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*Journal of the Cardiology Society of Serbia*

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# SRCE I KRVNI SUDOVI
# HEART AND BLOOD VESSELS

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# SRCE I KRVNI SUDOVI
## HEART AND BLOOD VESSELS

**Volumen 42 Broj 3 2023. godina**

## Sadržaj / *Content*

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Original article

# Adult congenital heart diseases - 10-years study in patients treated at the Institute for Cardiovascular Diseases of Vojvodina

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**Abstract**

**Introduction.** The number of adult patients with a congenital heart defect (adult congenital heart disease - ACHD) is higher than children born with the defect. The study aimed to examine the characteristics of patients with ACHD treated over a 10-year period at the Institute for Cardiovascular Diseases of Vojvodina (ICVDV).

**Methods.** A retrospective cohort study included patients examined and treated under the diagnosis of congenital heart defect at IKVBV from 2011 to 2021. Patients with ACHD were identified by searching the electronic database based on the ICD classification. In the examined group, we evaluated demographic characteristics, the presence of comorbidities, and complications that developed during follow-up in a predefined time period.

**Results.** Out of 106123 patients treated during the 10-year period, 0.8% were diagnosed with ACHD. The most frequently registered ACHD were atrial septal defect (ASD) with 49.1%, ventricular septal defect with 13.1%, congenital anomalies of the aortic valve 10%, and coarctation with aorta narrowing 6.2%. In comparison, complex defects like tetralogy of Fallot with 2.7% and transpositions of great arteries (1.2%) had lower prevalence. The most prevalent complications were heart rhythm disturbances in 44% and pulmonary hypertension in 15.2% of ACHD patients. The most common comorbidities were arterial hypertension (46.7%) and ischemic heart disease (20.5%).

**Conclusion.** The prevalence of ACHD was 0.8%. The most prevalent defects were from the group of septal defects. The most prevalent complications were heart rhythm disorders and pulmonary hypertension.

**Keywords** adult congenital heart diseases, complications, comorbidities

## Introduction

Congenital heart defects (CHDs) represent the most common anomalies, occurring in 0.8% to 1% of cases. Advances in diagnostics and therapeutics enable timely detection, often as early as the prenatal period, offering the potential for prompt intervention. Despite a trend toward primary surgical correction, in some complex cases, only palliative surgical procedures may be feasible.[1,2] Conversely, percutaneous techniques for addressing CHDs are widely applied when applicable, such as using occluders for atrial septal defects (ASDs). With improved treatment, a growing number of these patients reach adulthood (more than 90%), and it is now acknowledged that the number of adults with CHDs far exceeds the number of newborns with these defects. According to the 2020 recommendations of the European Society of Cardiology, the term "adults with CHD" has been replaced with "Adult Congenital Heart Disease (ACHD)".[2]

It is estimated that there are over 1.2 million ACHD patients in Europe[3] and over 1.6 million in the United States.[4] Many ACHD patients have experienced frequent hospitalizations, repeated surgeries and interventions, lifelong medication regimens, physical intolerance, reduced quality of life, and a shortened lifespan since a young age.[2] Additionally, in adulthood, these patients face a higher incidence of complications related to CHDs. They are at greater risk of arrhythmias and sudden cardiac death, with a threefold higher prevalence of atrial arrhythmias (AA) compared to the general population.[5] Infective endocarditis (IE) is also more common in ACHD patients, with a 30-140 times greater incidence than in the general population.[6]

Heart failure (HF) develops in 20-50% of ACHD patients and is the leading cause of death.[2] The true incidence may be even higher, as signs and symptoms of HF are often subtle. The pathophysiology of cardiorespiratory dysfunction is complex, and it involves elements seen in acquired HF, with the primary pathophysiological mech-

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anism being chronic pressure and/or volume overload.[7] Myocardial lesions (such as those resulting from bypass surgery, ventriculotomy, chronic hypoxia, etc.) also play a role in ADCH HF. These patients may also develop coronary artery disease (CAD) associated with aging or congenital coronary anomalies. They are also prone to developing other acquired heart diseases during their lifetime, including myocarditis, rheumatic or non-rheumatic valvopathies, and persistent tachyarrhythmias.

Among complications related to CHDs, pulmonary hypertension (PH), especially post-capillary PH, is common. In severe and inadequately treated cases of left-to-right shunt defects, pre-capillary PH (PAH) and pulmonary vascular disease (Eisenmenger syndrome) can develop. The development of aortic aneurysms and/or dissections is more often associated with arthropathies or post-interventional (formation of a "neo-aorta").[2] Patients with cyanotic CHD experience symptoms of hyperviscosity and numerous complications specific to different types of cyanotic and non-cyanotic CHDs.

Intensive monitoring and regular follow-up visits for all ACHD patients are needed to prevent complications and deterioration and to determine the appropriate timing for possible catheter-based or surgical procedures to improve long-term prognosis. Echocardiography plays a crucial role, along with magnetic resonance imaging (MRI) and/or computed tomography (CT) of the heart.[8,9]

In addition to complications stemming from the underlying disease and prolonged lifespan, ACHD patients are at greater risk of developing comorbidities such as hypertension, diabetes mellitus, hyperlipidemia, obesity, and atherosclerotic disease. Paradoxically, some studies report a higher prevalence of obesity and metabolic syndrome in this population.[10]

Beyond traditional risk factors for ischemic heart disease, ACHD patients are subject to other contributing factors for premature coronary disease, including obstructive left heart lesions, aortic stenosis, reperfusion injuries during surgery, turbulent blood flow across residual defects, coronary anomalies, and more.[2]

The incidence of cerebrovascular events (CVEs) is higher in ACHD patients compared to the general population, primarily attributed to the presence of interatrial shunts, leads, artificial materials in the heart, arrhythmias, and HF.(11) These patients also have an increased likelihood of developing chronic kidney disease (CKD) due to various factors, including blood hyperviscosity, alterations in renal blood flow, neurohormonal activation, and the impact of postoperative intensive care.[12]

The aim of our study was to investigate the characteristics of the ACHD patient population treated at the Institute for Cardiovascular Diseases of Vojvodina (ICVDV) and to explore the presence of specific complications and comorbidities.

## Methods

We conducted a retrospective cohort study. The study included patients with a congenital heart defect selected by diagnosis code for specific CHDs based on the International Classification of Diseases, 10th revision (ICD-10), and through notes associated with the given diagnosis containing words related to one of the CHDs. The following diagnosis codes for CHDs were specified: Q20.0-Q20.9; Q21.0-Q21.9; Q22.0-Q22.9; Q23.0-Q23.9; Q24.0-Q24.9, except Q24.6; Q25.0-Q25.9; Q26.0-Q26.9, except Q26.5 and Q26.6) and the codes for Marfan syndrome (Q87.4) and Turner syndrome (Q96), which are considered aortopathies, among others. For the search within diagnosis notes, the following words and abbreviations were provided: ASD, VSD, PDA, Eisenmenger, congenital, bicuspid valve, univalvular aortic valve, BAV, Fontan, univentricular heart, UVH, coronary anomalies, ALCAPA, ARCAPA, AAOCA, and coronary fistulas. Patients treated with the diagnoses above were categorized into the study group of ACHD patients. Exclusion criteria included patients diagnosed with persistent foramen ovale and mitral valve prolapse. A total of 926 patients meeting the inclusion criteria were identified. However, due to incomplete data in 90 patients, not all parameters could be analyzed. Demographic parameters were analyzed, along with complications and comorbidities that developed within a predefined time frame. Interventional procedures such as percutaneous coronary intervention (PCI) and the percutaneous placement of ASD occluders, pacemaker implantation, or implantable cardioverter-defibrillators (ICD) were also analyzed, as well as cardiothoracic surgical interventions.

The parameters were extracted from the patient's electronic records for predefined time frames. The data were finally checked by one investigator for missing or contradictory entries and for values beyond the normal range. The study was conducted according to the principles of the Declaration of Helsinki. The ethics committee approved the study of the ICVDV.

### Statistical analysis

Data were statistically processed using the Statistical Package for Social Sciences (SPSS) version 21. Standard descriptive statistical methods were employed, continuous variables were expressed as means and standard deviations, and categorical variables were expressed as absolute numbers and percentages. Values with a significance level of $p < 0.05$ were considered statistically significant.

## Results

Over the predefined 10-year period, a total of 106123 patients were examined and treated at the Institute for Cardiovascular Diseases of Vojvodina (ICDV). The prevalence of Adult Congenital Heart Disease (ACHD) was 0.8%, with an average patient age of 47.9 ± 36.4 years. Among the ACHD patients, 55% were females.

