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Insights in heart surgery 2022

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Insights in heart surgery: 2022

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Table of contents

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Editorial: Insights in heart surgery: 2022

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advances and challenges, insight and practice, innovation, coronary revascularization surgery, valve repair and replacement, aortic surgery, HOCM

Editorial on the Research Topic
Insights in heart surgery: 2022

Cardiac surgery continues to evolve over the years beyond current challenges, technologies, and "traditional" outcomes. This collection of articles "Insights into cardiac surgery" aims to highlight the latest advances in the field of cardiac surgery achieved during 2022.

Surgical approaches in cardiac surgery experienced a tremendous evolution in the last two decades. A lot of changes happened since the first operation performed by Goldwin et al. in 1958 (1) to treat hypertrophic obstructive cardiomyopathy (HOCM), including the advent of the Bentall technique for aortic root pathology, and the first coronary aortic bypass grafting (CABG), which today is the most commonly cardiac surgery procedure performed worldwide.

Different approaches have been previously described to treat HOCM (2). Raffa et al. introducing a method with the involvement of the subvalvular mitral apparatus [resection of anomalous muscular trabecula, accessory papillary muscles (PM), secondary chordae, and splitting of PM], showed excellent results including freedom from repeat intervention of 96% and significant symptomatic relief with NYHA and left ventricular obstruction reduction during midterm follow-up as well as a reduction in terms of mitral valve regurgitation incidence and septal thickness.

On the other hand, among aortic root repair strategies, Chang et al. suggested in case of pathological features of dissection, a sinus replacement technique using a patch trimmed to a scallop shape similar to Valsalva sinus, aiming to decrease severe aortic root bleeding. However, a cornerstone like the Bentall procedure created a race on describing the benefits of the modified technique in large clinical studies (3–5). In this context, Werner et al. closed the gap regarding long-term outcomes in patients undergoing the modified Bentall technique operation evidencing comparable results at 10-year follow-up with those of the general population. In this cohort of patients, the prosthesis choice in the so-called "gray area" (50–70 years old) is still controversial. Certainly, the advancement of transcatheter procedures (TAVR) with valve-in-valve aortic replacement and even the stentless valve prostheses, should be considered in the need of a reintervention (6) such as in the case of a "matryoshka procedure" (7). As a matter of fact, Chan et al. for aortic

valve replacement (SAVR), underlined that the use of biological aortic prostheses has increased significantly in recent years in all age groups while mechanical valves are still higher in patients requiring dialysis. Although SAVR is an effective treatment with very low in-hospital mortality, in the last years, SAVR's rate is reducing especially in patients with high risk, octogenarians, and those requiring redo surgery due to the advent of TAVR.

Despite the spread-out of percutaneous coronary revascularization (PCI) CABG remains the most common cardiac surgery procedure worldwide and the best option for multivessel disease to achieve complete revascularization. Pasierski et al. highlight the importance of complete revascularization even in patients with pre-existing AF showing improved long-term survival and a lower rate of reinterventions. The advent of new technologies for CABG has been shown to be a benefit in improving the outcomes and increasing the heterogeneity of the patients. In this context, grafts' availability is undoubtedly the first component needed to perform a CABG. In case of the lack of suitable autologous bypass material, Fusco et al. describe tissue-engineered vascular grafts (20 cm in length with an inner diameter of 3 mm) tested in animal models that showed good patency after 4 weeks.

Achieved the best available grafts, even their storage during the procedure, become crucial. Szalkiewicz et al. compare the use of saline with autologous blood vs. a preventive solution formulated with an endothelial damage inhibitor. The use of the second solution in the saphenous vein storage and testing during distal anastomosis has been described to be associated with lower levels of troponin after the procedure demonstrating superiority in preserving tissue functionality.

Beyond the surgical technique, in the current clinical practice, periprocedural risk predictors and optimization of medical therapy become fundamental before surgery to achieve a good outcome and to offer a tailored patient approach (8). For example, after tricuspid valve surgery (TVS) mortality remains high. In this particular group of patients, periprocedural risk predictors that impact long-term prognosis have not been fully investigated yet. Hasimbegovic et al. set the tone and paved the pathway to the adjustment of pre-procedural secondary prevention and optimization of medical therapy in patients undergoing TVS. Their "real world" study evidenced how patients with a high estimated plasma volume status (ePVS) have a significant impact on long-term outcomes after TVS. In this context, the author reported that the ePVS and Duarte's PVC were significantly lower in survivors. Risk predictors for long-term prognosis also included ePVS and gamma-glutamyltransferase levels.

Now more than ever, cardiovascular surgery feels the need to set a balance between adequate pre-operative patient medical optimization, the correct surgical procedure based on individual patient profiles, and the desire of treating complex conditions pushing forward the boundaries of the achievable. All of the articles in this Collection inspire, inform, and provide guidance and direction to researchers in the field, and could help us understand where cardiac surgery is going.

In conclusion, even if technology progresses by leaps and bounds significantly influencing surgical techniques and results, we must keep in mind that clinical success can be achieved only by multidisciplinary teamwork that adapts the chosen surgical strategy to the specific clinical profile of the individual patient.

Author contributions

MB, FC, BB, HTS, RJC and AD contributed to conception and design of the study. MB, BB, and AD wrote the first draft of the manuscript. MB, FC, BB, and AD wrote the second draft of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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ORIGINAL RESEARCH
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Deviations From the Ideal Plasma Volume and Isolated Tricuspid Valve Surgery—Paving the Way for New Risk Stratification Parameters

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Background: Congestion and plasma volume expansion are important features of heart failure, whose prognostic significance has been investigated in a range of surgical and non-surgical settings. The aim of this study was to evaluate the value of the estimated plasma volume status (ePVS) in patients undergoing isolated tricuspid valve surgery.

Methods: This study included patients who underwent isolated tricuspid valve surgery at the Vienna General Hospital (Austria) between July 2008 and November 2018. The PVS cut-off was calculated using ROC analysis and Youden's Index.

Results: Eighty eight patients (median age: 58 [IQR: 35-70] years; 44.3% male; 75.6% NYHA III/IV; median EuroSCORE II 2.65 [IQR: 1.70-5.10]; 33.0% endocarditis-related regurgitation; 60.2% isolated repair; 39.8% isolated replacement) were included in this study. Patients who died within 1 year following surgery had significantly higher baseline ePVS values than survivors (median ePVS 5.29 [IQR: −1.55-13.55] vs. −3.68 [IQR: −10.92-4.22]; $p = 0.005$). During a median actuarial follow-up of 3.02 (IQR: 0.36-6.80) years, patients with a preoperative ePVS ≥ -4.17 had a significantly increased mortality (log-rank $p = 0.006$).

Conclusions: ePVS is an easily obtainable risk parameter for patients undergoing isolated tricuspid valve surgery capable of predicting mid- and long-term outcomes after isolated tricuspid valve surgery.

Keywords: congestion, plasma volume status, tricuspid valve, isolated tricuspid valve surgery, mortality

INTRODUCTION

The prevalence of heart failure and acute decompensated heart failure in patients undergoing isolated tricuspid valve surgery is high, and its presence is associated with poor outcomes (1–3). Isolated tricuspid valve surgery is a comparatively rare procedure with a high mortality (1, 4–9). Due to the low overall number of isolated

tricuspid valve surgeries performed yearly, specific risk stratification parameters have not been explored as thoroughly as those in other types of cardiac surgery. Similarly, the relevance of noninvasive laboratory indicators of congestion has not been assessed in this patient collective. In this paper, we attempted to evaluate one such index, the estimated plasma volume status, for the risk stratification of patients undergoing isolated tricuspid valve surgery.

Congestion and volume overload, the hallmark features of heart failure, affect both the interstitial and the plasma space and develop gradually, with an initially asymptomatic clinical course. However, ultimately the majority of patients presenting with decompensated heart failure exhibit clinical signs of congestion (10, 11). The degree to which diuretic therapy affects congestion differs between the interstitial and intravascular compartments, which limits the usefulness of a mere weight-based assessment for tracking the success of in-hospital volume management of decompensated patients with heart failure (12, 13).

Although methods for assessing the degree of intravascular congestion via pressure measurement in the right atrium or the assessment of the pulmonary capillary wedge pressure are available, their invasiveness limits their applicability in day-to-day practice and they are thus mainly reserved for specific high-risk settings (10). Surrogate markers for the assessment of the intravascular volume overload, such as the brain natriuretic peptide (BNP), secreted in response to mechanical stretching of the cardiomyocytes in a volume overloaded left ventricle, have long been used to diagnose, assess the severity of and guide treatment of heart failure (14). The current gold standard for the direct measurement of the plasma volume is the nuclear medicine blood volume assessment. This set of methods is based on the injection of a tracker substance, followed by blood sampling to determine its dilution and subsequently extrapolate the dilution volume. Such dilution-based methods, albeit with the use of rudimentary dyes, were conducted as early as one century ago, but the time-consuming nature, the required expertise and their susceptibility to measurement errors have impeded their wider implementation (15–17). However, recent technical advances have resolved some of these issues and might make such techniques more useful in the emergency and other settings in the future (18).

Multiple methods use the patient's weight, hematocrit or hemoglobin for the non-invasive assessment of the plasma volume status (PVS), such as the Strauss, Duarte and Hakim formula (19–21). The correlation of these calculated estimates with symptoms and diagnostic markers of congestion has not been sufficiently elucidated, although initial findings have proposed some correlations with imaging modalities (22). In recent years, several studies have found compelling evidence for the prognostic value of the estimated PVS in cardiovascular disease. Duarte et al. found that PVS can predict the likelihood of early cardiovascular events following acute myocardial infarction with acute heart failure (20). Martens et al. found that PVS correlates with the measured plasma volume assessed by technetium red blood cell labeling and predicts overall mortality and heart-failure related hospitalization in a large cohort of patients with different etiologies of heart failure (23). Kobayashi et al. undertook an extensive assessment of Duarte's PVS in heart failure with a preserved ejection fraction (HFpEF) and found that it had a high prognostic value for adverse events, accurately reflected the degree of congestion, was not significantly impacted by renal function and could enhance existing risk stratification accuracy in conjunction with other established parameters (24). Similarly promising results for the use of PVS for risk stratification of HFpEF patients were also described by Huang et al. and Grodin et al. (25, 26). Tamaki et al. followed a group of patients admitted for acute decompensated heart failure and found that the plasma volume status correlated with overall mortality and rehospitalization for decompensated heart failure, findings similar to those of Yoshihisa et al. (27, 28). The value of PVS for risk stratification has been examined for a range of other applications, including left ventricular assist device (LVAD) recipients, coronary artery bypass grafting (CABG) or acute respiratory distress syndrome (ARDS) (29–31). Several studies have also looked at the potential of PVS for outcome and mortality prediction in patients undergoing interventions for valvular disease. A large-scale study of patients who underwent transcatheter aortic valve replacement (TAVR) by Shimura et al. found a link between a combined PVS and NYHA class stratification and mortality, as well as heart-failure-related rehospitalization (32). The association of PVS with outcomes following TAVR was also demonstrated by Seoudy et al. (33). A study by Schaefer et al. examined the association between PVS and mortality following mitral valve surgery (34).

However, the possible link between the calculated PVS and mortality following tricuspid valve surgery has not yet been explored. Thus, with this study we aimed to examine a possible link between the calculated PVS as a surrogate marker of congestion and the survival of patients undergoing isolated tricuspid valve surgery.

METHODS

Patient Selection and Preoperative Evaluation

For this study, data from 88 consecutive patients who underwent isolated tricuspid valve surgery at the Department of Cardiac Surgery, Medical University of Vienna between July 2008 and November 2018 was retrospectively analyzed. The isolated tricuspid valve surgery was conducted according to standard institutional operating procedure and the internal guidelines of the Division of Cardiac Surgery, Medical University of Vienna.

The preoperative patient assessment included a measurement of body weight, height, and standard laboratory tests. The etiology and degree of tricuspid valve regurgitation or tricuspid valve disease, as well as the presence of active endocarditis were recorded. A detailed patient history including comorbidities, risk factors, substance abuse and previous cardiac surgeries was collected. In accordance with routine practice, the EuroSCORE II and NYHA class were assessed.

This study was approved by the Ethics Committee of the Medical University of Vienna and was conducted in accordance

with the 1964 Declaration of Helsinki, as well as its later amendments, and did not receive any funding (EK: 1289/2019).

Plasma Volume Equations

The preoperative PVS values were calculated according to two separate formulae using the patient's weight, hemoglobin, and hematocrit.

First, the actual plasma volume (aPV) was calculated using the Hakim formula (19):

$$aPV = (1 - hematocrit) \times [a + (b \times weight)]$$

where hematocrit is given as a fraction and the weight refers to the weight in kilograms. The coefficient a has a value of 864 for female and 1,530 for male patients and the coefficient b has a value of 47.9 for female and 41.0 for male patients.

The ideal plasma volume (iPV) was calculated according to the equation previously published by Longo et al. (35):

$$iPV = c \times weight$$

where the weight is stated in kilograms and the coefficient c has a value of 40 for women and 39 for men. The PVS was calculated from the two abovementioned values using the following formula:

$$ePVS = \frac{aPV - iPV}{iPV} \times 100$$

The second method used to assess the plasma volume status was the Duarte formula (20):

$$Duarte's\ PVS = \frac{100 - hematocrit}{hemoglobin}$$

where the hemoglobin is stated in g/dl and the hematocrit is given in percentages.

Follow-Up

All adverse events following the surgery and prior to the patient discharge were internally documented. During the observational period, all visits to the outpatient clinics and inpatient stays from the electronic health record were recorded and analyzed. Information regarding survival of patients was either available within our electronic health record or was separately obtained from the national statistics department (Statistik Austria). The last date of follow-up was recorded as either death or the last documented living visit available within our electronic records. The primary endpoint of this study was the all-cause mortality.

Statistical Analysis

Statistical analyses were performed using the IBM SPSS 27.0 statistics software (SPSS Inc., Armonk, NY, USA) and the figures were created using GraphPad Prism V.8 (GraphPad Software, La Jolla, CA, USA). Continuous variables were reported as either the mean and standard deviation or median and interquartile range depending on their distribution pattern. The presence of a parametric distribution of metric variables was assessed using the Shapiro-Wilk test and visual analysis of the distribution. Categorical variables were recorded as the number of features with the corresponding percentage of patients. Categorical variables were compared using the Chi-square test or the Fisher's exact test. Group comparisons were conducted using either the student's t-test or the Mann-Whitney U-test for normally and non-normally distributed variables, respectively. The correlation between two metric variables was assessed via Spearman correlation coefficients. Survival analyses were performed via the Kaplan-Meier method and log-rank tests. Variables associated with a decreased survival during the follow-up period were identified using univariate and multivariate Cox regression models. Univariate p-values below 0.1 in the univariate analysis were considered for multivariate analysis. Variables not available for more than 5% of patients were not included in the multivariate analysis. Variables featured in the EuroSCORE II, or variables used for the calculation of or directly related to ePVS or Duarte's PVS were excluded from the multivariate analysis. In the multivariate analysis, a stepwise backward approach was applied. The accuracy of PVS in predicting the primary endpoint was examined using ROC-curve analysis based on the prediction of the 1-year mortality. The Youden Index was used to identify an ePVS of −4.17 as the optimal cut-off point. As a secondary analysis, the same procedure was applied to determine the optimal cut-off point for Duarte's PVS, which was found to be 4.79. Subsequently, the ePVS cut-off was used to stratify the patients into two groups (Group 1: ePVS < -4.17 vs. Group 2: ePVS ≥ -4.17). Two-sided p-values of <0.05 were considered statistically significant across the analysis.

RESULTS

Baseline Clinical Characteristics and Laboratory Parameters

A total of 88 patients undergoing isolated tricuspid valve surgery were included in this study. The median age of the patients was 58 years (IQR: 35-70 years), with a median follow-up time of 3.02 (IQR: 0.36-6.80) years. 38 patients (43.2%) had functional tricuspid regurgitation at baseline, whereas one fourth (25.0%) of all patients had active endocarditis at baseline. 19 patients (21.6%) had previously undergone a surgical left heart intervention and 23 patients (26.1%) had a lead passing through the tricuspid valve. One fifth of all patients ($n = 18$ [20.5%]) either had a previous history of intravenous drug use or were active intravenous drug users at baseline. Most patients had NYHA class III/IV ($n = 65$ [75.6%]). A comprehensive overview of the baseline clinical characteristics and risk factors is provided in **Table 1**.

Patients with an ePVS < -4.17 had received prior therapy with beta blockers more frequently ($p = 0.028$), suffered from functional tricuspid regurgitation more frequently than the cohort with an ePVS ≥ -4.17 ($p = 0.004$), exhibited fewer cases of endocarditis-related tricuspid regurgitation ($p = 0.011$), and had a lower prevalence of previous or active intravenous

TABLE 1 | Baseline characteristics of the overall and stratified cohort.

Baseline characteristics	Overall cohort $n = 88$	Group 1 (ePVS < -4.17) $n = 38$	Group 0 (ePVS ≥ -4.17) $n = 50$	*P*-value
Age (years)	58(35-70)	58(44-70)	59(33-70)	0.730
Gender (male)	39 (44.3%)	16 (42.1%)	23 (46.0%)	0.716
Height (cm)	170.0 (161-177)	180 ± 9	170 ± 10	0.830
Weight (kg)	71 (60-85)	80 (62-88)	66 (60-83)	0.074
BMI (kg/m2)	25.3 ± 4.5	26.9 (23.3-29.3)	23.5 (21.4-27.5)	0.038
LVEF (%)	60 (50-60)	60(46-60)	60 (50-60)	0.909
Previous anti-RAAS therapy	25 (28.4%)	12 (31.6%)	13 (26.0%)	0.565
Previous therapy with beta blockers	16 (18.2%)	11 (28.9%)	5 (10.0%)	0.028
sPAP (mmHg)	43(37-75)	43(34-50)	47(37-56)	0.294
Functional tricuspid regurgitation	38 (43.2%)	23 (60.5%)	15 (30.0%)	0.004
Endocarditis-related tricuspid regurgitation	29 (33.0%)	7 (18.4%)	22 (44.0%)	0.011
Tricuspid regurgitation etiology left-side related	15 (19.2%)	6 (18.2%)	9 (20.0%)	1.000
Active endocarditis	22 (25.0%)	3 (7.9%)	19 (38.0%)	0.001
Previous surgical left heart intervention	19 (21.6%)	9 (23.6%)	10 (20.0%)	0.677
Pacemaker/ICD	23 (26.1%)	6 (15.8%)	17 (34.0%)	0.054
Lead through the tricuspid valve	23 (26.1%)	6 (15.8%)	17 (34.0%)	0.054
Hemodynamic instability prior to surgery	4 (4.5%)	0 (0%)	4 (8.0%)	0.130
Any previous intravenous drug use	18 (20.5%)	3 (7.9%)	15 (30.0%)	0.015
Active intravenous drug use	7 (8.0%)	0 (0.0%)	7 (14.0%)	0.018
Any chronic hepatic condition	22 (25.0%)	4 (10.5%)	18 (36.0%)	0.007
Active hepatitis C viral infection	15 (17.0%)	3 (8.6%)	12 (24.0%)	0.084
EuroSCORE II	2.65 (1.70-5.10)	1.91 (1.22-3.71)	3.17 (2.10-6.65)	0.004
Active smoker	13 (14.8%)	4 (10.5%)	9 (18.0%)	0.379
Any previous regular smoking habit	23 (26.1%)	9 (23.7%)	14 (28.0%)	0.648
NYHA class III/IV	65 (75.6%)	24 (64.9%)	41 (83.7%)	0.044
Arterial hypertension	48 (54.5%)	19 (50.0%)	29 (58.0%)	0.455
Diabetes	12 (13.6%)	4 (10.5%)	8 (16.0%)	0.542
Previous myocardial infarction	4 (4.5%)	0 (0%)	4 (8.0%)	0.130
Previous stroke	7 (8.0%)	4 (10.5%)	3 (6.0%)	0.459
Chronic obstructive pulmonary disease	25 (28.4%)	11 (28.9%)	14 (28.0%)	0.922
Chronic kidney disease (GFR < 6 ml/min or renal replacement therapy)	33 (37.5%)	10 (26.3%)	23 (46.0%)	0.059
Ongoing dialysis	5 (5.7%)	1 (2.6%)	4 (8.0%)	0.384
Extracardiac arteriopathy	3 (3.4%)	0 (38.0%)	3 (6.0%)	0.255
Carotid disease	5 (5.7%)	3 (7.9%)	2 (4.0%)	0.648
eGFR (ml/min/1.73 m2)	68.8 (49.0-102.3)	81.2 (52.4-101.1)	63.1 (45.4-105.8)	0.209
Hematocrit (%)	35.9 ± 6.6	41.8 ± 3.2	31.5 ± 4.7	<0.001
Hemoglobin (g/dl)	11.9 ± 2.3	14.0 ± 1.4	10.4 ± 1.6	<0.001
Platelet count (G/l)	200 (155-275)	193 (164-246)	206 (118-287)	0.506
Erythrocyte count (T/l)	4.1 ± 0.8	4.7 ± 0.5	3.6 ± 0.6	<0.001
MCH (pg)	29.6 (27.5-31.1)	30.1 (28.4-31.4)	29.1 (27.3-30.9)	0.212
MCV (fl)	88.4 ± 6.0	89.2 ± 5.3	87.9 ± 6.5	0.304
proBNP (pg/ml)	1,147 (433-1882)	924 (474-1672)	1,480 (400-2,351)	0.183
Creatinine (mg/dl)	1.02 (0.86-1.35)	1,03 (0.91-1.33)	1.01 (0.85-1.40)	0.584
Creatinine kinase (U/l)	48 (31-95)	72 (41-116)	40 (19-65)	<0.001
Alkaline phosphatase (U/l)	112 (79-146)	103 (72-125)	127 (91-172)	0.006

(Continued)

TABLE 1 | Continued

Baseline characteristics	Overall cohort *n* = 88	Group 1 (ePVS < −4.17) *n* = 38	Group 0 (ePVS ≥ −4.17) *n* = 50	*P*-value
ASAT (U/l)	29 (21-41)	32 (22-43)	26 (19-38)	0.156
ALAT (U/l)	23 (17-33)	28 (21-36)	19 (12-28)	0.002
GGT (U/l)	110 (65-178)	109 (51-154)	122 (76-194)	0.259
LDH (U/l)	227 (193-303)	224 (199-289)	229 (174-304)	0.629
CRP (mg/dl)	0.63 (0.20-2.28)	0.33 (0.19-0.81)	1.29 (0.34-7.69)	<0.001
Total bilirubin (mg/dl)	0.87 (0.60-1.23)	0.87 (0.62-1.22)	0.86 (0.58-1.23)	0.860
Albumin (g/l)	40.6 (32.3-44.6)	43.6 (4.8)	34,4(9,0)	<0.001
Total protein (g/l)	73.0 (68.1-78.9)	76.1 (70.8-79.1)	71.2 (64.1-78.7)	0.033

Data is presented as number n (%), mean ± standard deviation (SD) or median (interquartile range). BMI, body mass index; LVEF, left ventricular ejection fraction; RAAS, renin-angiotensin-aldosterone system; sPAP, systolic pulmonary artery pressure; ICD, implantable cardioverter-defibrillator; NYHA, New York Heart Association; GFR, glomerular filtration rate; eGFR, estimated glomerular filtration rate; MCH, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; BNP, brain natriuretic peptide; ASAT, aspartate aminotransferase; ALAT, alanine aminotransferase; GGT, gamma-glutamyl transferase; LDH, lactate dehydrogenase; CRP, C-reactive protein.

TABLE 2 | Procedural characteristics and adverse events.

	Overall cohort *n* = 88	Group 1 (ePVS < −4.17) *n* = 38	Group 0 (ePVS ≥ −4.17) *n* = 50	*P*-value
Redo surgery	31 (35.2%)	14 (36.8%)	17 (34.0%)	0.782
Elective surgery	54 (61.4%)	32 (84.2%)	22 (44.0%)	<0.001
Urgent surgery	30 (34.1%)	6 (15.8%)	24 (48.0%)	0.002
Emergency surgery	4 (4.5%)	0 (0%)	4 (8.0%)	0.130
Cardiopulmonary bypass time (min)	114 (77-140)	127 (92-159)	93 (75-129)	0.041
Isolated tricuspid repair	53 (60.2%)	30 (78.9%)	23 (46.0%)	0.002
Ring annuloplasty	49 (55.7%)	30 (78.9%)	19 (38.0%)	<0.001
Isolated tricuspid replacement	35 (39.8%)	8 (21.1%)	27 (54.0%)	0.002
Sternotomy	77 (92.8%)	30 (88.2%)	47 (95.9%)	0.184
Mini-thoracotomy	6 (7.2%)	4 (11.8%)	2 (4.1%)	0.221
Beating heart surgery	28 (31.8%)	9 (23.7%)	19 (38.0%)	0.153
Blood transfusion required	55 (62.5%)	17 (44.8%)	38 (76.0%)	0.003
Erythrocyte concentrate (units)	1.0 (0.0-3.0)	0.0 (0.0-1.3)	2.0 (1.0-4.3)	<0.001
Postoperative acute kidney injury	6 (6.8%)	1 (2.6%)	5 (10.0%)	0.229
Postoperative renal replacement therapy	4 (4.5%)	1 (2.6%)	3 (6.0%)	0.631
Postoperative pericardial effusion	5 (5.7%)	2 (5.2%)	3 (6.0%)	1.000
Postoperative ECMO support	3 (3.4%)	1 (2.6%)	2 (4.0%)	1.000
New onset atrial fibrillation	9 (10.2%)	4 (10.5%)	5 (10.0%)	1.000
Postoperative pneumonia	3 (3.4%)	1 (2.6%)	2 (4.0%)	1.000
Postoperative stroke	0 (0.0%)	0 (0.0%)	0 (0.0%)	/
Postoperative myocardial infarction	0 (0.0%)	0 (0.0%)	0 (0.0%)	/
Wound complication	7 (8.0%)	2 (5.2%)	5 (10.0%)	0.694
Pulmonary embolism	1 (1.1%)	1 (2.6%)	0 (0%)	0.432
New pacemaker implantation	9 (10.2%)	4 (10.5%)	5 (10.0%)	1.000
Postoperative stay (days)	15(9-23)	12(8-19)	17(10-34)	0.039
Re-exploration for bleeding	12 (13.6%)	4 (10.5%)	8 (16.0%)	0.542
In-hospital death	7 (8.0%)	2 (5.2%)	5 (10.0%)	0.694
1-year death	18 (20.5%)	2 (5.2%)	16 (32.0%)	0.003
Death on last follow-up	34 (38.6%)	9 (23.7%)	30 (60.0%)	<0.001

Data is presented as number n (%), mean ± standard deviation (SD) or median (interquartile range). ECMO, extracorporeal membrane oxygenation.

TABLE 3 | ePVS and Duarte's PVS in survivors and non-survivors.

	ePVS survivors	ePVS non-survivors	*P*-value
1 year	−3.68 (−10.92-4.22)	5.29 (−1.55-13.55)	0.005
Overall follow-up	−4.80 (10.00)	3.04 (12.23)	0.001
	Duarte's PVS survivors	**Duarte's PVS non-survivors**	***P*-value**
1 year	4.84 (4.19-6.77)	6.78 (5.44-7.83)	0.006
Overall follow-up	4.66 (4.17-6.13)	6.02 (4.80-7.72)	0.002

Data is presented as mean ± standard deviation (SD) or median (interquartile range).

drug use ($p = 0.015$ and $p = 0.018$, respectively). The ePVS < -4.17 cohort had a lower EuroSCORE II ($p = 0.004$), a higher baseline hematocrit ($p < 0.001$) and hemoglobin ($p < 0.001$), erythrocyte count ($p < 0.001$) and higher levels of serum albumin ($p < 0.001$).

Surgical Characteristics and Adverse Events

The procedural characteristics and incidence of adverse postoperative events are shown in **Table 2**. Patients with an ePVS < -4.17 underwent elective surgery significantly more often ($p < 0.001$) and urgent surgery significantly less often ($p = 0.002$). These patients also underwent tricuspid repair more often and tricuspid replacement less often than the ePVS ≥ -4.17 group ($p = 0.002$). In terms of postoperative adverse events, the only significant difference between the groups was observed in the need for postoperative blood transfusion, which was required less often in the ePVS < -4.17 group ($p = 0.003$).

ePVS and Duarte's PVS in Survivors and Non-survivors

The difference in ePVS and Duarte's PVS in survivors and non-survivors at two timepoints during follow-up is shown in **Table 3**.

Survivors had a significantly lower ePVS after 1 year following the intervention (median ePVS −3.68 [IQR: −10.92-4.22] vs. 5.29 [IQR: −1.55-13.55], $p = 0.005$), and over the course of the overall follow-up (mean ePVS -4.80 ± 10.00 vs. 3.04 ± 12.23, $p = 0.001$).

Survivors had a significantly lower Duarte's PVS after 1 year following the intervention (median Duarte's PVS 4.84 [IQR: 4.19-6.77] vs. 6.78 [IQR: 5.44-7.83], $p = 0.006$), and over the course of the overall follow-up (median Duarte's PVS 4.66 [IQR: 4.17-6.13] vs. 6.02 [IQR: 4.80-7.72], $p = 0.002$).

There was a significant difference between both ePVS and Duarte's PVS in survivors and non-survivors at 1-year and during the overall follow-up period.

Survival Stratified According to the ePVS and Duarte's PVS Cut-Off

Kaplan-Meier curves illustrating the survival of patients stratified according to the ePVS and Duarte's PVS cut-offs are shown in **Figures 1**, **2**.

Patients with an ePVS of ≥-4.17 and patients with a Duarte's PVS of ≥4.79 had a significantly higher mortality over the follow-up period (median survival ePVS ≥ -4.17: 35.9 (95%CI: 0.0-80.7) months vs. median survival ePVS < -4.17: not reached during follow-up, $p = 0.006$; median survival Duarte's PVS ≥ 4.79: 35.8 (95%CI: 0.0-92.7) months vs. median survival Duarte's PVS ≤ 4.79: not reached during follow-up, $p = 0.007$). The cumulative probability of survival at 1 and 3 years for the ePVS ≥ -4.17 group was 65.9 and 47.7%, respectively, compared to 94.1 and 94.1% for the ePVS < -4.17 group. The cumulative probability of survival at 1 and 3 years for the Duarte's PVS ≥ 4.79 group was 64.7 and 48.6%, respectively, compared to 96.7 and 93.1% for the Duarte's PVS < 4.79 group.

Predictors of Mortality

Detailed results of the univariate and multivariate analysis for predictors of mortality are shown in **Table 4**. Variables included in the multivariate analysis included isolated tricuspid valve replacement, EuroSCORE II, functional regurgitation, alkaline phosphatase levels, gamma-glutamyltransferase levels, CRP, as well as ePVS and Duarte's PVS. Of these variables, only ePVS and gamma-glutamyltransferase reached significance in the multivariate analysis ($p = 0.04$ and $p = 0.027$), whereas EuroSCORE II approached significance ($p = 0.055$).

Additional Considerations: NYHA Class and Renal Function

A significantly higher proportion of patients with ePVS ≥ -4.17 had NYHA class III/IV (83.7 vs. 64.9% in patients with ePVS < -4.17; $p = 0.044$). The median survival was significantly longer in patients with NYHA I/II (log-rank $p = 0.035$), with 1-year and 3-year survival probabilities of 83.6 and 78.0% in NYHA I/II as compared to 74.9 and 63.2% in NYHA III/IV. Following the sub-stratification according to ePVS levels, the individual contribution of both parameters in terms of median survival became clearer (log-rank $p = 0.018$), with a 1-year survival probability of 90.9% in ePVS < -4.17 + NYHAI/II, as compared to 64.1% in ePVS ≥ -4.17 + NYHAIII/IV.

In our study, eGFR ≥ 60 ml/min/1.73 m^2 was not significantly associated with mortality (log-rank $p = 0.790$). Additionally, we found no significant correlation between ePVS and eGFR (r_s: −0.108; $p = 0.330$) and no significant difference between ePVS levels in patients with eGFR ≥ 60 ml/min/1.73 m^2 as compared to patients with eGFR < 60 ml/min/1.73 m^2.

DISCUSSION

This study provides a promising initial assessment of ePVS, an easily obtainable indicator of the plasma volume and degree of subclinical congestion, for the risk stratification of patients undergoing isolated tricuspid valve surgery.

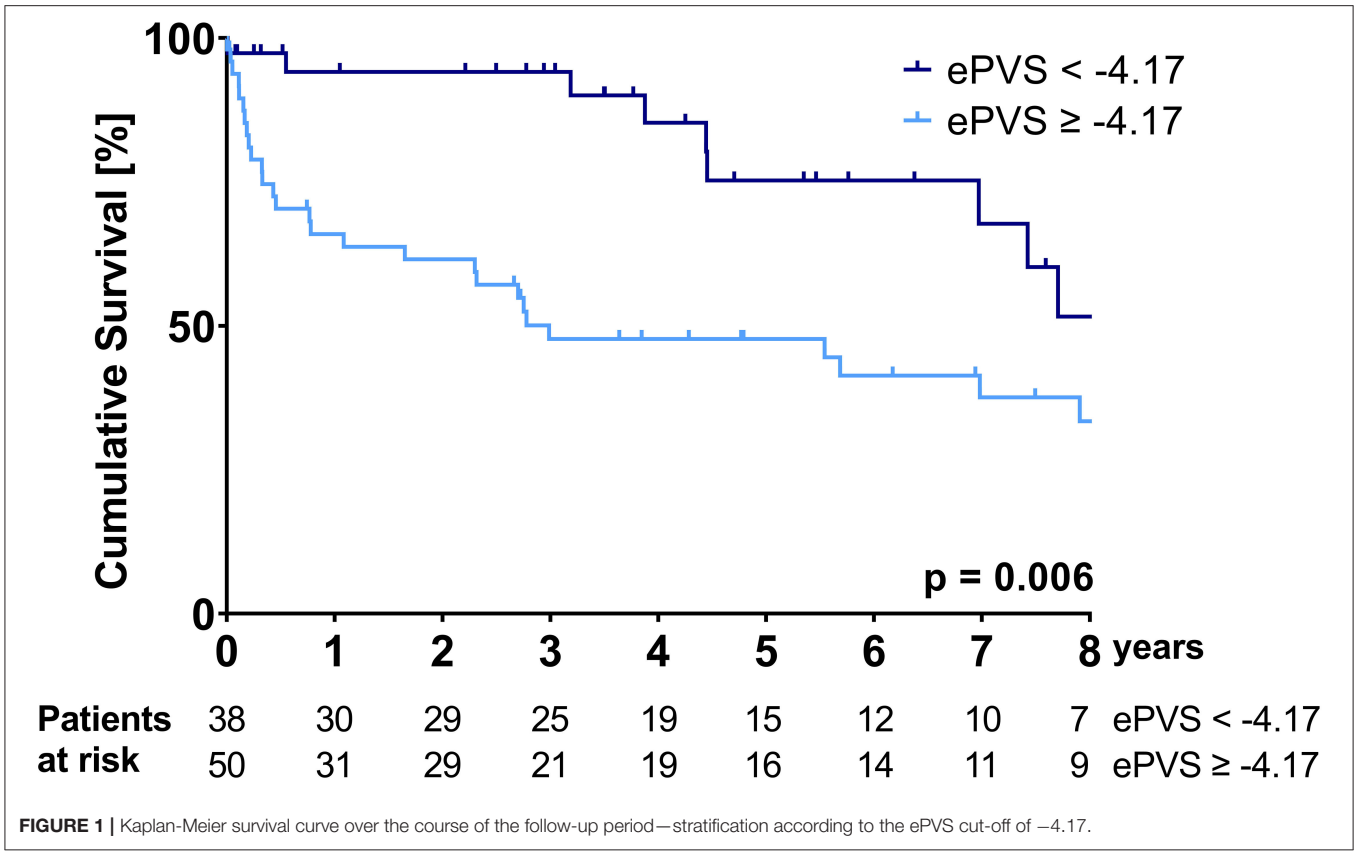

FIGURE 1 | Kaplan-Meier survival curve over the course of the follow-up period—stratification according to the ePVS cut-off of −4.17.

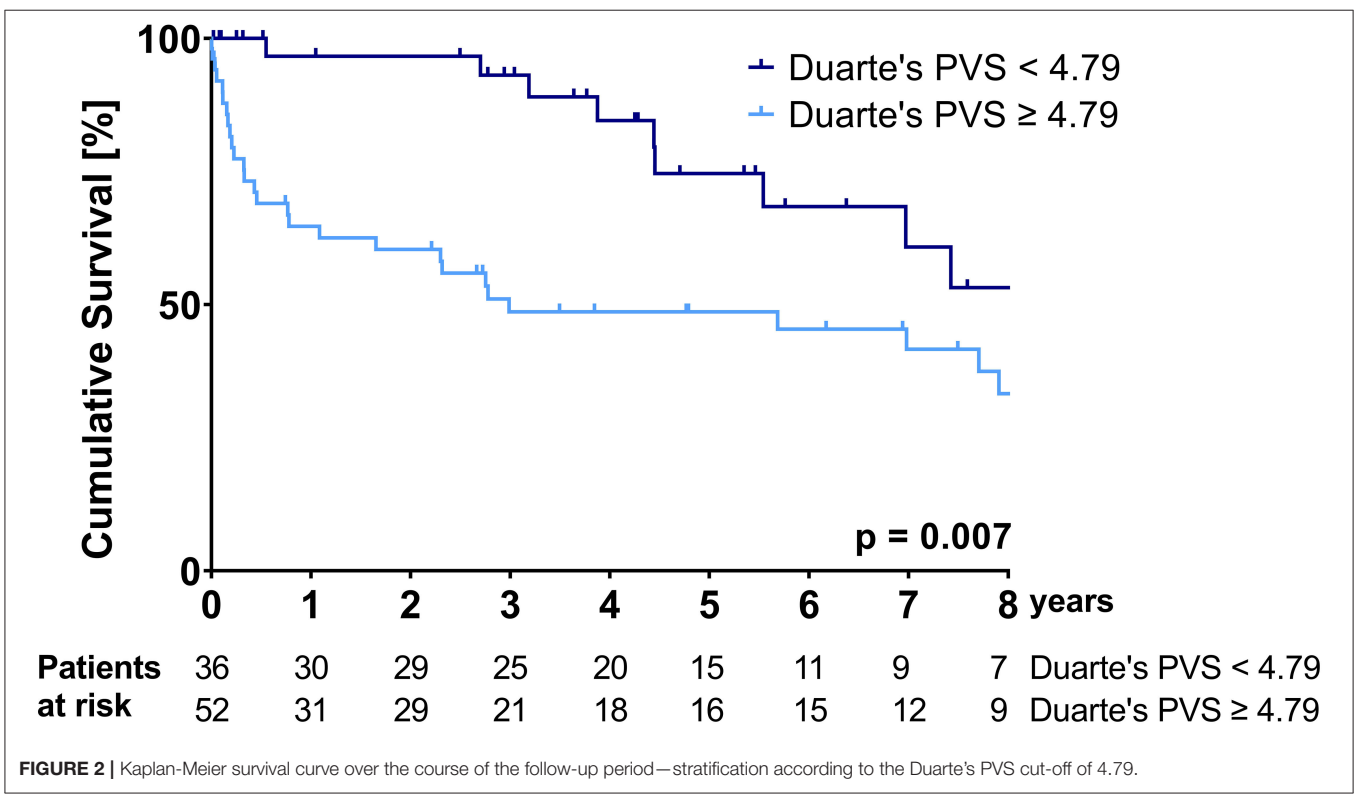

FIGURE 2 | Kaplan-Meier survival curve over the course of the follow-up period—stratification according to the Duarte's PVS cut-off of 4.79.

TABLE 4 | Predictors of mortality—univariate and multivariate analysis.

	Univariate analysis			Multivariate analysis		
Variable name	**Hazard ratio**	**95% confidence interval**	***P*-value**	**Adjusted hazard ratio**	**95% confidence interval**	***P*-value**
Age	1.026	1.006-1.046	0.010			
Baseline LVEF	0.966	0.940-0.993	0.014			
Elective surgery	0.519	0.275-0.980	0.043			
Urgent surgery	1.970	1.042-3.723	0.037			
Isolated TV repair	0.540	0.287-1.014	0.055			
Isolated TV replacement*	1.853	0.986-3.484	0.055			
EuroSCORE II*	1.054	1.018-1.092	0.003	1.039	0.999-1.079	0.055
NYHA class III/IV	2.667	1.035-6.872	0.042			
Diabetes mellitus	2.494	1.112-5.544	0.025			
Extracardiac arteriopathy	5.172	1.540-17.368	0.008			
Functional regurgitation*	0.561	0.282-1.113	0.098			
BMI	0.994	0.931-1.061	0.861			
Any previous intravenous drug use	1.129	0.541-2.354	0.746			
Active intravenous drug use	0.763	0.230-2.525	0.657			
Endocarditis related TR	1.078	0.552-2.102	0.827			
Any noncardiac chronic liver condition	1.805	0.936-3.480	0.078			
Active smoker	1.748	0.797-3.831	0.163			
Arterial hypertension	1.673	0.852-3.283	0.135			
Pacemaker/ICD	1.342	0.679-2.653	0.398			
COPD	1.343	0.690-2.613	0.385			
Chronic kidney disease	1.258	0.652-2.430	0.494			
Active endocarditis	0.966	0.462-2.091	0.927			
Pacemaker-related TR	1.382	0.576-3.320	0.469			
Redo surgery	0.790	0.359-1.403	0.323			
Previous surgical left heart valve intervention	0.894	0.391-2.044	0.791			
eGFR	0.990	0.979-1.001	0.074			
Hematocrit	0.935	0.889-0.984	0.010			
Hemoglobin	0.842	0.727-0.975	0.021			
Erythrocyte count	0.485	0.307-0.764	0.002			
proBNP	1.000	1.000-1.000	0.077			
Alkaline phosphatase*	1.005	1.002-1.008	0.001			
GGT*	1.003	1.000-1.006	0.026	1,004	1.001-1.007	0.004
CRP*	1.060	0.999-1.125	0.052			
Albumin	0.948	0.915-0.983	0.004			
Protein	0.981	0.959-1.003	0.094			
Sodium	0.940	0.883-1.001	0.052			
ePVS < -4.17*	0.360	0.170-0.765	0.008	0.431	0.188-0.905	0.027
Duarte's PVS < 4.79*	0.352	0.161-0.771	0.009			
Platelet count	0.999	0.995-1.002	0.445			
Creatinine	0.975	0.603-1.579	0.919			
LDH	0.999	0.998-1.001	0.558			
Total bilirubin	1.060	0.899-1.250	0.490			

Variables included in the multivariate Cox regression are indicated with an asterisk. LVEF, left ventricular ejection fraction; TV, tricuspid valve; NYHA, New York Heart Association; BMI, body mass index; ICD, implantable cardioverter-defibrillator; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; BNP, brain natriuretic peptide; GGM, gamma-glutamyltransferase; CRP, C-reactive protein; LDH, lactate dehydrogenase.

Heart failure is highly prevalent in patients undergoing isolated tricuspid valve surgery (2). Methods for noninvasively assessing the severity of congestion and identifying high-risk patients are required. Our study found a significant difference in baseline ePVS between patients who survived during the first year of follow-up and those who did not. This finding also remained valid for the overall follow-up period. The ePVS cut-off we identified from our 1-year follow-up data was a significant predictor of the overall all-cause mortality in both the univariate and multivariate analyses. The other predictor of overall mortality in the multivariate model was the level of gamma-glutamyltransferase (GGT), whereas the EuroSCORE II approached statistical significance. In order to expand the analysis to a non-weight dependent calculation, we also performed a second set of analyses using PVS values calculated by the Duarte formula. There were significant differences between Duarte's PVS in survivors and non-survivors, and Duarte's PVS was significant in the univariate Cox regression, but not in the multivariate analysis.

Isolated tricuspid valve surgery is performed substantially less frequently than other valve interventions (6). Almost four fifths of all surgeries involving the tricuspid valve in adults are performed concomitantly with other procedures (36). As indicated by the low interventional volumes, and when compared to the overall prevalence of tricuspid valve disease, the indication for tricuspid valve surgery was and is often set too conservatively or too late (37). Several factors related to an impaired immediate and long-term survival have been identified. Dreyfus et al. identified NYHA class III/IV as a predictor of mid-term mortality (3). In accordance with these findings, the ePVS ≥ -4.17 cohort, which had a lower overall survival, had a significantly higher proportion of NYHA III/IV patients. In our patient cohort, individuals with a higher NYHA class (III/IV) had a significantly lower survival compared to patients with NYHA class I/II. However, a sub-stratification according to the ePVS cut-off and NYHA class, despite being statistically significant, resulted in small group sizes and crossing survival curves. Thus, these results must be interpreted with caution and validated by future studies.

Interestingly, more patients in the ePVS < -4.17 cohort, which had a higher overall survival, suffered from functional tricuspid regurgitation, which was also linked to a poorer survival in the study by Dreyfus et al. (3). Tricuspid valve replacement was performed less often than tricuspid valve repair in this cohort, and less frequently when compared to the ePVS ≥ -4.17 cohort. Additionally, fewer in-hospital deaths were observed in the ePVS < -4.17 cohort. Tricuspid valve replacement was shown to carry a higher mortality compared to tricuspid valve repair by Zack et al., although other analyses have delivered conflicting findings (6, 38). The ePVS < -4.17 cohort had fewer cases of endocarditis-related tricuspid regurgitation and intravenous drug use. Intravenous drug users are known to have an impaired long-term survival following isolated tricuspid endocarditis-related surgery and are prone to a higher recurrence of valve endocarditis (39, 40). In the ePVS < -4.17 cohort, significantly more elective surgeries and significantly fewer urgent interventions were performed. Thus, ePVS could represent a surrogate parameter for late referral or delayed surgery. Delayed or urgently performed surgery has been linked to a worse outcome in isolated tricuspid valve surgery, which is also mirrored by the two (5.2%) in-hospital deaths in the ePVS < -4.17 cohort compared to five deaths (10.0%) in the ePVS ≥ -4.17 cohort. However, this finding did not reach statistical significance, possibly due to the small overall incidence of this outcome. Notably, patients with an ePVS < -4.17 had lower levels of GGT, although not statistically significant. In the multivariate analysis, higher GGT levels were statistically significant predictors of overall mortality. A large population study has identified elevated GGT levels as independent predictors of all-cause and cardiovascular mortality (41). Elevated GGT levels have also been described in patients in the beginning stages of heart failure and linked to their NYHA class (42). The third predictor of a poorer outcome was a higher EuroSCORE II, which was lower in the ePVS < -4.17 cohort, but did not reach statistical significance in the multivariate model. Notably, the EuroSCORE II was primarily developed with operative risk assessment in mind. Nonetheless, due to the included clinical parameters, it inevitably correlates with later outcomes, as demonstrated by Wang et al. for isolated tricuspid valve surgery (43, 44).

Our study identified an ePVS of -4.17 as the optimal cut-off point for ePVS when assessing the 1-year mortality following isolated tricuspid valve surgery. The ePVS cut-off most notably agrees with a -4 cut-off identified in a large cohort study by Ling et al. published in 2015, which included over 5,000 patients with heart failure and was also validated in a smaller outpatient cohort (45). This study also included an additional validation step which compared the calculated ePVS to the values obtained via the current gold-standard nuclear medicine plasma volume measurement technique and discovered a satisfactory correlation between the measured and calculated values (45). Notably, the same cut-off was the basis for a study in 600 TAVI patients, where patients with an ePVS past this cut-off also demonstrated significantly worse postinterventional outcomes (46). Slightly lower ePVS cut-offs in the same range were proposed by Martens et al. and Seoudy et al. (23, 33). In the study conducted by Martens et al. on a large cohort of heart failure patients the measured plasma volume and calculated ePVS were found to be comparable (23). In their mixed cohort of patients with HFpEF, heart failure with a mid-range (HFmEF) and reduced ejection fraction (HFrEF), a -6.5 cut-off was identified as the optimal cut-off in terms of heart failure related hospitalization and all-cause mortality (23). Seoudy et al. identified an ePVS cut-off of -5.4 as a significant predictor of these outcomes in a TAVI cohort at 1 year after the intervention (33). Interestingly, Schaefer et al. identified a higher ePVS cut-off of 3.1 when analyzing the correlation of the calculated plasma volume status with short- and long-term outcomes in patients undergoing mitral valve surgery (34). In summary, the ePVS cut-off identified by our study is in agreement with data from other trials in different patient collectives and thus provides initial proof that, on the one

hand, ePVS might represent a viable stratification parameter for patients undergoing isolated tricuspid valve surgery, and on the other hand, ePVS might represent an overarching heart failure-related stratification parameter that might play a key role in identifying at-risk cardiac surgery patients undergoing a number of different interventions.

