrated the benefits of SVR on NYHA class improvement and long-term survival. Furthermore, the value of pre- and postoperative MSCT assessment in patients undergoing SVR could be shown.

### 4.1. Improvement of NYHA functional class and survival after SVR

A significant improvement in NYHA functional class from a preoperative median class III to class II was observed following the operation, with 80.9% in NYHA class I or II. The NYHA class remained stable (median class II) at mid-term follow-up. This is consistent with the findings of previous studies (2.9 to 1.7, Athanasuleas et al. [50]; 2.5 to 1.4, Di Donato and coworkers [62]). Although Witkowski et al. [40] described a trend towards a better postoperative NYHA functional class in patients with greater volume reduction, this association was not found in this study. 1-, 5-, and 10-year survival free of adverse events was 83.5%, 69.6%, and 49% respectively. The mean time to LVAD was 3.8 years, to heart transplantation 2.6 years, and to all-cause mortality 4.1 years.

### 4.2. Superiority of SVR over conservative therapy

To the best of my knowledge, this is the first study that uses the Seattle Heart Failure Model to calculate predicted survival rates for patients on optimal medical therapy and compares them with the actual survival of patients undergoing SVR, thus addressing the lack of a control group in this retrospective study.

According to the European Society of Cardiology guidelines, all ischemic cardiomyopathy patients should receive optimal medical therapy [63]. The mortality reduction can be as high as 63% when the best heart failure medication is prescribed [64]; however, several other factors contribute to all-cause mortality. To address this

issue, the Seattle Heart Failure Model score [59] was developed to assess the survival on optimal medical therapy and the benefit of therapy modifications.

By comparing the predicted survival utilizing the baseline measurements and medication to the actual survival of patients undergoing SVR, this study was able to show a long-term survival benefit of operated patients, with 65.7% of the patients in the SVR group being alive and free of adverse events at 5 years compared to 51% of the patients on optimal medical therapy ( $p<0.001$ ). It is important to note that this benefit was not seen in the first two years, when there was no survival difference. These findings agree with the currently available evidence. For example, in a meta-analysis of all available studies [65], a survival benefit of isolated CABG in ischemic heart disease patients with a reduced ejection fraction of  $\leq 40\%$  compared to patients treated with conservative therapy was observed.

Furthermore, in the STICH trial, the benefit of bypass surgery over drug therapy in heart failure patients was investigated. 1212 patients (median age 60 years) with heart failure with reduced ejection fraction (LVEF  $\leq 35\%$ ), NYHA class II–IV and coronary heart disease, who did not have main stem stenosis or severe angina pectoris were randomized to bypass surgery or drug therapy. After five years, there was no significant difference in the primary endpoint all-cause mortality between the two groups, but bypass surgery was significantly superior to drug therapy for some secondary efficacy endpoints. After ten years of follow-up, the risk of death was also significantly reduced by bypass surgery (mortality 58.9% vs. 66.1%; HR 0.84 [95% CI 0.73; 0.97];  $p=0.02$ , NNT=14) [66].

#### **4.3. Change in volumetric, geometric, and functional parameters of the left ventricle**

The change in volumetric, geometric, and functional parameters of the left ventricle is in line with the findings of recent major SVR studies. The mean LVESVI reduction rate of 41.5% in this study is comparable to the studies by groups of Di Donato [25] and Dor [26], and the significant decrease in LVESVI (from  $102.9\pm 50.6$  mL/m<sup>2</sup> to  $58.6\pm 33.4$  mL/m<sup>2</sup> [ $p<0.001$ ]) and increase in LVEF ( $31.8\pm 10.5\%$  to  $39.3\pm 10.8\%$  [ $p<0.001$ ]) following the operation is similar to the results reported by other groups (Table 11).



**Table 11.** Overview of pre- and postoperative volumes and volumetric reductions reported in the different studies.

Author(s) (year)	No. of patients	Preoperative LVESVI	Postoperative LVESVI	Reduction (%)
Dor (1998) [67]	Akinetic: 51	188	70	62
	Dyskinetic: 49	160	48	70
Di Donato (2001) [68]	44	137	67	51
Di Donato (2001) [39]	245	112	46	58
Menicanti (2002) [69]	46	98	63	35
Athanasuleas (2004) [50]	671	80.4	56.6	30
Mickleborough (2004) [46]	41	97	65	33
Di Donato (2009) [16]	Type 1: 56	83	35	58
	Type 2: 55	87	39	55
	Type 3: 67	96	57	41
Jones (2009) [53]	161	83	67	19
Isomura (2011) [31]	90	87	63	27
Skelley (2011) [70]	87	108	65	39
Witkowski (2011) [40]	79	75	45	40
Wakasa (2014) [71]	596	107	70	34
Yoshida (2015) [72]	Group 1: 51	85	61	28
	Group 2: 60	159	108	32
Hrytsyna (2021)	124	102	58	43

#### 4.4. Predictors of in-hospital mortality

In-hospital mortality was 6.7% and thus equivalent to pooled early mortality estimated in the meta-analysis of various operative techniques by Klein and coworkers [52]. As in this study, cardiopulmonary bypass time, as a predictor of early mortality, was established by Salis et al. [73] and Vural et al. [74] as an independent predictor of perioperative mortality in patients undergoing SVR, and it was the only surgical predictor of 30-day mortality in a large cohort of patients with ischemic cardiomyopathy [75].