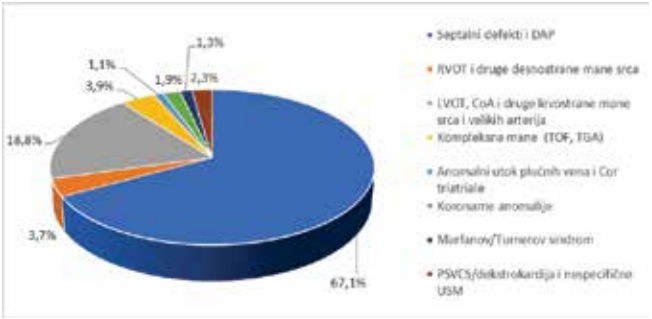
The atrial septal defect had the highest prevalence of 49.1%, VSD 13.1%, congenital aortic valve anomalies 10%, followed by coarctation of the aorta and other aortic stenoses 6.2%, while complex defects such as Tetralogy of Fallot (TOF) accounted for 2.7% and complete transposition of the great arteries (TGA) for 1.2% of cases (Table 1). The most prevalent ACHDs were within

**Table 1**. Different ACHDs with mean age±SD

| Different ACHDs | N | % | Age | SD |
|---|---|---|---|---|
| ASD | 455 | 49.1 | 52.6 | 16.98 |
| VSD | 121 | 13.1 | 40.6 | 17.82 |
| Aortic valve defects | 93 | 10 | 38.6 | 13.46 |
| Coarctation and other aorta narrowings | 57 | 6.2 | 45.6 | 18.16 |
| Pulmonary valve stenosis | 25 | 2.7 | 42.3 | 18.96 |
| T. Fallot | 25 | 2.7 | 38.6 | 15.11 |
| Persistent arterial duct | 23 | 2.5 | 44.9 | 19.57 |
| Aortic stenosis | 20 | 2.2 | 47.2 | 25.40 |
| Coronary anomalies | 18 | 1.9 | 50.6 | 19.73 |
| AV canal | 12 | 1.3 | 41.3 | 19.92 |
| Marfan/Turner Sy | 12 | 1.3 | 38.6 | 11.89 |
| Dextrocardia | 11 | 1.2 | 60.3 | 15.54 |
| Transposition | 11 | 1.2 | 32.0 | 15.46 |
| Other congenital septal defects | 9 | 1 | 45.2 | 12.02 |
| Cor triatriale | 6 | 0.6 | 58.0 | 18.85 |
| Ebstein's anomaly | 6 | 0.6 | 41.0 | 19.60 |
| Unspecific heart defects | 5 | 0.5 | 30.3 | 12.04 |
| Persistent left superior vena cava | 5 | 0.5 | . | . |
| Anomalous pulmonary vein drainage | 4 | 0.4 | 36.5 | .71 |
| Other aortic and mitral valve defects | 4 | 0.4 | 48.5 | 12.02 |
| TV/right heart malformation | 3 | 0.3 | 24.3 | 6.66 |
| Aortopulmonary window | 1 | 0.1 | 21.0 | . |

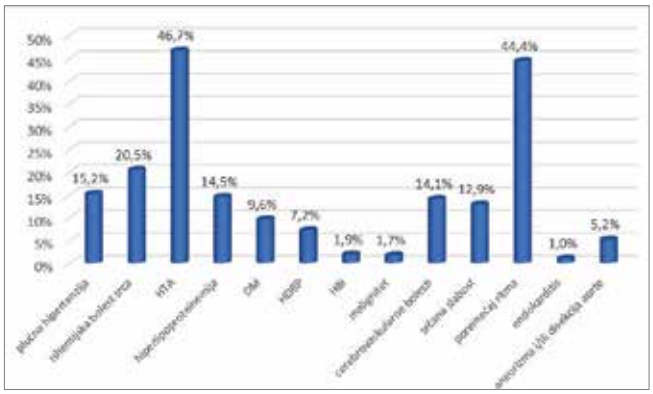
AV, atrioventricular; TV, tricuspid valve; N, number

**Figure 1.** Different comorbidities/complications in ACHD population




Legend: HTA, arterial hypertension; DM, diabetes mellitus; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; HF, heart failure; CVD, cerebrovascular disease; CAD, coronary artery disease; HLP, hyperlipoproteinemia; IE, infective endocarditis

**Figure 2.** Prevalence of complications and co-morbidities in ACHD




the septal defect group, including persistent arterial duct (PDA), which is an example of simple CHDs with left-to-right shunt. Next were anomalies associated with the left ventricular outflow tract (LVOT), including valvular, subvalvular, and supravalvular aortic stenoses, along with coarctation of the aorta (CoA) and malformations designated as other aortic abnormalities and left-sided heart defects.

Arrhythmia was the most common complication (44%) followed by pulmonary hypertension (PH) 15.2%, and heart failure (12.9%). Aneurysm and/or aortic dissection were less common (5.2%), and infective endocarditis (IE) was rare (1.1%). Regarding comorbidities among ACHD patients, hypertension (46.7%) and ischemic heart disease (IHD) (20.5%) were the most prevalent, followed by hyperlipoproteinemia (14.5%) and cerebrovascular diseases (14.1%). Diabetes mellitus (DM) was present in 9.6% of cases, followed by chronic obstructive pulmonary disease (COPD) (7.2%), CKD (1.9%), and malignancy (1.7%) (Figure 1).

Table 2 illustrates the distribution of these complications and comorbidities according to ACHD type. The most common complication was arrhythmia in the septal defect and PDA group (33.7%), and this same group had the highest prevalence of hypertension (34.9%). In the overall population, atrial rhythm disturbances were present in 19%, with atrial fibrillation (AF) occurring in 16.1% of cases. Chronic coronary syndrome was observed in 17.1% of ACHD patients (Table 3).

Cardiothoracic surgery was performed on a total of 141 patients (16.9%) during the 10-year treatment of ACHD patients, while septal ASD occluder implantation was required in 7.1% of cases. Pacemaker implantation was

**Table 2**. Complications by different ACHD

| | Septal defects and DAP | | RVOT | | LVOT, CoA | | Complex ACHD (TOF, TGA) | | APVD and cor triatriale | | Coronary anomalies | | Marfan/ Turner syndrome | | PSVCS/dextrocardia and unspecified | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Complications | N | % | N | % | N | % | N | % | N | % | N | % | N | % | N | % |
| Arrhythmias | 282 | 33.7 | 13 | 1.6 | 35 | 4.2 | 20 | 2.4 | 4 | 0.5 | 7 | 0.8 | 4 | 0.5 | 6 | 0.7 |
| IE | 4 | 0.5 | 2 | 0.2 | 1 | 0.1 | 0 | 0 | 0 | 0 | 0 | 0.0 | 1 | 0.1 | 0 | 0 |
| HF | 81 | 9.7 | 5 | 0.6 | 12 | 1.4 | 3 | 0.4 | 1 | 0.1 | 2 | 0.2 | 2 | 0.2 | 2 | 0.2 |
| Aneurism and/ or dissection | 15 | 1.8 | 0 | 0 | 29 | 3.5 | 0 | 0 | 0 | 0 | 1 | 0.1 | 2 | 0.2 | 1 | 0.1 |
| HTA | 292 | 34.9 | 8 | 1.0 | 61 | 7.3 | 8 | 1.0 | 2 | 0.2 | 10 | 1.2 | 2 | 0.2 | 7 | 0.8 |
| HLP | 91 | 10.9 | 3 | 0.4 | 17 | 2 | 1 | 0.1 | 2 | 0.2 | 5 | 0.6 | 0 | 0 | 2 | 0.2 |
| DM | 61 | 7.3 | 1 | 0.1 | 5 | 0.6 | 2 | 0.2 | 3 | 0.4 | 2 | 0.2 | 0 | 0 | 6 | 0.7 |
| CAD | 138 | 16.5 | 1 | 0.1 | 18 | 2.2 | 1 | 0.1 | 3 | 0.4 | 5 | 0.6 | 1 | 0.1 | 4 | 0.5 |
| COPD | 42 | 5.0 | 3 | 0.4 | 7 | 0.8 | 3 | 0.4 | 0 | 0 | 0 | 0 | 0 | 0 | 5 | 0.6 |
| CKD | 14 | 1.7 | 0 | 0 | 1 | 0.1 | 0 | 0 | 1 | 0.1 | 0 | 0 | 0 | 0 | 0 | 0 |
| CVD | 100 | 12.0 | 2 | 0.2 | 7 | 0.8 | 2 | 0.2 | 0 | 0 | 1 | 0.1 | 0 | 0 | 6 | 0.7 |
| Malignitet | 11 | 1.3 | 0 | 0 | 2 | 0.2 | 0 | 0 | 0 | 0 | 0 | 0.0 | 1 | 0.1 | 0 | 0 |

HTA, arterial hypertension; DM, diabetes mellitus; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; DAP, persistent arterial duct; LVOT, left-sided heart obstructive defects; CoA, aortic coarctation; RVOT, right-sided heart obstructive defects; TOF, tetralogy of Fallot; TGA, transposition of the great arteries; PSVCS, persistent left superior vena cava; HF, heart failure; CVD, cerebrovascular disease; CAD, coronary artery disease; HLP, hyperlipoproteinemia; APVD, anomalous pulmonary vein drainage

**Table 3**. Specific complications and comorbidities in ACHD

| Specific complications | N | % |
|---|---|---|
| AV block, bundle branch block and rhythm disturbances | 118 | 14.1 |
| Atrial rhythm disturbances | 167 | 19.9 |
| Ventricular rhythm disturbances | 57 | 6.8 |
| Sinus node disfunction | 6 | 0.7 |
| Unspecific rhythm disturbances | 39 | 4.7 |
| AF | 135 | 16.1 |
| Aneurism and/or dissection with rupture | 4 | 0.4 |
| Aneurism and/or dissection without rupture | 44 | 5.2 |
| precerebral arteries occlusion | 62 | 7.4 |
| Cerebrovascular events | 56 | 6.7 |
| Acute coronary syndrome | 28 | 3.3 |
| Chronic coronary syndrome | 143 | 17.1 |

AV, atrioventricular; AF, atrial fibrillation

necessary in 2.9% of patients, and implantable cardioverter-defibrillator (ICD) placement in 0.6%. Coronary angiography was performed in 23.7% of patients for the diagnosis and treatment of chronic or acute coronary syndrome, with percutaneous coronary intervention (PCI) performed in 5.1%.