Within our study, we also assessed a different approach to calculating the plasma volume from the hematocrit and hemoglobin values at baseline, as previously described by Duarte et al. (20). For Duarte's PVS, 4.79 was the optimal cut-off in our study. Notably, this cut-off is similar to the one identified by Lin et al. in patients with systolic heart failure (47). In their study, a Duarte's PVS higher than 4.35 was associated with more frequent hospitalization and a higher overall mortality (47). In a large cohort of patients admitted to the emergency department with dyspnea, Duarte's PVS higher than 4.17 and 5.12 in particular was linked to significantly worse in-hospital survival, whereas Duarte's PVS $>$ 5.12 increased the likelihood for the diagnosis of acute heart failure later on (48). Thus, the cut-off identified within our study lies well within the range of values identified by other studies.

In our study, ePVS calculated at baseline was a significant predictor of mortality. A study by Tamaki et al. evaluated the prognostic value of plasma volume calculations performed by all three aforementioned formulas: the Hakim, Strauss and Duarte formula for the prediction of outcomes of patients admitted for acutely decompensated heart failure following discharge (28). In their analysis, only ePVS calculated using the Hakim formula at baseline and before discharge reliably predicted the primary outcome (28). In a study by Kobayashi et al., Duarte's PVS measured at discharge was a reliable predictor of outcomes in patients admitted for acute decompensated heart failure, whereas the admission values and the overall change during the stay were not (24). This highlights the need for studies involving plasma volume status assessments during multiple timepoints to determine not only the optimal cut-off, but also the optimal timepoint for plasma volume calculations for patient risk stratification.

Despite the promising results, our study has a few limitations inherent to its retrospective character and small sample size. Most importantly, numerical echocardiography data were not electronically recorded for a large part of our patient collective, thus precluding us from conducting detailed analyses in this regard. Furthermore, the small sample size limited the combined sub-stratification analysis according to other key parameters, such as NYHA class.

In conclusion, ePVS is an easily obtainable risk score for patients undergoing isolated tricuspid valve surgery capable of predicting mid- and long-term outcomes after isolated tricuspid valve surgery. Our study proposes an ePVS cut-off of −4.17 for long-term risk stratification and a 4.79 cut-off for PVS calculated using Duarte's formula.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the corresponding author, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of the Medical University of Vienna, Vienna, Austria. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

MM, MR, and MA: conceptualization. MM and EH: methodology. BH, EH, and MM: formal analysis. GL, AK, DW, and MA: resources. MR and EH: data curation. EH and MM: writing—original draft preparation. PW, IC, MR, GL, AK, DW, and MA: writing—review and editing. EH and BH: visualization. MM: supervision. MR: project administration. All authors have read and agreed to the published version of the manuscript.

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Long Term Results of the Modified Bentall Procedure With Mechanical and Biological Composite Valve Grafts

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Objectives: Despite the evident shift toward biological prostheses, the optimal choice of valve remains controversial in composite valve graft (CVG) replacement. We investigated long-term morbidity and mortality after CVG implantation in an all-comer cohort with a subgroup analysis of patients aged 50–70 years stratified after valve type.

Methods: A total of 507 patients underwent the Bentall procedure with either a mechanical (MCVG, $n = 299$) or a biological (BCVG $n = 208$) CVG replacement between 2000 and 2020. A single-center analysis comprising clinical and telephone follow-up was conducted to investigate late mortality and morbidity

Results: The 30-day mortality in all patients [age 56 ± 14 years, 78.1% male, EuroSCORE II 3.12 (1.7; 7.1)] was 5.9%. Patients who were electively operated on had a 30-day mortality of 1.5% ($n = 5$) while it remained higher in urgent/emergent procedures ($n = 25$, 15.4%). Survival at 10 and 15 years was 78.19 ± 2.26% and 72.6 ± 3.2%, respectively. In patients aged 50–70 years ($n = 261$; MCVG = 151, BCVG = 110), survival did not differ significantly between the valve groups ($p = 0.419$). Multivariable analysis showed no significant impact of valve type on survival ($p = 0.069$). A time-varying relation with survival was notable, showing a higher risk in the MCVG group in the early postoperative phase, which declined compared to the BCVG group in the course of follow-up.

Conclusions: The Bentall technique presents with excellent mortality when performed electively. The type of valve prosthesis showed no statistically significant effect on mortality in patients aged 50–70 years. However, a time-varying relation showing an initially higher risk with MCVG which decreased compared to BCVG at long-term follow-up was notable. Further studies with even longer follow-up of BCVGs will clarify the ideal choice of prosthesis in this patient subset.

Keywords: modified Bentall procedure, composite valve graft replacement, valve-related adverse events, aortic valve replacement, aortic replacement

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INTRODUCTION

Initially, described in 1968 by Bentall and De Bono, composite valve graft (CVG) replacement, also known as the Bentall procedure, represented a novel surgical option for dilated aortic roots (1). The procedure underwent important modifications including, most notably, the abandonment of the wrap-inclusion technique due to albumin-coated Dacron prostheses and the implementation of the coronary-button technique (2) and has become a widely adopted standard of care for various root pathologies (3–5).

Although valve-sparing solutions are often the preferred approach in selected cases, CVG implantation remains universally applicable in an all-comer cohort and is not limited to favorable valve morphology. While earlier reports of patients with CVG only included mechanical conduits (5), the evident trend in surgical aortic valve replacement (SAVR) toward increased use of bioprosthetic valves has also led to a rising number of biological CVG implantations. However, the problem of the optimal choice of prosthesis in SAVR remains controversial in CVG replacement. Only a few studies have investigated the effect of the type of CVG on postoperative mortality and morbidity, and they have shown no relevant differences in postoperative mortality (6–8).

Herein, we report data on 507 patients with long-term follow-up and 21 years of experience with the Bentall procedure in a tertiary care center. Given the controversy regarding the optimal choice of conduit, a subgroup analysis of patients aged 50–70 years was performed to investigate the impact of valve choice on survival after CVG replacement.

MATERIALS AND METHODS

Ethics Statement

The following study was reviewed and approved by the ethical committee of the Medical University of Vienna (ethical-board number 2311/2020; date of approval 19.01.2021).

Patients

All patients who underwent aortic valve and associated aortic surgery between January 2000 and December 2021 were screened for their surgical procedure to identify patients who underwent CVG implantation after the modified Bentall technique. Patients who underwent root replacement that did not use CVGs and patients younger than 18 years were excluded. Retrospective data were obtained *via* the institutional database and prospective telephone follow-up was performed with assessment of adverse events (AEs) and reinterventions. Our institutional database is part of the Austrian quality-control system for cardiac surgery and is being monitored on a yearly basis. The stored mortality data are in concordance with the Austrian Federal Statistical-Agency and are updated annually.

Endpoint Definitions

The primary endpoint of this study was mortality in the overall cohort and subgroup of patients aged 50–70 years. Postoperative AEs were defined after the current Society of Thoracic Surgeons (STS)/American Association of Thoracic Surgery (AATS)/European Association for Cardio-Thoracic Surgery (EACTS) guidelines for reporting mortality and morbidity after cardiac valve interventions and were grouped into structural valve deterioration (SVD), non-structural valve dysfunction (NSVD), valve thrombosis, embolism, and bleeding events (9). Permanent neurological deficits which occurred when the patient emerged from anesthesia after the index operation were classified as perioperative stroke. Re-exploration for bleeding was classified as bleeding revision.

Surgical Technique and Conduit Selection

All cases in this study underwent the button Bentall technique, a modification of the original Bentall procedure (1), described by Kouchoukos et al. (2).

Surgical access over a median sternotomy was established. If necessary, right subclavian artery or femoral cannulation was performed before sternotomy. After the establishment of cardiopulmonary bypass and conduction of cardioplegic arrest with cold-blood cardioplegia, aortic root dissection was performed, the coronary buttons were mobilized, and the sinuses of Valsalva were excised. When a non-prefabricated graft was used, a CVG was composed by suturing the valve into a Dacron prosthesis (3–5 mm larger than valve size) with 5–0 polypropylene sutures in a running fashion. Following the first institutional use of a Valsalva conduit in 2006, the GelweaveTM Valsalva prosthesis (Terumo Aortic, Glasgow, UK) became the preferred option for non-prefabricated CVGs. Braided 2–0 polyester sutures with pledgets were placed from the ventricular to the aortic portion of the annulus to anchor the CVG. The second line of 2–0 sutures with pledgets anchoring the graft from the outside was performed for hemostatic reasons. The left coronary button was anastomosed to the CVG in an end-to-side fashion with a 6–0 polypropylene suture. The graft was subsequently pressurized with antegrade cardioplegia to check for bleeding and to distend the graft for correct evaluation of the right coronary artery (RCA) insertion before completion of the anastomosis. A thin strip of the autologous pericardium was routinely included in the button anastomoses for better hemostasis. Distal aortic anastomosis and concomitant procedures were performed according to the underlying pathology.

The valve choice was based on the patient's age, need for anticoagulation, and preference. Patients below 60 years of age more frequently received a mechanical CVG while patients over the age of 65 years routinely received biological CVGs. Some patients under the age of 60 opted for biological CVGs to avoid lifelong anticoagulation although they were advised about the risk of valve deterioration.

Statistical Methods

Continuous variables were described by mean (± standard deviation) or median (quartiles) in case of non-normal distributions and compared between groups of patients using the two-sample *t*-test or the Wilcoxon rank-sum test, respectively. Categorical data were compared using the chi-squared test or Fisher's exact test (if expected cell frequencies were <5).

TABLE 1 | Patient characteristics.

Variables	Overall cohort	50–70a		
	n = 507	MCVG (*n* = 151)	BCVG (*n* = 110)	*p*-value (50–70a)
Age (years)	56 ± 14	58 ± 6	64 ± 1	<0.001[a]
Sex (male)	396 (78.1%)	126 (83.4%)	89 (80.9%)	0.60[b]
BMI (kg/m²)	27 ± 4.4	27.7 ± 4.3	28.2 ± 4.5	0.41[a]
EuroSCORE II (%)	3.12 [1.7; 7.1]	2.2 [1.6–5.2]	3.45 [2.2; 7.03]	<0.001[c]
STS Prom (%)	0.89 [0.63; 1.47]	0.84 [0.61; 1.37]	0.87 [0.69; 1.40]	0.09[c]
Arterial hypertension	408 (80.5%)	127 (84.1%)	98 (89.1%)	0.25[b]
Diabetes	33 (6.5%)	10 (6.6%)	12 (10.9%)	0.22[b]
Dyslipidemia	264 (52.1%)	77 (51%)	67 (60.9%)	0.11[b]
Peripheral vascular disease	13 (2.6%)	4 (2.6%)	0	0.14[d]
Chronical lung disease	33 (6.5%)	13 (9.2%)	5 (5%)	0.23[b]
Atrial fibrillation/flutter	82 (16.2%)	29 (19.2%)	15 (13.6%)	0.24[b]
History of smoking	177 (34.9%)	48 (31.8%)	44 (40.0%)	0.17[b]
Preoperative creatinine (mg/dl)	1.06 ± 0.53	1.0 [0.85; 1.18]	0.97 [0.86; 1.15]	0.54[c]
Connective tissue disease	25 (4.9%)	4 (2.6%)	1 (0.9%)	0.31[d]
Previous cardiac surgery	64 (12.6%)	16 (10.6%)	13 (11.8%)	0.76[b]
Bicuspid valve	194 (38.3%)	64 (43.8%)	29 (26.4%)	0.004[b]

[a]*Two-sample t-test,* [b]*Chi-squared test,* [c]*Wilcoxon-rank-sum test,* [d]*Fisher's-exact test.*

The median follow-up times were calculated using the inverse Kaplan-Meier method (10).

The Kaplan-Meier method was used to calculate the cumulative survival probability (with 95% confidence intervals) of the study population. To compare the survival of the study cohort with an age- and sex-matched standard population, mortality data from 2013 (Austrian Federal Statistical-Agency "Statistics Austria") were used (11). The hypothetical cumulative survival of this age-sex-matched standard population was calculated using the life-table method. The comparison of survival of the study cohort to the standard population at time points of 2, 5, and 10 years was performed by z tests (standard population's survival as null hypothesis value).

To evaluate the potential valve type effect on survival, univariable and multivariable Cox proportional-hazards regression models were performed. The prognostic factors of age, EuroSCORE II ($\log_2$-transformed), reoperative status, and high-risk indication were included in the multivariable model in addition to the factor valve type (mechanical/biological) to account for imbalances with respect to these well-known confounding factors. Time-varying effects were tested in the Cox regression models to check the proportional hazards assumption. Since a statistically significant time-varying valve type effect was detected, this term was additionally included in the univariable and multivariable models. Directly adjusted survival curves are depicted to illustrate the multivariable adjusted valve type effect on survival. Survival times were censored after 10 years of follow-up to achieve comparable follow-up periods in these two cohorts.

Cumulative incidence functions were estimated to quantify the probability of valve-related adverse events (composite endpoint incorporating bleeding, thrombosis, embolization, and SVD) accounting for death as a competing event. Gray's test was used for group comparisons.

Two-sided $p < 0.05$ were considered statistically significant. The software SAS (SAS Institute Inc., 2016, Cary, NC, USA) was used for statistical calculations.

RESULTS

Characteristics and Procedural Details

Between January 2000 and December 2020, 507 patients underwent a modified Bentall procedure at our institution. The mean age in the overall cohort was 56 ± 14 years and 78.1% were male. The median (quartiles) EuroSCORE II was 3.12 (1.7; 7.1) and the median STS risk of mortality was 0.89 (0.63; 1.47). Patient characteristics are summarized in **Table 1**. Elective surgery was performed in 68% ($n = 345$) of patients. The indications for surgery were anulo-aortic ectasia ($n = 374$; 73.8%), aortic dissection ($n = 104$; 20.5%), endocarditis ($n = 16$; 3.2%), and others ($n = 13$; 2.6%). Biological CVGs and mechanical CVGs (MCVGs) were implanted in 208 (41%) and 299 patients (59%), respectively. Prosthetic conduits are listed in **Figure 1**. Implantation of MCVG was performed in 86.3% ($n = 132$) of cases between 2000 and 2010 and in 47.2% ($n = 167$) of cases between 2011 and 2020 ($p < 0.001$). Procedural details are summarized in **Table 2**.

The median follow-up for the primary endpoint survival was 81.5 (35.5; 127.1) months with 3,129 patient-years and a maximum of 243 months. The median follow-up for AEs was 47.9 (5.1; 104.7) months with a total of 2,230 patient years. In patients aged 50–70 years, the median survival follow-up was 102.8 months in the MCVG group (57.8 months for AEs) and

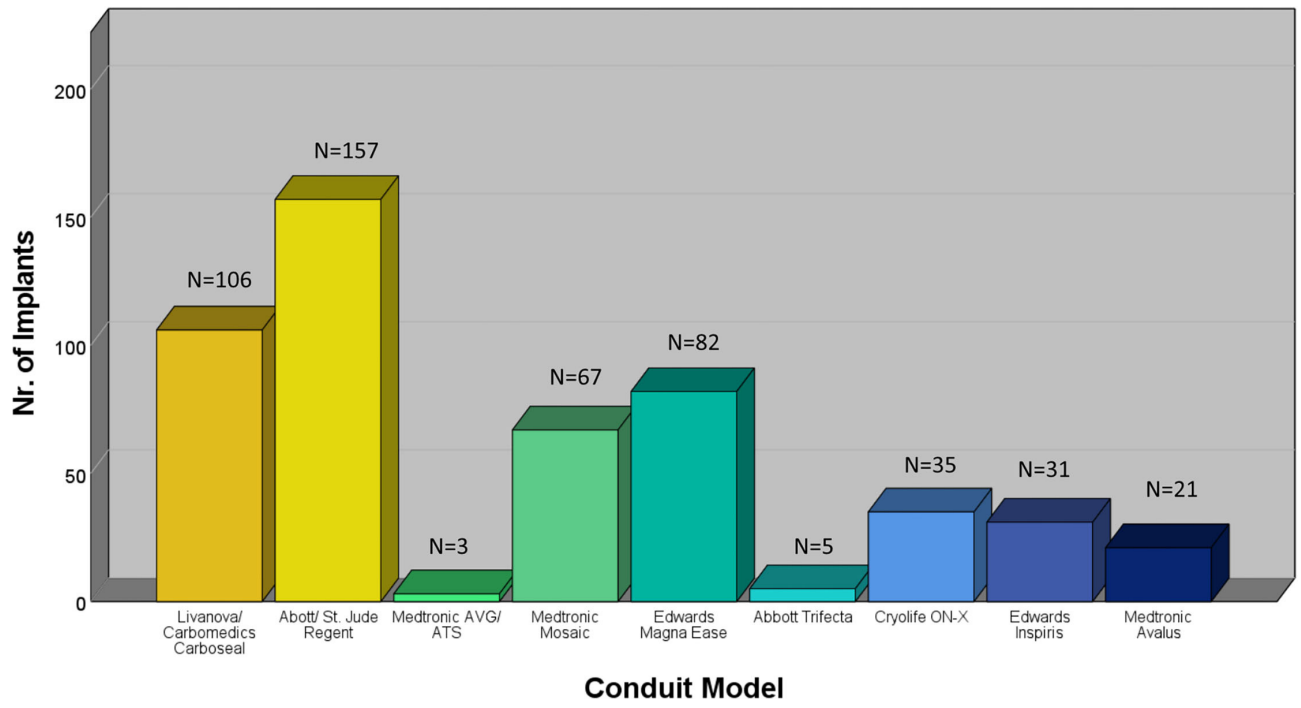

FIGURE 1 | Prosthetic valve models used for composite graft implantation in the study cohort.

55.1 months in the biological CVG (BCVG) group (37.2 months for AEs).

Post-operative Mortality

The 30-day mortality in all patients was 5.9% ($n = 30$) with one case of intraprocedural mortality (0.2%). No significant difference in 30-day mortality was observed between patients who received a MCVG ($n = 18$) vs. BCVG ($n = 12$, $p = 0.9$). Patients who underwent surgery for acute type-A dissection presented with a higher 30-day mortality ($n = 21$, 20.2%, $p < 0.001$), as did patients who underwent urgent/emergent procedures ($n = 25$, 15.4%, $p < 0.001$). Patients who underwent elective surgery had a low 30-day mortality rate of 1.5% ($n = 5$). Survival at 5, 10, and 15 years was 84.1 ± 1.8, 78.2 ± 2.3, and 72.6 ± 3.2%, respectively. Our study cohort's survival was compared to an age- and sex-matched Austrian standard population (**Figure 2**). Survival was significantly lower in patients who underwent CVG implantation than in a standard population at 2 years (97.6 vs. 87.8; $p < 0.0001$) and 5 years (93.2 vs. 84.1; $p < 0.0001$) but not at 10 years (82.6 vs. 78.2; $p = 0.12$).

Morbidity and Repeat Surgery

Overall, 37 patients (7.3%) received temporary mechanical circulatory support within 30 days after surgery, with 34 cases of extracorporeal membrane-oxygenation (ECMO) implantation ($n = 6.7\%$) and two cases (0.4%) of intra-aortic balloon pump implantation. Indications for ECMO implantation in the patients receiving a BCVG were severely reduced left ventricular function ($n = 2$) after CBP, left ventricular failure after ventricular rupture ($n = 1$), biventricular failure ($n = 4$) due to myocardial stunning, right ventricular failure ($n = 2$), combined respiratory and hemodynamic instability ($n = 2$), and cardiopulmonary resuscitation with pulseless electrical activity at the 29th postoperative day (POD). Of those patients, two patients died within 30 days after the index surgery.

Revision surgery for bleeding or tamponade was necessary in 45 patients (re-exploration $n = 33$, 6.5%; subxiphoidal drainage $n = 12$, 2.4%). Perioperative stroke was observed in 24 cases (4.7%) and perioperative transient-ischemic attacks (TIAs) occurred in 4 patients (0.8%). Early permanent pacemaker implantation (<14 days postoperative) was necessary for 13 patients (2.3%). Two patients (1% BCVG) presented with SVD after receiving a BCVG, and NSVD was observed in one case (0.2%) with severe paravalvular dehiscence after implantation of an MCVG (the patient eventually died due to prohibitive surgical risk). Valve thrombosis was diagnosed in two patients (0.4%) with an MCVG, and surgical extirpation was required in both cases. Embolic events were observed in 27 patients (5.3%), of which 24 (4.7%; stroke $n = 19$, TIA $n = 5$) presented as cerebral and three (0.6%) as peripheral. Bleeding events were reported in 32 patients (6.3%), stratified into 12 cerebral and 20 peripheral bleeding events. Endocarditis was observed in 19 patients (3.7%), of whom 9 (1.8%) underwent root rereplacement.

Repeat surgery on the thoracic aorta, aortic valve, or coronaries was performed in 35 patients (6.9%). Valve-related reoperations ($n = 9$; 1.8%) were performed due to endocarditis requiring root rereplacement in 8 cases (1.6%) and valve thrombus requiring extirpation in one case (0.2%). Eighteen

TABLE 2 | Procedural details.

Variables	Overall cohort	50–70a		
		MCVG ($n = 151$)	BCVG ($n = 110$)	p-value (50–70a)
Operative status				**0.24[a]**
Elective	345 (68.1%)	97 (64.2%)	80 (72.7%)	
Urgent	66 (13%)	18 (11.9%)	11 (10%)	
Emergent	95 (18.7%)	36 (23.8%)	18 (16.4%)	
Salvage	1 (0.2%)	0	1 (0.9%)	
Indication				**0.34[a]**
Anulo-aortic ectasia	374 (73.8%)	106 (70.2%)	85 (77.3%)	
Dissection	104 (20.5%)	36 (23.8%)	20 (18.2%)	
Endocarditis	17 (3.4%)	7 (4.6%)	2 (1.8%)	
Other	12 (2.4%)	2 (1.3%)	3 (2.7%)	
Concomitant procedures	189 (37.3%)	54 (35.8%)	42 (38.2%)	0.69[b]
Coronary bypass	88 (17.4%)	21 (13.9%)	12 (19.1%)	0.26[b]
Mitral	33 (6.5%)	9 (6%)	6 (5.5%)	0.87
Tricuspid	9 (1.8%)	2 (1.3%)	3 (2.7%)	0.41
Atrial-Fibrillation	10 (2%)	3 (2%)	4 (3.6%)	0.42
Aortic				
Hemiarch	73 (14.4%)	26 (17.2%)	16 (14.5%)	0.56[b]
Total-Arch	22 (4.3%)	5 (3.3%)	4 (3.6%)	1.0[a]
Elephant-Trunk	6 (1.2%)	0	2 (1.8%)	0.18[a]
Circulatory arrest	198 (39.1%)	60 (39.7%)	46 (41.8%)	0.74[b]
Aortic cross-clamp (min)	131 [107; 164]	126.5 [103; 158]	135 [115; 174]	0.02[c]
Extracorporeal circulation (min)	184 [150; 235]	174 [139; 226]	192.5 [161; 236]	0.02[c]

[a] *Fisher's-exact test.*
[b] *Chi-squared test.*
[c] *Wilcoxon-rank-sum test.*

patients (3.7%) underwent aortic-related repeat surgery with 2 cases (0.4%) of root rereplacement, 1 case (0.2%) of sinotubular-junction pseudoaneurysm, 5 cases (1%) of arch replacement, 9 cases (1.8%) of thoracic endovascular aortic repair, and one case (0.2%) of thoracoabdominal replacement. Coronary-related reoperations ($n = 8$; 1.6%) were performed due to coronary button pseudoaneurysm ($n = 3$; 0.6%), kinking of the proximal RCA ($n = 2$; 0.4%), kinking of a vein-graft to the RCA ($n = 1$; 0.2%), necessity of bypass revision with simultaneous thrombus extirpation and ventricular assist-device implantation ($n = 1$; 0.2%), and ischemic cardiogenic failure ($n = 1$; 0.2%). Second repeat surgery was performed in seven patients (1.4%) with three cases (0.6%) of root rereplacement and four cases of aortic procedures (0.8%). Altogether, rereplacement of the root was performed in 13 patients (2.6%) in the overall cohort. The annualized event rate of root rereplacement was 0.6% in all patients. Postoperative mortality and morbidity are summarized in **Table 3**.

Mortality and Morbidity in Patients Aged 50–70 Years

In patients aged 50–70 years ($n = 261$; MCVG = 161, BCVG = 110), the 30-day mortality was 6.5% ($n = 16$) with no significant differences between valve types (MVCG $n = 11$, 6.8%, BCVG 4.5% $n = 5$, $p = 0.36$). The Kaplan-Meier estimated freedom from mortality at 1, 5, and 10 years was 89.8 ± 2.5, 83.1 ± 3.3, and 79.7 ± 3.7% in the mechanical cohort and 89.3 ± 3.1, 83.4 ± 4.1, and 68 ± 6.9% in the biological cohort, respectively, with no statistically significant differences (log-rank $p = 0.419$; **Figure 3A**). When compared to an age- and sex-matched Austrian standard population, freedom from mortality was significantly lower in the MCVG cohort at 2 (98.4 vs. 86.7%, $p = 0.0004$) and 5 years (95.4 vs. 83.1%, $p = 0.0017$), but not at 10 years (88.6 vs. 79.6%, $p = 0.052$). In the BCVG cohort, survival was significantly lower at 2 years (97.2 vs. 88.1%, $p = 0.013$), but not at 5 (92.4 vs. 83.4%, $p = 0.06$) or 10 years (81.9 vs. 68%, $p = 0.17$; **Figure 3B**).

To investigate the effect of valve type on mortality in this subset, univariate and multivariable Cox proportional-hazards regression models were created. According to the number of observed events ($n = 47$), the four relevant prognostic confounders of age, EuroSCORE II ($\log_2$-transformed), previous cardiac surgery, and high-risk indication (aortic-dissection/endocarditis) were included in the multivariable model to evaluate the adjusted effect of valve type on survival. All variables except valve type were statistically significant prognostic factors for mortality following univariate analysis (**Table 4**). When adjusting for the confounders (multivariable model) and including the statistically significant time-varying effect of valve type ($p = 0.034$), the initially negative effect of

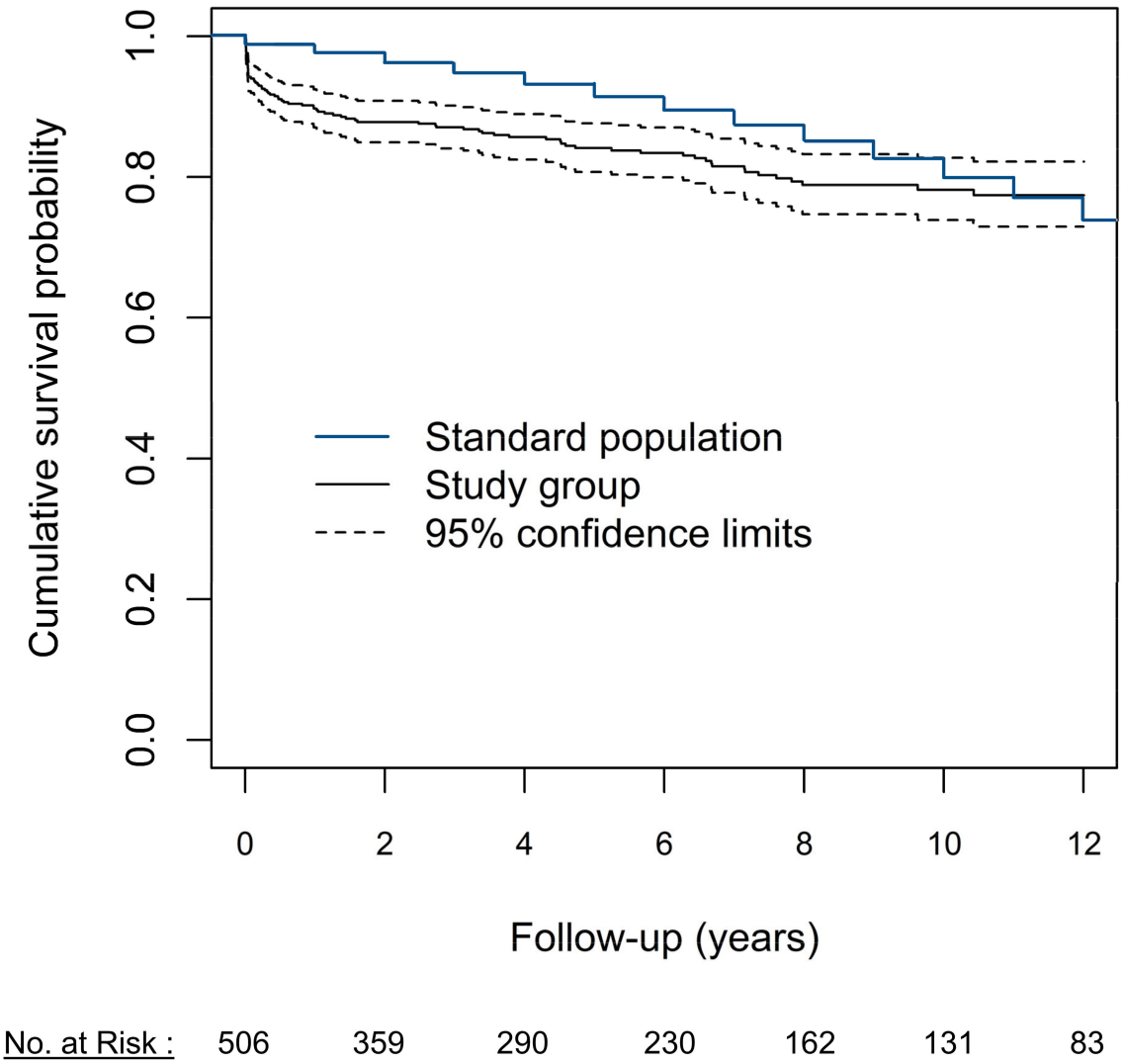

FIGURE 2 | Survival of the overall cohort compared to an age- and sex-matched Austrian standard population.

the MCVG was found to later change to a decreased risk for mortality compared to the BCVG. However, the overall valve type effect remained statistically non-significant ($p = 0.069$). To illustrate the time-varying valve type effect, landmark analyses were performed at the landmark time points 2 and 5 years after CG replacement (**Supplementary Material**). A direct adjusted survivor function was created to illustrate this trend in patients aged 50–70 years (**Figure 4**). As a sensitivity analysis, a sub-analysis was performed on a 1:1 matched cohort based on patients age (categorized in 5-years increments), EuroSCORE II (categorized in deciles), and BAV (bicuspid vs. non-bicuspid valve) (**Supplementary Material**).

To assess valve-related AEs, a composite endpoint incorporating bleeding, thrombosis, embolization, and SVD was assessed. A cumulative incidence function with death as competing event showed no differences between the two groups ($p = 0.695$) with a CI at 1, 5, and 10 years of 7.9 ± 2.4, 14.3 ± 3.6, and 20.5 ± 4.8% in the MCVG cohort and 7.6 ± 2.8, 9.1 ± 3.2, and 18.7 ± 6% in the BCVG cohort, respectively (**Figure 5**).

DISCUSSION

Within this study, we investigated long-term mortality and morbidity in a large single-center cohort of 507 patients who underwent CVG implantation after the modified Bentall procedure, and performed a specific subset analysis of patients between the ages of 50–70 years at index surgery.

Our study presents the following principal findings: (1) the modified Bentall procedure continues to represent the gold-standard for an all-comer cohort with aortic root pathologies and can be performed with excellent early mortality comparable to isolated aortic valve replacement (1.5%) in elective cases; (2) In the specific subset of patients aged 50–70 years, no clear survival benefit was shown for any type of prosthetic

TABLE 3 | Post-operative morbidity and mortality.

Clinical events	Overall cohort	50–70a		
		MCVG ($n = 151$)	BCVG ($n = 110$)	*p*-value (50–70a)
30-day mortality	30 (5.9%)	11 (7.3%)	5 (4.5%)	0.36
ECMO (<30 days)	34 (6.7%)	4 (2.6%)	12 (10.9)	0.003
Perioperative stroke	24 (4.7%)	8 (5.3%)	8 (7.3%)	0.51[c]
Early pacemaker (<14 days)	13 (2.6%)	4 (2.6%)	3 (2.7%)	1.0[d]
Bleeding revision/drainage	45 (8.9%)	5 (3.3%)	13 (11.8%)	0.007[c]
Root rereplacement[a]	0.6% ppy ($n = 13$)	0.6% ppy ($n = 4$)	0.3% ppy ($n = 1$)	
SVD[a]	<0.01% ppy ($n = 2$)	0% ppy	0.3% ppy ($n = 1$)	
NSVD[a]	<0.01% ppy ($n = 1$)	0% ppy	0% ppy	
Embolic events[a]	1.2% ppy ($n = 27$)	2% ppy ($n = 13$)	1.1% ppy ($n = 4$)	
Bleeding[a]	1.4% ppy ($n = 32$)	1.4% ppy ($n = 9$)	1.7% ppy ($n = 6$)	
Endocarditis[a]	0.9% ppy ($n = 19$)	0.8% ppy ($n = 5$)	1.1% ppy ($n = 4$)	
Bleeding/embolization/thrombus/SVD[b]	/			0.70[e]
1 year		7.9% [4–13.5]	7.6% [3.3–14.2]	
5 years		14.3% [8.2–22.1]	9.1% [4.2–16.5]	
10 years		20.5% [12–30.6]	18.7% [8.7–31.8]	

[a]*Annualized event-rates (event per patient year = ppy).*
[b]*Cumulative incidence with death as competing event.*
[c]*Chi-squared test.*
[d]*Fisher's exact test.*
[e]*Gray's test.*

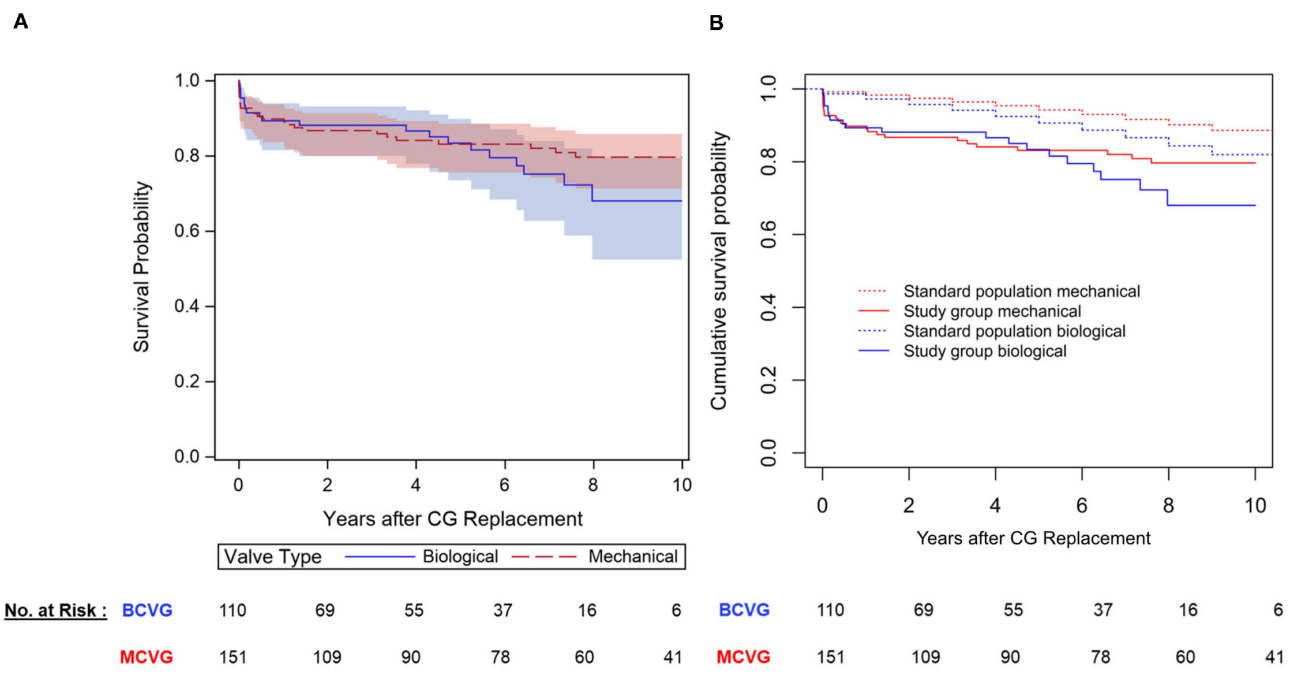

FIGURE 3 | Survival in patients aged 50–70 years. **(A)** Kaplan-Meier (KM)-estimated survival stratified after valve type **(B)** KM-estimated survival of each valve type compared to a group-specific age- and sex-matched Austrian standard population.

valve, however, there was a strong tendency for an initially higher risk with MCVG which decreased compared to BCVG at long term follow-up; (3) In patients aged 50–70 years, no difference in the incidence of a composite endpoint comprising valve-related morbidity was observed between mechanical and biological CVGs.

The observed 30-day mortality in our overall cohort was 5.9%, with no significant differences between mechanical and

TABLE 4 | Univariable and multivariable Cox regression models for post-operative mortality (50–70a).

Prognostic factor	Univariable models		Multivariable model	
	HR [95% CI]	*P*-value	HR [95% CI]	*P*-value
Age (years)	1.063 [1.01–1.12]	0.0127	1.07 [1.01–1.13]	0.02
EuroSCORE II (log_2-transformed)	1.79 [1.42–2.17]	<0.0001	1.66 [1.29–2.14]	<0.001
Previous cardiac surgery	2.8 [1.39–5.65]	0.004	1.32 [0.611–2.86]	0.48
Indication (dissection/endocarditis)	2.98 [1.67–5.32]	0.0002	1.54 [0.79–3]	0.21
Valve type (mechanical)		0.079[b]		0.069[c]
6 months[a]	0.71 [0.39–1.29]		1.29 [0.64–2.58]	
1 year[a]	0.60 [0.32–1.13]		1.08 [0.52–2.24]	
5 years[a]	0.40 [0.17–0.94]		0.71 [0.28–1.80]	
9 years[a]	0.35 [0.14–0.90]		0.61 [0.22–1.70]	

[a]*After surgery.*
[b]*Overall p-value (time-dependent effect: p = 0.04).*
[c]*Overall p-value (time-dependent effect: p = 0.033).*

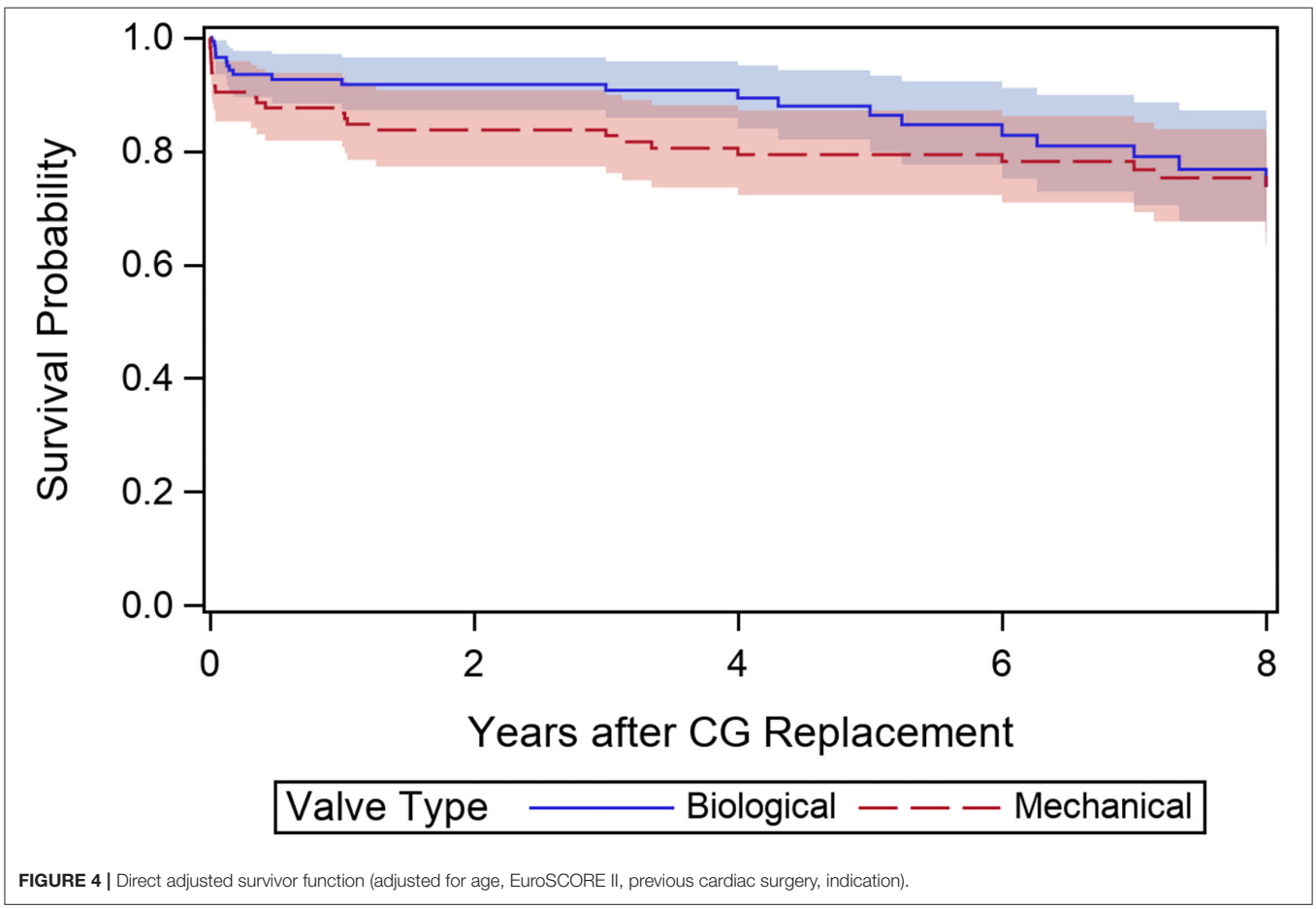

FIGURE 4 | Direct adjusted survivor function (adjusted for age, EuroSCORE II, previous cardiac surgery, indication).

biological CVGs, which is comparable to other collectives in the literature. Di Marco et al. reported on the currently largest single-center cohort (n = 1,045) after MCVG and BCVG implantation, showing operative mortality of 5.3% without significant differences between valve types (3). The Leipzig group reported hospital mortality of 3.9% in their overall cohort of 597 patients who were implanted with MCVGs and BCVGs (4). In a different single-center cohort of 593 patients with only MCVGs, the 30-day mortality was 3.2%, with 2.5% in elective cases and 6.5% in urgent cases (5). A meta-analysis published in 2016, including 46 studies with 7,629 patients undergoing a Bentall procedure, showed a pooled early mortality of 6%

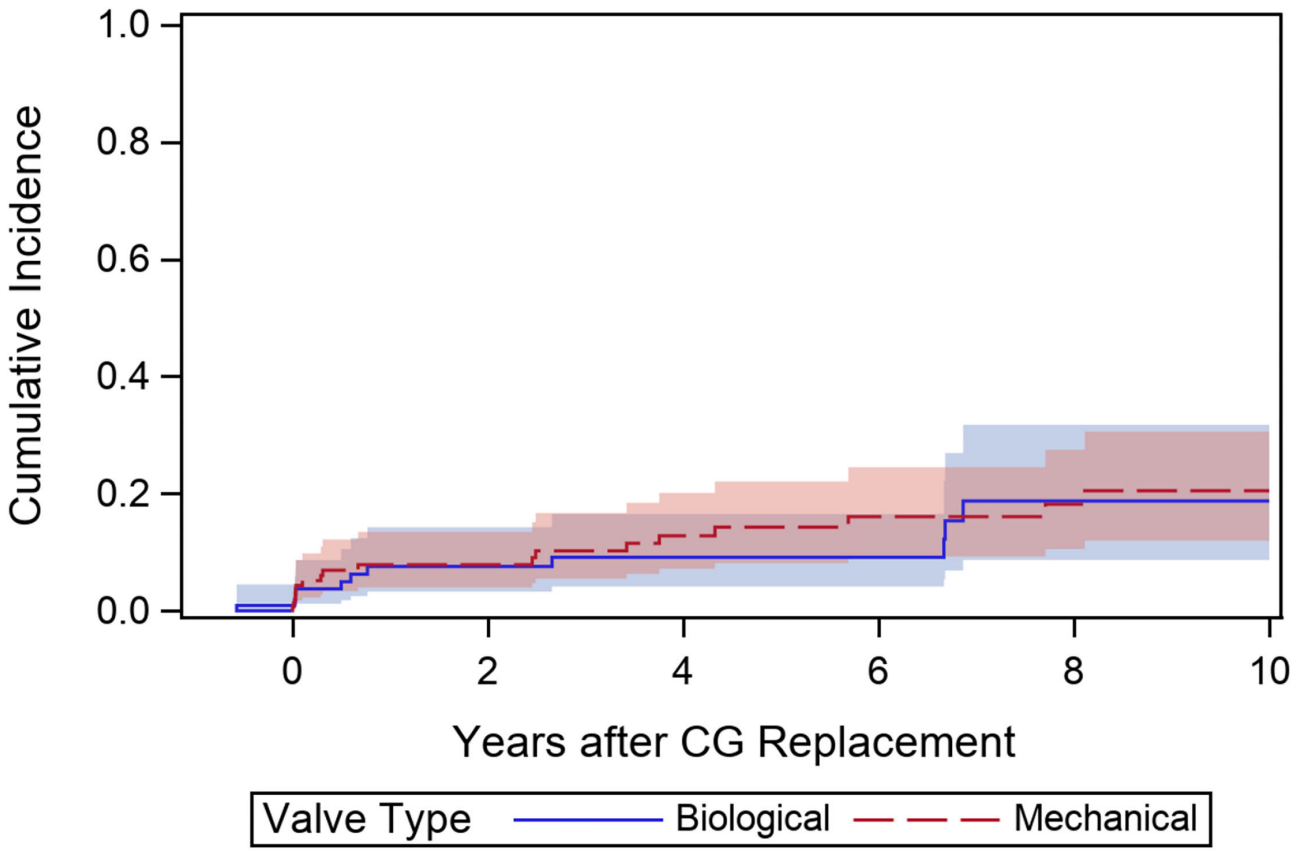

FIGURE 5 | Cumulative incidence function for a composite endpoint for valve-related morbidity including bleeding events, embolic events, valve thrombosis, and structural valve deterioration in patients aged 50–70a.

(12). We observed low 30-day mortality of 1.5% in patients who underwent elective CVG implantation, which is comparable to isolated SAVR and represents an excellent safety profile for an aortic root procedure. The low mortality of elective cases might be attributable to the standardization of the procedure within the last 20 years including modifications, such as the button technique and the broad implementation of temporary mechanical circulatory support. However, in urgent/emergent cases and type-A dissection, the Bentall procedure remains at higher risk as indicated by the 30-day mortality in our collective and within the literature (3, 4, 13).

