Interdisciplinary and cross-sectoral perioperative care model in cardiac surgery: ERAS implementation in the setting of minimally invasive heart valve surgery (INCREASE) –results of a randomized controlled trial

Johannes Petersen, Sina Stock, Christian Brettschneider, Luisa Dolata, Christian Dumps, Bernd Löwe, Eric Nijman, Ann-Kathrin Ozga, Hermann Reichenspurner, Mona Elisabeth Schmid, Leonie Schulte-Uentrop, Eik Vettorazzi, Antonia Zapf, Inke Zastrow, Susanne G. R. Klotz, Evaldas Girdauskas

Angaben zur Veröffentlichung / Publication details:

Petersen, Johannes, Sina Stock, Christian Brettschneider, Luisa Dolata, Christian Dumps, Bernd Löwe, Eric Nijman, et al. 2026. "Interdisciplinary and cross-sectoral perioperative care model in cardiac surgery: ERAS implementation in the setting of minimally invasive heart valve surgery (INCREASE) –results of a randomized controlled trial." *European Journal of Cardio-Thoracic Surgery* 68 (2): ezag061. https://doi.org/10.1093/ejcts/ezag061.

European Journal of Cardio-Thoracic Surgery 2026, 68(2), ezag061
https://doi.org/10.1093/ejcts/ezag061 Advance Access publication 31 January 2026

ORIGINAL ARTICLE

Cite this article as: Petersen J, Stock S, Brettschneider C, Dolata L, Dumps C, Löwe B *et al*. Interdisciplinary and Cross-Sectoral Perioperative Care Model in Cardiac Surgery: ERAS Implementation in the Setting of Minimally Invasive Heart Valve Surgery (INCREASE)—Results of a Randomized Controlled Trial. Eur J Cardiothorac Surg 2026; doi:10.1093/ejcts/ezag061.

Interdisciplinary and Cross-Sectoral Perioperative Care Model in Cardiac Surgery: ERAS Implementation in the Setting of Minimally Invasive Heart Valve Surgery (INCREASE)—Results of a Randomized Controlled Trial

Johannes Petersen[*,1,2]; Sina Stock[3]; Christian Brettschneider[4]; Luisa Dolata[5]; Christian Dumps[6]; Bernd Löwe[7]; Eric Nijman[8]; Ann-Kathrin Ozga[9]; Hermann Reichenspurner[1,2]; Mona Elisabeth Schmid[3]; Leonie Schulte-Uentrop[10]; Eik Vettorazzi[9]; Antonia Zapf[9]; Inke Zastrow[5]; Susanne G.R. Klotz[11]; Evaldas Girdauskas[1,2,3]

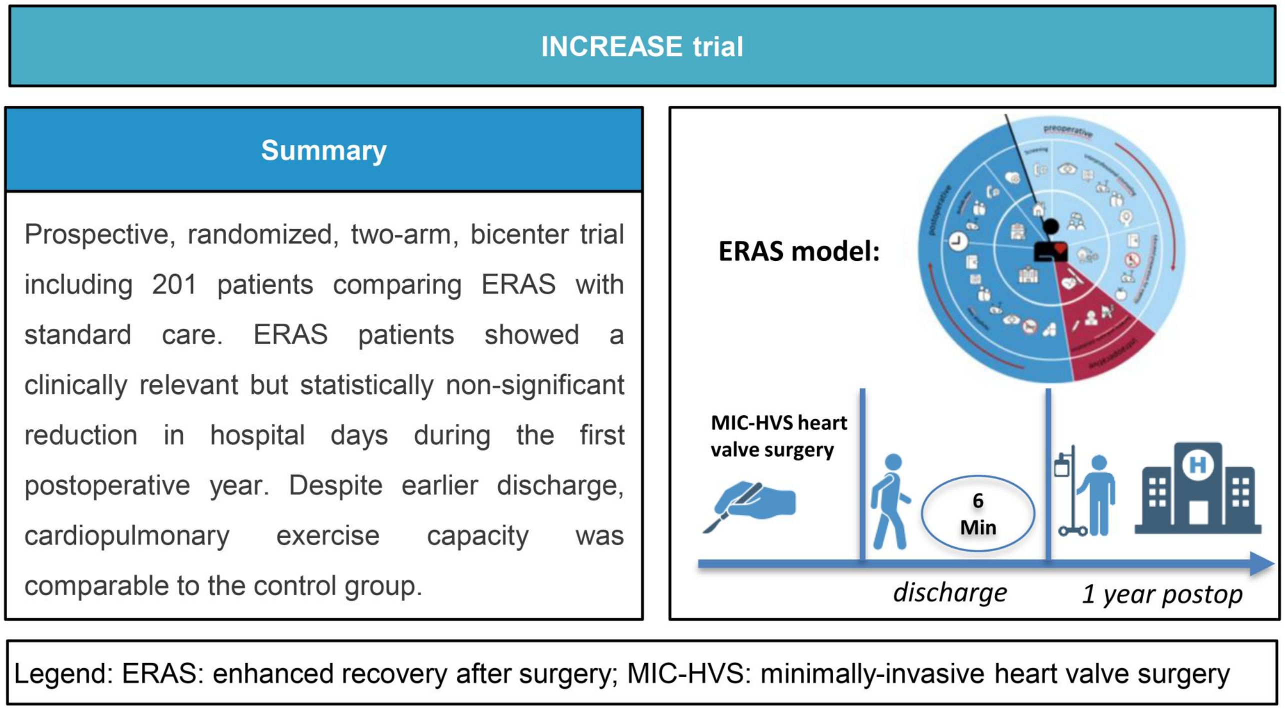
[1]Department of Cardiovascular Surgery, University Heart and Vascular Center, University Medical Center Hamburg-Eppendorf, Hamburg 20251, Germany
[2]DZHK (German Centre for Cardiovascular Research), partner site North, Hamburg, Germany
[3]Department of Cardiothoracic Surgery, University Hospital Augsburg, 86156 Augsburg, Germany
[4]Department of Health Economics and Health Services Research, University Medical Center Hamburg-Eppendorf, 20251 Hamburg, Germany
[5]Department of Patient and Care Management, University Medical Center Hamburg-Eppendorf, 20251 Hamburg, Germany
[6]Anesthesiology and Operative Intensive Care, Faculty of Medicine, University of Augsburg, 86156 Augsburg, Germany
[7]Department of Psychosomatic Medicine and Psychotherapy, University Medical Center Hamburg-Eppendorf, 20251 Hamburg, Germany
[8]Department of Physiotherapy and Occupational Therapy, University Hospital Augsburg, 86156 Augsburg, Germany
[9]Institute of Medical Biometry and Epidemiology, University Medical Center Hamburg-Eppendorf, 20251 Hamburg, Germany
[10]Department of Anesthesiology, Center of Anesthesiology and Intensive Care Medicine, University Medical Center Hamburg-Eppendorf, 20251 Hamburg, Germany
[11]Department of Physiotherapy, University Medical Center Hamburg-Eppendorf, 20251 Hamburg, Germany

*Corresponding author. Department of Cardiovascular Surgery, University Heart and Vascular Center, University Medical Center Hamburg-Eppendorf, Martinstrasse 52, 20251 Hamburg, Germany (joh.petersen@uke.de).

Received: September 10, 2025; Revised: December 23, 2025; Accepted: January 6, 2026

Author Contributions: Johannes Petersen, Sina Stock, Susanne G.R. Klotz, and Evaldas Girdauskas contributed equally to this work.