## Discussion

Patients with ACHD are becoming increasingly prevalent in adult cardiology as more children and young adults with complex, palliatively managed CHDs survive into adulthood. In Japan, the number of adults with ACHD equaled that of children with CHDs in 1997, with an estimated annual growth rate of 5%.[13] Our study found a 0.8% prevalence of ACHD during a ten-year follow-up, corresponding to the estimated prevalence in children (0.8-1%). A Canadian study reported a prevalence of CHDs of 4.09 per 1000 adults, or 5.78 per 1000 in the general population in 2000.[14] However, it should be noted that the registered number of ACHD patients in our study is not representative of the general population, as some adult ACHD patients gravitate towards other specialized cardiology centers with experience in managing CHDs.

Studies have demonstrated an increasing number of adults with ACHD and a higher proportion of severe defects. A Canadian study between 1983 and 2000 reported a prevalence of severe CHDs of 1.45 per 1000 children and 0.38 per 1000 adults, constituting 12% and 9% of all defects, respectively. The average age of all patients with severe CHDs increased from 11 years in 1985 to 17 years in 2000.[10] From 1996 to 2007, the number of simple CHDs steadily increased, while the number of severe CHDs significantly increased from 2008/2009[15]. In our studied ACHD group, simple defects were more prevalent compared to severe ACHD (TOF, TGA, atrioventricular canal). Authors report a prevalence of complex ADCH being twice more compared to our population.[14]

Among our ACHD patients, the most common conditions were ASD (49.1%), VSD (13.1%), congenital aortic valve anomalies (10%), followed by coarctation of the aorta and other aortic stenosis (6.2%). Other studies reported different prevalence rates, with VSD (19.2%), ASD (13.0%), TOF (9.3%), univentricular heart (9.4%), and CoA (7.0%).[15] A study in the same country but on newborns and infants up to 3 months reported the following prevalences: VSD (48.9%), ASD (17.0%), valvular pulmonary stenosis (6.1%), PDA (4.3%), and CoA (3.6%)[16]. Although many muscular VSDs spontaneously close in early childhood, this defect remains the most common in later years.[17)]

Countries with lower living standards, especially in Asian regions, exhibit a heightened occurrence of ASDs. This may be correlated with environmental factors such as

air pollution.[18] ASD is considered a simple CHD, and considerable defects have a good prognosis if identified and treated timely. The chosen treatment method is percutaneous septal occluder implantation, which was performed in 7.1% of our ACHD patients.

The third most prevalent defect in our group were aortic valve anomalies (most commonly BAV), presented in 10% of cases. This percentage is likely even higher, as BAV was initially reported as congenital aortic stenosis (2.2%) or as part of anomalies involving the aortic and mitral valves (0.4%). BAV occurs in 2% of the general population and does not always manifest as hemodynamic abnormalities. Valve dysfunction is reported in 16%-68% of cases, with dominant stenosis in 19.5% and regurgitation in 26.2%. Aortic dilation occurs in 84.8% of cases, more commonly in the ascending portion (81.3%) than in the aortic root (3.5%). BAV, aortopathies, and defects that require surgical correction in the aortic root present the risk factor for aortic dissection and/or aneurysms.[19]

Among other complications that can result from CHDs, stroke and arrhythmias are most frequently mentioned[2]. United States study from 1998 to 2011 reported a 91% increase in hospitalizations for ACHD patients compared to a 21% increase in patients without ACHD.[20] ACHD patients in our study had a high incidence of stroke 12.9%. ACHD patients are at higher risk of developing all types of arrhythmias, particularly atrial arrhythmias related to cardiac surgery and cardiac remodeling, while left atrial enlargement promotes atrial fibrillation (AF).[2] In a large study involving 38,428 ACHD patients, 15% had atrial arrhythmias, and the risk increased with age. The appearance of atrial arrhythmias increased the risk of any adverse event, with a 50% increase in mortality, doubling morbidity for cerebrovascular events and heart failure, and a threefold increase the risk of cardiac interventions.[5] In our study population, rhythm disturbances were common, with atrial arrhythmias being the most prevalent. The occurrence of atrial arrhythmias in our ACHD patients were higher when compared to other studies, likely due to the higher prevalence of septal defects[2]. ACHD patients are more likely to develop AF, even at a younger age.[5]

Individuals with CHDs are 15-100 times more likely to develop infective endocarditis (IE), with its occurrence more frequently associated with defects affecting the valves[6]. Pulmonary arterial hypertension (PAH) represents a complication of CHDs (PAH-CHD) that is sought to be avoided through early recognition of congenital defects and timely treatment. PAH-CHD is characterized by elevated pulmonary vascular resistance (PVR).[2,21] Post-capillary PH is more common and results from pressure "transmission" to the pulmonary circulation due to increased left ventricular filling pressure in cases of LV dysfunction or AV valve regurgitation when PVR is normal. Our study group had a 15.2% prevalence of PH, with over 95% of cases being secondary. We identified six cases of Eisenmenger syndrome, two of which had ASD and four had VSD.

Considering the older age of ACHD patients, it is expected that, in addition to their primary condition, they would have a higher risk of developing acquired diseases due to exposure to conventional risk factors for cardiovascular disease. In a cohort analysis of 250 patients[22] with ACHD, with an average age of 51±15 years and 53% of them being male, selective coronary angiography was performed for reasons unrelated to suspected CAD. Significant CAD was found in 9.2% of the participants, and its frequency was similar to that in the general population. Analysis of traditional risk factors for CAD concluded that they hold equal importance in prevention as in the general population. The strongest predictors of coronary disease were hypertension (HTA) and hyperlipidemia, with a prevalence of 29.3% for HTA and 19.1% for hyperlipidemia. None of the included cyanotic ACHD patients (7.2%) in the study had significant CAD. The occurrence of HTA and CAD in our study group was higher compared to data in other studies, while the prevalence of diabetes mellitus (DM) and hyperlipidemia was in line with previously published results in other studies. ACHD patients more frequently presented with chronic coronary syndrome. Approximately 2% of ACHD patients have congenital anomalies of coronary vessels, and it remains unexplored to what extent they contribute to the clinical manifestations of CAD.

Current epidemiological data indicate that CKD occurs more frequently among ACHD patients (in 30-50% of cases), especially in cyanotic defects and at an earlier age. Mild renal dysfunction was present in 41% of patients, while moderate to severe dysfunction was observed in 9%.[23] They are at 10-100 times greater risk of CVE despite the absence of classical cardiovascular risk factors. A large Danish study encompassing all adult ACHD patients from 1963 to 2017 revealed that the risk of myocardial infarction (MI) at the age of 30 was 0.7% in ACHD patients, compared to 0.1% in the general population cohort. At the age of 60, the respective risks were 7.4% versus 2.9%.[11] In this study the occurrence of stroke is associated with the following conditions: ASD (4%); closed ASD or VSD (1.4%); corrected TOF (2.4%); Eisenmenger's physiology (5.1%); other cyanotic ACHD (23.3%); mechanical valves (3.3%); absence of sinus rhythm (25%); implanted pacemakers (7%); endocarditis (2%); cardiac surgical interventions (11%); and percutaneous interventions (2%).(24) In our cohort, 6.78% of the total number of ACHD patients experienced a stroke.

## Conclusion

The prevalence of congenital heart diseases in our adult population is 0.8%. The most common defects in adulthood are septal defects, while anomalies of the aortic valve rank second. The most frequent complications are cardiac rhythm disorders and pulmonary hypertension, with the most common comorbidities being hypertension and CAD.

