

# SUPPLEMENTARY MATERIALS

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**Contributors:** The Principal investigators and members of the Steering Committee were involved in design of the trial, enrollment, clinical follow up of the patients, data analysis and writing of the manuscript.

**Acknowledgements:** We thank to all the patients who agreed to participate, to the study coordinators, and all the physicians and nurses who with their work and commitment helped to conduct the study.

## **2. SUPPLEMENTAL METHODS**

### **2.1. Inclusion criteria**

- Men and women of any ethnic origin aged  $\geq 18$  years
- Written informed consent
- Standard echocardiographic criteria for diagnosing severe aortic stenosis (defined as V max across the aortic valve  $> 4\text{m/s}$  or P mean  $\geq 40\text{mmHg}$  and AVA  $\leq 1\text{cm}^2$  or AVAi  $\leq 0.6\text{cm}^2/\text{m}^2$  at rest)
- Without reported symptoms
- Society of Thoracic Surgeons (STS) score  $< 8\%$

### **2.2. Exclusion criteria**

- Participation in another clinical trial within 30 days prior randomization
- Pregnant or nursing women
- Mental condition rendering the patient unable to understand the nature, scope and possible consequences of the study or to follow the protocol
- Positive stress-test defined as:
  - a. Anginal chest pain during testing



- b. Syncope or dizziness during testing
  - c. Decrease in systolic blood pressure during exercise  $\geq 20$ mmHg
  - d. Malignant arrhythmia during exercise testing (VT or VF)
- Left ventricular ejection fraction  $< 50\%$  at rest
  - Very Severe AS defined as  $V_{max} > 5.5$  m/s at rest
  - Significant disease of other valves: Mitral stenosis with  $P_{mean} > 5$ mg, or any significant regurgitation  $\geq 3+$
  - Recent previous myocardial infarction ( $< 1$  year)
  - Need for additional aortic root replacement (i.e Bentall) or ascending aorta surgery in asymptomatic patients undergoing AVR
  - Previous coronary bypass surgery
  - Previous any heart valve surgery
  - Impaired renal function, i.e. creatinine  $>200$   $\mu$ mol/L or glomerular filtration rate  $< 30$  mL/min/1.73 m<sup>2</sup>
  - Significant pulmonary hypertension at rest (systolic AP pressure  $> 50$ mmHg)
  - Uncontrolled hypertension at rest (systolic pressure  $>180$  mmHg or diastolic pressure  $>100$  mmHg)
  - Significant co-morbidity with reduced life expectancy ( $< 3$  years)
  - Uncontrolled diabetes mellitus (HbA1C  $> 9\%$ )
  - Significant COPD (FEV1  $< 70\%$  of predicted value)

Any type of atrial fibrillation including present or documented history of atrial fibrillation

### **2.3 Exercise testing**

Exercise testing has been performed according to local practice and experience, either Treadmill (Bruce protocol) or semi-supine ergobicycle (Ramp R15w protocol).

For patients who exercised on semi-supine ergobicycle first 3 min of pedaling was without workload. After that there was incremental increase in workload, 15w for every minute. On treadmill, the levels were changed every 3 minutes with standard (according to Bruce protocol) increase in speed and slope.

During exercise special attention was on AS symptom onset. Test was stopped if emergence of symptoms was observed (presyncope, syncope, dizziness, dyspnea, chest pain). Patients were encouraged to exercise as much as possible. Exercise testing was carried out following the current American Society of Echocardiography Guidelines for Performance of Stress Echocardiography<sup>12</sup>. During exercise-testing, patients underwent 12-lead ECG monitoring, and blood pressure was measured every 3 min during exercise, at peak effort, and 3 min later. The criteria for interrupting either test was severe chest pain, dizziness/syncope, ST-segment shift  $\geq 2$  mm diagnostic for ischemia in the setting of LV hypertrophy, extreme dyspnea/fatigue, excessive increase (systolic blood pressure  $>240$  mm Hg, diastolic blood pressure  $>120$  mm Hg), or drop in blood pressure ( $\geq 20$ mmHg).