#### 4.5. Preoperative predictors of an adverse outcome

The findings of this study confirm several predictors of risk that were reported in previous survival studies of heart failure patients: Renal function and diabetes, identified as predictors of postoperative adverse events in patients undergoing SVR in this study, were among the most consistent and strongest predictors of risk of death in heart failure patients in 48 studies [76]. In a retrospective study of patients undergoing SVR utilizing data from the Society of Thoracic Surgeons' National Cardiac Database [51], creatinine > 2 mg/dl, insulin-dependent diabetes, and severe MR were identified as strong predictors of an adverse procedural outcome. In another study [77], renal failure was the only independent predictor of mortality in patients with a baseline LVESVI > 100 mL/m<sup>2</sup>.

In agreement with previous studies (Menicanti et al. [38], Wakasa and coworkers [71], Sartipy and associates [45]), also in this study the preoperative MR grade was one of the independent predictors of adverse events in patients undergoing SVR. Intermediate mortality was significantly increased in patients with moderate to severe MR at baseline (69.4% vs. 86.8% at 1 year,  $p=0.018$ ). Postinfarction MR is a known predictor of mortality, associated with increased LV volumes and depressed LV function [78]. In patients with ischemic cardiomyopathy, MR was associated with an increased risk of mortality independently of the baseline characteristics and degree of ventricular dysfunction [79], and even mild MR led to increased mortality and risk of congestive heart failure [80]. In experimental studies, MR occurred only when global LV function was affected and was not associated with the dysfunction of regional wall adjacent to the papillary muscles [81], suggesting that significant dilatation was needed

to produce MR [82]. However, Yiu et al. [77] observed that MR can be difficult to assess in the setting of left ventricular dysfunction, as similar types of wall motion abnormalities can result in MR of different grades of severity and morphology.

Baseline LVEDD, another major predictor in this study, has also been established as a predictor of an adverse outcome and failed reverse remodeling following restrictive mitral annuloplasty in patients with ischemic MR by Braun et al. [42] and Bax et al. [83]. The authors suggested that, in the setting of an LVEDD > 65 mm, additional SVR might be needed in addition to annuloplasty to improve outcome. In this study, the survival was significantly reduced in patients with a preoperative LVEDD exceeding 60.5 mm. Di Donato et al. [25] suggested that LVEDD > 65 mm predicts the postoperative LVESVI > 60 ml/m<sup>2</sup>, but this finding could not be confirmed in this study. LVEDD can be easily measured using TTE during preoperative assessment; however, Mickleborough and coworkers [46] questioned the significance of the measurement of the short axis and long axis diameter in the dilated ventricle with an asymmetric shape. Buckberg and associates [84] suggested that ischemic cardiomyopathy is associated with non-homogenous dilation of the ventricle beyond the plane of papillary muscles, where LVEDD is measured, making this parameter not reliable for prediction or follow-up in aneurysmatic ventricles. Di Donato group [85] proposed that the evaluation of the shape of the ventricle should involve assessing the apical distal half of the ventricle, where major shape changes occur. This information might be of greater importance for the planning of the surgical strategy, especially regarding the choice of the best strategy for MR therapy. To address this issue, the RESTORE group proposed a novel conicity index, a ratio between apical and short axis [85]. A better assessment of volumetric and geometric parameters of the whole ventricle not relying on volumetric assumptions can also be achieved through preoperative MSCT imaging.

However, a variety of preoperative predictors reported in previous studies were not predictive in our study:

We found no association of baseline LVEF with a long-term adverse outcome, an often-reported finding of previous SVR studies [46], [54].

Contrary to studies, suggesting that a baseline LVESVI < 60 ml [54] or < 100 ml [41], [72] is required for a good outcome following SVR, no influence of the baseline LVESVI

could be established in this study. Instead, the achieved postoperative LVESVI was a strong predictor of adverse event-free survival.

#### **4.6. Postoperative predictors of an adverse outcome**

A postoperative LVESVI > 55 mL/m<sup>2</sup> was identified as the only postoperative predictor of adverse events and should thus be considered as target volume for an effective procedure. Other SVR studies [25], [40] have established an LVESVI > 60 mL/m<sup>2</sup> as another common cut-off. A 5-fold increased risk of an adverse event was described in patients undergoing SVR with a postoperative LVESVI > 60 mL/m<sup>2</sup> [40]. In our study, for every 10 mL/m<sup>2</sup> increase in postoperative LVESVI, the probability to suffer from an adverse event increased by 20%.

This suggests that SVR can be safely performed even in patients with severely dilated ventricles, but only when a target volume of LVESVI < 55 mL/m<sup>2</sup> is likely to be achieved. In most patients with extremely dilated ventricles, the achievement of this target volume will not be possible (in this cohort, a beneficial LVESVI < 55 mL/m<sup>2</sup> was achieved only in 21.4% of the patients with a preoperative LVESVI > 100 mL/m<sup>2</sup>), and even if the NYHA functional class improves, the survival will be reduced. In this setting, a preoperative LVESVI > 100 mL/m<sup>2</sup> can be considered as a risk factor of insufficient SVR, but it cannot be regarded as a definitive predictor of mortality or contraindication to SVR. To underline the importance of postoperative LVESVI for SVR outcome, our group recently developed a method to project the achievable residual volume based on preoperative MSCT (Solowjowa et al. [86]).