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## Sažetak

### *Adultne kongenitalne bolesti srca – desetogodišnje lečenje pacijenata u Institutu za kardiovaskularne bolesti Vojvodine*

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***Uvod.*** *Broj odraslih bolesnika sa urođenom srčanom manom (adultnom kongenitalnom srčanom bolešću - ACHD) je danas veći od broja dece rođenih sa manom. Cilj rada bio je ispitivanje karakteristika bolesnika sa ACHD lečenih u 10 godišnjem periodu na Institutu za kardiovaskularne bolesti Vojvodine (IKVBV).*

***Metodologija.*** *Retrospektivna kohortna studija uključila je bolesnike pregledane i lečene pod dijagnozom urođene srčane mane na IKVBV od 2011–2021. godine. Pretraživanjem elektronske baze na osnovu MKB klasifikacije izdvojene su dijagnoze prema kojima su identifikovani bolesnici sa ACHD. Kod ispitivane grupe evaluirali smo demografske karakteristike, prisustvo komorbiditeta i komplikacija koje su se razvile tokom praćenja u predefinisanom vremenskom periodu.*

***Rezultati.*** *Od ukupno 106 123 bolesnika lečenih u toku 10 godišnjeg perioda 0.8% je imalo dijagnostikovanu ACHD. Najčešće registrovane ACHD su: defekt atrijalnog septuma (ASD) 49.1%, defekt ventrikularnog septuma13.1%, urođene anomalije aortne valvule 10%, koarktacija aorte i druga suženja aorte 6.2%, dok je udeo kompleksnih mana, tetralogije Fallot 2.7% i transpozicije velikih arterija 1.2%. Od mogućih komplikacija najzastupljenije su: poremećaj srčanog ritma 44% i plućna hipertenzija 15.2%. Od komorbiditeta najzastupljenije su arterijska hipertenzija (46.7%) i ishemijska bolest srca (20.5%).*

***Zaključak.*** *Prevalenca ACHD je 0.8%, najzastupljenije su mane iz grupe septalnih defekata. Najčešće komplikcije kod ACHD bile su poremećaj srčanog ritma i plućna hipertenzija, dok su najčešći komorbiditeti bili ishemijska bolest srca i arterijska hipertenzija.*

***Ključne reči:*** *adultne kongenitalne srčane bolesti, ACHD, urođene srčane mane, komplikacije, komorbiditeti*

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Original article

# Echocardiographic Society of Serbia (ECHOS) survey on the use of echocardiography in pulmonary hypertension

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**Abstract**

**Introduction.** Pulmonary hypertension (PH) is a chronic progressive disease affecting about 1% of the world population. The Echocardiographic Society of Serbia (ECHOS) conducted a national survey to assess the use of echocardiographic parameters for non-invasive assessment of the likelihood of PH and its early detection in real-life practice.

**Methods**. The survey consisted of 23 questions on demographics, routine assessment of right heart morphology and function, echocardiographic parameters used to screen for PH and report writing standards. The survey was sent as an online questionnaire by email to all members of ECHOS.

**Results**. A total of 150 (22.7%) members responded to the survey. Echocardiographic examinations are most commonly performed by cardiologists (51%) with more than 10 years of experience in echocardiography (46%). More than half of the survey participants (55%) routinely assess right ventricular (RV) function and morphology. Echocardiographic parameters used to assess PH such as RV outflow tract flow profile and pulmonary artery diameter are routinely assessed by half of the respondents, while other parameters such as right atrial area are less commonly evaluated (23%). Systolic RV function is routinely assessed by the majority of respondents (90%), as is systolic RV pressure (97%). In patients with pulmonary thromboembolism, an echocardiographic examination is performed routinely during hospitalisation (95%). When screening for PH, all respondents assess left ventricular function. Most survey respondents consider routine assessment of RV parameters to be clinically important and believe that targeted echocardiographic courses are required to improve PH screening (96%).

**Conclusion**. This survey highlights the lack of standardised echocardiographic assessments in screening for PH among ECHOS members. There is a need for targeted echocardiographic education that would improve routine echocardiographic practise in assessing right heart function and the likelihood of PH.

**Kew words** Echocardiographic Society of Serbia, ECHOS, pulmonary hypertension, survey

## Introduction

Pulmonary hypertension (PH) is a chronic progressive disease affecting approximately 1% of the world population[1] The estimated time from onset of symptoms to PH diagnosis is > 2 years.[2] Because of the high morbidity and mortality, early detection and referral to a PH centre is critical. PH is invasively defined by right heart catheterization (RHC) as mean pulmonary artery pressure (mPAP) > 20 mmHg at rest.[2] However, echocardiography plays an essential role in the detection and follow-up of patients with PH. It provides a comprehensive assessment of hemodynamic parameters and right ventricular (RV) function, which in turn allows echocardiographic estimation of PH probability. The key parameter for assessing the likelihood of PH is elevated systolic pulmonary artery pressure (sPAP), estimated by measuring peak tricuspid regurgitation (TR) velocity. Other parameters of RV function and morphology are also used to assign PH probability (low, intermediate, high). These parameters include: enlargement of the right ventricle and atrium, flattening of the interventricular septum (IVS), indices of RV systolic function, including tricuspid annular plane systolic excursion (TAPSE), RV fractional area change (FAC), tricuspid annular velocity (S' wave), RV free-wall strain, RV ejection fraction (RVEF) derived from 3D echocardiography, as well as RV outflow tract Doppler profile (midsystolic

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**Table 1.** Characteristics of survey participants

| Age | Number (%) |
|---|---|
| < 35 years | 30 (20%) |
| 35-50 years | 63 (42%) |
| >50 years | 57 (38%) |
| Experience in echocardiography | |
| < 5 years | 56 (37%) |
| 5-10 years | 25 (17%) |
| > 10 years | 69 (46%) |
| Level of training/specialty | |
| Cardiologist | 76 (51%) |
| Internal Medicine specialist | 44 (29%) |
| Resident | 27 (18%) |
| Pulmologist | 1 (0.7%) |
| Pediatric cardiologist | 1 (0.7%) |
| Medical doctor | 1 (0.7%) |
| Affiliation | |
| Primary Care Centre | 14 (9%) |
| Secondary Care Centre | 36 (24%) |
| Tertiary Care Centre | 85 (57%) |
| Private Practice | 15 (10%) |

**Table 2.** Echocardiographic assessments

| RV morphology and function | |
|---|---|
| Routinely | 83 (55%) |
| Only when referred for RV assessment | 1 (1%) |
| Only in decompensated heart failure | 10 (7%) |
| Only when suspected of RV dysfunction by initial echocardiographic view | 56 (37%) |
| Pulmonary artery diameter | |
| Routinely | 83 (55%) |
| Only in suspected PH | 43 (29%) |
| Never | 24 (16%) |
| RVOT flow profile assessment | |
| Routinely | 86 (57%) |
| Only in suspected PH | 43 (29%) |
| Never | 21 (14%) |
| RV free-wall diameter | |
| Routinely | 26 (17%) |
| Only in suspected PH | 94 (63%) |
| Never | 30 (20%) |
| RV diameter | |
| Routinely | 119 (79%) |
| Only in suspected PH | 23 (15%) |
| Never | 8 (5%) |
| RA area | |
| Routinely | 35 (23%) |
| Only in suspected PH | 57 (38%) |
| Never | 58 (39%) |
| Agitated saline contrast use in enlarged RV | |
| Routinely | 12 (8%) |
| Only in suspected PH | 63 (42%) |
| Never | 75 (50%) |

PH ,pulmonary hypertension; RA, right atrium; RV, right ventricle; RVOT, right ventricular outflow tract

"notching", decreased pulmonary ejection acceleration time), pulmonary artery diameter (PA), inferior vena cava (IVC) diameter and inspiratory collapsibility, and a recently introduced parameter TAPSE/sPAP, which is a non-invasive measure of RV-PA coupling.[2]

PH is classified into 5 groups (Group 1: pulmonary arterial hypertension, Group 2: PH associated with left heart disease, Group 3: PH associated with lung diseases and/or hypoxia, Group 4: PH associated with pulmonary artery obstruction (including chronic thromboembolic PH (CTEPH)), Group 5: PH with unclear and/or multifactorial mechanisms).[2] As left heart disease is the most common cause of PH, it is important to assess left-sided valvular heart disease and left ventricular (LV) systolic and diastolic function.

The Echocardiographic Society of Serbia (ECHOS) conducted a nationwide survey to assess the use of echocardiographic parameters for non-invasive assessment of the likelihood of PH and its early detection in real life clinical practice. The goal of the survey is to determine the degree of use of current recommendations for echocardiographic detection of PH.

## Methods

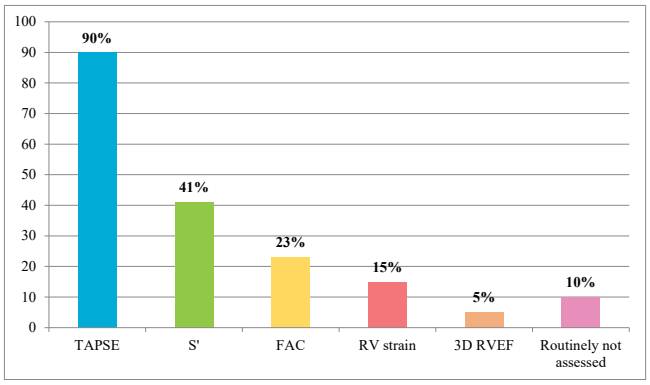
The survey was designed by ECHOS Research Committee as an online questionnaire that was sent to all members of ECHOS by email. All members (660 at the time of the survey) were invited to complete an online questionnaire anonymously by selecting one or more answers to each question. The survey was conducted from May 4 to June 4, 2023, and included 23 questions on demographics, routine assessment of right heart morphology and function, echocardiographic parameters used for screening at PH, and report writing standards. Questions were based on current European Society of Cardiology (ESC) and European Association of Cardiovascular Imaging (EACVI) guidelines and related to the use of echocardiographic parameters in the assessment of PH. All respondents agreed that the obtained data could be used for academic purposes and for scientific publications.

