MEDICAL UNIVERSITY - SOFIA
DEPARTMENT OF CARDIOVASCULAR SURGERY
AND INVASIVE CARDIOLOGY
"ST. EKATERINA" HOSPITAL

Dr. Stanislava Vasileva Stoycheva

SURGICAL TREATMENT OF HIGH-RISK PATIENTS WITH AORTIC STENOSIS

A B S T R A C T

Dissertation work for the acquisition of the educational and scientific degree "PhD"

Professional field 7.1 Medicine

Doctoral Program: "Cardiovascular Surgery"

Scientific supervisor:

Prof. Dr. Gencho Nachev, MD, PhD

Sofia

2025

The dissertation is written on 142 standard typewritten pages and is illustrated with 41 diagrams, 8 figures, 1 scheme and 11 tables . The bibliography contains 124 literary sources, which are in Latin.

The dissertation work has been discussed and directed for public defense by the Department Council at the Department of Cardiovascular Surgery and Invasive Cardiology, Medical University - Sofia.

The dissertation candidate is an assistant professor in the same department and works at the Cardiac Surgery Clinic of the University Multi-profile Hospital for Active Treatment "St. Catherine", Sofia.

The public defense of the dissertation will take place on March 27, 2025 at 2:00 p.m. in the auditorium of St. Catherine University Hospital, Sofia, 52A Pencho Slaveykov Blvd. , before a scientific jury consisting of:

1. *Prof. Dr. Dimitar Georgiev Petkov, MD, PhD*
2. *Prof. Dr. Valentin Stefanov Govedarski, MD, PhD*
3. *Prof. Dr. Plamen Georgiev Panayotov, MD, PhD*
4. *Assoc. prof. Dr. Vladimir Borisov Kornovski,MD*
5. *Assoc. prof. Dr. Nadelin Krasimirov Nikolov, MD*

The materials for the defense are available in the Science Department of the Faculty of Medicine at the Medical University - Sofia, as well as on the website of the Medical University - Sofia.

Contents

List of abbreviations

ACEI - Angiotensin-Converting Enzyme Inhibitors

AF - atrial fibrillation

AS - aortic stenosis

AVA - Aortic Valve Area

AVN - atrioventricular node

AVR - aortic valve replacement

BP- blood pressure

BSA - Body Surface Area

CABG - Coronary Artery Bypass Grafting

CKD - chronic kidney disease

COPD - chronic obstructive pulmonary disease

CT - cardiac computed tomography

DSE - Dobutamine Stress Echo

ECC - extracorporeal circulation

ECG - electrocardiography

EchoCG - echocardiography

EOA - Effective Orifice Area

EuroSCORE II - European System for Cardiac Operative Risk Evaluation

FC - functional class

FEV - forced expiratory volume

GIT - gastrointestinal tract

LV - left ventricle

LVEF - left ventricular ejection fraction

MSG - mean systolic gradient

POD - postoperative day

PPM - Patient - Prosthesis Mismatch

PSG - peak systolic gradient

SA block – sinoatrial block

SAVR - Surgical Aortic Valve Replacement

SR - sinus rhythm

TAVI - Transcatheter Aortic Valve Implantation

TEE - transesophageal echocardiography

I. INTRODUCTION

The treatment strategy for aortic valve stenosis (AS) is a major topic in many current scientific publications due to its severe clinical and economic consequences. AS has been identified as one of the most common valvular diseases in developed countries, second only to mitral valve disease, with an incidence expected to double over the next 50 years [1].

Aortic valve stenosis is a progressive disease that, if left untreated, usually leads to life-threatening consequences [2]. The increased resistance against which the left ventricle pushes is initially compensated by hypertrophy of its walls, with subsequent left ventricular failure.

Surgical aortic valve replacement (SAVR) has always been considered the gold standard for the treatment of severe symptomatic aortic stenosis, with excellent results [3,4]. However, the incidence of postoperative complications is directly dependent on the type and severity of other comorbidities - diabetes, renal or hepatic failure, COPD, etc. The operation is performed under conditions of extracorporeal circulation and aortic cross clamping, the duration of which is directly associated with increased postoperative morbidity and mortality [5,6], especially in high-risk patients. And new technologies and surgical techniques aimed at reducing adverse postoperative events are one of the main goals of modern cardiac surgery.

Sutureless valves are a new generation of surgical bioprostheses with a unique design that facilitates their implantation and reduces the duration of the surgical procedure. There is growing evidence that aortic valve replacement using sutureless bioprostheses is associated with better postoperative outcomes in patients with intermediate and high surgical risk [7,8]. Their use is particularly attractive in minimally invasive surgical approaches [9–11].

This dissertation aims to clarify the effect of the use of Perceval sutureless aortic valves in high-risk patients with aortic stenosis on early postoperative morbidity and mortality and to evaluate the results after one year of follow-up. In particular, the effect of using a completely new treatment strategy, including minimally invasive surgical access and implantation of sutureless valves. In order to increase the objectivity of the study, the data of the group of patients undergoing the new strategy were compared

with those of a similar group of patients who were operated on using the traditional method - complete median sternotomy and implantation of standard stented bioprostheses.

III. AIM AND OBJECTIVES

1. AIM

To assess the applicability and effectiveness of a new generation of surgical sutureless valve bioprostheses in the treatment of high-risk patients with severe aortic stenosis.

2. OBJECTIVES

1. Determining the baseline characteristics of the study population and defining groups;

2. Analysis of intraoperative data and comparison between groups;

3. Comparative analysis of early results in the first 24 hours after surgery;

4. Comparative analysis of postoperative outcomes from the second postoperative day until discharge;

5. Follow-up of patients in the second and fourth weeks after discharge;

6. Analysis of one-year survival;

7. Development of an algorithm for setting indications for sutureless valve implantation;

IV . MATERIALS AND METHODS

The study included 64 patients indicated for cardiac surgery due to high-grade aortic stenosis, operated on at the University Hospital "St. Catherine", Sofia in the period from 04.2015 to 07.2022. The study is retrospective, and the included patients were selected according to previously set inclusion and exclusion criteria. All patients underwent cardiac surgery under ECC conditions, with moderate hypothermia with aortic cross clamping and cardioplegic arrest, achieved with blood cardioplegia, administered ante- and retrogradely according to the hospital protocol. The mean age of the patients was 70.18 ± 4.04, with a median of 69. Of these, 28 or 44% were women, and 36 (56%) were men. The distribution of men and women is clearly presented in diagram 1.

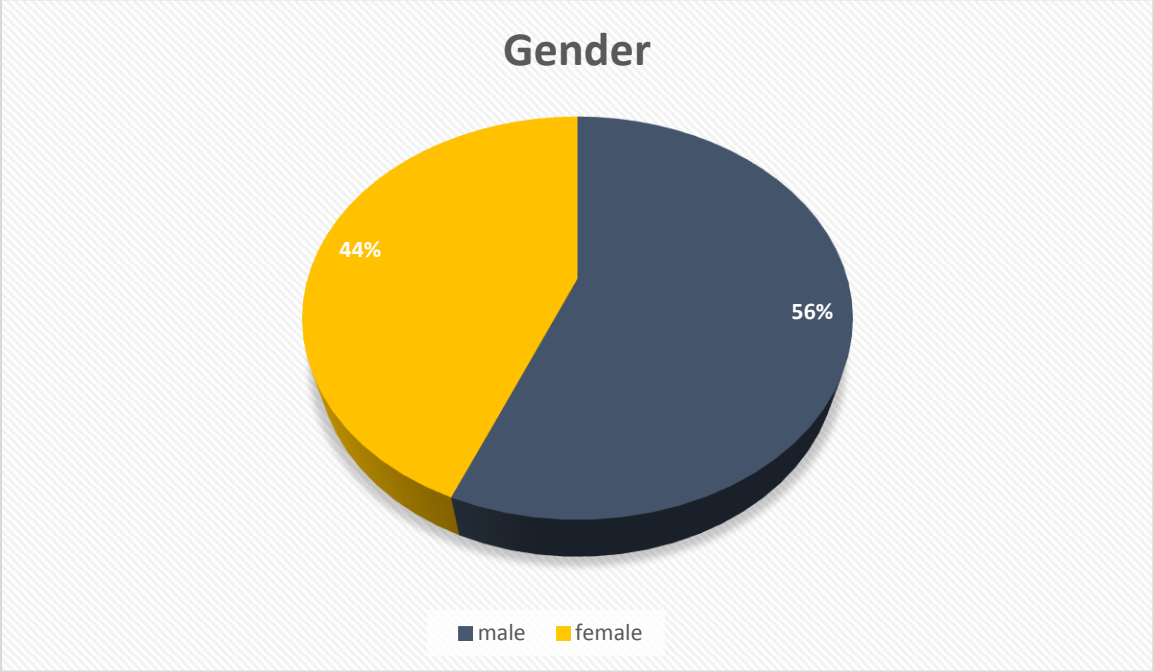


Diagram 1. Distribution of patients by gender

1. Inclusion and exclusion criteria

Patients were selected according to the following inclusion criteria:

1. Isolated symptomatic high-grade aortic stenosis - Mean gradient above 40 mmHg , representing the main indication for cardiac surgery;
2. Age over 65 years;
3. Calculated preoperative EuroScore II > 6% ;
4. Left ventricular ejection fraction above 35%;

The following exclusion criteria were met:

1. Patients with other concomitant cardiac pathology requiring combined surgical intervention - concomitant coronary artery disease, mitral valve disease, aneurysm and/or dissection of the ascending aorta, annuloaortic ectasia, etc.
2. Age under 65 years;
3. Calculated preoperative EuroScore II < 6% ;
4. Having had previous heart surgery;
5. Active endocarditis;
6. Left ventricular ejection fraction below 35%;

2. Study design

The study is retrospective, and for this purpose, ‘’St. Catherine” University Hospital provided a complete package of pre-, intra- and postoperative data for all patients included in the study. The study is structured as follows:

2.1 Patient selection

Patient selection was performed according to the specified inclusion and exclusion criteria described above.

2.2 Recording patient baseline characteristics

- **GENDER**
- **AGE**
- **RISK FACTORS**

- Diabetes mellitus and insulin therapy;
- Arterial hypertension and taking antihypertensive therapy;
- *Chronic obstructive pulmonary disease* , proven and documented, FEV_1 % below 50%;
- *Chronic renal failure* , proven and documented with serum creatinine levels above 353 and/or glomerular filtration rate below 60 ml/min/1.73 m²
- *Extracardiac arteriopathy - presence of claudication; carotid artery stenosis over 50%, peripheral vascular disease, amputation, etc.;*
- *Pulmonary arterial hypertension* with measured mean pulmonary artery pressure values above 30 mmHg;
- Limited mobility due to proven and documented concomitant musculoskeletal or neurological dysfunction;
- Obesity - over 2 degree;
- *Smoking* , history of at least 15 cigarettes per day;

- **FUNCTIONAL CLASS ,** reported according to the NYHA classification , patients with the following classes were registered:

- *Second class;*
- *Third grade;*
- *Fourth grade;*

- **LEFT VENTRICULAR EJECTION FRACTION;**

- **EuroScore;**

- **THICKNESS OF THE SEPTUM AND POSTERIOR WALL OF THE LEFT VENTRICLE,** measured in millimeters during transthoracic echocardiography performed immediately before surgery;

- **AORTIC VALVE GRADIENTS -** peak and mean systolic gradient, measured during transthoracic echocardiography performed immediately before surgery;

- **body surface area – BSA m2**

2.3 Operative techniques and operative approaches.

The main **surgical intervention** in this study was aortic valve replacement using two types of biological valve prostheses:

- Surgical sutureless bioprostheses;
- Standard biological prostheses on a stent;

Operational accesses:

- Complete median sternotomy;
- Upper J- sternotomy;

-Registering the duration of extracorporeal circulation;
-Register the duration of the cross clamping time;

2.4 Formation of main groups

The study compares the results of two main groups, and the principle for their structuring is explained in detail in the next chapter.

2.5. Comparison of baseline characteristics of patients from the main groups.

Comparison using statistical methods between the baseline characteristics of patients from both groups and determination of similarity.

2.6 Recording the results.

- intraoperative results

- Average ECC period
- Average cross clamping time

-early postoperative results - up to 24 hours after surgery

- monitoring and postoperative assessment of the function of the biological valve prosthesis from a control EchoCG;
- Postoperative bleeding - milliliters
- Duration of mechanical ventilation - hours;
- Need for catecholamine support;
- need for analgesia;
- need for a temporary pacemaker;

-recording the results for the entire hospital stay:

- monitoring and evaluation of the biological valve prosthesis by daily control transthoracic EchoCG;
- intensive care unit stay in days;
- total hospital stay in days;
- need for permanent pacemaker implantation;

- Adverse events in the postoperative period:

- Postoperative infusion with Catecholamines;
- Postoperative respiratory failure;

- Postoperative renal failure;
- Bleeding/pericardial drainage revisions;
- Neurological complications;
- Sepsis;
- Wound infections;

2.7.Follow up

Patients were followed up until the end of the first postoperative month, with control examinations conducted in the outpatient clinic of St. Catherine's University Hospital on the second and fourth weeks, and deaths were recorded.

2.8.Comparison of patient outcomes from the main groups.

The data recorded in the individual protocols are entered into MicroSoft Office Excel tables and compared with statistical methods appropriate for the type of variable being studied (quantitative or qualitative) as well as its distribution.

2.9 Analysis of results and drawing conclusions.

3. Diagnostic methods

3.1 Output characteristics

The baseline characteristics were registered according to the data in the available medical documentation from the archive of St. Catherine University Hospital, including epicrities of bedsores, test results, control examinations, surgical protocols, resuscitation and temperature lists, decurses and histories of the disease, which reflected the main surgical pathology, concomitant diseases and risk factors for each of the patients included in the study.

Nine preoperative risk factors were reported in the study. The sum of the number of risk factors is greater than the number of the study population because most of the patients had more than one risk factor. The largest proportion of patients is with arterial hypertension and obesity, followed by patients who smoke and those with diabetes

mellitus. Then come patients with extracardiac arteriopathy, which reflects the presence of stenosis > 50% of one or both carotid arteries, claudication or peripheral vascular disease. The proportion of patients with concomitant chronic obstructive pulmonary disease is large. Due to the requirement for selection of high-risk patients, the proportion of patients with preoperative renal failure also occupies a large share in the studied population. Patients with pulmonary hypertension and limited mobility are represented to a lesser extent.

Due to the requirement to select patients with high surgical risk, the proportion of patients with three or more risk factors exceeds 70%.

The data from the anamnesis and physical examination were recorded in detail in the study and according to them the initial selection of candidates for inclusion was carried out. Due to the extreme increase in risk, all patients with registered recent (up to three months before the surgical intervention) cerebral circulation disorders, acute myocardial ischemia, GIT bleeding, acute surgical abdomen, severe diarrhea, etc. were also excluded from the study.

3.2. Instrumental studies

3.2.1. Laboratory tests

All patients admitted to the cardiac surgery clinic at St. Catherine Hospital are examined according to a protocol with a laboratory set.

Hemostasis parameters were used to monitor the effect of preoperative anticoagulant therapy and determine the risk of increased postoperative bleeding. All patients screened for inclusion in the study had their anamnestic and laboratory data on antiplatelet and anticoagulant therapy recorded, which should be discontinued for a minimum of 5 days before surgery. If a failure to meet this requirement was found to increase the risk of increased postoperative bleeding, the candidate was also excluded. All patients with severe anemia, evidence of cytolysis, or acute organ ischemia were also excluded.

3.2.2. Electrocardiography

ECG was performed in all patients, both preoperatively and during the entire stay of the patients, as well as at all control examinations. If preoperative ECG data for acute

myocardial ischemia were established in the accompanying documentation, the patient was also excluded from the study population. The type of heart rhythm, the presence of newly appeared AV - block and the need for permanent pacemaker implantation were also monitored with ECG.

3.2.3 Echocardiography

Echocardiography (EchoCG) was performed on all patients included in the study at admission, during the hospitalization period, as well as during all established control examinations. Standard positions were used: parasternal position long and short axis, apical position in four-chamber, two-chamber and five-chamber views. Two-dimensional imaging (2D), M mode, color Doppler, pulse Doppler, continuous Doppler were applied . Ejection fraction was measured using the Simpson method . Current international recommendations for echocardiographic evaluation of patients with aortic stenosis were followed, peak, mean systolic gradient, peak transvalvular velocity (Vmax) and valve area were measured. Information on the severity of the defect and the state of cardiac function was obtained from parameters such as stroke volume, Doppler velocity index, degree of valve calcification, LV function, the presence or absence of LV hypertrophy, as well as the absence or presence of accompanying lesions of the other heart valves, and the diameters and impositions in the cardiac cavities in systole and diastole. Transesophageal echocardiography (TEE) in patients with AS should be considered when transthoracic echocardiography (TTE) is of suboptimal quality. TEE is very useful when a detailed assessment of the functional valve anatomy is needed. Intraoperative TEE is used to assess the immediate results of the operation and the presence of prosthesis dysfunction. Echocardiographic parameters included in this study are

- ejection fraction;
- thickness of septum and posterior wall of left ventricle;
- peak systolic and mean systolic gradient across the aortic valve;

The remaining data from the EchoCG were used to clarify the diagnosis, to monitor the outcome of the operation, as well as to register complications in the early postoperative period - prosthetic function - regurgitation or stenosis, LV dysfunction, pericardial tamponade.

3.2.4. Heart and lung radiography

A study that was performed as standard in all patients in the study both preoperatively and during the hospital stay. It provides information about the size of the cardiac shadow, dilation of the cardiac cavities, the presence of inflammatory changes and congestive areas of the lung parenchyma, the presence of pericardial and pleural effusions, etc. Specific data from the radiographic examination were not included in the study.

3.2.5. Cardiac catheterization and coronary angiography

All patients included in the study were over 65 years of age and were indicated for preoperative cardiac catheterization with coronary angiography. According to the results of coronary angiography, left ventriculography and aortography, candidates with significant coronary artery stenosis requiring aorto-coronary bypass were identified and they were excluded from the study. The characteristics of the selected candidates studied in this study did not include specific data from the invasive examination - gradients, pressures, ventriculography data.

3.2.6. Computed tomography and tomoangiography

In all patients indicated for surgical access through upper J -sternotomy, preoperative computed tomography (CT) was performed to assess the anatomical features - distance and position of the aorta relative to the sternum, level of the aortic valve relative to the ribs and intercostal spaces and condition of the peripheral arteries, as well as the degree of calcification of the valve and aortic root and their diameters. The results of the CT of the patients were not included in the study, but were used only to assess the possibility of performing SAVR with minimized access - upper partial J - sternotomy.

4. Drug therapy

Preoperative drug therapy of patients in the study population was determined by the degree of aortic stenosis, the presence and type of heart failure, as well as concomitant diseases. Statin intake and appropriate antihypertensive therapy were recorded in all patients participating in the study.