The optimal valve choice in the so-called "gray area" of patients aged 50–70 years has been a matter of discussion in past decades and remains controversial. Nevertheless, the trend toward an increasing number of bioprostheses used in SAVR continues and is also present in CVG replacement. In our series, 86.3% of patients between 2000 and 2010 received an MCVG, while BCVG implantation was more frequent between 2010 and 2020 with 53% ($p < 0.001$). Evidence on valve choice in the Bentall procedure is limited as only a few studies have investigated the effect of valve type, especially in patients aged 50–70 years. An earlier analysis, including BCVG, stentless prostheses, and MCVG, showed no differences regarding early and midterm mortality between mechanical and biological solutions (6). In a more recent publication with two equally sized ($n = 138$) propensity-matched CVG cohorts stratified after valve type, no differences in early and late mortality were observed between the groups (7). Follow-up was limited with mean values ranging from 29 months in the biological group to 40 months in the mechanical group. In the only subgroup analysis of patients aged 50–70 years, Etz et al. reported no significant differences in long-term survival, reinterventions rates, or stroke (4). They concluded that BCVG might be an equivalent alternative to MCVG in this patient subset. However, their conclusion is challenged by more recent evidence from larger retrospective analyses in SAVR patients. Particularly, a California state-wide analysis showed improved survival in patients with mechanical AVR below the age of 55 and data from the nationwide SWEDEHEART registry reported a survival benefit of mechanical over biological prostheses in patients aged up to 69 years at replacement (14, 15). Even though we did not find a statistically significant effect of valve type on mortality, a time-varying effect with initially increased risk for MCVG which later decreased compared to BCVG was notable ($p = 0.069$). Similar results were observed in an Italian multicentric-registry comparing MCVG and BCVG implantation, where a

non-significant ($p = 0.09$) trend to improved late survival in MCVG patients was reported (8). A possible factor contributing to the initially increased mortality in the MCVG cohort might be a numerically higher number of urgent (MCVG 11.9% vs. BCVG 10%) and emergent (MCVG 23.8% vs. BCVG 16.4%) procedures (nonetheless, surgical indication, including dissection and endocarditis, was not a predictive factor for mortality in the multivariable model). Patients in the BCVG group showed a trend toward decreased survival in long-term follow-up, which can be partially explained by an older cohort with a numerically higher burden of comorbidities (although statistically non-significant). Further considerations, such as the impact of structural deterioration remain speculative, as only one case of SVD and one root rereplacement in the BCVG aged 50–70a were observed in our cohort with no significant differences in reinterventions. Our cohort presented a median survival follow-up of 102.8 months in the MCVG group (57.8 months for AEs) and 55.1 months in the BCVG group (37.2 months for AEs). SVD, which remains the burden of bioprosthetic valves, usually occurs after 5 years postoperatively. As we recently showed, a rapid increase in SVD events in certain valve types can be expected starting 6 years after surgery with aortic valve reinterventions as a negative predictor of survival in SAVR (16). Longer follow-up times in this subset (50–70a) will be needed to obtain a more comprehensive picture of the effects of SVD in CVG replacement. The survival benefit of mechanical valves in patients who have undergone SAVR aged up to 55/69 years shown by recent analyses (14, 15) and the absence of evidence of survival benefits for BCVG should not be neglected when opting for the optimal CVG choice in patients aged 50–70 years.

Interestingly, the incidence of a composite endpoint for valve-related morbidity did not differ between the MCVG and BCVG cohorts aged 50–70 years (**Figure 5**). No significant difference in the number of bleeding or embolic events was observed between the groups. This might be attributable to improved management of anticoagulation in patients receiving mechanical prostheses, including self-measurement strategies and lower thrombogenicity of modern mechanical valves.

Study Strengths and Limitations

This study presents one of the largest single-center cohorts of patients who underwent a modified Bentall procedure at a tertiary care center with a relevant number of patients aged 50–70 years at the time of surgery. Due to its retrospective nature, this study presents has some limitations. Although patient follow-up was meticulously performed, it was naturally hindered by patient refusal, relocation, and death. In a single-center cohort, a specific set of surgeons is represented and may thus introduce an unknown bias. Biological CVGs have been implanted more frequently in the latter half of the study period. Therefore, follow-up in this group is inevitably proportionally shorter compared to MCVGs. Consequently, analyses between the valve groups in patients aged 50–70 years were limited to 10 years of follow-up. The present study is retrospective in nature and, therefore, its results cannot substitute those of a prospective randomized trial which would randomize eligible patients to either mechanical or biological CVG replacement.

CONCLUSION

The modified Bentall technique presents satisfactory results in an all-comer series with low mortality when electively performed, but remains a high-risk procedure when performed in urgent or emergent cases. The choice of valve conduit showed no statistically significant effects on mortality in patients aged 50–70 years. However, there was a strong tendency for an initially higher risk with MCVG, which decreased compared to BCVG at long-term follow-up. Further studies with longer follow-up of biological valve conduits are needed to determine the ideal choice of valve in this specific patient subset.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethical Committee of the Medical University of Vienna (ethical-board number 2311/2020; date of approval 19.01.2021). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

PW was responsible for conceptualization, data curation, investigation, formal analysis, methodology, and writing. JG and IC were responsible for data curation, resources, review, and editing. AKa was responsible for the methodology, resources, and formal analysis. EO, SM, and M-ES were responsible for reviewing, editing, and conceptualization. AKo and GL were responsible for the review with editing and supervision. MA was responsible for conceptualization, review with editing, and supervision. ME was responsible for conceptualization, project administration, reviewing, editing, and supervision. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.867732/full#supplementary-material

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The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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ORIGINAL RESEARCH
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Perioperative and Short-Term Outcomes of Sinus Replacement and Conservative Repair for Aortic Root in Acute Type A Aortic Dissection: A Prospective Cohort Study

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Background: To compare outcomes between sinus replacement (SR) and conservative repair (CR) for dissected roots with normal size.

Methods: From October 2018 to April 2021, a prospective cohort study was carried out. Patients were assigned to two groups (SR group and CR group) according to whether they underwent sinus replacement. Propensity score matching was applied to adjust preoperative variables and Kaplan–Meier method was used for survival analysis.

Results: Three hundred and eighty-seven patients were enrolled. In the whole cohort, 18 patients (4.7%) died postoperatively. The operative mortality of SR group was comparable to CR group (3.2% vs. 6.0%, $p = 0.192$ before matching; 3.5% vs. 7.0%, $p = 0.267$ after matching) and the incidence of hemostasis management under restarted cardiopulmonary bypass for root bleeding was lower in SR group (1.6% vs. 7.0%, $p = 0.002$ before matching; 2.1% vs. 8.5%, $p = 0.03$ after matching). The median follow-up duration was 12 months. There were 3 reoperations in the CR group. The estimated cumulative event rate of reoperation was 1.1 % at 12 months and 1.6% at 24 months in CR group, with a trend of a lower rate in the SR group (log-rank $p = 0.089$ before matching, $p = 0.075$ after matching). There was one late death in each group. The estimated cumulative event rate of death was 3.8% at 12 months and 24 months in the SR group, and was 6.6% in the CR group with no significant difference (log-rank $p = 0.218$ before matching, $p = 0.120$ after matching). Aortic regurgitation significantly improved postoperatively and remained stable during follow-up.

Conclusions: Sinus replacement is a simple, safe, and effective technique for repairing severely dissected sinus with a comparable time spent in operation and excellent immediate and short-term results. It had the advantages of eliminating false lumen and avoiding aortic root bleeding.

Keywords: aortic dissection, aortic root repair, prospective cohort study, propensity score matching, sinus replacement

INTRODUCTION

Surgical treatment of acute type A aortic dissection (ATAAD) is challenging and management of the involved aortic root is a key point. In the guidelines, the aortic root involved in dissection should be replaced when its diameter is larger than 45 mm (1). For those aortic roots with normal size, the conservative repair is preferred, accompanied by an estimated freedom from root reoperation of 82–100% at 5 years and 69–93% at 10 years (2). The reoperation was closely related to pathological features and operation choice (3–5). Among various techniques, sinus replacement (SR) (or other names like single patch technique, patch neointima technique) presented with excellent early and long-term results according to our experience and previous research (6, 7). To compare the outcomes between sinus replacement and other conservative repair techniques, we conducted a prospective cohort study from October 2018 to April 2021. In this study, we analyzed the perioperative and short-term outcomes to demonstrate more reliable evidence about aortic root management in ATAAD.

MATERIALS AND METHODS

Study Cohort

The study was approved by the Ethics Committee of Fuwai Hospital in September 2018 and the approval number was 2018-1094. From October 2018 to April 2021, patients with ATAAD were recruited for this prospective cohort study in our institution. The inclusion criteria were as follows: (1) aortic sinus or root being involved; (2) open surgical repair being performed. All the inclusion criteria must be met simultaneously. The exclusion criteria were as follows: (1) having connective tissue diseases; (2) aortic root diameter being more than 45 mm and requiring aortic root replacement; (3) having three aortic sinuses involved simultaneously. One exclusion criterion was enough to reject the candidate. The patients accepted sinus replacement or other conservative repair techniques at surgeons' discretion and then they were assigned to the SR group and CR group. Based on a two-tailed $\alpha = 0.05$, power $(1 - \beta) = 0.90$, and relative risk of aortic root reoperation = 0.125 (based on data from a previous study [2]and our estimation), a sample size of 180 for each group was originally calculated for comparison between the two groups. Taking into account an anticipated 10% loss to follow-up rate, 200 patients were selected for each group to ensure an adequate final sample size. The flow chart of patient enrollment was shown in **Supplementary Figure I**. Written informed consent was obtained from all participating patients before the start of the study.

Definition and Classification

Acute aortic dissection was defined as a dissection operated on no later than 14 days after the onset of symptoms. Aortic regurgitation (AR) grade was defined as: 0 = none or trivial, 1 = mild, 2 = moderate, 3 = moderate to severe, and 4 = severe. The classification proposed by Neri et al. (8) was used for coronary artery involvement. Restarted CPB referred to a reoperation under restarting cardiopulmonary bypass (CPB) or cross-clamp for bleeding or myocardial ischemia in the same surgery. The primary end-point was defined as aortic root reoperation during follow-up. The second end-point was defined as death during follow-up.

Surgical Procedures

A standard median sternotomy was performed for all patients. The strategy of initial arterial cannulation and cardiopulmonary bypass was decided individually, according to the operation method choice, surgeon's preference, and patient's status.

Sinus replacement was conducted as follows: ascending aorta was transected 1 cm above sinotubular junction and the intimal flap of the involved sinus was removed maintaining a remanent edge of 5 mm apart from the cusp insertion. Dissecting aortic root from surrounding tissue was troublesome so adventitia was reserved to omit to separate an involved root. A patch deriving from artificial graft was trimmed to a scallop shape similar to native Valsalva sinus. A 5-0 running polypropylene suture was used to sew the patch and remanent intima and adventitia together. Of note, the bottom of the patch should be sewed to the aortic annulus (**Figures 1A–C**). If we performed sinus replacement in the left or right coronary sinus we would judge the severity of the dissected coronary artery by Neri classification. In type A, the intima of the coronary orifice was trimmed into a button with a 5 mm circumferential cuff. The intimal button was attached snugly to the adventitia by running suture. After sinus replacement was performed as mentioned above, a circular hole was created on the patch for receiving the coronary button. Then the button was re-implanted to the patch using a 5-0 running polypropylene suture (**Figures 2A–C**). In types B and C, we selected coronary artery bypasses grafting (CABG) for security. The avulsed commissure was attached to adventitia using interrupted mattress suture with the pledge. Then the root stump was prepared for proximal anastomosis. In the CR group, two approaches were used at the surgeon's discretion: neomedia technique and adventitial inversion technique, as the previous study described (9, 10). Neomedia technique was inserting a shaped patch into the false lumen of the root and then intima, the patch, and adventitia were anastomosed with graft. The adventitial inversion technique referred to invert the redundant adventitia overlapping the intima to reinforce anastomosis. These two techniques could reinforce the sutural margin of the aortic root. A total arch replacement was routinely applied in our institution to repair the involved arch. Frozen elephant trunk or endovascular stents were used distally. When the dissection was limited to ascending aorta or proximal arch, isolated ascending aorta replacement or hemi-arch replacement was recommended. Hypothermic circulatory arrest (HCA) and antegrade selective cerebral perfusion were used for arch repair.

Follow-Up

Data was obtained from each patient's medical chart during regular visits to the outpatient clinic or by telephone contact. The survivors received follow-up using transthoracic echocardiography, CT scan, or both. Survival, reoperation, and AR grade were investigated.

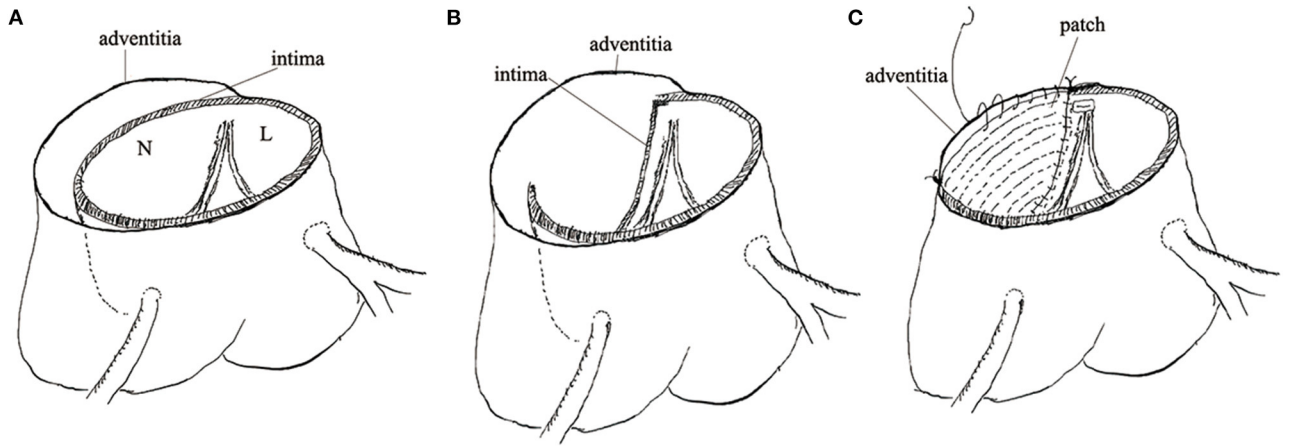

FIGURE 1 | The technical details of sinus replacement. **(A)** Showed deeply dissected non-coronary sinus. **(B)** Showed the intimal flap removed. **(C)** Showed the scallop-shaped patch sewed with remanent intima and adventitia together.

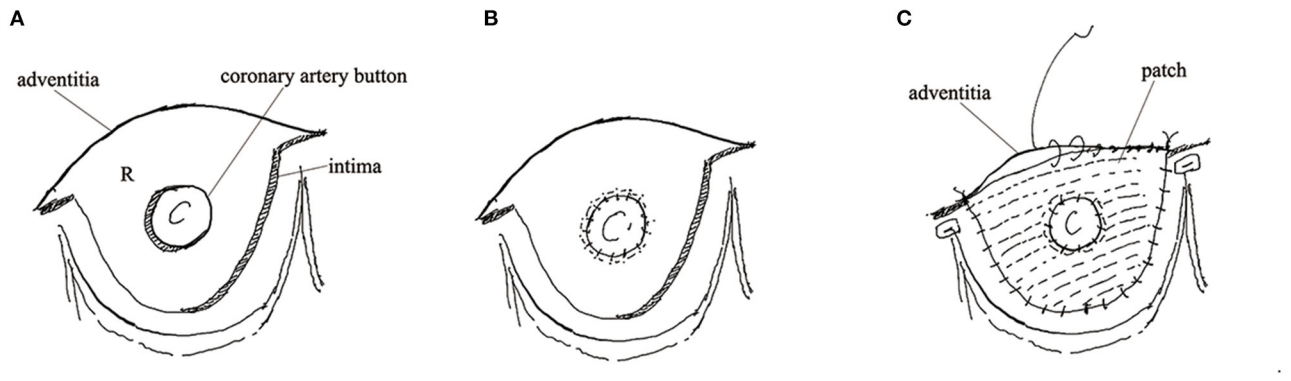

FIGURE 2 | The technical details of sinus replacement. **(A)** Showed the intima of coronary orifice trimmed into button. **(B)** Showed the intimal button attached snugly to the adventitia. **(C)** Showed the patch and the re-implanted button.

Statistical Analysis

Data were presented as mean and SD for continuous data conforming to the normal distribution and as number (%) for categorical data. Shapiro–Wilk test was used to evaluate the normality of continuous data. The mean of two continuous normally distributed variables was compared by independent samples Student's *t*-test. Wilcoxon signed-rank test was used to compare non-normal continuous variables. Comparison of categoric variables between groups was analyzed by likelihood ratio Chi-square test or Fisher's exact test.

Propensity score matching was applied to achieve balanced exposure groups at baseline (i.e., minimal confounding). The probability of each patient having an aortic sinus replacement (i.e., the propensity score) was calculated using a logistic regression model. Covariates adjusted and evaluation of propensity score model was demonstrated in **Supplementary Table I**. Patients were then matched one-to-one using nearest neighbor matching and caliper width of 0.1 of SD of the logit of the propensity score. After propensity score matching, a comparison of continuous data conforming to normal distribution between groups was analyzed by paired *t*-test. Wilcoxon signed-rank test was used to compare non-normal continuous variables. Paired Chi-square test was used to compare multiple categorical variables between the two groups. McNemar test was used to compare binary variables between the two groups. Univariate logistic regression analysis was used to calculate the relative risk (RR) of sinus replacement after matching. Kaplan–Meier method was used for survival analysis and log-rank test was used to compare the difference in cumulative event rate. The competing risk model was constructed by subdistribution hazard function to control the effect of long-term mortality on the primary outcome:long-term risk for reintervention. Statistical significance was denoted by p-values < 0.05. The statistical analyses were conducted by SAS (version 9.4, SAS Institute Inc., Cary, NC, USA).

TABLE 1 | Baseline characteristics.

Variable	Unmatched			*P*	Matched			*P*
	Overall *n* = 387	SR group *n* = 187	CR group *n* = 200		Overall *n* = 284	SR group *n* = 142	CR group *n* = 142	
Age, year (X ±SD)	52.3 ± 11.5	51.6 ±11.0	52.9 ± 11.9	0.27	53.2 ± 11.2	53.2 ± 10.9	53.2 ±11.6	0.98
BMI (X ±SD)	26.6 ±4.3	26.7 ±4.7	26.5 ± 3.9	0.80	26.3 ± 4.4	26.3 ± 4.9	26.4 ± 3.8	
Male (*n*, %)	263(68.0)	130(69.5)	133(66.5)	0.53	194(68.3)	97(68.3)	97(68.3)	1.00
HT (*n*, %)	325(84.0)	150(80.2)	175(87.5)	0.05	239(84.2)	113(79.6)	126(88.7)	0.05
CAD (*n*, %)	60(15.5)	23(12.3)	37(18.5)	0.09	37(13.0)	20(14.1)	17(12.0)	0.72
DM (*n*, %)	12(3.1)	5(2.7)	7(3.5)	0.64	10(3.5)	3(2.1)	7(4.9)	0.34
COPD (*n*, %)	3(0.8)	2(1.1)	1(0.5)	0.61*	3(1.1)	2(1.4)	1(0.7)	1.00
CRI (*n*, %)	9(2.3)	3(1.6)	6(3.0)	0.51*	7(2.5)	3(2.1)	4(2.8)	1.00
Previous heart surgery (*n*, %)	3(0.8)	1(0.5)	2(1.0)	0.22*	3(2.1)	1(0.7)	2(1.4)	0.22
VMS (*n*, %)	3(0.8)	3(1.6)	0(0.0)	0.11*	0(0.0)	0(0.0)	0(0.0)	NA
Initial tear (*n*, %)				0.05				0.98
aAO	289(74.7)	133(71.1)	156(78.0)		220(77.5)	110(77.5)	110(77.5)	
Arch	85(22.0)	50(26.7)	35(17.5)		57(20.1)	28(19.7)	29(20.4)	
DTA	13(3.4)	4(2.1)	9(4.5)		7(2.5)	4(2.8%)	3(2.1)	
Type of CAI (left) (*n*, %)				0.04*				1.00
No	361(93.3)	169(90.4)	192(96.0)		270(95.1)	136(95.8)	134(94.4)	
A	26(6.7)	18(9.6)	8(4.0)		14(4.9)	6(4.2)	8(5.6)	
B	0(0.0)	0(0.0)	0(0.0)		0(0.0)	0(0.0)	0(0.0)	
C	0(0.0)	0(0.0)	0(0.0)		0(0.0)	0(0.0)	0(0.0)	
Type of CAI (right) (*n*, %)				0.01*				0.86
No	265(68.5)	116(62.0)	149(74.5)		202(71.1)	97(68.3)	105(73.9)	
A	98(25.3)	60(32.1)	38(19.0)		65(22.9)	35(24.6)	30(1.1)	
B	17(4.4)	6(3.2)	11(5.5)		11(3.9)	6(4.2)	5(3.5)	
C	7(1.8)	5(2.7)	2(1.0)		6(2.1)	4(2.8)	2(1.4)	
Scr, μmol/L(X ±SD)	96.4 ± 35.8	95.4 ± 37.3	97.4 ± 34.4	0.58	93.4 ± 31.5	89.5 ± 28.8	97.2 ± 33.7	0.03
Lac,mmol/L (media *n*, IQR)	1.47 (1.06–2.17)	1.54 (1.14–2.20)	1.41 (1.03–2.16)	0.28§	1.43 (1.08–2.13)	1.45 (1.14–2.17)	1.38 (1.06–2.03)	0.99§
GPT, IU/L (media *n*, IQR)	22.0 (15.0–36.0)	23.0 (15.0–35.0)	20.0 (14.0–36.0)	0.40§	23.0 (14.0–36.0)	22.0 (14.0–32.0)	25.0 (14.0–37.0)	0.72§
TnI, ng/ml (X ±SD)	0.05 ±0.19	0.05 ±0.11	0.05 ±0.24	0.84	0.05 ±0.16	0.05 ±0.11	0.04 ±0.20	0.58
Root diameter, mm (X ±SD)	37.5 ± 4.3	38.0 ± 4.3	37.1 ± 4.4	0.03	37.7 ± 4.5	38.0 ± 4.3	37.4 ± 4.6	0.09
AR (*n*, %)				0.003*				0.28
No or trivial	176(45.5)	76(40.6)	100(50.0)		124(43.7)	55(38.7)	69(48.6)	
Mild	155(40.1)	75(40.1)	80(40.0)		115(40.5)	57(40.1)	58(40.8)	
Moderate	39(10.1)	28(15.0)	11(5.5)		31(10.9)	23(16.2)	8(5.6)	
Moderate-severe	12(3.1)	8(4.3)	4(2.0)		10(3.5)	7(4.9)	3(2.1)	
severe	3(0.8)	0(0.0)	3(1.5)		2(0.7)	0(0.0)	2(1.4)	

SR, sinus replacement; CR, conservative repair; HT, hypertension; CAD, coronary artery disease; DM, diabetes mellitus; CRI, chronic renal insufficiency; VMS, visceral malperfusion syndrome; aAO, ascending aorta; DTA, descending thoracic aorta; CAI, coronary artery involvement; Scr, serum creatinine; Lac, lactic acid; IQR, Interquartile Range; GPT, glutamic-pyruvic transaminase; TnI, troponin I; AR, aortic regurgitation.

**Fisher's exact test was used.*

§*Wilcoxon signed-rank test was used.*

RESULTS

Baseline Characteristics and Operative Outcomes

At the end of the study, 387 effective cases were collected, with 187 cases in the SR group and 200 cases in the CR group. In the whole cohort, the average age was 52.3 ±11.5 years, with a male preponderance (68.0%). Coronary artery involvement occurred more frequently in SR group (9.6% vs. 4.0%, $p = 0.04$ for left coronary artery; 38.0% vs. 25.5%, $p = 0.01$ for right coronary artery). The grade of aortic regurgitation differed significantly between the two groups ($p = 0.003$). The patients' baseline characteristics are presented in **Table 1**. Altogether, 142 pairs of patients were well-matched across groups

TABLE 2 | Operative characteristics.

Variable	Unmatched			*P*	Matched			*P*
	Overall *n* = 387	SR group *n* = 187	CR group *n* = 200		Overall *n* = 284	SR group *n* = 142	CR group *n* = 142	
SP (*n*, %)	187(48.3)	187(100.0)	0(0.0)	–	142(50.0)	142(100.0)	0(0.0)	–
LCS	17(9.1)	17(9.1)	0(0.0)		13(4.6)	13(9.2)	0(0.0)	
RCS	53(28.3)	53(28.3)	0(0.0)		36(12.7)	36(25.4)	0(0.0)	
NCS	123(65.8)	123(65.8)	0(0.0)		92(32.4)	92(64.8)	0(0.0)	
Commissure reattachment (*n*, %)	142(36.7)	66(35.3)	76(38.0)	0.58	105(37.0)	52(36.6)	53(37.3)	0.90
Arch repair (*n*, %)				0.95*				0.96
None	7(1.8)	4(2.1)	3(1.5)		7(1.8)	4(2.8)	3(2.1)	
HAR	17(4.4)	8(4.3)	9(4.5)		11(3.9)	5(3.5)	6(4.2)	
TAR	363(93.8)	175(93.6)	188(94.0)		266(93.7)	133(93.7)	133(93.7)	
DTA management (*n*, %)				0.08				0.60
None	48(12.4)	20(10.7)	28(14.0)		38(13.4)	16(11.3)	22(15.5)	
FET	308(79.6)	157(84.0)	151(75.5)		224(78.9)	116(81.7)	108(76.1)	
Endovascular stent	31(8.0)	10(5.3)	21(10.5)		22(7.7)	10(7.0)	12(8.5)	
CABG (*n*, %)	64(16.5)	34(18.2)	30(15.0)	0.40	47(16.5)	28(9.7)	19(13.4)	0.16
CPB duration, min(X ±SD)	183.5 ± 71.6	184.7 ± 61.9	182.5 ± 79.7	0.76	185.8 ± 74.0	185.7 ± 62.0	185.8 ± 84.6	0.99
Cross-clamp duration, min (X ±SD)	112.2 ± 41.9	114.7 ± 43.6	109.9 ± 40.3	0.26	113.1 ± 39.7	114.3 ± 39.9	112.0 ± 39.6	0.62
HCA duration, min(X ±SD)	14.0 ± 9.3	14.3 ± 8.8	13.7 ± 9.7	0.53	13.6 ± 9.3	13.9 ± 9.2	13.6 ± 9.4	0.94
Operation duration, hour, (X ±SD)	6.4 ± 1.9	6.3 ± 1.7	6.5 ± 2.0	0.20	6.4 ± 1.9	6.3 ± 1.7	6.4 ± 2.1	0.46

*SR, sinus replacement; CR, conservative repair; LCS, left coronary sinus; RCS, right coronary sinus; NCS, none coronary sinus; HAR, hemi-arch replacement; TAR, total arch replacement; DTA, descending thoracic aorta; FET, frozen elephant trunk; CABG, coronary artery bypass grafting; CPB, cardiopulmonary bypass; HCA, hypothermic circulatory arrest. *Fisher's exact test was used.*

regarding baseline characteristics, consistent with the right half of **Tables 1**–**3**. The absolute standardized mean differences between the two groups regarding baseline characteristics are shown in **Supplementary Table II**.

In the SR group, 181 patients had one sinus replacement and 6 patients had two sinuses replacements. The noncoronary sinus was most frequently involved and was replaced in 123 patients. In the whole cohort, 64(16.5%) patients underwent CABG for coronary artery involvement or coronary artery disease. All the concomitant operations were distributed similarly between the two groups. The main time variables including CPB duration, cross-clamp duration, HCA duration, and operation duration were comparable with no significant difference. Operative characteristics are listed in **Table 2**.

The operative mortality of the whole cohort was 4.7% (18 patients), 6 in the SR group and 12 in the CR group. The main presumed causes of death were acidosis and multiple organ failure (8 cases), circulatory failure (5 cases), and stroke (5 cases). The operative mortality of SR group was comparable to CR group (3.2% vs. 6.0%, $p = 0.192$ before matching; 3.5% vs. 7.0%, $p = 0.267$ after matching). Significantly fewer patients needed restarted CPB for root bleeding in SR group (1.6% vs. 7.0%, $p = 0.002$ before matching; 2.1% vs. 8.5%, $p = 0.03$ after matching). The other perioperative outcomes are demonstrated in **Table 3**. There was no significant association between sinus replacement and operative mortality after matching (RR = 0.48; 95% CI 0.16–1.45). A comparison of operative and perioperative outcomes across the three root management groups is shown in **Supplementary Table IV**.

Follow-Up Results

During a median follow-up of 12 (Interquartile Range [IQR] 9–17) months, five and four patients were lost to follow-up in the SR group and CR group, respectively, and 20 patients were lack of latest echocardiography data. There was one late death in each group (unknown reason) and 3 patients received reoperation due to residual aortic root dissection in the CR group. No patients had aortic regurgitation more than moderate during follow-up in both groups. Postoperative deaths were included in the estimation of long-term mortality. No reoperation occurred in the SR group. The estimated cumulative event rate of reoperation was 1.1 % at 12 months and 1.6% at 24 months in the CR group (**Figure 3A**). The estimated cumulative event rate of death was 3.8% at 12 months and 24 months in SR group, and was 6.6% at 12 months and 24 months in the CR group (**Figure 4A**), respectively. No matter before or after matching, there was no significant difference in the long-term cumulative event rate of reoperation in the SR group (log-rank $p = 0.089$ before matching, $p = 0.075$ after matching), and no significant difference in the cumulative event rate of death among the two groups (log-rank $p = 0.218$ before matching, $p = 0.120$ after matching), as shown in **Figures 3**, **4**. In competing risk analysis, there was no significant difference in the cumulative event rate of reoperation after controlling the effect of long-term mortality

TABLE 3 | Perioperative outcome characteristics.

Variable	Unmatched			*P*	Matched			*P*
	Overall *n* = 387	SR group *n* = 187	CR group *n* = 200		Overall *n* = 284	SR group *n* = 142	CR group *n* = 142	
MV duration, hour (median, IQR)	21.0 (13.0–44.0)	21.0 (13.0–56.0)	21.0 (13.0–41.5)	0.34§	19.0 (13.0–40.0)	20.0 (13.0–43.0)	18.5 (13.0–40.0)	0.59§
ICU stay, day (X ±SD)	5.4 ± 4.7	5.5 ± 5.1	5.3 ± 4.2	0.66	5.0 ± 4.3	5.0 ± 4.8	5.0 ± 3.7	0.97
Operative mortality (*n*, %)	18(4.7)	6(3.2)	12(6.0)	0.19	15(5.3)	5(3.5)	10(7.0)	0.27
Restarted CPB for root bleeding (*n*, %)	17(4.4)	3(1.6)	14(7.0)	0.002	15(5.3)	3(2.1)	12(8.5)	0.03
PMI (*n*, %)	1(0.3)	0(0.0)	1(0.5)	1.00*	1(0.3)	0(0.0%)	1(0.7)	1.00
Reoperation for bleeding (*n*, %)	7(1.8)	2(1.1)	5(2.5)	0.45*	2 (0.7)	0(0.0)	2(1.4)	0.50
IABP (*n*, %)	1(0.3)	0(0.0)	1(0.5)	1.00*	1(0.4)	0(0.0)	1(0.7)	1.00
ECMO (*n*, %)	4(1.0)	0(0.0)	4(2.0)	0.12*	4(1.4)	0(0.0)	4(2.8)	0.13
Stroke (*n*, %)	8(2.1)	1(0.5)	7(3.5)	0.07*	5 (1.8)	0(0.0)	5(3.5)	0.06
CRRT (*n*, %)	23(5.9)	12(6.4)	11(5.5)	0.70	14(4.9)	7(4.9)	7(4.9)	1.00
Paraplegia (*n*, %)	6(1.6)	0(0.0)	6(3.0)	0.03*	3(1.1)	0(0.0)	3(2.1)	0.25

SR, sinus replacement; CR, conservative repair; MV, mechanical ventilation; IQR, Interquartile Range; ICU, intensive care unit; CPB, CABG, coronary artery bypass grafting; PMI, myocardial infarction; IABP, intra-aortic balloon pump implantation; ECMO, extracorporeal membrane oxygenation; CRRT, continuous renal replacement therapy.

§*Wilcoxon signed rank test was used.*

**Fisher's exact test was used.*

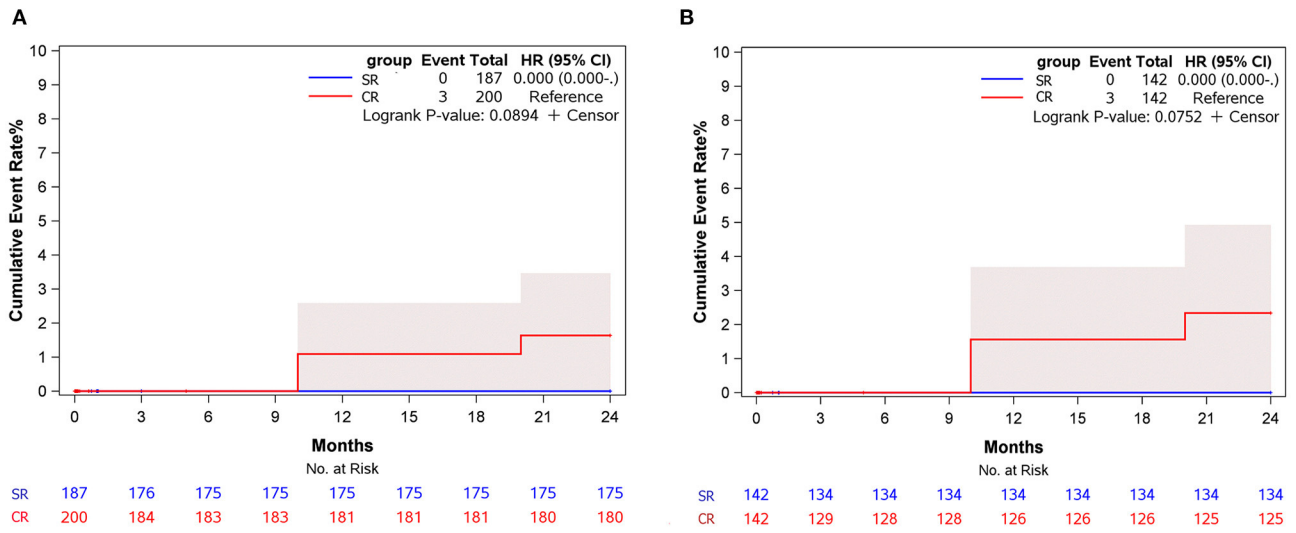

FIGURE 3 | Cumulative event rate of reoperation at 24 months of follow-up for subjects in different surgical groups. **(A)** Before matching. **(B)** After matching.

(Multivariate subdistribution hazard model analysis can be seen in **Supplementary Table III** and survival curves are shown in **Supplementary Figure II**).

DISCUSSION

This study is important because it compares different aortic root repair strategies prospectively. The main findings of our study can be summarized as follows:

1) Regarding pathological features of dissection, sinus replacement was a safe and simple technique with a comparable operative mortality and time spent in operation.
2) Sinus replacement had an advantage in decreasing severe aortic root bleeding that needed to be restarted cardiopulmonary bypass.
3) In short-term follow-up, there was no reoperation in the sinus replacement group.

Even in the third decade of the twenty-first century, treatment of ATAAD is also a challenging task. The management of aortic roots is crucial. For those people with connective tissue disease or a large root (diameter > 45mm), aortic root replacement is appropriate (1).

When the aortic root can be preserved, restoring aortic valve competency and avoiding catastrophic bleeding should be

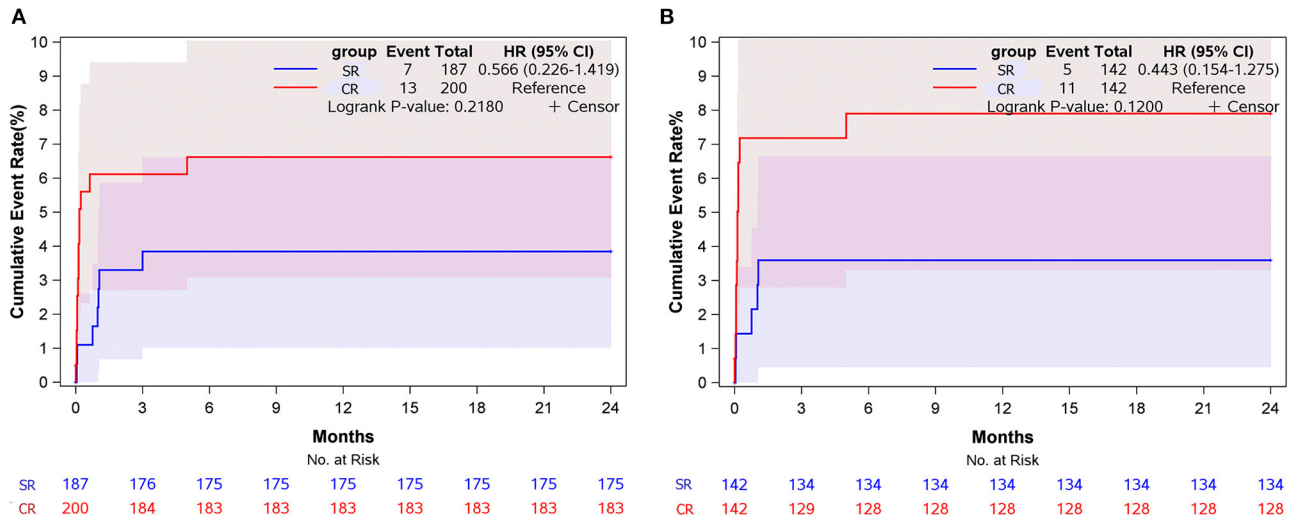

FIGURE 4 | Cumulative event rate of death at 24 months of follow-up for subjects in different surgical groups. **(A)** Before matching. **(B)** After matching.

considered. To eliminate residual dissection and avoid proximal catastrophic bleeding due to vulnerable tissue, multiple root repair techniques using prosthetic and biologic materials have been reported (6, 7, 9, 10).

In our center, we carried out sinus replacement for the patients with severely dissected sinus and preservable roots. This technique had remarkable feasibility because tailoring and suturing the patch were simple and easily observable. The thin and flexible vascular graft patch had no influence on root morphology. We could add stitches on the patch without concerning frail adventitia tearing and catastrophic bleeding. Differing from other methods, we just removed intima but reserved adventitia on basis of two considerations: first, the avulsed intima had lost its structural function and could not hold the suture well; second, dissecting adventitia from surrounding tissues was time-consuming and might lead to adventitia rupture and subsequent bleeding.

In this prospective cohort study, the duration of CPB, cross-clamp HCA, and operation in the SR group was no longer than that of the CR group. The time variables were comparable to Urbanski's study (6). It can be believed that sinus replacement was feasible without wasting time.

Overall, compared with previous studies (6, 7, 9, 10), we had a lower operative mortality and a comparable incidence of main complications in this study. The operative mortality was comparable between the two groups before and after matching. We considered that perioperative death was multifactorial in ATAAD treatment. In this study, management of aortic root was not a risk factor for death after adjusting for other lethal comorbidities. Coronary malperfusion was an independent risk factor of mortality (11) and a successful management of the involved coronary artery was necessary for rescuing patients. The management of the involved coronary artery was reported by several studies (8, 12, 13). For the patients whose coronary orifice was dissected circumferentially, we selected reimplantation of the coronary orifice to the patch in the SR group. The intima of the coronary orifice was trimmed into a button without separating adventitia from surrounding tissue. This was a more precise repair of the coronary orifice. In the CR group, intermittent pledgetted stitches around the orifice or CABG were either choice for circumferentially dissected coronary orifice. According to our strategy, CABG was used as a standard approach for main trunk dissection and detachment of orifice. Fortunately, there were no coronary artery-related events and deaths in both groups. Sinus replacement did not increase operative mortality.

It seemed to be expected that a significantly lower incidence of root bleeding requiring restarted CPB occurred in the SR group. We considered that the intima completely detaching from adventitia was not strong enough to hold the suture. If the intima was not removed completely, once anastomotic bleeding occurred, adding stitches on fragile adventitia and intima would lead to catastrophic bleeding. The sinus replacement technique could avoid these troubles to some extent. Because we preserved adventitia and sutured it with patch together, there was also a space between adventitia and patch. Tight stitching was needed to prevent blood from leaking into this space.

Regarding follow-up, we just presented short-term results. Three patients received reoperation of aortic root due to residual dissection in the CR group. In the SR group no reoperation occurred. There were no significant differences in the cumulative event rate of reoperation between the two groups, even after adjusting by competing risk analysis. This might attribute to the short follow-up time and few reoperation events. The excellent mid-and long-term result of a similar technique was found in Irimie et al. report (14). In their study, there was no aortic root reoperation during follow-up with a mean duration of 70 months. As we speculated before, complete removal of dissected intima could eliminate residual false lumen of the aortic root and decrease the risk of reoperation.

Mazzucotelli et al. (15) found that preservation of the aortic valve during surgery for ATAAD may be a valuable choice

regardless of the severity of AR. The same conclusion was drawn by Rylski et al. (9) and Ro et al. (16). Indeed, aortic regurgitation secondary to aortic dissection is commonly due to detachment of aortic valve commissure and resuspension of the commissures could typically preserve aortic valve competency. In this study, as many as 36.7% of patients received commissure reattachment. The grade of AR significantly improved postoperatively and remained stable during follow-up no matter what approaches were used to repair the root. In the present study, the follow-up duration was short and the stability of aortic valve function needed long-term observation.

This study has some limitations. First, up to 8 surgeons attended this study and performed these procedures, so the differences in technique might increase the uncertainty of the results. Second, the follow-up duration was short and long-term results needed to be determined in the future.

CONCLUSION

Sinus replacement was a safe and simple technique with a comparable operative mortality and time spent in operation. It also had an excellent immediate and short-term results. It had the advantages of eliminating false lumen, preventing severe root bleeding, and might avoid residual aortic root dissection and reoperation.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of Fuwai Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

YC: data curation and writing—original draft. XQ: conceptualization, methodology, investigation, and funding acquisition. HG, YW, CY, XS, BW, QM, YS: investigation. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.880411/full#supplementary-material

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Septal Thickness Does Not Impact Outcome After Hypertrophic Obstructive Cardiomyopathy Surgery (Septal Myectomy and Subvalvular Mitral Apparatus Remodeling): A 15-Years of Experience

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Background: The aim of this study was to assess the impact of septal thickness on long-term outcomes of surgical treatment for hypertrophic obstructive cardiomyopathy (HOCM) and correction of mitral subvalvular anomalies.

Methods: Sixty-six consecutive patients (58 ± 12 years, 56% female) undergoing extended septal myectomy and subvalvular mitral apparatus remodeling from 2007 to 2021 were retrospectively reviewed. Patients were divided into 2 groups according to septal thickness: moderate [< 18 mm, 29 patients (44%)] and severe [≥ 18 mm, 37 patients (56%)]. End points included survival, symptom improvement, reduction of left ventricle outflow tract (LVOT) gradient, resolution of mitral regurgitation (MR), and reoperation.

Results: The mean interventricular septal thickness was 19 ± 3 mm, 15.8 ± 0.8 mm in patients with moderate and 21.4 ± 3.2 mm in those with severe hypertrophy. Preoperative data, intraoperative variables, postoperative complication rates, pre-discharge echocardiographic and clinical parameters did not differ between the two study groups [except for procedures involving the posterior mitral leaflet ($p = 0.033$) and septal thickness after myectomy ($p = 0.0001$)]. Subvalvular apparatus remodeling (secondary chordae of mitral valve resection and papillary muscle and muscularis trabecula procedures including resection, splitting, and elongation) was invariably added to septal myectomy (100%). Four (6%) procedures involved the posterior mitral leaflets. Mitral valve replacement was carried out in two patients (3%, $p = 0.4$). Reoperation

for persistent MR was necessary in one patient (1%, $p = 0.4$). Neither iatrogenic ventricular septal defect nor in-hospital mortality occurred. During follow-up (mean 4.8 ± 3.8 years), two deaths occurred. NYHA class was reduced from 2.9 ± 0.7 to 1.6 ± 0.6 ($p < 0.0001$), the LVOT gradient from 89.7 ± 34.5 to 16.3 ± 8.8 mmHg ($p < 0.0001$), mitral valve regurgitation grade from 2.5 ± 1 to 1.2 ± 0.5 ($p < 0.0001$), and septal thickness from 18.9 ± 3.7 to 13.9 ± 2.7 mm ($p < 0.0001$).

Conclusions: Regardless of septal thickness, subvalvular apparatus remodeling with concomitant septal myectomy can provide satisfactory long-term outcomes in terms of symptom improvement, LVOT obstruction relief, and MR resolution (without mitral valve replacement in most cases) in patients with HOCM.

Keywords: hypertrophic obstructive cardiomyopathy, mitral valve repair, mitral approach, systolic anterior motion, extensive myectomy

INTRODUCTION

Transaortic surgical septal myectomy (1) for the treatment of hypertrophic obstructive cardiomyopathy (HOCM) is associated with low operative morbidity and mortality, and reduction of the outflow gradient (2, 3). Systolic anterior motion (SAM) of the anterior mitral leaflet (AML) as a contributor to the pathophysiology of left ventricle outflow tract (LVOT) obstruction has been addressed (4–6) and in patients without severe hypertrophy (7, 8), SAM and mitral abnormalities (e.g., leaflet elongation and a wide array of malformations of the papillary muscles (PM) and chordae) may influence the dynamic obstruction of LVOT. In this context, the correction of subvalvular mitral apparatus abnormalities in addition to septal myectomy has been advocated (6, 8, 9) in order to abolish the LVOT gradient and to restore mitral competence. Although a matter of debate (10), these procedures include secondary chordae cutting (11), anterior leaflet plication (12) or extension (13), reorientation of PM (14), edge-to-edge repair (15), and mitral valve (MV) surgery (6, 7, 9, 16). MV replacement has been also reported (7, 16) if SAM and severe mitral regurgitation (MR) are challenging to manage.

The role of septal thickness in long-term outcomes of correction of subvalvular mitral apparatus abnormalities during myectomy is an under-studied matter of debate.

In this study we sought to assess the implications of septal thickness in long-term clinical and echocardiographic outcomes of patients requiring subvalvular MV remodeling (6, 9) in addition to extended septal myectomy.

MATERIALS AND METHODS

This retrospective and monocentric study was approved by the ethics committee of our institute (IRRB/35/16) and individual consent was obtained from each patient.

Study Population

The study included 66 consecutive adult patients with HOCM treated surgically by extended septal myectomy and subvalvular MV remodeling between March 2007 and September 2021 at our institution. The patients had peak LVOT gradients ≥ 50 mmHg at rest or during stress and drug-refractory disabling symptoms (17) and were divided in 2 groups according to the septal thickness: moderate [< 18 mm, 29 patients (44%)] and severe [≥ 18 mm, 37 patients (56%)]. The cutoff of 18 mm was decided according to data available in the literature (7, 8). The 66 patients operated on represent 37% of 178 patients referred to our dedicated hypertrophic obstructive cardiomyopathy out-patient clinic who underwent surgery. Exclusion criteria were: history of mitral operation (including Mitraclip). Emergency operations and patients having undergone previous surgical myectomy or alcoholization were included.

Review of hospital records and analysis of preoperative history and reports, operative notes, and postoperative and follow-up echocardiography reports were carried out using a dedicated database.

Diagnosis

All patients underwent preoperative Doppler transthoracic echocardiogram examination. Measurements of septal thickness were performed at end-diastole, in short-axis views from the mitral and mid left ventricle levels. Resting LVOT velocity was measured by continuous-wave Doppler of the outflow tract from an apical window. In HOCM patients who had a resting LVOT gradient < 30 mmHg but manifested drug refractory symptoms, provocative maneuvers such as the Valsalva were used during examination. Less symptomatic patients with LVOT gradient > 50 mmHg at rest underwent stress-echocardiogram. MV anatomy and function were evaluated by transthoracic and transesophageal echocardiogram (TEE) using an interactive approach. The degree of MR was measured by Doppler color flow imaging and quantitatively graded as mild (1 + /4 +), moderate (2 + /4 +), moderate-to-severe (3 + /4 +) and severe (4 + /4 +). A thorough analysis of the mitral subvalvular anomalies, including fibrotic and retracted secondary chordae inserted on the AML, abnormal chordae tendineae attached to the ventricular septum or free wall, and PM abnormalities was performed (6, 18). Cardiovascular magnetic resonance imaging providing detailed information on cardiac morphology, ventricular function, and myocardial

tissue characteristics was not routinely performed. Most patients underwent pre-operative genetic and electrophysiology consults. Coronary anatomy was evaluated by angiograms and computed tomography scans. Intraoperative specimens were evaluated by pathologists.