In this study, an LVESVI volume reduction of 42% (n=65, 53.3% of patients with MSCT studies) was required to achieve a significant survival benefit (85.3 vs. 61.7%, *p*=0.003). This volume reduction is consistent with the mean LVESVI reduction rates in recent SVR studies [25], [26]), however, it is dependent on the mean baseline LVESVI of the cohorts and will vary between different studies (Table 11).

#### **4.7. Impact of aneurysm localization on outcome following SVR**

In this study, the scar segmentation analysis using MSCT showed a good outcome in patients with isolated antero-apical aneurysms. These patients were characterized by a lower baseline LVESVI, greater intraoperative LVESVI reduction, and significantly

lower postoperative LVESVI. A significantly lower survival was found in patients with additional involvement of basal anterior, basal antero- and inferoseptal, and mid inferoseptal segments (56.3% vs. 73.5% at 5 years,  $p=0.020$ ). Vural et al. [74] suggested that the performance of the unaffected remote myocardium is associated with the postoperative rate of adverse events (early mortality, low cardiac output syndrome, and poor long-term survival). In a CMR study [87] patients with less scarring in the basal segments showed a greater increase in LVEF following SVR. It can be hypothesized, that patients with localizations beyond the antero-apical region have less myocardial reserve and more extensive myocardial resection is required, thus risking a creation of a more restrictive ventricle. A less viable myocardium leads to reduced postoperative contractile force improvement. In cases of isolated antero-apical LVA localization, the aneurysm can be reached more easily, and SVR can be performed more efficiently. However, in a recent study analyzing the predictive power of regional cardiac function in the STICH population, no segments of significant importance could be identified and baseline LVESVI was found to be the only independent predictor of mortality in ischemic cardiomyopathy patients [88]. As suggested in a systematic review of SVR predictors [52], the striking discrepancy regarding predictors in different SVR studies might be explained by the heterogeneity of the functional capacity of the remote myocardium. In our study scarification of the myocardium was assessed before the operation using MSCT. Multimodality imaging, including strain echocardiography (Dandel et al. [89], Nemchyna et al. [20]), may be helpful for a more accurate preoperative assessment of remote myocardium viability and surgical strategy planning.

#### **4.8. Role of imaging in SVR**

This study used various geometric, volumetric, and functional measurements to predict SVR outcome. The results support the contention that the preoperative assessment of the left ventricle by means of echocardiography and MSCT is useful in selection of patients who would benefit from SVR due to adequate LV volume reduction (Solowjowa et al. [86]). TTE is a fast and cost-effective modality to initially assess ventricle volumes, geometry (LVEDD), and functional parameters (LVEF, MR grade); however, its measurements are observer-dependent and can be inadequate in aneurysmatic ventricles. MSCT was used in this study not only to assess the

geometric, volumetric, functional parameters, but also the local wall motion abnormalities of the myocardium. Of all the parameters assessed by imaging studies before the operation, LVEDD and MR grade on TTE were the only independent predictors of an adverse outcome in our study. Although no preoperative parameters measured by MSCT were predictive of outcome, the postoperative LVESVI achieved following SVR was the only predictor of adverse event-free survival. Using MSCT, ventricular volume reduction during SVR can be planned thoroughly, considering the baseline LVESVI and individual anatomical constellations, such as involvement of septum, mitral annulus dilation, or papillary muscle involvement. The residual LVESVI can be visualized and calculated based on preoperative CT, thus guiding surgical decision-making (Solowjowa et al. [86]).

One criticism of the STICH trial was the utilization of predominantly echocardiographic volumetry for surgery planning and postoperative assessment. Of 555 patients included in a subset analysis [56], only 195 (35.1%) had paired cardiac magnetic resonance studies, while 276 (49.7%) had echocardiography and 84 (15.1%) radionuclide imaging studies that were used for the final analysis. Volumetric and functional measurements acquired under different imaging modalities are known to be not interchangeable [29]. This study employed complete MSCT datasets acquired under a uniform protocol and analyzed by a single investigator, so the probability of bias is low.

#### **4.9. Significance of concomitant CABG and mitral valve surgery in SVR**

In this study, an improvement of the NYHA functional class and functional parameters was observed even in patients in whom no myocardial revascularization was performed due to chronic complete occlusion of the target vessels, and there was no survival difference between both groups.

There is an ongoing debate whether concomitant MVS should be performed in patients undergoing SVR. Di Donato and coworkers [62] postulated that SVR alone can significantly reduce ischemic functional MR, which is a result of distorted ventricular geometry and increased distance between the papillary muscles. However, Klein and associates [90] also suggested that MVS might be needed in cases of moderate to severe MR in order to achieve a survival benefit and low MR recurrence rates. No survival benefit of adding MVS to SVR could be identified in this study. This agrees

with currently available evidence. A meta-analysis of 11 studies did not show additional functional or survival benefits when adding valve repair to CABG in patients with moderate ischemic functional MR [91]. This was confirmed by Di Donato group for patients with mild preoperative MR undergoing SVR [62].