Graphical abstract



Abstract

Objectives: Enhanced recovery after surgery (ERAS) protocols are patient-centred, interprofessional perioperative care models aimed at reducing hospital stays, complications, healthcare costs, and improving patient satisfaction. Evidence for ERAS in cardiac surgery is scarce; therefore, we aimed to assess its efficacy and safety in minimally invasive heart valve surgery (MIHS).

Methods: Interdisciplinary Perioperative Care in Minimally Invasive Heart Valve Surgery (INCREASE) is a randomized-controlled trial that compares ERAS with standard care in MIHS. The intervention group (IG) received ERAS-based treatment; the control group (CG) standard care. Co-primary end-points were in-hospital stay for cardiovascular reasons within 1 year postoperatively (superiority hypothesis) and physical performance (6-minute walk test [6MWT]) at discharge (non-inferiority hypothesis). Superiority hypothesis was tested primarily in surgically treated patients (modified intention to treat population), while non-inferiority hypothesis was tested in per protocol population.

Results: In total, 201 patients scheduled for MIHS were randomized (IG: 101; CG: 100). Total weighted in-hospital stay within 1 year was non-significantly shorter in the IG (adjusted mean difference −2.7 days, 95% confidence interval (CI) (−6.3, 0.9), 1-sided $P = .07$). Sensitivity analyses favoured the IG (adjusted ratio 0.71, 95% CI, 0.6, 0.85). For 6MWT, adjusted mean difference was −14%, 95% CI (−43%, 15%) exceeding the non-inferiority margin of −15% (1-sided $P = .48$). Without baseline adjustment, 6MWT values revealed a mean difference between groups of −1%, 95% CI (−10%, 8%), reaching non-inferiority of the IG. Safety outcomes were comparable with the exception of an unexpected higher rate of postoperative atrial fibrillation in patients randomized to ERAS.

Conclusions: ERAS is feasible and safe in MIHS. The trial did not demonstrate a reduction in length of hospital stay during the first postoperative year in the population studied. Exploratory analyses suggest that further evaluation of ERAS concepts is justified.

Keywords: minimally invasive heart valve surgery; enhanced recovery after surgery; ERAS; physiotherapy; psychosomatic medicine; advanced practice nurse.

Introduction

In recent years, cardiac surgery has undergone a paradigm shift towards minimally invasive techniques with the goal of reducing surgical trauma and optimizing patient recovery.[1] Concurrently, there have been advances in perioperative care, with enhanced recovery after surgery (ERAS) protocols emerged for improving postoperative outcomes.

Enhanced recovery after surgery is a comprehensive, patient-centred strategy that involves the entire health-care team, aiming to accelerate patient recovery after major surgery. Originating in colorectal surgery in the 1990s, ERAS has since expanded to all surgical disciplines, including cardiac surgery in the early 2000s.[2] Due to the invasiveness and risk of postoperative morbidity of cardiac surgery, ERAS implementation proved challenging. The establishment of the ERAS Cardiac Society in 2017 marked a milestone, providing consensus-based guidelines.[3] Their implementation has led to the establishment of ERAS programmes in numerous institutions, leading to reduced complications, shorter hospital stays, and improved patient satisfaction, all while maintaining safety standards.[4-6] The introduction of minimally invasive heart surgery (MIHS) in the late 1990s marked the development of techniques specifically designed to minimize surgical trauma and thereby enhance postoperative recovery. As such, MIHS aligns seamlessly with the principles of ERAS, supporting its core objectives of reducing physiological stress, and promoting faster functional recovery.[7]

Despite the growing body of literature supporting ERAS in cardiac surgery, the overall level of evidence for individual guideline recommendations remains low.[3] Most studies are limited by methodological weaknesses, including retrospective designs and small sample sizes. High-quality prospective trials are notably scarce, underscoring the need for more rigorous investigation to substantiate and refine the existing recommendations.

To address this evidence gap, the Interdisciplinary Perioperative Care in Minimally Invasive Heart Valve Surgery (INCREASE) trial was initiated. The INCREASE study focuses on holistic, patient-centred care through a standardized ERAS protocol combined with a MIHS approach.[8] The INCREASE study tested 2 co-primary end-points: first, that the intervention group (IG) would have a shorter hospital stay within the first postoperative year than the control group (CG) (superiority hypothesis); and second, that despite earlier discharge, the IG would achieve 6-minute walking test (6MWT) results not inferior to those of the CG (non-inferiority hypothesis).

Methods

Study design

Written informed consent was obtained from each study participant and the Ethics Committees of the Medical Association Hamburg, Germany (2020-10276-BO-ff) and of the Ludwig-Maximilians-University Munich, Germany (21-0703) approved the investigation. The study was conducted in accordance with the Declaration of Helsinki[9] and registered in ClinicalTrials.gov (NCT04 977362 assigned July 27, 2021). The study protocol was published[8] and follows the CONSORT 2010 statement.[10]

The INCREASE trial is a randomized, parallel, 2-arm bicentre trial designed to compare the IG, treated according to ERAS protocol, and the CG which received the treatment as usual.

Sample size calculation

The calculation of the sample size was based on the 2 co-primary end-points: (1) total number of cardiac-related hospital days within the first postoperative year, and (2) physical performance at hospital discharge, assessed by the 6-minute walk test (6MWT). For the first co-primary end-point, a superiority hypothesis was made assuming that the length of hospitalization would be shorter in the IG than in the CG. For the second co-primary end-point, a non-inferiority hypothesis was assumed, stating that the patients in the IG, although discharged earlier, will achieve values of the 6MWT not inferior to the CG. A minimal clinically important difference was considered to be 10% (about 50 m). Accordingly, we have chosen 15% as the non-inferiority margin, which corresponds to 45 meters. Both primary null hypotheses must be rejected for the study to be considered successful.

The type I error was fixed at $\alpha = 0.025$ based on the 1-sided test, while the power was set to 90% for the individual hypotheses to ensure an overall power of at least 80%.

When using the 2-sample t-test based on unequal variances, the sample size required to prove superiority in the IG regarding hospitalization was 138 patients in total, assuming a mean length of stay of 6.1 days with an SD of 2.5 days in the IG, as compared to 8.0 days with an SD of 4.1 days in the CG.

When using the 2-sample t-test assuming equal variances, the sample size required to prove non-inferiority in 6MWT was 168 patients in total, assuming a mean walking distance of 300 metres (SD 89 m) for both groups.[11] A deviation −15% (ie, −45 m) was defined as non-inferiority margin. Given a dropout rate of 10%, the total sample size required was 186 patients. All sample size calculations were conducted using NCSS PASS 15 (Utah, United States). For details see Holland et al.[12]

Randomization and blinding

Patients were randomly assigned to either the IG or CG at a 1:1 ratio stratified by centre (for details, see Holland et al[12]). The enrolment period extended from July 23, 2021 (first patient randomized) to February 28, 2023 (last patient randomized). Due to the different interventions in the 2 study groups, it was not possible to blind the patients, medical staff, and the assessors of the end-points. However, the assessors were not involved in the perioperative care process. The analysis of the study data was carried out by blinded statisticians.

Inclusion/exclusion criteria

All patients underwent minimally invasive surgery via a right anterior mini-thoracotomy for mitral valve surgery, or a partial upper sternotomy for aortic valve surgery. The study inclusion and exclusion criteria are listed in **Table 1**.