### **2.4 Aortic valve replacement procedure**

Before the AVR patients were informed about the advantages and disadvantages of each prosthesis type. The selection of the aortic valve prosthesis was made considering patient's

choice, indications by the actual aortic valve surgery guidelines<sup>26-27</sup> as well as surgeon's decision according to institutional protocols. After these considerations, surgeon decided on the surgical approach between conventional and minimally invasive, using full median sternotomy or partial j-sternotomy. Consistent with the chosen surgical approach, standard or mini cardiopulmonary bypass (CPB) circuit under full heparinization on the arrested heart was used. Standard aortic cannulation was used, and venous cannulation was adjusted to the type of the CPB. Myocardial protection was achieved with the use of cardioplegic solution and selected by the institutional protocol and surgeon's preference adjusted to each patient. Standard surgical technique was used according to the type of surgery. Postoperatively, all patients were treated with unfractionated or low-molecular weight heparin until removal of chest tubes and warfarin or aspirin were initiated thereafter, according to guidelines and local practices. After the hospital discharge, patients with a biological prosthesis were treated with warfarin with a target International Normalized Ratio (INR) between 2 and 3 for 2-3 months. Patients with a mechanical prosthesis were anticoagulated lifelong with a target INR between 2-3.

### **3. DEFINITIONS OF ENDPOINTS**

Operative mortality was defined as death within 30 days of surgery. Cardiovascular mortality was defined as sudden cardiac death, death from myocardial infarction, heart failure, complications of cardiac surgery or percutaneous coronary intervention, stroke or other cardiovascular disease. Sudden cardiac death was defined as either witnessed instantaneous unexpected death, or unwitnessed unexpected death, if other causes of death were excluded with reasonable certainty. Unplanned hospitalization due to the heart failure was defined as an

unplanned urgent admission for the management of congestive heart failure lasting at least 24 hours. Acute myocardial infarction was defined as detection of rise and/or fall of cardiac biomarkers (preferably high-sensitive troponin) with at least one value above the 99th percentile of the URL together with evidence of myocardial ischemia with at least one of the following:

- Symptoms of ischemia
- ECG changes indicative of new ischemia (new ST-T changes or new left bundle branch block [LBBB])
- Development of pathological Q waves in the ECG

Periprocedural Acute myocardial infarction was defined as > 10 fold in increase in high sensitive Troponin.

Stroke was defined as an acute symptomatic episode of neurological dysfunction attributed to a vascular cause, sub-classified as follows:

- Ischemic stroke is defined as an acute symptomatic episode of focal cerebral, spinal, or retinal dysfunction caused by an infarction of central nervous system tissue
- Hemorrhagic stroke is defined as an acute symptomatic episode of focal or global cerebral or spinal dysfunction caused by a non-traumatic intra-parenchymal, intraventricular, or subarachnoid hemorrhage
- Undetermined stroke is defined as a stroke with insufficient information to allow categorization as Ischemic or Hemorrhagic as defined above

## 4. Supplementary Results

**Supplementary Table 1.** Patient enrollment per participating centers

University Clinical Centre of Serbia, Belgrade, Serbia	Principal Investigator: Marko Banovic	115 patients
Clinical Center Zvezdara, Belgrade, Serbia	Principal Investigator: Goran Loncar	1 patient
Novi Sad, Serbia	Principal Investigator: Lazar Velicki	3 patients
Zagreb, Croatia	Principal Investigator: Hrvoje Gasparovic	4 patients
Aalst, Belgium	Principal Investigator: Martin Penicka	11 patients
Vilnius, Lithuania	Principal Investigator: Sigita Glaveckaite	5 patients
Katowice, Poland	Principal Investigator: Marek Deja	8 patients
Turin, Italy	Principal Investigator: Stefano Salizzoni	2 patients
Prague, Czech Republic	Principal Investigator: Martin Kotrc	8 patients