In the early postoperative period, all patients received intravenous heparin infusion, followed by acenocoumarol replacement after extubation. Anticoagulant therapy with acenocoumarol was continued until the third month after surgery, and in the absence of other indications for anticoagulation (atrial fibrillation, deep venous thrombosis) after a control examination in the hospital, it was discontinued and replaced with an antiplatelet agent.

5. Risk assessment

Risk assessment was performed on all patients in the study using the EuroScore-II system . EuroSCORE (European System for Cardiac Operative Risk Evaluation) is a system that allows the calculation of the risk of death after cardiac surgery. EuroSCORE II is presented at the EACTS Congress in Lisbon on October 3, 2011 , is an update of the EuroSCORE logistic model, using similar methodology.[120] It is recommended for risk assessment in cardiac surgery in adults. The model takes into account 18 parameters, including the patient's gender and age, comorbidities, cardiac status, and the indicated surgery, and calculates an expected operative mortality expressed as a percentage.[121] High-risk patients are those with a calculated EuroScore-II value of more than 6%.[120]

The system is free for online use at: http://www.euroscore.org/calc.html.

Patients included in the study had a preoperative risk calculated by EuroScore-II > 6%. The risk in the study population ranged from 6.16 to 13.2, and the mean value was even higher - 8.34 ± 1.29%. The median was close to the mean value and was 8.31.

6. Preoperative functional class

The functional class (FC) of the patients participating in the study was determined according to the NYHA classification. None of the patients had a preoperative functional class below second.

The largest proportion of patients with NYHA class III is 40 (62.5%) of the population. These are patients with a clinic of fatigue and shortness of breath during light physical exertion. In the second functional class there are 15 patients or 23.5%. Patients in IV FC are 14%, i.e. nearly 2/3 of all patients included in the study have pronounced manifestations of heart failure above the third FC.

7. Preoperative ejection fraction

In all patients in the study, the ejection fraction was monitored using the Simpson method. Preoperatively, the EF of the patients included in the study ranged from 35% to 65%. The mean EF of the entire group was 49.71 ± 6.94% with a median of 50.

8. Presence of left ventricular hypertrophy

8.1 Interventricular septum thickness

The assessment and severity of preoperative left ventricular hypertrophy is determined by the thickness of the interventricular septum and the posterior wall of the left ventricle. Their values are expressed, measured in millimeters after preoperative TTE.

The registered septal thickness measurements of the studied patients ranged from 12 mm to 18 mm. The mean septal thickness in the entire studied population was 14.34 ± 1.39 mm, median 14.

8.2 Back wall thickness

The thickness of the posterior wall of the left ventricle, measured in millimeters, was recorded in a similar manner. For those included in the study, it ranged from 11.5 to

15 mm. The mean thickness of the posterior wall of the left ventricle in the entire population was 13.24 ± 1.16, and the median was 13.

9. Preoperative aortic valve gradient

Peak and mean transvalvular gradients were measured by continuous wave Doppler TTE from the best available window (apical, suprasternal, right parasternal). Peak gradient was calculated as $4V^2$ max according to Bernoulli's equation. Mean gradient was calculated as the integral of the velocity curve during one systole. Peak gradients of native aortic valves in the entire population ranged from 63 to 110.3. The mean peak gradient was 83.65 ± 13.19 mmHg, with a median of 85.

The measured values of mean transvalvular gradient in mmHg were also recorded , which ranged from 31 to 69 mmHg . The mean value was 47.09 ± 7.59 mm Hg , with a median of 46.

10. Major surgical intervention

The main intervention in this study was surgical replacement of the aortic valve using biological prostheses. All patients were operated on in the cardiac surgery clinic of St. Ekaterina Hospital, Sofia. Two types of surgical approaches were used in the study - median longitudinal sternotomy or upper partial J - sternotomy. All cardiac surgeries were performed under ECC and aortic cross clamping with cardioplegic arrest, provided by infusion of cold blood cardioplegia antegrade and retrograde into the coronary sinus, according to the clinic's protocol. The surgeries were performed under moderate hypothermia. Two types of biological prostheses were used in the study - biological seamless valves and standard biological valve prostheses on a stent.

11. Average ECC period

The mean duration of the ECC period of the patients included in this study ranged from 41 to 102 min. The mean ECC period for all patients was 59.56 ± 13.27 min, with a median of 57.

12. Surgical technique

12.1 Surgical technique using surgical sutureless bioprostheses

The surgical technique was standardized in all patients in the study, in which the Perceval S (LivaNova PLC, London, UK) biological sutureless prosthesis was used. The Perceval sutureless valve includes a biological component of bovine pericardium, treated to reduce the risk of calcification, and a self-expanding and elastic nitinol stent, coated with a thin Carbofilm™ coating to improve biocompatibility. The stent consists of two rings, as well as nine connecting struts, designed to support the valve and keep it in place after implantation, without the need for permanent sutures. The design of the stent mimics the anatomy of the aorta and, as a result of its flexibility, follows the movements of the aorta, and relieves stress on the leaflets. (Figure 6.) [122]

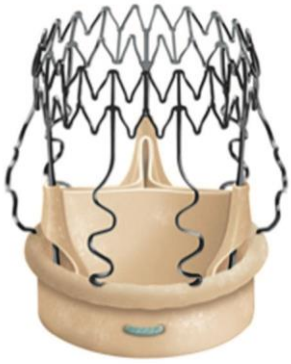


Figure 6. Perceval S bioprosthesis made of bovine pericardium and a nitinol stent skeleton.

The surgical approach in patients who received a sutureless valve in this study was an upper partial J- sternotomy to the 4th intercostal space on the right .

After performing the described Upper J-sternotomy, the patients are heparinized with a systemic dose of 450 UI/kg and after reaching a value of over 450 sec. for the activated clotting time, through oxygen sutures applied in the standard positions used in operations with complete sternotomy, the distal part of the ascending aorta and right atrium are cannulated , followed by initiation of cardiopulmonary bypass. A venting catheter is placed in the LV through the upper right pulmonary vein. And the aorta is clamped. Cardioplegic arrest is achieved by administering cold blood cardioplegic

solution ante- and retrogradely. Antegrade administration of cardioplegia is performed in the aortic root, and in patients with concomitant aortic insufficiency above the second degree, the cardioplegic solution is administered by selective cannulation of both coronary ostia. Retrograde delivery of cardioplegia was achieved by cannulation of the coronary sinus. After establishing cardiac arrest, a transverse/oblique aortotomy was performed approximately 1 to 2 cm above the sinotubular junction, higher than the traditional technique. The native valve was removed and the annulus was decalcified. After using special sizers, the appropriate size of the seamless valve prosthesis was selected. There are four sizes available and are arranged according to their diameter in the following order - S , M , L , XL . The valve sizes and their corresponding aortic annulus diameter (mm) and effective valve orifice (cm2) are presented in Table 3.[123]

Table 1: Perceval sizes and in vitro projected EOAs

Perceval sizes	S		M		L		XL	
Annulus diameter (mm)	19 (min)	21 (max)	21 (min)	23 (max)	23 (min)	25 (max)	25 (min)	27 (max)
In vitro EOAs (cm^2)	2.07	2.20	2.47	2.63	2.81	2.95	3.11	3.43

Table 3.

Implantation of this valve is considered possible when the size of the aortic annulus is between 19 mm and 27 mm and the ratio between the sinotubular diameter and that of the aortic annulus is no more than 1.3.

Three 3/0 (4/0) prolene guidewires are placed at the nadir of each leaflet. The appropriately sized prosthesis is crimped onto a holder. The three guidewires are passed through three loops factory-installed on the prosthesis and the prosthesis is positioned over the aortic annulus. The holder is removed and the prosthesis is opened using the release system. By inflating a balloon to 4 atm for 30 sec and irrigating the prosthesis with warm saline due to the thermospecific properties of the nitinol stent,

the prosthesis is further adhered to the annulus. The balloon is removed and the prosthesis is inspected for leaflet position and function. The guidewires are removed and the aortotomy is closed as usual. All patients undergo transesophageal echocardiography to assess proper prosthesis implantation and the presence of paraprosthetic insufficiency. In case of malposition, the prosthesis can be removed by rotating the “χ-maneuver”, crimped again and can be reimplanted again, however, each subsequent attempt increases the risk of damage to the crimping path.[124]

12.2 Surgical technique using biological prostheses on a stent.

All patients in the study who had their aortic valve replaced with a standard biological prosthesis received the Mitroflow prosthesis (Sorin Group USA Inc, Arvada, Colo) .

Figure 8. Mitroflow bioprosthesis

The Mitroflow valve is also constructed from bovine pericardium, which is preserved with glutaraldehyde and sutured to a polyester-coated polymer stent. A radiopaque, silicone ring is attached to the outer perimeter of the inlet side of the valve. The available sizes of this prosthesis are 19 mm, 21 mm, 23 mm, 25 mm, and 27 mm. The sizes of the prostheses and their corresponding aortic annulus diameter (mm) and effective valve orifice (cm2) are presented in Table 4.

VALVE SPECIFICATIONS

Mitroflow Aortic Pericardial Heart Valve – Model 12

	A*	B*	C*	D*	
Model	Inside Diameter (mm)	Outside Diameter (mm)	Overall Height (mm)	Sewing Ring Width (Relaxed) (mm)	** Effective Orifice Area (cm^2)
12A19	15.4	18.5	11	21	1.6
12A21	17.3	20.6	13	24	2.0
12A23	19.0	22.6	14	26	2.4
12A25	21.0	25.0	15	28	3.0
12A27	22.9	27.2	16	32	3.5

*Dimensions illustrated in Fig. 11 below

** In vitro data on file

Table 4. https://www.accessdata.fda.gov/cdrh_docs/pdf6/p060038c.pdf

The operative approach in these patients is a complete median sternotomy again with standard cannulation of the aorta and right atrium, left ventricular vent through the upper right pulmonary vein. Cardioplegic arrest is in a similar way, again with ante and retrograde administration of cold blood cardioplegic solution under moderate hypothermia. An oblique aortotomy and decalcification of the aortic annulus are performed. After measurement, the appropriate size valve is implanted using single U-shaped Cardioxyl 2/0 sutures with felt. Standard closure of the aortotomy follows.

13. Formation of main groups

All patients included in the study were operated on at the University Hospital "St. Catherine", Sofia in the period 04.2015 to 07.2022 and met the initially defined inclusion and exclusion criteria. All patients underwent aortic valve replacement due to the presence of isolated symptomatic high-grade AS. The results of two main groups of patients are compared. **Control group** - formed by 30 patients (46.9% of the study population), operated on in the above-mentioned period through a complete median sternotomy, in which the aortic valve was replaced with a standard biological prosthesis on a stent. **Study group** - formed by patients with minimally invasive access (J - sternotomy), in which a sutureless valve was implanted in place of the stenotic aortic valve. It is composed of 34 patients or 53.1% of the study population. The operations on patients from both groups were performed under the same conditions - extracorporeal circulation, moderate hypothermia, aortic clamping and cardioplegic arrest, performed by blood cardioplegia according to the hospital protocol, delivered

antegrade and retrograde through the coronary sinus. Hereinafter in the text these groups will also be referred to as: minimally invasive group and control group. The distribution of patients in both groups is presented in diagram 12.

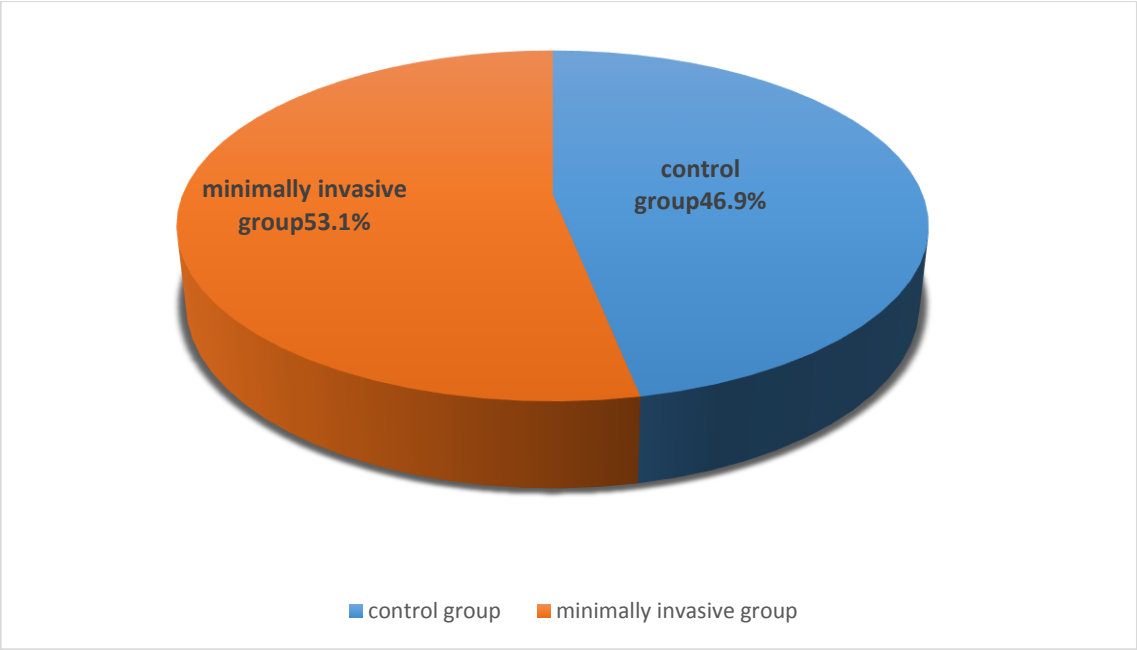


Diagram 12. Distribution of patients in the two groups

STATISTICAL METHODS

The data were entered and processed with the statistical packages IBM SPSS Statistics 25.0. and MedCalc Version 19.6.3., as well as Excel of Office 2021. A value of $p<0.05$ was accepted as the level of significance at which the null hypothesis is rejected.

The following statistical methods were used in the processing and comparison of characteristics and results:

1. Descriptive analysis – the frequency distribution of the considered features presented in tabular form. Quantitative variables are presented as mean value ± standard deviation or median value depending on the type of their distribution. Categorical variables are demonstrated in percentages (%).

2. Graphical analysis – for visualization of the obtained results.

3. Comparing relative shares.

4. Fisher's exact test, Fisher-Freeman-Halton exact test and χ2 test – for testing hypotheses about the existence of a relationship between categorical variables.

5. Nonparametric Kolmogorov-Smirnov and Shapiro-Wilk test – to check the distribution for normality.

6. Student's T-test - for testing hypotheses about the difference between the arithmetic means of two independent samples.

7. Nonparametric Mann-Whitney test – for testing hypotheses about the difference between two independent samples.

8. Wilcoxon nonparametric test – for testing hypotheses about the difference between two dependent samples.

9. Friedman's nonparametric test – for testing hypotheses about differences between several dependent samples.

14. Comparison of baseline characteristics of the main groups

The comparison of the baseline characteristics of the two main groups was performed to establish the degree of similarity between their shares in order to establish comparability of the final results, and to maximally limit the influence of all other factors, except the type of surgical access and the type of prosthesis used.

14.1 Comparison by gender

The comparison of patients by gender between groups and P values are presented in Figure 13.

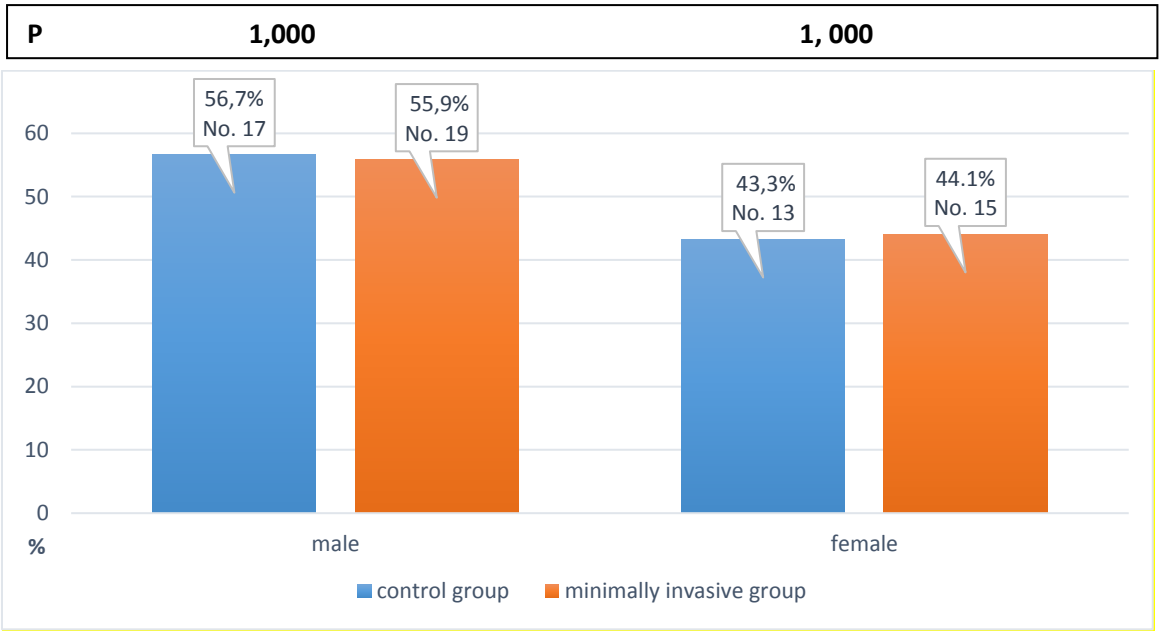


Chart 13. Comparison of patients by gender

Given the P values, the two groups do not differ statistically significantly according to the distribution of the groups by gender.

14.2 Comparison by average age

The comparison of the mean age of the patients is presented in diagram 14. The Shapiro-Wilk test showed that the age did not have a normal distribution in both groups. For comparison, a non-parametric two-sample Kolmogorov-Smirnov test was used, in which the medians were compared. The test did not show a significant difference between the groups in terms of age, **P= 0.417** . Therefore, the groups do not differ in terms of the age of the patients included in them and are comparable.

	Control group	Minimally invasive group
	N=30	N= 34
	Mean Age 69,73 ± 4,24	Mean age 70,59 ± 4,24
	(from 65 to 78)	(from 65 to 79)
	median 68	Median 69

Chart 14. Comparison between groups by average age.

14.3 Comparison of groups according to the distribution of risk factors

The comparison between groups according to the distribution of patients' risk factors is presented in diagram 15.