In this study, adverse events occurred more often in the perioperative period in the MVS group patients (16.7% vs. 6.5%,  $p=0.046$ ), and the survival after discharge from the hospital was reduced, although not statistically significant (81.7% vs. 61% in the MVS group at 3 years,  $p=0.064$ ). Significant early mortality remains problematic when dealing with concomitant MVS in SVR. Interestingly, 13 endpoints occurred during the first postoperative year after the operation in the MVS group, but no events occurred in the following 2 years. These results are similar to those of recent studies: In a large cohort of patients reported by Menicanti et al. [38], an operative mortality of 13% in patients undergoing concomitant MVS compared with 3% in patients without valve surgery was observed. Increased early mortality was observed in a study of patients undergoing SVR with concomitant intraventricular papillary muscle imbrication without a mitral ring [69], with operative mortality at 15% and a 1-year survival of 62.7%. Reporting similar operative mortality in patients undergoing SVR and concomitant MVS, Jeganathan and coworkers [92] suggested that in high-risk patients with a baseline LVEDD>65 mm, LVESVI>100 ml/m<sup>2</sup>, and extensive regions of non-viable myocardium, heart transplantation or LVAD should be considered as alternatives. In a systematic review of 62 SVR studies, concomitant MVS was associated with an increased risk of early and late mortality [52]. It should be noted that the ventricle is already larger in patients eligible to MVS than in other LVA patients and that heart failure is highly symptomatic due to substantial MR. This makes the procedure high-risk, especially considering extended clamp and perfusion time (one of the predictors of in-hospital mortality in our study) required to perform MVS. However, once the target LVESVI<55 mL/m<sup>2</sup> can be achieved, the results are excellent. The findings of this study show no clear survival benefit in patients undergoing concomitant MVS, with a high rate of adverse events observed in the first year after the operation. The interpretation of this finding remains difficult, as patients undergoing MVS are characterized by high-grade MR, a predictor of increased mortality in this study as well as in others [45] [71]. This analysis does not allow for distinguishing between the risks posed by preoperative MR and the MVS itself. However, we identified a group of patients with moderate MR

not receiving MVS and showing good adverse event-free survival. These patients did not differ in preoperative LVESVI, LVEF, CI, and NYHA functional class from patients with mild or no MR. This suggests that moderate MR cannot be considered a definitive indication for MVS, and each case should be reviewed individually under special consideration of the postoperative ventricular function and volumes and the achievable LVESVI.

Residual mild MR, as measured in TTE early after the operation, did not affect the NYHA functional class at follow-up and was not associated with increased mortality (68% vs. 69.6% at 5 years,  $p=0.114$ ); however, there were no cases of significant postoperative MR in this study. Di Donato and coworkers [68] and Barletta et al. [93] proposed ignoring mild and even moderate MR after the SVR, as it was often a result of the surgery and did not have an impact on the survival at the late follow-up. This is an interesting finding, as even light MR was found to be an independent predictor of post-MI cardiovascular mortality in the Survival and Ventricular Enlargement Study [94]. These findings once again suggest that the ventricular pathology is of utmost importance and should be the primary target of surgical correction, while MR is likely to be stabilized by the normalization of the ventricular geometry.

In conclusion, based on the results of this study, no definitive statement on the role of concomitant MVS in patients undergoing SVR can be made. Each case should be reviewed individually based on pre- and intraoperative imaging, as the morphology of MR can be very different in dilated ventricles. MVS appears to be associated with an increased rate of adverse events early after the operation, and thus careful consideration is required before adding it to SVR. It can be postulated that, in SVR patients, the main focus should be on the LVESVI reduction, and the decision to perform MVS should be made individually in cases of significant ventricular and annular dilation as well as papillary muscle dysfunction.

#### **4.10. Study limitations**

This study has all known limitations of a retrospective non-randomized study.

Prediction in the setting of ischemic cardiomyopathy is difficult due to the interplay of different factors influencing each other. The extent of akinesia/dyskinesia, amount of



residual viable myocardium, valvular pathology, coronary status, clinical symptoms, and comorbidities can vary greatly in patients. To account for all these characteristics, extensive statistical modeling and large cohorts of patients are needed. Prospective trials are required for a more controlled patient selection. As discussed in detail in Chapter 1.6, the STICH trial only partially met this goal.

Another limitation of this study is that the ventricles were assessed early after the operation, when reverse remodeling is the result of immediate surgical volume reduction. To understand the adaptive changes of the remote zones of the ventricle and possible redilatation mechanisms, repeated studies with sufficient time intervals are needed. These data would possibly help identify a different set of predictors of failed reverse remodeling. Another limitation of this study is survivor bias, as MSCT was only performed in patients without major preoperative or in-hospital complications, thus limiting the identification of morphological predictors in this group of sicker patients.

Detecting cut-offs in relatively small databases represents a major statistical problem. After identifying significant predictors, cut-offs should be calculated using larger databases and validated in real-world populations.

Because of the study's retrospective nature, missing data was a major issue. As the data was not missing at random, no methods of multiple imputation could be used and the cases with missing data were removed from the statistical analysis.

Furthermore, in this study operative results of a single center with extensive experience are presented, but they may differ in the setting of clinics in which SVR is performed rarely.