## Results

A total of 150 (22.7%) members of ECHOS participated in the survey (Table 1). Most respondents were over 35 years of age (80%) and had more than 10 years of experience in echocardiography (46%). Echocardiographic examinations were predominantly performed by cardiologists (51%) who were from tertiary care centres (57%). Most survey participants consider routine assessment of RV parameters to be clinically important and believe that targeted echocardiographic courses are necessary for PH screening (96%).

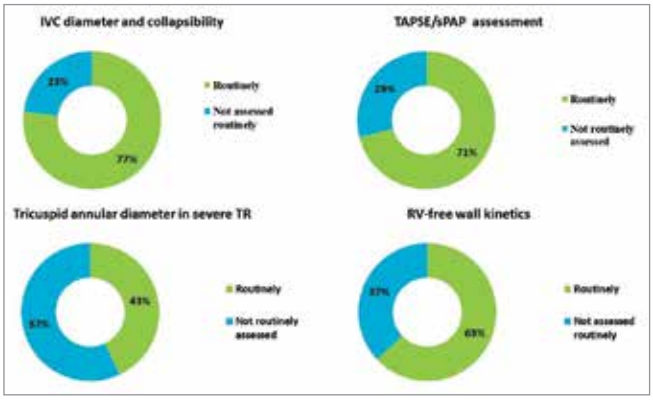
The function and morphology of the RV was routinely assessed in only 55% of cases (Table 2). The RV systolic function is most commonly assessed with TAPSE, followed by tricuspid S' velocity and FAC (Figure 1). Most reports (79%) routinely include RV diameter. More than one-third of survey respondents (39%) never report

**Figure 1.** Percentual use of echocardiographic parameters in assessment of right ventricular systolic function



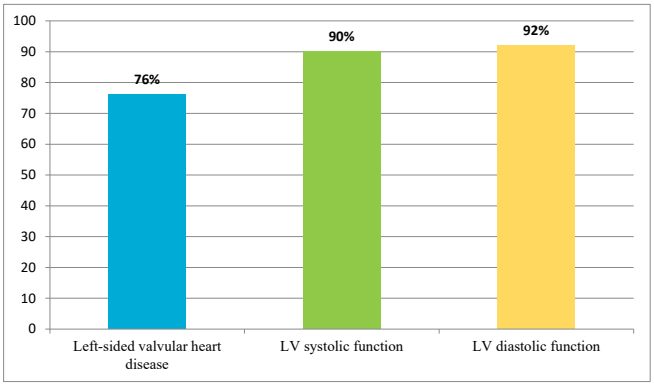

3D, three dimensional; FAC, fractional area change; RV, right ventricular; RVEF, right ventricular ejection fraction; S', peak systolic tricuspid annular velocity; TAPSE, tricuspid annular plane systolic excursion

**Figure 3**. Routine assessment of echocardiographic parameters



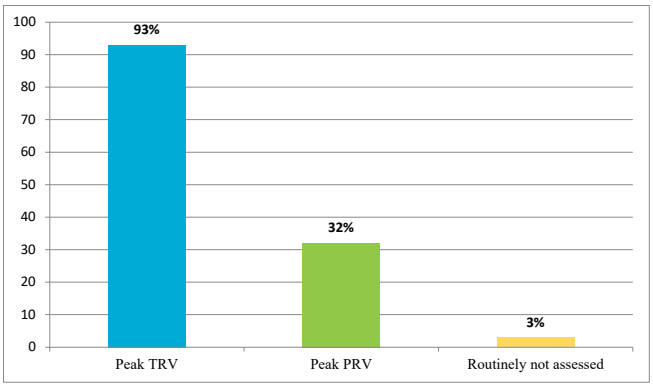

IVC, inferior vena cava; RV, right ventricle; sPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation

**Figure 5**. Left ventricular (LV) echocardiographic parameters assessment when evaluating pulmonary hypertension probability



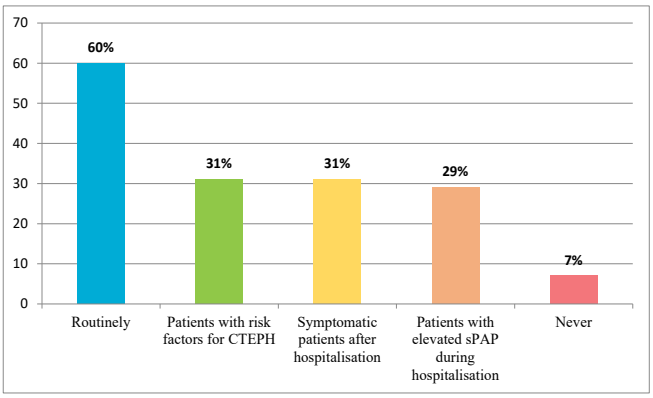

right atrial area (RAA) area, and almost as many respondents (38%) report it only when PH is suspected. RV free wall motion is not routinely assessed in 37% of cases. Half of the respondents never perform agitated saline contrast in the presence of an enlarged RV. Pulmonary artery diameter and flow profile are routinely assessed in 55% and 57%, respectively (Table 2).

**Figure 2.** Percentual echocardiographic assessment of systolic pulmonary artery pressure




PRV, pulmonary regurgitation velocity; TRV, tricuspid regurgitation velocity

**Figure 4.** Echocardiographic follow-up of patients 3-6 months after hospitalisation for pulmonary thromboembolism




CTEPH, chronic thromboembolic pulmonary hypertension; sPAP, systolic pulmonary artery pressure

Further, systolic PA pressure is usually calculated by measuring maximum tricuspid regurgitation velocity (93%) (Figure 2). RV-PA 'Coupling' (TAPSE/sPAP) is estimated by only 27% of respondents. RV wall thickness is most commonly measured when PH is suspected (63%). About half of the respondents report the phase of cardiac cycle (systole or diastole) when they observe a flattened interventricular septum (55%). Inferior vena cava diameter and inspiratory collapsibility is routinely assessed in 77% of participants (Figure 3).

In addition, almost all routinely perform an echocardiographic examination during hospitalisation for pulmonary embolism (PE) (95%). There are different standard protocols for follow-up for CTEPH in patients after acute PE (Figure 4).

Finally, all respondents assess left ventricular function in the PH probability assessment, while the assessment of LV function is not standardised (Figure 5).

## Discussion

This is the first survey on the use of echocardiographic parameters in assessing the likelihood of PH in Serbia. The aim of this survey was to assess the implementation of the new ESC guidelines for PH detection and follow-up in our echocardiographic community.

## PH probability

Increased PA pressure over time leads to RV overload and dysfunction, which can be detected by echocardiography[3-5]. However, echocardiography is not sufficient to diagnose PH, but only to assess the likelihood of PH and thus indicate the need for RHC. There is no single echocardiographic parameter that is sufficient to conclude PH. Therefore, it is necessary to perform a comprehensive echocardiographic exam to assess systolic pressure PA and additional signs suggestive of PH: increased RV diameter, RA area, IVS flattening, distended IVC with decreased inspiratory collapsibility, shortened RV outflow tract acceleration time of pulmonary ejection, decreased RV systolic function and the presence of pericardial effusion.[2]

This survey showed that routine assessment of RV function and morphology was suboptimal (45%), especially considering that most respondents were cardiologists with more than 10 years of echocardiographic experience working in tertiary centres. sPAP is most commonly assessed by measuring peak TR velocity or by measuring peak pulmonary regurgitation velocity if TR is not available. This is in line with the guidelines, which state that TR velocity above 2.8 m/s implies a PH probability. However, almost a quarter of respondents does not usually estimate IVC diameter and inspiratory collapsibility, i.e. right atrial pressure, which is important for accurate estimation of sPAP. According to the guidelines, the degree of echocardiographic PH likelihood can be altered if additional indices from at least two of three categories are present (LV and RV relationship parameters, PA parameters and IVC and RA parameters). Therefore, the assessment of additional echocardiographic signs can be crucial. Furthermore, standard and advanced echocardiographic parameters of RV structure, function and haemodynamics correlate with functional status and natriuretic peptide levels and may be useful for follow-up in patients with precapillary PH.[6]