Intervention (ERAS) group

Intervention group patients were treated according to the ERAS protocol, which includes pre-, intra-, and

Table 1. Study Inclusion and Exclusion Criteria

Inclusion criteria	**Exclusion criteria**
Indication for elective minimally invasive aortic or mitral valve surgery	Urgent or emergency surgery
Sufficient language skills and ability to understand the nature and extent of the individual requirements for participation in the ERAS model	Severe comorbidities, including: • advanced tumour disease with life expectancy < 1 year • chronic obstructive pulmonary disease (GOLD III or IV) • renal failure requiring dialysis • liver cirrhosis (child stage B + C) • residual neurological impairment after stroke (hemiplegia/severe limitation of movement and/or neuropsychological disorder that resulted in an inability to adhere to the prescribed physiotherapy protocol • previous cardiac surgery • major depressive disorder • addictive disorder (eg, alcohol, drugs)
Classification as "FIT" or "pre-FRAIL" using the LUCAS (Longitudinal Urban Cohort Ageing Study) functional index	Lack of social environment that ensures supportive patient care

Abbreviation: ERAS, enhanced recovery after surgery.

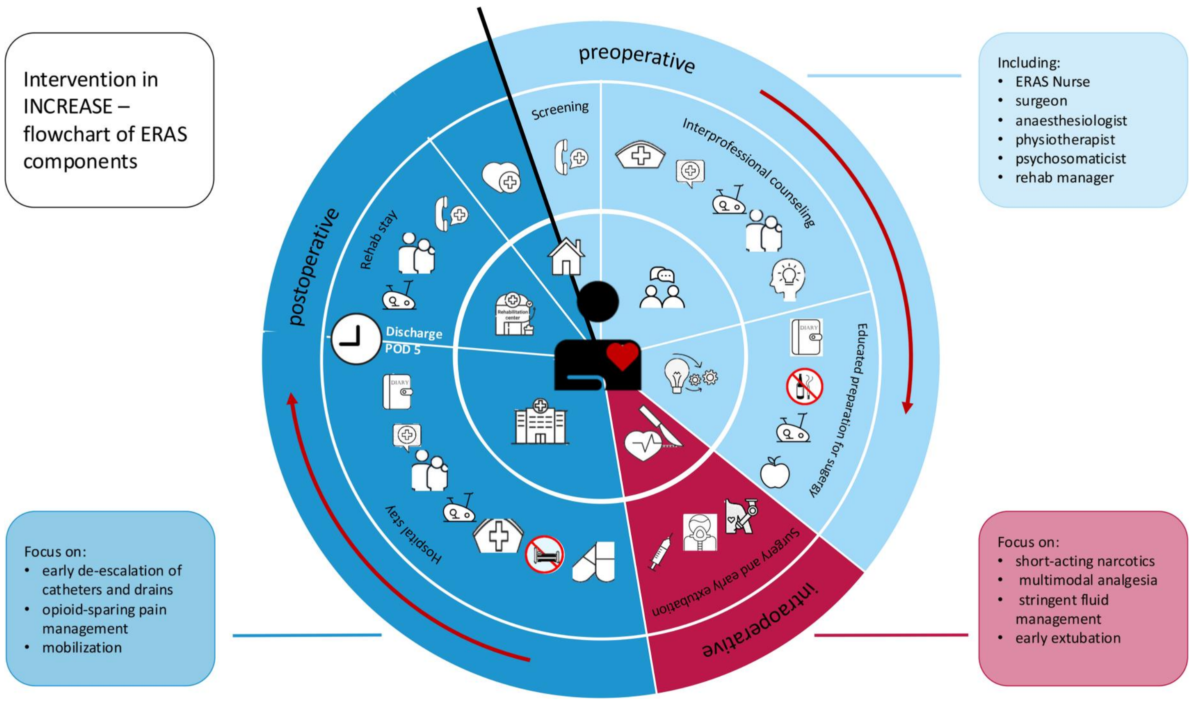


Figure 1. Intervention in INCREASE—Flowchart of ERAS Components. Abbreviations: ERAS, enhanced recovery after surgery; INCREASE, Interdisciplinary Perioperative Care in Minimally Invasive Heart Valve Surgery.

postoperative interventions.[12] ERAS components are displayed graphically in **Figure 1**.

Preoperative interventions

Prehabilitation began 2-4 weeks before surgery with an outpatient educational session. This included a structured interview with a surgeon, anaesthetist, ERAS nurse, physiotherapist, and psychosomatics specialist. Participants were provided with the INCREASE diary, enabling them to document their in-hospital course and recovery process. Preconditioning involved nutrition optimization, personalized exercise, and psychological support. Admission occurred the day before surgery and included a final briefing by ERAS team.

Intraoperative interventions

The details have been described previously.[13] Briefly, the cardiopulmonary bypass flow was targeted to ≥3.2 L/m^2/min and restrictive fluid management was implemented to achieve a negative/zero fluid balance at the end of the procedure. Short-acting anaesthetic drugs, advanced cerebral monitoring and regional anaesthesia (eg, ultrasound-guided serratus anterior plane block) were routinely used.

Postoperative interventions

All IG patients were extubated in the operating room or directly after transfer to the postanaesthesia care unit. The extubation criteria for the IG were haemodynamic stability with no significant signs of bleeding and adequate oxygenation and ventilation ($PaO_2 \geq 60$ mm Hg on $FiO_2 \leq 0.4$). Postoperative protocol has been described previously.[5] The first physiotherapy session was conducted at 3 hours after surgery. Chest tubes, invasive arterial lines, and central venous catheters were removed during the first 12 hours postoperatively. Daily interprofessional rounds and individualized, high-intensity physiotherapy were conducted until discharge.

Control group

Control group received the standard care without any prehabilitation. Patients were transferred intubated to the intensive care unit (ICU) and extubated according to hospital standard in case of awake neurological status with adequate cough and gag reflex and satisfactory chest X-ray. The CG received routine physiotherapy, including 1 ICU and 1 ward visit. There was no psychosomatic support or counselling by an ERAS nurse.

Both groups had the same discharge criteria such as (1) adequate oxygenation on room air, (2) stable sinus rhythm or well-controlled atrial fibrillation, (3) dry surgical wounds without signs of infection or dehiscence, and (4) independent ambulation and ability to perform basic self-care with (5) adequately controlled pain with oral analgesia.

Time points of measurements

The outcomes were assessed at 4 time points: baseline measurement (t0) was conducted prior to any group-specific interventions. Consequently, the t0 assessment in the IG was conducted immediately prior to the outpatient educational session, while it was on the day of hospital admission in the CG. The t1 assessment was conducted on the day before discharge in both groups. Three-month follow-up (t2) was done via telephone, whereas 12-month follow-up (t3) was performed in person at 1 year after surgery.

Outcomes

The 2 co-primary outcomes were (1) total number of in-hospital days for cardiac reasons within the first postoperative year and (2) functional capacity as measured by the 6MWT at the time of hospital discharge (see **Appendix: Table A1** for detailed cardiac reasons).

Safety events included re-thoracotomy, resuscitation, extracorporeal membrane oxygenation, mediastinitis, stroke, myocardial infarction, in-hospital death, and hospital readmission.

Data analysis

Categorical data were presented using absolute and relative frequencies. Continuous data were summarized by mean, standard deviation, median, first and third quantiles, and minimum and maximum. No significance tests were performed to compare baseline characteristics between the groups; rather, clinical relevance of any imbalance was considered.