Surgical Technique

Complete surgical details have been reported previously (6), **Figure 1**. The operations were guided by TEE with particular attention paid to the septal anatomy and thickness, and MV apparatus. Briefly, all operations were performed through a full sternotomy, with aorta and right atrial cannulation and intermittent antegrade cold blood cardioplegia, and with mild hypothermia (34°C). Transaortic myectomy was performed in all patients starting at nadir of the right coronary sinus, and extended apically to achieve exposure of the PM bases. Muscular resection was extended toward the lateral ventricular wall up to the left trigone. The PM were carefully inspected to detect any hypertrophy, fusion, displacement, anomalies, or aberrances (e.g., bifurcation and fibrosis). Subvalvular mitral apparatus remodeling included (1) resection of all anomalous muscular trabecula and accessory PM; (2) resection of fibrotic, thickened, and agglutinated secondary chordae tendineae from the tip of the PM to the ventricular surface of the anterior mitral leaflet; and (3) splitting of hypertrophied and thickened PM. In cases of mitral leaflet repair, bicaval cannulation and a left or right atrial approach was used. The leaflet repair was done after myectomy and after the complete "release" of the AML obtained by the resection of diseased secondary chordae "anchoring" the leaflet itself to the PM and the septum. Further procedures on cardiopulmonary bypass were performed if necessary. After weaning from cardiopulmonary bypass and before protamine administration, a pharmacological stress test with adrenaline (from 5 to 10 mcg) was performed to assess for any residual LVOT gradient, SAM, and MR by the induction of tachycardia and systemic hypertension.

Outcomes

Primary outcomes of the study were survival, symptom improvement [decrease in New York Heart Association (NYHA) functional class], reduction of LVOT gradient, and resolution of MR. Secondary outcomes included postoperative complications and reoperation for recurrence of LVOT obstruction and severe MR.

Follow-Up Data

Yearly patient follow-up included physical examination, chest X-ray, electrocardiogram, transthoracic echocardiogram, and blood tests, and was performed in our dedicated outpatient clinic or by telephone interview. At September 1, 2021, the follow-up was 100% complete. The longest follow-up time was 14.6 years.

Statistical Analysis

Continuous variables were expressed as mean, standard deviation, and range. Categorical variables were expressed as absolute value and percentage. The comparison between (1) patients with septal thickness < 18 mm and ≥ 18 mm; (2) NYHA, LVOT gradient, septum thickness, and residual MR before and after surgery were assessed by Chi-Square test, Fisher's exact test, and logistic regression. Linear regression analysis was also applied to assess association with outcomes with septal thickness considered as a continuous predictor. Freedom from events at follow-up was assessed with Kaplan–Meier estimator and log-Rank test. Data management and analysis were done with SAS version 9.4. All p-values of < 0.05 were considered statistically significant.

RESULTS

Patient Characteristics

The preoperative characteristics of the patients are depicted in **Table 1**. No major differences were observed between the two groups. The mean age was 58 ± 12 years, with 29 males and 37 females. Although patients were treated medically with β-blockers and/or calcium-channel blockers, all were symptomatic in NYHA class I-II ($n = 15$), III ($n = 40$), or IV ($n = 11$). Nine patients (13%) had a history of acute pulmonary edema and one (1%) was hospitalized at our institute due to cardiogenic shock. One patient underwent a second reoperation because of failure of previous surgeries performed elsewhere. History of previous alcoholization was recorded in one patient.

The mean interventricular septal thickness was 19 ± 3 mm, 15.8 ± 0.8 mm in patients with moderate and 21.4 ± 3.2 mm in those with severe hypertrophy. Six (9%) patients had an extreme septal thickness (≥ 26 mm). Intraventricular peak gradient was 89 ± 34 mmHg. MR was graded 1 + and 2 + /4 + in 29 patients, 3 + /4 + in 25 patients, and 4 + /4 + in 12 patients. The average length of the AML and posterior mitral leaflet were 26 ± 3 mm and 16 ± 3 mm, respectively. A significant difference in neither preoperative clinical characteristics nor in echocardiographic data were detected between patients with moderate and severe septal thickness.

Perioperative Outcomes

Surgical data and postoperative outcomes are summarized in **Table 2**. Intraoperative data, postoperative complication rate, and pre-discharge echocardiographic and clinical parameters did not differ between the two study groups [except for procedures involving the posterior mitral leaflet ($p = 0.033$) and septal thickness after myectomy ($p = 0.0001$)]. The analysis of the LVOT demonstrated thickened secondary chordae tendineae tractioning the AML to the interventricular septum in 64 patients (97%) and PM malformations in 55 patients (83%) including PMs hypertrophy (25 patients, 37%), accessory PMs (17 patients, 25%) and PMs fusion (13 patients, 20%). Surgical myectomy was performed in all patients (100%). Subvalvular mitral apparatus remodeling by means of secondary MV chordae resection (97%) and PM procedures (resection, splitting, and elongation; 83%) was added to myectomy where indicated. The mean number of resected secondary chordae was 3 ± 1.

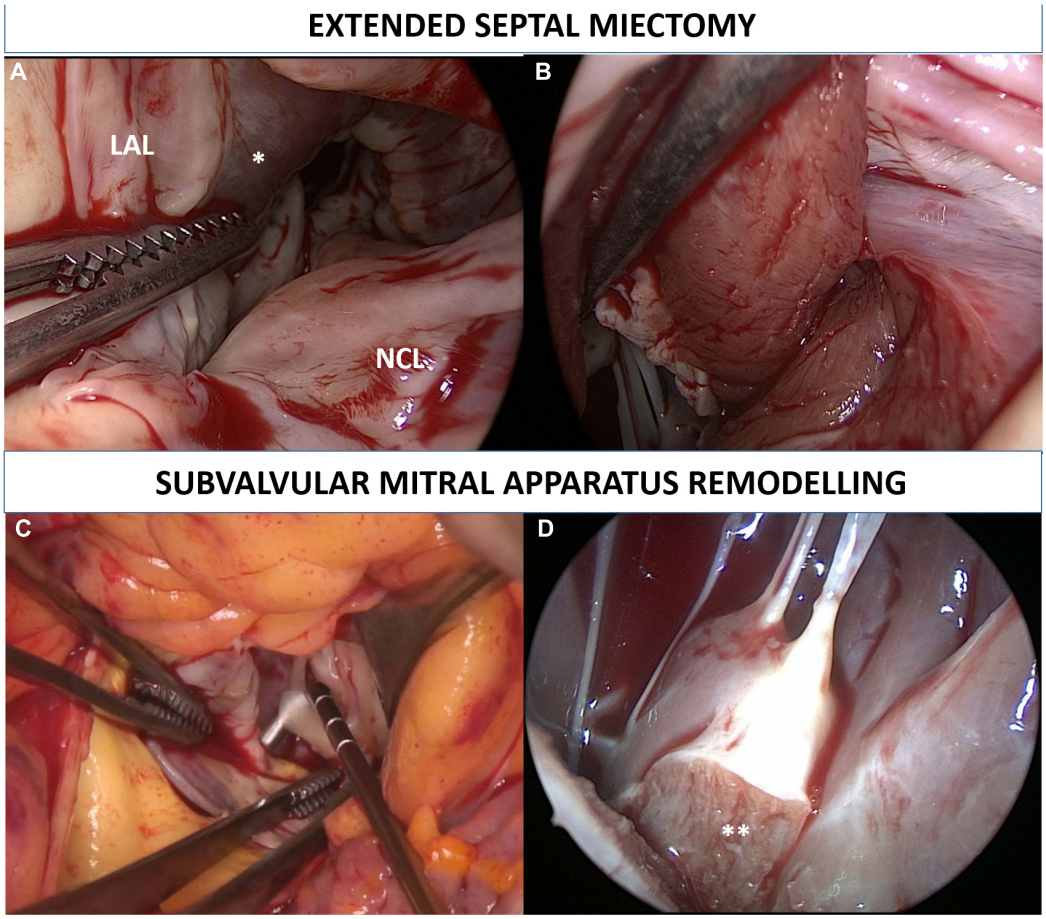

FIGURE 1 | Extended septal myectomy. Surgical view of the left ventricle outflow tract before the procedure is depicted in panel **(A)**. Transaortic myectomy was performed in all patients starting at nadir of the right coronary sinus, and extended apically to achieve exposure of the papillary muscles bases. Muscular resection was extended toward the lateral ventricular wall up to the left trigone **(B)**. Subvalvular mitral apparatus remodeling included (1) resection of fibrotic, thickened, and agglutinated secondary chordae tendineae from the tip of the papillary muscles to the ventricular surface of the anterior mitral leaflet **(C)**; (2) resection of all anomalous muscular trabecula and splitting (**) of hypertrophied and thickened papillary muscles **(D)**. LAL, left aortic leaflet; NCL, non-coronary leaflet. *Interventricular septum bulging.

In 4 patients, due to redundancy and excessive tissue of the posterior mitral leaflet, resection and shortening of the leaflet itself was performed. Of note, all four of these patients were in the moderate septal thickness group. Intuitively, the septal thickness reduction was greater in the group with septal thickness less than 18 mm (12.7 ± 1.4 mm vs. 15 ± 2.9 mm, $p = 0.0001$). Two patients required valve replacement due to persistent severe MR after LVOT obstruction resolution. One patient, at the beginning of our experience in 2007, underwent early reoperation (during the same hospitalization) after a complicated postoperative course. A mechanical mitral prosthesis for recurrent SAM and severe MR was implanted on postoperative day 55 and the patient was discharged on post-operative day 6. In a 58-year-old female patient, a mechanical prosthesis was necessary after 3 failed attempts (including posterior leaflet shortening) to correct severe MR, although complete LVOT obstruction and SAM resolution were obtained. In this case, the AML was dysplastic and retracted. Aortic valve replacement (6 patients) and coronary artery bypass (2 patients) were also performed. No iatrogenic ventricular septal defect occurred. Intraoperative, in-hospital, and 30-day mortality were 0%. No patients developed complete atrioventricular block, but 3 patients (4%) required pacemaker implantation because of tachy-brady syndrome. Pre-discharge pharmacological treatment included b-blockers (56 patients, 85%), diuretics (52 patients, 79%), renin-angiotensin-aldosterone system inhibitors (23 patients, 35%) and calcium channel blockers (4 patients, 6%).

Follow-Up Results

The mean follow-up time was 4.8 ± 3.8 years (range 0–14.5). Two deaths occurred, one at 83 days after surgery due to gastrointestinal bleeding and cardiogenic shock. The same patient was admitted in cardiogenic shock before HOCM surgery and a postmortem autopsy showed severe myocardial fibrosis, suggesting irreversible diastolic dysfunction. A late death

TABLE 1 | Baseline characteristics.

	All, $n = 66$	Septal thickness < 18 mm ($n = 29$)	Septal thickness ≥ 18 mm ($n = 37$)	*P*-value
Female sex	37 (56)	20 (54)	17 (46)	0.08
Age (years)	58.4 ± 12.5 (26–80)	59.5 ± 11.7 (36–80)	57.5 ± 13.2 (26–75)	0.5
BMI (kg/m^2)	27.6 ± 3.4 (20–39)	26.8 ± 3.1 (20–35)	28.3 ± 3.4 (21–39)	0.07
Family history for HOCM	22 (33)	9 (13)	13 (20)	0.7
Family history for SCD	23 (34)	9 (13)	14 (21)	0.6
Previous alcoholization	1 (1)	1 (1)	0 (0)	0.4
Syncope/lipothimia	15 (22)	6 (9)	9 (13)	0.7
Angina	33 (50)	12 (18)	21 (32)	0.3
Acute pulmonary edema	9 (13)	4 (6)	5 (7)	1
Pre-operative NYHA functional class	2.9 ± 0.7 (1–4)			0.6
I–II, n (%)	15 (22)	6 (9)	9 (13)	
III, n (%)	40 (61)	18 (28)	22 (33)	
IV, n (%)	11 (17)	5 (7)	6 (10)	
Pre-operative atrial fibrillation	37 (56)	13 (19)	24 (37)	0.1
Pre-operative SAM	53 (80)	22 (41)	31 (59)	0.5
Pre-operative ICD	13 (19)	3 (4)	10 (15)	0.1
Pre-operative LVEF (%)	64.2 ± 7.1 (40–83)	63.9 ± 5.3 (55–75)	64.5 ± 8.3 (40–83)	0.7
Pre-operative SPAP (mmHg)	27.4 ± 11.1 (19–70)	28.8 ± 12.8 (19–70)	26.4 ± 9.6 (20–58)	0.3
Pre-operative LVOT gradient* (mmHg)	89.7 ± 34.5 (28–174)	95.5 ± 35.6 (28–174)	85.1 ± 33.4 (40–165)	0.2
Pre-operative septal thickness (mm)	18.9 ± 3.7 (14–29)	15.8 ± 0.8 (14–17)	21.4 ± 3.2 (19–29)	0.7
Pre-operative MR grade	2.5 ± 1 (0–4)			0.4
1 + and 2 + /4 +	29 (43)	14 (21)	15 (22)	
3 + /4 +	25 (39)	9 (13)	16 (26)	
4 + /4 +	12 (18)	6 (9)	6 (9)	
Anterior mitral leaflet length (mm)	26.5 ± 3.8 (18–35)	26.2 ± 3.5 (21–32)	26.7 ± 4 (18–35)	0.6
Posterior mitral leaflet length (mm)	16.6 ± 3.7 (8–24)	17.5 ± 2.8 (11–22)	16 ± 4.2 (8–24)	0.1

BMI, body mass index; HOCM, Hypertrophic obstructive cardiomyopathy; SCD, sudden cardiac death; NYHA, New York Heart Association; SAM, systolic anterior motion; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; SPAP, systolic pulmonary artery pressure; LVOT, left ventricle outflow tract; MR, mitral regurgitation.

**Peak gradient at rest.*

Continuous variables were expressed as mean, standard deviation and range.

Categorical variables were expressed as absolute value and percentage.

occurred in one patient due to pneumonia 717 days after surgery. This patient underwent reoperation 97 days after HOCM surgery because of endocarditis of the aortic prosthesis and pacemaker lead. Follow-up data are available in **Table 2**. Recurrence of SAM was detected in 7 patients without significant obstruction. Severe MR occurred in one patient who is currently under close follow-up for asymptomatic MR. Two patients with obesity had NYHA III symptoms at follow-up.

At the last available follow-up, the survival and freedom from reoperation was 96%. NYHA class was reduced from 2.9 ± 0.7 to 1.6 ± 0.6 ($p < 0.0001$), the LVOT gradient from 89.7 ± 34.5 to 16.3 ± 8.8 mmHg ($p < 0.0001$), MV regurgitation grade from 2.5 ± 1 to 1.2 ± 0.5 ($p < 0.0001$), and septal thickness from 18.9 ± 3.7 to 13.9 ± 2.7 mm ($p < 0.0001$), **Figure 2**. Freedom from composite end points at follow-up by means of recurrent LVOT obstruction (peak gradient ≥ 20 mmHg), MR ≥ 3 + /4 + , and NYHA ≥ 3 are depicted in **Figure 3**. Seven patients (10%) showed a mean LVOT peak gradient of 35.8 ± 2.6 mmHg and a mean NYHA class 2.2 ± 0.4 (in two patients were detected a 2 + /4 + grade of MV regurgitation. All these patients are medically treated and strictly followed at out outpatients clinic. Details of these patients are depicted in **Supplementary Table 1**.

Further linear regression analysis of LVOT obstruction ($p = 0.2232$), SAM ($p = 0.2982$), and MR ($p = 0.6468$) recurrence with septal thickness as the continuous variable did not show any statistical relationship.

DISCUSSION

This study reports the long-term clinical and echocardiographic outcomes of subvalvular mitral anomalies correction with concomitant extended septal myectomy in HOCM patients with moderate (< 18 mm) and severe (≥ 18 mm) inteventricular septal thickness.

Our 15-year experience demonstrates that (1) HOCM is a wide spectrum of disease in which both septal hypertrophy and the MV apparatus invariably contribute to dynamic LVOT obstruction; (2) the subvalvular mitral apparatus (chordae and PM) promote SAM and contribute to obstruction; (3) regardless of septal thickness, subvalvular apparatus remodeling

TABLE 2 | Intraoperative results, early and long term outcomes.

	All, *n* = 66	**Septal thickness < 18 mm (*n* = 29)**	**Septal thickness ≥ 18 mm (*n* = 37)**	***P*-value**
Aortic cross-clamp (min)	41.4 ± 10.6 (20–80)	41.9 ± 10.9 (20–65)	41.1 ± 10.6 (24–80)	0.7
Cardiopulmonary bypass (min)	56.5 ± 12.7 (25–105)	56.8 ± 13.7 (25–88)	56.2 ± 12.1 (38–105)	0.8
Resected cords (n)	3.5 ± 1.6 (0–8)	3.5 ± 1.6 (0–8)	3.5 ± 1.6 (0–7)	0.9
Procedures on papillary muscles (n)	1.3 ± 0.8 (0–3)	1.4 ± 0.9 (0–3)	1.2 ± 0.8 (0–2)	0.4
Mitral valve replacement	2 (3)	0	2 (3)	0.4
Intraoperative mitral valve replacement for MR	1 (1)	0	1 (1)	0.4
Posterior mitral leaflet shortening	4 (6)	4 (6)	0 (0)	**0.033**
Other procedures	6 (9)	4 (6)	2 (3)	0.3
Blood transfusion	37 (56)	17 (25)	20 (30)	0.8
Re-exploration	1 (1)	1 (1)	0 (0)	0.4
Low cardiac output syndrome	2 (3)	1 (1)	1 (1)	1
Sepsis	3 (4)	1 (1)	2 (3)	1
Post-operative atrial fibrillation	33 (50)	11 (16)	22 (34)	0.1
Post-operative PM implantation	3 (4)	2 (3)	1 (1)	0.5
Post-operative Complete AV block	0			
Iatrogenic ventricular septal defect	0			
Length of stay (days)	10.6 ± 8.3 (5–62)	10.1 ± 6 (5–33)	10.9 ± 9.8 (5–62)	1
Pre-discharge SAM	2 (3)	1 (1)	1 (1)	1
Pre-discharge				
LVOT gradient* (mmHg)	15.4 ± 8.5 (0–33)	14.7 ± 8 (0–30)	16 ± 8.8 (0–33)	0.5
Septal thickness (mm)	14 ± 2.6 (7–16)	12.7 ± 1.4 (10–16)	15 ± 2.9 (7–16)	**0.0001**
NYHA functional class	1.3 ± 0.5 (1–3)			0.7
I–II	63 (95)	27 (41)	36 (55)	0.7
III	3 (5)	2 (3)	1 (1)	
MR grade	1.2 ± 0.6 (0–3)			0.2
≤ 1 + /4 +	50 (75)	25 (37.5)	25 (37.5)	
2 + /4 +	15 (22)	4 (6)	11 (16)	
3 + /4 +	1 (3)	0	1 (3)	
Hospital mortality	0			
Follow-up				
SAM	7 (11)	2 (3)	5 (8)	0.5
LVOT gradient* (mmHg)	16.3 ± 8.8 (6–40)	18.2 ± 9.2 (6–40)	14.8 ± 8.2 (8–39)	0.1
Septal thickness (mm)	13.9 ± 2.7 (9–16)	12.9 ± 1.9 (10–18)	14.8 ± 3 (9–16)	**0.0068**
NYHA functional class	1.6 ± 0.6 (1–3)			0.9
I	27 (43)	11 (17)	16 (25)	
II	35 (54)	16 (25)	19 (29)	
III	2 (3)	1 (1)	1 (1)	
MR grade	1.2 ± 0.5 (0–4)			0.6
≤ 2 + /4 +	62 (98)	28 (44)	34 (54)	
4 + /4 +	1 (2)	0	1 (1)	
Reoperation at follow-up for MR	0			
Exitus at follow-up	2 (3)	1 (1.5)	1 (1.5)	1

MR, mitral regurgitation; PM, pacemaker; AV, atrio-ventricular; SAM, systolic anterior motion. LVOT, left ventricle outflow tract; NYHA, New York Heart Association.
**Peak gradient at rest.*
Continuous variables were expressed as mean, standard deviation and range.
Categorical variables were expressed as absolute value and percentage.
Bold values are referred to the significative p value.

added to septal myectomy can provide satisfactory early- and long-term outcomes in terms of symptom improvement, LVOT obstruction, and MR resolution; (4) conservative procedures on the subvalvular mitral apparatus ("remodeling") can correct SAM and MR and avoid, in most cases, MV replacement; (5) surgical remodeling of the subvalvular apparatus does not impair MV function at long-term follow-up; and (6) a dedicated HOCM team (dedicated clinical

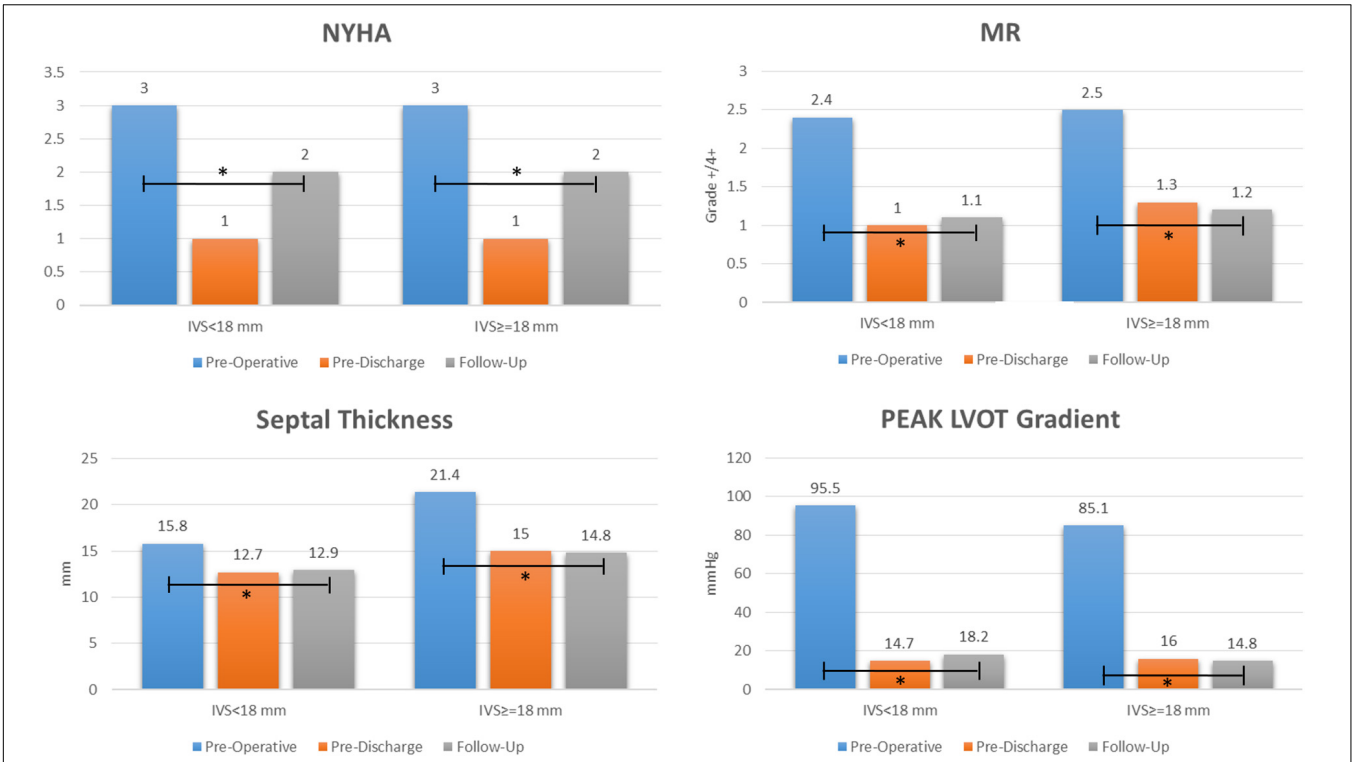

FIGURE 2 | Early and long term outcome after extended septal myectomy and subvalvular mitral apparatus remodeling. NYHA: New York Heart Association; MR: mitral regurgitation; LVOT: left ventricle outflow tract; IVS: interventricular septum. "*" explains the events.

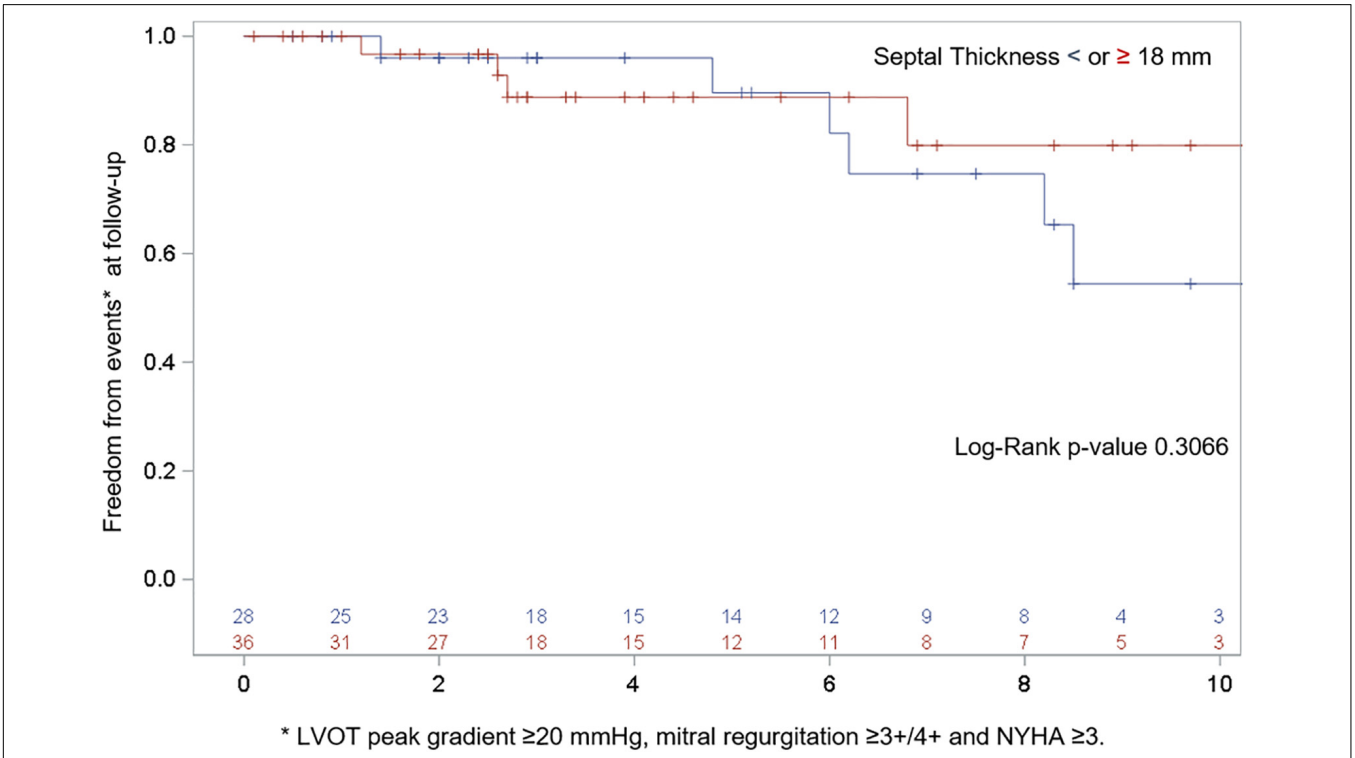

FIGURE 3 | Freedom from composite end points at follow-up by means of recurrent LVOT obstruction (peak gradient ≥ 20 mmHg), MR ≥ 3 + /4 + and NYHA ≥ 3. *$p = 0.0001$.

and interventional cardiologists, radiologists, surgeons, pathologists, and geneticists) is crucial to assess patients with hypertrophic cardiomyopathy and for planning the most appropriate treatment.

In our series, septal myectomy was performed in all cases, confirming the well-defined role of this technique for the relief of drug-refractory symptoms in patients with LV outflow obstruction (1–3, 17). Presently, the mortality rate after this procedure is below 1% (19, 20) and approaching zero in some series (21).

Concerns surround managing patients with moderate hypertrophy (7, 8, 11) in which the role of the MV in LVOT obstruction is predominant (4–6). Isolated myectomy should be considered cautiously because of iatrogenic ventricular septal defect occurrence and the insignificant relief of symptoms and LVOT obstruction (22). In fact, less marked septal basal hypertrophy may not be the sole cause of LVOT obstruction (8) and this clinical picture has been reported to be associated with mitral valvular and subvalvular anomalies (7, 8). These variants include changes in the MV leaflets (elongation, laxity, calcifications) and, more often, aberrancies of PM and secondary chordae (4, 5). We defined the complex anatomy of the LVOT in patients with HOCM as a "crowded" LVOT (18) in which, historically, replacement of the MV and subvalvular apparatus resection was the only viable option to treat the SAM-mediated obstruction and MR (22). In 2019, The Society of Thoracic Surgeons reported results of septal myectomy in the United States from a national database of more than 2,300 patients (16). About 1/3 of septal myectomy cases required MV operation ($n = 801$), including mitral repair (62%) and replacement (38%). Replacement compared to repair was associated with an increased risk of in-hospital mortality (4.4% vs. 1.9%) and MV surgery in addition to isolated septal myectomy (mortality 1.6%) was associated with an increased composite risk [OR 1.81, 95% confidence interval (CI): 1.39 to 2.36, $p < 0.0001$]. In the series by Lapenna et al. (7) the long-term mortality was higher in 23 patients with moderate septal thickness that required MV replacement plus septal myectomy compared to those with septal myectomy alone ($n = 41$) or septal myectomy plus MV repair ($n = 12$). In a prospective clinical trial (NCT02054221), 88 patients were randomized to MV replacement or repair during myectomy. At 2-year follow-up, the rates of overall survival, freedom from sudden cardiac death, and freedom from thromboembolic events were significantly higher in the repair group (23). Finally, the same group conducted a meta-analysis of over 2,762 patients with HOCM and MR (24) reporting a strong clinical benefit of MV repair compared to replacement in adult patients with HOCM.

The superiority of MV repair is well established for degenerative MV disease (25) and all efforts should be made to preserve the MV in patients with HOCM.

There is debate whether myectomy alone is enough to achieve the best outcome even in patients with moderate septal thickness. A dedicated high-volume center (10) reported on 1,486 surgical HOCM patients stratified by basal septal thickness (< 18 mm, $n = 369$; 18–21 mm, $n = 612$; and > 21 mm, $n = 505$). All patients underwent septal myectomy alone, regardless of septal thickness and degree of SAM-related MR. Concomitant MV procedures were performed for patients with intrinsic MV disease (66%) or insufficient intraoperative results in terms of residual mitral regurgitation (30%) and gradient (2%) after extended septal myectomy. In the group with septum < 18 mm, at early postoperative follow-up, moderate/severe mitral regurgitation was documented in only 2% of patients and SAM in 27.5%, with no difference compared to patients with a baseline septum ≥ 18 mm. The lack of long-term follow-up echocardiographic data is the major limitation of this study.

On the other hand, subvalvular mitral procedures are routinely performed at other dedicated HOCM centers with excellent results (6, 9, 11–13). For instance, the role of diseased secondary chordae in obstruction, especially in cases of a relatively thin septum, has been demonstrated by Ferrazzi et al. (11) Anomalous chordae resection (median of 3, range 1–8) associated with a shallow myectomy in 39 patients (with a ventricular septal thickness ≤ 19 mm) showed better clinical and hemodynamic results compared with a control group (only myectomy, 29 patients).

Our series provides long-term clinical and echocardiographic outcomes of procedures involving the subvalvular mitral apparatus during HOCM surgery. Release of the AML achieved by the technique described allows for coaptation of the mitral leaflet far from the septum and provides resolution of LVOT obstruction. Neither ventricular septal defect nor hospital mortality occurred. Intraoperative MV replacement because of a failed procedure due to severe MR recurrence was necessary in one patient. Pacemaker implantation rate was consistent with data from another single-center report (16). Our research highlights the complex anatomic interactions among the basal septal hypertrophy, mitral valvular and subvalvular abnormalities and SAM-in HOCM moreover when the septal thickness is less marked (91% of patients showed a septal thickness ≤ 24 mm), and contributes further data to the debate over surgical myectomy or alcoholization, though the use of the latter has increased in Europe in recent decades (25). This study also reports the definitive benefits of subvalvular mitral apparatus procedures added to septal myectomy in experienced centers. Preoperative planning, based on individual anatomic findings, and tailored surgical treatment resulted in excellent outcomes.

This is a single-center series of consecutive patients retrospectively reviewed. The small sample size and the lack of certain data (e.g., type of HOCM and hypertrophy localization, weight of the resected muscle, histopathologic analysis and cardiac magnetic resonance findings) should be considered its major limitations.

CONCLUSION

Subvalvular apparatus remodeling added to septal myectomy can provide satisfactory early and long-term

outcomes in terms of symptom improvement, LVOT obstruction relief, and MR resolution in patients with HOCM regardless of septal thickness.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available due to the nature of this research, participants of this study did not agree for their data to be shared publicly, so supporting data is not available. Requests to access the datasets should be directed to GR, giuseppe.raffa78@gmail.com.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by IRCCS-ISMETT. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

GR: conceptualization, formal analysis, methodology, supervision, validation, and writing—original draft. EF, CL, AP, AR, and MG: data curation and validation. MK and SL: methodology and writing—review and editing. SS, MT, VS, MM, and GM: data curation and supervision. MP: conceptualization, supervision, and validation. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.853582/full#supplementary-material

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Clinical Insights to Complete and Incomplete Surgical Revascularization in Atrial Fibrillation and Multivessel Coronary Disease

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Objectives: Although endorsed by international guidelines, complete revascularization (CR) with Coronary Artery Bypass Grafting (CABG) remains underused. In higher-risk patients such as those with pre-operative atrial fibrillation (AF), the effects of CR are not well studied.

Methods: We analyzed patients' data from the HEIST (HEart surgery In AF and Supraventricular Tachycardia) registry. Between 2012 and 2020 we identified 4770 patients with pre-operative AF and multivessel coronary artery disease who underwent isolated CABG. We divided the cohort according to the completeness of the revascularization and used propensity score matching (PSM) to minimize differences between baseline characteristics. The primary endpoint was all-cause mortality.

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Results: Median follow-up was 4.7 years [interquartile range (IQR) 2.3–6.9]. PSM resulted in 1,009 pairs of complete and incomplete revascularization. Number of distal anastomoses varied, accounting for 3.0 + –0.6 vs. 1.7 + –0.6, respectively. Although early (< 24 h) and 30-day post-operative mortalities were not statistically different between non-CR and CR patients [Odds Ratio (OR) and 95% Confidence Intervals (CIs): 1.34 (0.46–3.86); P = 0.593, Hazard Ratio (HR) and 95% CIs: 0.88 (0.59–1.32); P = 0.542, respectively] the long term mortality was nearly 20% lower in the CR cohort [HR (95% CIs) 0.83 (0.71–0.96); P = 0.011]. This benefit was sustained throughout subgroup analyses, yet most accentuated in low-risk patients (younger i.e., < 70 year old, with a EuroSCORE II < 2%, non-diabetic) and when off-pump CABG was performed.

Conclusion: Complete revascularization in patients with pre-operative AF is safe and associated with improved survival. Particular survival benefit with CR was observed in low-risk patients undergoing off-pump CABG.

Keywords: atrial fibrillation, CABG, complete revascularization, survival, long-term

INTRODUCTION

Although never compared directly in a randomized controlled trial (RCT), complete revascularization (CR) during coronary artery bypass grafting (CABG) is considered to be superior to incomplete revascularization (ICR) in multi-vessel coronary artery disease (MV-CAD). The benefit is thought to originate from reduced risk of future cardiovascular events, namely periprocedural myocardial infarction (MI) and repeat revascularization (RR). Many observational studies, as well as insights from subgroup analysis of RCTs reinforced this notion (1–3). Several RCTs which investigated CR in the context of percutaneous intervention (PCI) for ST-elevation myocardial infarction (STEMI) have shown the benefit of complete, compared to ICR for MV-CAD (4–6). However, surgical revascularization is still the first-choice procedure in high-risk non-acute MI patients, specifically those with diabetes (7) and intermediate-to-high anatomical complexity coronary disease (8).

The 2018 ESC/EACTS guidelines on myocardial revascularization emphasized that the expected highest completeness of revascularization should guide the choice of treatment strategy (9). The question arises if surgeons should attempt CR at all costs and, if not, what type of risk factors may discourage them from pursuing one. Atrial fibrillation (AF) is an independent predictor of mortality and morbidity after CABG (10, 11). Apart from an increased risk of stroke, AF is also associated with an over a fourfold increased risk of developing heart failure (12). Moreover, an impaired graft flow in AF CABG patients was observed (13). Most reports estimate the pre-op AF prevalence in CABG patients at 6–10%, but in some reports, it was as high as 20% (14). Because of aging of the society, the prevalence of AF is likely to rise.

The disparity in reported results of CR in CABG, and the shortage of evidence in high-risk patients, requires further investigation (15, 16). The current study aimed to address whether there exists a survival benefit with CR in MV-CAD and underlying AF.

PATIENTS AND METHODS

Study Population and Clinical Variables

Because of the retrospective nature of the study, the ethics committee approval was waived. Our investigation was a part of the HEIST (Heart Surgery In atrial fibrillation and Supraventricular tachycardia) Registry (NCT04860882). We included consecutive AF patients, over 18 year old, admitted to 8 tertiary centers in Poland, Netherlands, and Italy between January 2012 and December 2020 who had isolated CABG for MV-CAD performed (**Supplementary Figure 1**). Patients who (1) had no diagnosis of AF; (2) had CABG with concomitant valvular or aortic procedures, were not included in the study. Similarly, (3) patients with single-vessel CAD or (4) patients in whom the number of distal anastomoses and/or type of graft material used could not be determined were excluded from the analyses. (5) Patients undergoing hybrid revascularization by intention-to-treat protocol, or who were admitted for (6) staged revascularization strategy or (7) re-do surgery were not included.

Endpoints and Definitions

The primary endpoint was all-cause mortality following complete vs. incomplete surgical revascularization for MV-CAD. We defined CR as grafting two significantly stenotic lesions in two-vessel disease and three lesions in three-vessel disease of different territories: right coronary artery (RCA), left anterior descending- (LAD), and circumflex- (Cx) artery. Additional grafts to the diseased systems were encouraged and when the number of grafts was greater than the number required for CR, the approach was considered as "supracomplete" revascularization (SCR). Only the coronary vessels with significant stenosis were bypassed. We defined ICR as failure to graft two significantly

TABLE 1 | Pre-operative characteristics after PS-matching.

	Total (2018)	Non-CR (1009)	CR (1009)	*P*-value
Baseline characteristics				
Age years [median (IQR)]	70 (64–76)	70 (64–76)	70 (64–76)	0.792
Male gender	1589 (78.7)	795 (78.8)	794 (78.7)	0.99
EuroSCORE II	1.91 (1.21,3.19)	1.92 (1.22, 3.19)	1.90 (1.18, 3.19)	0.760
Diabetes	899 (44.5)	457 (45.3)	442 (43.8)	0.531
Insulin ± oral hypoglycemic drugs	372 (18.4)	186 (18.4)	186 (18.4)	0.99
Smoking	1247 (61.8)	628 (62.2)	619 (61.3)	0.714
Hypertension	1829 (90.6)	917 (90.9)	912 (90.4)	0.760
Hyperlipidemia	1293 (64.1)	656 (65.0)	637 (63.1)	0.404
BMI [median (IQR)]	28.69 (25.78–31.70)	28.70 (25.65, 31.71)	28.69 (25.95, 31.67)	0.815
Pulmonary hypertension[a]	154 (7.6)	86 (8.5)	68 (6.7)	0.154
Renal impairment	1128 (55.9)	570 (56.5)	558 (55.3)	0.622
Dialysis (regardless of CC)	26 (1.3)	13 (1.3)	13 (1.3)	0.99
Peripheral artery disease	515 (25.5)	263 (26.1)	252 (25.0)	0.610
Cerebrovascular disease	162 (8)	75 (7.4)	87 (8.6)	0.368
History of stroke	73 (3.6)	34 (3.4)	39 (3.9)	0.634
History of TIA/RIND	72 (3.6)	28 (2.8)	44 (4.4)	0.071
chronic lung disease	111 (5.5)	56 (5.6)	55 (5.5)	0.99
LVEF (%) [median (IQR)][a]	50 (40–55)	50 (40–55)	49 (40–55)	0.527
3 vessel CAD	1609 (79.7)	813 (80.6)	796 (78.9)	0.376
Previous MI	1076 (53.3)	517 (51.2)	559 (55.4)	0.067
Previous PCI	304 (15.1)	152 (15.1)	152 (15.1)	0.99
NYHA IV	31 (1.5)	14 (1.4)	17 (1.7)	0.718
CCS 4	194 (9.6)	93 (9.2)	101 (10.0)	0.597
ACS	95 (4.7)	47 (4.7)	48 (4.8)	0.99

[a]*Missing data.*

PS, propensity score; IQR, interquartile range; BMI, body mass index; PA, pulmonary artery; CC, creatinine clearance; TIA, transient ischemic attack; LVEF, left ventricle ejection fraction; CAD, coronary artery disease; VD, vessel disease; MI, myocardial infarction; PCI, percutaneous coronary intervention; NYHA, New York Heart Association; CCS, Canadian Cardiovascular Society; ACS, Acute Coronary Syndrome.

stenotic lesions in two-vessel disease and three lesions in three-vessel disease of different territories for whatever reason (15). Each distal anastomosis was counted as a separate graft, e.g., sequential conduit was counted as more than one graft. Whenever the territory that sequential graft supplied couldn't be determined from the registry or this data was missing, it was not taken into consideration when assessing the completeness of revascularization. We report data on early post-operative (< 24 h) mortality rates, in-hospital complications, lengths of stay in the intensive care unit (ICU) and in the hospital (HLoS).

Statistical Analyses

Continuous variables were summarized as mean with standard deviation if normally distributed; non-normal distributions were summarized as median with IQR and compared with the Mann–Whitney U test or standard *t*-test, as appropriate. Categorical variables [number (%)] were compared with the Fisher exact test. Propensity matching was generated for each patient from a non-parsimonious multivariable logistic regression model that was based on baseline characteristics (age, number of vessels diseased, comorbidities, EuroSCORE II, LVEF, CCS, NYHA, and others listed in **Table 1**) and procedural [concomitant ablation, type of surgery (Off-Pump, On-Pump), procedure urgency] covariates as independent variables with treatment type (CR vs. non-CR) as a dependent variable. We used and opt-match and matchIt packages, 1-to-1 pairing, without replacement within a specific caliper width of 0.2 standard deviation of the propensity score. We computed standardized mean differences (SMDs) to verify the balance between CR versus non-CR groups after matching (**Supplementary Figure 2**). Risk Ratios (RRs) were used for in-hospital outcomes, whereas Cox proportional-hazards models were used to determine factors related to the event-free survival at long-term follow-up. We calculated Hazard Ratios (HRs) point estimate and 95% confidence intervals (95% CIs) with ensuing statistical models. Mortality was assessed with Kaplan–Meier survival curves fitted after PS matching. As a further sensitivity analysis, defined subgroup analyses were performed to assess the mortality in different scenarios. STATA MP v13.0 software (StataCorp, College Station, TX, United States) and R (with Rcmdr package and EZR software) were used for computations.

RESULTS

We identified 4,770 patients with pre-operative AF undergoing CABG; of those, in 3,193 (66.9%) patients, CR according to predefined criteria was achieved. During the 9-year follow-up, there were no marked differences in the proportion of complete vs. ICR, nor there were

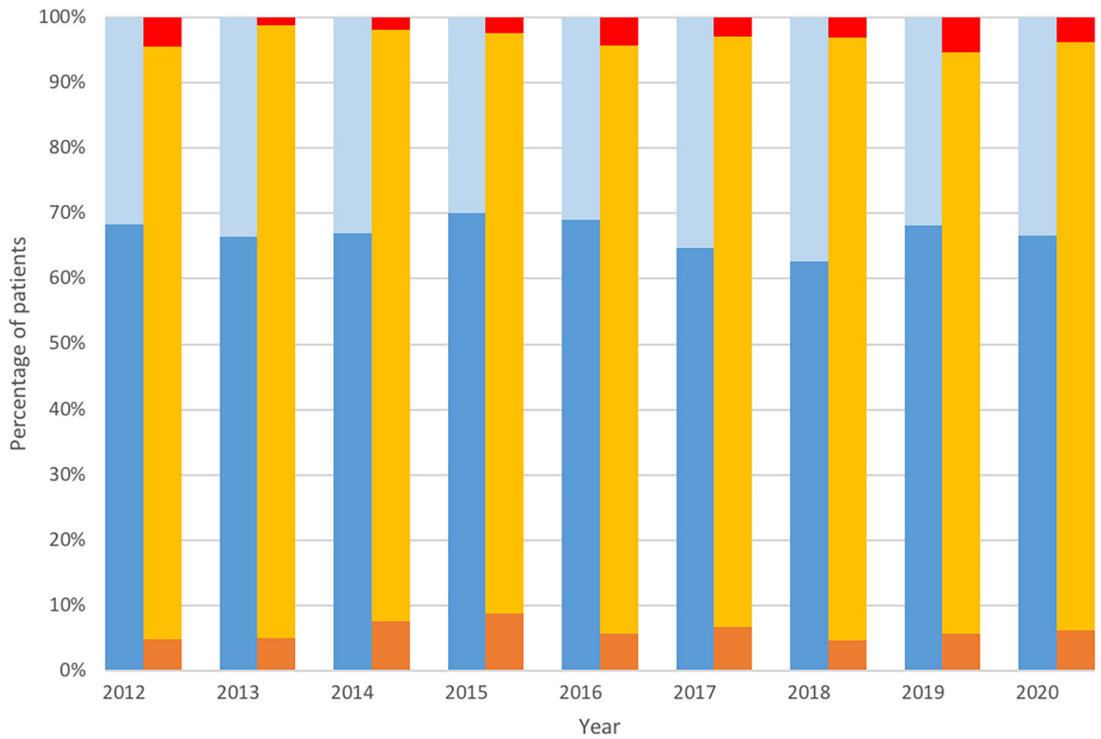


FIGURE 1 | Temporal trends in completeness of revascularization and utilization of arterial grafting. Complete revascularization (dark blue), non-complete revascularization (light blue), multiple arterial grafting (orange), single arterial grafting (yellow), total arterial revascularization (red).

any differences in the adoption of multi-arterial grafting (MAG) (**Figure 1**). Using the propensity score matching (PSM) model, two groups of 1,009 patients each were determined, by pairing non-CR patients with CR controls to achieve similar baseline (**Table 1**) and surgical (**Table 2**) characteristics. We report details on matching quality in **Supplementary Figure 2**.

TABLE 2 | Operative characteristics after PS-matching.

	Total (2018)	Non-CR (1009)	CR (1009)	*P*-value
Procedural characteristics				
Critical pre-operative state	43 (2.1)	22 (2.2)	21 (2.1)	0.99
IABP	8 (0.4)	4 (0.4)	4 (0.4)	0.99
iv. inotropes	35 (1.7)	19 (1.9)	16 (1.6)	0.734
Mechanical vent	8 (0.4)	5 (0.5)	3 (0.3)	0.726
Emergency surgery	74 (3.7)	37 (3.7)	37 (3.7)	0.99
OPCAB	1031 (51.1)	531 (52.6)	500 (49.6)	0.182
CPB (min)[a]	74 (55–95)	60 (45–74)	90 (71–109)	< 0.001
X-clamp (min)[a]	41 (29–54)	32 (24–41)	50 (40–61)	< 0.001
Conversion to ONCAB	17 (0.8%)	11 (1.1)	6 (0.6)	0.330
Concomitant ablation	79 (3.9)	41 (4.1)	38 (3.8)	0.819

[a]*Missing data.*
PS, propensity score; CPR, cardiopulmonary resuscitation; IABP, intra-aortic balloon pump; iv, intravenous; OPCAB, Off-Pump Coronary Artery Bypass; ONCAB, On-Pump Coronary Artery Bypass; CPB, cardiopulmonary bypass; LAAO, left atrial appendage occlusion; ±; SD, Standard Deviation.

Baseline and Surgical Characteristics

Baseline characteristics were balanced between groups, with similar EUROSCORE values [median (IQR): 1.92 (1.22–3.19) and 1.90 (1.18–3.19), respectively in patients with incomplete and CR]. The median age was identical in both groups – 70 years (64–76). Of included patients, 78.8% (non-CR) vs. 78.7% (CR) were men, 80.6% of non-CR patients in comparison with 78.9% in the CR group had a 3-vessel coronary artery disease (p = 0.376). Concomitant ablation was performed in 4.1% of non-CR and 3.8% of the CR group; 531 (52.6%) non-CR and

TABLE 3 | Grafts and anastomoses after PS-matching.