**Supplementary Table 2.** Post-operative hemodynamic variables

	Early surgery group	Conservative treatment group	P
EF post surgery (%)	66.1±8.2	67.0±7.75	0.75
P <sub>mean</sub> post surgery (mmHg)	13.9±5.2	15.5±7.0	0.51
V <sub>max</sub> post surgery (m/s)	2.4±0.5	2.5±0.5	0.61

**Supplementary Table 3.** Complications after surgery (within 30-day after surgery)

	Early surgery group (n=72)	Conservative treatment group (n=25)
Stroke/TIA	2 (2.8%)	0
Acute myocardial infarction	0	0
Bleeding	3 (4.2%)	0
Major vascular complication	0	0
Acute kidney injury	0	0

(stage 3 and 4)		
New onset AF	9 (12.5%)	5 (20%)
Permanent pacemaker implantation	0	0
Endocarditis	1 (1.4%)	0
Paravalvular leak	2 (2.8%)	0
Reoperation	2 (2.8%)	0
Death	1 (1.4%)	1 (4%)

TIA – transient ischemic attack, AF – atrial fibrillation

**Supplementary Table 4.** Case Fatalities in both groups

Early surgery group	Age	Days from randomization to death	Explanation	Conservative treatment group	Age	Days from randomization to death	Explanation
Patient 1	77	74	SCD at home (while waiting for scheduled SAVR)	Patient 1	65	2001	SCD at home
Patient 2	83	158	Significant paravalvular leak (reoperated)	Patient 2	63	787	SCD at home
Patient 3	76	286	Postoperative aortic regurgitation	Patient 3	65	531	hemorrhagic stroke

			followed with progressive heart failure				
Patient 4	73	437	Perivalular abscess (reoperated)	Patient 4	68	199	SCD during sleep
Patient 5	77	73	Post-op arrhythmia that led to HF, cardiogenic shock and ultimately death	Patient 5	76	731	SCD at home
Patient 6	68	1248	Ischemic stroke (mechanical valve)	Patient 6	64	1079	Pancreatic cancer
Patient 7	46	866	SCD (collapsed on the street)	Patient 7	87	446	SCD at home
Patient 8	69	1261	hemorrhagic stroke (mechanical valve)	Patient 8	82	504	Progressive HF result cardiac arrest in hospital
Patient 9	70	196	SCD (daughter found her death in the apartment)	Patient 9	68	69	Pneumonia followed with ARDS
				Patient 10	78	1107	Pneumonia (Covid-19 related)
				Patient 11	71	300	Sepsis (phlegmona of the right arm followed with sepsis)
				Patient 12	75	652	Pneumonia (Covid-19



							related)
				Patient 13	71	421	Pneumonia (Covid-19 related)
				Patient 14	75	799	SCD at home
				Patient 15	69	1264	hemorrhagic stroke
				Patient 16	82	985	Progressive dementia

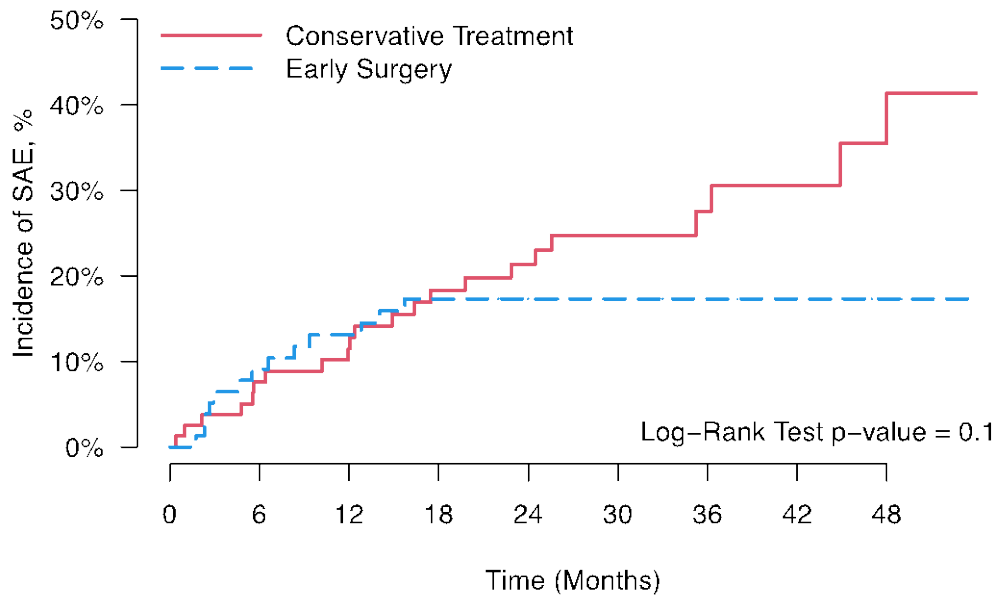
SCD – sudden cardiac death, CVI – cerebrovascular insult, COVID-19 – corona virus disease 19