P	1,000	0,801	0,683	0,536	0,816	0,901	0,647	0,847	0,827

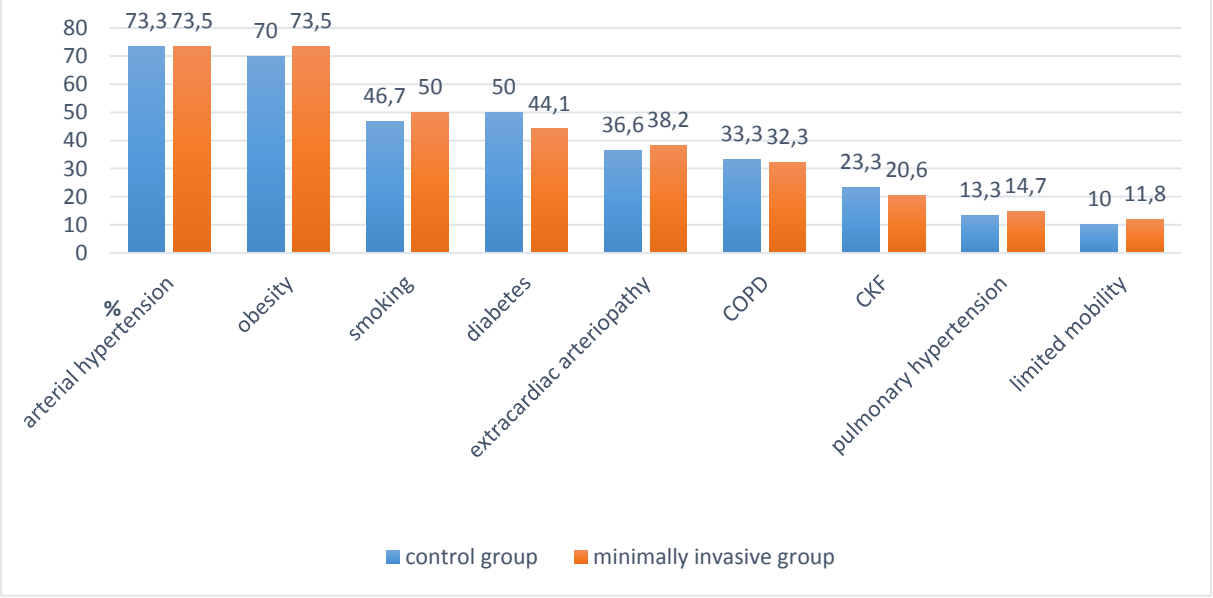


Diagram 15. Comparison of groups according to the distribution of risk factors.

The distribution of risk factors among patients in the groups is presented in percentages (%) in diagram 15. A statistically significant difference is considered to be P < 0.05. It is clearly seen from the diagram that no P value is significant and therefore the two main groups do not differ from each other in the percentage distribution of the registered risk factors. The comparison between patients in the groups and according to the average number of risk factors per patient is demonstrated in table 5. Despite the higher percentage in the minimally invasive group compared to the control group, with two, three and four risk factors per patient, the P values define these differences as insignificant and the expected results of the two groups will be comparable.

Distribution by average number of risk factors per patient

Number of risk factors	Control group Number/percentage	Minimally invasive group Number/percentage	P
0	0 / 0%	0 / 0%	NS
1	1 / 3.3%	1 / 2.9%	
2	11 / 36.7%	13 / 38.2%	
3	16 / 53.3%	21 / 61.8%	
4	5 / 16.7%	7 / 20.6%	
5	2 / 6.7%	2 / 5.9%	

Table 5 .

14.4 Comparison of groups according to preoperative functional class

The comparison between patients from the two main groups in terms of preoperative functional class according to the NYH A classification is demonstrated in diagram 16.

P	**0,376**	**0,719**	**0,847**

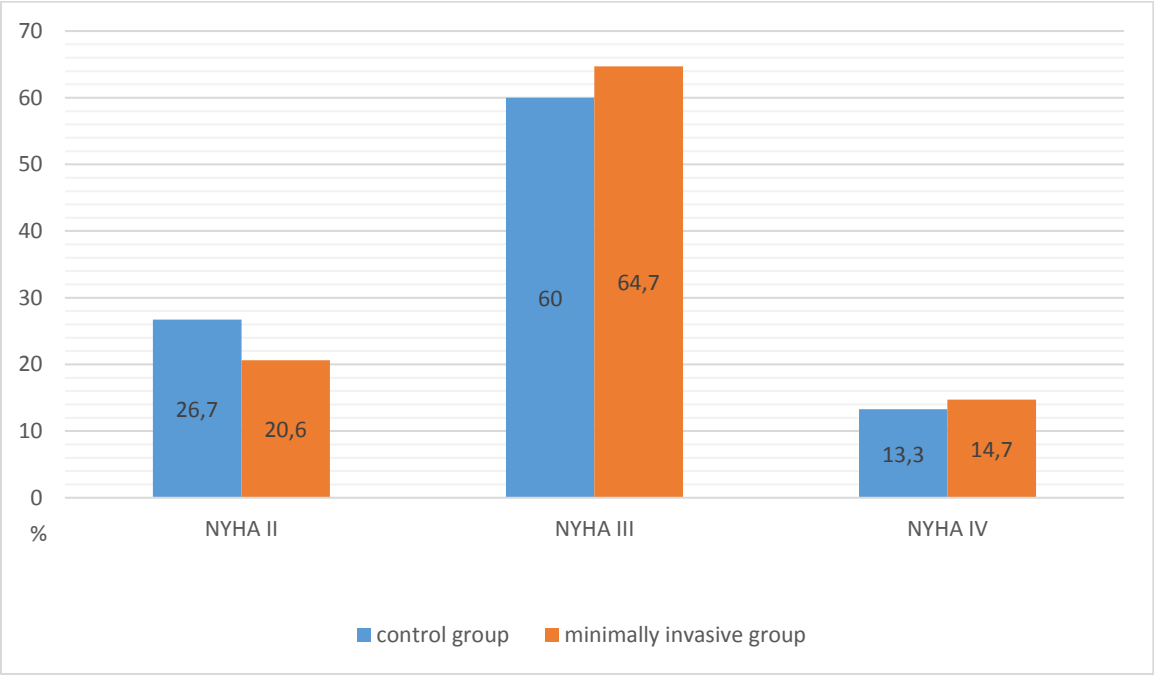
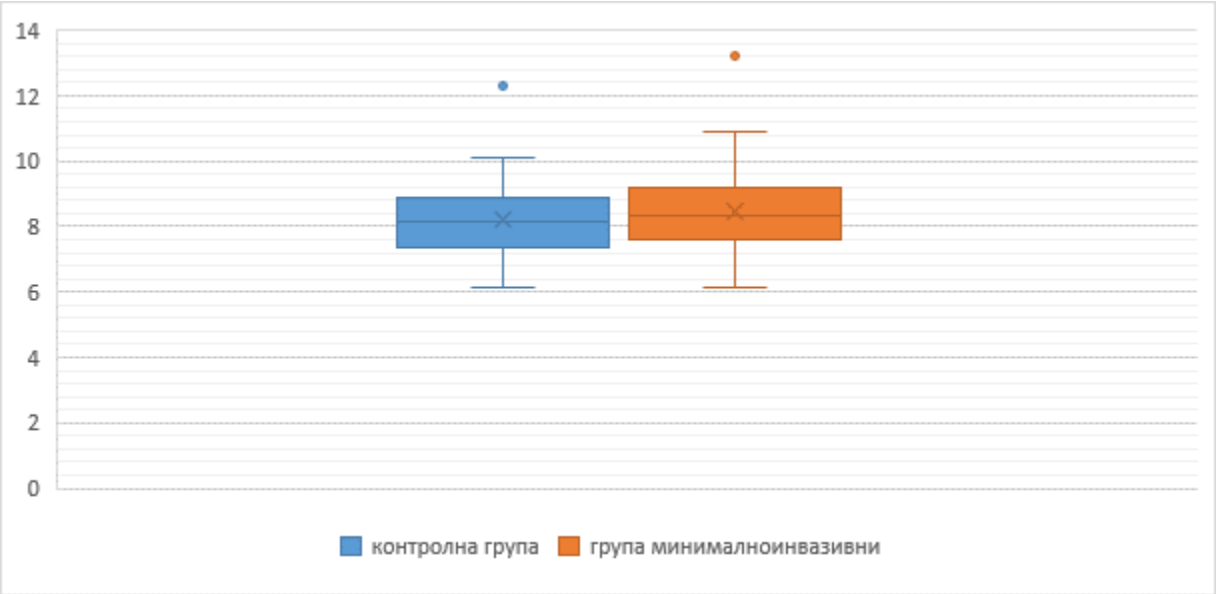


Diagram 16. Comparison of groups according to FC.

A slightly higher percentage of patients in the second FC than the control group and a slightly higher percentage of patients in the third and fourth FC in the group with minimally invasive access are noted. Statistical processing did not show significance of these differences. Therefore, the groups do not differ in the distribution of patients according to preoperative FC.

14.5 Comparison between groups according to preoperative risk calculated using the EuroScore system.

The distribution of patients from the two main groups according to the EuroScore indicator is presented graphically in diagram 17. The Shapiro-Wilk test for this parameter also shows that there is no normal distribution for both groups. The comparison requires the use of the non-parametric two-sample Kolmogorov-Smirnov test, in which we again compare the medians.



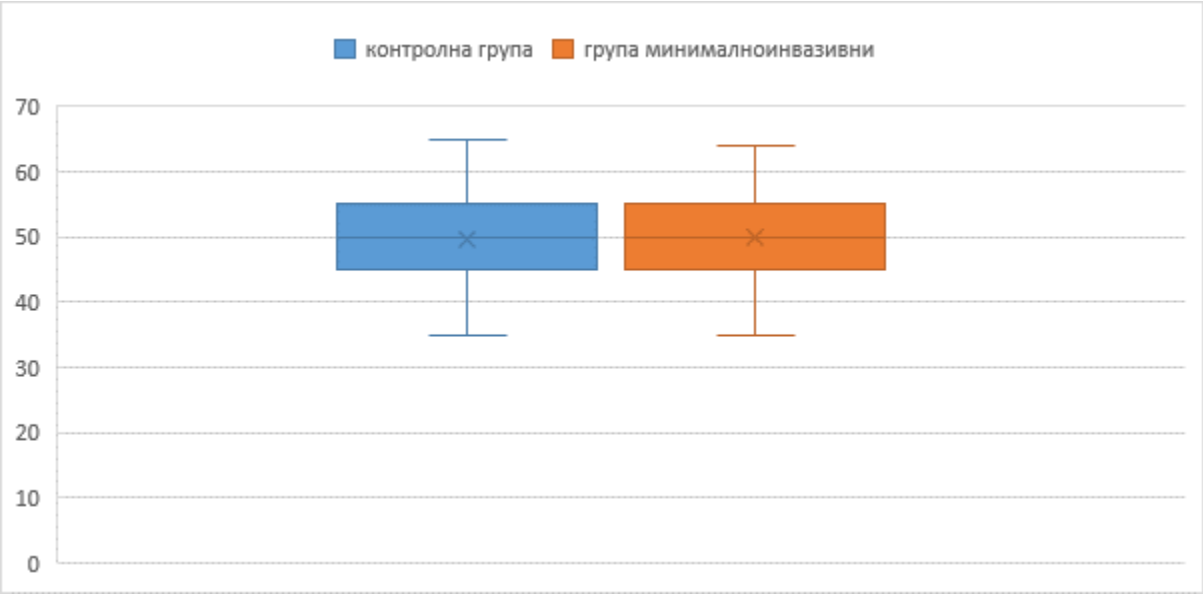
Control group	Minimally invasive group
N=30	N= 34
Mean EuroScore 8,22 ± 1,18	Mean EuroScore 8,45 ± 1,39
Median 8,18	Median 8,35

Diagram 17. Comparison of groups according to the calculated EuroScore.

The calculated value of **P = 0.097** indicates that there is no statistically significant difference between the two main groups on this indicator.

14.6 Comparison of groups according to preoperative ejection fraction

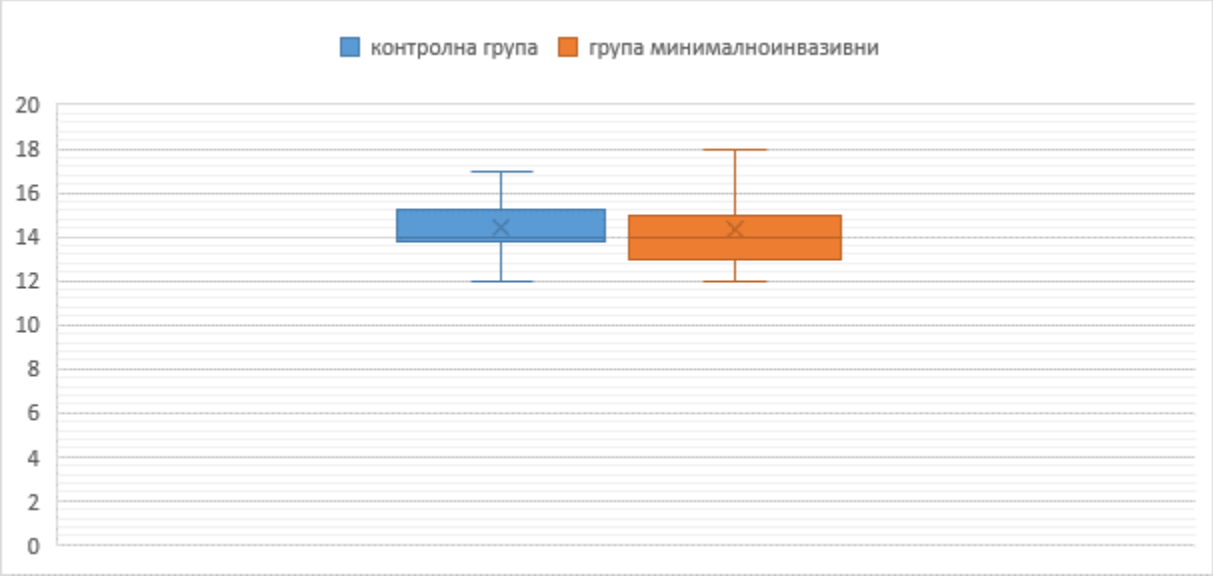
The comparison between the two main groups according to the preoperative left ventricular ejection fraction is presented in diagram 18. Due to the lack of normal distribution of this quantitative indicator in the two groups, the Kolmogorov-Smirnov test was again used and their medians were compared. No statistically significant difference was reported, **P= 0.924** . The groups did not differ statistically according to the values of the preoperative ejection fraction and were comparable according to this indicator.



Control group	Minimally invasive group
N=30	N= 34
Mean EF 49,63 ± 7,12%	Mean EF 49,91 ± 7,09%
Median 50	Median 50

Diagram 18. Comparison of groups according to average EF.

14.7 Comparison of groups according to preoperatively measured septal and posterior wall thickness



Control group	Minimally invasive group
N=30	N= 34
Mean interventricular septum 14,4 ± 1,33 мм.	Mean interventricular septum 14,26 ± 1,46 мм
Median 14	Median 14

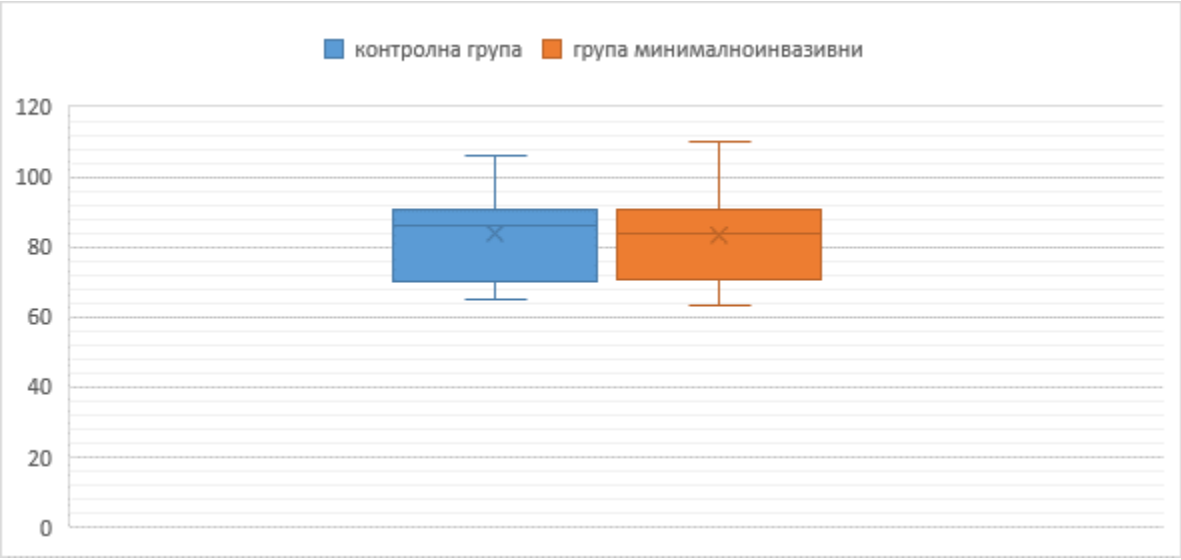
Diagram 19. Comparison of groups according to preoperative septal thickness.

The distribution of patients from the two main groups according to septal thickness is presented in diagram 19.The medians of the individual groups are the same and their comparison shows no statistically significant difference, **P= 0.504.**

The values of the thickness of the posterior wall of the left ventricle between the two groups were also compared (13.26 ± 1.19 mm, median 13 in the control group and 13.23±1.15mm, median 13.5 in the minimally invasive group) . The medians of the two groups have approximate parameters and the Kolmogorov-Smirnov test shows no statistically significant difference in these indicators **, P= 0.649** .

14.8 Comparison of groups according to preoperatively measured aortic valve gradients

It is important to compare the groups according to the values of peak and mean systolic gradients of the aortic valve. The comparison between the main groups according to the mean value of peak systolic gradient is demonstrated in diagram 21. The mean values of PSG in both groups are close to each other. Since the Shapiro-Wilk test shows a lack of normal distribution, their medians were compared again using the Kolmogorov-Smirnov test. The medians are different in values, but close to each other and their comparison did not report a statistically significant difference, **P= 0.321** .



Control group	Minimally invasive group
N=30	N= 34
Mean PSG 83,97 ± 12,9 ммHg	Mean PSG 83,38 ± 13,6 ммHg
Median 86	Median 83,5

Diagram 21. Comparison of groups according to PSG values.

The comparison between the groups regarding the values of the mean systolic gradient of the aortic valve demonstrated that the medians were very close to each other and the Kolmogorov-Smirnov test showed no statistically significant difference between the groups regarding this quantitative indicator, **P= 0.807** .

14.9 Comparison of groups according to measured body surface area depending on gender

The body surface area of all patients was calculated based on their respective kilograms and height in centimeters. The included patients were divided into subgroups according to their gender. Table 6.

POL	BSA (m^2) **Control group**	BSA (m2) **Minimally invasive group**
MEN	1.98 ± 2.03	1.92 ± 1.65
WOMEN	1.82 ± 1.45	1.79 ± 1.13

Table 6. Body surface area of patients

The comparison of the mean values of BSA ± standard deviation between the respective subgroups did not show a significant difference – for men **P= 0.745,** and for the included females - **P= 0.579.**

15. Summary and analysis of the comparison of baseline characteristics between the two main groups.

All comparisons between baseline characteristics - demographics, and risk factors of the patients included in the study did not show any statistically significant differences. This conclusion allows us to assume with a high degree of certainty that the comparison of results between the two main groups is possible and the conclusions based on these comparisons will be valid.