## CTEPH

Echocardiography is indicated for risk stratification of patients with acute pulmonary embolism (PE).[7] It can provide information about RV overload, the presence of right-to-left shunts, patent foramen ovale and right ventricular thrombi, which are associated with increased mortality. The survey found that almost all respondents regularly performed an echocardiographic examination in patients with acute PE. However, there were significant differences regarding the echocardiographic follow-up of these patients (Figure 4). According to the guidelines,[2] echocardiographic follow-up is indicated in patients who have persistent dyspnoea or functional limitations after the acute PE and in asymptomatic patients with risk factors for CTEPH (recurrent PE or deep vein thrombosis, echocardiographic signs of RV overload during acute PE, persistent perfusion defects, permanent intravascular devices, thrombophilic disorders, malignancy) or a high CTEPH prediction score.[8]

## Advanced echocardiographic techniques

The survey results show that RV systolic function is most commonly assessed with standard transthoracic echocardiography, while advanced echocardiographic techniques, such as RV strain and three-dimensional RVEF were less commonly used. This is in line with the previous ECHOS survey of echocardiographic practise in Serbia, which showed low availability of advanced echocardiographic techniques (speckle tracking strain echocardiography and three-dimensional echocardiography, 19% and 11%, respectively.[9] However, it should be emphasised that it has been suggested that speckle-tracking strain and three-dimensional echocardiographic indices might perform better than conventional echocardiographic parameters in assessing regional and global RV dysfunction in patients with PH.[10] In addition, 3D RV strain and 3D RV EF were found to be independent predictors of mortality in PH patients.[10]

## RV-PA coupling

RV-PA coupling reflects the relationship of RV contractility and RV afterload. With increased PA pressure and increased RV afterload, RV contractility increases through hypertrophy and RV remodelling as an adaptive response.[11] Because RV-PA is an invasive parameter measured during RHC, several non-invasive surrogate parameters have been proposed.[12] The new guidelines introduced the TAPSE/sPAP ratio as a non-invasive measure of RV-PA coupling.[2] In our survey, only 29% of respondents rated this parameter. This is probably due to the fact that TAPSE/sPAP has only recently been introduced and it takes time to be fully implemented in clinical practice.

## Conclusions

This is the first national survey of echocardiographic assessment of the likelihood of PH and its early detection. The survey revealed a lack of standardised echocardiographic assessments when screening for PH. There is a need for targeted echocardiography courses that would improve routine echocardiographic practice in assessing right heart function and evaluating the likelihood of PH to promote early treatment and management of PH.

**Conflict of interest:** None to declare.

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## Sažetak

### *Istraživanje Ehokardiografskog društva Srbije (ECHOS) o primeni ehokardiografije kod plućne hipertenzije*

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***Uvod.*** *Plućna hipertenzija (PH) je progresivna hronična bolest koja pogađa oko 1% globalne populacije. Ehokardiografsko udruženje Srbije (ECHOS) je sprovelo nacionalnu anketu sa ciljem da se ispita način procene ehokardiografskih parametara koji su ključni za neinvazivno određivanje verovatnoće PH i njeno rano prepoznavanje u svakodnevnoj praksi.*

***Metode.*** *Anketa sastavljena od 23 pitanja o demografskim podacima, rutinskoj proceni funkcije i morfologije desnog srca, ehokardiografskim parametrima kod sumnje na PH i standardima pisanja izveštaja, poslata je elektronskom poštom svim ECHOS članovima.*

***Rezultati.*** *Anketu je popunilo 150 članova (22.7%). Ehokardiografske preglede najčešće obavljaju kardiolozi (51%) sa preko 10 godina iskustva (46%). Oko polovine anketiranih članova (55%) rutinski procenjuje funkciju i morfologiju desne komore (DK). Parametre procene postojanja PH, kao šte su profil protoka u izlaznom traktu DK, dijametar plućne arterije, rutinski se procenjuju u oko polovini slučajeva, dok se pojedini parametri kao što je površina desne pretkomore rutinski procenjuju ređe (23%). Sistolna funkcija DK rutinski se procenjuje u većini slučajeva (90%), kao i sistolni pritisak u DK (97%). Rutinski ehokardiografski pregled kod pacijenata sa dokazanom plućnom tromboembolijom se radi tokom iste hospitalizacije (95%). Kod sumnje na postojanje PH, svi anketirani članovi procenjuju funkciju levog srca. Većina smatra da je rutinska procena parametara DK važna u kliničkoj praksi i da su potrebni fokusirani kursevi iz ehokardiografije u prepoznavanju PH (96%).*

***Zaključak.*** *Anketa ukazuje na suboptimalnu primenu ehokardiografskih parametara i tehnika u rutinskoj praksi u cilju prepoznavanja PH. Postoji potreba za fokusiranim ehokardiografskim edukacijama u cilju unapređivanja ehokardiografske prakse u proceni funkcije desnog srca i verovatnoće postojanja PH.*

***Ključne reči:*** *Ehokardiografsko udruženje Srbije, ECHOS, plućna hipertenzija, anketa*

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Review article

# Treatment approach for patients with MINOCA: What we know today and what to expect tomorrow?

Ivan Bešenji, Milenko Čanković

*Institute of Cardiovascular Diseases, Sremska Kamenica, Medical Faculty, University of Novi Sad*

**Abstract** Myocardial infarction with non-obstructive coronary arteries (MINOCA) is a clinical entity characterized by the presence of symptoms of myocardial infarction (MI) and evidence of myocardial ischemia, despite coronary angiography revealing insignificant coronary artery disease. Therefore, this condition presents significant diagnostic and therapeutic challenge. This paper provides a concise overview of therapeutic strategies for MINOCA patients, highlighting the complexities and approaches to managing this unique patient population. The multifactorial etiology of MINOCA requires an adapted approach, so the therapeutic approach to patients with MINOCA is primarily focused on addressing the underlying causes and minimizing the risk of future cardiac events.

**Key words** MINOCA, therapy, adverse events

## Introduction

When we talk about myocardial infarction with non-obstructive coronary arteries (MINOCA), it is important to note that many healthcare institutions still do not have a well-organized diagnostic process in their clinical practice, either due to lack of knowledge or lack of clear recommendations from clinical guidelines. Therefore, there is a need for an appropriate and valid diagnostic protocol to be applied in clinical practice when treating these patients in order to avoid relying solely on cardiologists for making the diagnosis.[1] So far, only the American Heart Association (AHA) has attempted to summarize and align the diagnostic path and treatment of MINOCA in its scientific statement, where a diagnostic algorithm was proposed, but clear guidelines regarding the use of additional diagnostic methods alongside coronary angiography were not provided, most likely due to limited evidence-based data.[2] Understanding the fundamental etiological factors is crucial for selecting the most effective therapeutic approach in MINOCA. Treating all cases in the same way does not yield consistent results. For example, what may benefit a specific subgroup of patients may be ineffective or even harmful to others. For instance, the use of Dual Antiplatelet Therapy (DAPT) may increase the risk of bleeding, and the use of beta-blockers may cause constriction of coronary arteries in patients with epicardial artery spasm by unmasking α-adrenoreceptors.[3] Because of these considerations, the term MINOCA should not be used as a specific diagnosis but rather as a "working diagnosis." Through an appropriate diagnostic process, which includes both invasive and non-invasive tests, we can gradually uncover the underlying mechanisms and apply the appropriate treatment approach.

## Medical therapy – available data

The diagnostic criteria for MINOCA are proposed as follows: 1) meeting the universal definition criteria for acute myocardial infarction (AMI), 2) angiographically verified coronary arteries without obstruction (with stenosis less than 50%), 3) no obvious specific clinical cause for acute presentation (elevated troponin levels). The etiology of MINOCA is diverse and can be categorized into coronary, cardiac, and extracardiac factors. Coronary factors include rupture or erosion of an occult plaque, coronary spasm, spontaneous coronary artery dissection, coronary embolism, and coronary microvascular disorders. Cardiac factors encompass myocarditis, Takotsubo syndrome, cardiomyopathies, cardiac trauma, and tachyarrhythmias. Extracardiac factors include stroke, pulmonary embolism, sepsis, kidney failure, and hypoxemia. Consequently, MINOCA should be viewed as a working diagnosis that requires further investigation into its underlying cause.[2,4,5]

Although identifying the underlying etiology of MINOCA can guide appropriate and personalized long-term treatment, there is limited data on the optimal pharmacotherapeutic approach. In a large study involving 9,136 patients, registered in the SWEDEHEART registry, diagnosed with MINOCA, the use of statins and renin-angiotensin system inhibitors significantly reduced the rate of major cardiovascular events (MACE, defined as mortality from any cause, as well as hospitalization due to myocardial infarction, ischemic stroke, or heart failure) during an average follow-up of 4.1 years. There was a trend towards reducing events with the use of beta-blockers, while the use of DAPT as the primary therapy for atherosclerotic obstructive coronary disease did not significantly affect the clinical outcomes of patients. However, it is important to note that the study group was highly heterogeneous, as the specific pathogenetic

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mechanism leading to MINOCA had not been identified, and medical therapy was not tailored accordingly.[6]

***DAPT***. Two secondary analyses of randomized controlled trials (RCTs) have assessed the effect of antiplatelet therapy in patients diagnosed with MINOCA. In the CURRENT-OASIS7 trial, a total of 23,783 patients with myocardial infarction, of whom 1,599 (6.7%) had MINOCA, were included. In this study, compared to DAPT based on clopidogrel, intensive therapy does not seem to provide additional benefit, but there is an indication of potential harm. There was no difference in bleeding events among patients with MINOCA.[7] In the PURSUIT trial, which included a total of 5,767 patients with non-ST segment elevation myocardial infarction (NSTEMI), of whom 366 (6%) had MINOCA, it was found that these patients did not benefit from eptifibatide therapy, whereas patients with obstructive coronary disease did. There was no increased frequency of bleeding events in MINOCA patients in this study either.[8]

Several retrospective studies have assessed the effect of secondary prevention on clinical outcomes in patients with MINOCA.[9,10,11] In none of these studies was DAPT associated with a reduction in the frequency of MACE. Overall, current evidence on the role of antiplatelet therapy in patients with MINOCA comes from registries or secondary analyses of RCTs and is therefore of low quality.[7-13] However, available evidence suggests that antiplatelet therapy is not associated with an improvement in clinical outcomes.