Two-factorial analysis of variance with unequal variances was used for the analysis of "days in hospital for cardiac reasons" with treatment group and study centre as covariates. The days in hospital were weighted with the individual study duration. An analysis of covariance was used for the analysis of "6MWT at discharge" with treatment group, study centre, and baseline value of the 6MWT as covariates. For the 6MWT analysis a relative scale, that is, difference of mean 6MWT distance in the IG and in the CG divided by the mean 6MWT distance in the CG was used. Adjusted mean values are presented with corresponding 1-sided 97.5% confidence intervals and *P*-values.

If the assumption of normal distributed residuals was not met, a data transformation (eg, logarithmic transformation) or an alternative model (eg, negative binomial model) was used as a sensitivity analysis.

The intention to treat (ITT) population included all randomized patients. The modified intention to treat (mITT) population considered all patients who underwent surgery, whereas the per protocol population (PP) included those patients who underwent surgery and had no major protocol violations (see **Appendix: Table A2**). The mITT population was primarily used to test the superiority hypothesis "days in hospital," and the PP population for the non-inferiority end-point "6MWT at discharge," according to the ICH E9 guideline. The PP population was used for the sensitivity analysis of the end-point "days in hospital." Worst-case and multiple imputation sensitivity analyses were used for the end-point "6MWT at discharge" (see **Appendix: Table A3** for further details). Furthermore, a model without adjustment for baseline 6MWT was evaluated. Statistic software R Version 4.4.2 (Vienna, Austria) was used, including the basic packages, as well as MASS, car, nlme, and Amelia packages.

Results

Study cohort

A total of 251 patients were systematically screened for study inclusion. Of these, 201 patients were deemed eligible, consented to participate, and were subsequently randomized. Eleven patients who had been randomized (3 IG and 8 CG) did not undergo the surgery for various reasons and were therefore excluded from primary outcome analysis. Consequently, 190 mITT patients (93 IG and 97 CG) were available for the primary end-point "days in hospital" analysis. Seventeen patients (11 IG and 6 CG) had major protocol deviations, while the remaining 173 patients (82 IG and 91 CG) served as PP population. The patients' flowchart is displayed in **Figure 2**.

Baseline characteristics (mITT population)

The baseline characteristics of the mITT population are outlined in **Table 2**. The information for the ITT population can be found in **Appendix: Table A4**. The mean age of the sample was 57.31 (12.93) years (CG: 58.49 [12.42] years; IG: 56.14 [13.38] years) and 27.9% ($n = 56$) of the patients were female. The most prevalent valve disease was mitral regurgitation ($n = 99$; 49.3%), followed by aortic stenosis ($n = 57$; 28.4%). The most prevalent cardiovascular comorbidities were arterial hypertension (51.0%) and hyperlipidaemia (32.0%). The demographics and preoperative characteristics were comparable between IG and CG.

Perioperative characteristics (mITT population)

Mitral valve repair (48.4%) was the most common procedure, followed by aortic valve replacement (34.2%) and repair (14.2%) (see **Table 3**). Concomitant procedures included tricuspid valve repair in 2.6% of cases. Aortic

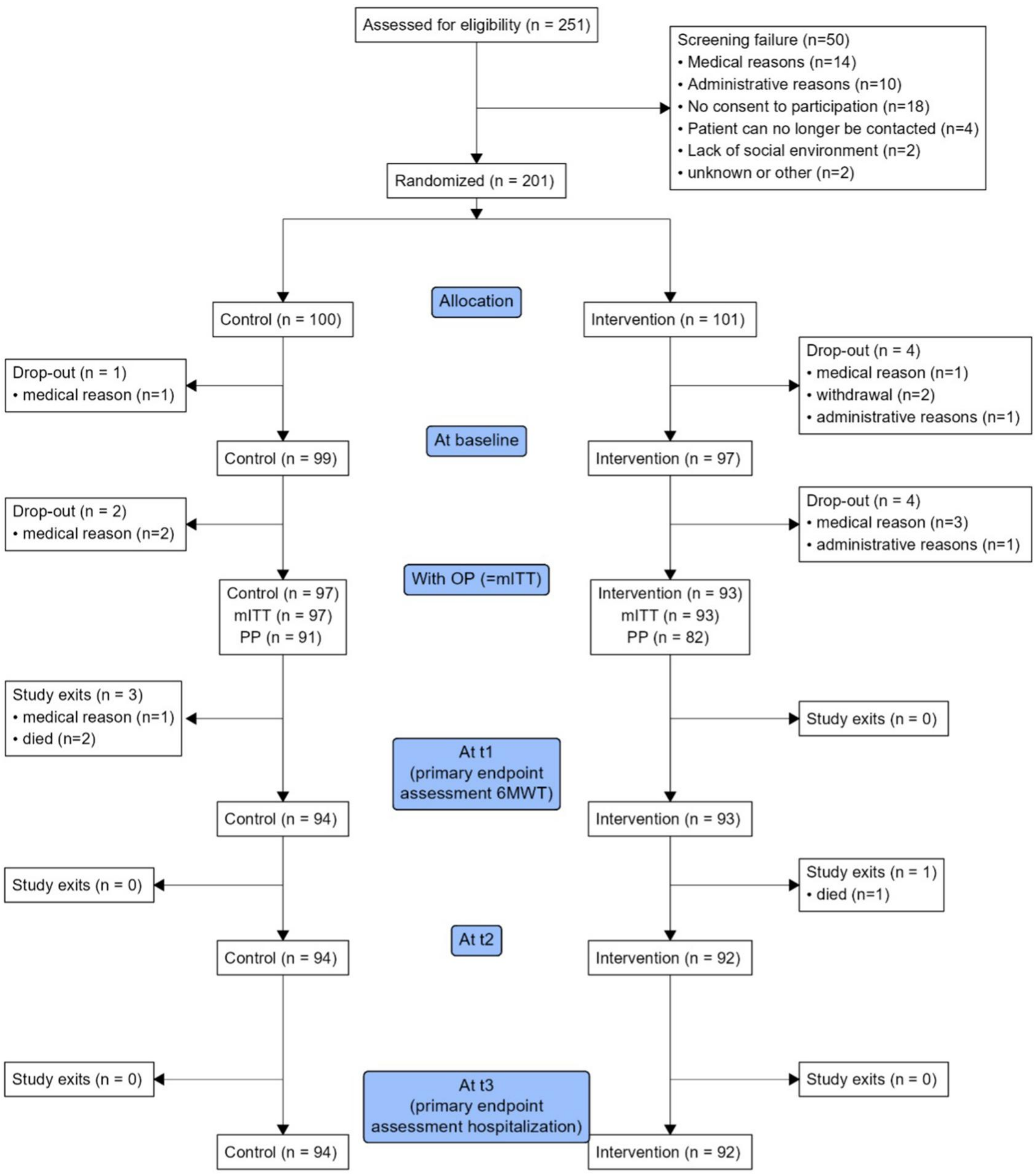


Figure 2. Flowchart of the Study Cohort. Abbreviations: miTT, modified intention to treat; 6MWT, 6-minute walk test; PP, protocol population.