#### **4.11. Research outlook**

The results of this study as well as other research results of our group (Solowjowa et al. [34], Penkalla et al. [95], Saito et al. [96], Solowjowa et al. [86], Nemchyna et al. [20]) demonstrate that MSCT and 2D speckle-tracking echocardiography represent excellent diagnostic tools for the preoperative and postoperative assessment. Furthermore, both proved to be useful predictors of outcome in patients planned for SVR and should continue to be integrated in clinical decision-making for SVR.

Artificial intelligence algorithms in the form of deep learning that integrate multimodal data sources and hybrid methodologies [97] will enable improved characterization, modeling, and virtual treatment of individual patients, thereby optimizing the surgical and interventional procedure and predicting outcome on a patient-by-patient basis.

#### **4.12. Summary of major study findings**

This study showed a good long-term survival and acceptable operative mortality in patients undergoing SVR. A significant survival benefit at 5-year follow-up compared to predicted survival in heart failure patients treated with conservative therapy could be demonstrated.

In most patients improvement of functional parameters and significant volume reduction were achieved, followed by a decrease in the NYHA functional class at early follow-up and sustained improvement of heart failure symptoms at late follow-up.

An extended operative perfusion time was the most significant predictor of in-hospital mortality. Preoperative predictors of an adverse outcome (all-cause mortality, left ventricular assist device implantation, and heart transplantation) were diabetes, glomerular filtration rate, LVEDD, and MR grade measured by transthoracic echocardiography. Preoperative LVESVI as measured by MSCT did not influence the survival following SVR.

Postoperative LVESVI, however, was the only postoperative predictor of an adverse event-free survival. A postoperative LVESVI  $\leq 55$  mL/m<sup>2</sup> should be considered the main surgical target. For every 10 mL/m<sup>2</sup> increase in postoperative LVESVI, the probability to suffer from an adverse event increased by 20%.

When the localization of the aneurysm was limited to the antero-apical region, a favorable outcome was observed. In cases of additional involvement of basal segments, an adverse outcome was common.

MSCT imaging was employed to assess myocardial scarification, aneurysm localization, ventricular geometry, and possible volumetric reduction. To the best of my knowledge, this is the first study of such extent, involving pre- and postoperative MSCT

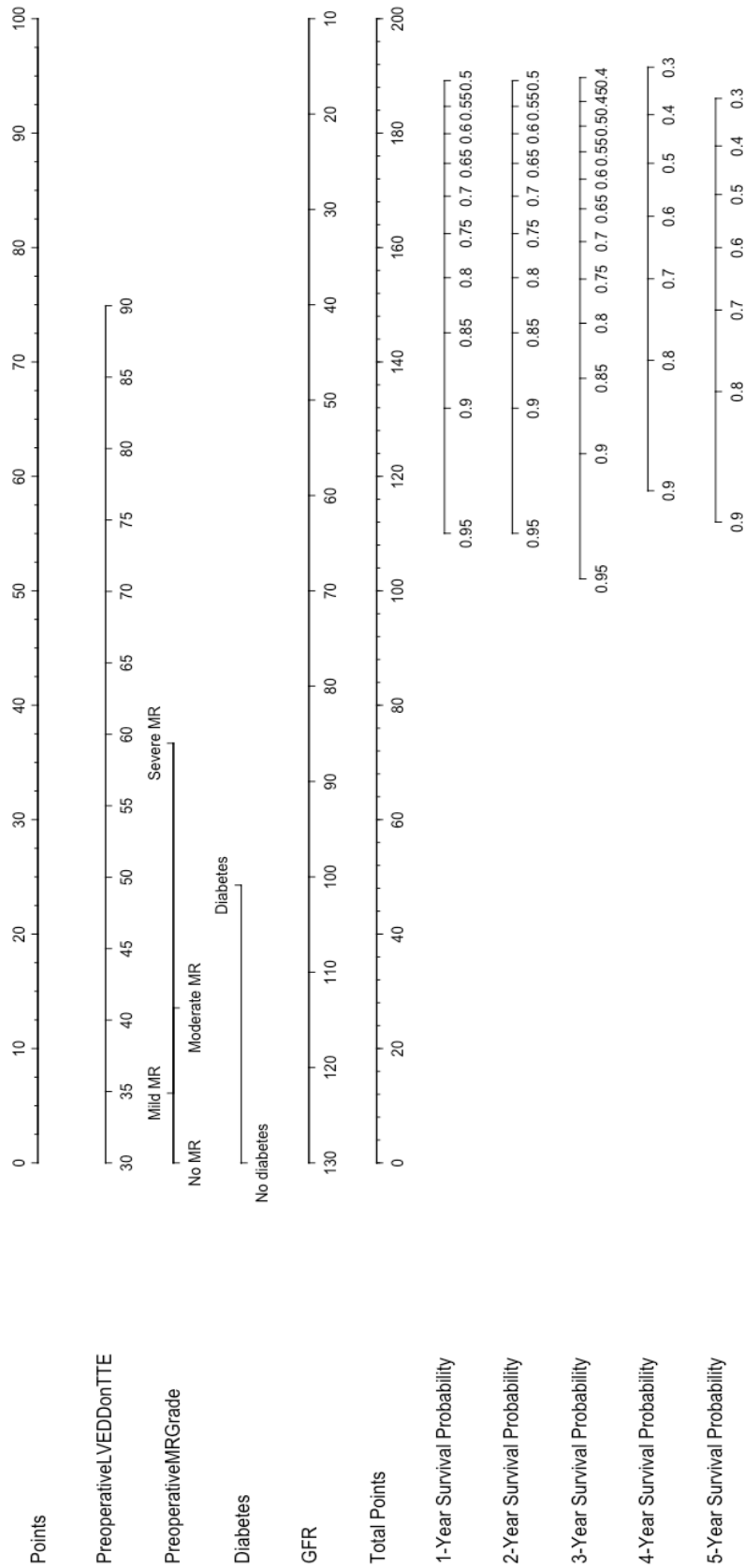
assessment in patients undergoing SVR. Based on the findings of this study, preoperative MSCT imaging is recommended for planning the best surgical strategy.