	Total (2018)	Non-CR (1009)	CR (1009)
LIMA	1860 (92.2)	914 (90.5)	950 (94.2)
RIMA	83 (4.1)	35 (3.5)	48 (4.8)
BIMA	77 (3.8)	34 (3.4)	43 (4.3)
Pedicled IMA[a]	619 (30.7)	295 (34.6)	324 (38.0)
Skeletonized IMA[a]	1085 (53.8)	557 (65.4)	528 (62.0)
Radial artery	44 (2.2)	25 (2.5)	19 (1.9)
Multiple arterial grafts	203 (10.1)	82 (8.1)	121 (12.0)
Total Arterial Revascularization	42 (2.1)	0 (0.0)	42 (4.2)
Number of anastomoses (Mean + –SD)		2 (1–2)	3 (3–3)

[a]*Missing data.*
LIMA/RIMA/BIMA, Left/Right/Bilateral Internal Mammary Artery; RA, Radial Artery. ±; SD, Standard Deviation.

TABLE 4 | In-hospital outcomes after PS-matching.

	Non-CR (1009)	CR (1009)	Risk ratio (95% CIs)	*P*-value
Early post-operative mortality (< 24 h)	7 (0.7)	8 (0.8)	1.14 (0.42–3.14)	0.288
Cardiac tamponade and/or rethoracotomy for bleeding	31 (3.1)	51 (5.1)	1.65 (1.06–2.55)	0.032
Respiratory failure	60 (5.9)	74 (7.3)	1.23 (0.89–1.71)	0.245
Neurologic complications	25 (2.5)	21 (2.1)	0.84 (0.47–1.49)	0.655
Multiorgan failure	21 (2.1)	21 (2.1)	1.00 (0.55–1.82)	1.000
Gastrointestinal complications	13 (1.3)	16 (1.6)	1.23 (0.6–2.55)	0.709
Acute kidney failure and/or dialysis	32 (3.2)	34 (3.4)	1.06 (0.66–1.71)	0.901
Superficial sternal wound infection	19 (1.9)	21 (2.1)	1.11 (0.60–2.04)	0.873
Deep sternal wound infection	18 (1.8)	14 (1.4)	0.78 (0.39–1.56)	0.594
Mediastinitis	4 (0.4)	6 (0.6)	1.50 (0.42–5.3)	0.753
PPI	4 (0.4)	4 (0.4)	1.00 (0.25–3.99)	1.000
ECMO	1 (0%)	1 (0%)	1.00 (0.06–15.97)	1.000
IABP	18 (1.8%)	21 (2.1%)	1.17 (0.63–2.18)	0.628

PS, propensity score; CIs, confidence intervals; MI, myocardial infarction; ICU, intensive care unit; PPI, permanent pacemaker implantation; ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump.

FIGURE 2 | Long-term mortality, propensity matched Kaplan–Meier survival curves between the two groups: CR vs. non-CR CABG for the analysis of long-term survival. Hazard Ratios and respective 95% Confidence Intervals.

500 (49.6%) CR patients were operated on without the use of cardio-pulmonary bypass ($p = 0.182$). As expected, the number of distal anastomoses varied between groups (1.7 ± 0.6 non-CR vs. 3.0 ± 0.6 CR, $P < 0.001$). **Table 3** lists information regarding grafts and anastomoses.

Clinical Outcomes

In-hospital outcomes and post-operative complications were consistent between groups (**Table 4**). Early mortality (24 h) and 30-day mortality were unaffected by CR [Odds Ratio (OR) and 95% Confidence Intervals (CIs): 1.34 (0.46–3.86), $P = 0.593$, Hazard Ratio (HR) and 95% CIs: 0.88 (0.59–1.32), $P = 0.542$, respectively]. Cardiac tamponade and/or re-thoracotomy for bleeding occurred in 3.1 vs. 5.1% and was statistically more frequent in the CR group [Risk Ratio (RR) and 95% CIs, 1.65 (1.06–2.55), $P = 0.032$]. Cardiopulmonary bypass (CBP) and aortic X-clamp times were significantly longer in the CR group: the median of CBP time was 65 vs. 79 min ($P \leq 0.001$) in the CR and non-CR group and respectively 34 vs. 40 min ($P \leq 0.001$) of aortic X-clamp time. In the long-term follow-up [As stated in the abstract median follow up was 4.7 years (2.3–6.9)], CR was associated with significantly lower mortality [HR (95% CIs) 0.83 (0.71–0.96), $P = 0.011$] (**Figure 2**).

The CR group was further divided into patients who underwent complete- and "supracomplete" revascularization. The latter was associated with an even greater reduction in mortality HR (95% CIs) 0.76 (0.59–0.97), $P = 0.023$ (for SCR vs. ICR). Between ICR, CR, and SCR we observed a significant trend toward lower mortality (log rank $P = 0.032$, **Figure 3**).

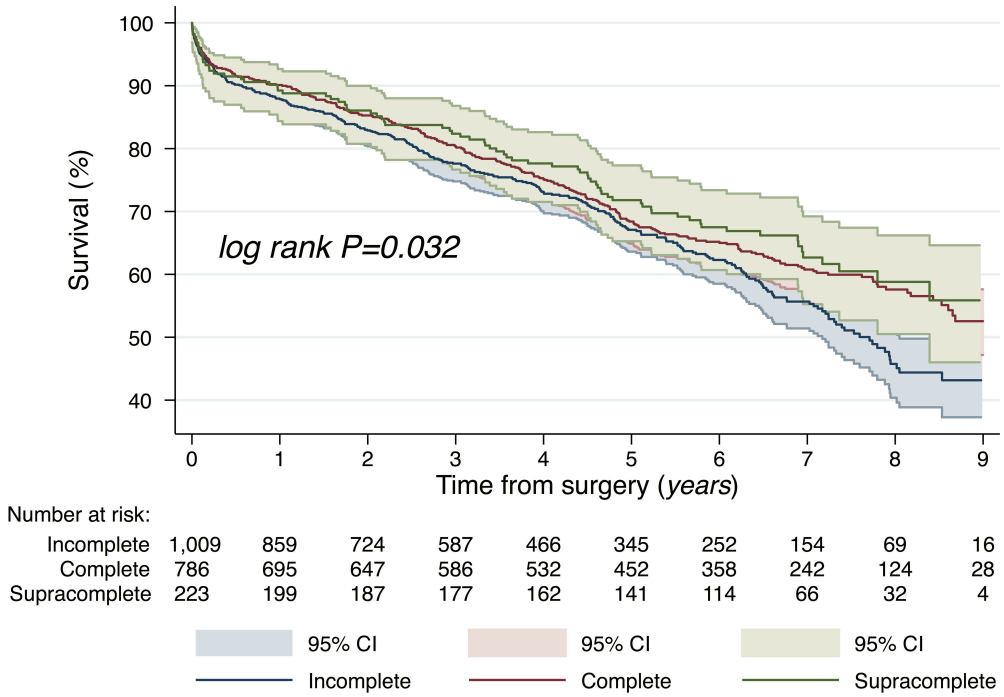


FIGURE 3 | Long-term mortality, propensity matched Kaplan–Meier survival curves between three groups: CR, non-CR, SCR CABG. Logrank test for differences in survival between groups. CR, complete revascularization; SCR, "supracomplete" revascularization.

In subgroup analyses, the benefit of improved long-term survival was sustained across diverse patient populations. Especially beneficent were younger (< 70 years old.) patients [HR (95% CIs) 0.67 (0.53–0.85), P = 0.001 for < 70 year old Vs. HR (95% CIs) 0.94 (0.78–1.13), P = 0.497 for ≥ 70 year old; P interaction = 0.027]. The effect was also more pronounced in patients with lower EuroSCORE II, without diabetes and when off-pump CABG was performed. Further details on the subgroup analyses are shown in **Figure 4**.

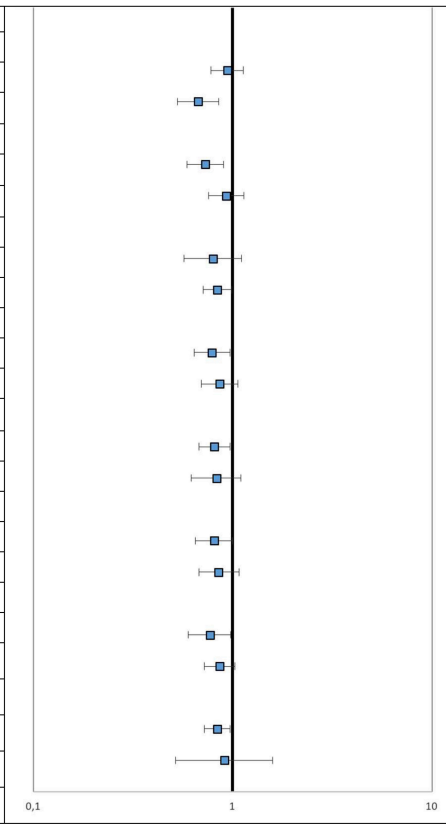
DISCUSSION

The current analysis is the first to focus on the long-term results of complete and incomplete surgical revascularization for MV-CAD in patients with pre-existing AF. Its main findings are as follows; (1) there was a high rate of ICR; (2) long-term benefit of CR; (3) even greater benefit with a higher number of additional grafts; (4) low prevalence of MAG and TAR in the population of AF patients, without significant temporal trends.

Complete revascularization, especially achieved through CABG, is characterized by improved long-term survival and a lower rate of reinterventions compared with ICR (1–3). It remains to be established whether this distinction is specifically because of ICR as a surgical method, deficiency, or anatomical obstacles during CABG or, whether the ICR is only a marker of more advanced and progressive coronary disease. The ICR usually indicates complex coronary pathology, with unfavorable outcomes originating from the patient's baseline risk profile. In reality, even though ICR may contrarily influence long-term results (17), it may be the most appropriate treatment method in a specific subset of prohibitive-risk patients. When the risks of surgery must be minimized to reduce perioperative mortality and complications, target vessel revascularization represents possibly the best feasible course of action (6).

Patients presenting with AF are at markedly elevated, yet non-prohibitive, operative risk, nor is AF itself accounted for in prognostic scores (e.g., EuroSCORE II). Although, the prevalence of AF in patients undergoing CABG is much lower than in patients undergoing mitral valve surgery (18, 19), up to 20% of patients presenting for coronary surgical procedures may have preoperative AF (14, 20), which is often used as a marker for high-risk patients (10, 11, 21). This percentage rises with age and decreased left ventricular function, which is seen in an increasing number of patients referred for CABG surgery. Although no data exists on performing CR in this population, because of their high-risk nature, surgeons may be reluctant to aim for CR as it is associated with longer operative time. Until now, no single study has focused on a comparison of CR/ICR in the AF population undergoing CABG.

One subgroup analysis of the Atrial Fibrillation undergoing Coronary Artery Stenting (AFCAS) registry focusing on the impact of ICR, has shown that of 445 (46.8%) PCI subjects in whom physicians opted for ICR, at 1-year follow-up, had a higher rate of the composite endpoint of acute MI, stent thrombosis and RR, compared to patients with CR (13.9% vs. 9.4%, p = 0.003) (22). In an adjusted multivariable analysis, only creatinine clearance (inverse relationship) and ICR were



	Hazard Ratio (95%CIs)	P_{value}	$P_{interaction}$
Age ≥ 70 yrs			
Yes	0.94 (0.78 – 1.13)	0.497	0.027
No	0.67 (0.53 – 0.85)	0.001	
Type of surgery			
Off-pump	0.73 (0.59 – 0.90)	0.004	0.105
On-pump	0.93 (0.76 - 1.14)	0.475	
Coronary Artery Disease			
2-VD	0.80 (0.57 - 1.11)	0.176	0.797
3-VD	0.84 (0.71 - 0.99)	0.036	
Diabetes			
Yes	0.79 (0.64 - 0.97)	0.028	0.571
No	0.86 (0.70 - 1.06)	0.157	
LVEF ≤ 50%			
Yes	0.81 (0.68 - 0.97)	0.018	0.887
No	0.83 (0.62 - 1.10)	0.194	
Previous MI			
Yes	0.81 (0.65 - 1.00)	0.053	0.765
No	0.85 (0.68 - 1.08)	0.186	
Euroscore			
< 2%	0.77 (0.60 - 0.98)	0.031	0.476
≥ 2%	0.86 (0.72 - 1.03)	0.105	
Type of conduits			
SAG	0.84 (0.72-0.97)	0.021	0.786
MAG	0.91 (0.52-1.59)	0.740	

CIs. confidence intervals; LVEF. left ventricle ejection fraction MI. myocardial infarction; SAG, single arterial grafting; MAG, multiple arterial grafting

FIGURE 4 | Subgroup Analysis, Hazard Ratios and 95% Confidence Intervals (Cis) for death from any cause in CR as compared to non-CR according to selected characteristics; CR, complete revascularization; VD, vessel disease; LVEF, left ventricle ejection fraction; MI, myocardial infarction.

independently associated with a higher risk of the composite endpoint [HR (95% CIs) 1.66, (1.10–2.50), $p = 0.013$] (22).

The latest reports and registries analyses present data on safety and efficacy of surgical CR in AF. In a study of 900 patients with end-stage renal disease, where 14.1% of all patients had pre-existing AF, emergency surgery, diabetes mellitus, the number of vein grafts and age were identified as risk factors for mortality (23). CR, the use of an internal thoracic artery and the sinus rhythm pre-op were recognized as beneficial factors for long-term survival (23). Although AF was not identified as an independent risk factor for perioperative mortality ($p = 0.59$), it was an independent predictor for late mortality ($p < 0.001$) (23). In an analysis of the KROK registry Off-Pump CABG offered a 30-day survival benefit to patients undergoing CABG surgery and presenting with underlying AF (24). On-Pump CABG, on the other hand, was associated with significantly improved long-term survival. CR was possible in 67.5% of patients and was significantly higher, by 10%, in patients undergoing On-Pump CABG (73.3 vs. 62.6%; $P < 0.001$) (24).

One finding of the preset report requires special attention; it was demonstrated that "supra-complete" revascularization, may further improve survival in AF patients undergoing CABG. A study by Schwann et al. investigated the effects of SCR in SAG and MAG and concluded that it conveyed a survival benefit in patients with 3-VD in a single arterial grafting group (which is the majority in our study) (25). Conversely, Chu et al. observed no survival benefit with multiple grafts to each myocardial territory (26). Supra-complete revascularization could be beneficial in several ways, by securing the vulnerable myocardium during the early phase post-op, particularly prone to arrhythmias and disturbances in blood flow, or protecting distal coronary arteries from MI in long-term when functionally non-significant and non-revascularized lesions become significant (27). However, aiming for SCR must increase operative times and since its benefit is not well established the surgeons face a difficult decision. Our results suggest that preoperative AF, although a poor prognostic factor in general, should not be deemed prohibitive while considering additional grafts to each coronary territory.

Several factors, beyond the completeness of the revascularization, can influence the outcome in the AF population. Analysis of the KROK registry (28) showed a significant survival benefit associated with concomitant surgical ablation (SA) in the setting of CABG. The same analysis showed that it remains severely underused, as it was performed only in 4.4%. Recent guidelines give a recommendation to concomitant SA during CABG surgery. Considering that both CR and SA

prolong operative times, surgeons might decide to choose SA over the additional graft that would ensure completeness of the revascularization. Our results suggest that in non-prohibitive risk patients, both SA and CR should be aimed for. Another analysis of the KROK registry showed that patients undergoing multiple arterial grafting have survival benefits at long-term follow-up (13 years post-op) as compared to single arterial grafting (29). This benefit was further sustained in subgroup analyses, yet most appraised in low risk patients (< 70-year-old; EuroSCORE < 2; no diabetes) and when CR was achieved (P = 0.009). Some studies suggest that benefit with the CR may be conferred to SAG patients, wheares when multiple arterial grafts are used their superior patency could neutralize survival benefit associated with completeness of revascularization (30). Indeed, in our sensitivity analysis the benefit in MAG group was non-significant, although it has to be noted that the number of MAG patients was low.

LIMITATIONS

Our study has several limitations. First, only all-cause mortality assessment is possible; the information regarding the cause of death, reinterventions, MIs, heart failure hospitalizations, adherence to anticoagulation therapy, or angiographic patency follow-up is not recorded in the registry. Second, although we addressed a potential selection bias, with propensity score matching according to baseline clinical variables, several confounders could prevail, an important of which is the lack of coronary angiograms that would allow us to access the percentage of chronic total occlusions. Additionally, we did not include the grafting choice (arterial vs. venous grafting) and patient allocation in the propensity score model. Third, detailed anatomy of coronary vessels is not available and therefore the feasibility of CR in each case could not be assessed. Finally, our data regarding coronary revascularization concerns CABG surgery only. Perhaps, some patients, in whom CR during surgery was deemed infeasible, could benefit from a staged hybrid revascularization with PCI as a second stage. Unfortunately, the registry at that time did not gather data regarding subsequent interventions.

CONCLUSION

In this multicenter retrospective propensity-matched study of patients with preoperative AF, CR during CABG was associated with improved long-term survival. The particular benefit was observed in lower-risk patients. A significant trend was observed toward lower mortality with "supracomplete" revascularization.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

MP, JS, JF, and MKow: conception and design. PS, RLo, MD, WWo, JR, MJ, MZ, and KB: administrative support. JS, RLi, GF, AK, WWa, AŁ, SS, DJ, FJ, MM, GM, and GR: provision of study materials or patients. NP-S, SM, TL, DR, and AS: collection and assembly of data. MP, MKow, MKoł, PGM, PM, and DF: data analysis and interpretation. MP, JS, JF, MKow, MKoł, and SM: manuscript writing. All authors approved the final manuscript.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.910811/full#supplementary-material

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Graft preservation confers myocardial protection during coronary artery bypass grafting

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Background: During on-pump coronary artery bypass grafting (ONCAB), graft flushing for distal anastomoses testing also perfuses the downstream myocardium. This single-center retrospective study evaluated the impact of specific preservation solutions on myocardial protection during ONCAB.

Materials and methods: Between July 2019 and March 2020 either DuraGraft (DG) or 0.9% Saline/Biseko (SB) was applied to 272 ONCAB. Overall, 166 patients were propensity-matched into two groups. Cardiac enzymes [high-sensitive Troponin I (hs-TnI) and creatine kinase (CK)] were evaluated 7 days post-surgery.

Results: Post-surgery, hs-TnI values were significantly lower from 3 to 6 h (h) up to 4 days in the DG group: 3–6 h: 4,034 ng/L [IQR 1,853–8,654] vs. 5,532 ng/L [IQR 3,633—8,862], $p = 0.05$; 12–24 h: 2,420 ng/L [IQR 1,408–5,782] vs. 4,166 [IQR 2,052–8,624], $p < 0.01$; 2 days: 1,095 ng/L [IQR 479–2,311] vs. 1,564 ng/L [IQR 659–5,057], $p = 0.02$ and at 4 days: 488 ng/L [IQR 232–1,061] vs. 745 ng/L [IQR 319–1,820], $p = 0.03$. The maximum value: 4,151 ng/L [IQR 2,056–8,621] vs. 6,349 ng/L [IQR 4,061–12,664], $p < 0.01$ and the median area under the curve (AUC): 6,146 ng/L/24 h [IQR 3,121–13,248] vs. 10,735 ng/L/24 h [IQR 4,859–21,484], $p = 0.02$ were lower in the DG group. CK values were not significantly different between groups: maximum value 690 [IQR 417–947] vs. 631 [464–979], $p = 0.61$ and AUC 1,986 [1,226–2,899] vs. 2,081 [1,311–3,063], $p = 0.37$.

Conclusion: Repeated graft flushing with DG resulted in lower Troponin values post-surgery suggesting enhanced myocardial protection compared to SB. Additional studies are warranted to further assess the myocardial protection properties of DG.

KEYWORDS

vein graft preservation, storage solutions, myocardium, protection, coronary artery

Introduction

Although graft storage solutions (GSS) are known to influence graft failure rates following coronary artery bypass grafting (CABG), their impact on myocardial protection in the context of ischemia reperfusion injury (IRI) during cardiopulmonary bypass remains unknown. Saphenous vein grafts (SVG) remain the most commonly used conduits in CABG procedures (1). However, SVGs are prone to vein graft disease and failure. While graft failure and the documented early pathohistological or functional changes in SVG are initiated by various means including underlying harvesting techniques (2), inadequate tissue protection during graft storage appears to be the main trigger (3). Although saline and autologous blood are frequently used as GSS, their use is inadequate to maintain graft patency compared to subsequent GSS (3–5). DuraGraft (DG; Marizyme, Jupiter FL, United States) is an endothelial damage inhibitor, formulated into a preventive solution to protect the integrity and function of the graft when used in this manner. Several *in vitro* studies have shown the protective potential of DG (6–9). Recent research demonstrated reduced graft intimal hyperplasia in SVGs treated with DG (10), and a large-scale retrospective analysis from the Boston West Roxbury Veterans Hospital suggested that treatment of SVGs is associated with significantly lower rates of repeat revascularization and major adverse cardiac events compared to saline (11). While DG has demonstrated its capacity for vascular graft preservation, its potential for myocardial protection in on-pump coronary artery bypass grafting (ONCAB) after intracoronary perfusion by graft flushing for distal anastomosis leak testing during cardiopulmonary bypass remains unclear. In this study, we examined the impact of DG on myocardial protection. This was evaluated by assessing the post-operative biomarker release profile following SVG storage in DG and its downstream intracoronary infusion (*via* the distal anastomosis) in patients undergoing ONCAB procedures and compared to 0.9% Saline/Biseko (SB; control).

Patients and methods

Study design

This study was a retrospective single-center analysis of cardiac biomarker release in patients undergoing ONCAB whose SVGs were treated with DG or SB at the Vienna Heart Center, Floridsdorf Nord, Austria between July 2019 and March 2020. Both GSS were applied separately in different subsequent time intervals. Every patient underwent ONCAB with the treatment of at least one SVG with one of the indicated GSS. Follow-up was conducted by outpatient management and telephone follow-up to obtain information on post-operative myocardial infarction (MI), repeat revascularization, and death. Mortality data were obtained by request from the mortality registry of Statistic Austria, the Austrian statistical office. Ethics approval for the study protocol was received by the local ethics committee.

Surgical technique

In all ONCAB procedures, aortic cross-clamping was implemented. Cardioplegia was applied in standard antegrade and/or retrograde fashion using cold blood cardioplegia. SVGs were harvested by either the open or endoscopic technique. After harvesting and preparation, grafts were stored and flushed either in DG or SB until distal anastomosis was carried out. If arterial grafts were used, only the radial artery was stored in either GSS. After completion of the distal anastomosis in sequential, graft-to-graft, or direct single anastomosis fashion, a careful repeated graft flushing with the respective GSS was performed for leak testing.

Laboratory evaluation of cardiac markers

Cardiac enzymes high-sensitive Troponin I (hs-TnI) and creatine kinase (CK) were measured pre-surgery, 1–3 , 3–6, and 12–24 h after CABG, and once daily up to 7 days post-CABG. Measurement of both cardiac markers was conducted each by the Abbott Alinity assay. Hs-TnI-related detection limits are 1 ng/L, with sex-specific normal upper reference limit of 34.2 ng/L for men and 15.6 ng/L for women. CK-related detection limits are 7 U/L, with sex-specific normal upper reference limit of 200 U/L for men and 168 U/L for women.

Graft storage solutions

DuraGraft (Marizyme, Jupiter FL, United States) is a GSS which preserves endothelial function and structure during CABG procedures. DG contains L-glutathione, L-ascorbic acid, L-arginine, glucose, and balanced salts for minimizing ischemic and metabolic damage to the conduits during graft preservation,

Abbreviations: AUC, area under the curve; CABG, coronary artery bypass grafting; CK, creatine kinase; DG, duragraft; GSS, graft storage solution; Hs-TnI, high-sensitive Troponin I; IRI, ischemia reperfusion Injury; IQR, interquartile range; MI, myocardial infarction; ONCAB, On-pump coronary artery bypass grafting; PCI, percutaneous coronary intervention; PSM, propensity score matching; SB, saline/biseko; SVG, saphenous vein grafts.

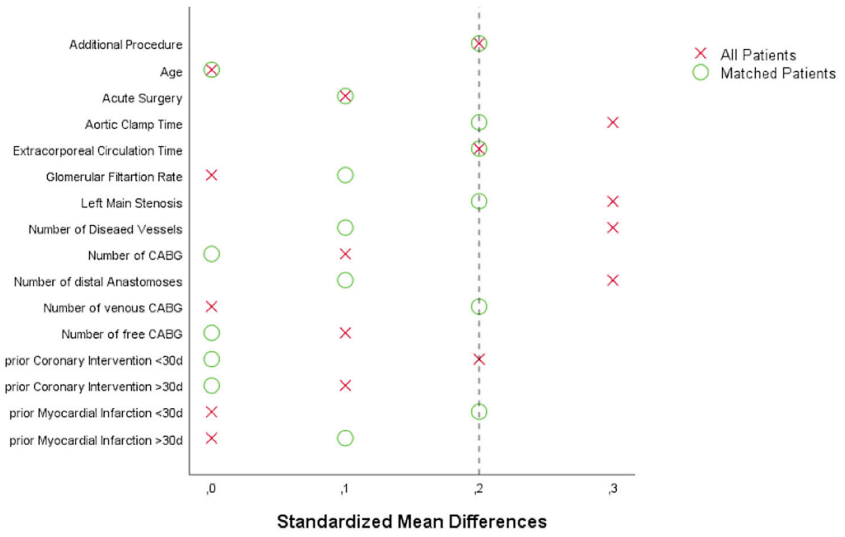

FIGURE 1
Love plot visualizing covariate balancing according to standardized mean differences before and after propensity score matching: CABG, coronary artery bypass grafting.

TABLE 1 Patient baseline characteristics.

	Unmatched			Matched		
n (%)	DuraGraft *n* = 100	Saline/Biseko *n* = 172	*p*-value	DuraGraft *n* = 83	Saline/Biseko *n* = 83	*p*-value
Male	89 (89.0)	136 (79.1)	0.04	73 (88.0)	71 (85.5)	0.65
Age (years), median (IQR)	72 (62 – 75)	70 (61 – 76)	0.77	71 (62 – 75)	69 (62 – 75)	0.81
BMI, median (IQR)	27.7 (24.9 – 30.4)	27.2 (24.8 – 30.3)	0.52	28.4 (25.2 – 30.8)	26.9 (24.9 – 30)	0.22
EuroSCORE II, median (IQR)	1.7 (1.1 – 3.3)	1.7 (1.1 – 3.1)	0.59	1.6 (0.9 – 3.1)	1.6 (0.9 – 3.1)	0.81
Hypertension	87 (87.0)	147 (85.5)	0.73	72 (86.7)	74 (89.2)	0.63
Hyperlipidemia	78 (78.0)	135 (78.5)	0.93	65 (78.3)	63 (75.9)	0.71
Diabetes mellitus			0.89			0.82
IDDM	7 (7.0)	13 (7.6)		6 (7.2)	8 (9.6)	
NIDDM	37 (37.0)	68 (39.5)		30 (36.1)	31 (37.3)	
None	56 (56.0)	91 (52.9)		47 (56.6)	44 (53)	
Chronic heart failure	24 (26.1)	32 (19.8)	0.24	18 (22.2)	14 (17.9)	0.50
GFR (ml/min), median (IQR)	76.5 (57 – 88)	73 (59 – 86)	0.66	78 (59 – 90)	74 (64 – 88)	0.92
Stroke	4 (4.0)	17 (9.9)	0.80	3 (3.6)	4 (4.8)	1.00
COPD	23 (27.4)	49 (35.8)	0.20	18 (26.1)	20 (29)	0.70
Smoker			0.001			0.03
Active	19 (20.4)	54 (32.0)		14 (17.9)	24 (30.0)	
Former	31 (33.3)	23 (13.6)		27 (34.6)	14 (17.5)	
None	43 (46.2)	92 (54.4)		37 (47.4)	42 (52.5)	
Atrial fibrillation	15 (15.0)	28 (16.3)	0.78	13 (15.7)	11 (13.3)	0.66
Prior MI > 30 days	18 (18.2)	28 (16.3)	0.69	14 (16.9)	17 (20.5)	0.55
Prior MI ≤ 30 days	21 (21.0)	36 (21.1)	0.99	19 (22.9)	14 (16.9)	0.44
Prior PCI > 30 days	15 (15.0)	29 (16.9)	0.69	14 (16.9)	15 (18.1)	0.84
Prior PCI ≤ 30 days	5 (5.0)	16 (9.3)	0.20	5 (6.0)	6 (7.2)	0.76

BMI, body mass index; COPD, chronic obstructive pulmonary disease; EuroSCORE II, updated European system for cardiac operative risk evaluation; GFR, glomerular filtration rate; IDDM, insulin dependent diabetes mellitus; IQR, interquartile range; NIDDM, not insulin dependent diabetes mellitus; Prior MI ≤ 30 days/ > 30 days, preoperative myocardial infarction within/beyond 30 days prior surgery; Prior PCI ≤ 30 days/ > 30 days, preoperative percutaneous coronary intervention within/beyond 30 days prior surgery.

graft handling, and IRI. Moreover, the pH is buffered in the physiologic range. Biseko (Biotest Pharma GmbH, Dreieich, Germany), which is known to be used off-label for graft storage, is an ionized plasma derivate containing human serum protein, albumin, and human immunoglobulin. Saline 0.9% was added due to the lower volume of Biseko. Additionally, heparin was added to both DG and SB during their preparation for surgical application.

Statistical analysis

Categorical variables, shown as numbers and percentage, were compared by Chi-Square test or Fisher-Exact test for small sample size correction. Continuous variables, expressed as median and interquartile range (IQR), were compared by Mann–Whitney–*U*-test. Propensity score matching (PSM) was performed to minimize potentially responsible bias for the

TABLE 2 Procedural characteristics and concomitant procedures.

	Unmatched			Matched		
***n* (%)**	**DuraGraft *n* = 100**	**Saline/Biseko *n* = 172**	***p*-value**	**DuraGraft *n* = 83**	**Saline/Biseko *n* = 83**	***p*-value**
Acute procedure	29 (29.0)	59 (34.3)	0.37	25 (30.1)	30 (36.1)	0.41
Left main stenosis	31 (31.0)	77 (44.8)	0.03	30 (36.1)	38 (45.8)	0.21
Number of vessels diseased, median (IQR)	3 (3 – 3)	3 (2 – 3)	0.18	3 (2 – 3)	3 (2 – 3)	0.44
Number distal anastomoses, median (IQR)	3 (3 – 3)	3 (2 – 3)	0.02	3 (3 – 3)	3 (2 – 3)	0.36
Number of central anastomoses, median (IQR)	1 (1 – 2)	1 (1 – 2)	0.91	1 (1 – 2)	1 (1 – 2)	0.95
Number of CABG, median (IQR)	3 (2 – 3)	3 (2 – 3)	0.54	3 (2 – 3)	3 (2 – 3)	0.72
Number of free CABG, median (IQR)	2 (1 – 2)	2 (1 – 2)	0.69	2 (1 – 2)	2 (1 – 2)	0.83
Number of venous CABG, median (IQR)	1 (1 – 2)	1 (1 – 2)	0.77	1 (1 – 2)	1 (1 – 2)	0.41
LIMA			0.34			0.43
In situ	93 (93.0)	151 (87.8)		77 (92.8)	73 (88)	
Free graft	0 (0.0)	2 (1.2)		0 (0.0)	1 (1.2)	
None	7 (7.0)	19 (11.0)		6 (7.2)	9 (10.8)	
RIMA			0.60			0.41
In situ	8 (8.0)	9 (5.2)		8 (9.6)	4 (4.8)	
Free graft	9 (9.0)	19 (11.0)		9 (10.8)	12 (14.5)	
None	83 (30.5)	144 (83.7)		66 (79.5)	67 (80.7)	
BIMA	17 (17.0)	28 (16.3)	0.88	17 (20.5)	16 (19.3)	0.85
Radial artery	1 (1.0)	7 (4.1)	0.27	1 (1.2)	4 (4.8)	0.37
Vein harvest			0.94			0.67
Endoscopic	41 (54.7)	62 (54.9)		35 (56.5)	27 (50.9)	
Surgical	20 (26.7)	28 (24.8)		16 (25.8)	13 (24.5)	
Both	14 (18.7)	23 (20.4)		11 (17.7)	13 (24.5)	
Concomitant surgeries						
Additional cardiac procedure	39 (39)	51 (29.8)	0.12	28 (33.7)	19 (22.9)	0.12
Valvular procedure	32 (32)	42 (24.4)	0.18	22 (26.5)	16 (19.4)	0.36
Aortic valve replacement	14 (16.3)	31 (18)	0.17	19 (22.9)	12 (14.5)	0.16
Mitral valve replacement	4 (4.0)	3 (1.7)	0.27	0 (0.0)	0 (0.0)	
Mitral valve repair	3 (3.0)	12 (7)	0.17	3 (3.6)	5 (6)	0.72
Tricuspid valve replacement	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Tricuspid valve repair	1 (1.0)	2 (12)	1.00	0 (0.0)	0 (0.0)	
MAZE	8 (8.0)	7 (4.1)	0.17	6 (7.2)	1 (1.2)	0.12
LAA	8 (8.0)	8 (4.7)	0.26	6 (7.2)	3 (3.6)	0.50
Procedural characteristics						
Aortic cross clamp time (minutes), median (IQR)	79 (63 – 103)	71 (57.3 – 91)	0.01	74 (62 – 93)	70 (57 – 89)	0.07
Extracorporeal circulatory time (minutes), median (IQR)	123 (102 – 143)	112.5 (97.3 – 139)	0.09	119 (101 – 140)	110 (93 – 135)	0.14

BIMA, bilateral internal mammary artery; CABG, coronary artery bypass grafting; IQR, interquartile range, LAA, left atrial appendage occlusion; LIMA, left internal mammary artery; RIMA, right internal mammary artery.

evaluation of biomarker values and cardiac adverse events between both study groups. Matching was conducted by a multivariate logistic model, which consisted of 1-to-1 patient pair formation, nearest-neighbor matching, and no case-replacement. The corresponding caliper of 0.15 was chosen. The model incorporated the following variables: additional cardiac procedure, age, acute surgery, aortic clamp time, extracorporeal circulation time, glomerular filtration rate, left main stenosis, number of diseased vessels, number of CABG, number of distal anastomoses, number of venous CABG, number of free CABG, prior percutaneous coronary intervention (PCI) ≤30 days, prior PCI >30 days, prior MI ≤30 days, and prior MI >30 days.

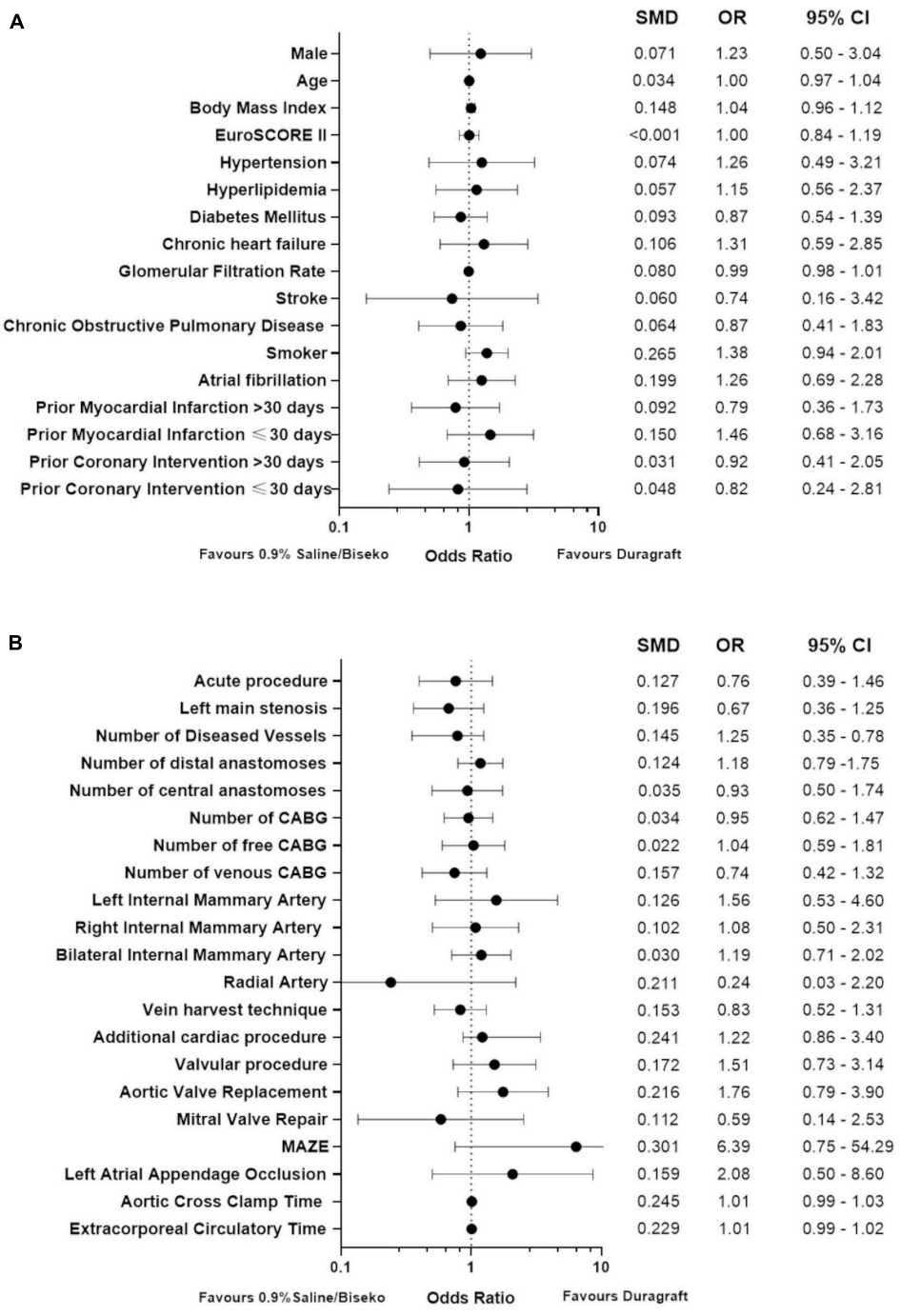

FIGURE 2
Forest plot presenting diagnostic odds ratios and effect size of baseline **(A)** and procedural variables **(B)** after propensity score matching; CABG, coronary artery bypass grafting; SMD, standardized mean differences, OR, odds ratio, 95% CI, 95% confidence interval.

Covariate balancing was evaluated according to calculating standardized mean differences with a value of ≤0.2 considered as sufficient equilibrium of these covariates between the groups (Figure 1). Differences in prevalence of baseline and procedural variables between both groups of patients were evaluated by diagnostic odds ratios according to logistic regression and effect size estimation according to standardized mean differences. The area under the curve (AUC) was calculated from the plasma biomarker concentrations vs. the time after surgery. Data analysis was conducted by SPSS statistical software version 25 (IBM Corp, Armonk, NY, United States). *P*-values of <0.05 were considered statistically significant.

Results

Pre- and peri-procedural data

The SVGs of 100 patients were treated with DG and 172 patients with SB. After PSM, 83 patients within each group were selected. The corresponding Love plot (Figure 1) provides visualization of covariate balancing of all included baseline (Table 1) and procedural variables (Table 2) in the propensity model. The included covariates were equally distributed between both groups according to standardized mean differences, which did not exceed rounded maximum values of 0.2. Therefore, the conducted PSM might be considered valid. Moreover, diagnostic odds ratios with associated 95% confidence intervals and effect size according to given standardized mean differences of all baseline and procedural variables of the propensity-matched patient population are presented in a given Forest plot (Figure 2). After PSM, only documented smokers (DG: 17.9 vs. SB: 30.0%; $p = 0.03$) and those on whom the concomitant MAZE procedure (DG: 7.2 vs. SB: 1.2%; $p = 0.12$) were conducted were distributed unequally between both groups according to an increased effect size for the given variables, with values of standardized mean differences of 0.265; OR: 1.38; 95% CI: 0.94–2.01, and 0.301; OR: 6.39; 95% CI: 0.75–54.29, respectively. Although both variables revealed a higher prevalence within the DG group, both groups appeared overall homogenized after PSM as the remaining baseline and procedural characteristics were equally distributed within the patient population (Figure 2).

Evaluation of cardiac biomarkers

Data on post-procedural laboratory values (Tables 3, 4) revealed a typical post-operative monophasic course for both hs-TnI and CK (Figure 3). Hs-TnI values were comparable pre-surgery (DG: 11 [5–28] vs. SB: 8 [3–28], $p = 0.22$). Post-surgery, hs-TnI values were significantly lower from 3 to 6 h until the measurement at 4 days in the DG group: 3–6 h: 4,034 ng/L [IQR 1853–8654] vs. 5,532 ng/L [IQR 3633–8862], $p = 0.05$; 12–24 h: 2,420 ng/L [IQR 1408–5782] vs. 4166 [IQR 2052–8624], $p < 0.01$; 2 days: 1,095 ng/L [IQR 479–2311] vs. 1,564 ng/L [IQR 659–5057], $p = 0.02$, and at 4 days: 488 ng/L [IQR 232–1061] vs. 745 ng/L [IQR 319–1820], $p = 0.03$. Noteworthy, hs-TnI values only reached borderline significance at 3 days: 709 ng/L [IQR 321–1696] vs. 950 ng/L [IQR 332–2105], $p = 0.08$. The maximum value and the median AUC were also significantly lower after graft treatment with DG (maximum value: 4,151 ng/L [IQR 2056–8621] vs. 6,349 ng/L [IQR 4061–12664], $p < 0.01$ and AUC: 6,146 ng/L/24 h [IQR 3121–13248] vs. 10,735 ng/L/24 h [IQR

TABLE 3 Median values and interquartile ranges of high-sensitive Troponin I in nanograms/liter post-CABG after propensity matching.

Troponin, median (IQR), *n*	DuraGraft *n* = 83	Saline/Biseko *n* = 83	*p*-value
Pre-surgery	11 (5-28), 73	8 (3-28), 80	0.22
1-3 h	2147 (1155-3855), 80	2790 (1425-4033), 78	0.25
3-6 h	4034 (1853-8654), 63	5532 (3633-8862), 62	0.05
12-24 h	2420 (1408-5782), 83	4166 (2052-8624), 83	<0.01
2 days	1095 (479-2311), 83	1564 (659-5057), 83	0.02
3 days	709 (321-1696), 75	950 (332-2105), 79	0.08
4 days	488 (232-1061), 66	745 (319-1820), 69	0.03
5 days	354 (123-941), 56	696 (176-1318), 46	0.17
6 days	301 (149-915), 53	561 (241-1061), 58	0.18
7 days	186 (83-588), 58	249 (70-697), 44	0.81
Max value	4151 (2056-8621), 83	6349 (4061-12664), 83	<0.01
AUC	6146 (3121-13248), 83	10735 (4859-21484), 83	0.02

AUC, area under the curve; CABG, coronary artery bypass grafting; IQR, interquartile range.

TABLE 4 Median values and interquartile ranges of creatine kinase in units/liter post-CABG after propensity matching.

Creatine kinase, median (IQR), *n*	DuraGraft *n* = 83	Saline/Biseko *n* = 83	*p*-value
Pre-surgery	93 (71–150), 75	89 (64–120), 82	0.32
1–3 h	388 (286–563), 83	347 (267–483), 81	0.05
3–6 h	476 (303–730), 63	478 (373–639), 60	0.75
12–24 h	578 (339–815), 82	571 (400–863), 83	0.56
2 days	412 (249–654), 83	483 (308–684), 83	0.14
3 days	239 (153–396), 76	290 (160–460), 79	0.16
4 days	161 (99–276), 67	208 (136–324), 70	0.07
5 days	140 (95–280), 59	161 (95–271), 48	0.62
6 days	85 (55–169), 52	108 (74–160), 58	0.09
7 days	89 (56–158), 56	93 (66–123), 43	0.75
Max value	690 (417–947), 83	631 (464–979), 83	0.61
AUC	1986 (1226–2899), 83	2081 (1311–3063), 83	0.37

AUC, area under the curve; CABG, coronary artery bypass grafting; IQR, interquartile range.

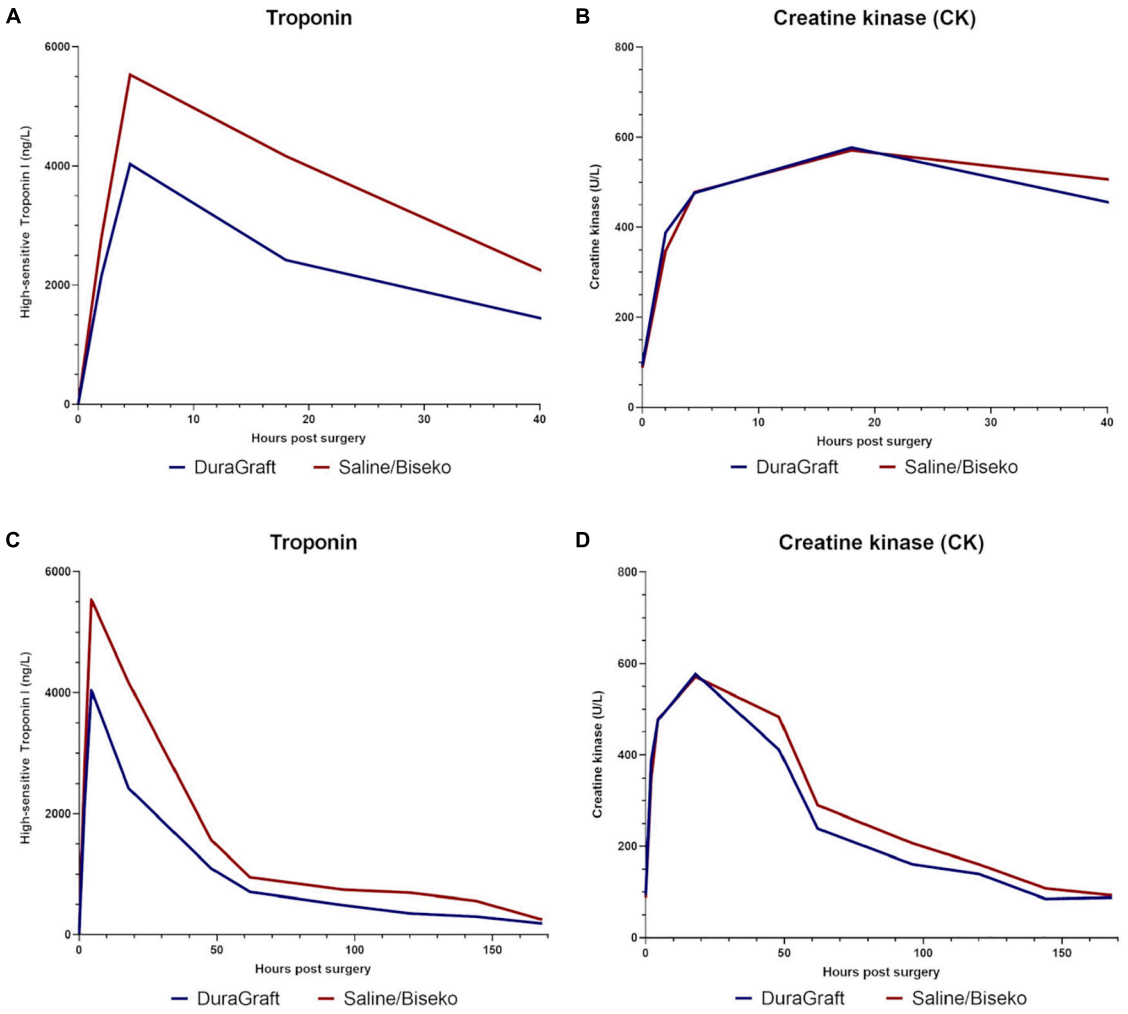

FIGURE 3
Median values of high-sensitive Troponin I in nanogram/liter and creatine kinase in units/liter within the first hours post-surgery **(A,B)**, and during the overall hospital stay **(C,D)**.

4859–21484], $p = 0.02$). CK values in the DG group appeared to be slightly higher at 1–3 h (388 U/L [IQR 286–563) vs. 347 U/L [IQR 267–483], $p = 0.05$, while lower values in DG patients at 4 days (161 U/L, [IQR 99–276] vs. 208 U/L (136–324), $p = 0.07$) and at 6 days (85 U/L [IQR 55–169] vs. 108 U/L [IQR 74–160], $p = 0.09$) did not reach complete statistical significance.