Table 2. mITT Population: Demographics and Baseline Characteristics

	Control group ($n = 97$)	Intervention group ($n = 93$)	Total ($n = 190$)
Age (years)	58.43 (12.47)	55.85 (13.53)	57.17 (13.03)
Male gender	69/97 (71.1%)	71/93 (76.3%)	150/190 (73.3%)
Body mass index	26.32 (3.47)	26.17 (3.64)	26.25 (3.55)
Coronary artery disease	7/97 (7.2%)	7/93 (7.5%)	14/190 (7.4%)
Diabetes mellitus	8/97 (8.2%)	5/93 (5.4%)	13/190 (6.8%)
Hyperlipidaemia	32/97 (33.0%)	29/93 (31.2%)	61/190 (32.1%)
Arterial hypertension	48/97 (49.5%)	46/93 (49.5%)	94/190 (49.5%)
Pulmonary disease	4/97 (4.1%)	2/93 (2.2%)	6/190 (3.2%)
Atrial fibrillation	19/97 (19.6%)	17/93 (18.3%)	36/190 (18.9%)
History of stroke	1/97 (1.0%)	0/93 (0.0%)	1/190 (0.5%)
History of pacemaker implantation	1/97 (1.0%)	1/93 (1.1%)	2/190 (1.1%)
Valve disease			
Predominant aortic valve stenosis	26/97 (26.8%)	26/93 (28.0%)	52/190 (27.4%)
Predominant aortic valve insufficiency	14/97 (14.4%)	15/93 (16.1%)	29/190 (15.3%)
Predominant mitral valve stenosis	0/97 (0.0%)	1/93 (1.1%)	1/190 (0.5%)
Predominant mitral valve insufficiency	52/97 (53.6%)	41/93 (44.1%)	93/190 (48.9%)
Aneurysm of the ascending aorta	2/97 (2.1%)	6/93 (6.5%)	8/190 (4.2%)
Aneurysm of the aortic root	3/97 (3.1%)	4/93 (4.3%)	7/190 (3.7%)

Table 3. mITT Population: Perioperative Characteristics

	Control group ($n = 97$)	Intervention group ($n = 93$)	Total ($n = 190$)
Aortic valve replacement	33/97 (33%)	33/93 (35.5%)	66/190 (34.2%)
Aortic valve repair	12/97 (12.4%)	15/93 (16.1%)	27/190 (14.2%)
Mitral valve replacement	3/97 (3.1%)	2/93 (2.2%)	5/190 (2.6%)
Mitral valve repair	49/97 (50.5%)	43/93 (46.2%)	92/190 (48.4%)
Concomitant procedures			
Tricuspid valve repair	3/97 (3.1%)	2/93 (2.2%)	5/190 (2.6%)
Aortic root surgery	3/97 (3.1 %)	5/93 (5.4%)	8/190 (4.2%)
Replacement of ascending aorta	11/97 (11.3%)	11/93 (11.8%)	22/190 (11.6%)
Procedural time	216.9 (75)	200.5 (50.9)	208.9 (64.7)
Cardiopulmonary bypass time (minutes)	138.9 (52.1)	129.6 (37.5)	134.4 (45.7)
Aortic cross-clamp time (minutes)	85.1 (28.5)	82.8 (28.8)	84.0 (28.6)

cross-clamp time was 82.8 (28.8) minutes in the IG and 85.1 (28.5) minutes in the CG, respectively. The mean cardiopulmonary bypass time was 129.6 (37.5) minutes in the IG and 138.9 (52.1) min in the CG.

In-hospital days within the first postoperative year (superiority hypothesis)

The total weighted in-hospital days within the first postoperative year was 9.03 (11.62) (median [first, third quantile]: 5.63 [4.74, 8.43]) days in the IG and 11.69 (13.11) (median [first, third quantile]: 7.30 [6.11, 10.77]) days in the CG in the mITT population (see **Appendix: Table A5**). The (centre-adjusted) mean difference was −2.67 (95% confidence interval (CI): −6.25, 0.90), 1-sided $P = .07$, indicating that, on average, cardiac-related hospital days were reduced by −2.67 days in the IG vs CG, which exceeded the initial assumption of −1.9 days. However, the observed standard deviation was larger than that assumed in the sample size calculation, and therefore the difference was not significant.

As an exploratory post-hoc analysis within the mITT population, postoperative in-hospital stay until discharge were evaluated. Postoperative in-hospital stay was 6.49 (1.66) days in the IG (median [first, third quantile]: 6.04 [5.17, 7.00]) and 8.89 (3.99) days in the CG (median [first, third quantile]: 7.94 [6.77, 9.35]). This indicates a shorter postoperative stay in the IG.

Sensitivity analysis using PP population revealed the total weighted in-hospital stay of 7.95 (6.18) days in the IG and 11.04 (11.42) days in the CG. The adjusted mean difference between the IG and the CG was −3.09 (95% CI, −5.82, −0.36), 1-sided $P = .01$. Further sensitivity analysis was conducted due to a skewed distribution of residuals. Sensitivity analysis using the negative binomial model revealed that IG exhibited a reduced hospital stay when compared to CG with an adjusted ratio of 0.71 (95% CI, 0.60-0.85; 2-sided $P < .01$). Another sensitivity analysis employing log-transformed data revealed that IG had a shorter in-hospital stay when compared to the CG with an adjusted ratio of 0.76 (95% CI, 0.64-0.91; 2-sided $P < .01$). The distribution of the observed total weighted in-hospital days within the first postoperative year is displayed in **Figure 3** (see also **Appendix: Figure A1** for further information).

6MWT at hospital discharge (non-inferiority hypothesis)

In the PP population, the 6MWT at hospital discharge measured 380.0 (117.5) m in the IG vs 382.8 (106.0) m in the CG (**Figure 4**). The baseline 6MWT values were 557.89 (111.61) m and 528.51 (106.99) m, respectively. The adjusted (for baseline 6MWT and centre) mean difference in 6MWT at discharge between the IG and the CG was −14% (95% CI, −43%, 15%; 1-sided $P = .48$) with the lower limit of the confidence interval exceeding the non-inferiority margin of −15%. Therefore, non-inferiority could not be proven. The observed standard deviation was larger than assumed in the sample size calculation.

Sensitivity analyses were performed using multiple imputation and worst-case imputation (see **Figure 5** and **Appendix: Figures A2 and A3**). Using the multiple imputed data, we found the adjusted mean difference in 6MWT at discharge between the IG and the CG of −8% (95% CI, −43%, 28%; 1-sided $P = .66$) in the PP population.

Further comparison of 6MWT at discharge between the groups was performed without adjustment for baseline 6MWT (see **Figure 5** and **Appendix: Figure A3**). In the absence of adjustment for baseline 6MWT values, the mean difference between the IG and the CG was −1% (95% CI, −10%, 8%; 1-sided $P < .01$) in the PP population, reaching the non-inferiority in the IG.

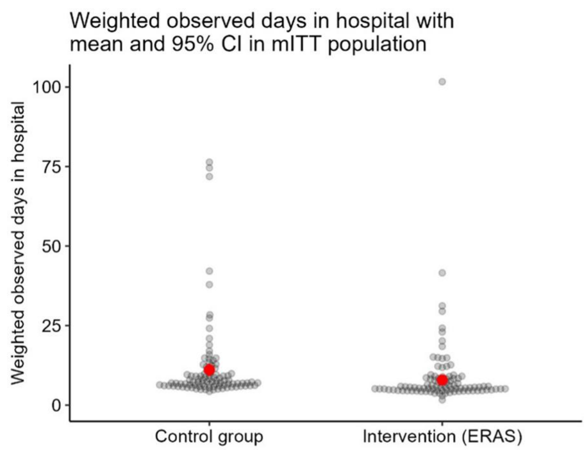


Figure 3. Observed Total Weighted Days in Hospital due to Cardiac Reasons in the mITT Population in the First Postoperative Year with Mean and 95% CI. Abbreviations: CI, confidence interval; ERAS, enhanced recovery after surgery; miTT, modified intention to treat.