V. RESULTS

The results were recorded as described in the study design. No patients dropped out during the follow-up and all selected endpoints were recorded. The comparative statistical analysis of the data from the two main groups included intraoperative results, early postoperative results – up to 24 hours after the surgical intervention, results of the entire hospital stay and data from the control examinations at the second and fourth weeks after discharge. An analysis of one-year mortality was also performed.

1. Intraoperative data analysis and comparison between groups

1.1 Determination of intraoperative characteristics

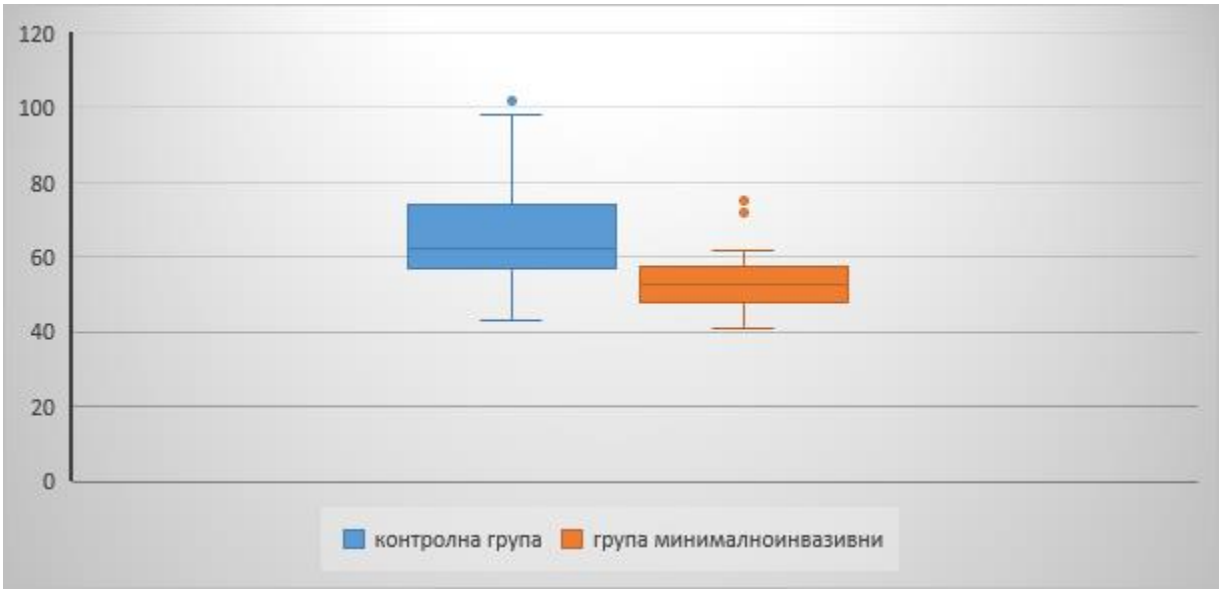
The characteristics on which the conclusions of this study will be based were determined when choosing the study design. The intraoperative data of both groups include two main intraoperative characteristics.

-Registering the duration of extracorporeal circulation;

-Register the duration of the cross clamping time;

1.2 Comparison between groups according to the duration of ECC

The distribution of patients from the two main groups according to the duration of ECC is presented in diagram 23.



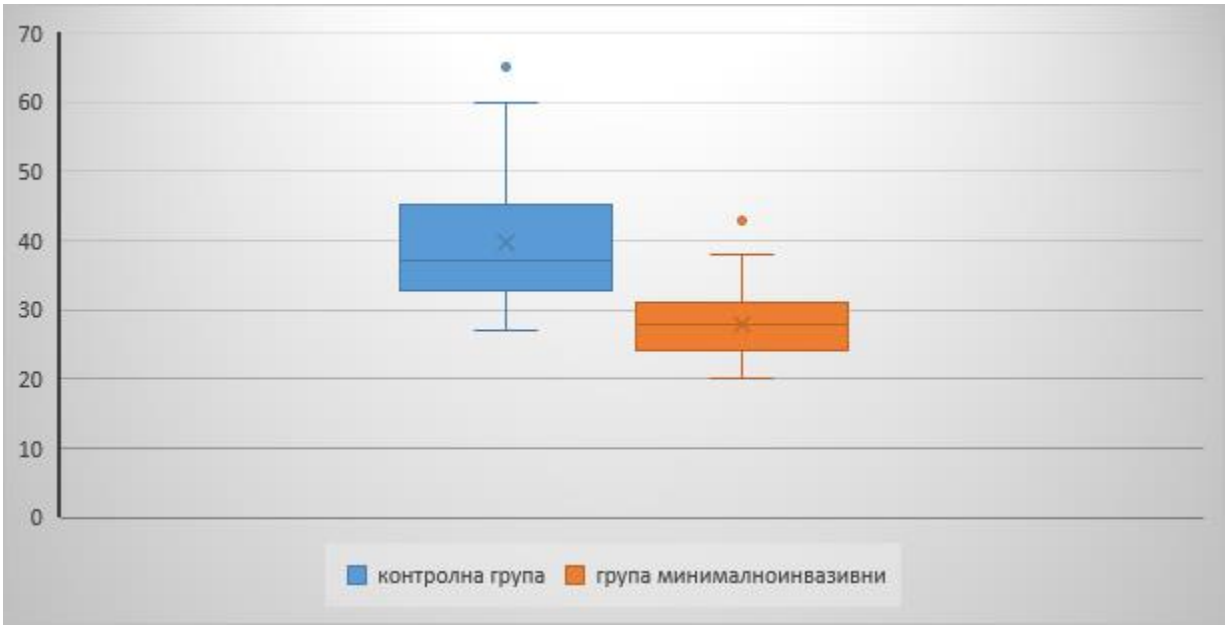
Control group	Minimally invasive group
N=30	N= 34
Mean ECC 66,57 ± 14,9 min	Mean ECC 53,38 ± 7,49 min.
Median 62,5	Median 52,5

Diagram 23. Distribution of patients from the two main groups according to the duration of ECC

The control group had higher ECC duration and a significantly wider range of standard deviation. When comparing the medians of the two groups with the two-sample test, it was found that there was a statistically significant difference between the two groups in terms of ECC duration, **P= 0.00001, which was shorter in the minimally invasive group.**

1.3 Comparison between groups according to the duration of clamping time

Similarly, a statistical comparison of the mean cross clamping time was performed. In the control group, the mean cross clamping time ± standard deviation was **39.6 ± 9.54 min, with a median of 37.** In the group with a minimally invasive approach and sutureless biological valves used, the same value was : **27.8 ± 5.24min., with a median of 28.** Statistical comparisons between these two results presented a value of **P < 0.00001,** i.e. the presence of a statistically significant difference in favor of the minimally invasive group.



Control group	Minimally invasive group
N=30	N= 34
Mean cross clamp time 39,6 ± 9,54 мин.	Mean cross clamp time 27,8 ± 5,24мин.
Median 37	Median 28

Diagram 24. Distribution of the two groups by average cross clamping time

1.4 Summary of the comparison of the two main groups according to the recorded intraoperative characteristics.

After the overall statistical processing of the data regarding the two main registered intraoperative characteristics - mean ECC period and mean duration of cross clamping time, a statistically significant difference was found between the two groups for both indicators, with the obtained values of **P < 0.05.** The relatively shorter ECC period and shortened clamping time are in favor of the group with minimally invasive access and the use of sutureless biological valves.

2. Comparison of early postoperative outcomes and complications up to the twenty-fourth hour after surgery

2.1 Echocardiography monitoring and assessment of the function of the biological valve prosthesis.

Conducting a control EchoCG is a mandatory procedure for evaluating the implanted biological valve prosthesis. The evaluation of patients from the group with a sutureless biological valve is routine practice and is performed intraoperatively, by TEE, immediately after leaving the ECC. When implanting a biological prosthesis on a stent, TEE is not a routine procedure, and the EchoCG assessment of the functioning of the prosthesis is performed with a control TTE performed in the intensive care unit, immediately after the patient is removed from the operating room. Table 8 shows the distribution by size of the implanted biological valve prostheses for all patients participating in the study. It is clearly demonstrated that in the control group the largest proportion of valves with size No. 21 – 40% and No. 23 – 30% in total 70%, and for the group with minimally invasive access the largest proportion of patients with size M – 35.3%, corresponding to a 21-23 mm effective opening, followed by size L – 32.3%, corresponding to a 25 mm effective opening, the proportion of patients in whom size XL was used is significantly higher – 20%

Type of prosthesis		**Control group**	**Minimally invasive group**
Biological prosthesis on a stent	No. 19	2 (6.7%)	-
	No. 21	12 (40%)	-
	No. 23	9 (30%)	-
	No. 25	6 (20%)	-
	No. 27	1 (3.3%)	-
Sutureless biological prosthesis/annulus size	S 19 - 21 mm	-	4 (11.8%)
	M21 - 23mm	-	12 (35.3%)
	L 23- 25 mm	-	11 (32.3%)
	XL 25 – 27 mm	-	7 (20.6%)

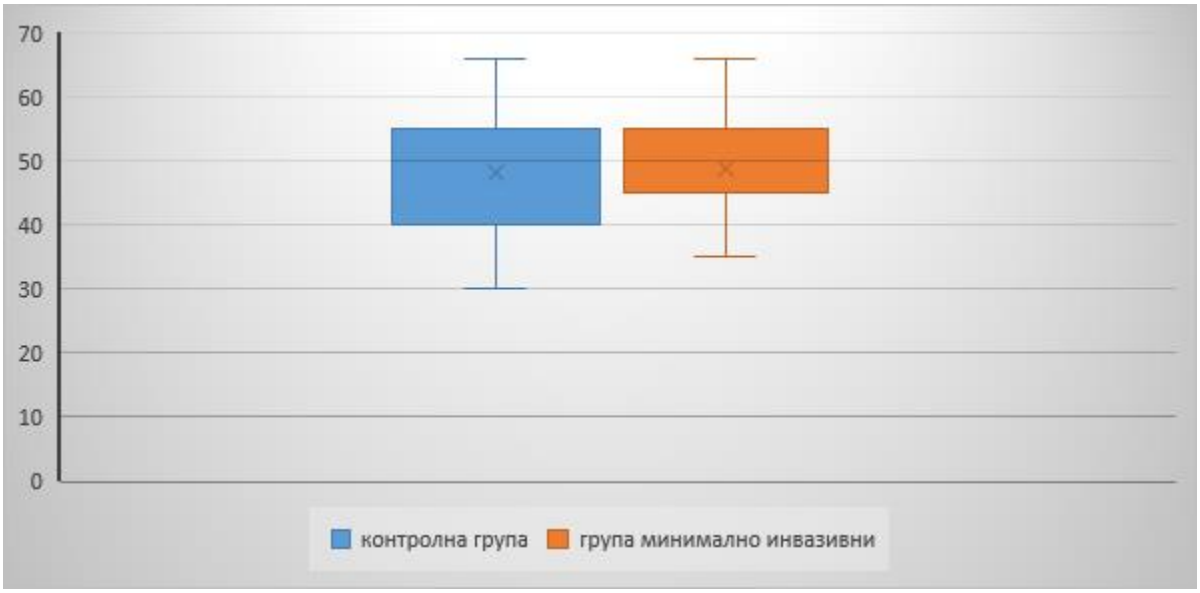
Table 8. Size distribution of implanted biological valve prostheses

This distribution shows that patients with a prosthesis size greater than 23 in the minimally invasive approach group were nearly 53%, in contrast to the control group, where this proportion was only 23%. This result may be associated with more optimal hemodynamics for a larger proportion of patients with a sutureless valve implanted.

2.1.1 Postoperative assessment of LV ejection fraction and comparison between groups

During the control echocardiograms during the first 24 hours, all participants in the study were assessed for - LV ejection fraction, valve function - presence and degree of intra or paraprosthetic insufficiency, peak systolic and mean systolic gradients across the prosthesis.

Diagram 25 presents the distribution of patients from both groups according to the mean value of the postoperative ejection fraction up to the 24th postoperative hour.



Control group	Minimally invasive group
N=30	N= 34
Mean postop EF 48,06 ± 9,69 %	Mean postop EF 48,76 ± 6,45%
Median 50	Median 50

Diagram 25. Postoperative ejection fraction

Despite the registered wider range of values of the postoperative ejection fraction of the patients from the control group, when comparing the medians of the participants from the two groups, no significant difference was found - **P = 0.848.**

2.1.2 Postoperative aortic regurgitation and comparison between groups

In the control group, one patient with up to the first degree of central aortic insufficiency was registered - 3.33%, in the minimally invasive group there was also

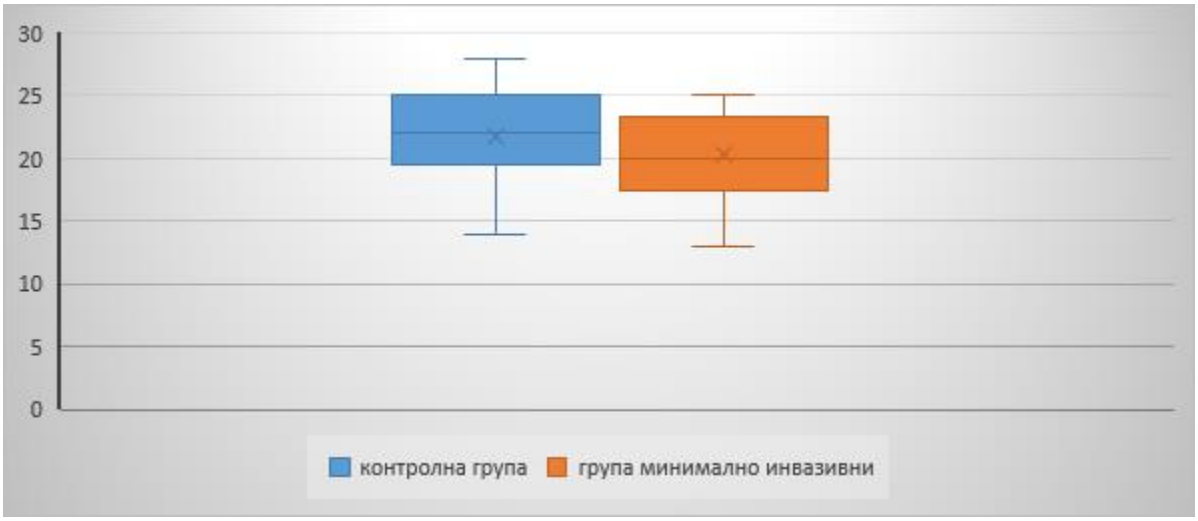
only one patient - 2.94% with a similar finding. Their comparison did not show a statistically significant difference, **P = 1.000** . In both groups, no patients with a higher degree of central intraprosthetic insufficiency were registered.

With paraprosthetic aortic insufficiency of up to the first degree, 1 patient was registered in the control group - 3.33%, while in the group with seamless bioprostheses used, two - 5.88%. Despite the higher relative proportion in the minimally invasive group, the difference was not found to be statistically significant - P = 0.479. Patients with paraprosthetic insufficiency higher than the first degree were not registered in either group.

2.1.3 Gradients across valve prostheses and comparison between groups.

The detection of high peak and mean systolic gradients is an important predictor of the presence of patient-prosthesis mismatch, which is an important problem in all operated patients and largely determines their long-term prognosis. These facts have made the selection of an appropriate size valve prosthesis corresponding to the patient's body surface area and the prevention of patient-prosthesis mismatch a primary issue of pre- and intraoperative evaluation.

According to the presented distribution, the recorded values of the peak systolic gradient of the two groups do not differ significantly - **P= 0.118** .



Control group	Minimally invasive group
N=30	N= 34
Mean PSG 21,7 + - 3,98 mmHg	Mean PSG20,24 + - 3,64 mmHg
Median 22	Median 20

Diagram 28. Peak systolic gradient

Comparison of medians of mean peak gradient also showed no difference between groups, **P = 0.577** .

The risk of patient-prosthesis mismatch was increased in cases with preoperatively determined small aortic annulus diameter. To further assess the role of prosthesis selection in these cases, an additional subanalysis of measured gradients was performed only for patients with anatomically small aortic annulus, established preoperatively, in which prostheses with a size ≤ 21 mm were implanted. In the patients from the control group – two or 6.7%, prosthesis number 19 was placed, and 12 patients or 40% of the group number 21. In the group with minimally invasive access, 4 of the patients (11.82%) were implanted with an S size sutureless valve. Another 12 patients or 35.3% were implanted with an M size prosthesis. Statistical analysis did not show a significant difference between the groups in terms of the proportion of patients with a small aortic annulus.

The measured gradients across the prostheses and the indexed values of the effective prosthetic area were the indicators we used to assess the adequacy of hemodynamics when implanting each of the two types of prostheses in the subgroup with an anatomically small aortic annulus.

For statistical comparisons, we used the EchoCG-determined values of EOA index value, as well as the mean value of the peak systolic gradient for the subgroup. The results obtained are presented in Table 9. Postoperatively measured peak transvalvular gradient was lower in the sutureless valve group (15 ± 7 mm Hg vs. 20 ± 11 mm Hg; p = 0.02). Effective valve area and its indexed mean were significantly higher again in the minimally invasive group (1.12 ± 0.2 cm2/m2 vs. 0.82 ± 0.1 cm2/m2; p = 0.002).

parameter	Control group sample N =14 (46.7 %)	A sample of a group of minimally invasive N =16 (47%)	P-value
Prosthesis size mm	19mm 21 mm Avg.20.7	S (19-21 mm) M (21-23 mm) Avg. 21.5	**P<0.05**
Avg. EOA (cm ^{2})	**1.72 ± 0.85**	**2.48 ± 0.56**	
Avg. iEOA (cm ^{2} /m ^{2})	**0.82 ± 0.1**	**1.12 ± 0.2**	
Avg. Peak transvalvular gradient (mmHg)	**20 ± 11 mmHg**	**15 ± 7 mmHg**	

Table 9. Hemodynamic parameters of prostheses in the subgroup with small aortic annulus

The results obtained in this subgroup comparison confirm the claim that the use of sutureless biological valves in patients with small aortic annulus reduces the risk of developing patient-prosthesis mismatch and is superior to conventional bioprostheses.

2.2 Postoperative blood loss

Postoperative blood loss was one of the endpoints according to the initial study design to assess the impact of access on the amount of postoperative blood loss. The mean blood loss for the control group was **412.3 ± 113 ml, with a median of 410** . for patients in the minimally invasive group, the value of this indicator was **205.3 ± 60.7 ml, with a median of 210.** The lower blood loss recorded was the basis for the additionally recorded reduced need for blood transfusion in the minimally invasive group (1.4 vs. 2.6 units, P < 0.001). In both groups, there were no patients recorded who underwent revision due to significant postoperative bleeding.

2.3 Duration of mechanical ventilation

The duration of postoperative mechanical ventilation depends on multiple factors - cardiovascular, respiratory, neurological, metabolic, the type of surgical intervention, and the patient's condition after surgery.