Adverse events

After PSM, the median hospital stay in days (DG: 16.5 [IQR 12–22] vs. SB: 15 [IQR 12–22]; $p = 0.62$), all-cause mortality (DG: 6.0 vs. SB: 2.4%, $p = 0.44$), and cardiac-related mortality (DG: 2.4 vs. SB: 0.0%, $p = 0.70$) did not differ between both groups over the median follow-up of 4 (IQR 0–22) months (**Table 5**). Noteworthy, all mortality events occurred within 1-year of follow-up. Progression of heart failure was the cause of death in the four patients with cardiac death.

Comment

This study shows that the use of DG for leak testing during distal anastomosis and its subsequent application to the downstream myocardium appears to be associated with improved myocardial protection in patients undergoing ONCAB, identified by significantly lower hs-TnI levels including the maximum value and AUC during the early post-operative phase after CABG when compared to SB. In contrast, values of CK were comparable between both groups within the observation period, which may be due to CK being a

TABLE 5 Cardiac adverse events after matching over the median follow-up of 4 (IQR 0–22) months.

n (%)	DuraGraft *n* = 83	Saline/Biseko *n* = 83	*p*-value
Mortality	5 (6.0)	2 (2.4)	0.44
30-day Mortality	3 (3.6)	2 (2.4)	1.00
Cardiac related mortality	2 (2.4)	0 (0.0)	0.70
MI	1 (1.2)	3 (3.6)	0.62
PCI	1 (1.2)	6 (7.2)	0.18
Stroke	3 (3.6)	2 (2.4)	1.00
New onset of atrial fibrillation	23 (27.7)	16 (19.3)	0.27
AV-Block (II° and III°)	1 (1.2)	1 (1.2)	1.00
Pacemaker implantation	1 (1.2)	2 (2.4)	1.00
Pneumonia	7 (8.4)	7 (8.4)	1.00
Hospital stay in days, median (IQR)	16.5 (12–22)	15 (12–22)	0.624

AV-Block, atrioventricular block; Cardiac related Death, composite endpoint of events of progressing or acute onset of heart failure; MI, myocardial infarction; PCI, percutaneous coronary intervention.

non-specific cardiac enzyme, while Troponin I is highly specific for myocardial injury (12).

Several factors influence cardiac marker increase, such as the complexity of the CABG procedure (13, 14) and renal impairment (15). From a clinical perspective, the observed overall lower early post-operative Troponin levels in the DG group might be a predictor of better overall patient outcomes when considering that increased Troponin values have been described to predispose to increased early and long-term mortality and cardiac-related complication rates (13, 14, 16).

In our study, peak values for hs-TnI were reached within temporal proximity of 3–6 h in both groups post-surgery, and the most significant difference in absolute hs-TnI values was seen at 12–24 h after surgery. Afterward, in both groups, values decreased in a logistic linear fashion. Overall, enzyme increase during ONCAB indicates ischemic myocardial damage (17). Sufficient administration of cardioplegia for adequate myocardial protection during on-pump cardiac surgery is crucial. Insufficient protection of the heart during on-pump runs leads to increased local metabolic stress which can be particularly problematic for the right ventricle and in the context of inefficient retrograde application of cardioplegia (18). Since DG has been designed to prevent IRI in vascular conduits, one may hypothesize that additional specific administration of DG into the downstream myocardium *via* systematic flushing of the distal anastomosis during leak testing may protect the downstream myocardium from IRI as well and enhance myocardial protection, which was reflected by significantly lower post-operative troponin values in our study.

DuraGraft, as well as its precursor GALA solution, on which the basis of DG was developed, has demonstrated superiority in preserving tissue functionality over saline and other GSS in human venous and free arterial conduits by reducing oxidative stress (6, 8, 9) and through the actions of L-arginine (a key component of DG) to sustain NO concentration, thereby maintaining endothelial function and preventing hyperplasia (19). In direct comparison, saline fails to prevent oxidative damage and downstream IRI (6), while its acidic pH (5.5) might induce solution damage as well (3).

On the other hand, Biseko enables superior preservation of graft patency by decreased risk of vasospasm (20) and endothelial pressure damage due to graft flushing (21) when compared to saline; however, Biseko does not protect against ischemic injury. One may speculate that in line with its established protective impact on the endothelium of vascular conduits (6, 8, 9), DG might also have similar beneficial effects on the endothelial integrity and function of the coronary vasculature in the treated territory, which could ultimately explain myocardial protection. This might be particularly driven by L-, which is one of the main components in DG, and which is known (i) to enhance coronary blood flow by enhanced vasodilation following intracoronary application (22) and simultaneously (ii) to reduce IRI (23).

However, if and to what extent the observed positive effects on myocardial protection and its underlying mechanisms are directly comparable to the previously described protective impact of DG on vascular conduits needs further in-depth investigation. Nevertheless, if proven valid, this concept could have great clinical relevance in future on-pump revascularization strategies, especially when considering the frequently seen challenges with inadequate myocardial protection and associated poor recovery of the right ventricle after CABG procedures.

Limitations

This was a retrospective, non-randomized study, hence all established limitations do apply. No additional cardiac imaging for evaluation of myocardial protection and graft patency was conducted. Intraoperative intracoronary flow measurement could not be evaluated retrospectively. Measurement of the myocardial fraction of CK and CK-MB was not done in this study, but may have yielded statistically significant differences, and thus, may be considered for future studies. Finally, this study was not powered for clinical outcome events.

Conclusion

In this study, the administration of DG into the downstream myocardium during graft flushing for leak testing of the distal anastomosis was associated with improved perioperative myocardial protection as measured by significantly

lower troponin levels when compared to SB in patients undergoing ONCAB.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethic committee of the city of Vienna. The patients/participants provided their written informed consent to participate in this study.

Author contributions

PS: conceptualization, data curation, formal analysis, investigation, methodology, project administration, supervision, validation, visualization, writing – original draft, and writing – review and editing. ME and BW: conceptualization, investigation, methodology, project administration, supervision, validation, and writing – review and editing. PH, ZA, IC, MM, TA, and MG: conceptualization and writing – review and editing. All authors contributed to the article and approved the submitted version.

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Conflict of interest

Author ME was the PI of the European DuraGraft registry and the chair of the registry scientific advisory committee and is a consultant to Somahlution.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Small-diameter bacterial cellulose-based vascular grafts for coronary artery bypass grafting in a pig model

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Surgical revascularization is the gold standard in most cases of complex coronary artery disease. For coronary artery bypass grafting, autologous grafts are state-of-the-art due to their long-term patency. A non-negligible amount of patients lack suitable bypass material as a result of concomitant diseases or previous interventions. As a promising alternative, tissue-engineered vascular grafts made of biomaterials such as bacterial cellulose (BC) are gaining more and more attention. However, the production of small-diameter grafts (inner diameter $<$ 6 mm) of application-oriented length ($>$ 5 cm) and their *in vivo* long-term patency remain challenging. In this study, grafts of 20 cm in length with an inner diameter of 3 mm were generated in a custom-made bioreactor. To potentially improve graft compliance and, therefore *in vivo* patency, BC was combined with an embedded cobalt–chromium mesh. The grafts were designed for *in vivo* endothelialization and specific surgical properties and implanted as an aortocoronary bypass in a left anterior descending occluded pig model (n = 8). Coronary angiography showed complete patency postoperatively at 4 weeks. Following 4 weeks *in vivo*, the grafts were explanted revealing a three-layered wall structure. Grafts were colonized by smooth muscle cells and a luminal layer of endothelial cells with early formation of *vasa privata* indicating functional remodeling. These encouraging findings in a large animal model reveal the great potential of small-diameter BC grafts for coronary and peripheral bypass grafting.

KEYWORDS

coronary artery, vascular graft, cellulose, surgery, tissue engineering

Introduction

Coronary and peripheral vascular diseases are the leading cause of death worldwide (1). Every year more than 350,000 people die in the USA because of coronary artery disease (2). In the case of complex multivessel coronary artery disease, myocardial revascularization by coronary artery bypass grafting (CABG) is the state-of-the-art therapeutic procedure. Commonly, CABG requires autologous bypass grafts such as the internal thoracic artery, the great saphenous vein, and the radial artery. Their availability is restricted due to multivascular diseases, poor graft quality, and previous surgeries. Furthermore, the long-term patency of vein grafts seems to be limited and inferior when compared with arterial grafts (3). Moreover, a second surgical site increases the risk of complications such as wound infection, postoperative pain, and bleeding. For large-diameter peripheral bypass grafting, vascular prostheses made of Dacron® or polytetrafluoroethylene (PTFE) are commercially available. When applied as small-diameter vascular grafts (inner diameter < 5 mm), these materials showed an increased risk of thrombosis and intimal hyperplasia, resulting in a poor *in vivo* long-term patency (4). These findings restricted the use of these materials as well as the use of cryopreserved homografts as early as 1980. Various studies were undertaken with the result that these materials were left for the small diameter application and scientific interest was drawn toward engineering different forms of artificial grafts (5, 6). The patency rates varied but in conclusion showed a dramatic low rate at 12 months of up to 80% failure rate depending on the implantation site. For peripheral applications, the rates remained slightly higher at 40% patency after 1 year (5). Since the early days of cardiac surgery, tissue-engineered biomaterials grafts (TEVG) made of various biomaterials have been considered a promising alternative. As one prominent example, antithrombotic vascular grafts made of extracted human fibroblasts were implanted successfully *in vivo* from Cytograft Tissue Engineering Inc. (Novato, USA) (7). However, in clinical practice, no TEVG has been implemented for arterial bypass grafting. Another favorable biomaterial used for vascular grafts is bacterial cellulose (BC), which is excreted extracellularly by certain bacteria species, namely AcetoBacter Xylinum (ABX) (8). This biomaterial has been used for many biomedical applications like skin substitutes and is now explored for TEVGs (9). In addition to its biocompatibility and unique biomechanical properties, its nanofibrillar structure allows vascular remodeling by endothelial cells (ECs) and smooth muscle cells (SMCs). Preliminary results from studies applying BC grafts for peripheral bypass grafting in large animal models are promising, although they are limited by the restricted *in vivo* long-term patency (10, 11).

Since the limited *in vivo* patency of previous BC grafts might be related to a compliance mismatch between the graft and the native vessel, potential modifications of BC graft compliance have been discussed (12).

In the past, manufacturing small-diameter BC-vascular grafts (inner diameter < 6 mm) of application-oriented length (> 5 cm) has been challenging. Furthermore, these grafts have not been applied as coronary artery bypass grafts in a large animal ischemic heart model so far. Therefore, this study aimed to generate a small-diameter BC-vascular graft of more than 15 cm in length for CABG in a pig model as a proof of concept study.

Materials and methods

Generation of bacterial cellulose-vascular grafts

Cultivation of AcetoBacter xylinum

The bacterial strain used to produce BC was ABX subsp. sucrofermentas Toyosaki et al. (ATCC© 700178^{TM}). Deep-frozen cultures were stored at –70°C. Hestrin–Schramm medium containing glucose 50% (2.0% w/v), yeast extract (0.5%), proteose peptone (0.5%), Na_2HPO_4 (0.27%), and citric acid (0.115%) was used for cultivation. The cultivation medium containing suspended ABX was incubated at 26°C for 18 days under static conditions at room oxygen.

Bioreactor-based culture of the reinforced bacterial cellulose-vascular grafts

Bacterial cellulose (BC)-vascular grafts are generated in a customized open rotating bioreactor (**Supplementary Figure 1**). The bioreactor contains four independent units. Each unit consists of a horizontally rotating steel shaft (outer diameter = 2 mm) covered by a silicone tube (outer/inner diameter = 3/2 mm). For BC fermentation, glucose-based medium containing glucose 50% (2.381% w/v), KH_2PO4 (0.7%), $MgSO_4 \times 7\ H_2O$ (0.213%), H_3BO_3 (0.00043%), nicotinamide (0.00007%), $FeSO_4 \times 7\ H_2O$ (0.00095%), Na_2HPO_4 (0.134%), $(NH_4)_2SO_4$ (0.354%), and ethanol (0.473%) was used. The bioreactor was filled with bacterial suspension (fermentation media + bacteria) up to the level of the silicone-covered steel shafts. Each unit was controlled by a stepper motor with a rotational speed of 30 rpm. BC fermentation process lasts 5 days at 26–28°C. BC is produced at the air-liquid interface by Acetobacter Xylinus. Steel shaft rotation is necessary for wrapping the BC layers around the silicon tube over the fermentation time. After 2.5 days of culture, the steel shafts with the preliminary BC grafts were removed from the bioreactor. Knitted VEST® cobalt–chromium meshes from Vascular Graft Solutions (VGS, Tel-Aviv, Israel, outer-diameter 5 mm) were placed over the grafts and incubated at 26–28°C for 2.5 days more. After harvesting, the grafts were purified from bacteria in NaOH solution for 11 days. On day 8, each graft was

heated up to 60°C for 4 h. For storage, the grafts were placed horizontally in sterile glass tubes at 2–8°C in standard sodium chloride solution after being autoclaved at 121°C in ddH_2O.

In vitro assessments

Micro-computed tomography

Micro-CT was applied to determine the mesh position along the graft. The cross-sectional center of both, the inner and outer layer of BC as well as the mesh was computed at different positions, and their deviation was calculated. For the X-ray tomography high-resolution analysis and three-dimensional rendering, phoenix nanotom® m from GE Sensing and Inspection Technologies (Hürth, Germany), respectively, VGStudio MAX 2.1® from Volume Graphics GmbH (Heidelberg, Germany) were used.

Scanning electron microscopy

Scanning electron microscopy (SEM) was applied to investigate the morphology of the inner and outer surfaces as well as the cross-sectional surface of the grafts. Samples were ultra-rapidly frozen in nitrogen slush and freeze-dried for 12.5 h. The dry samples were sputtered with 20 nm gold by an EM ACE 600 Sputter Coater® from Leica (Austria) and analyzed by the Nova NanoSem 230® from FEI (Netherlands).

Mechanical characterization of the vascular graft

A different batch from the vascular grafts implanted was used to assess the mechanical properties of the generated BC vessels.

For longitudinal tensile testing, tubular samples of 4 cm in length were set to a tensile testing machine from MTS Systems Corporation (Eden Prairie, MN, USA). Each sample was stretched longitudinally with a constant rate of 15 mm/s, and displacement and force at the breaking point were recorded. Due to the BC reinforcement with an embedded support device, the stress at break was assigned to the mechanically superior mesh. To determine the force at the break of mechanically inferior BC layers, a force decrease of more than 0.1 N within 0.1 s was defined as significant for all tensile testing.

For circular tensile testing, tubular samples of 0.5 cm in length were stretched circularly with a constant rate of 15 mm/s.

For suture retention testing, tubular samples of 2 cm in length were sutured by 14 stitches with a stitch-edge distance of approximately 1 mm, with double-armed 7-0 non-resorbable Prolene® from Ethicon (Bridgewater, MA, USA). The prepared samples were stretched longitudinally with a constant rate of 15 mm/s.

Surgical procedure

Approval and standards

The research protocol was coordinated and approved by the national ethics committee of Israel under the national registration number IL-16-11-369. All facilities and activities at Lahav C.R.O. (D.N. Negev, Israel) were accredited and monitored in accordance with GLP and ISO 9001 (2015) standards for quality and service. This study was conducted in accordance with the Israeli National Council of Animal Experimentation. This study adhered to the ARRIVE Guidelines and was designed and performed under consideration of the 3Rs (Replace, Reduce, and Refine) principles for animal experimentation.

Animals

Eight healthy female pigs with a weight of 78–91 kg were purchased by Lahav C.R.O. (D.N. Negev, Israel). Standard diet (soft food) expanded for pigs from AMBAR Feed mill (Granot M.P. Heffer 3881100, Israel) were provided. Housing started at least 10 days prior to intervention to adapt the animals to the experimental environment.

Surgery

The selected pigs were fasted for 24 h before anesthesia to prevent vomiting. For preparation, all animals were washed, shaved, and disinfected. Preoperative antibiotics were administered in the usual manner. All surgical procedures were performed under aseptic conditions in an operating suite dedicated to veterinary surgery and under general anesthesia: Prior to the surgeries, 2 mg/kg xylazine (Anased®, AKORN, USA) + 10 mg/kg ketamine (Clorkeam®, Vetoquinol, France) were administered by intramuscular injection. Anesthesia was induced by inhalation of 3% isoflurane (Piramal Critical Care, USA) *via* a mask and intravenous administration of 5–10 mg diazepam per animal (Diazepam-Ratiopharm®, Ratiopharm, Germany). During surgeries, anesthesia was maintained by the administration of 1–3% isoflurane. Animals were intubated and ventilated *via* a ventilator, breathing parameters were constantly monitored (ECG, pulse oximetry, rectal temperature, blood pressure, and CO_2). Antibiotic prophylaxis was administered using 0.1 ml/kg Pen&strep® (200 mg/ml penicillin + 250 mg/ml streptomycin, Norbrook, USA). A single shot of 200 mg amiodarone (Cordarone, Pfizer Inc., USA) was administered i.v. to all animals preoperatively. After intubation, the animals were placed in a supine position with their legs attached to the operating room table. After conventional sternotomy, pericardiotomy was performed. The left anterior descending (LAD) artery was identified and ligated after 30 min of preconditioning (3 times for 5 min closure and 3 times for 5 min of flow using an elastic band and a tourniquet system). Within the first days after surgery, the animals

TABLE 1 Bacterial cellulose (BC)-vascular graft morphological and mechanical features (n = 3).

Morphological properties				
BC graft inner diameter	BC graft outer diameter	CoCr mesh diameter	BC graft length	BC graft wall thickness
3 mm	9.45 ± 0.43 mm	5 mm	20 cm	2.73 ± 0.21 mm
Mechanical properties				
Longitudinal tensile test		Circumferential tensile test		Suture retention test
2.85 ± 2.08 N		0.98 ± 0.42 N		8.83 ± 1.47 N

were monitored routinely and further analgesia was given as necessary.

Off-pump coronary artery bypass grafting model

Coronary artery bypass grafting (CABG) was performed on the beating heart utilizing a stabilizer and an intracoronary shunt by two experienced cardiac surgeons. For routine anticoagulation during CABG, heparin was administered, aiming for an activated clotting time greater than 400 s, and later antagonized with protamine. The graft was implanted in the middle segment of the LAD distally to the occluded section. After completion of the anastomosis with the ascending aorta, intraoperative flow measurement (Medistim, Norway) was conducted to validate the patency of the graft. For antithrombotic prophylaxis, aspirin (100 mg/day) was administered daily during the postoperative period. Termination was performed 4 weeks post-implantation. Cardiac arrest was induced by injecting a 20% solution of pentobarbital (Pental Veterinary, CTS Chemical Industries, Israel).

In vivo assessments

The primary endpoint was graft patency after CABG and 4 weeks of follow-up determined by angiography and intraoperative flow measurement prior to model termination. The secondary endpoint was vascular remodeling defined by the presence of endothelial cells in the inner lumen.

Primary endpoint

Postoperative assessment and follow-up

Right after the CABG procedure, coronary angiography was performed. Four weeks after implantation, an angiographic assessment was repeated, and thereafter, the grafts were explanted *in toto* with attached cardiac and aortic segments. Angiography was used to assess the patency of the grafts, in particular, grafts were classified as fully open or partially narrowed, or fully closed according to the established scoring system by Fitz Gibbon et al. for grading distal, proximal anastomoses in the early stage after CABG (13).

Secondary endpoint

Histologic analysis

Samples from two grafts from both anastomotic sites and the middle section of the graft were prepared and embedded in paraffin, cross-sectioned, and stained with hematoxylin and eosin (HE staining) for histologic assessment. For immunofluorescence staining, the following antibodies were used: rabbit anti-laminin (ab11575, dilution at 1:200) and goat anti-smooth muscle actin (SMA) (ab7817, dilution at 1:400) from Abcam (UK), goat anti-vascular endothelial (VE) cadherin (sc6458, dilution at 1:100) from Santa Cruz Biotechnology (Dallas, US), mouse anti-CD31 (MCA1746GA, dilution at 1:100) from AbD Serotec (Germany), mouse anti-CD68 (BA4D5, dilution at 1:50) from AbD Serotec (Germany). All secondary antibodies were diluted 1:200 (Life Technologies, USA). Cell nuclei were stained with 4',6-diamidino-2-phenylindole (DAPI) (0.125 mg/ml) (Sigma-Aldrich, Germany).

Results

In vitro characterization of the vascular graft

All grafts met the predefined criteria, particularly, having a length of 20 cm and an inner diameter of 3 mm, a wall thickness of 2.73 ± 0.21 mm, and an outer diameter of 9.45 ± 0.43 mm (**Table 1**). Micro-CT revealed a homogenous inner layer of BC and centralization of the mesh along with the graft (**Figures 1A,B**). BC was combined with a highly flexible and kink-resistant cobalt–chromium mesh embedded within the graft wall. The mesh was covered entirely from both sides by BC without an external connection (**Figures 1C,D**). Furthermore, SEM revealed an even luminal porous surface (**Figures 1E,F**).

Longitudinal and circumferential tensile testing resulted in a force at break of 2.85 ± 2.08 N and 0.98 ± 0.42 N, respectively. The suture retention testing resulted in a force at break of 8.83 ± 1.47 N.

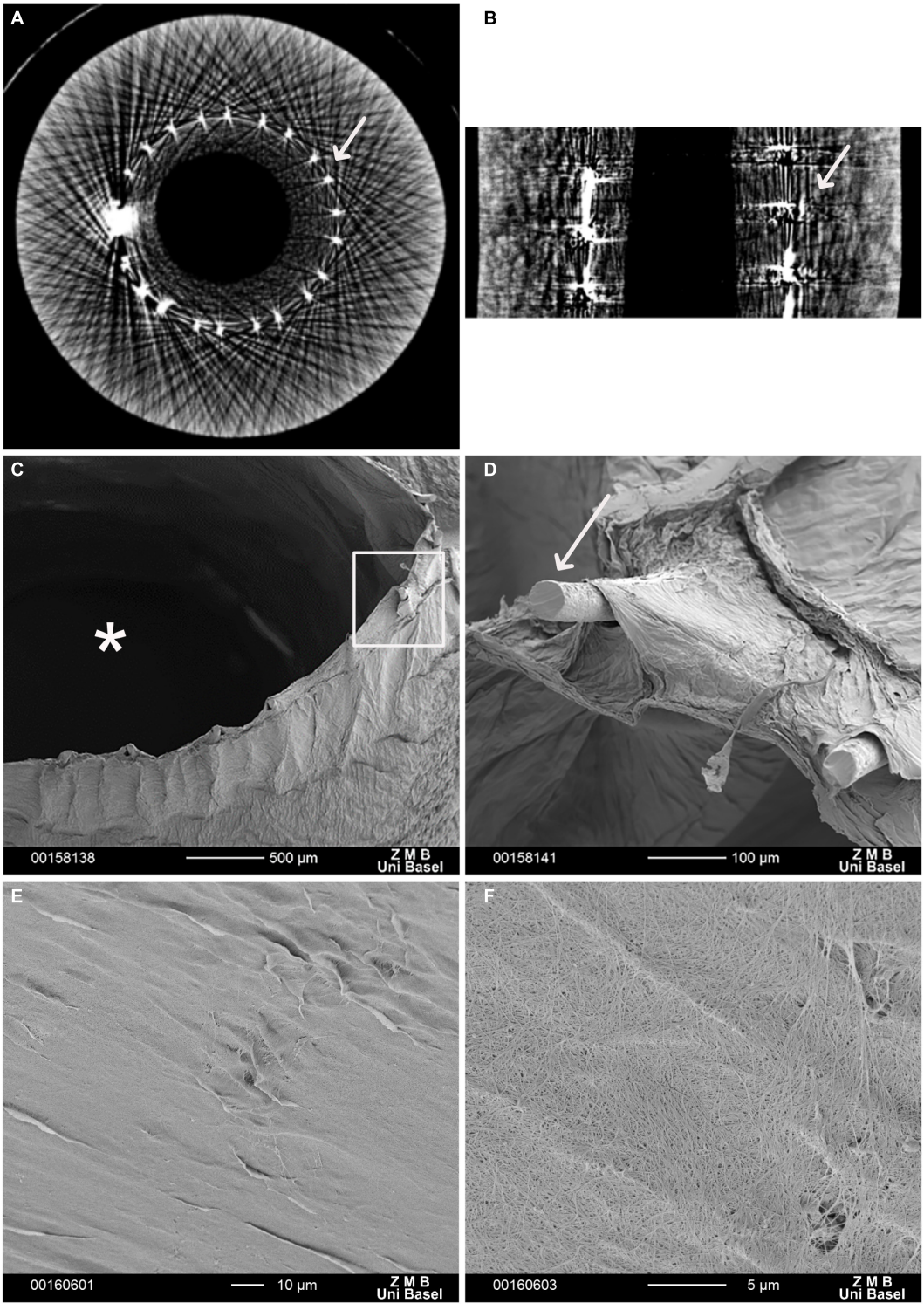

FIGURE 1
Electron microscopy of a vascular graft. Micro-computed tomography (Micro-CT) scan. **(A)** Cross section, **(B)** longitudinal section of the reinforced bacterial cellulose (BC)-based vascular graft. White arrows indicate the Co-Cr mesh scanning electron microscopy (SEM). **(C)** In the cross-section, the structure of the graft comprising an inner BC layer defining the graft lumen (*), the embedded metallic mesh, and an outer BC layer is visible. **(D)** The enlargement (rectangular frame) shows the ends of the mesh wires (arrow). These protruding ends result from cutting and further processing of the vascular graft. **(E,F)** BC-vascular graft luminal surface. **(F)** At higher magnification, porosity of BC-vascular graft luminal surface.

In vivo coronary artery bypass grafting pig model

Intraoperatively, the surgical handling of the graft was reported comparable to arterial grafts in terms of elasticity and wall rigidity. The vessel was blood tight when anastomosed and did not show any effect of kinking or twisting. The artificial "adventitia" stayed adherent and did not show any signs of delamination. The BC-vascular graft handling has been evaluated by two experienced cardiac surgeons.

There were no complications arising from neither the BC nor the embedded CoCr mesh and no bleeding from the anastomotic site has been observed after the reversal of heparin. The graft presented visible pulsation without signs of rupture or dissection once it was de-clamped (**Figure 2** and **Supplementary Video 1**).

Postoperative assessment and follow-up

The initial postoperative angiography conducted directly after finishing the CABG procedure revealed sufficient graft patency of the implanted BC graft in all eight animals. There were no signs of graft dissection or narrowing at the distal anastomotic site (**Figure 3A**). All animals recovered within 24 h, consuming solid food and water 24 h after surgery.

Coronary angiography 4 weeks after CABG confirmed sufficient graft patency without signs of graft dissection or burst in all animals (**Figure 3B**; **Table 2**). None of the animals showed a completely closed lumen of the graft, dissection, ruptures, or bleeding during the 4-week period when evaluated with angiography.

In vivo cellularization of the vascular grafts

Four weeks after implantation, the cobalt–chromium mesh appeared still centered and embedded into the BC layers. BC layers were still visible (**Figure 4**). However, it was possible to observe the presence of SMCs and ECs covering the BC-vascular graft luminal surface suggesting a possible remodeling of the graft in the long term (**Figure 5**). The remodeling of the graft and the endothelialization were more evident in the anastomotic sites compared to the center of the graft following 1 month upon implantation (**Figures 4**, **5**). Macrophages have been not detected (**Figures 5C,F**). Only in one case of endocarditis, inflammatory cells were found within the implant.

The presence of *vasa privata*, namely blood vessels belonging to a specific organ, nourishing, and perfusing it, was investigated. Functional *vasa privata* through the vascular wall were seen in the analyzed grafts (**Figure 6**). The *vasa privata* were composed of clear endothelial and smooth muscle cell layers and vascular basal membrane as shown by the presence of laminin.

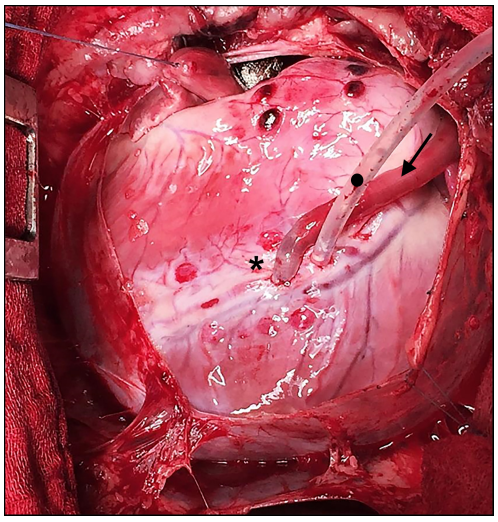

FIGURE 2
Intraoperative situs during off-pump coronary artery bypass grafting (CABG). Bacterial cellulose (BC) graft as a coronary bypass (arrow in direction of flow) after distal anastomosis to the occluded left anterior descending (LAD) (*) using an elastic band with a tourniquet (●).

Besides, there were no signs of thrombosis or luminal narrowing as seen in the case of neointimal hyperplasia.

Discussion

Due to rising life expectancy and the increasing prevalence of vascular diseases, there is a growing need but limited availability of autologous vascular grafts for surgical revascularization. In the context of peripheral and CABG, TEVGs made of biomaterials appear to be promising alternatives. However, complex manufacturing of particularly small-diameter grafts of sufficient length and their limited long-term *in vivo* patency appears to be challenging and represents the limiting factors for their clinical introduction. Consequently, the aim of this study was to generate a novel BC-vascular graft of sufficient length for CABG procedures, precisely greater than 15 cm featuring a small inner diameter of less than 6 mm. Through various improvements, the herein described grafts overcome various limitations of previously reported biological grafts: short and simple production, sufficient mechanical strength, and a satisfactory length of 20 cm for cardiovascular applications. The main aim of the graft design was to allow the *in vivo* endothelialization process to avoid any time-consuming pre-seeding or cell expansion step. Beyond manufacturing and *in vitro* characterization, this was the first attempt to implant

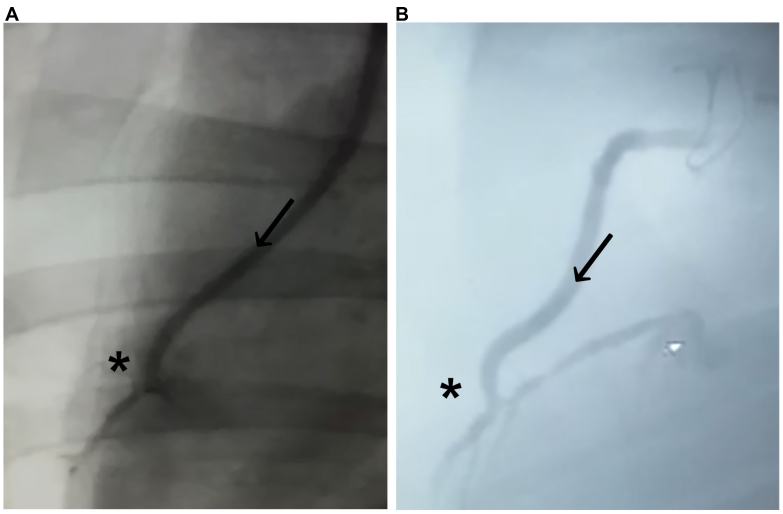

FIGURE 3
Coronary angiogram of the implanted graft. **(A)** Immediately after implantation and **(B)** 4 weeks after implantation. Bacterial cellulose (BC)-vascular graft shows good postoperative results with a complete patency profile as coronary artery bypass and antegrade flow through the BC graft (arrow in direction of the flow) toward the distal anastomosis (*).

TABLE 2 Coronary angiography 4 weeks after coronary artery bypass grafting (CABG) (scoring).

Patency-scoring	Graft 1	Graft 2	Graft 3	Graft 4	Graft 5	Graft 6	Graft 7	Graft 8
100% opened								
> 75% opened								
< 75% opened								
100% closed								

Grey boxes are indicating the patency scoring level of each graft.

a BC-vascular graft as a coronary artery bypass graft in a large animal ischemic heart model.

In the past, one of the first BC small-diameter vascular grafts was described in 2001. Although much smaller with a luminal diameter of only 1 mm and inferior to the herein described grafts regarding mechanical strength, the great potential of BC grafts for cardiovascular applications was demonstrated. The microvascular graft was implanted as carotid interponat in a small-animal model and remained patent for 4 weeks (14). Since then, the methods of graft production and biomechanical characteristics have been continuously improved.

Among various features of BC-vascular grafts, burst pressure is a key indicator of mechanical strength and clinical applicability. Bodin et al. have shown that BC-vascular graft burst pressure strength increased at an oxygen ratio of 100% compared to a ratio of 21, 35, or 50%. This is most likely because BC-producing bacteria are obligate aerobes and produce more BC with higher density under more favorable environmental conditions (15). Comparing the burst pressure of different vascular grafts, native BC grafts compete with autologous venous grafts but not with arterial grafts. The latter is characterized by a thicker wall, physiologically withstanding higher blood pressure in the arterial system (16, 17). For saphenous vein grafts, a burst pressure of about 1,600 mmHg has been reported. Internal mammary artery grafts withstand a pressure higher than 3,100 mmHg (16). After CABG procedures, venous grafts, physiologically designed to withstand low pressure within the venous system, have to withstand high pressure within the arterial system. Insufficient wall strength of venous grafts favors micro lesions leading secondarily to intimal hyperplasia. Reactive migration and proliferation of vascular SMCs result in an extracellular matrix of connective tissue, consecutively, leading to graft stenosis and occlusion (18). In general, intimal hyperplasia is considered a major cause of graft failure (19). Therefore, BC grafts have to fulfill specific requirements for compliance and mechanical strength. Since all the herein described grafts remained patent for over 4 weeks, sufficient compliance and mechanical strength are presumed.

As highlighted above, coronary angiography 4 weeks after CABG revealed complete patency. To the best of our knowledge, this was the first time that BC grafts were implanted as coronary bypass grafts in a large animal model. So far, BC grafts were tested prevalently as interponat in the common carotid artery

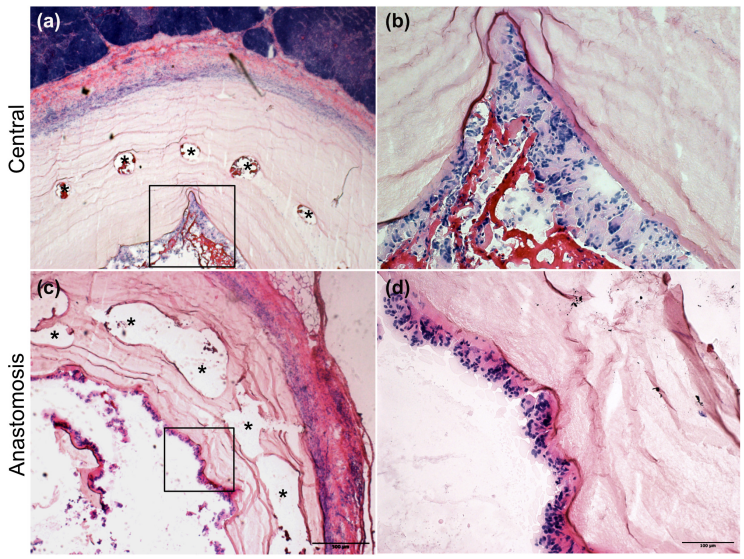

FIGURE 4
H&E staining of the explanted grafts 4 weeks after implantation. The explanted Bacterial cellulose (BC)-vascular graft reveals a three-layered wall structure indicating remodeling by host cells. Representative images of the vascular grafts at the central part **(a,b)** and at the anastomosis site **(c,d)** at high 20 × **(b,d)** and low 4 × **(a,c)** magnifications. *indicates the empty holes left from the embedded mesh, which were removed during the histological process.

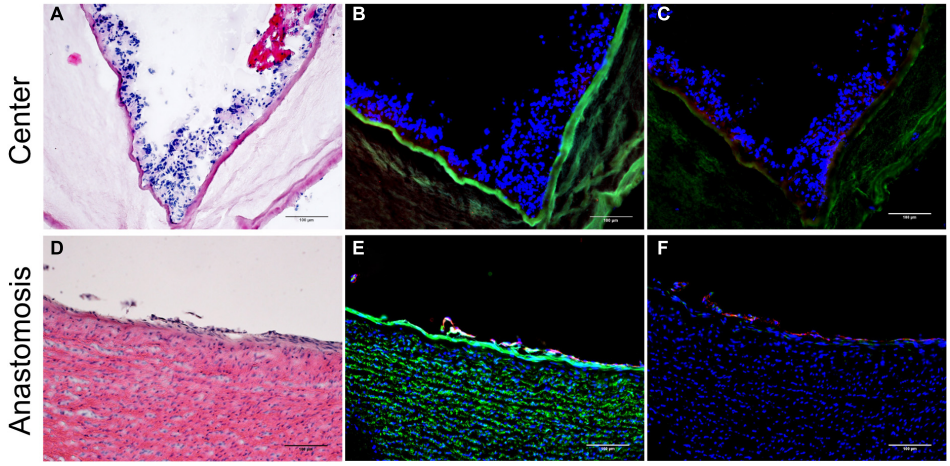

FIGURE 5
Inner layer of the vascular grafts 4 weeks after implantation. Representative images of the vascular grafts at the central part **(A–C)** and at the anastomosis site **(D–F)** stained with H&E **(A,D)** and immunofluorescence antibodies specific for Ve-Cadherin (red), α-SMA (cyan), laminin (green) **(B,E)**, and for CD31 (red) and CD68 (green) **(C,F)**. Nuclei were stained with DAPI (blue) **(B,C,E,F)**. Scale bar = 100 μm.

in various animal models. This is due to the favorable cervical accessibility and the possibility of implanting short grafts of a few centimeters and even millimeters. Wippermann et al. performed carotid replacement in a large animal model. For carotid interposition, grafts up to 10 mm in length with an inner diameter of 3.0–3.7 mm were applied in eight domestic pigs. After 3 months, a patency of 87.5% was reported. While one graft was found occluded due to collapsed vascular walls, the others showed no signs of thrombosis, dilatation, dehiscence, or aneurysm formation (10). Malm et al. tested BC grafts with an increased length in a long-term animal study. Samples up to 40 mm length and an inner diameter of 4 mm were implanted bilaterally in the common carotid arteries of eight sheep. Five cases of acute thrombosis and severe anemia occurred in the early postoperative period. From the three-remaining sheep, all grafts remained patent after 3 months and five of six, respectively, 83.3% after 6 months. The sheep with unilateral occlusion had to be euthanized after 8 months revealing an

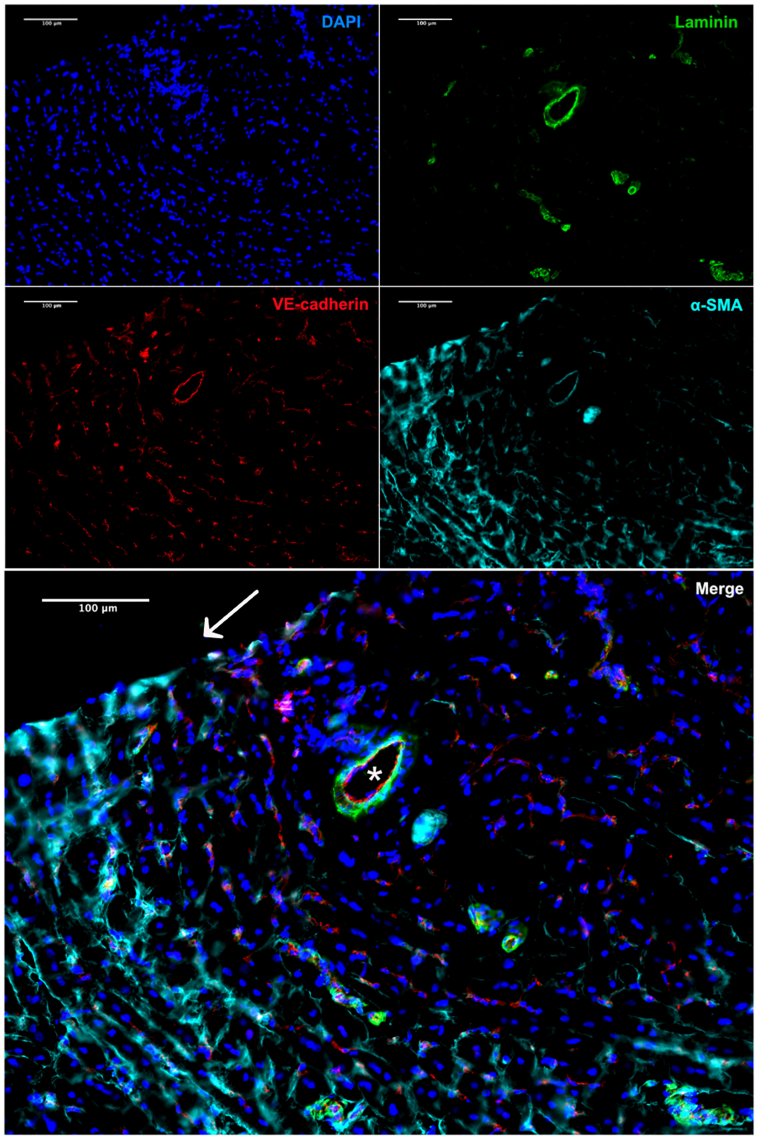

FIGURE 6
Immunofluorescence staining of the explant 4 weeks after implantation. Vasa privata (*) within the remodeled BC-vascular graft wall (anti-VE-cadherin in red, anti-αSMA in cyan, and anti-laminin in green). Nuclei were stained with DAPI. Scale bar = 100 µm.

organized thrombosis and signs of intimal hyperplasia in the perianastomotic region. Thirteen months after implantation the grafts from the remaining two sheep were explanted revealing 75% patency (11). Although various experimental studies display the great potential of BC grafts for a broad field of cardiovascular application, there has been no clinical translation yet. This requires even better long-term results without thrombotic complications.

As mentioned before, the grafts were explanted after 4 weeks. According to our findings, the explanted grafts were well-integrated into the surrounding host tissue without signs of inflammation. All of them revealed a native-like three-layered wall structure showing a layer of ECs with the basal lamina, a concentric layer of SMCs, and an outer layer of fibroblasts. The presence of various cell types and the occurrence of *vasa privata* confirm the suitability of the BC fibril network as a scaffold for cellularization (20, 21). Since the histological findings indicate sufficient graft remodeling within 4 weeks, the pre-procedural step of cell harvesting, expansion, and seeding prior to implantation is unnecessary in this graft type. This represents an important feature in terms of clinical translation as these three steps are time-consuming, and time the patients do not have prior to a CABG procedure. Nevertheless, it seems very important to gain a better understanding of *in vivo* cellularization dynamics and conditions in order to create an optimal graft environment. By continuous optimization of BC

grafts such as surface modification, *in vivo* endothelialization might be further sped up.

The study has one major limitation. Since the main aim was to implant the BC-vascular graft as a coronary bypass graft in a large animal model as proof of concept, *in vivo* testing was carried out only in eight domestic pigs without a control group as a proof-of-concept study. Larger and controlled animal studies are required to verify the results, especially in the medium-and long-term.

In conclusion, small-diameter BC-vascular grafts with an application-oriented length of more than 15 cm can be generated. Furthermore, these grafts reveal great potential when applied as a coronary bypass graft in an ischemic heart model in pigs. The grafts showed a three-layered structure composed of an inner endothelial layer with SMCs beneath and *vasa privata* formation. In the future, more animal studies are needed to determine the potential of BC-vascular grafts for cardiovascular applications beyond CABG. In case of continued successful *in vivo* testing, coronary and peripheral artery bypass grafting with BC grafts should be evaluated.

Data availability statement

The original contributions presented in this study are included in the article/**Supplementary material**, further inquiries can be directed to the corresponding author.

Ethics statement

The research protocol was coordinated and approved by the National Ethics Committee of Israel under the national registration number IL-16-11-369. All facilities and activities at Lahav C.R.O. (D.N. Negev, Israel) were accredited and monitored in accordance with GLP and ISO 9001 (2015) standards for quality and service. This study was conducted in accordance with the Israeli National Council of Animal Experimentation. This study adhered to the ARRIVE Guidelines.

Author contributions

BW: concept or design of the work. MG and BW: acquisition of data. FM, DF, AM, BP, and BW: analysis and interpretation of data and drafting the manuscript. All authors revising the manuscript critically for important intellectual content and approved of the version of the manuscript to be published.

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Conflict of interest

This study was supported by grants of the Department of Cardiac Surgery of the University Hospital Basel and the University of Basel awarded to the PI BW. Another grant from Jubilaeumsstiftung/Novartis was awarded to BW for a visiting fellowship for tissue engineering. Further, BW, MG, and FE were supported from Vascular Graft Solutions (VGS, Tel Aviv-Jaffa, Israel). No other potential conflict of interest relevant to this article was reported.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.881557/full#supplementary-material

SUPPLEMENTARY FIGURE 1
Customized bioreactor used for bacterial cellulose (BC)-vascular graft production. **(A)** Bioreactor scheme consists of a culture chamber filled with bacteria suspension, four rotating steel shafts covered by a silicon tube, and four stepper motors. **(B)** Picture of the bioreactor during the fermentation process.

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Incidence, management, and prognosis of post-ischaemic ventricular septal defect: Insights from a 12-year tertiary centre experience

Henri Treille de Grandsaigne[1,2], Frédéric Bouisset[2], Jean Porterie[3], Caroline Biendel[1,2], Bertrand Marcheix[3], Olivier Lairez[2], François Labaste[4], Meyer Elbaz[2], Michel Galinier[1,2] and Clément Delmas[1,2]*

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Background: Among mechanical complications of acute myocardial infarction, ventricular septal defect (VSD) is uncommon but still serious. The evolution of emergency coronary revascularisation paradoxically decreased our knowledge of this disease, making it even rarer.

Aim: To describe ischaemic VSD incidence, management, and associated in-hospital and 1-year outcomes over a 12-years period.

Methods: A retrospective single-centre register of patients managed for ischaemic VSD between January 2009 and December 2020.

Results: Ninety-seven patients were included representing 8 patients/ years and an incidence of 0.44% of ACS managed. The majority of the patients were 73-years-old males ($n = 54$, 56%) with STEMI presentation ($n = 75$, 79%) and already presented with Q necrosis on ECG ($n = 70$, 74%). Forty-nine (51%) patients underwent PCI, 60 (62%) inotrope/vasopressors infusion, and 70 (72%) acute mechanical circulatory support (IABP 62%, ECMO 13%, and Impella® 3%). VSD surgical repair was performed for 44 patients (45%) and 1 patient was transplanted. In-hospital mortality was 71%, and 86% at 1 year, without significant improvement over the decade. Surgery appears to be a protective factor [0.51 (0.28–0.94) $p = 0.003$], whereas age [1.06 (1.03–1.09), $p < 0.001$] and lactate [1.16 (1.09–1.23), $p < 0.001$] were linked to higher 1-year mortality. None of the patients that were managed medically survived 1 year.

Conclusion: Post-ischaemic VSD is a rare but serious complication still associated with high mortality. Corrective surgery is associated with better survival, however, timing, patient selection, and a place for mechanical circulatory support need to be defined.

KEYWORDS

acute cardiac care, acute coronary syndrome, mortality, complication, epidemiology

Introduction

Ventricular septal defect (VSD) is an uncommon but serious mechanical complication of myocardial infarction (MI), most often associated with an acute ST-elevation MI (STEMI), related to the acute occlusion of a major epicardial vessel. If its prevalence was relatively high during the pre-thrombolytic era, 1 to 2% (1), technical improvements in coronary revascularisation and the development of pre-hospital networks have made it even rarer (0.2%) (2, 3). VSD is the least rare mechanical complication (0.21%) of MI, compared to mitral regurgitation due to papillary muscle ischaemic rupture (0.05%), and free wall rupture (0.01%) (3). In addition, whatever the mechanical complication, its occurrence is five times more likely in STEMI vs. non-STEMI (3). The admissible pathophysiological argument is that longer and deeper ischaemia would produce such necrosis that it has noteworthy anatomical repercussions (4).