No survival or functional difference was observed between patients receiving concomitant CABG and patients in whom revascularization was not performed.

The MR grade decreased significantly in all patients undergoing SVR. However, increased early mortality was observed in patients undergoing concomitant mitral valve repair due to moderate to severe MR. No definitive statement on the necessity of concomitant MVS could be made based on the findings of this study and an individual assessment is required in each case. Trivial residual MR following SVR does not influence survival.

## 5. Appendix

**Figure A.** Nomogram of adverse event–free survival in patients undergoing SVR.



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## 7. Affidavit

### Eidesstattliche Versicherung

„Ich, Yuriy Hrytsyna, versichere an Eides statt durch meine eigenhändige Unterschrift, dass ich die vorgelegte Dissertation mit dem Thema:

#### **Predictors of early and late survival after surgical ventricular restoration of antero-apical left ventricular aneurysms**

selbstständig und ohne nicht offengelegte Hilfe Dritter verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel genutzt habe.

Alle Stellen, die wörtlich oder dem Sinne nach auf Publikationen oder Vorträgen anderer Autoren/innen beruhen, sind als solche in korrekter Zitierung kenntlich gemacht. Die Abschnitte zu Methodik (insbesondere praktische Arbeiten, Laborbestimmungen, statistische Aufarbeitung) und Resultaten (insbesondere Abbildungen, Graphiken und Tabellen) werden von mir verantwortet.

[Für den Fall, dass Sie die Forschung für Ihre Promotion ganz oder teilweise in Gruppenarbeit durchgeführt haben:] Ich versichere ferner, dass ich die in Zusammenarbeit mit anderen Personen generierten Daten, Datenauswertungen und Schlussfolgerungen korrekt gekennzeichnet und meinen eigenen Beitrag sowie die Beiträge anderer Personen korrekt kenntlich gemacht habe (siehe Anteilserklärung). Texte oder Textteile, die gemeinsam mit anderen erstellt oder verwendet wurden, habe ich korrekt kenntlich gemacht.

Meine Anteile an etwaigen Publikationen zu dieser Dissertation entsprechen denen, die in der untenstehenden gemeinsamen Erklärung mit dem/der Erstbetreuer/in, angegeben sind. Für sämtliche im Rahmen der Dissertation entstandenen Publikationen wurden die Richtlinien des ICMJE (International Committee of Medical Journal Editors; [www.icmje.org](http://www.icmje.org)) zur Autorenschaft eingehalten. Ich erkläre ferner, dass ich mich zur Einhaltung der Satzung der Charité – Universitätsmedizin Berlin zur Sicherung Guter Wissenschaftlicher Praxis verpflichte.

Weiterhin versichere ich, dass ich diese Dissertation weder in gleicher noch in ähnlicher Form bereits an einer anderen Fakultät eingereicht habe.

Die Bedeutung dieser eidesstattlichen Versicherung und die strafrechtlichen Folgen einer unwahren eidesstattlichen Versicherung (§§156, 161 des Strafgesetzbuches) sind mir bekannt und bewusst.“

Datum

Unterschrift

## Anteilserklärung an etwaigen erfolgten Publikationen

Yuriy Hrytsyna hatte folgenden Anteil an den folgenden Publikationen, die im Zusammenhang mit seiner Promotion entstanden:

### Abstract 1:

Solowjowa N, Nemchyna O, Hrytsyna Y, Meyer A, Pasic M, Falk V, Knosalla CH, Cardiac computed tomography for therapy targeting in surgical repair of anteroapical left ventricular aneurysms: assessment of aneurysm volume and of anticipated residual left ventricular volume. In: European Heart Journal - Cardiovascular Imaging, Volume 22, Issue Supplement 1, January 2021

- Erfassung von Daten und Erstellung der Datenbank
- Statistische Analyse und Interpretation der Daten

### Abstract 2:

Nemchyna O, Dandel M, Solowjowa N, Hrytsyna Y, Stein J, Soltani S, Knierim J, Felix S, Falk V, Knosalla C. Strain Study in Patients after Surgical Ventricular Repair: Prognostic Role of Strain Parameters and Evaluation of Left-Ventricle Remodeling. In: Thoracic and Cardiovascular Surgeon; 2020. p. S9-10.

- Erfassung von Daten und Erstellung der Datenbank
- Statistische Analyse und Interpretation der Daten

### Abstract 3:

Solowjowa N, Nemchyna O, Hrytsyna Y, Meyer A, Pasic M, Falk V, Knosalla C. Repair of Anteroapical Left Ventricular Aneurysms Guided by Use of Cardiac Computed Tomography: Assessment of Aneurysm Volume and of Anticipated Residual Left Ventricular Volume. In: Thoracic and Cardiovascular Surgeon; 2020. p. S34.