The recorded duration of mechanical ventilation is presented in hours and covers the period from the moment the patient was removed from the operating room to the intensive care unit until the time of extubation. The number of patients and their distribution according to the postoperative duration of mechanical ventilation is presented in diagram 29.

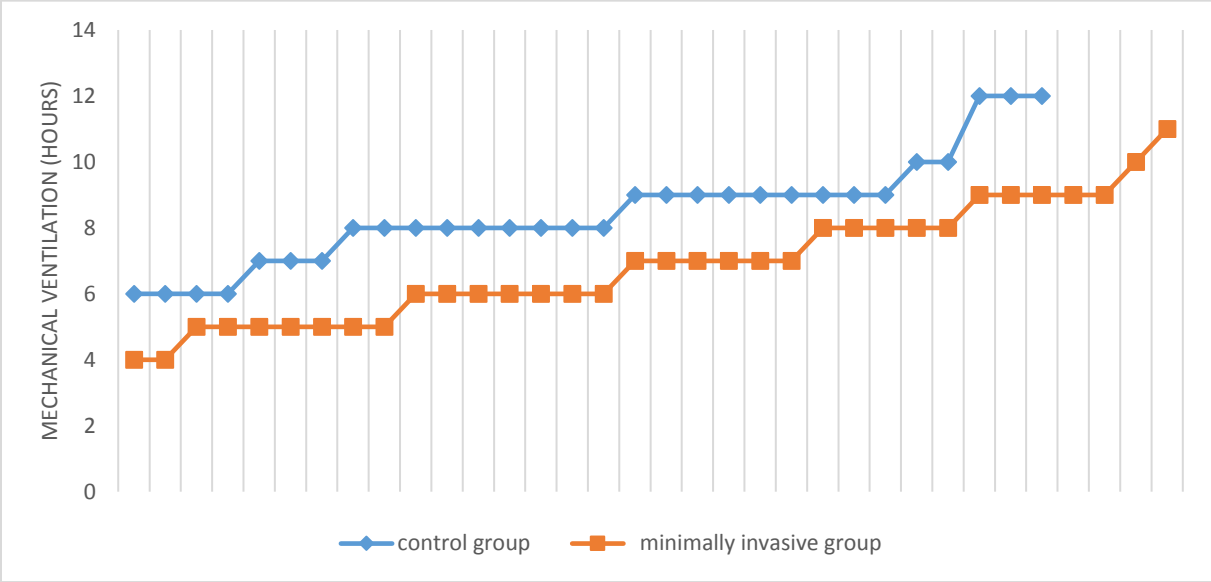


Diagram 29. Mechanical ventilation

The mean duration of intubation for patients in the control group was **8.47 ± 1.63 h, with a median of 8** , and for the group with minimally invasive access **6.85 ± 1.76 h, with a median of 7.** The Mann-Whitney test showed a statistically significant difference between the groups, **P = 0.0006, which favored the minimally invasive patients** .

2.4 Need for catecholamine support

Due to the presence of severe left ventricular hypertrophy and the risk of subendocardial ischemia, the use of catecholamines in patients with aortic stenosis should be minimized. However, a large percentage of patients in both groups of this study received a low-dose dopamine infusion of 3 μg /kg/min . The recorded data show that 12 patients or 40% of the control group required dopamine infusion during the first 24 hours of surgery. In the Perceval group , 14 patients or 41.1% received

catecholamine support. The percentages of the two main groups are similar and the difference was not considered significant **, P=0.912** .

2.5 Need for additional analgesia

Postoperative pain after standard sternotomy in cardiac surgery is an important factor, the adequate management of which reduces the risk of developing adverse hemodynamic and pulmonary complications. Proper management of postoperative pain allows early extubation, mobilization and shortens the stay in the intensive care unit. Pharmacological therapy includes parenteral opioids or nonsteroidal anti-inflammatory drugs. The comparison between the two groups was performed according to the need for analgesia up to the 24th postoperative hour. Data were used on the type and quantity of the administered medications according to the resuscitation lists of the patients participating in the study - Fentanyl, Paracetamol, Morphine, Ketoprofen 100mg/2 ml. The results of the comparative analysis show that all patients from both groups needed infusions of at least two ampoules of the listed medications during the first 24 hours - together or in combination.

A third or more doses were administered to 17 patients or 56.7% of the total median sternotomy group, and to 16 patients or 47% of the J-sternotomy group. Despite the different percentage of patients in the two groups, the reported difference was not found to be significant, **P=0.375.**

2.6 Postoperative heart rate and need for a temporary pacemaker

The registered heart rhythm variants of the studied population from the early postoperative period are four - SR, AF, AV-block, SA-block. In addition to these four variants, which are present in over 90% of the patients' ECG recordings, two additional heart rhythm states are also recorded, which are observed episodically in some of the patients, these are - episodes of AF and episodes of using a temporary pacemaker due to bradycardia.

An episode of AF in this study is defined as a recorded episode of AF lasting less than 24 hours, followed by restoration of normal HR.

Episodes of temporary pacemaker use are understood as the registration of reversible postoperative bradycardia, with a frequency below 60/min and a duration of less than 24 hours. The reasons for this need are temporary AV block, SA block or sinus bradycardia. In patients with an episode duration of more than 24 hours and reliable ECG criteria for the presence of a conduction block, a permanent pacemaker is implanted. This part of the population is the subject of a separate analysis and is discussed in detail in the upcoming chapter.

In the early postoperative period, the postoperative rhythm in 66.7% (20 patients) of the control group was sinus, in the patients from the group with Perceval prostheses this was reported in 47% or 16 patients. With AV-block or SA block there were 6 patients (20%) from the control group. And in the group with sutureless valves this percentage was – 35.3% or 12 patients. An episode of AF was reported in 13.3% of the control patients, and in the group with minimally invasive access these patients were 17.7%. Despite the known difference in this percentage distribution, the statistical analysis did not report any significance in terms of the proportion of sinus rhythm (P = 0.073) and AF (P = 0.465). Regarding the registered episodes of AV block, a clearly expressed significant difference was found with a value of **P = 0.0431** , which is in favor of patients with conventional prostheses.

2.7 Summary of immediate postoperative results and comparison between groups

Table 10 presents the summary results of patients from both groups, registered and followed up during the first 24 hours of the surgical intervention. The analyzed indicators, registered as an immediate postoperative result (up to 24 hours after leaving the operating room), show the presence of significant differences between the groups in terms of the measured transvalvular gradients, the effective opening of the valve prostheses, especially in patients with a small aortic annulus, which are in favor of the group of minimally invasive patients. The differences in the need for hemotransfusion and its amount, as well as the duration of mechanical ventilation, which are in favor of patients with partial sternotomy, were also reported as significant. The differences in the presence of para and intraprosthetic insufficiency were not reported as significant,

although it was higher in patients in the group with seamless biological valves (5.88%). No significant differences were observed when comparing the needs for catecholamine support and analgesia during the first 24 hours. Patients with restored sinus rhythm prevailed in the control group, while the percentage of patients with AV block was higher in the Perceval group (35.3%), and this difference was statistically significant.

Features	Control group	Minimally invasive group	P
EF (%)	**48.06 ± 9.69**	**48.76 ± 6.45**	**0.848**
Intraprosthetic insufficiency (≤grade 1)	**1 (3.33%)**	**1 (2.94%)**	**1,000**
Intraprosthetic insufficiency (≤grade 2)	**0(0%)**	**0(0%)**	
Paraprosthetic insufficiency (≤grade 1)	**1 (3.33%)**	**2 (5.88%)**	**0.479**
Paraprosthetic insufficiency (>2nd degree)	**0(0%)**	**0(0%)**	
PSG (mmHg)	**21.7 ± 3.98**	**20.24 ± 3.64**	**0.118.**
MSG (mm Hg)	**11.26 ± 2.55**	**10.93 ± 2.54**	**0.577**
Prosthesis size mm	19mm 21 mm	S (19-21 mm) M (21-23 mm)	**P<0.05**
EOA (cm^2)	**1.72 ± 0.85**	**2.48 ± 0.56**	
iEOA (cm^2 / m^2)	**0.82 ± 0.1**	**1.12 ± 0.2**	
Peak transvalvular gradient (mmHg)	**20 ± 11 mmHg**	**15 ± 7 mmHg**	
Bleeding in 24 hours (ml)	**412.3 ± 113**	**205.3 ± 60.7**	
Amount of erythrocyte concentrate transfusions	**2.6 units**	**1.4 units**	**<0.001**
Duration of mechanical ventilation (h)	**8.47 ± 1.63**	**6.85 ± 1.76**	**0.0006**
Catecholamine support	**12 (40%)**	**14 (41.1%)**	**0.912**
Analgesia with two infusions	**30 (100%)**	**34(100%)**	

Analgesia with three or more infusions	**17(56.7%)**	**16(47%)**	**0.375**
Heart rate			
Sinus rhythm	**20(66.7%)**	**16(47%)**	**0.073**
AV block/SA block	**6 (20%)**	**12(35.3%)**	**0.0431**
AF	**4 (13.3%)**	**6 (17.7%)**	**0.465**

Table 10. Summary of patient outcomes from both groups during the first 24 hours.

3. Analysis of early postoperative results and comparison between groups

Early postoperative outcomes in this study are understood as variables reflecting the patient's condition, which were recorded from the 2nd day after surgery until the day of discharge. All patients participating in the study were monitored daily during their entire hospital stay. Laboratory tests, control chest radiography and TTEhoCG data were recorded. All patients were under constant monitoring of vital signs - blood pressure, ECG monitoring of heart rate, saturation, central venous pressure, monitoring of twenty-four-hour diuresis and recording of the total water-salt balance, until the day of their discharge.

3.1 Control transthoracic echocardiography

During the daily transthoracic EchoCG in the postoperative period until the moment of discharge, LV EF, valve prosthesis function, peak and mean systolic gradient values, presence of paraprosthetic or intraprosthetic insufficiency were recorded. Postoperative monitoring of the amount of pericardial effusion is also important, by TTE based on measuring the detachment between the pericardium and the heart in millimeters, which is converted into the amount of fluid according to the formula used daily at the University Hospital “St. Catherine”. Additionally, the hemodynamic significance of the established effusion is assessed.

Comparison of the data from the control echographic examinations did not show any statistically significant difference between the groups in terms of the measured EF. There were also no statistically significant differences in the measured gradients - PSG and MSG, and their order remained unchanged during the entire postoperative stay.

No additional paraprosthetic or intraprosthetic insufficiency was registered. By the time of discharge in the control group, only 1 patient remained with grade 1 intraprosthetic insufficiency (3.33%) and another one with paraprosthetic insufficiency up to grade 1. In the group with seamless biological valves, only two or 2.94% with central aortic insufficiency were registered during the entire hospital stay, and the number of patients with paraprosthetic insufficiency remained two or 5.88%. In the median sternotomy group, two patients with echographic and clinical data for hemodynamically significant pericardial effusion were registered - 6.67%. One of the patients underwent pericardial drainage on the 4th postoperative day, and the other patient from the group on the 6th postoperative day. In the minimally invasive access group, one patient or 2.94% with significant pericardial effusion was registered, in which subxiphoid drainage was performed. Statistical analysis of this difference showed that it was not significant

(**P= 0.157**).

3.2 Catecholamine support

The need for catecholamine support gradually decreased. After the second postoperative day (POD), dopamine infusion was withheld in four or 13.3% of the patients in the control group, and in the minimally invasive group this proportion was 5.89% (2 patients). After the third POD, the infusion was continued in 2 of the control group and discontinued on the fourth, and in the two patients in the minimally invasive group it was discontinued before the end of the second POD. The distribution of patients in the two groups according to catecholamine infusion until the second POD is presented in diagram 33. The difference in the shares of patients with a need for catecholamines until the second POD is clearly visualized, and it is considered significant. Which allows the conclusion that with similar baseline characteristics, patients in the group with sutureless bioprostheses had a reduced need for catecholamine support, and when such was used, it was for a significantly shorter period.

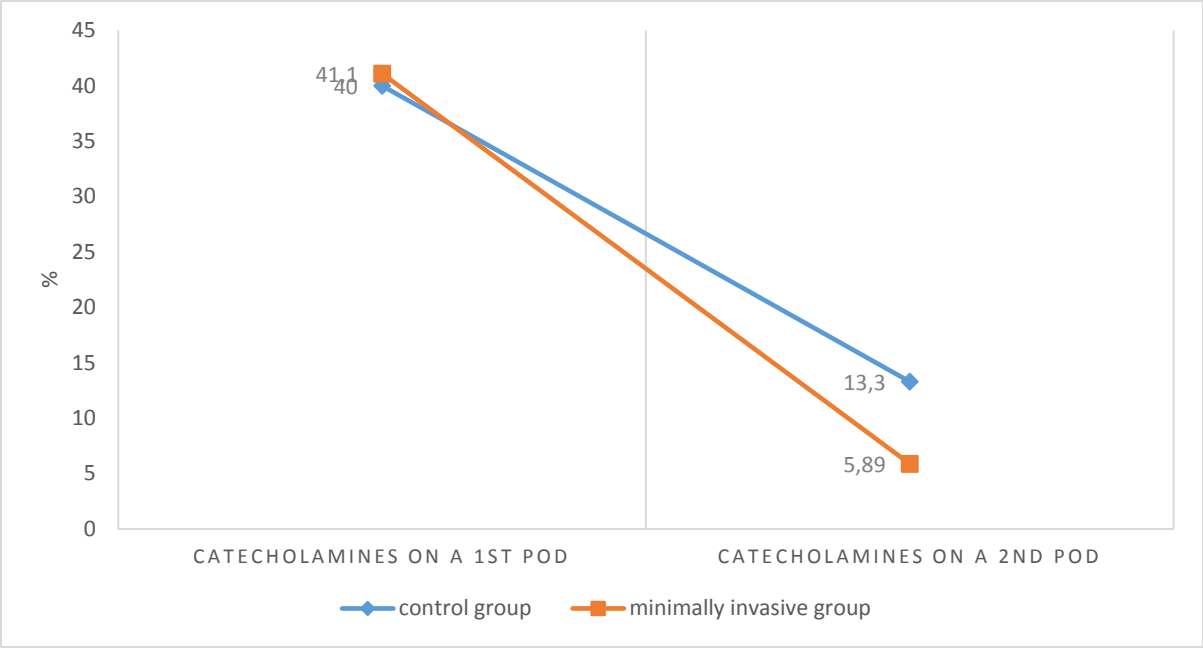


Diagram 33. Catecholamine support with Dopamine, for the 1st and 2nd POD.

3.3 Need for permanent pacemaker implantation

In patients who developed postoperative AV block/SA block, which is not overcome after the second POD and with certain ECG criteria, the implantation of a permanent pacemaker is indicated. In the control group, the patients with AV block at the first POD are - 6 or 20%, in only 1 of them (3.33% of the group) the sinus rhythm has not been restored after the second POD and this necessitated the implantation of a permanent pacemaker. In the group with implanted sutureless bioprostheses, the percentage of patients with AV block/SA block is higher. Already during the first POD it is - 35.3%, 12 patients. Due to the lack of restoration of supraventricular rhythm in 3 of them (8.82%) after the second POD, the implantation of a permanent pacemaker was necessary. Despite this higher proportion, the statistical analysis did not report significant statistical significance of this difference, **P = 0.131** . The distribution of patients in percentages according to the need for permanent pacemaker implantation is presented in diagram 34. The comments made so far and the relatively higher proportion of patients in need of a pacemaker in the group with sutureless valve prostheses are clearly demonstrated.

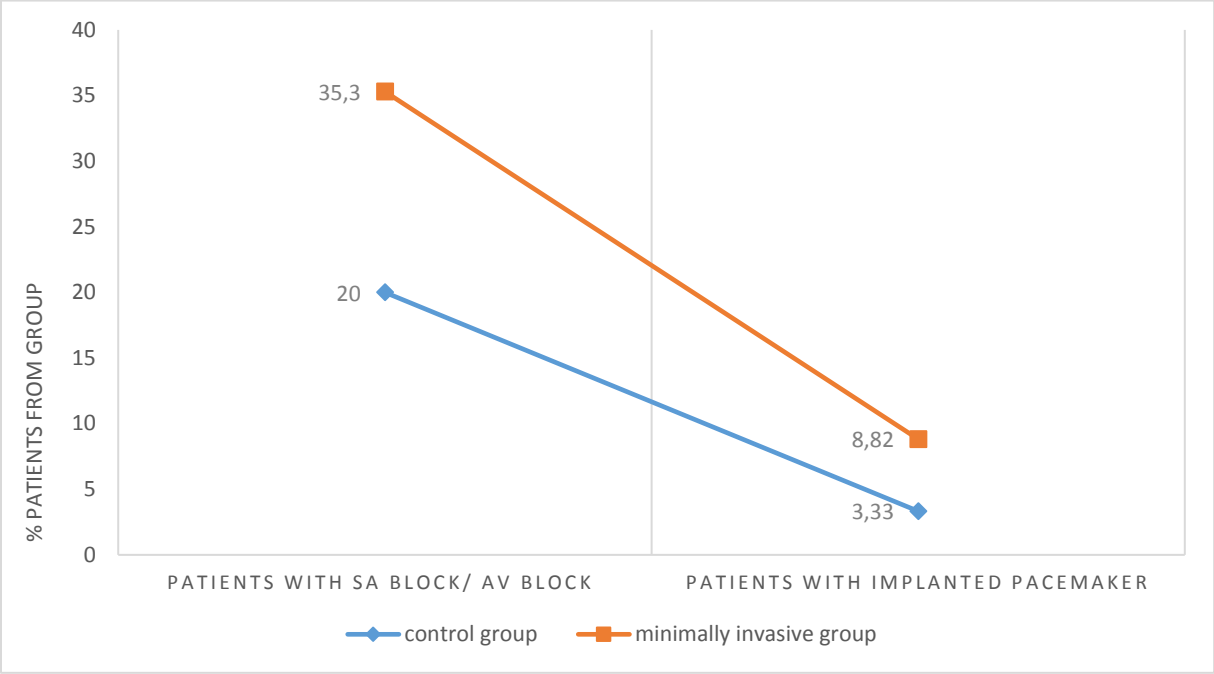


Diagram 34. Need for a pacemaker for the 1st and 2nd POD .

3.4 Other adverse events in the postoperative period

The following conditions were analyzed as additional adverse events in the postoperative period of hospital stay for this population - respiratory failure, renal failure, neurological complications, sepsis, wound infections.

According to the baseline characteristics, the two main groups showed approximately similar percentages of patients with concomitant chronic obstructive pulmonary disease (COPD) and documented FEV1 % <50%. Their share comprised 33.3% of the control group and 32.3% of the minimally invasive group. In the postoperative period, despite the targeted postoperative management of respiratory function allowing early extubation, a small percentage of patients developed short-term episodes of acute respiratory failure, which were amenable to management with drug therapy (bronchodilators, corticosteroids), oxygen treatment via mask, or intermittent use of mandatory non-invasive ventilation with positive airway pressure (CPAP). The registered shares of patients with such complications were, respectively, 13.3% (4 patients) in the control group and 5.88 (2 patients) in the minimally invasive group. In

all these patients, acute respiratory failure was managed with the described methods, without the need for re-intubation and mechanical ventilation.