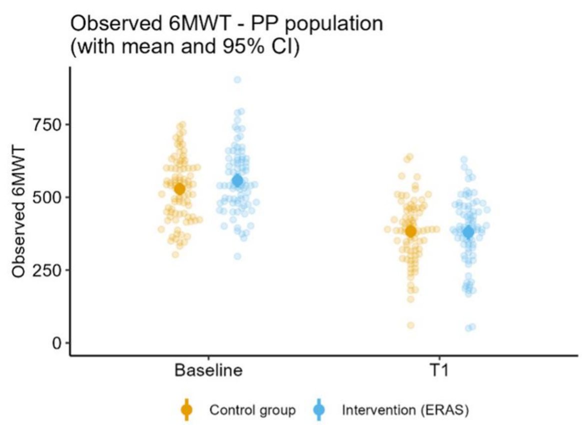


Figure 4. Observed 6MWT Values with Means and 95% CI (PP Population). Abbreviations: CI, confidence interval; 6MWT, 6-minute walk test; PP, protocol population.

Safety events (mITT population)

The total number of adverse events in both groups is summarized in **Table 4**. The most common event was postoperative atrial fibrillation, occurring 34 times in the IG group vs 17 times in the CG group. There were 2 occurrences of postoperative stroke in the CG, whereas there was no stroke in the IG. Rethoracotomy due to bleeding was necessary in 4 cases in the IG vs 3 in the CG. One 1-year postoperative death occurred in the IG and 2 in the CG.

Discussion

The INCREASE trial aimed to compare the ERAS vs standard of care in MIHS regarding in-hospital stay within first postoperative year (superiority hypothesis), and the physical performance measured by 6MWT at hospital discharge (non-inferiority hypothesis). In summary, the objective of the INCREASE trial was to prove that ERAS-treated patients, despite an earlier hospital discharge, obtain physical fitness that is not inferior to that of patients who were treated "as usual." The trial offers novel evidence on perioperative care in cardiac surgery using a multiprofessional ERAS approach.

In-hospital days within the first postoperative year

The implementation of ERAS has historically been driven by the objective of reducing in-hospital stay. Prior to the advent of ERAS, numerous fast-track protocols had been implemented, demonstrating a reduction in in-hospital stay.[14] Moreover, recent retrospective studies showed that the adherence to ERAS recommendations[3] might reduce both the ICU and in-hospital stays.[4,5,13] Consistent with these previous findings, our exploratory post-hoc analysis of postoperative in-hospital days until discharge supports the notion that ERAS may contribute to a shorter hospital stay. In this analysis, patients in the IG showed a reduction in postoperative in-hospital stay compared with the CG. Although the analysis was not prespecified and should therefore be interpreted cautiously, the results align with the existing body of evidence, indicating that ERAS can facilitate earlier discharge after cardiac surgery.

Most studies focused exclusively on the period until discharge, neglecting the interval beyond the index hospital stay. The INCREASE trial is the first to focus on the

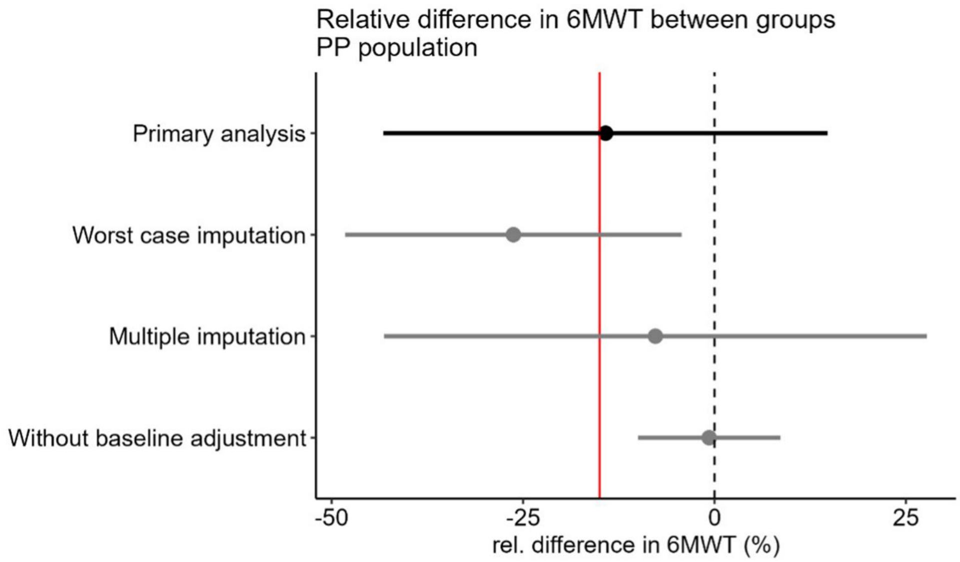


Figure 5. Effect Estimate of 6MWT in PP Population. Primary analysis and sensitivity analyses. Abbreviations: 6MWT, 6-minute walk test; PP, protocol population.

Table 4. mITT Population: 1-Year Postoperative Adverse Events

	Control group ($n = 35$[a])	Intervention group ($n = 51$[a])	Total ($n = 86$[a])
Postoperative atrial fibrillation	17/35	34/51	51/86
Postoperative stroke	2/35	0/51	2/86
Transient ischaemic attack	3/35	0/51	3/86
Permanent pacemaker implantation	2/35	4/51	6/86
Rethoracotomy due to bleeding	3/35	4/51	7/86
Wound healing disorder	2/35	2/51	4/86
Postcardiotomy syndrome	3/35	6/51	9/86
Postoperative ECMO support	1/35	0/51	1/86
Mortality	2/35	1/51	3/86

[a] *n* refers to the total number of adverse events. It does not represent the number of patients. Multiple adverse events may occur per patient.
Abbreviation: ECMO, Extracorporeal Membrane Oxygenation.

cumulative in-hospital stay within the first postoperative year. ERAS intervention yielded a mean reduction of 2.7 cardiac-related hospital days within 1 year when compared to the CG, although not statistically significant. Sensitivity analysis in the PP population showed a relevant reduction of in-hospital stay by −3.09 days (95% CI, −5.82, −0.36) in the IG vs CG. Furthermore, sensitivity analyses using negative binomial model or logarithmic transformation to consider the large skewness, revealed that IG patients exhibited a reduced duration of hospitalization with an estimated factor of approximately 0.71 (95% CI, 0.60, 0.85) and 0.76 (95% CI, 0.64-0.91), respectively. And hence, although the primary confirmatory analysis did not show superiority of days in hospital in the IG, sensitivity analysis gives hints that days in hospital might be reduced in the IG. This finding is reassuring and has significant implications for clinical practice. First, it provides a solid argument against the widespread opinion that ERAS-treated patients might be discharged too early and at cost of later rehospitalization. The safety of earlier discharge in ERAS patients has been confirmed by comparable safety profile in both study arms and similar readmission rates during the first postoperative year. Second, the findings of the INCREASE trial indicate a substantial economic benefit due to shorter initial in-hospital stay, along with a reduction of total in-hospital days within the first postoperative year. Moreover, the earlier discharge of patients was shown to have numerous benefits for the patients' empowerment. Apart from decreasing the psychological stress and the regain of independence, early discharge improves the overall quality of life of patients and reduces the risk of hospital-acquired complications due to a shorter exposure to hospital environment.[15] However, the incidence of postoperative atrial fibrillation (POAF) was twice as high in the ERAS IG. This may have resulted in longer hospital stays in the year following surgery. Therefore, ERAS protocols require mandatory POAF prevention measures, as recommended by the ERAS guidelines.[3] Another possible impact could have been the differences in type of valve procedures between randomized groups (aortic and mitral). However, the subgroup analysis comparing patients with aortic valve disease and patients with mitral valve disease did not indicate any difference in the efficacy of the intervention for the 2 types of valve surgery: the effects were of similar magnitude and the interaction *P*-values were above .15.