A study that assessed the role of DAPT therapy without stent implantation in patients with plaque erosion-induced myocardial infarction, documented using optical coherence tomography (OCT) was called the EROSION study.[14] During a 30-day follow-up, the use of DAPT with aspirin and ticagrelor was associated with a significant reduction in thrombus volume and a low rate of adverse events. Furthermore, during one-year follow-up, 92.5% of patients with plaque erosion-induced myocardial infarction treated with DAPT without stent implantation were free from MACE. One patient had to discontinue DAPT due to gastrointestinal bleeding.[15] In the final report after four years, 21% of patients underwent revascularization of the target vessel.[16] This study provides compelling data supporting the effectiveness of DAPT involving aspirin and ticagrelor in plaque erosion-induced myocardial infarction. However, this was a pilot study without randomization and an open-label design with a surrogate primary outcome. Therefore, this hypothesis should be adequately confirmed through RCTs with an adequate number of patients and clinical outcomes as endpoints.

The role of DAPT in patients with Spontaneous Coronary Artery Dissection (SCAD) is a subject of debate. SCAD is a condition that typically results in acute coronary syndrome (ACS). In most cases, SCAD leads to simultaneous and significant coronary artery narrowing (>50% stenosis), making it a rare cause of MINOCA.(5) Some experts argue that DAPT may increase the risk of bleeding and the expansion of the hematoma/dissection, while others contend that the rupture of the vessel's intima may be prothrombotic, and the additional use of clopidogrel alongside aspirin may be justified.[17] Data from the DISCO registry suggest that in patients managed conservatively, DAPT may be associated with worse clinical outcomes compared to therapy with a single antiplatelet agent (SAPT).[18] The authors assessed MACE, defined as death from any cause, non-fatal myocardial infarction, and any unplanned percutaneous coronary intervention (PCI) after 12 months. DAPT, mainly with aspirin and clopidogrel (63%), was associated with an increase in MACE compared to aspirin SAPT therapy (93%). This difference was due to recurrent infarction and urgent revascularization shortly after the initial presentation of SCAD. Currently, there are no randomized clinical trials on this topic, and available evidence suffers from limitations of retrospective registries.

While vasospastic angina has been the subject of continuous research, specific data on MINOCA resulting from coronary vasospasm are limited. Lin et al.(19*)* conducted a systematic review and meta-analysis evaluating the role of low-dose aspirin in patients with vasospastic angina without significant coronary lesions. The authors included six studies encompassing a total of 3,661 patients. The primary outcome was MACE, defined as cardiac death, ACS, hospitalization for unstable angina, PCI, symptomatic arrhythmia, appropriate implantable cardioverter-defibrillator use, and cardiogenic shock. Aspirin was not associated with a reduction in MACE. However, this analysis did not include any RCTs, and there was very high heterogeneity in the results within the included studies.

The role of DAPT in coronary vasospasm was prospectively assessed in the multicenter VA-Korean registry.[20] Researchers compared the effect of DAPT with aspirin and clopidogrel versus aspirin alone on MACE. The primary outcome was time to composite events, including death from any cause, acute coronary events, and symptomatic arrhythmia after 3 years of follow-up. Patients treated with DAPT had worse clinical outcomes compared to those treated with aspirin alone. Patients presenting as ACS and smokers had a higher risk of cardiovascular events. However, RCTs did not include this analysis.

There have been differing results regarding the role of antiplatelet therapy in Takotsubo syndrome (TTS) to date. In a single-center retrospective registry of TTS patients assessing clinical outcomes during hospitalization, authors found that the use of DAPT with aspirin and clopidogrel was associated with a lower incidence of MACE.[21] MACE was defined as heart failure during hospitalization, in-hospital death, stroke, or respiratory failure requiring mechanical ventilation. However, it's important to note that a small sample size and retrospective methodology are significant limitations to consider. On the other hand, in a systematic review and meta-analysis involving nearly two thousand patients, DAPT was associated with an increase in cardiovascular events and mortality.[22] Bleeding rates were not reported.

**ACEi and ARB**. Earlier in the text, it was mentioned that the SWEDEHEART study[4] demonstrated a significant reduction in the rate of MACE with the use of renin-angio-

tensin system inhibitors, but it did not compare angiotensin II receptor type I blockers (ARBs) and angiotensin-converting enzyme inhibitors (ACEi). In a retrospective study by Ahn JH et al. aimed at comparing the impact of ACEi and ARB, it was shown that the frequency and risk of MACE were similar in both groups of patients[23]. Regarding cardiovascular event-related mortality, it was similar in both treatment groups, consistent with previous RCTs comparing ACEi and ARB.[24,25] However, the results indicate that ACEi reduce the risk of recurrent myocardial infarction more significantly compared to ARB. These results can be interpreted as a specific effect of ACEi through the suppression of angiotensin II and preservation of bradykinin, ultimately leading to the prevention of endothelial dysfunction.[26,27]

**STATINS**. Masson W et al. conducted a meta-analysis[28] whose results suggest that statin therapy has a positive impact on clinical outcomes in MINOCA patients. The use of statins has proven beneficial in reducing the risk of MACE and mortality in this group of patients. The results imply that statin therapy has prognostic value in improving outcomes in these patients.

## What to expect?

Available research has mainly focused on assessing the role of traditional cardiovascular drugs (such as ACE inhibitors, ARBs, statins, beta-blockers, and DAPT) in the treatment of MINOCA, with only a few currently active RCTs exploring the best approach and pharmacological treatment. It's worth mentioning a few upcoming prospective studies. One of these currently active clinical trials is the *MINOCA-BAT* study, which aims to determine whether therapy with oral beta-blockers or ACEi/ARBs can reduce the incidence of all-cause mortality, recurrent hospitalizations for myocardial infarction, ischemic stroke, or heart failure in patients discharged after MINOCA with left ventricular ejection fraction ≥40%.[29,30]

StratMed-MINOCA[15] is an ongoing clinical trial that will analyze whether early risk stratification through coronary microcirculation dysfunction (defined by a microvascular resistance index ≥25), combined with therapy using the cardioprotective mineralocorticoid antagonist eplerenone, can reduce changes in N-terminal pro-brain natriuretic peptide (NT-pro-BNP) levels as a marker of myocardial damage in MINOCA patients.[31]

The currently active clinical trial *PROMISE17* aims to evaluate whether a "personalized medicine approach," which involves comprehensive diagnostic analysis followed by tailored pharmacological treatment targeting the underlying cause, is more effective than "standard therapy", which includes coronary angiography with conventional treatment for myocardial infarction, including DAPT for all patients, beta-blockers, statins, and ACEi/ARBs. The goal is to determine whether this personalized medicine approach can improve the prognosis and quality of life for MINOCA patients.[32,33]

One of the most interesting upcoming trials is a randomized trial *of beta-blockers and antiplatelet drugs in SCAD patients*, where 600 patients will be randomized in a 2x2 factorial design to assess the safety and efficacy of beta-blockers and DAPT in SCAD patients.[34]

## Conclusions

The role of pharmacological therapy in patients diagnosed with MINOCA remains poorly defined. Currently, most scientific evidence and guidelines are supported by low-quality studies. It's important to note that there are no RCTs evaluating the role of medication therapy in the entire cohort of these patients or for any of its specific etiologies. In clinical practice, the management of most MINOCA cases is based on studies of patients with obstructive coronary artery disease. RCTs are essential to determine the role of medication therapy and given the complex etiology and limited amount of evidence, medical treatment remains uncertain.