Because this is a cohort constructed with inclusion criteria selecting high-risk patients, the proportion of patients with preoperative chronic renal failure was high - 23.3% of the control group and 20.6% in the minimally invasive group. Postoperative need for prolonged veno-venous hemofiltration due to acute chronic renal failure was recorded in 2 patients (6.67%) of the control group and in 1 patient (2.94%) of the sutureless valve group, and statistical analysis did not find significance of this difference.

In the postoperative period, no severe neurological complications with residual symptoms were recorded in either group. In 1 patient (2.94%) from the minimally invasive group, an episode of transient ischemic attack was recorded, without gross neurological deficit, the symptoms of which subsided after treatment within the next few hours of their appearance. The performed head CT scan did not reveal any changes that could be associated with ischemic foci.

No patient had a clinical presentation or even symptoms that could be associated with sepsis. Positive blood cultures with significant bacteremia and occasional fever were reported in 2 patients (6.67%) from the control group, who underwent an extended seven-day antibiotic course, after which laboratory and clinical markers normalized. In the J -sternotomy group, positive blood cultures and septic conditions were not registered. No patient from either group developed severe wound infections.

Diagram 35 presents the percentage distribution of adverse events in the postoperative period.

P	0.0593	0.157	0.068	NS	1.000

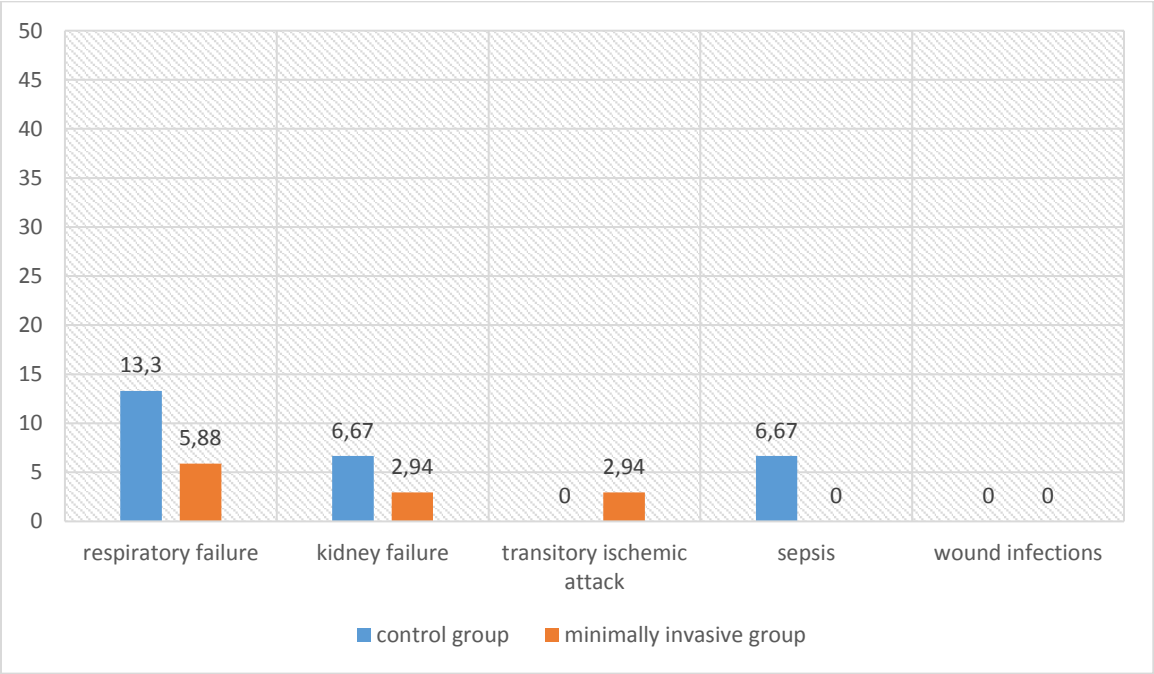


Diagram 35. Distribution of adverse events in the postoperative period

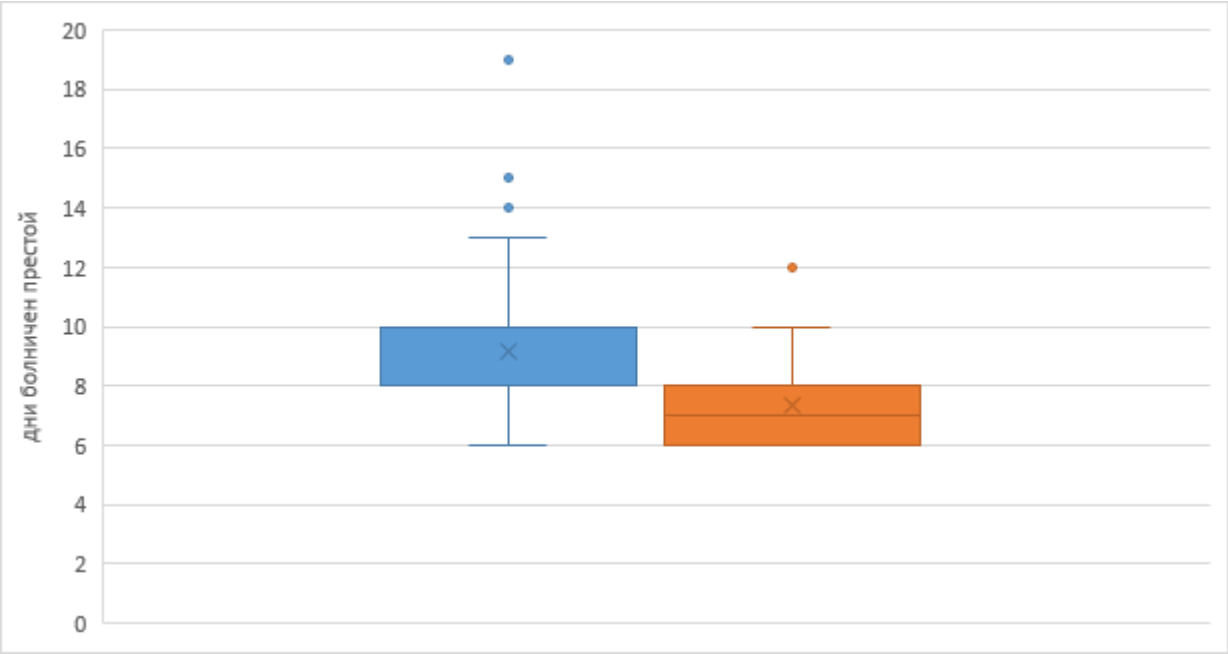
Statistical comparisons between the two groups regarding these data did not show any significance of the registered differences.

3.5 Average length of stay in intensive care

The length of stay in intensive care was monitored and recorded in days for all patients in this study. The Shapiro-Wilk test showed that the mean length of stay in intensive care was not normally distributed, so the Kolmogorov-Smirnov test was used for comparison, comparing medians. The reported mean length of stay in intensive care for patients in the control group was 3.27 ± 1.05 days, with a median of 3. For the partial sternotomy group, the reported mean length of stay was 2.59 ± 1.42 days, with a median of 2. Despite the apparently higher mean length of stay in intensive care reported in days in favor of the control group, a significant difference between the two main groups was not reported, **P = 0.124** .

3.6 Average hospital stay

The average hospital stay of patients in the control group was 9.17 ± 2.95 days, with a median of 8. In the group with minimally invasive access, the average hospital stay was 7.35 ± 1.45 days, with a median of 7. Due to the asymmetric distribution of this quantitative indicator in both groups, their medians were again used for comparison between the groups. The comparison is demonstrated in diagram 37.



Control group	Minimally invasive group
N=30	N= 34
Average hospital stay 9,17 ± 2,95 дни	Average hospital stay 7,35 ± 1,45 дни
Median 8	Median 7

Diagram 37. Average hospital stay

The comparison of medians showed a statistically significant difference between the groups - P= 0.0003 . Hospital stay was significantly shorter in patients with minimally invasive access.

3.7 Summary of postoperative results

The pooled analysis of the postoperative outcomes of the patients included in the study did not reveal any statistically significant differences between the two main groups in

terms of almost all compared variables, with the exception of the average hospital stay, which was significantly shorter in the group with minimally invasive surgery.

4. Comparison of the Follow up data

Patients included in the study were followed up for up to one month after discharge from hospital, with follow-up examinations performed in the outpatient clinic of St. Catherine University Hospital on the second and fourth weeks. At each of the follow-up examinations, a thorough history and status of the patient was taken, blood pressure values were measured, ECG monitoring was performed, and transthoracic EchoCG was performed. All changes in ejection fraction and valve prosthesis function were recorded, and the results obtained were compared with those recorded during the hospital stay.

During the follow-up, no new or increased para- or intraprosthetic insufficiency was registered in either group. No statistically significant difference was found in the measured transvalvular gradients (both in PSG and MSG). In both groups, an increase in the Functional Class was recorded at the end of the follow-up period compared to that registered preoperatively. Even before the end of the follow-up, there was no patient in the fourth FC. A total of 15 patients from the study population were in the third FC, with 8 or 26.7% of them in the control group, and 7 (20.6%) in the group with minimally invasive access. A total of 49 patients were in the second FC. Twenty-two were in the control group (73.3%), and 27 (79.4%) were in the group with seamless biological valve prostheses. When comparing the two main groups, no statistical difference was found in these share distributions.

According to the design of this study, at the end of the follow-up period, the patients' EF was also recorded. There was an overall increase in the mean EF in both groups, with no significant statistical difference between them **(P= 0.415).**

5. One-year survival analysis

During the early postoperative stay, mortality in both groups was zero. During the first month of follow-up period, there was also no patient who died. According to the calculated preoperative mean EuroScore, the expected one-month mortality should

have been 8.34%. By the end of the first postoperative year, the total mortality of the entire population reached 4.67%, which is three patients. In the group with minimally invasive access, 1 patient (2.94%) died at the eighth month, and in the control group, two patients (6.67%) died - one at the sixth month and one at the eleventh month. The total mortality for a period of 1 year is illustrated in diagram 40. The statistical analysis showed no significant difference between the groups in terms of the percentage of patients who died and their one-year survival.

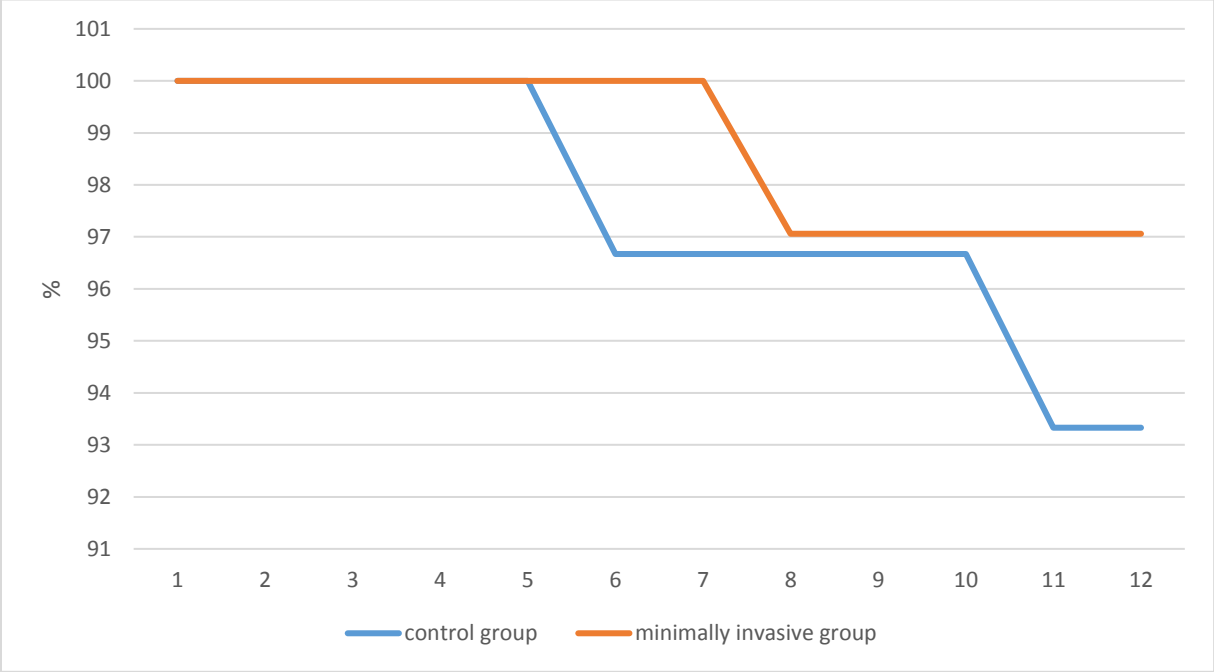


Chart 40. Total mortality by the end of the first year in percent

6. Summary of late postoperative results

The follow-up of the patients in the study covered the period from the operation until the end of the first postoperative month, during which better results were recorded in the group with the implanted seamless bioprosthesis. Further follow-up was not performed because each of the patients had subsequent check-ups with their regional cardiologist.

The advantage of the group with minimally invasive access is expressed in the lower proportion of adverse events in the postoperative period. And although this

difference is significant only for a few of the registered variables, it was not reported once in favor of the control group. Based on these results, it can be stated with great certainty that, if not a categorical advantage, then the lack of a significant difference in the frequency of adverse events makes the application of the new generation of sutureless biological aortic prostheses safe with reliable data for excellent effectiveness.

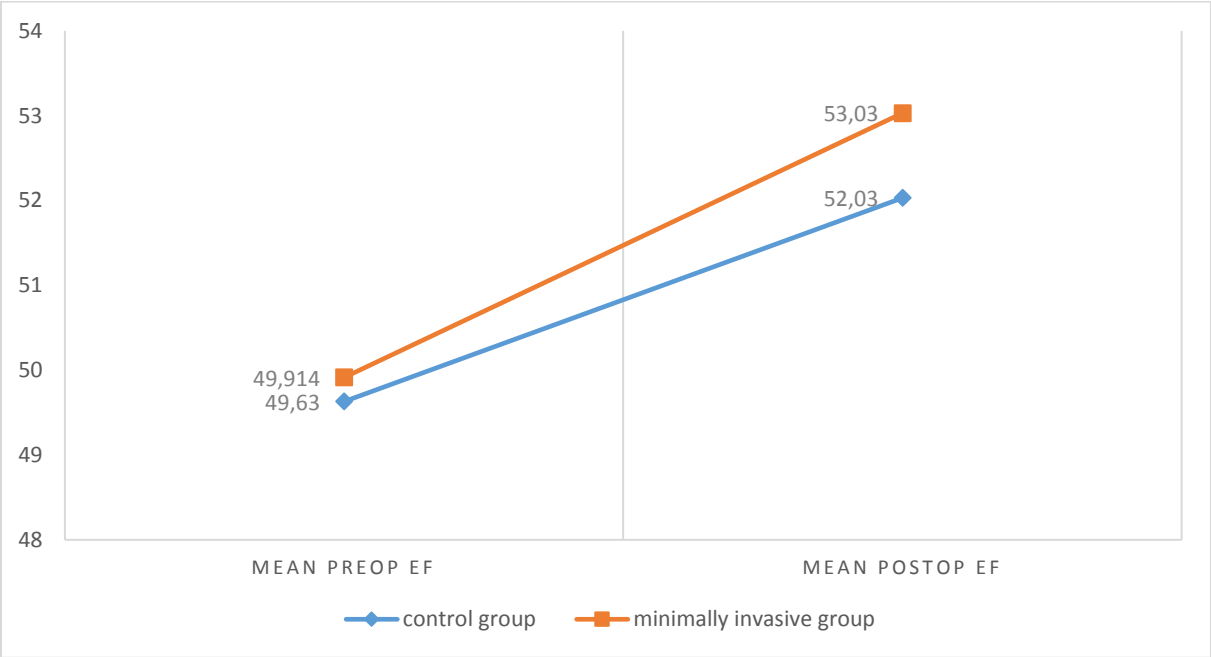


Diagram 41. Evolution of left ventricular ejection fraction

At the end of the follow-up period, the patients' FC showed a general trend of improvement in both groups, and the evolution of the Ejection Fraction compared to the preoperative values, even for this short follow-up period, demonstrated an advantage for the group with sutureless valves. This result is illustrated in diagram 41.

The registered total mortality is based on telephone calls and data from the National Social Security Institute system, the distribution of deaths by the end of the first year did not show any significant difference between the groups.

VI . DISCUSSION

Aortic stenosis is one of the most common valvular diseases in developed countries. The overall prevalence among the European population aged 55–74 years is 2.9% and reaches 13.6% in those aged >75 years.

Surgical aortic valve replacement has always been considered the gold standard for the treatment of severe symptomatic aortic stenosis, with excellent results, especially in asymptomatic patients with preserved functional status. However, the frequency of postoperative complications is directly dependent on the type and extent of other concomitant diseases. Therefore, the introduction of new technologies and surgical techniques, allowing the reduction of adverse postoperative events, has become a priority goal for cardiac surgery. Sutureless valves are a new generation of surgical bioprostheses with a unique design that facilitates their implantation and reduces the duration of the surgical procedure. The ability of these prostheses to limit the harmful effects of one of the main problems in aortic valve replacement - "patient-prosthesis mismatch" in patients with a small aortic annulus, which has been shown to significantly shorten the expected survival after surgery , is another factor proving the benefit of their widespread use.

This study also reflects the state of the problem in Bulgaria and offers an option for its solution, which is adequate and relevant all over the world.

1. Analysis of the study population

The study included 64 patients indicated for cardiac surgery due to high-grade AS, operated on at the University Hospital "St. Catherine", Sofia for the period 04.2015 to 07.2022. The study is retrospective, with a selection of patients subject to previously set inclusion and exclusion criteria. The general baseline characteristics of the studied group of patients show that in this sample of patients there are no statistically significant differences in terms of gender distribution - 28 women (44%) and 36 (56%) men. The average age of the patients included in the study is 70.18 ± 4.04, with a median of 69.

This study aims to investigate the impact of two competing surgical strategies on the outcomes of patients with severe AS and high operative risk, defined by the inclusion of patients with multiple comorbidities, considered as risk factors. The introduction of inclusion criteria selected a specific study population, in which patients with two and three risk factors predominated, followed by patients with four risk factors. All patients in the study were risk assessed using one of the two most widely used scoring systems for expected perioperative mortality (up to one month after surgery) - EuroScore-II, which according to the predefined inclusion criteria should be > 6%. The calculated risk ranged from 6.16 to 13.2 with a high mean value of 8.34 ± 1.29%. The median is close to the mean value and is 8.31. The most significant contribution to the high values of the calculated expected postoperative mortality is the relatively advanced age of the patients and the significant share of concomitant diseases and risk factors in the selected population - renal failure, COPD, peripheral vascular disease.