Physical performance at hospital discharge

In the PP population, the difference in 6MWT distance at hospital discharge between the IG and CG exceeded the non-inferiority margin established within the baseline-adjusted model and hence non-inferiority could not be shown in the primary confirmatory analysis. In the additional sensitivity analysis that ignored the baseline 6MWT, the non-inferiority criteria was fulfilled, and hence, there is at least a hint that despite earlier hospital discharge, patients in the IG demonstrated non-inferior physical performance to CG when baseline differences were disregarded.

The simple, safe, and low-cost 6MWT is a well-established tool for assessing patients' physical performance and functional status after cardiac surgery.[11] Concerning postoperative outcomes, it is recognized that functional exercise capacity declines immediately following cardiac surgery.[16] The observed reduction in 6MWT distance in both groups when comparing preoperative and postoperative measurements aligns with this evidence and highlights the impact of pre-existing heart disease, hospitalization, and the surgical procedure on physical performance. This phenomenon emphasizes the critical role of rehabilitation strategies in optimizing postoperative recovery.

Consequently, the postoperative decline in 6MWT distance observed in both groups is consistent with expectations. However, the preoperative 6MWT was higher in the IG, resulting in a greater postoperative decline. Established determinants of 6MWT performance at hospital discharge following cardiac surgery include the type of surgery, operative time, baseline functional capacity, and body mass index.[17] Importantly, these factors were comparable between groups, owing to the randomized design of this study. This raises the question of why preoperative 6MWT distances differed between the IG and CG. A potential contributor may be the timing of the preoperative 6MWT assessment. In the IG, it was conducted 2-4 weeks before surgery as part of the interprofessional prehabilitation programme, whereas in the CG, it was performed the day before surgery. Psychological factors, known to strongly influence physical performance, may have contributed to this disparity. As demonstrated in previous studies, anxiety and psychological distress can negatively affect 6MWT outcomes.[18] Both factors demonstrate higher levels of intensity on the day immediately prior to surgery compared to 2-4 weeks before the procedure. This finding could offer a potential explanation for the preoperative advantage observed in the IG, thus necessitating further investigation into the interplay between psychological factors, timing of assessment, and physical performance metrics like the 6MWT. However, this remains a hypothetical interpretation. While a divergence in preoperative 6MWT distance was observed between the groups, its clinical relevance appears limited. Evidence from previous studies suggests that a minimum difference of at least 30 meters in 6MWT distance is required to be considered clinically meaningful.[12,19] In this study, the observed preoperative difference (527.4 [105.8] m in the CG vs 549.7 [118.5] m in the IG) did not meet this threshold, indicating a limited clinical impact. Another aspect to consider when interpreting the 6MWT results is the higher-than-anticipated variability, which can be explained by the age distribution of the patients. The patients were aged between 19 and 76 years in both groups. As outlined by Fiorina et al,[11] 6MWT distance is affected by age. Additionally, the 6MWT can be influenced by physical factors, such as pulmonary disease (5 patients in the CG compared to 2 in the IG) or a history of stroke (1 vs 0 patients). Since baseline measure took place after randomization, patients already knew which group they were randomized to. Therefore, knowing which group they belong to might change their performance (this is called Lord's Paradox).

From a clinical perspective, it is noteworthy that 6MWT distances at hospital discharge were very comparable between the 2 per protocol populations (380.0 [117.5] m in the IG vs 382.8 [106.0] m in the CG), meeting the non-inferiority in the baseline-unadjusted model. Importantly, a 6MWT distance exceeding $>$300 m at hospital discharge has been associated with reduced mortality and rehospitalization rates following cardiac surgery.[20] Both groups surpassed this critical threshold, suggesting a favourable prognosis with low risks of complications and rehospitalization. A key consideration pertains to the earlier hospital discharge of the IG by −3.09 days (95% CI, −5.82, −0.36) in the per protocol population, consequently facilitating an earlier 6MWT assessment. Despite this earlier measurement, the 6MWT distances were comparable, indicating that patients in both groups were similarly "fit" at the time of hospital discharge. Therefore, the 6MWT served as a critical safety and functional assurance end-point. By demonstrating non-inferiority between study groups on the 6MWT at the time of discharge, we provide robust evidence that the accelerated discharge ERAS protocol does not compromise patients' functional capacity.

In general, the multidisciplinary ERAS care within a dedicated ERAS-programme benefits patients by improving clinical outcomes (eg, reduced postoperative complications and better pain control), facilitating faster functional recovery (eg, earlier mobilization and improved physical performance) and reducing hospital stays.

Limitations

Despite the randomized controlled trial's status as the gold standard, the present study has several limitations. The study was not possible to blind which could introduce bias into the study. However, it is not possible to blind the patients because the IG included several additional elements, such as prehabilitation 2-4 weeks prior to surgery and physiotherapy. Most of the medical staff (physicians and nurses on the ward) were unaware of which patients were in the intervention or CG, in order to avoid influencing discharge decisions based on randomization. In addition, the statistician was blinded to reduce bias. Moreover, the model assumptions for the primary model in the analysis of hospital days were not fulfilled, which was predominantly due to much higher than expected levels of variation and skewness of the data. Consequently, the results of the pre-specified primary analysis should be interpreted with caution. This aspect must be taken into consideration when interpreting the study's findings. Results of the sensitivity analyses have to be confirmed by another confirmatory study.

Conclusion

The ERAS protocol is feasible and safe in MIHS. Concerning the hospitalization in the first postoperative year, ERAS patients showed a clinically relevant, although statistically non-significant, reduction in hospital days in comparison to the CG. Despite earlier hospital discharge, ERAS patients demonstrated similar cardiopulmonary exercise capacity to the CG in a non-confirmatory sensitivity analysis. However, it should be noted that, according to the specific study design, the primary end-point was not achieved. Nevertheless, the findings of sensitivity analyses support the assumed effects and justify the pursuit of the research question in further studies.

Acknowledgements

The authors would like to thank all patients who participated in the study. Furthermore, the authors wish to thank the persons who contributed to the success of this study: Jelena Bagnjuk, Anke Begerow, Christian-Alexander Behrendt, Tamara Betz, Sandra Brandt, Jens Brickwedel, Caroline Clifford, Daniel Hofbauer, Gesche Ketels, Hans-Helmut König, Helene König, Sebastian Kohlmann, Daria Schefer, Philipp Simon, and Christian Zöllner.