**Supplementary table 5.** List of serious adverse events

<b>Serious Adverse Events</b>	<b>Group</b>	
	<b>Conservative group</b>	<b>Early surgery group</b>
pericardial effusion (needing hospitalization)	0	1
Aortic valve related symptoms ¶	15	0
Aortic valve reoperation	0	3
Bleeding requiring hospital admission	1	4
Hospitalization due to the Colon Cancer	0	1
Paroxysmal atrial fibrillation needing hospital treatment	1	1
Pneumonia	3	1
Hospitalization due to Prostatic cancer	1	0
Hospitalization due to the urinary bladder cancer	1	0
Hip trauma leading to hip surgery	0	1
Pleural effusion (needing hospital treatment)¶	1	1
<b>Total</b>	<b>23</b>	<b>13</b>

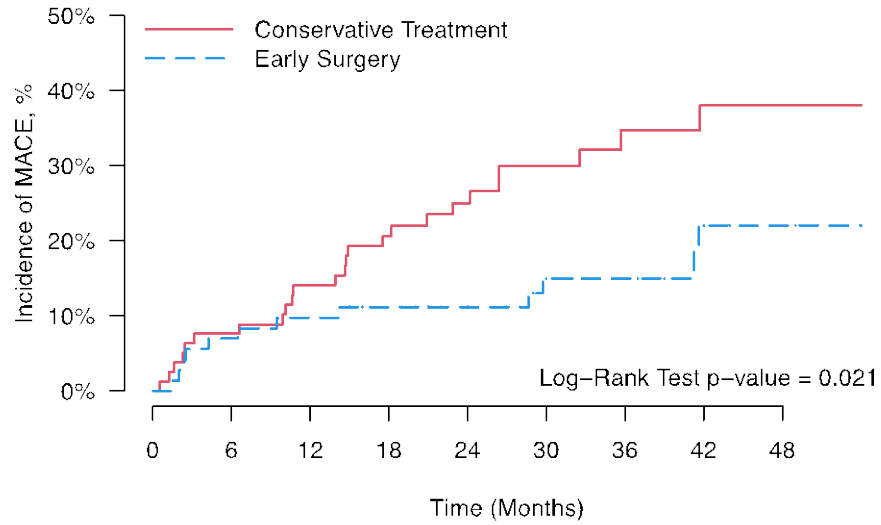
¶ Post-operative pleural effusion, Aortic valve related symptoms include: syncope/dizziness, chest pain and pronounced dyspnea without signs of HF

**Supplementary Figure 1.** Kaplan-Meier cumulative incidence rates estimates of serious adverse events (SAE, intention to treat analysis)



79	73	67	58	50	36	26	17	10
78	69	63	57	51	41	34	21	11

**Supplementary Figure 2.** Kaplan-Meier cumulative incidence rates estimates of primary endpoint excluding 6 subjects who were not operated within early surgery group



79	73	66	59	49	36	25	19	12
72	67	64	60	54	44	37	22	13

**Supplementary Figure 3.** Subgroup analysis assessing heterogeneity of treatment effect. Subgroups were selected at the analysis stage based on their clinical significance and without having access to outcome data. Individual parameters were dichotomized by median value except for age using cut-off 65 years and LVEF using cut-off of 60%.