The main surgical intervention for the treatment of AS in this study was the surgical replacement of the damaged aortic valve of the patients with two types of biological valve prostheses. All patients were operated on in the cardiac surgery clinic of St. Ekaterina Hospital, Sofia. The valve prostheses were performed through two main surgical approaches - median longitudinal sternotomy for implantation of conventional biological valve prostheses - Mitroflow and upper partial J- sternotomy for implantation of sutureless biological valve prostheses - Perceval . All cardiac surgeries were performed under conditions of ECC, aortic cross clamping and cardioplegic myocardial arrest, provided by infusion of cold blood cardioplegia, antegrade and retrograde into the coronary sinus according to the clinic's protocol. All surgeries were performed under moderate hypothermia - 32° C. The average ECC period for all patients was 59.56 ± 13.27 min., with a median of 57.

All patients included in the study had proven symptomatic high-grade AS and were indicated for accelerated aortic valve replacement, with the decision of a cardiac surgical committee.

Two main groups of patients were defined. The control group was formed by 30 patients (46.9% of the study population), operated in the above-mentioned period by means of a complete median sternotomy and a biological prosthesis on a stent was used. The other main group was formed by patients with a minimally invasive approach (J-sternotomy), in whom a sutureless valve prosthesis was implanted. These were 34

patients or 53.1% of the study population. All patients in the study were at high perioperative risk as determined by the presence of a significant percentage of comorbidities and risk factors in the population. The retrospective nature of the study and the lack of randomization are the main shortcomings of the study, which limit to some extent the weight of the conclusions reached.

2. Comparison between baseline characteristics of the two groups

The two main groups were compared according to their baseline characteristics in order to establish the degree of comparability between them. The baseline characteristics were gender, age, risk factors, NYHA functional class , preoperatively calculated according to the EuroScore system, risk of early mortality, left ventricular ejection fraction, septal and posterior wall thickness in millimeters, aortic valve gradients and body surface area. No significant statistical differences were found (at a pre-defined threshold of $P<0.05$) between the two formed main groups. as in the rank of quantitative, as well as in the proportion of qualitative characteristics. This conclusion allows the results achieved with the two surgical strategies in the main groups to be compared and the differences reported between them to be analyzed for significance with the appropriate statistical methods, selected according to the nature of the variables studied and the type of their distribution.

3. Results

The results of the study are the product of a comprehensive comparative analysis of the postoperative data of patients from the two main groups. They include the following variables:

- intraoperative results - duration of ECC periods and aortic cross clamping,
- early postoperative results (up to 24 hours after surgery),
- results of the postoperative hospital stay
- results reported during the follow-up period - check-ups in the second and fourth weeks of discharge,
- analysis of overall mortality by the end of the first year after surgery.

The comparison between the results achieved in the two main groups using statistical methods showed the following trends:

Duration of ECC and duration of cross clamping time. The recorded mean ECC period for the control group was 66.57 ± 14.9 min, and the one achieved in the minimally invasive group was 53.38 ± 7.49 min. Regarding the average period of aortic cross clamping, the following average values were obtained - 39.6 ± 9.54 min. for the control group and 27.8 ± 5.24 min. for the group with sutureless valves. The statistical analysis of these results, conducted with the Mann-Whitney U- test for rank comparison of two independent samples, found that the registered differences were statistically significant. The shorter ECC period and cross clamping time are entirely in favor of the minimally invasive group. According to the evidence presented in the literature review, the duration of ECC and aortic cross clamping are independent risk factors for increased postoperative morbidity and mortality, especially in patients with AS. Therefore, the significant reduction in the duration of these two periods achieved in the minimally invasive group has a proven potential to limit the development of the risks associated with them. The main reason for this result is the innovative design of the conceptually new generation of prostheses used, the implantation of which is significantly facilitated and requires the imposition of only three guiding threads that do not tie, followed by a short additional adhesion (< 1 min), by inflating the prosthesis with a balloon to 4 atm . The achieved result confirms the data from other studies conducted outside Bulgaria that the use of sutureless biological valve prostheses in aortic valve prosthetics reduces the duration of ECC and aortic cross clamping time and has the potential to reduce the associated adverse effects and complications of surgical therapy in AS, especially in high-risk patients.

Early postoperative outcomes (up to 24 hours postoperatively) were also analyzed in detail. The recorded characteristics included data from - control Echocardiograms (EF, valve prosthesis function, presence of para- or intraprosthetic insufficiency, transprosthetic gradients). The average measured value of EF in this period was 48.06 ± 9.69% for the control group and 48.76 ± 6.45% for the minimally invasive group. The statistical comparison of these results did not reveal any significant difference in this indicator. In none of the operated patients in either group was there any defect in the function of the prostheses, as well as the presence of intra- or paraprosthetic insufficiency higher than the first degree. With up to the first degree of central aortic

insufficiency in the control group, 1 patient was registered - 3.33%, a similar finding was also found in only one patient (2.94%) from the group with sutureless biological valves. The comparison of the shares did not reveal any statistically significant difference. The number of patients with registered paraprosthetic insufficiency below the first degree in the control group was one (3.33%), and in the minimally invasive group – two (5.88%). Despite the higher percentage of patients with up to the first degree paraprosthetic insufficiency in the Perceval group , statistical analysis showed no significant difference between the two groups. Many similar studies have reported a similarly low rate of mild paraprosthetic insufficiency in Perceval prostheses, without evidence of a negative effect of this finding on the function of the prosthesis and an increase in risk for the patient.

Correct measurement of the annulus, correct selection of an appropriate size prosthesis and thorough annular decalcification are the most critical factors in the implantation of the used sutureless bioprostheses, which determine their postoperative function . Recording errors in the implementation of these key moments of implantation is a direct cause of the realization of the following complications - paravalvular regurgitation (most often when choosing a larger than necessary prosthesis) intraprosthetic regurgitation (when implanting a prosthesis with a smaller than necessary diameter), in more severe cases these errors can even lead to migration of the valve prosthesis or in extreme disproportion with implantation of a prosthesis much larger than the annulus - rupture of the aortic root or LV outflow tract, due to excessively increased tension on the walls of the aortic root. Sometimes these errors can cause stent invagination, fatal arrhythmia, severe regurgitation with hemodynamic collapse. No such complication was recorded in this study, which can be explained by the punctual adherence to the implantation protocol and strict intraoperative control via TEE .

Patient - prosthesis mismatch (PPM) is an important risk factor for reduced long-term mortality and increased morbidity in patients undergoing aortic valve replacement. Most authors believe that PPM has a complex impact, caused by: higher transvalvular gradients, decreased cardiac index, delayed postoperative regression of left ventricular hypertrophy, worsening of NYHA functional class. The problem is not uncommon and can be prevented by correctly choosing a valve prosthesis that is appropriate in size for the patient's body surface area. The risk of PPM is particularly pronounced in

patients with a small aortic annulus. To assess the safety and effectiveness of the new generation of seamless valve prostheses, we performed an additional subanalysis by comparing the registered values of postoperatively measured EchoCG gradients and effective valve openings in a subgroup of patients with preoperatively established small aortic annulus ≤ 21 mm. Of the patients in the control group, there were 16 patients, two of them (6.7%) had prosthesis number 19, and the remaining 12 patients (40%) from the group number 21. In the group with minimally invasive access, the number of similar patients was also 16, 4 of them (11.82%) were implanted with a sutureless prosthesis valve - S size, which corresponds to the effective opening of the annulus with a diameter of 19mm-21mm. The other 12 patients (35.3%) from the same group were implanted with an M size prosthesis, which corresponds to an annular diameter of 21mm-23mm. The comparison of the baseline characteristics of the patients forming these two subgroups - gender and body surface area, did not reveal any differences between them. The statistical analysis, conducted using the T-test method, allowed a comparison between the echocardiographic measurements of the patients forming the described subgroups. Postoperatively measured peak transvalvular gradient was lower in the sutureless valve group (15 ± 7 mm Hg vs. 20 ± 11 mm Hg; p = 0.02). The indexed effective valve area was again in favor of the same group (1.12 ± 0.2 cm2/m2 vs. 0.82 ± 0.1 cm2/m2; p = 0.04). Statistical analysis of these results found that the difference was significant. As noted above, PPM is a major problem in aortic valve replacement, and its avoidance should be a primary goal for the surgeon. If it is impossible to implant an appropriately sized prosthesis, the use of different techniques for aortic root expansion or the implantation of a homograft, but all these operations require additional extension of the aortic cross clamping time period and ECC, which is not a good alternative in high-risk patients. The results obtained from the present study fully confirm the statement, that the use of seamless biological valves in patients with a small aortic annulus significantly reduces the risk of developing prosthesis-patient mismatch and makes them a mandatory option in cases of AS with a small aortic annulus and high operative risk.

The next task of the study was to assess the efficacy and safety of the access by comparing the data reflecting postoperative blood loss. The mean blood loss for the control group was 412.3 ± 113 ml, with a median of 410, and for the minimally invasive group the mean value of this indicator was 205.3 ± 60.7 ml, with a median of 210.

Statistical processing of this result showed that this difference was significant and in favor of the partial sternotomy group. The registered lower blood loss was also identified as a direct reason for the reduced need for red blood cell concentrate transfusion in the minimally invasive access group compared to those operated on with a complete sternotomy (mean 1.4 vs. 2.6 units, P <0.001). This result confirms the conclusions of numerous similar studies supporting the thesis that that the main source of bleeding in cardiac surgery is the sternum. The risk of increased blood loss when using the J -sternotomy arises from the fact that it extends into the fourth right intercostal space, which can cause injury to the right internal thoracic artery, accompanied by increased blood loss. This risk requires increased attention when closing the sternal wound and may be one of the main reasons for the reduced amount of postoperative bleeding.

The next difference between the characteristics of the two groups in the study, which showed statistical significance, was observed in the analysis of the duration of mechanical ventilation, expressed in hours (the period from the moment the patient was taken from the operating room to the intensive care unit until the time of extubation). The average duration of intubation for patients in the control group was 8.47 ± 1.63 hours, and for the group with minimally invasive access 6.85 ± 1.76 hours, $p < 0.05$. A number of factors have a major influence on the duration of mechanical ventilation in the early postoperative period, but the surgical access and the associated pain are one of the main ones. Early extubation is an important component of the so-called Fast - track Recovery , rapid recovery protocols that significantly reduce recovery time after heart surgery, hospital stay and hospital costs. In addition to reduced bleeding levels, J -sternotomy also provides another important advantage for patients - preserving the integrity of the lower half of the sternum and the stability of the chest, which preserves the mechanics of respiratory movements.

Due to the presence of severe left ventricular hypertrophy and the risk of subendocardial ischemia, catecholamine support in patients with AS should be avoided to the minimum possible. However, in the study population, the need for catecholamine administration was reported in 12 of the patients (40%) in the control group during the first 24 hours. In the Perceval group, 14 patients (41.1%) received catecholamine support. This difference was not considered significant.

Postoperative pain after cardiac surgery has a multifactorial etiology. Skin incision, tissue dissection, sternal retraction, chest tube placement, endotracheal

intubation, and sternal osteosynthesis directly injure tissues and induce the release of a panel of proinflammatory mediators, including nitric oxide and cytokines. These mediators activate afferent nociceptive fibers and cause nociceptive pain. More severe sternal retraction can also lead to rib fracture, which is a leading cause of severe postoperative pain syndrome that limits rehabilitation and impedes rapid postoperative recovery. Pain limits satisfactory coughing and deep breathing. This leads to the accumulation of secretions in the bronchial passages and an increased risk of hypoventilation, atelectasis, and pneumonia, important factors predetermining an increased risk of prolonged hospital stay, mechanical ventilation, and the need for antibiotic treatment. A comparison between the perception of pain and its magnitude in the study patients was based on the recorded need for analgesia up to the 24th postoperative hour. Adequate postoperative analgesia technique allows early extubation, mobilization, and discharge from the intensive care unit. Pharmacological therapy in the form of parenteral opioids or nonsteroidal anti-inflammatory drugs is the mainstay of analgesic therapy for postoperative pain management in cardiac surgery. The results of the comparative analysis show that all patients in both groups received at least two infusions during the first 24 hours as monotherapy or as a combination of the above analgesics. In 17 patients (56.7%) from the total median sternotomy group, an increased need for analgesia was reported with the application of a third and more applications of analgesics, and in the J-sternotomy group, the dose share consisted of 16 patients (47%). Despite the numerous literature data reporting significantly lower levels of postoperative pain in favor of patients with partial sternotomy compared to complete sternotomy, no such trend was reported in our study, P=0.375.

The registered heart rhythm variants of the studied population during the early postoperative period are four - SR, AF, AV-block, SA-block. Their distribution is as follows:

- sinus rhythm - 66.7% (20 patients) from the control - 47%(16)
- AV block or SA block - 6 patients (20%) from the control group - Perceval - 35.3% (12)
- Atrial fibrillation - 13.3% of the control group - 17.7% in the group with minimally invasive access.

Despite the differences in percentage distribution, statistical significance was not observed for sinus rhythm (P = 0.073) and atrial fibrillation (P = 0.465). In contrast, we found a significant difference in the proportions of patients with AV block or SA block

between the two main study groups, P = 0.0431. All of these patients required temporary pacemaker implantation.

In summary, data processing from the first 24 postoperative hours showed the presence of several important statistically significant differences between the two main groups.

The control EchoCG revealed lower values of the measured transprosthesis gradients and increased indexed effective valve opening in patients with small aortic annulus from the group with sutureless bioprostheses, P<0.05.

The differences in the number of blood transfusions performed and the average value of registered blood loss were also reported as significant, again in favor of the group with minimally invasive access.

The difference between the groups was also statistically significant in terms of the duration of mechanical ventilation, which was shorter in patients with partial sternotomy.

No significant differences were noted regarding the presence of para- and intraprosthetic insufficiency, although the percentage of residual paraprosthetic insufficiency in the group with sutureless biological valves was higher (5.88%).

Differences in the need for catecholamine support were also not reported. The results of the comparisons between patients with increased need for analgesia were similar. Despite the presence of numerous publications in the literature that demonstrate significantly higher success rates in these characteristics in favor of minimally invasive surgery. This result is probably due to the small number of patients included in our study.

Patients with restored sinus rhythm prevailed in the control group, while the proportion of patients with AV block was higher in the Perceval group (35.3%).

Data reported for the second postoperative day showed the following trends.

The conducted control ultrasound examinations established the presence of statistically significant differences between the groups in terms of ejection fraction. No significant change in these values was found within each individual patient during the entire follow-up period. No statistically significant changes were observed in the measured transprosthetic gradients. No new cases of paraprosthetic or intraprosthetic insufficiency were reported. By the time of discharge from the hospital, one patient (3.33%) remained in the control group with intraprosthetic regurgitation and one patient

had paraprosthetic insufficiency with a magnitude of up to the first degree. In the group with sutureless biological valves, 2.94% were registered with central aortic insufficiency throughout the entire hospital stay, and in another 5.88% low-grade (up to the I degree) paraprosthetic insufficiency was found.

Despite the lack of revisions or cases of uncontrolled postoperative bleeding in the entire study population, three of the patients required evacuation of hemodynamically significant pericardial effusion during their hospital stay. This occurred in two (6.67%) patients in the median sternotomy group. In the first patient, pericardial drainage was performed on the 4th postoperative day, and in the other patient on the 6th postoperative day. In the minimally invasive group, this complication was recorded in only 1 patient (2.94%), who also underwent subxiphoid drainage. Despite the higher percentage in favor of the control group, the difference was not considered statistically significant (P= 0.157).

Despite the lack of significant difference between the groups regarding the need for catecholamine support during the first 24 hours of the surgical intervention, the analysis of the data recorded during the second SOD showed a significant trend for a reduced need for catecholamine support in the minimally invasive access group (13.3%) compared to the control group (5.89%). These results indicate that in the minimally invasive group, the need for catecholamine support is exhausted in a shorter period . An important role in registering this result is played by the good hemodynamics and function of the seamless biological valves, proven by the measurement of lower gradients and increased effective area, as well as of course the shortened periods of aortic clamping and duration of ECC.

Episodes of AV block/SA block lasting more than 24 hours are the main reason for implantation of a permanent pacemaker. In the studied groups, their distribution is as follows - the control group 1 patient (3.33%), in the group with implanted seamless bioprostheses this share is higher and reaches - 8.82% (three patients). Despite the higher percentage of patients with implanted permanent pacemaker in the group with minimally invasive access, the reported difference was not statistically significant (P=0.131). Numerous articles in the literature also demonstrate a higher percentage of patients requiring implantation of a permanent pacemaker after using a sutureless bioprosthesis compared to those treated with conventional aortic valve prostheses. According to the literature, factors that are essential for reducing the need for

permanent pacemaker implantation are: correct decalcification of the annulus, selection of the correct size of the prosthesis, precise positioning of the guiding sutures and balloon dilatation without overinflation. The Perceval S sutureless aortic bioprosthesis relies on maintaining its stable position by the radial force that its nitinol frame exerts on the aortic wall. It is believed that compression of the conduction system by this radial force is the main mechanism of postoperative conduction disturbances after aortic valve prosthesis using a sutureless bioprosthesis. This is in contrast to standard valve prosthesis, where compression of the conduction system is caused by postoperative edema and may reverse after its resolution. The present study demonstrated the presence of such a difference, but it was not considered significant.

As additional adverse events in the postoperative period, the following conditions were analyzed in this study - respiratory failure, renal failure, neurological complications, sepsis, wound infections.

Patients in the study were those with proven and documented FEV1% below 50%. Their share in the control group was 33.3% (10 patients), and in the minimally invasive group they were 32.3% (11 patients). This high level of such patients in the study population is due to the criteria for their selection, the aim of which was to create a cohort with high perioperative risk. The two main groups did not differ in terms of the distribution of patients in them according to this baseline indicator. In the postoperative period, a small percentage of COPD patients developed short-term respiratory failure, which was controlled with medication (bronchodilators, corticosteroids) and oxygen therapy, various methods of non-invasive ventilation (CPAP, full face mask) and enhanced respiratory rehabilitation. The number of patients registered with respiratory failure in the control group was four or 13.3%, and their number in the group with minimally invasive access was two or 5.88%. This difference is in favor of the minimally invasive strategy, but the statistical processing of the data failed to report the presence of significance.

Again, due to the selected high-risk patient population, the distribution of patients with CKD in both groups was significantly higher than in the normal population. The two groups did not differ significantly in terms of preoperative proportions of these baseline characteristics - control group - 23.3%, minimally invasive - 20.6% (7). The need for prolonged veno-venous hemofiltration after the surgical intervention was recorded in 2 patients (6.67%) from the control group and in 1 patient (2.94%) from the

group with seamless valves, a difference that was again not considered significant. Although the pronounced advantage of the minimally invasive group was a sought-after outcome in this study, the presumed benefit to patients from shortening the periods of aortic cross clamping and ECC did not have a strong enough impact to register a significant advantage in terms of the development of acute renal failure. A likely reason for reporting the present result is the fact that the aortic cross clamping times and the duration of ECC in the control group were not significantly prolonged, despite their significantly shortened values in the minimally invasive group. The conclusion that can be drawn based on this finding and the data from the literature is that the study confirms the 60-min limit for aortic cross clamping as an essential factor in reducing postoperative morbidity.