Author contributions

Johannes Petersen (Methodology, Validation, Investigation, Data curation, Writing—original draft, Visualization), Sina Stock (Methodology, Validation, Investigation, Data curation, Writing—original draft, Visualization), Christian Brettschneider (Conceptualization, Methodology, Formal analysis, Data curation, Writing—review & editing, Visualization), Luisa Dolata (Methodology, Investigation, Writing—review & editing), Christian Dumps (Methodology, Investigation, Writing—review & editing), Bernd Löwe (Methodology, Investigation, Writing—review & editing), Eric Nijman (Methodology, Investigation, Writing—review & editing), Ann-Kathrin Ozga (Conceptualization, Methodology, Formal analysis, Data curation, Writing—review & editing, Visualization), Hermann Reichenspurner (Methodology, Investigation, Writing—review & editing), Mona Elisabeth Schmid (Methodology, Investigation, Writing—review & editing), Leonie Schulte-Uentrop (Methodology, Investigation, Writing—review & editing), Eik Vettorazzi (Conceptualization, Methodology, Formal analysis, Data curation, Writing—review & editing, Visualization), Antonia Zapf (Conceptualization, Methodology, Formal analysis, Data curation, Writing—review & editing, Visualization), Inke Zastrow (Methodology, Investigation, Writing—review & editing), Susanne G.R. Klotz (Conceptualization, Methodology, Software, Validation, Investigation, Data curation, Writing—original draft, Supervision, Project administration, Funding acquisition), and Evaldas Girdauskas (Conceptualization, Methodology, Software, Validation, Investigation, Data curation, Writing—original draft, Supervision, Project administration, Funding acquisition)

Supplementary material

Supplementary material is available at *EJCTS* online.

Conflicts of interest

None declared.

Funding

This study was funded by the Innovationsausschuss in the Gemeinsamer Bundesausschuss with resources of the Innovationsfonds for the promotion of new forms of care (Section 92a (1) SGB V) (funding code: 01NVF19028). The funders were not involved in any step of the study project including study design, data collection, data management, data analysis, data interpretation, and issues regarding publication of the results.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

References

[1] Chitwood WR Jr. Historical evolution of robot-assisted cardiac surgery: a 25-year journey. *Ann Cardiothorac Surg*. 2022;11:564-582. https://doi.org/10.21037/acs-2022-rmvs-26
[2] Wilmore DW, Kehlet H. Management of patients in fast track surgery. *BMJ*. 2001;322:473-476. https://doi.org/10.1136/bmj.322.7284.473
[3] Engelman DT, Ben Ali W, Williams JB, et al. Guidelines for perioperative care in cardiac surgery: enhanced recovery after surgery society recommendations. *JAMA Surg*. 2019;154:755-766. https://doi.org/10.1001/jamasurg.2019.1153
[4] Williams JB, McConnell G, Allender JE, et al. One-year results from the first US-based enhanced recovery after cardiac surgery (ERAS Cardiac) program. *J Thorac Cardiovasc Surg*. 2019;157:1881-1888. https://doi.org/10.1016/j.jtcvs.2018.10.164
[5] Gebauer A, Konertz J, Petersen J, et al. The impact of a standardized enhanced recovery after surgery (ERAS) protocol in patients undergoing minimally invasive heart valve surgery. *PLoS One*. 2023;18:e0283652. https://doi.org/10.1371/journal.pone.0283652
[6] Petersen J, Kloth B, Konertz J, et al. Economic impact of enhanced recovery after surgery protocol in minimally invasive cardiac surgery. *BMC Health Serv Res*. 2021;21:254. https://doi.org/10.1186/s12913-021-06218-5

[7] Reichenspurner H, Welz A, Gulielmos V, Boehm D, Reichart B. Port-access cardiac surgery using endovascular cardiopulmonary bypass: theory, practice, and results. *J Card Surg*. 1998;13:275-280. https://doi.org/10.1111/j.1540-8191.1998.tb01068.x

[8] Klotz SGR, Ketels G, Behrendt CA, et al. Interdisciplinary and cross-sectoral perioperative care model in cardiac surgery: implementation in the setting of minimally invasive heart valve surgery (INCREASE)-study protocol for a randomized controlled trial. *Trials*. 2022;23:528. https://doi.org/10.1186/s13063-022-06455-x

[9] World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA*. 2013;310:2191-2194. https://jamanetwork.com/journals/jama/fullarticle/193387

[10] Schulz KF, Altman DG, Moher D; CONSORT Group. CONSORT 2010 statement: updated guidelines for reporting parallel group randomized trials. *Ann Intern Med*. 2010;152:726-732. https://doi.org/10.7326/0003-4819-152-11-201006010-00232

[11] Fiorina C, Vizzardi E, Lorusso R, et al. The 6-min walking test early after cardiac surgery. Reference values and the effects of rehabilitation programme. *Eur J Cardiothorac Surg*. 2007;32:724-729. https://doi.org/10.1016/j.ejcts.2007.08.013

[12] Holland AE, Spruit MA, Troosters T, et al. An official European Respiratory Society/American Thoracic Society technical standard: field walking tests in chronic respiratory disease. *Eur Respir J*. 2014;44:1428-1446. https://doi.org/10.1183/09031936.00150314

[13] Kubitz JC, Schulte-Uentrop L, Zoellner C, et al. Establishment of an enhanced recovery after surgery protocol in minimally invasive heart valve surgery. *PLoS One*. 2020;15:e0231378. https://doi.org/10.1371/journal.pone.0231378

[14] Di Eusanio M, Vessella W, Carozza R, et al. Ultra fast-track minimally invasive aortic valve replacement: going beyond reduced incisions. *Eur J Cardiothorac Surg*. 2018;53:ii14-ii18. https://doi.org/10.1093/ejcts/ezx508

[15] Aggarwal K, Singh B, Banker H, et al. Exploring the ramifications of delayed hospital discharges: impacts on patients, physicians, and healthcare systems. *Cureus*. 2024;16:e61249. https://doi.org/10.7759/cureus.61249

[16] Petersen J, Vettorazzi E, Winter L, Schmied W, Kindermann I, Schäfers H-J. Physical and mental recovery after conventional aortic valve surgery. *J Thorac Cardiovasc Surg*. 2016;152:1549-1556.e2. https://doi.org/10.1016/j.jtcvs.2016.07.072

[17] Oliveira GU, Oliveira Carvalho V, de Assis Cacau LP Jr, et al. Determinants of distance walked during the six-minute walk test in patients undergoing cardiac surgery at hospital discharge. *J Cardiothorac Surg*. 2014;9:95. https://doi.org/10.1186/1749-8090-9-95

[18] Borgmann M, Ivanda M, Hadizamani Y, et al. Does the 6-minute walk test in hospitalized COPD patients exclusively correlate with lung function parameters or should psychological factors also be taken into account? *PLoS One*. 2020;15:e0232587. https://doi.org/10.1371/journal.pone.0232587

[19] Shoemaker MJ, Curtis AB, Vangsnes E, Dickinson MG. Clinically meaningful change estimates for the six-minute walk test and daily activity in individuals with chronic heart failure. *Cardiopulm Phys Ther J*. 2013;24:21-29. https://doi.org/10.1097/01823246-201324030-00004

[20] Chen YC, Chen KC, Lu LH, Wu YL, Lai TJ, Wang CH. Validating the 6-minute walk test as an indicator of recovery in patients undergoing cardiac surgery: a prospective cohort study. *Medicine (Baltimore)*. 2018;97:e12925. https://doi.org/10.1097/MD.0000000000012925

European Journal of Cardio-Thoracic Surgery, 2026, 68, ezag061
https://doi.org/10.1093/ejcts/ezag061
Original article