- Erfassung von Daten und Erstellung der Datenbank
- Statistische Analyse und Interpretation der Daten

### Abstract 4:

Solowjowa N, Nemchyna O, Hrytsyna Y, Meyer A, Pasic M, Falk V, Knosalla C. Surgical Repair of Anteroapical Left Ventricular Aneurysms guided by Cardiac Computed Tomography: Assessment of Aneurysm Volume and of Anticipated Residual Left Ventricular Volume. In: Clinical Research in Cardiology; 2020. p. P1550.

- Erfassung von Daten und Erstellung der Datenbank
- Statistische Analyse und Interpretation der Daten

Abstract 5:

Solowjowa N, Hrytsyna Y, Meyer A, Pasic M, Falk V, Knosalla C.

Survival determinants and improvement of heart failure symptoms after surgical repair of anteroapical left ventricular aneurysms guided with multislice computed tomography.

47th Annual Meeting of the German Society for Thoracic and Cardiovascular Surgery (DGTHG), Leipzig, 17.-20.02.2018.

In: Thoracic and Cardiovascular Surgeon 2018;66(Suppl. 2):S97.

- Erfassung von Daten und Erstellung der Datenbank
- Statistische Analyse und Interpretation der Daten

Abstract 6:

Solowjowa N, Hrytsyna YY, Meyer AM, Pasic M, Falk V, Knosalla C.

Surgical Repair of Anteroapical Left Ventricular Aneurysms Guided with Multislice Computed Tomography: Survival Determinants and Improvement of Heart Failure Symptoms.

In: Abstractbook of the 54th Annual Meeting of the Society of Thoracic Surgeons; 2018 Jan 27-31; Fort Lauderdale, Florida; 2018: 192.

- Erfassung von Daten und Erstellung der Datenbank
- Statistische Analyse und Interpretation der Daten

Abstract 7:

Solowjowa N, Meyer A, Hrytsyna Y, Pasic M, Falk V, Knosalla C.

Mitral Valve Reverse Remodeling after Surgical Repair of Acquired Left Ventricular Aneurysms of Posterior versus Anterior Localization Assessed with Multislice Computed Tomography.

EuroEcho Imaging 2017. 21th Annual Meeting of the European Association of Echocardiography, Lisbon, Portugal, 06.-09.12.2017.

In: European Heart Journal Cardiovascular Imaging 2017;18(Suppl 3):iii232 (P977).

- Erfassung von Daten und Erstellung der Datenbank
- Statistische Analyse und Interpretation der Daten

Abstract 8:

Solowjowa N, Penkalla A, Hrytsyna Y, Pasic M, Falk V, Knosalla C.

Reverse remodeling of mitral valve apparatus after surgical repair of acquired left ventricular aneurysms of posterior versus anterior localization assessed with multislice computed tomography.

46th Annual Meeting of the German Society for Thoracic and Cardiovascular Surgery (DGTHG), Leipzig, 11.-14.02.2017.

Thoracic and Cardiovascular Surgeon 2017;65(Suppl 1):S63.

- Erfassung von Daten und Erstellung der Datenbank
- Statistische Analyse und Interpretation der Daten

Abstract 9:

Solowjowa N, Hrytsyna Y, Dandel M, Pasic M, Falk V, Knosalla C.  
Repair of anteroapical left ventricular aneurysms guided with multislice computed tomography: update of single center experience.  
82. Jahrestagung der Deutschen Gesellschaft für Kardiologie – Herz- und Kreislaufforschung e.V., Mannheim, 30.03.-02.04.2016.  
In: Clinical Research in Cardiology 2016;105(Suppl 1):P1830.

- Erfassung von Daten und Erstellung der Datenbank
- Statistische Analyse und Interpretation der Daten

Abstract 10:

Solowjowa N, Musayeva L, Hrytsyna Y, Knosalla C, Falk V.  
Functional anatomy of the mitral valve and left ventricle in ischemic mitral regurgitation assessed with multislice computed tomography.  
45th Annual Meeting of the German Society for Thoracic and Cardiovascular Surgery, Leipzig, Germany, 13.-16.02.2016.  
In: Thoracic and Cardiovascular Surgeon 2016;64(Suppl 1):S65.

- Erfassung von Daten und Erstellung der Datenbank
- Statistische Analyse und Interpretation der Daten

Abstract 11:

Solowjowa N, Musayeva L, Hrytsyna Y, Knosalla C, Falk V.  
Functional anatomy of the mitral valve-left ventricle complex in patients with ischemic cardiomyopathy as assessed with multislice computed tomography: characteristics associated with mitral regurgitation.  
Annual Scientific Meeting of the International Society for Minimally Invasive Cardiothoracic Surgery (ISMICS), Berlin, Germany, 03.-06.06.2015.  
Innovations: Technology and Techniques in Cardiothoracic and Vascular Surgery 2015;10(2S):S21-22.

- Erfassung von Daten und Erstellung der Datenbank
- Statistische Analyse und Interpretation der Daten

Abstract 12:

Solowjowa N, Musayeva L, Hrytsyna Y, Knosalla C, Falk V.  
Potential of multislice computed tomography in assessment of functional anatomy of the mitral valve and left ventricle in ischemic mitral regurgitation.  
19th Annual Meeting of the European Association of Cardiovascular Imaging (EACVI), Seville, Spain, 02.-05.12.2015.  
European Heart Journal Cardiovascular Imaging 2015;16(Suppl 2):ii166.