The study did not report any patients with permanent gross neurological deficit. In the partial sternotomy group, one patient with a transient ischemic attack episode was registered, who recovered completely without residual symptoms within 24 hours. It can be concluded that the access does not affect the development of neurological complications and the upper sternotomy is a safe alternative to the standard access with regard to this type of complications, which can dismiss as unfounded some concerns about increased difficulties in decalcification and deaeration of the cardiac cavities when using a minimally invasive approach.

The cases with a developed clinical picture of postoperative sepsis in the studied population are zero. In 2 patients (6.67%) from the control group with single febrile episodes, significant bacteremia was detected, registered with a positive blood culture. In both cases, a seven-day antibiotic treatment was performed, which allowed complete control of the condition with normalization of the clinic and laboratory markers of inflammation. In the group with J-sternotomy, positive blood cultures and septic conditions were not registered.

In both groups, there were no patients with severe wound infections requiring targeted surgical treatment.

In summary, the proportions of all studied adverse events and complications of the postoperative period showed low levels in the studied population. The differences in the distribution of all these characteristics within the main groups were in favor of the minimally invasive group, but statistical methods did not establish the significance

of these results. Despite the logically sustained expectation of a significant advantage of minimally invasively treated patients, due to the significantly shorter duration of ECC and cross clamping time, which are important predictors of increased morbidity and mortality in such high-risk populations. An important role in reducing the risk should also be played by the minimally invasive approach, which has been categorically proven to be a direct cause of reduced postoperative blood loss (205.3 ± 60.7 ml vs. 412.3 ± 113 ml) and the need for blood transfusions (1.4 vs. 2.6 units, $P < 0.001$). These advantages were reflected in the lack of worsening of the degree of renal failure after surgery and the duration of mechanical ventilation, characteristics on which the strategy adopted in the minimally invasive group probably has a stronger influence. In our study, there was no significant difference between the proportions of patients with neurological complications in the two main groups. All intracardiac procedures require careful deaeration of the left heart chambers to prevent the occurrence of systemic air embolism, which can lead to severe neurological and myocardial dysfunction. Deaeration during minimally invasive access poses certain challenges due to the limited access to the pericardial space and the difficulty of direct manipulation of the heart. However, despite the limited scope for applying such maneuvers, according to the data used in the study, minimal access was not identified as a risk factor for the development of such severe complications associated with difficult deaeration, and therefore can be recommended as a safe and secure alternative to conventional sternotomy even in similar populations of patients with high surgical risk.

The analysis of the results regarding the reported days, mean ICU stay and mean hospital stay revealed the following trends: The reported mean ICU stay for the patients in the control group was 3.27 ± 3.05 days, with a median of 3. For the partial sternotomy group, the reported mean stay was 2.59 ± 1.42 days, with a median of 2. Despite the higher mean ICU stay for the patients in the control group, the difference was not reported as significant, $P= 0.124$. Regarding the mean hospital stay, the data show that for the control group it is 9.17 ± 2.95 days, with a median of 8, and for the minimally invasive access group - 7.35 ± 1.45 days, with a median of 7. Statistical comparison of this result showed a significant difference between the groups, $P = 0.0003$. Therefore, it can be confidently assumed that the strategy of minimal access and implantation of a sutureless valve prosthesis is a reliable predictor of reduced hospital stay and rapid postoperative recovery.

4. Folow up

Patients included in the study were followed up until the end of the first month after discharge, with follow-up examinations performed in the outpatient clinic of St. Catherine University Hospital on the second and fourth weeks. The results of the patient follow-up showed no significant differences between the groups regarding the recorded ultrasound parameters at the time of discharge - transprosthetic gradients, and no new patients with para- or intraprosthetic insufficiency were reported. In both groups, an increase in the Functional Class was recorded at the end of the follow-up period compared to the preoperatively registered one. Not a single patient from the entire population was in the fourth FC. In the third FC, 15 patients from the studied population remained, 8 of them (26.7%) were from the control group, and 7 (20.6%) were from the group with minimally invasive access. A total of 49 patients were under the second FC. Twenty-two were from the control group (73.3%), and 27 (79.4%) were from the group with seamless biological valves. When comparing the two main groups, no statistical difference was found in terms of FC at the fourth week after discharge. The main reason for the overall increase in the mean FC in both groups was the surgical correction of the AS itself, and not the type of bioprosthesis used.

The mean EF at the end of the 1st month in the control group was 52.03 ± 6.74%, with a median of 50. In the group with seamless valves, this value at the end of the 1st month was 53.03 ± 5.04%, with a median of 55. No statistically significant difference was found between the two groups (P= 0.415). Further follow-up and analysis of these indicators was not conducted according to the study design. The short postoperative follow-up period is one of the shortcomings of the study, but its main goal is to evaluate the effectiveness of the newly proposed strategy for surgical treatment of AS with implantation of sutureless bioprostheses in a minimized surgical approach - upper partial with ternotomy. The proposed follow-up period in the presented study design was accepted as completely sufficient.

5. Mortality

The overall mortality rate of all patients in the study population for one year is 4.67%, which corresponds to three patients. According to the calculated preoperative average EuroScore, the expected mortality rate in the study population should be 8.34%.

In the group with minimally invasive access, 1 patient (2.94%) died at the eighth month, and two patients (6.67%) died in the control group - one at the sixth month and one at the eleventh month.

All three patients died after the third month and outside our institution, and the event was registered according to the data of the relatives, which makes it incorrect to comment on the specific cause of death. The analysis that was made was based on the registered data from the preoperative period, the intraoperative indicators and those reported during the hospital stay and the control examinations at the 2nd and 4th weeks after discharge.

For the control group - one of the deceased patients was 74 years old, with high-grade AS, a developed clinical picture and several episodes of syncope before seeking medical help and being hospitalized in our hospital. The patient's EuroScore was 10.24%. His preoperative EF was -38%, and the preoperatively reported FC was Third. As accompanying diseases, obesity, arterial hypertension, insulin-dependent diabetes with poor control of blood sugar levels for 15 years, and COPD were registered. Aortic valve prosthesis was performed as planned using the conventional method with an ECC duration of 58 min. The postoperative period was relatively tense with the need for Dopamine infusion and an extended hospital stay. On the 11th postoperative day, the patient was discharged with a EF of 40%, compensated up to a second FC. At the follow-up examinations, the patient had normal function of the biological prosthesis, preserved EF as at discharge. The patient did not have other follow-up examinations in our clinic, and after a telephone conversation with the relatives, it was established that the patient died at the sixth postoperative month.

The other deceased patient from the control group was a 72-year-old man with comorbidities of obesity, arterial hypertension, peripheral arteriopathy and CKD. EuroScore- 9.18%, preoperative EF- 42%. Aortic valve prosthesis was performed using a biological prosthesis. During the resuscitation period, the patient was on

catecholamine support with Dopamine. An exacerbation of CKD followed, requiring renal replacement therapy with veno-venous hemofiltration. The patient was discharged from the clinic on the 14th postoperative day with a EF close to the preoperative value. No new complaints and complications on the control examinations. Again, according to data from relatives, the patient died on the 11th postoperative month in a hospital at his place of residence during emergency hospitalization with clinical data of transient ischemic attack and heart and kidney failure exacerbated on this background.

The deceased patient from the minimally invasive group was a 71-year-old man with concomitant diseases: obesity - grade III , arterial hypertension, COPD and pulmonary hypertension, systolic pressure in the pulmonary artery - 100 mmHg . LV EF was 45%. The preoperatively calculated EuroScore was 10.32%. Aortic valve prosthesis was performed using a seamless bioprosthesis and minimally invasive access. The patient had a protracted postoperative period of Dopamine infusion. With a developed clinical picture of respiratory failure in the early postoperative period, which was controlled with bronchodilators, corticosteroids and CPAP procedures within two days. After a protracted hospital stay, the patient was discharged on the 13th postoperative day, rehabilitated to a second FC, and the described condition was maintained during the control examinations conducted at the 2nd and 4th weeks. The patient died on the 8th month of dehospitalization again in another medical institution with a picture of ischemic stroke and data on severe respiratory failure.

All three deceased patients were high-risk, with serious concomitant risk factors and a reduced preoperative EF. They had a difficult postoperative period with the development of acute renal or respiratory failure. These characteristics do not allow us to differentiate a single factor responsible for the fatal outcome, since all three patients are at high risk and there is no medical data on the condition of the patients after the mandatory control examinations at the 2nd and 4th weeks after their discharge from hospital. From the analysis of the deceased patients in the sample participating in our study and the nearly twofold difference in mortality rate (2.94 % in the minimally invasive group and 6.67% in the control group), we can state that the use of sutureless bioprostheses is a safe and effective method for the treatment of high-grade AS, which does not increase, and even has the potential to reduce, one-year mortality, especially in high-risk patients similar to those included in this study.

VII . CONCLUSIONS

1. The two main groups formed are comparable according to their initial characteristics;

2. Good patient selection is a prerequisite for good results and, above all, for the absence of serious complications;

3. The duration of ECC and aortic cross clamping time are shorter when using sutureless bioprostheses for aortic valve replacement, which is of particular importance in high-risk patients since the ECC period and ischemic time are independent predictors of early morbidity and mortality;

4. The use of sutureless bioprostheses in aortic valve replacement is an efficient and reliable method for treating high-risk patients with high-grade aortic stenosis

5. Thorough annular decalcification, appropriately selected valve size, correctly positioned guiding sutures, and inflation of the prosthesis to the appropriate atmospheres without overinflation are the main key stages determining the risk of postoperative para- or intraprosthetic insufficiency;

6. The use of sutureless biological valves in patients with small aortic annulus demonstrates improved indexed EOA and a reduced risk of developing patient-prosthesis mismatch compared to those registered with implantation of conventional bioprostheses.

7. Sutureless biological valves are suitable for implantation in patients with severe aortic root calcification;

8. Sutureless valves are the gold standard when using minimally invasive access for aortic valve replacement;

9. Significant differences in favor of the J -sternotomy group are:

- reduced postoperative blood loss,
- reduced need for blood transfusions,
- shortened duration of mechanical ventilation;

10. The use of sutureless valves carries a higher risk of conduction disorders and implantation of a permanent electrical stimulator;

11. The number and severity of adverse events was significantly lower in the minimally invasive access group, which is confirmed by the rapid recovery and shorter hospital stay of patients in this group;

12. The two groups did not differ significantly in terms of one-year mortality;

VIII . INDICATIONS AND ALGORITHM FOR THE USE OF SUTURELESS BIOPROSTHESES IN AORTIC VALVE REPLACEMENT

1. Indications

Based on the results and conclusions of this study, indications for implantation of a sutureless aortic prosthesis in aortic valve replacement were defined:

1. Isolated symptomatic aortic stenosis is the main indication for performing this type of cardiac surgery;

2. Patients > 65 years of age, in whom the use of a biological prosthesis is appropriate;

3. Patients with aortic annulus size between 19 and 27 mm.

4. Calculated preoperative EuroScore II > 6% and a decision by a cardiac surgical committee that the patient is suitable for surgical treatment despite his increased risk;

5. Patients with one or more concomitant diseases requiring the shortest possible period of ECC and aortic cross clamping time, in order to reduce perioperative risk;

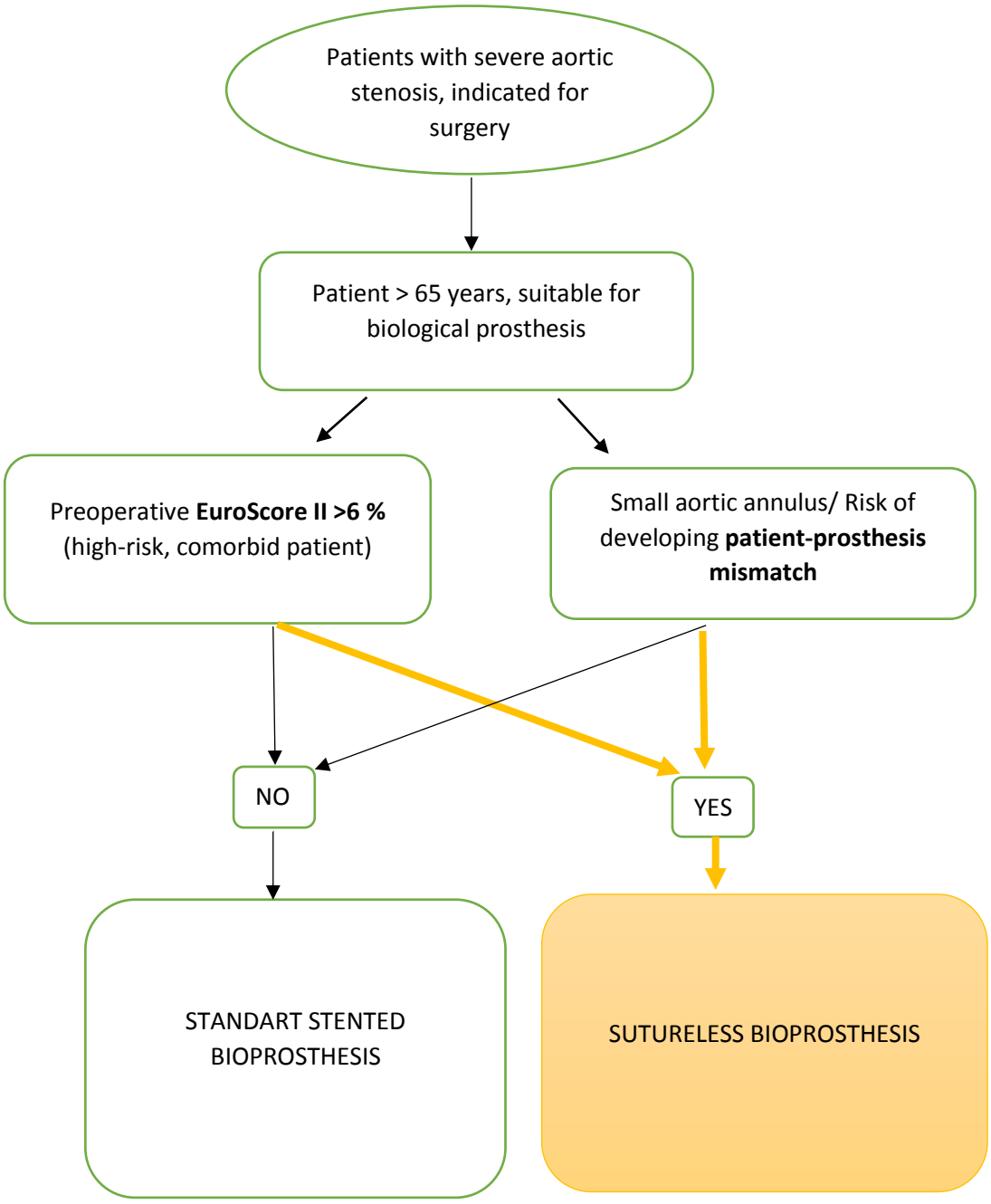
6. Patients with a small aortic annulus and a high risk of developing patient-prosthesis mismatch;

7. Patients with severe aortic root calcification;

8. Patients with suitable anatomy for the use of minimally invasive access for aortic valve replacement;

2. Algorithm for implantation of a sutureless bioprosthesis in aortic valve replacement

According to what has been said so far, the main result of this study is the creation of an algorithm for the selection of patients with AS suitable for implantation of a sutureless biological valve. It is entirely based on the analysis of the characteristics of the patients from this study and the achieved results. The algorithm is presented in Scheme 1.



scheme 1.

IX . CONTRIBUTIONS ACCORDING TO THE AUTHOR

1. In this dissertation, a comprehensive comparative analysis of two groups of high-risk patients with isolated symptomatic high-grade aortic stenosis, operated on under ECC conditions, has been made – in the one group, forming the minimally invasive group, the main surgical access was J -sternotomy and a new generation of sutureless biological prosthesis for aortic valve prosthesis was used, and in the other, the so-called control group, the operation was performed with a complete median sternotomy, and the valve was replaced with a conventional biological prosthesis on a stent.

2. For the first time in Bulgaria, a retrospective non-randomized study of surgical treatment in high-risk patients with high-grade aortic stenosis has been conducted;

3. For the first time in Bulgaria, an analysis of the results of the treatment of high-risk patients with AS, through the implantation of a new generation of sutureless bioprostheses, is being conducted;

4. The intraoperative, early and late postoperative outcomes of the included patients with high surgical risk undergoing two surgical alternatives for aortic valve replacement were analyzed in detail;

5. An analysis of one-year survival in high-risk patients with AS undergoing surgical treatment was performed;

6. Data from numerous other studies confirm that sutureless valve prostheses have excellent hemodynamic characteristics, good early and late postoperative results, and shorter hospital stays. Their implantation brings benefits , expressed in reduced morbidity.

7. Comparing the two groups in terms of postoperative results, it was proven that the implantation of sutureless bioprostheses through minimally invasive access is a good alternative to the standard approach and an effective method for treating high-risk patients with AS;

8. The benefit of using sutureless prostheses in AS to prevent the risk of patient-prosthesis mismatch is confirmed, especially in high-risk patients with a small aortic annulus.

9. Partial superior sternotomy has been confirmed to be a safe and effective approach for performing aortic valve replacement in high-risk patients.

10. An algorithm has been developed for indicating the implantation of sutureless biological valve prostheses;

X. PUBLICATIONS RELATED TO THE DISSERTATION

1. Implantation of Suture-less Aortic Valve Prosthesis in High-Risk Patients via Upper Ministerotomy. [Abstract]

Publisher's details: BULGARIAN thoracic, cardiac and vascular surgery – Sofia: Univ. Publishing House "St. Kliment Ohridski", 2022, issue 1, p. 66. ISSN 1313-9339

Co-authors: D. Kyuchukov, S. Stoycheva, D. Petkov, G. Nachev

2. Florida Sleeve method for aortic root reconstruction. Clinical case. [Abstract]

Publisher's details: BULGARIAN thoracic, cardiac and vascular surgery – Sofia: Univ. Publishing House "St. Kliment Ohridski", 2022, issue 1, p. 63. ISSN 1313-9339

Co-authors: D. Kyuchukov, Doychev, S. Stoycheva, G. Nachev

3 . Isolation of pulmonary veins in patients with atrial fibrillation without mitral valve disease undergoing elective heart surgery.

Publisher data: Journal of Cardiothoracic Surgery. 2019 volume 14, Article number: 154 , O47, page 14 . doi 10.1186/s13019-019-0971-2. ISSN 1749-8090

SCOPUS/ 2019 /

Co-authors: Kyuchukov D, Baev B, Iliev R, Stoycheva S, Nachev G.