Despite its rarity, ischaemic VSD is still associated with high mortality if medically managed (above 90% mortality at 30 days) and its management remains challenging (1, 5). The only curative therapy is then surgical septum repair, mostly by VSD patch closure using the double ventriculostomy technique, which remains a high-risk procedure mainly due to recent infarction, depressed ventricular function, and often precarious hemodynamics. VSD repair is still associated with high postoperative mortality (33% to 61 %) (1, 5–7). Moreover, surgery timing is also pivotal (8), as suggested by the higher mortality observed among the patients undergoing surgery before day 7 (54% vs. 17%) (9), even if these observations are probably subject to selection bias. Finally, discussion on the timing of surgery and the better results observed in the case of delayed surgery raises the question of the waiting conditions. During this time frame, physicians should be able to stabilize the patient's hemodynamics, correct any organ failure, and unload the ventricles in order to promote myocardial recovery before VSD correction. Acute mechanical circulatory support (aMCS) is thus often discussed for this purpose; however, the type and timing of its deployment are still a matter of debate (10).

We aimed to assess the evolution of incidence, management, and prognosis of ischaemic VSD during the last 10 years in a large tertiary center in western Europe.

Methods

Population

All the consecutive patients managed for ischaemic VSD at Toulouse University Hospital between 01/01/2009 and 31/12/2020 were retrospectively included in this study. The patients were found *via* the local PMSI (Programme de Médicalisation des Systèmes d'Information) (ICD codes 10 X and Y), with a retrospective control carried out using the intensive cardiac care unit register. According to the French ethical and regulatory law, retrospective studies based on the exploitation of usual care data do not need to be submitted to an ethical committee but have to be covered by the reference methodology of the French National Commission for Informatics and Liberties (CNIL). After evaluation and validation by the data protection officer and according to the General Data Protection Regulation, this study completed all the criteria and was registered in the register of retrospective studies of the Toulouse University Hospital (number RnIPH 2020–115) and covered by the MR-004 (CNIL number: 2206723 v 0).

Data collection

Clinical data were collected at admission and during hospitalization, together with a previous history of heart disease, cardiovascular risk factors, and comorbidities. Transthoracic echocardiography (TTE) was performed in all cases and data obtained were collected (left and right ventricle diastolic and systolic function, size and localization of the VSD). Biological monitoring included blood gas and arterial lactate, prothrombin ratio, NT-pro-BNP, aspartate aminotransferase, alanine aminotransferase, total bilirubin and creatinine levels, and estimated glomerular filtration rate. The EuroSCORE II was calculated for all patients.

Statistics

Continuous variables were expressed as means ± standard deviation or as medians with interquartile ranges (IQR) when not normally distributed. Nominal variables were expressed in numbers and percentages. The association between the mean values of continuous variables was assessed using the Mann-Whitney rank sum test or Student's t-test when appropriate. Nominal variables were assessed by the χ^2 test or Fisher's exact test when appropriate. The patients were separated into two groups based on in-hospital (Supplementary Table S1) or 1-year (Table 1) mortality. Regression analysis was performed using variables with a p-value < 0.05 to analyse variables associated with the criteria of mortality with results reported as odds ratios (OR) with 95% confidence intervals (CI) for in-hospital mortality. A Cox analysis was performed to analyse the factors associated with 1-year mortality and the results were reported as a hazard ratio (HR) with 95% CI (Table 2). A p-value inferior to 0.05 was considered significant. Stata® (14.2 version) software was used for statistical analyses.

TABLE 1 Description of the population at admission, management, and outcomes according to their 1-year mortality.

	Global population ($n = 97$)	Non-survivors at 1 year ($n = 83$)	Survivors at 1 year ($n = 14$)	*p*-value
Age, years old	73 +/- 11	74 +/- 9	63 +/- 13	<0.001
Male sex, *n* (%)	54 (55.7)	45 (54.2)	9 (64.3)	0.48
Cardiovascular risk factors, *n* (%)				
Smokers ($n = 95$)	37 (38.9)	27 (33.3)	10 (71.4)	< 0.01
Diabetes ($n = 96$)	30 (31.3)	26 (31.7)	4 (28.6)	0.82
Dyslipidemia ($n = 95$)	32 (33.7)	26 (32.1)	6 (42.9)	0.43
Hypertension ($n = 95$)	53 (55.8)	45 (55.6)	8 (57.1)	0.91
Obesity (BMI > 30) ($n = 90$)	17 (18.9)	12 (15.8)	5 (35.7)	0.08
Medical history, *n* (%)				
Ischaemic cardiomyopathy ($n = 94$)	9 (9.6)	8 (10)	1 (7.1)	0.73
PAD ($n = 95$)	7 (7.4)	6 (7.4)	1 (7.1)	0.97
CKD ($n = 95$)	6 (6.3)	4 (4.9)	2 (14.3)	0.18
Clinical characteristics at admission, n (%)	35 (40.2)	28 (37.8)	7 (53.9)	0.27
Right HF signs ($n = 87$)				
Left HF signs ($n = 92$)	54 (58.7)	47 (60.3)	7 (50)	0.47
Hemodynamics instability ($n = 97$)	53 (54.6)	47 (56.6)	6 (42.9)	0.33
Electrocardiogram at admission, *n* (%)				
STEMI ($n = 95$)	75 (79)	66 (81.5)	9 (64.3)	0.14
Q wave	70 (73.7)	60 (74.1)	10 (71.4)	0.83
Angiocoronarography, *n* (%)				
Culprit lesion location ($n = 91$)				0.75
LAD	51 (56)	43 (55.8)	8 (57.1)	
RCA	37 (40.7)	31 (40.3)	6 (42.9)	
Cx	3 (3.3)	3 (3.9)	0 (0)	
Ad-hoc revascularisation	49 (50.5)	42 (50.6)	7 (50)	0.96
Significant other coronary artery disease ($n = 91$)				0.63
One-vessel disease	37 (40.7)	30 (39)	7 (50)	
Two-vessel disease	33 (36.3)	28 (36.4)	5 (35.7)	
Tri-vessel disease	21 (23.1)	19 (24.7)	2 (14.3)	
Biology at admission				
Lactates (mmol/l) ($n = 84$)	2.65 [1.75–4.7]	2.8 [1.8–5.4]	1.4 [1.2–2.2]	< 0.01
PTT (%) ($n = 91$)	66 +/- 19	65 +/- 20	73 +/- 12	0.13
Hepatic cytolysis (n x Normale) ($n = 90$)	6 (2–17)	7 (2–18)	3 (2–11)	0.19
Total bilirubin (mmol/l) ($n = 88$)	21.8 +/- 13.6	22.8 +/- 14.4	16.4 +/- 5.2	0.10
pH ($n = 91$)	7.39 +/- 0.12	7.37 +/- 0.13	7.45 +/0.06	0.06
Troponin (n x Normale) ($n = 95$)	420 [217–1,192]	427 [227–1,192]	427 [227–1,192]	0.24
Natriuretic peptid (n x Normale) ($n = 66$)	20 (9–49)	23 (10–53)	9 (7–19)	0.03
eGFR (MDRD) ml/min/1.73 m^2 ($n = 96$)	43 [28–73]	40 [28–69]	66 [37–85]	0.08
Echocardiography (TTE or TOE), *n* (%)	44 +/- 13	44 +/- 13	40 +/- 15	0.28
LVEF (%) ($n = 96$)				
RV dilatation ($n = 88$)	50 (56.8)	39 (52.7)	11 (78.6)	0.07
RV dysfunction ($n = 92$)	44 (47.8)	38 (48.7)	6 (42.9)	0.68
VSD characteristics				
Size by TTE (mm) ($n = 67$)	14 +/- 8	13 +/- 7	16 +/- 11	0.23
Surgical size (mm) ($n = 38$)	23 +/- 13	23 +/- 14	26 +/- 10	0.51
VSD localization ($n = 96$)				0.70

(Continued)

TABLE 1 (Continued)

	Global population ($n = 97$)	Non-survivors at 1 year ($n = 83$)	Survivors at 1 year ($n = 14$)	*p*-value
Basal	28 (29.2)	25 (30.5)	3 (21.4)	
Median	16 (16.7)	14 (17.1)	2 (14.3)	
Apical	52 (54.3)	43 (52.4)	9 (64.3)	
EuroSCORE 2 ($n = 95$)	42.4 +/- 20.7	44.9 +/- 19.7	28 +/- 20.9	< 0.01
VSD management				
Inotrops or vasopressors	60 (61.9)	56 (67.5)	4 (28.6)	< 0.01
IABP	60 (61.9)	48 (57.8)	12 (85.7)	0.04
VA-ECMO	13 (13.4)	12 (14.5)	1 (7.1)	0.45
Impella®	3 (3.1)	2 (2.4)	1 (7.1)	0.34
All acute MCS	70 (72.2)	58 (69.9)	12 (85.7)	0.22
Surgical closure	44 (45.4)	32 (38.6)	12 (85.7)	< 0.01
Percutaneous closure	4 (4.1)	4 (4.8)	0 (0)	0.40
Heart transplantation	1 (1)	0 (0)	1 (7.1)	0.01
Length of stay (days) ($n = 96$)	7 (3–12)	6 (3–10)	16 (11–27)	< 0.01
ICU/ICCU LOS				
Total LOS	8 (3–16)	6 (3–12)	23 (16–46)	< 0.01

BMI, body mass index; CKD, chronic kidney disease; Cx, circonflex coronary artery; eGFR, estimated glomerular filtration rate; HF, heart failure; IABP, intra-aortic balloon pump; ICU, intensive care unit; ICCU, intensive cardiac care unit; LAD, left anterior descending artery; LOS, length of stay; LVEF, left ventricular ejection fraction; MCS, mechanical circulatory support; PAD, peripheral arterial disease; PTT, prothrombin time; RCA, right coronary artery; RV, right ventricle; TOE, transesophagal echocardiography; TTE, transthoracic echocardiography; VA-ECMO, veno-arterial extracorporeal membrane oxygenation; VSD, ventricular septal defect.

TABLE 2 Factors associated with in-hospital mortality by Cox regression analysis.

	Univariate analysis			Multivariate analysis		
	OR	CI 95%	*p* value	OR	CI 95%	*p* value
Age (for each supplementary year)	1.06	[1.02–1.11]	< 0.01	1.06	[1.01–1.12]	0.02
Active smocker	0.42	[0.17–1.04]	0.06	-	-	-
Chronic renal failure	0.39	[0.07–2.06]	0.26	-	-	-
Biology						
Lactates (for each supplementary mmol)	1.35	[1.01–1.81]	0.04	-	-	-
TP (for each supplementary %)	0.97	[0.95–1.01]	0.10	-	-	-
Hepatic cytolysis > 20 N	3.40	[1.06–10.9]	0.04	-	-	-
Management						
VSD surgical repair	0.09	[0.03–0.28]	< 0.01	0.14	[0.04–0.45]	< 0.01
Amine use	3.78	[1.50–9.49]	< 0.01	3.08	[1.22–11.4]	< 0.01

CI, confidence interval; HR, hazard ratio; N, normal; PT, prothrombin time; VSD, ventricular septal defect.

Results

Population

Over a period of 12 years, a total of 97 patients with ischaemic VSD were included (Table 1), with a mean of 8 per year. Figure 1 shows VSD cases by year in comparison with STEMI and non-STEMI in our center and associated VSD incidence which varied between 0.10 % (2015) to 0.73 % of ACS (2020).

Patients were predominantly male ($n = 54$, 56%) with a mean age of 73 ± 11 years old. Cardiovascular risk factors were frequent but ischaemic cardiomyopathy was previously known for only 9 patients (9.6%). At admission 44 patients (45%) were in cardiogenic shock, 57 (59%) presented with left heart failure, and 39 (40%) with right heart failure signs. An ECG showed a Q wave of sequelae for 70 (74%). TTE showed a left (LVEF 44%) and right ventricles dysfunction (RV dilation 57% and/or dysfunction 48%). The VSD was apical for 52 patients (54%), with a mean size of 14 mm.

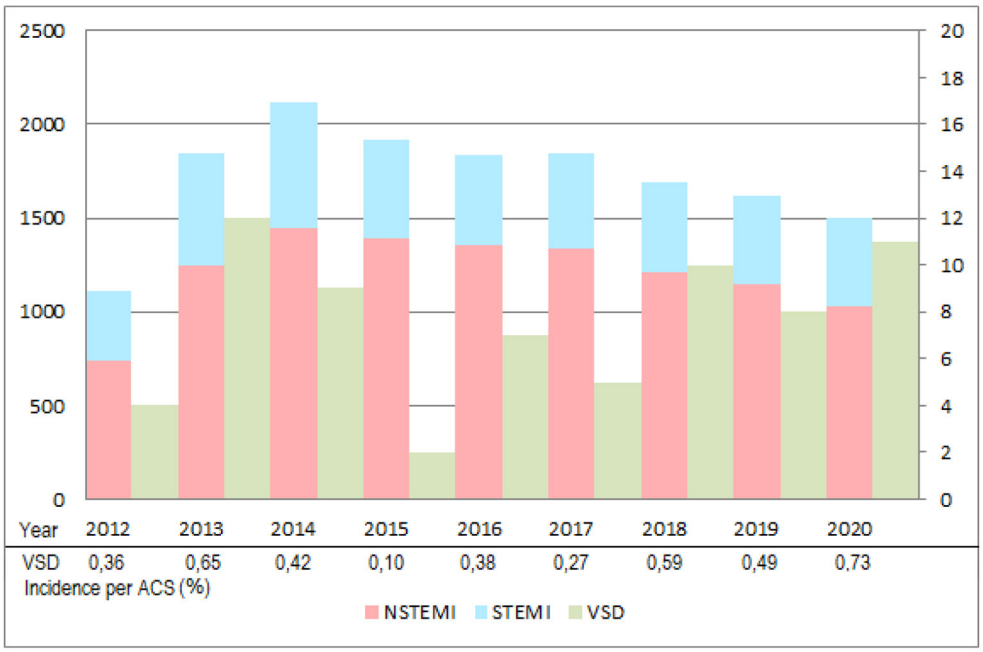

FIGURE 1
Annual numerical comparison of acute coronary syndromes (Non-STEMI and STEMI) and ischemic VSD managed between June 2012 and December 2020. Number of Non-STEMI (red) and STEMI (blue) per year are reported on the left axis although VSD (green) is reported on the right. Patients before January 2012 were nor reported since an old data system did not permit a systematic counting of all consecutive cases. ACS, acute coronary syndrome; NSTEMI, non-ST-elevated myocardial infarction; STEMI, ST-elevated myocardial infarction; VSD, ventricular septal defect.

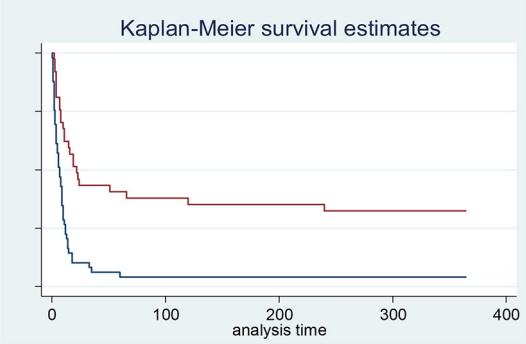

FIGURE 2
Ischemic ventricular septal defect survival according to the realization of surgical repair (red curve) or not with only medical management (blue curve). Log-rank test p-value < 0.001. On 97 patients. 11 patients were lost of follow-up and not included in survival analysis.

Patients had one-vessel disease in 40% of the cases and the left anterior descending artery was the culprit vessel for 50 patients (56%).

Management

An *ad hoc* revascularisation was performed for 49 patients (51%), despite a mean delay from initial symptoms of 52 h. Inotrope/vasopressor support was needed for 60 patients (62%) and mechanical circulatory support for 70 (72%), mainly by IABP ($n = 68$, 86%). The patients supported by an aMCS were younger (71 +/- 10 vs. 77 +/- 9 yo, $p = 0.01$), with less peripheral artery disease (2.9 vs. 20%, $p = 0.002$), with larger VSD (26 +/- 13 vs. 15 +/- 5 mm, $p = 0.03$). They were also more managed by inotropes/vasopressors (71.4 vs. 37.4%, $p = 0.002$) with more surgical closures attempted (51.4 vs. 29.6%, $p = 0.05$) and a higher length of stay in the critical care unit (9 vs. 3 days, $p = 0.002$) (Supplementary Table S1). For 44 patients (45%), a surgical VSD repair was performed and for 1 patient (1%) a heart transplant was required, with a mean delay to the procedure of 10.6 days. A percutaneous closure technique was attempted for 4 patients (4%) considered to be at prohibitive risk for surgery.

Outcomes

In-hospital and 1-year mortality rates were 71% and 86%, respectively (Figures 2 , 3). A total of 28 patients (28.9%) were

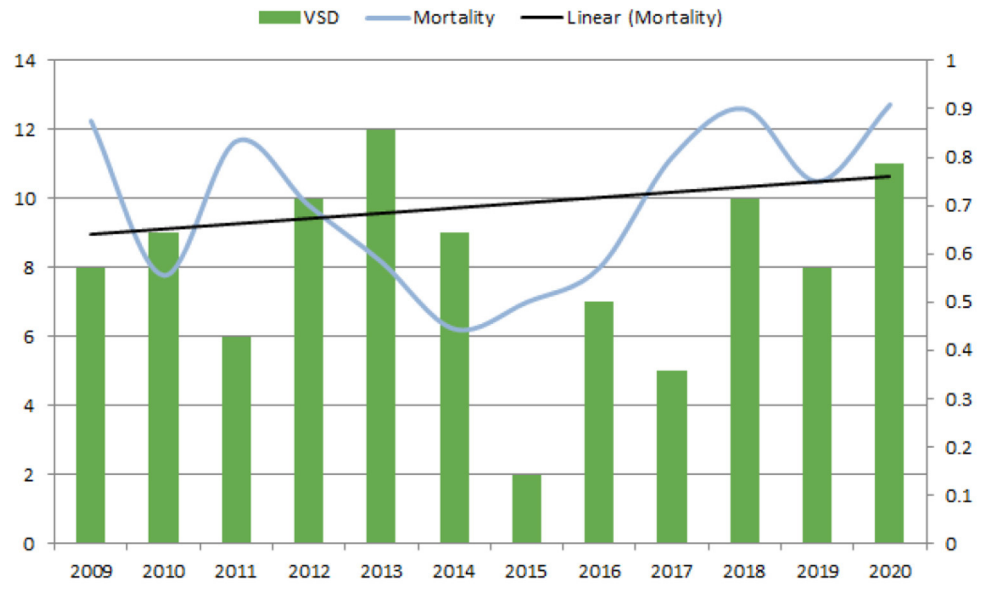

FIGURE 3
Annual VSD count between 2009 and 2020 and associated 1-year mortality. Left axis reports number of ischemic VSD per year. Right axis reports the ischemic VSD 1-year associated mortality. VSD, ventricular septal defect.

TABLE 3 Factors associated with 1-year mortality by Cox regression analysis.

	Univariate analysis			Multivariate analysis		
	HR	CI 95%	*p* value	R	CI 95%	*p* value
Age (for each supplementary year)	1.05	[1.02–1.08]	< 0.01	0.06	[1.03–1.09]	< 0.01
Active smockers	0.46	[0.27–0.73]	< 0.01	-	-	-
Chronic kydney disease	0.48	[0.15–1.54]	0.22	-	-	-
Biology						
Lactates (for each supplementary mmol)	1.17	[1.11–1.24]	< 0.01	10.16	[1.09–1.23]	< 0.01
PTT (for each supplementary %)	0.98	[0.96–0.99]	< 0.01	-	-	-
Hepatic cytolysis (> 20 N)	1.52	[0.93–2.48]	0.09	-	-	-
Management						
VSD surgical repair	0.33	[0.20–0.55]	< 0.01	00.51	[0.28–0.94]	0.03
Amine use	1.99	[1.19–3.34]	< 0.01	-	-	-

CI, confidence interval; HR, hazard ratio; N, normal; PT, prothrombin time; VSD, ventricular septal defect.

discharged from the hospital: their mean LVEF was 38% and in 7 cases (24%) a residual shunt was present.

Non-survivors at 1 year were older (74 vs. 63 yo, $p < 0.001$) with more severe organ dysfunction as reflected by higher lactate (2.8 vs. 1.4 mmol/l, $p = 0.005$) and natriuretic peptide (23 vs. 9 x N, $p = 0.003$) at admission. Non-survivors were more likely to have undergone inotrope/vasopressors support (67.6% vs. 28.6 %, $p = 0.006$) and less surgical repair (38.6% vs. 85.7%, $p = 0.001$) than survivors. The EuroSCORE II value was significantly higher for non-survivors (44.9% vs. 28% for survivors, $p < 0.001$). No significant difference was found according to medical history, VSD type, and position or type of aMCS (Supplementary Figure S1). The characteristics of patients according to in-hospital mortality are described in Supplementary Table S2.

Factors associated with higher in-hospital mortality in multivariate analysis were age [OR 1.06 (1.01–1.12) for each supplementary year, $p = 0.02$] and amines support requirement [OR 3.08 (1.22–11.4), $p = 0.002$], whereas surgery was associated with lower mortality [0.14 (0.04–045), $p = 001$] (Table 2).

Factors associated with 1-year mortality were age [1.06 (1.03–1.09), $p < 0.001$] and lactate [1.16 (1.09–1.23), $p < 0.001$], whereas surgery was associated with lower mortality [0.51 (0.28–0.94) $p = 0.003$] (Table 3). Additionally, we did not observe a decrease in 1-year mortality in the most recent period. On the contrary, we observed a trend of higher mortality (Figure 3).

For the 44 patients who underwent surgical septum repair, in-hospital and 1-year mortality were significantly lower than for medically managed patients (48% vs. 57% and 73% vs. 100%, respectively) (Figure 2). No significant difference was found among patients surgically managed on mean surgery delay or surgical technique used according to their in-hospital and 1-year vital status (Supplementary Table S3). No significant difference in survival was observed according to the use of aMCS or according to aMCS type (Supplementary Figures S1, S2).

Discussion

Thanks to a 12-years retrospective analysis of our tertiary centre's experience, we demonstrated (1) the scarcity of post-ischaemic VSD (mean of 8 patients per year either <0.8% of ACS managed), (2) its severe prognosis close to 1 on 3 deceased at hospital discharge and up to 100% at 1 year in case of medical treatment, and (3) factors associated with worse prognosis were age, amine use, and lactate increase, (4) whereas surgery seems to be the only effective treatment with a 1-year survival of 27%.

As in a recent large retrospective multicentric registry (The CAUTION study $n = 475$ patients in 26 sites) (11), we found no prognosis improvement during the last decade despite refinements in interventional cardiology, heart surgery, mechanical circulatory support, and intensive care. Despite not reporting specific analysis by time period, we did not find any mortality difference between periods with the persistence of severe prognosis with in-hospital mortality around 80% and up to 100% 1-year mortality for medically managed patients.

This observation is surprising and there are questions regarding its causes. One possible explanation is the lack of expertise even in tertiary centers due to the scarcity of the disease (8 per year even in our reference center), preventing substantial practice enhancement. Another explanation is that today, the majority of patients arrive at our tertiary center contrary to before when they were probably less referred and died in primary or secondary centers. But, the absence of difference in terms of severity (data not shown) or incidence change during a 10-year period is not in favor of this. We only found a numerical VSD increase in 2020 which could be linked to the SARS-CoV-2 pandemic as previously explained, particularly by latency in management (12).

Another potential explanation is based on non-considered cofactors such as the systemic inflammatory response syndrome which could play an important role in the worsening of the associated MOF but also in the widening of the VSD. So, it might be a potential therapeutic target in these severe patients. But despite attractive pathophysiological hypotheses, inflammatory blocking or modulation (by anti-IL6, anti-TNF for example) and blood purification techniques (such as Cytosorb®) have yielded conflicting results (13, 14). They should only be discussed in the most severe patients as a rescue strategy based, for example, on a high level of plasma IL-6 or on the need for high doses of vasopressors, as recently suggested.

We reported a predominance of apical VSD with moderate RV dysfunction as previously reported (11). Interestingly, the VSD site was not prognostic in our study although the posterior position was associated with higher in-hospital mortality in the CAUTION study (11). The smaller population reported here may explain this difference. Due to the retrospective design of the study, TTE data were incomplete without standardization to evaluate and describe the RV function preventing any specific analysis.

As in previous reports (11), nearly half of patients were in cardiogenic shock at initial management (45%). The initial haemodynamic instability was related not only to the early prognosis but also to the patient's long-term prognosis, as highlighted by the multivariate analysis. This also confirms the prognostic weight of age at treatment. Only surgery was associated with a better prognosis (52% survival at hospital discharge and 27% at 1 year). This association was significant with in-hospital mortality [OR 0.14 (0.04–0.45), $p < 0.001$] and persisted with 1-year mortality [OR 0.51(0.28–0.94), $p = 0.03$] reaffirming the pivotal place of surgery in the management of post-MI VSD patients.

The place, type, and timing of aMCS could not be discussed with our cohort since the timing of insertion was not collected and the majority of patients received IABP ($n = 68$, 74%). Other devices were marginal (3 Impella® and 13 ECMO), preventing any conclusion contrary to the previous meta-analyses (15, 16). Dedicated studies may help the decision on timing and type of aMCS but these seem impossible to conduct due to the scarcity of this complication and the absence of consensual management even in a unique center. Direct LV and/or RV venting sounds attractive based on physiological and *ex-vivo* simulating studies but no specific studies to date report its use in these complex cases (17). Direct LV unloading is associated with a decrease in LVEDP and PCWP and an increase in coronary perfusion, suggesting higher potential LV recovery and preventing the worsening of the RV function associated with renal and hepatic failure (17). Nevertheless, the enthusiasm for direct ventricle venting could be moderated by the risk of worsening mechanical complications and systemic embolism due to its intra-cavity position. Further, all aMCS available are associated with potential adverse events in particular haemolysis, bleedings, limb ischaemia, and vascular complications (from 3.0% for IABP to 5.6% for Impella and 15.8% for ECMO) that potentially worsen the patient prognosis with a significant association with in-hospital mortality in a recent comparative

observational study (56.3% with ECMO vs. 33.8% with Impella and 26.2% with IABP) (18). Despite frequent adverse events, the use of aMCS is sometimes mandatory in order to prevent the aggravation of cardiac and multi-organ failure and the death of the patient. The type and timing of device implantation are subject to debate without consensus to date. ECMO is probably the higher circulatory support and the best way to perfuse and oxygenate peripheral organs but several preclinical and clinical studies have shown the association between an increase in LV afterload and an increase in LVEDP and PCWP (19). LV overload seemed to correlate with the intensity of flow and was associated with the worst prognosis including mortality, especially in the case of LV failure (20, 21). In the case of VSD, these effects potentially lead to a worsening of the left-to-right shunt with an increased risk of RV dysfunction and death. Another possibility is to associate an early and systematic left heart decompression with an IABP association, a percutaneous balloon atrioseptostomy or a direct LV-unloading (22, 23). So, a combination of multiple aMCSs could improve peripheral organ perfusion while unloading the LV and RV. The combination of ECMO and Impella (ECMELLA), seems to provide the greatest degree of overall circulatory support while simultaneously unloading the LV (24) and may be a good alternative. But a combination of multiple aMCSs increases associated adverse events as recently demonstrated (24). This should be a case-by-case discussion in the absence of clear recommendations. In all cases, the choice should also depend on the aMCS availability and the multidisciplinary expertise and practice of the center. An important point seems to emerge from the literature, namely the early implantation of aMCS, whatever its type, aimed at preventing multiorgan organ failure and preserving RV and LV functions (11, 25).

Finally, the place of percutaneous closure is still debated, fuelled by contradictory literature. Patient selection and an expert team showed interesting results but, in our study, it was only proposed as a last line of treatment in very severe cases with a 100% in-hospital mortality. The low level of local expertise in this highly technical area may also have contributed to our poor results. Recently a large UK national registry (372 patients with post-MI VSD), showed that percutaneous closure has been increasingly used in clinical practice over recent years accounting for 31.6% of ischaemic VSD patients' management alone and for 7.4% in association with surgical repair. They did not find a difference in long-term mortality between patients managed by surgical or percutaneous closure (61.1% vs. 53.7%, $p = 0.17$), but in-hospital mortality was lower in the surgical group (55.0% vs. 44.2%, $p = 0.048$). Interestingly, the percutaneous approach [aHR 1.44 (1.01–2.05), $p = 0.04$], and the number of vessels with coronary artery disease [aHR 1.22 (1.01–1.47), $p = 0.043$] were two of the three independent factors associated with long-term mortality, suggesting better results for the surgical approach (26). Surgery and percutaneous closure should not be opposed but may be combined since 16.1% of percutaneous patients subsequently had surgery and 7.8% of surgical patients subsequently had percutaneous treatment. This justifies a multidisciplinary approach in expert centers, allowing a patient-centered approach in terms of medical management, type of device, and timing of implantation, but also of VSD closure strategy.

Limits

The retrospective and monocentric design of our study with a collection over 12 years explain most of the limits of our manuscript and preclude the conclusion or generalization of our results. The timing of aMCS implantation and explantation was not reported, preventing any analysis of its effect on outcomes. Moreover, the number of patients supported by aMCSs other than IABP [$n = 15$ with Impella (whatever its type) and/or ECMO] do not allow specific and independent analysis. Finally, no dedicated protocol was available to harmonize VSD patients' management during the study period, explaining different types and timing of aMCS implantation, but also differences in medical management and surgical closure indication. Nevertheless, the persistence of high mortality of the post-ischemic VSD remains a real conclusion. The outstanding questions concern, on the one hand, the medical treatment put in place and the need to optimize and formalize it; and on the other hand, the question of patients who are contraindicated to surgery, which in fact condemns them to almost certain death ("self-fulfilling prophecy"). This reinforces the absolute necessity of implementing standardized multidisciplinary management and decision-making protocols.

Conclusion

A post-ischaemic ventricular septal defect is an uncommon but still severe complication, involving <0.8% of all ACS and associated with an in-hospital mortality of 73% and 1-year mortality of 86%. Surgery remains the only treatment associated with better survival but is not feasible for all patients. Patient selection and the timing of surgery, as well as the type of aMCS in the waiting period or alternative therapies, should be addressed by larger multicentre dedicated studies.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent for

participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

Conceptualization: CD, HT, and FB. Data curation: HT, JP, CD, CB, FL, BM, OL, ME, MG, and CD. Formal analysis: FB, HT, and CD. Methodology and visualization: CD and FB. Project administration: CD and MG. Supervision: CD. Validation: HT, CD, FB, ME, and CD. Writing—original draft: HT and CD. Writing—review and editing: All authors. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.1066308/full#supplementary-material

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Effect of posterior pericardiotomy in cardiac surgery: A systematic review and meta-analysis of randomized controlled trials

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Background: Posterior pericardiotomy (PP) has been shown to reduce the incidence of pericardial effusion and postoperative atrial fibrillation (POAF) after cardiac surgery. However, the procedure and the totality of its effects are poorly known in the cardiac surgery community. We performed a study-level meta-analysis of randomized controlled trials (RCTs) to evaluate the impact of PP in cardiac surgery patients.

Methods: A systematic literature search was conducted on three medical databases (Ovid MEDLINE, Ovid Embase, Cochrane Library) to identify RCTs reporting outcomes of patients that received a PP or no intervention after cardiac surgery. The primary outcome was the incidence of POAF. Key secondary outcomes were operative mortality, incidence of pericardial and pleural effusion, cardiac tamponade, length of stay (LOS), pulmonary complications, amount of chest drainage, need for intra-aortic balloon pump, and re-exploration for bleeding.

Results: Eighteen RCTs totaling 3,531 patients were included. PP was associated with a significantly lower incidence of POAF (odds ratio [OR] 0.45, 95% confidence interval [CI] 0.32–0.64, $P < 0.0001$), early (OR 0.18, 95% CI 0.10–0.34, $P < 0.0001$) and late pericardial effusion (incidence rate ratio 0.13, 95% CI 0.06–0.29, $P < 0.0001$), and cardiac tamponade (risk difference −0.02, 95% CI −0.04 to −0.01, $P = 0.001$). PP was associated with a higher incidence of pleural effusion (OR 1.42, 95% CI 1.06–1.90, $P = 0.02$), but not pulmonary complications (OR 0.82, 95% CI 0.56–1.19; $P = 0.38$). No differences in other outcomes, including operative mortality, were found.

Conclusions: PP is a safe and effective intervention that significantly decreases the incidence of POAF and pericardial effusion following cardiac surgery.

Systematic review registration: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=261485, identifier: CRD42021261485.

KEYWORDS

cardiac surgery, posterior pericardiotomy, postoperative atrial fibrillation, pericardial effusion, meta-analysis

1. Introduction

Despite advances in postsurgical management, postoperative atrial fibrillation (POAF) still represents the most frequent complication following cardiac surgery, resulting in a substantial clinical and economic burden (1–3). An important trigger of POAF, among others, seems to be the accumulation of fluid in the posterior pericardium (4, 5). Since its introduction in 1995, posterior pericardiotomy (PP) has been hypothesized to reduce the incidence of POAF and pericardial effusion by means of an incision in the posterior pericardium, allowing pericardial fluid to drain into the left pleural space (6).

Over the past two decades, multiple randomized controlled trials (RCTs) have tested this intervention, providing data on its high efficacy in reducing POAF (7–24). However, the procedure and the totality of its benefits and safety profile are poorly known in the cardiac surgery community.

We conducted a systematic review and study-level meta-analysis to evaluate the outcomes of patients that received a PP in addition to cardiac surgery compared to patients that received no additional intervention.

2. Methods

This review was registered with the National Institute for Health Research International Registry of Systematic Reviews (PROSPERO; CRD42021261485). The manuscript follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline (25).

2.1. Search strategy

A qualified librarian (MD) performed a systematic literature search to identify potential studies comparing the outcomes of patients that received cardiac surgical procedures and PP to patients that received a cardiac surgical procedure and no PP. Searched were originally run on July 2021 and updated on December 28, 2021 using the following databases (Ovid MEDLINE, Ovid EMBASE, and The Cochrane Library) from inception to present. The search strategy for Ovid MEDLINE is available in Supplementary Table 1.

2.2. Study selection and data extraction

After deduplication, title and abstracts of the remaining articles were screened against predefined inclusion and exclusion criteria by two authors (GS and RP-O) independently. Any discrepancies were adjudicated by the senior author (MG). All relevant English-written RCTs reporting outcomes of adult patients (≥18 years old) undergoing open heart surgery with and without a concomitant PP procedure were considered for inclusion. All the studies that were not RCTs were excluded. The full text of the selected manuscripts was retrieved for a second round of screening. The references were also reviewed for pertinent studies not identified through the initial search. The quality assessment of the included RCTs was performed using The Cochrane Collaboration's Risk of Bias 2 (RoB 2) tool for randomized trials (26).

The PP procedure was defined as any incision in the posterior pericardium allowing drainage of the pericardial cavity into the left pleural space, with or without the insertion of a chest tube in the posterior pericardial space. A detailed description of the steps to perform a PP has been previously published (27).

Two authors (GS and RP-O) separately performed data extraction and the accuracy was verified by the senior investigatto (MG). The following variables were extracted from each RCT: study characteristics (first author, year of publication, publishing journal, country, type of cardiac surgery, and sample size), patient demographics (age, sex, smoking status, hypertension, diabetes, and dyslipidemia), and key outcomes.

2.3. Outcomes

The primary outcome was the incidence of POAF. The secondary outcomes were operative mortality, early and late pericardial effusion, cardiac tamponade, pleural effusion, amount of total chest drainage (mediastinal plus pleural drainage), duration of intensive care unit (ICU) and hospital length of stay (LOS), pulmonary complications, need for intra-aortic balloon pump (IABP), and re-exploration for bleeding. For the secondary outcomes, individual study definitions were used.

2.4. Statistical analysis

The number of events of short-term outcomes was extracted for each group and pooled with an inverse variance method and described as odds ratio (OR) with 95% confidence interval (CI). When both groups reported zero events, risk difference (RD) was used as pooled estimate.

For the only follow-up outcome (late pericardial effusion), we took into account the variability in the lengths of follow-up in each study and therefore incidence rate ratio (IRR) were pooled for this outcome. IRRis the ratio of the number of events and the number of patient-years. Inverse variance method with both fixed- and random-effect models was used to pool this estimate.

The standardized mean difference (SMD) with 95% CI was used to compare chest drainage, as well as ICU and hospital LOS between patients with and without PP.

The I^2 was used to evaluate statistical heterogeneity that is the proportion of the variability in the estimates due to heterogeneity rather than by chance. A value of 25, 50, and 75% identified low, moderate and high heterogeneity, respectively. Egger's test and inspection of funnel plot was used to assess the presence of small-study effect.

A leave-one-out approach was used as sensitivity analysis for the primary outcome: the meta-analytic estimates were recalculated by excluding one study per time. Also, meta-regression was performed by regressing the estimates against the preoperative characteristics (age, female sex, hypertension, dyslipidemia, smoking, and diabetes), and the type of surgery (coronary artery bypass grafting [CABG], aortic valve replacement [AVR], or other valve surgery).

In all analyses, the control group was the reference group. Statistical analyses were performed in R (version 4.2.0; R Project; R Foundation for Statistical Computing, Vienna, Austria) using the packages: meta, dmetar. A P-value < 0.05 was used as threshold for statistical significance.

3. Results

3.1. Study characteristics

Of the 4,017 screened articles, 18 articles published between 1997 and 2021 met our inclusion criteria and were included in the present analysis (7–24). The PRISMA flow diagram outlining the study selection process is provided in Supplementary Figure 1.

Assessment of study quality using the RoB 2 tool showed that all but four (15, 17, 18, 21) RCTs had an unclear risk of bias regarding allocation concealment and blinding of researchers and participants. Details of the quality assessment are provided in Supplementary Table 2.

Ten (55.5%) of the included RCTs were conducted in Turkey, three (16.6%) in Iran, while China, Egypt, England, Thailand, and the United States contributed with one RCT (5.6%) each. Thirteen (72.2%) RCTs included patients undergoing isolated CABG, three (16.7%) enrolled patients undergoing either isolated CABG or CABG with valve surgery, one (5.6%) RCT enrolled patients undergoing valve and/or aortic surgery, and one (5.6%) included CABG, AVR, and aortic surgery patients. Characteristics of the included RCTs are provided in Table 1.

3.2. Patient characteristics

A total of 3,531 patients were pooled in the analysis. The number of patients in the included RCTs ranged from 20 to 458, with a median sample size of 146 (interquartile range: 100–209). Overall, 1,745 (49.4%) patients received a PP and 1,786 (50.6%) underwent cardiac surgery without PP.

Men represented 62.2% of the studied population (62.8 and 61.7% of the PP and control groups, respectively). The mean age range was 40.9 to 67.3 years in the PP group and 43.2 to 68.2 years in the control group. The prevalence of diabetes ranged from 17.3 to 65% in the PP group and from 10 to 56.9% in the control group. The prevalence of dyslipidemia ranged from 36 to 75% in the PP group and from 35.3 to 71.2% in the control group. The prevalence of smoking ranged from 0 to 76.1% in the PP group and from 20 to 74% in the control group. The prevalence of hypertension ranged from 20 to 80% in the PP group and from 36 to 90% in the control group.

3.3. Meta-analysis

Compared to the no intervention group, patients with a PP had a significantly lower risk of POAF (OR 0.45, 95% CI 0.32–0.64, $P < 0.0001$; Figure 1), early pericardial effusion (OR 0.19, 95% CI 0.10–0.34, $P < 0.0001$; Figure 2), late pericardial effusion (IRR 0.14, 95% CI 0.07–0.30, $P < 0.0001$; Figure 3), and cardiac tamponade (RD −0.02, 95% CI −0.04 to −0.01, $P = 0.001$; Supplementary Figure 2). Patients with a PP had a higher risk of pleural effusion (265/1,165, 22.7%) compared to the no intervention group (203/1,173, 17.3%) (OR 1.42, 95% CI 1.06–1.90, $P = 0.02$; Supplementary Figure 3).

The leave-one-out analysis confirmed the solidity of the main analysis (Supplementary Figure 4).

No difference in operative mortality, pulmonary complications (84/1,168 [7.2%] in the PP group vs. 107/1,205 [8.9%] in the control group), need for IABP, re-exploration for bleeding, ICU LOS, hospital LOS, or chest drainage (range/mean volume in PP group: 450–1,421 ml/746 ml; range/mean volume in control group: 266–1,153 ml/696 ml) was found between groups (Supplementary Figures 5–11). A summary of all the outcomes and their reporting in each of the included RCTs are provided in Table 2 and Supplementary Table 3, respectively.

TABLE 1 Summary of the included RCTs.

References	Journal (2020 IF)	Country	Type of procedure	Sample size (men, %)	No of patients per arm	Outcomes and results
Arbatli et al. (7)	*The Journal of Cardiovascular Surgery (1.888)*	Turkey	CABG	113 (89, 79%)	PP: 54 Control: 59	**Main outcomes assessed** POAF, pericardial effusion, pleural effusion **Assessment modalities** Continuous telemetry + EKG, echocardiography, chest X-rays **Main findings** No difference in POAF between PP and control groups ($P = 0.32$). The incidence of POAF was higher in patients with mild to moderate compared to those with no or minimal pericardial effusion ($P = 0.017$). Pericardial effusion was lower in the PP group ($P = 0.02$). No significant difference in pleural effusion between groups.
Asimakopoulos et al. (8)	*The Journal of Thoracic and Cardiovascular Surgery (5.209)*	UK	CABG	100 (NR)	PP: 50 Control: 50	**Main outcomes assessed** POAF **Assessment modalities** Continuous telemetry + EKG **Main findings** No significant difference in the incidence of AF between groups.
Bakhshandeh et al. (9)	*Asian Cardiovascular and Thoracic Annals (0.49)*	Iran	CABG/ Valve surgery	410 (164, 40%)	PP: 205 Control: 205	**Main outcomes assessed** POAF, pericardial effusion **Assessment modalities** Not stated for POAF, echocardiography **Main findings** No significant difference in POAF between groups. At all time points, the majority of patients who underwent PP were free of effusion, but none of those in the control group were free of effusion ($P < 0.05$).
Cakalagaoglu et al. (10)	*The Heart Surgery Forum (0.676)*	Turkey	CABG/ Valve surgery	100 (83, 83%)	PP: 50 Control: 50	**Main outcomes assessed** POAF, pericardial effusion **Assessment modalities** Continuous telemetry + EKG, echocardiography, chest X-ray **Main findings** No significant difference in POAF. Before discharge, the control group had a significantly higher number of patients with moderate, large, and very large pericardial effusions compared with the PP group.
Ekim et al. (11)	*Medical Science Monitor (2.649)*	Turkey	CABG	100 (65, 65%)	PP: 50 Control: 50	**Main outcomes assessed** POAF, pericardial effusion, pleural effusion **Assessment modalities** Continuous telemetry + EKG, echocardiography. Not stated for pleural effusion. **Main findings** Early pericardial effusion was significantly lower in the PP group ($P = 0.0001$). The number of patients who developed POAF was significantly lower in the PP group compared with the control group (10 vs. 30%, $P < 0.01$). No difference in the incidence of pleural effusion was found.

(Continued)

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TABLE 1 (Continued)

References	Journal (2020 IF)	Country	Type of procedure	Sample size (men, %)	No of patients per arm	Outcomes and results
Erdil et al. (12)	*Journal of Cardiac Surgery (1.62)*	Turkey	Valve surgery/ Aortic	100 (39, 39%)	PP: 50 Control: 50	**Main outcomes assessed** Pericardial effusion, pleural effusion **Assessment modalities** Echocardiography. Not stated for pleural effusion. **Main findings** Early pericardial effusion developed in 4/50 (8%) patients of the PP group and in 19/50 (38%) of the control group ($P < 0.001$). No late pericardial effusion in the PP group, 9/50 (18%) in control group ($P < 0.003$). No significant difference in the incidence of pleural effusion between groups.
Farsak et al. (13)	*European Journal of Cardio-Thoracic Surgery (4.191)*	Turkey	CABG	150 (51, 34%)	PP: 75 Control: 75	**Main outcomes assessed** POAF, pericardial effusion, pleural effusion **Assessment modalities** Continuous telemetry + EKG, echocardiography. Not stated for pleural effusion. **Main findings** POAF developed in 7 patients (9.3%) in the PP group and 24 patients (32%) in the control group ($P < 0.001$). Early pericardial effusion developed in 42.6% (32/75) of the control group and in 10.6% (8/75) of the PP group ($P < 0.0001$). No late pericardial effusion developed in the PP group, while 7 (9.3%) developed in the control group ($P < 0.013$). No significant difference in pleural effusion.
Fawzy et al. (14)	*Interactive CardioVascular and Thoracic Surgery (1.905)*	Egypt	CABG	200 (132, 66%)	PP: 100 Control: 100	**Main outcomes assessed** POAF, pericardial effusion **Assessment modalities** Continuous telemetry + ECG, echocardiography. **Main findings** The incidence of POAF was significantly lower in the PP group than in the control group (13 vs. 30%, $P = 0.01$). Postoperative pericardial effusion was significantly lower in the PP group (15 vs. 50 patients, $P = 0.04$).
Gaudino et al. (15)	*Lancet (79.321)*	USA	CABG/ AVR/ Aortic surgery	420 (318, 76%)	PP: 212 Control: 208	**Main outcomes assessed** POAF, pericardial effusion, pleural effusion **Assessment modalities** Continuous telemetry and daily EKG, echocardiography, chest X-rays. CT scan in case of moderate-large pericardial effusion. **Main findings** POAF in PP group 37/212 (18%) compared to 66/208 (32%) in the no intervention group (aOR 0.44, 95% CI: 0.27–0.70; $P < 0.0005$). Pericardial effusion in PP 27/212 (12%) vs. 44/208 (21%) in the control group (RR 0.58, 95% CI: 0.37–0.91). No significant difference regarding pleural effusion.

(Continued)

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TABLE 1 (Continued)

References	Journal (2020 IF)	Country	Type of procedure	Sample size (men, %)	No of patients per arm	Outcomes and results
Haddadzadeh et al. (16)	*Acta Medica Iranica (0.26)*	Iran	OPCABG	207 (142, 69%)	PP: 105 Control: 102	**Main outcomes assessed** POAF, pericardial effusion **Assessment modalities** Continuous telemetry + EKG, echocardiography **Main findings** No significant difference between the two groups regarding POAF or pericardial effusion.
Kaya et al. (17)	*Kardiochirurgia i Torakochirurgia Polska (0.23)*	Turkey	CABG	96 (77, 80%)	PP: 30 Control: 66	**Main outcomes assessed** POAF, pericardial effusion **Assessment modalities** Continuous telemetry + EKG, echocardiography **Main findings** No significant differences were found between the groups regarding POAF ($P = 0.392$). The incidence of moderate to severe pericardial effusion in PP group was significantly lower than in the other groups on the 30th post-operative day ($P = 0.028$).
Kaya et al. (18)	*Interactive CardioVascular and Thoracic Surgery (1.905)*	Turkey	CABG	142 (118, 83%)	PP: 70 Control: 72	**Main outcomes assessed** POAF, pericardial effusion, pleural effusion **Assessment modalities** Portable EKG telemetry, echocardiography. Not stated for pleural effusion **Main findings** POAF occurred in 27.78% of the cases in the open group and 8.57% of the patients in the closure group ($P = 0.003$). Difference in pericardial effusion favored the closure group ($P = 0.039$). No significant difference in pleural effusion between groups.
Kaya et al. (19)	*Thoracic and Cardiovascular Surgeon (1.827)*	Turkey	CABG	210 (164, 78%)	PP: 103 Control: 107	**Main outcomes assessed** POAF, pericardial effusion, pleural effusion **Assessment modalities** Portable EKG telemetry, echocardiography. Not stated for pleural effusion **Main findings** Statistically significant results were obtained in the amount of PE ($P = 0.034$ on POD 2; $P = 0.019$ on POD 5) and POAF ($P = 0.019$) in favor of the study group. No significant difference regarding pleural effusion.
Kaygin et al. (20)	*The Tohoku Journal of Experimental Medicine (1.848)*	Turkey	CABG	415 (212, 51%)	PP: 213 Control: 212	**Main outcomes assessed** POAF, pericardial effusion, pleural effusion **Assessment modalities** Not stated for POAF and pleural effusion. Echocardiography. **Main findings** POAF ($P < 0.0001$), early ($P < 0.001$) and late pericardial effusion ($P < 0.0001$) occurred more frequently in the control group compared with the PP group. PP was associated with an increase in pleural effusion requiring intervention ($P = 0.002$).