- Erfassung von Daten und Erstellung der Datenbank
- Statistische Analyse und Interpretation der Daten



## **8. Curriculum Vitae**

Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht.

## 9. List of Publications

### Articles

1. Hrytsyna Y, Kneissler S, Kaufmann F, Müller M, Schoenrath F, Mulzer J, Sündermann SH, Falk V, Potapov E, Knierim J. Experience with a standardized protocol to predict successful explantation of left ventricular assist devices. In: Journal of Thoracic and Cardiovascular Surgery. 2021: first published online Jan 9
2. Nemchyna O, Soltani S, Solowjowa N, Schoenrath F, Hrytsyna Y, Unbehaun A, Kempfert J, Stein J, Knosalla C, Hagendorff A, Knebel F, Falk V, Knierim J. Validity of visual assessment of aortic valve morphology in patients with aortic stenosis using two-dimensional echocardiography (Olena Nemchyna and Sajjad Soltani contributed equally to first authorship). In: Int J Cardiovasc Imaging 2020: first published online Oct 11.

### Abstracts

1. Solowjowa N, Nemchyna O, Hrytsyna Y, Meyer A, Pasic M, Falk V, Knosalla CH, Cardiac computed tomography for therapy targeting in surgical repair of anteroapical left ventricular aneurysms: assessment of aneurysm volume and of anticipated residual left ventricular volume. In: European Heart Journal - Cardiovascular Imaging, Volume 22, Issue Supplement 1, January 2021
2. Nemchyna O, Dandel M, Solowjowa N, Hrytsyna Y, Stein J, Soltani S, Knierim J, Felix S, Falk V, Knosalla C. Strain Study in Patients after Surgical Ventricular Repair: Prognostic Role of Strain Parameters and Evaluation of Left-Ventricle Remodeling. In: Thoracic and Cardiovascular Surgeon; 2020. p. S9-10.
3. Solowjowa N, Nemchyna O, Hrytsyna Y, Meyer A, Pasic M, Falk V, Knosalla C. Repair of Anteroapical Left Ventricular Aneurysms Guided by Use of Cardiac Computed Tomography: Assessment of Aneurysm Volume and of Anticipated Residual Left Ventricular Volume. In: Thoracic and Cardiovascular Surgeon; 2020. p. S34.
4. Solowjowa N, Nemchyna O, Hrytsyna Y, Meyer A, Pasic M, Falk V, Knosalla C. Surgical Repair of Anteroapical Left Ventricular Aneurysms guided by Cardiac Computed Tomography: Assessment of Aneurysm Volume and of Anticipated Residual Left Ventricular Volume. In: Clinical Research in Cardiology; 2020. p. P1550.

5. Solowjowa N, Hrytsyna Y, Meyer A, Pasic M, Falk V, Knosalla C.  
Survival determinants and improvement of heart failure symptoms after surgical repair of anteroapical left ventricular aneurysms guided with multislice computed tomography.  
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In: Thoracic and Cardiovascular Surgeon 2018;66(Suppl. 2):S97.
6. Solowjowa N, Hrytsyna YY, Meyer AM, Pasic M, Falk V, Knosalla C.  
Surgical Repair of Anteroapical Left Ventricular Aneurysms Guided with Multislice Computed Tomography: Survival Determinants and Improvement of Heart Failure Symptoms.  
In: Abstractbook of the 54th Annual Meeting of the Society of Thoracic Surgeons; 2018 Jan 27-31; Fort Lauderdale, Florida; 2018: 192.
7. Solowjowa N, Meyer A, Hrytsyna Y, Pasic M, Falk V, Knosalla C.  
Mitral Valve Reverse Remodeling after Surgical Repair of Acquired Left Ventricular Aneurysms of Posterior versus Anterior Localization Assessed with Multislice Computed Tomography.  
EuroEcho Imaging 2017. 21th Annual Meeting of the European Association of Echocardiography, Lisbon, Portugal, 06.-09.12.2017.  
In: European Heart Journal Cardiovascular Imaging 2017;18(Suppl 3):iii232 (P977).
8. Solowjowa N, Penkalla A, Hrytsyna Y, Pasic M, Falk V, Knosalla C.  
Reverse remodeling of mitral valve apparatus after surgical repair of acquired left ventricular aneurysms of posterior versus anterior localization assessed with multislice computed tomography.  
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In: Thoracic and Cardiovascular Surgeon 2017;65(Suppl 1):S63.
9. Solowjowa N, Hrytsyna Y, Dandel M, Pasic M, Falk V, Knosalla C.  
Repair of anteroapical left ventricular aneurysms guided with multislice computed tomography: update of single center experience.  
82. Jahrestagung der Deutschen Gesellschaft für Kardiologie – Herz- und Kreislaufforschung e.V., Mannheim, 30.03.-02.04.2016.  
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10. Solowjowa N, Musayeva L, Hrytsyna Y, Knosalla C, Falk V.  
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In: European Heart Journal Cardiovascular Imaging 2015;16(Suppl 2):ii166.

## 10. Acknowledgements

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