(Continued)

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TABLE 1 (Continued)

References	Journal (2020 IF)	Country	Type of procedure	Sample size (men, %)	No of patients per arm	Outcomes and results
Kongmalai et al. (21)	*Journal of the Medical Association of Thailand (0.09)*	Thailand	CABG	20 (10, 50%)	PP: 10 Control: 10	**Main outcomes assessed** POAF, pericardial effusion, pleural effusion **Assessment modalities** Continuous telemetry + EKG, echocardiography, chest X-rays. **Main findings** No significant differences in POAF ($P = 1$) and early pericardial effusion ($P = 1$). The incidence of pleural effusion was higher in the PP group ($P = 0.028$).
Kuralay et al. (22)	*The Journal of Thoracic and Cardiovascular Surgery (5.209)*	Turkey	CABG	200 (150, 75%)	PP: 100 Control: 100	**Main outcomes assessed** POAF, pericardial effusion, pleural effusion **Assessment modalities** Continuous telemetry + EKG, echocardiography, Not stated for pleural effusion. **Main findings** POAF developed in 6 patients (6%) in PP group and in 34 patients (34%) in the control group ($P = 0.0000007$). The incidence of early and late pericardial effusion was significantly more frequent in the control group ($P < 0.001$ for both). No statistically significant difference was found regarding pleural effusion.
Sadeghpour et al. (23)	*Multidisciplinary Cardiovascular Annals (NA)*	Iran	CABG	80 (63, 79%)	PP: 40 Control: 40	**Main outcomes assessed** Pericardial effusion **Assessment modalities** Echocardiography **Main findings** Early pericardial effusion was more frequent in the control group (45 vs. 15%; $P = 0.01$). Late pericardial effusion was also more frequent in the control group (57 vs. 15%; $P = 0.01$).
Zhao et al. (24)	*Journal of International Medical Research (1.671)*	China	CABG/ Valve surgery	458 (263, 57%)	PP: 228 Control: 230	**Main outcomes assessed** POAF, pericardial effusion, pleural effusion **Assessment modalities** Not stated for POAF. Echocardiography **Main findings** The incidence of POAF in the PP group was significantly lower compared with the control group ($P = 0.044$). The incidence of small ($P = 0.004$) and moderate-to-large ($P = 0.02$) pericardial effusion in the PP group was significantly lower than in the control group. The incidence of moderate-to-large pleural effusion in the PP group was significantly higher than in the control group ($P = 0.015$).

aOR, adjusted odds ratio; AVR, aortic valve replacement; CABG, coronary artery bypass grafting; CT, computerized tomography; EKG, electrocardiography; IF, impact factor; NA, not available; NR, not reported; OPCABG, off-pump coronary artery bypass grafting; PO, postoperative day; POAF, postoperative atrial fibrillation; PP, posterior pericardiotomy; RCT, randomized controlled trial; SD, standard deviation.

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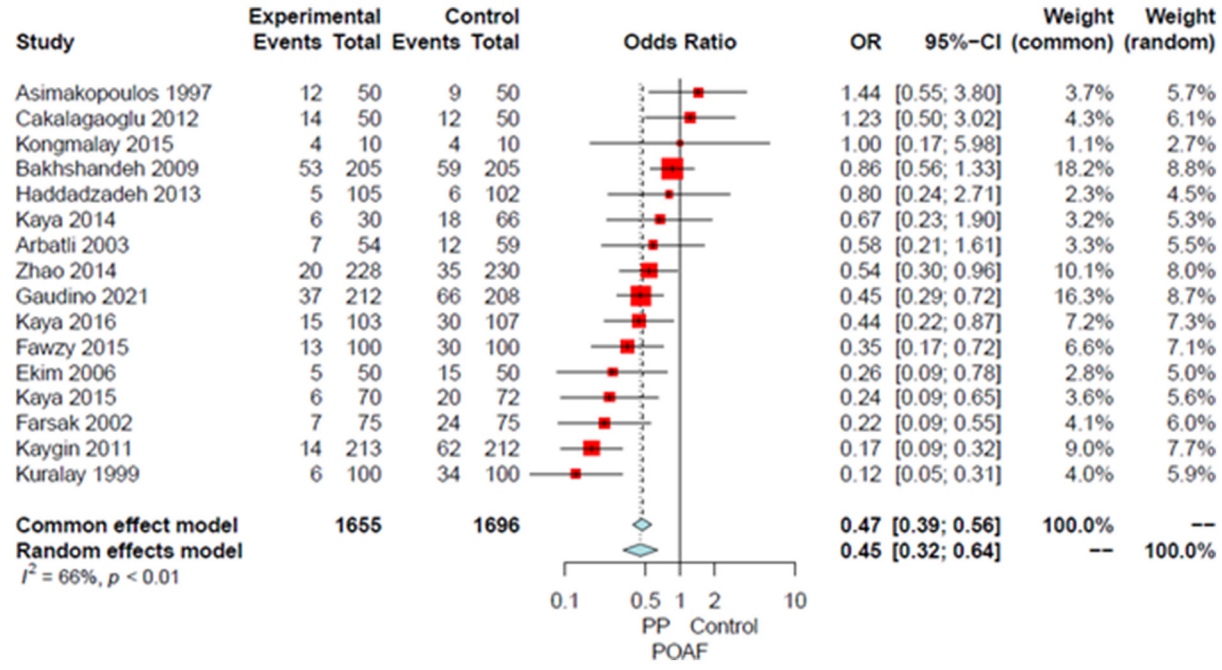

FIGURE 1
Forest plot for postoperative atrial fibrillation. CI, confidence interval; OR, odds ratio; POAF, postoperative atrial fibrillation; PP, posterior pericardiotomy.

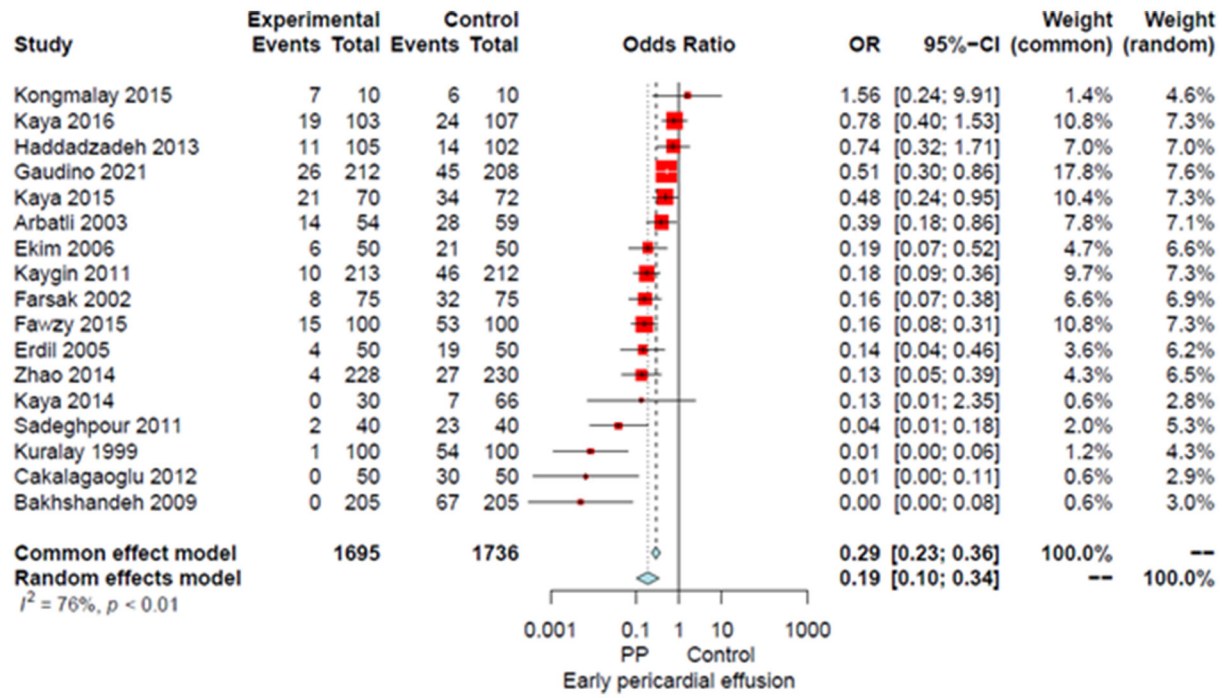

FIGURE 2
Forest plot for early pericardial effusion. CI, confidence interval; OR, odds ratio; PP, posterior pericardiotomy.

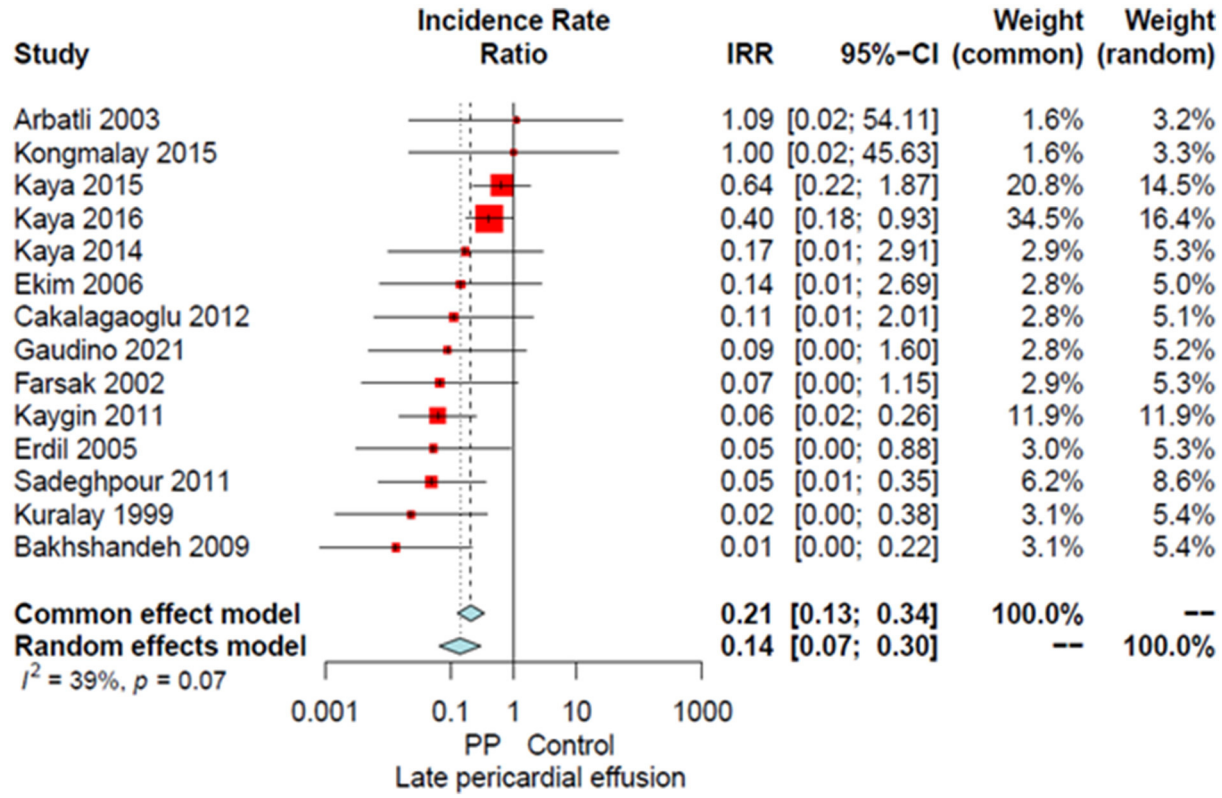

FIGURE 3
Forest plot for late pericardial effusion. CI, confidence interval; IRR, incidence rate ratio; PP, posterior pericardiotomy.

TABLE 2 Summary of the primary and key secondary outcomes.

Outcome	No. of studies	Events	Patients	Effect estimate (95% CI), *P*-value	Heterogeneity (I^2, *P*-value)
POAF	16	660	3,351	OR = 0.45 (0.32–0.64), $P < 0.0001$	65.8%, $P < 0.001$
Operative mortality	11	33	2,123	RD = −0.002 (−0.01 to 0.01), $P = 0.66$	0.0%, $P = 0.99$
Early pericardial effusion	17	678	3,431	OR = 0.19 (0.10–0.34), $P < 0.0001$	76.3%, $P < 0.001$
Late pericardial effusion	14	-	2,566	IRR = 0.14 (0.07–0.30), $P < 0.0001$	38.5%, $P = 0.07$
Chest drainage	14	-	2,019	SMD = 0.10 (−0.13 to 0.34), $P = 0.4$	86.3%, $P < 0.001$
Cardiac tamponade	15	62	3,144	RD = −0.02 (−0.04 to −0.01), $P = 0.001$	55.5%, $P = 0.01$
Pleural effusion	11	468	2,338	OR = 1.42 (1.06–1.90), $P = 0.02$	38.4%, $P = 0.09$
Hospital LOS*	10	-	1,641	SMD = −0.11 (−0.29 to 0.06), $P = 0.21$	60.7%, $P = 0.01$
ICU LOS*	6	-	1,243	SMD = 0.06 (−0.15 to 0.27), $P = 0.57$	62.9%, $P = 0.02$
Pulmonary complications	12	191	2,373	OR = 0.82 (0.56–1.19), $P = 0.30$	7.1%, $P = 0.38$
Need for IABP	9	105	2,096	RD = 0.003 (−0.01 to 0.02), $P = 0.62$	0.0%, $P = 0.97$
Re-exploration for bleeding	14	100	2,944	OR = 0.78 (0.52 to 1.19), $P = 0.25$	0.0%, $P = 0.93$

*Measured in days. CI, Confidence interval; IABP, intra-aortic balloon pump; ICU, intensive care unit; IRR, incidence rate ratio; LOS, length of stay; OR, odds ratio; POAF, postoperative atrial fibrillation; RD, risk difference; SMD, standardized mean difference.

TABLE 3 Results of meta-regression for the primary outcome.

Variables	Beta ± SE, *P*-value
Age	0.0675 ± 0.0486, $P = 0.17$
Female sex	−0.0039 ± 0.0116, $P = 0.74$
Diabetes	−0.0105 ± 0.0120, $P = 0.39$
Dyslipidemia	0.0146 ± 0.0474, $P = 0.76$
Smoking	−0.0178 ± 0.0157, $P = 0.26$
Hypertension	0.0141 ± 0.0133, $P = 0.29$
CABG	−0.0099 ± 0.0102, $P = 0.33$
Valve surgery	0.0125 ± 0.0084, $P = 0.14$
Aortic valve replacement	0.0001 ± 0.0153, $P = 0.99$

CABG, coronary artery bypass grafting; SE, standard error.

No evidence of publication bias was observed based on the Egger's intercept test ($P = 0.75$) (Supplementary Figure 12).

3.4. Meta-regression

Meta-regression failed to identify any significant association between the tested variables and the OR for the POAF (Table 3).

4. Discussion

This meta-analysis of 18 studies found that patients with PP had a significantly lower incidence of POAF, early and late pericardial effusion, and cardiac tamponade; there was a significantly higher incidence of pleural effusion, but not an increased risk of pulmonary complications. No other differences in outcomes were found.

POAF is the most frequent complication following cardiac surgery, occurring in approximately one third of the patients (1, 28). POAF has been associated with extended postoperative LOS and increased hospital costs (28), as well as with major adverse postoperative outcomes including renal and heart failure, stroke, and mortality (4, 28, 29). Despite many attempts with medical therapy to prevent POAF, its incidence remains high (30). PP provides a safe and virtually zero-cost surgical alternative for the prevention of POAF. Notably, there has been only one report of complications related to PP (graft herniation) (31), and no there are no reports on damage to the phrenic nerve or the esophagus during PP. None of the studies included in this meta-analysis reported phrenic nerve or esophageal injuries.

Since the procedure was first described by Mulay et al. (6), several RCTs have tried to shed light on the relationship between PP and POAF (7–11, 13–22, 24, 32). However, most of these studies were limited in methodological quality and inadequately powered to yield statistically significant results. This prompted our group to perform the first high-quality, adequately powered RCT on the effect of posterior pericardiotomy on POAF, the Posterior Left Pericardiotomy for the prevention of AtriaL Fibrillation after Cardiac Surgery (PALACS) trial (15), which included 420 cardiac surgery patients undergoing CABG, AVR, and/or aortic surgery, notably excluding mitral and tricuspid surgeries.

In the PALACS trial, we found a significantly lower incidence of POAF among patients randomized to PP (17 vs. 32%, $P = 0.0007$), and a lower incidence of postoperative pericardial effusion in the PP group (12 vs. 21%, relative risk 0.58, 95% CI 0.37–0.91), but no difference in the incidence of cardiac tamponade or pleural effusion was found. In this meta-analysis, both outcomes reached statistical significance, with the incidence of cardiac tamponade being lower in the PP group and the incidence of pleural effusion being higher in PP patients. An important finding of the present analysis is that despite the higher incidence of pleural effusion, patients with PP did not have an increased risk of pulmonary complications.

This study has the following limitations. Although our systematic review identified the best available evidence evaluating the impact of PP on postoperative outcomes, the present study cannot control for individual biases of the included studies. Additionally, there was variability in POAF detection methods, perioperative management, PP technique, and in the definition and reporting of outcomes of interest. More importantly, clinical outcomes of relevance to POAF like stroke and transient ischemic attack (TIA) were not reported in most studies (88.9%) and could not be pooled for analysis.

To conclude, our meta-analysis of 18 studies found that PP is associated with a lower incidence of POAF, pericardial effusion, and cardiac tamponade, but increased incidence of pleural effusion.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding authors.

Author contributions

GS, MG, and TS : concept and design. GS and MD: systematic search. GS and RP-O: drafting the article. MR, AD, and MG: statistics. GS, RP-O, BB, MY, and DS: data collection. All authors analyzed the data interpretation, critical revision of the article, and approval of the article.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.1090102/full#supplementary-material

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Trend and early outcomes in isolated surgical aortic valve replacement in the United Kingdom

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Objective: Surgical aortic valve replacement (SAVR) is traditionally the gold-standard treatment in patients with aortic valve disease. The advancement of transcatheter aortic valve replacement (TAVR) provides an alternative treatment to patients with high surgical risks and those who had previous cardiac surgery. We aim to evaluate the trend, early clinical outcomes, and the choice of prosthesis use in isolated SAVR in the United Kingdom.

Methods: All patients (*n* = 79,173) who underwent elective or urgent isolated surgical aortic valve replacement (SAVR) from 1996 to 2018 were extracted from the National Adult Cardiac Surgery Audit database. Patients who underwent additional procedures and emergency or salvage SAVR were excluded from the study. Trend and clinical outcomes were investigated in the whole cohort. Patients who had previous cardiac surgery, high-risk groups (EuroSCORE II >4%), and predicted/observed mortality were evaluated. Furthermore, the use of biological prostheses in five different age groups, that are <50, 50–59, 60–69, 70–79, and >80, was investigated. Clinical outcomes between the use of mechanical and biological aortic valve prostheses in patients <65 years old were analyzed.

Results: The number of isolated SAVR increased across the study period with an average of 4,661 cases performed annually after 2010. The in-hospital/30-day mortality rate decreased from 5.28% (1996) to 1.06% (2018), despite an increasing trend in EuroSCORE II. The number of isolated SAVR performed in octogenarians increased from 596 to 2007 (the first year when TAVR was introduced in the UK) to 872 in 2015 and then progressively decreased to 681 in 2018. Biological prosthesis usage increased across all age groups, particularly in the 60–69 group, from 24.59% (1996) to 81.87% (2018). There were no differences in short-term outcomes in patients <65 years old who received biological or mechanical prostheses.

Conclusion: Surgical aortic valve replacement remains an effective treatment for patients with isolated aortic valve disease with a low in-hospital/30-day mortality rate. The number of patients with high-risk and octogenarians who

underwent isolated SAVR and those requiring redo surgery has reduced since 2016, likely due to the advancement in TAVR. The use of biological aortic prostheses has increased significantly in recent years in all age groups.

KEYWORDS

aortic valve, trend, surgical aortic replacement, transcatheter and surgical aortic valve replacement, United Kingdom

Introduction

Surgical aortic valve replacement (SAVR) has been the treatment for patients with aortic valve disease since it was first performed in 1960 (1, 2), with biological and mechanical prostheses most commonly used to replace the native diseased valve. The long-term outcome and freedom from structural valve degeneration for SAVR remain excellent (3, 4). However, the choice of the ideal valve in relation to the specific age group remains controversial.

The recent advancement of transcatheter aortic valve replacement (TAVR) provides an alternative treatment. The PARTNER 1, 2, and 3 trials have shown the benefits of TAVR in all patients with aortic stenosis, regardless of surgical risk (5–7). TAVR also provides an alternative to patients with the previous SAVR/TAVR with an option of valve-in-valve transcatheter aortic valve replacement (ViV TAVR). This has been suggested to result in a reduction in mechanical valve use worldwide (8, 9).

We aim to evaluate the trend and clinical outcomes in isolated SAVR in the United Kingdom and also focus on the volume of SAVR in the high-risk cohort, redo surgery, and the choice of prosthesis use. Finally, early clinical outcomes in patients who received mechanical or biological prostheses under the age of 65 were compared.

Materials and methods

All patients undergoing elective or urgent isolated SAVR in the United Kingdom from 1996 to 2018 were extracted from the National Adult Cardiac Surgery Audit (NACSA) database. The NACSA database prospectively collects data on all major heart operations conducted on National Health Service patients in the United Kingdom since April 1996. The definitions of database variables were used, and a description of the database was previously described (10).

Patients were divided into five different age groups: less than 50 years old, 50–59 years old, 60–69 years old, 70–79 years old, and above 80 years old. The surgical volume and choice of aortic valve prostheses (biological vs. mechanical) across the five age groups were investigated. The choice of aortic valve prostheses used in patients with chronic kidney disease undergoing dialysis was also evaluated (As defined in one of the three categories—1. dialysis for acute renal failure: onset within 6 weeks of cardiac surgery, 2. dialysis for chronic renal failure: onset more than 6 weeks prior to cardiac surgery, and 3. no dialysis but pre-operative acute renal failure (anuria or oliguria <10 ml/h). The trend in patients who underwent previous cardiac surgery and the volume of SAVR performed in patients with low- (<2%), intermediate- (2–4%), and high-risk (>4%) as defined by the EuroSCORE II was also evaluated (11). The observed mortality was defined as 30-day or in-hospital mortality after the index operation. The expected mortality was calculated using the EuroSCORE II. Moreover, the early clinical outcomes in patients who received mechanical or biological prostheses under the age of 65 were compared using propensity score matching. Sixty-five was selected as a cutoff based on the 2020 ACC/AHA Guideline for the Management of Patients with Valvular Heart Disease (12).

Patients who underwent additional procedures, major aortic surgery, emergency, or salvage SAVR were excluded from the study. Missing data in the choice of prostheses were also excluded in this study (n = 3,309, 4.18%).

Ethics statement

The study is part of a research project approved by the Health Research Authority (HRA) and Health and Care Research Wales (HCRW). As the study included retrospective interrogation of the NACSA database, the need for individual patient consent was waived off (HCRW) (IRAS ID: 278171) in accordance with the research guidance. The study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments. The General Data Protection Regulations were strictly followed for the use of all data.

Statistical analysis

Continuous variables are reported as mean and standard deviation (SD). Categorical variables are reported as frequencies

Abbreviations: NACSA, National Adult Cardiac Surgery Audit; PSM, propensity score matching; SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement; ViV TAVR, valve-in-valve transcatheter aortic valve replacement.

and percentages. Pearson's chi-squared test, Wilcoxon rank-sum test, and one-way/multi-factor analysis of variance were used to compare two categorical variables, for comparison between two means of continuous, independent samples, and to compare between three continuous variables, respectively.

Propensity score matching (PSM) was performed to create a quasi-experimental design by balancing measured confounding factors between the two groups. A 1:1 nearest neighbor matching without replacement with a caliper width of 0.2 standard deviations of the logit of the propensity scores was performed using the pre-operative characteristics listed in **Table 3**. Missing continuous variables data (left ventricular ejection fraction and body mass index) were imputed with the median value in the data after the application the of exclusion criteria listed above. After matching, all standardized mean differences for the covariates were checked. The adequate balance was set to be below 0.1.

The effectiveness of the PSM was visualized with a Love plot to report the covariate balance with all variables before and after the matching. This is shown in the **Supplementary Figure 1**. Binary logistic regression was performed using the baseline patient demographics and comorbidities to predict factors associated with the use of biological aortic valve prostheses. The results are demonstrated as odds ratio (OR) and 95% confidence interval (95% CI). A *P*-value of < 0.05 is deemed statistically significant.

R (Version 4.1.1) and R Studio (Version 1.4.1103, RStudio, PBC) were used to perform the statistical analysis. The following packages were used: tidyverse, MatchIt, sjPlot, and ggplot2. Graphs and tables were created using R Studio (Version 1.4.1103, RStudio, PBC) and Microsoft Office 365 (Version 16.0.14026, 64 bits).

Results

A total of 79,173 patients underwent isolated SAVR in the study period. The mean age was 67.99 (SD 12.48) years old, and 32,799 (41%) were female. The mean BMI was 28.35 (SD 5.64), and LVEF was 53.60 (SD 10.89). About 81% (n = 64,457) were performed in an elective setting. The median post-operative length of stay was 6 days (IQR 5–7 days). The most common surgical incision was median sternotomy (88.7%), followed by partial/hemisternotomy (9.05%). In patients who underwent minimally access SAVR, 4.9% required conversion to median sternotomy.

Etiology

The most common etiology was aortic stenosis (66.8%) followed by mixed aortic stenosis and regurgitation (18.3%) and aortic regurgitation (14.9%). The native valve pathology was most likely due to degeneration (76.1%) followed by congenital (9.4%). Infective endocarditis and rheumatic heart disease accounted for 3.6 and 2.3% of total cases, respectively.

Predicted/observed mortality

The number of isolated SAVR increased across the study period with an average of 4,661 cases performed annually after 2010 (**Figure 1**). The in-hospital/30-day mortality rate decreased from 3.28% (2000) to 1.06% (2018), despite an increasing trend in EuroSCORE II. The observed/expected mortality has significantly reduced over the study period and was below 1.0 since 2011. The trend of observed and expected mortality rates is shown in **Figure 2**.

Isolated SAVR in octogenarians, intermediate- and high-risk groups, and patients who underwent previous cardiac surgery

The number of isolated SAVR in octogenarians increased from 596 to 2007 (the first year when TAVR was introduced in the UK) to 872 in 2015. Since then, the number of isolated SAVR has reduced to 823, 752, and 681 in 2016, 2017, and 2018, respectively.

There was an increasing trend of patients with intermediate-risk who underwent isolated SAVR, particularly after 2010 (>20% of all isolated SAVR). In patients with high-risk, a downward trend was observed since 2016. Redo-isolated SAVR peaked in 2007 (14.26% of all isolated SAVR performed) and gradually declined to 8.27% in 2018 (**Figure 3**).

Choice of aortic valve prostheses

Biological aortic prosthesis use increased across all age groups from 1996 to 2018. Nearly, all patients above 70 s

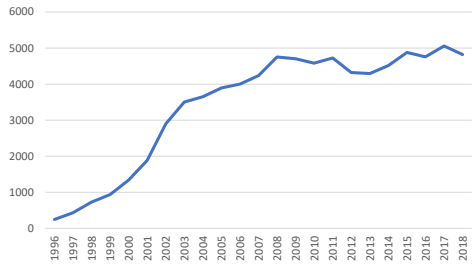

FIGURE 1
Number of isolated surgical aortic valve replacement performed in the United Kingdom from 1996 to 2018 recorded in the national database.

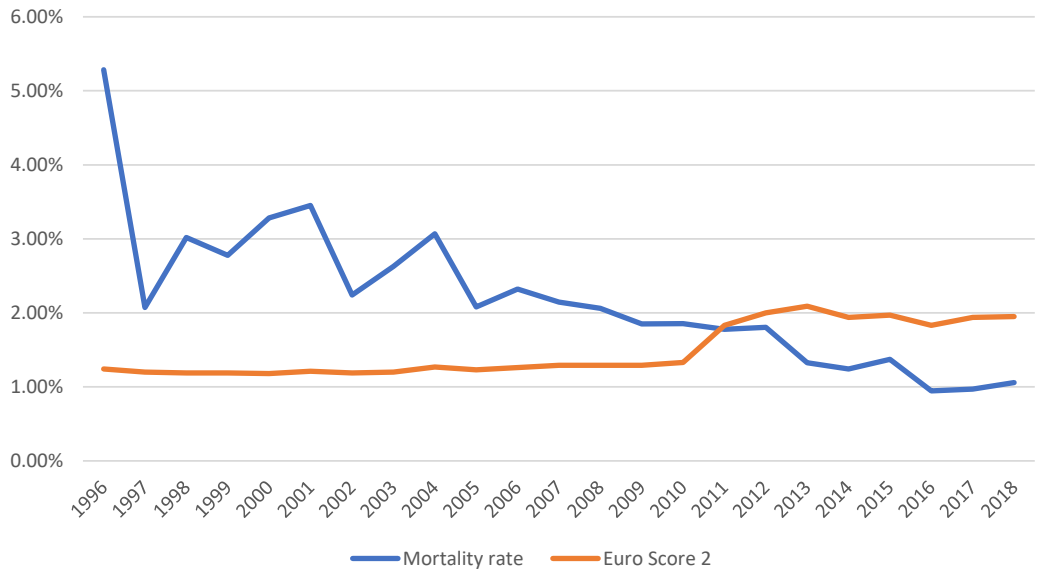

FIGURE 2
Trend of observed and expected mortality rates in patients who underwent isolated surgical aortic valve replacement in the United Kingdom from 1996 to 2018.

received a biological prosthesis since 2010 (98.09 and 99.52% in the 70–79 and >80 groups, respectively in 2018). The increase in the adoption of biological prostheses was most apparent in the 60–69 groups, from 24.59% to 1996 to 81.87% in 2018. There was also increased use of bioprostheses in patients below the age of 50 (28% in 2018) (**Figure 4**).

Choice of aortic valve prostheses in patients with chronic kidney disease requiring dialysis

Eighty-two patients had acute renal failure requiring dialysis within 6 weeks before SAVR; of these, 74.39% (n = 61) received a mechanical prosthesis. In patients with chronic renal failure requiring long-term dialysis, 60.2% (n = 150) received a mechanical prosthesis. One hundred and four patients (85.95%) with acute renal failure who did not undergo dialysis prior to surgery received a mechanical prosthesis.

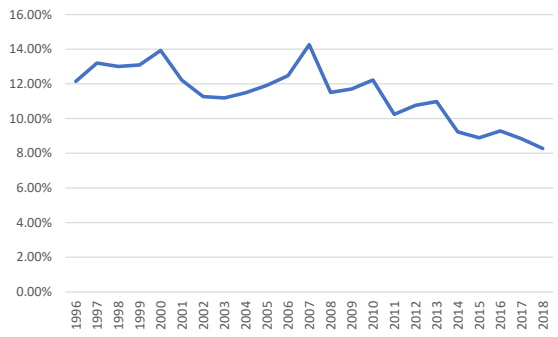

FIGURE 3
Proportion of isolated surgical aortic valve replacement patients who underwent previous cardiac surgery from 1996 to 2018.

Factors predicting the use of biological aortic valve prostheses

Pre-operative characteristics including age, EuroSCORE II, and patients with pre-operative neurological dysfunction were more likely to receive a biological aortic valve prosthesis. On the other hand, female sex, patients with pre-operative atrial fibrillation and peripheral vascular disease were more likely to receive a mechanical prosthesis (**Table 1**).

Early clinical outcomes between biological and mechanical prosthesis in patients <65 years old

After propensity score matching, there were no differences between patients <65 years old who received either biological or mechanical aortic valve prostheses in mortality, return to the theater (including for bleeding and tamponade), post-operative neurological events, dialysis, and deep sternal wound infection. The aortic cross-clamp time and cardiopulmonary bypass time were lower in patients who received mechanical

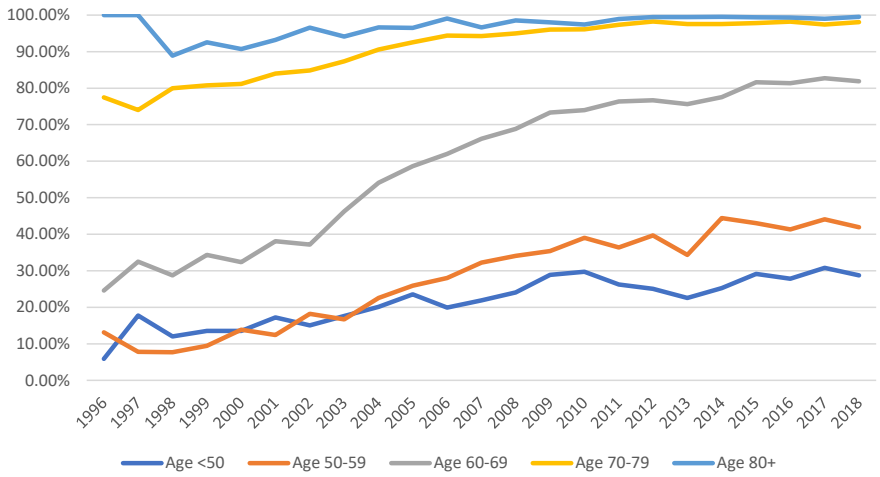

FIGURE 4
Trend of the proportion of bioprostheses used (against mechanical prostheses) across all five age groups from 1996 to 2018 (dark blue: <50, orange: 50–59, gray: 60–69, yellow: 70–79, and pale blue: >80).

aortic valves (Table 2). The pre-operative characteristics are shown in Table 3.

Discussion

Our study demonstrated that SAVR remains an effective treatment with low mortality for patients with isolated aortic valve disease. The number of patients with high-risk, octogenarians undergoing isolated SAVR, and those requiring redo surgery has reduced in recent years, likely due to the advancement in TAVR. The use of biological aortic prostheses has increased significantly in recent years in all age groups.

Despite the increment in EuroSCORE II, the overall mortality rate has continued a downward trend to 1.06% in 2018. The observed mortality rate has outperformed the predicted mortality rate by nearly 50% in 2016–2018. The mortality rate in the United Kingdom has further reduced since the last report (13) and other reports in the literature (9, 14).

The increased use of bioprostheses we observed reflects a similar trend in the literature. Jiménez-García et al. (9) reported a five-fold use of bioprostheses from 2001 to 2015 using the Spanish National Hospital Discharge Database, although the age groups were not specified. Alkhouli et al. (8) reported

TABLE 1 Factors predicting the use of biological (age, LVEF, current smoker, EuroSCORE II, and neurological dysfunction) or mechanical (female sex, urgent operation, peripheral vascular disease, and pre-operative atrial fibrillation) prostheses (CI, confidence interval, BMI, body mass index, LVEF, left ventricular ejection fraction, PVD, peripheral vascular disease, AF, atrial fibrillation).

Pre-operative characteristics	Odd ratios (95% CI)	*P*
Age (year)	1.14 (1.14–1.14)	<0.001
Female sex	0.96 (0.91–1.00)	0.043
BMI	1.00 (0.99–1.00)	0.137
LVEF	1.02 (1.02–1.02)	<0.001
Urgent operation	0.83 (0.78–0.88)	<0.001
Smoking (Current)	1.18 (1.09–1.27)	<0.001
Pulmonary disease	0.94 (0.89–1.00)	0.061
PVD	0.72 (0.65–0.79)	<0.001
Pre-operative AF	0.56 (0.53–0.60)	<0.001
Euro Score II	1.51 (1.46–1.57)	<0.001
Neurological dysfunction	1.57 (1.35–1.82)	<0.001

TABLE 2 Intra- and post-operative outcomes of patients <65 years old receiving biological or mechanical prostheses.

Characteristics	Biological (*n* = 9,246)	Mechanical (*n* = 9,246)	*p*-value
CPB (Minute)	99.17 (45.76)	95.71 (44.04)	<0.001
XClamp (Minute)	74.16 (32.10)	72.11 (29.84)	<0.001
Mortality	81 (0.9%)	86 (0.9%)	0.73
Return to theater	422 (5.2%)	428 (5.1%)	0.93
Postop stroke			0.92
TIA	34 (0.4%)	33 (0.4%)	
CVA	38 (0.5%)	42 (0.5%)	
Postop dialysis	107 (1.3%)	119 (1.4%)	0.62
Postop DSWI	12 (0.5%)	15 (0.5%)	0.85

Data are expressed as mean ± SD. N/A, not applicable, OR, odds ratio, CI, confidence interval, XClamp, cross-clamp, CPB, cardiopulmonary bypass, DSWI, deep sternal wound infection, TIA, transient ischemic attack, CVA, cerebral vascular accident, Postop, post-operative.

TABLE 3 Pre-operative characteristics of the biological and mechanical prostheses in patients <65 years old before and after propensity score matching.

Pre-operative characteristics	Pre PSM			Post PSM			
	Biological (*n* = 15,989)	Mechanical (*n* = 9,927)	*P*-value	Biological (*n* = 9,246)	Mechanical (*n* = 9,246)	SMD	*p*-value
Age (Year)	52.53 (9.69)	56.94 (9.01)	<0.001	56.07 (8.54)	56.56 (9.15)	−0.0546	<0.001
Gender (Male)	11,417 (71%)	6,774 (68%)	<0.001	2,890 (31%)	2,875 (31%)	0.0035	0.81
BMI	28.70 (5.85)	28.79 (5.19)	0.14	28.63 (5.64)	28.85 (5.93)	0.0368	0.027
CCS grade			<0.001				0.41
0	9,667 (60%)	6,143 (62%)		5,788 (63%)	5,662 (61%)	0.0281	
1	24, 18 (15%)	1,334 (13%)		1,218 (13%)	1,280 (14%)	−0.0197	
2	2,662 (17%)	1,750 (18%)		1,583 (17%)	1,635 (18%)	−0.0148	
3	967 (6.0%)	563 (5.7%)		527 (5.7%)	541 (5.9%)	−0.0065	
4	275 (1.7%)	137 (1.4%)		130 (1.4%)	128 (1.4%)	0.0019	
NYHA status			<0.001				0.59
1	3,604 (23%)	1,805 (18%)		1,790 (19%)	1,743 (19%)	0.0132	
2	6,638 (42%)	4,325 (44%)		4,049 (44%)	4,011 (43%)	0.0083	
3	4,840 (30%)	3,205 (32%)		2,899 (31%)	2,965 (32%)	−0.0153	
4	907 (5.7%)	592 (6.0%)		508 (5.5%)	527 (5.7%)	−0.0087	
Preop AF	850 (5.3%)	404 (4.1%)	<0.001	341 (3.7%)	388 (4.2%)	−0.0257	0.076
Previous MI			0.36				0.95
No	15,384 (96%)	9,516 (96%)		8,881 (96%)	8,884 (96%)	−0.0016	
1	555 (3.5%)	377 (3.8%)		336 (3.6%)	331 (3.6%)	0.0028	
2 Or more	50 (0.3%)	34 (0.3%)		29 (0.3%)	31 (0.3%)	−0.0037	
Previous PCI			<0.001				0.86
No	15,728 (98%)	9,651 (97%)		9,022 (98%)	9,036 (98%)	−0.0092	
24 h before op	18 (0.1%)	13 (0.1%)		10 (0.1%)	11 (0.1%)	−0.0030	
same admission	9 (<0.1%)	420 (0.8%)		6 (<0.1%)	7 (<0.1%)	−0.0033	
Previous admission	234 (1.5%)	252 (2.5%)		208 (2.2%)	192 (2.1%)	0.0010	
LVEF	53.38 (6.09)	53.49 (713)	<0.001	53.52 (6.21)	53.53 (6.92)	0.0021	<0.001
Diabetes			<0.001				0.79
No	14,547 (91%)	8,682 (87%)		8,167 (88%)	8,163 (88%)	0.0013	
Diet control	265 (1.7%)	219 (2.2%)		186 (2.0%)	199 (2.2%)	−0.0096	
Drug control	823 (5.1%)	722 (7.3%)		634 (6.9%)	613 (6.6%)	0.0087	
Insulin	354 (2.2%)	304 (3.1%)		259 (2.8%)	271 (2.9%)	−0.0075	
Smoking			0.004				0.65
Non-smoker	7,605 (48%)	4,516 (45%)		4,279 (46%)	4,221 (46%)	0.0126	
Ex-smoker	6,709 (38%)	3,956 (40%)		3,651 (39%)	3,709 (40%)	−0.0128	
Current smoker	2,305 (14%)	1,455 (15%)		1,316 (14%)	1,316 (14%)	0.00	
Pulmonary disease	1,704 (11%)	1,250 (13%)	<0.001	1,141 (12%)	1,111 (12%)	0.0098	
NeuroDys	271 (1.7%)	340 (3.4%)	<0.001	231 (2.5%)	225 (2.4%)	0.0036	0.78
PVD	677 (4.2%)	453 (4.6%)	0.21	400 (4.3%)	411 (4.4%)	−0.0057	0.69
Creatinine > 200	282 (1.8%)	200 (2.0%)	0.15	156 (1.7%)	172 (1.9%)	−0.0123	0.37
Euro Score II	1.00 (1.00)	1.18 (1.48)	<0.001	1.06 (1.21)	1.09 (1.11)	−0.0194	<0.001

AF, atrial fibrillation, CCS, canadian cardiovascular society, PCI, percutaneous coronary intervention, BMI, body mass index, NYHA, New York Heart Association, LMS, left main stem disease, MI, myocardial infraction, LVEF, left ventricular ejection fraction, NeuroDys, neurological dysfunction, ES2, EuroSCORE II, PSM, propensity score matching, SMD, standardized mean difference, PVD, peripheral vascular disease.

the age group-specific use of bio/mechanical prostheses in the United States using the Nationwide Inpatient Sample. They observed a significant reduction in the use of mechanical prostheses among patients aged 50–70 years between 2008 and 2017. This is similar to our finding in which more than 80% of patients aged 60–69 received a biological aortic valve. However, the use of mechanical valves remains higher in the 50–59 age group in the United Kingdom (58% in 2018) compared with 37 and 22% among the 56–60 and 50–55 age groups in the United States (8).

The durability of bioprostheses remains an important topic when used in young patients. The freedom from structural valve deterioration has been reported at 81.7% at 15 years and 52% at 20 years post-SAVR (15); hence, the need to repeat interventions should be taken into consideration. The advancement of TAVR, valve-in-valve transcatheter aortic valve replacement (ViV TAVR), has become an alternative treatment in patients with the previous SAVR. In addition to avoidance of anticoagulation, these may be the explanation for the observed reduction in the use of mechanical prostheses. However, a higher rate of prosthesis–patient mismatch, paravalvular leak, and coronary obstruction, in ViV TAVR compared to native valve TAVR has been reported (16, 17).

In our report, we observed a higher proportion of mechanical valves used in patients requiring dialysis. With the high risk of early structural deterioration in biological prostheses, there seems to be a preference for the use of the mechanical valve in this subgroup. This is in line with literature reports. Uzuka et al. (18) reported the risk of early structural deterioration in the biological valve to be approximately 50% at 6 years (compared to 0% in the control arm). Chi et al. (19) also demonstrated the survival benefits of implanting mechanical prostheses in patients with dialysis.

Currently, the European guideline recommends that patients above the age of 75 should consider TAVR after Heart/Valve team evaluation (20), while the American guideline had a cutoff of 65 years old (12). The National Institute for Health and Care Excellence recommends SAVR as a first-line interventions and TAVR for patients who are at high surgical risk or if surgery is unsuitable (21). However, with the results of the UK TAVI trials, the authors predicted that the volume of TAVR will continue to increase and exceed SAVR in the United Kingdom (22). Indeed, in the NACSA 2022 reports, the ratio of TAVR to SAVR rose from 1.2:1 to 2.3:1, which dramatically accelerated during the COVID-19 pandemic (23). The annual volume of TAVR has already exceeded SAVR in the USA and Germany (24, 25).

Our study demonstrated similar short-term outcomes regardless of the valve of choice in non-elderly patients, which echo the findings reported in the literature. Most studies showed the risk of re-intervention is higher in bioprostheses although the risk of major bleeding is lower. However, the long-term survival benefits remain controversial with some studies demonstrating a survival benefit with mechanical valves (26–28) while some did not (29–32). Although the survival benefits could be due to primary valve failure, which could be less of an issue due to the advancement of TAVR, particularly in patients who are at high risk for a redo of SAVR.

Limitations

There are several limitations of the study. First, the impact of SVAR on the clinical practice may not be fully evaluated, in a patient with extra pathology such as mitral valve/aortic/coronary artery disease requiring concomitant procedures. The choice of prostheses in these patients was not evaluated in this report. In addition, patients with aortic stenosis and coronary artery disease may undergo TAVR and their coronary artery disease managed at a later stage, while in the surgical arm, these patients will undergo both coronary artery bypass graft and SAVR at the same time. The morphology (bicuspid and tricuspid) was not coded in the database and remains an important limitation as patients with bicuspid valves are more likely to be referred for a SAVR. The lack of TAVR registry data to compare the volume of SAVR against TAVR is another major limitation.

The lack of pre- and post-operative precise echocardiographic data limited the sub-analysis for patients who underwent SAVR with different pathologies. In addition, the database did not collect certain post-operative outcomes and follow-up data; hence, information on pacemaker implantation, repeat valve intervention, endocarditis, and structural valve deterioration is not available. Finally, the database requires input from all healthcare professionals, missing data are seen in several non-mandatory items, and these are instead presented as a percentage. Overall, the mandatory items, particularly items essential for EuroSCORE II risk stratification, are well maintained with an acceptable rate (<5%) of missing data since the 2,000s.

Despite the application of PSM, it is possible that residual bias is present in the analysis since the propensity-matched model can account only for measured confounders and not for the unmeasured confounders (e.g., frailty).

Conclusion

Our data show that isolated SAVR is a safe and effective treatment with very low in-hospital mortality for patients with aortic valve disease. The advancement of transcatheter aortic valve replacement is the likely explanation for the reduction of SAVR in patients with high-risk, octogenarians, and those requiring redo surgery. The option of valve-in-valve transcatheter aortic valve replacement may also be one of the

causes for the observed use of biological aortic prostheses which has increased significantly in recent years in all age groups.

Data availability statement

The datasets presented in this article are not readily available because Ethical approval required. Requests to access the datasets should be directed to NICOR, nicor.auditenquiries@nhs.net.

Ethics statement

The studies involving human participants were reviewed and approved by Health Research Authority (HRA) and Health and Care Research Wales (HCRW) (IRAS ID: 278171). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

JC: conceptualization, data curation, formal analysis, methodology, writing—original draft, and writing—reviewing and editing. AD: data curation, formal analysis, methodology, writing—original draft, and writing—reviewing and editing. TD: data curation, formal analysis, methodology, and writing—reviewing and editing. DF, SS, and PN: conceptualization and writing—reviewing and editing. GA: conceptualization, supervision, methodology, and writing—reviewing and editing. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.1077279/full#supplementary-material

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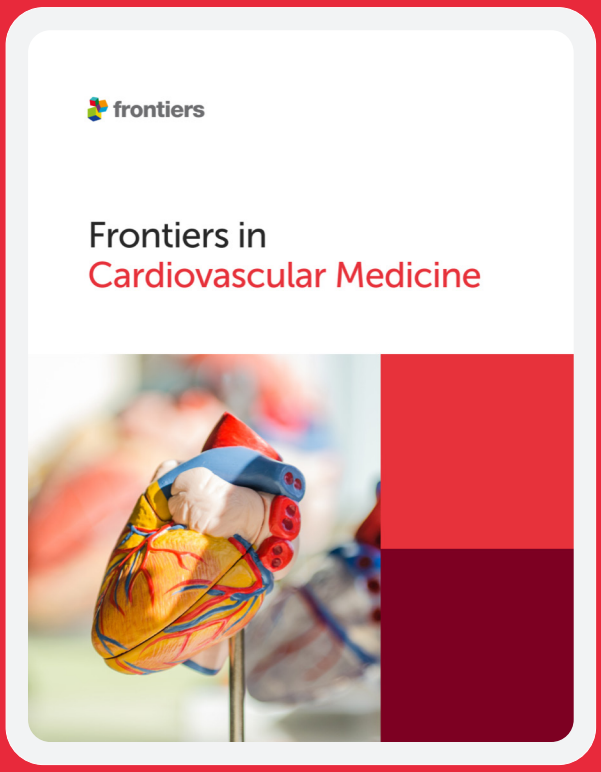

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