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## *Sažetak*

## *Pristup lečenju pacijentiama sa MINOCA-om: Šta znamo i šta očekivati sutra?*

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*Infarkt miokarda bez opstrukcije koronarnih arterija (engl. Myocardial infarction with non-obstructive coronary arteries - MINOCA) je klinički entitet koji karakteriše prisustvo simptoma infarkta miokarda (IM) i dokaz o ishemiji miokarda, uprkos koronarnoj angiografiji koja otkriva nesignifikantnu koronarnu bolest. Stoga, ovo stanje predstavlja značajni dijagnostički i terapijski izazov. Ovaj rad pruža sažet pregled terapijskih strategija za pacijente kojima je dijagnostikovan MINOCA, naglašavajući složenost pristupa ovoj jedinstvenoj populaciji pacijenata. Multifaktorska etiologija MINOCA-e zahteva prilagođen terapijski pristup ovim bolesnicima te je fokus na rešavanju osnovnih uzroka i na minimiziranju rizika od budućih srčanih događaja.*

***Ključne reči:*** *MINOCA, terapija, MACE*

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Review article

# The development of the TAVI program in Serbia – ten-years of experience

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**Abstract** Aortic stenosis (AS) is the most common valvular disease requiring surgical (SAVR) or transcatheter intervention (TAVI) in Europe and North America. The first TAVI was performed in 2002 in order to treat in-operable patients with AS, and the initial ESC guidelines recommended this procedure in patients with a high risk of SAVR. According to ESC guidelines for the treatment of valvular diseases from 2021, the decision on the treatment modality of AS is defined by the Heart team, and SAVR is recommended in younger patients with a low risk of surgery (<75 years STS-PROM/EuroScore II<4%), and TAVI is recommended in elderly patients ≥75 years or in patients with high operative risk (STS-PROM/EuroScore II>8%) or in patients not suitable for surgery. In addition, large randomized clinical studies (PARTNER 3, Evolut Low Risk and NOTION studies) showed that TAVI is also safe in patients with a low operative risk (STS-PROM/EuroScore II<4%), and not inferior to SAVR (UK TAVI trial). The first TAVI procedure in Republic of Serbia was performed on April 22, 2014 during BASIC 8+ congress. In the period of 2014-2023, 444 TAVI procedures were performed in Republic of Serbia, with exponential increase in in the last 2 years.

**Kew words** aortic stenosis, surgical aortic valve replacement (SAVR), transcatheter aortic valve intervention (TAVI)

## Introduction

Aortic stenosis (AS) is the most common primary valve lesion requiring surgery (SAVR) or transcatheter intervention (TAVI) in Europe and North America.[1,2] AS prevalence is rising rapidly as a consequence of the aging population.[3,4] SAVR was the therapy of choice in patients with symptomatic AS, but the mortality after isolated surgical procedures is 1–3% in patients under 70 years, and 4–8% above 70 years.[1,2] As an alternative of SAVR, transcatheter aortic valve implantation (TAVI) was proposed and initiated in 2002,[5] and in a short period achieved clinical acceptance and recommendations by the guidelines in the high-risk surgical patients.[1-6]

## Management of aortic stenosis according to ESC guidelines 2021

Use of SAVR and TAVI as complementary treatment options has allowed a substantial increase in the overall number of patients with aortic stenosis undergoing surgical or transcatheter intervention in the past decade.[6] ESC guidelines[1] suggested that randomized clinical trials (RCT) have assessed the two modes of intervention across the spectrum of surgical risk in predominantly elderly patients. These trials using surgical risk scores to govern patient selection demonstrated that TAVI is superior to medical therapy in extreme-risk patients and non-inferior to SAVR in high[7-11] and intermediate-risk patients at follow-up extending to 5 years.[12-17] In addition, PARTNER 3 and Evolut Low Risk trials demonstrated that TAVI is non-inferior to SAVR in low-risk patients at 2-year follow-up.[18-22] Rates of vascular complications, pacemaker implantation, and paravalvular regurgitation are consistently higher after TAVI, whereas a severe bleeding, acute kidney injury, and new-onset AF are more frequent after SAVR. Likelihood of paravalvular regurgitation has been reduced with newer transcatheter heart valve designs, but still pacemaker implantation (and new-onset left bundle branch block) may have long-term consequences[23-25] requiring further refine-

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**Table 1.** Number of TAVI procedures in Republic of Serbia since 2014

| Year | University Clinical Center of Serbia | Institute for CVD Dedinje | Institute for CVD Sremska Kamenica | Military Medical Academy | Total |
|---|---|---|---|---|---|
| 2014 | 5 | / | / | / | 5 |
| 2015 | 2 | 2 | 2 | / | 6 |
| 2016 | 1 | / | / | / | 1 |
| 2017 | / | / | / | 2 | 2 |
| 2018 | / | / | / | 2 | 2 |
| 2019 | / | 24 | / | 1 | 25 |
| 2020 | / | 9 | / | / | 9 |
| 2021 | / | 23 | / | / | 23 |
| 2022 | 30 | 166 | 24 | / | 220 |
| 2023 | 39 | 65 | 47 | / | 151 |

ments. Most patients undergoing TAVI have a swift recovery, short hospital stay, and rapidly return to normal activities. Despite these benefits, there is a wide variation in worldwide access to the procedure as a result of high device costs as well as different levels of health care resources[26].

In the summary the latest ESC guidelines form 2021 recommend that aortic valve intervention should be performed in Heart valve Centers (IC).[1] The choice between SAVR and TAVI must be based upon careful evaluation of Heart team (IC). SAVR is recommended in younger patients with low risk for surgery (<75 years STS-PROME/EuroScore II<4%) (IB), and TAVI is recommended in older patients ≥75 years or in patients with high surgery risk (STS-PROME/EuroScore II>8%) or in patients unsuitable for surgery (IA).[1]

## TAVI in clinical randomized trials

In the last fourteen yours,14 RCT for TAVI were published including more than 9000 patients. Initially TAVI was recommended for high-risk patients. From 2019, TAVI has been assessed in low and intermediate risk patient. The PARTNER 3[18,19] and Evolut Low Risk trials[20] demonstrated that TAVI is non-inferior SAVR in low-risk patients at 2-year follow-up. In the Partner 3 trial there were no significant between-group differences in major vascular complications, new permanent pacemaker insertions, or moderate or severe paravalvular regurgitation. Among patients with severe aortic stenosis who were at low surgical risk, the rate of the composite of death, stroke, or rehospitalization at 1 year was significantly lower with TAVI than with surgery. Importantly, patients in the low-risk trials were predominantly male and relatively elderly (e.g. PARTNER 3: mean age 73.4 years; <70 years 24%, 70-75 years 36%, >75 years 40%, >80 years 13%). Results of the Evolut Low Risk study[23] suggested that in the patients with severe aortic stenosis who were at low surgical risk, TAVI with a self-expanding supraannular bioprosthesis was noninferior to surgery with respect to the composite end point of death or disabling stroke at 24 months.[18,19]

The Nordic Aortic Valve Intervention (NOTION trial)[16] was designed to compare transcatheter aortic valve replacement (TAVI) to surgical aortic valve replacement (SAVR) in patients 70 years or older with isolated severe aortic valve stenosis. NOTION trial demonstrated that there was no statistical difference for major clinical outcomes 5 years after TAVI with a self-expanding prosthesis compared to SAVR. Higher rates of prosthetic regurgitation and pacemaker implantation were seen after TAVI.[16]

The latest published study for TAVI in low risk-patients was UK TAVI trial[27]. In this randomized clinical trial conducted at 34 UK centers, 913 patients aged 70 years or older with severe, symptomatic aortic stenosis and moderately increased operative risk due to age or comorbidity were enrolled. This study proved that in patients aged 70 years or older with severe, symptomatic aortic stenosis and moderately increased operative risk, TAVI was non inferior to surgery with respect to all-cause mortality at 1 year.

There is some new potential indication fields for TAVI, which include asymptomatic severe aortic stenosis (RECOVERY, AVATAR, ENVOLVED and EARLY TAVR trials) and moderate AS “at risk“ (UNLOAD, PROGRESS, EXPAND TAVR II trials).

## Implementation of TAVI in Republic of Serbia

From 2014-2023 year in Republic of Serbia (RS) 444 TAVI procedures was performed. The first TAVI procedure in Republic of Serbia was performed on April 22, 2014 during BASIC 8+ congress. In the 2014 year 5 TAVI procedures was done in University Clinical Center of Serbia, next 6 TAVI procedures was done during 2015 (two TAVI during BASIC 9+), after that TAVI was done sporadically until 2019, when Institute for cardiovascular disease Dedinje started with commercial TAVI program and number of TAVI procedures in RS raised (Table 1). In 2022, Republic Fund for Health insurance started with noncommercial TAVI program and provided 141 self-expandable valves including 111 Evolute (Medtronic) and 30 Portico (Abbot) valves. For 2023 and 2024, 300 valves will be provided including 225 Evolute (Medtronic), 45 Portico (Abbot), and 30 balloon-expandable Myval (Meril Lifesciencies).

The first results of TAVI procedures in Serbia was published 2016[28] demonstrating all successful interventions

without significant periprocedural complications. In this initial group of patients, immediate hemodynamic improvement was obtained in all patients (peak gradient 94.2 ± 27.6 to 17.6 ± 5.2 mmHg, p < 0.001, mean pressure gradient 52.8 ± 14.5 to 8.0 ± 2.1 mmHg, p < 0.001). None of the patients developed heart block, stroke, vascular complication or significant aortic regurgitation. After 6 months, the survival was 100% with New York Heart Association (NYHA) functional improvement in all the patients[28]. All the initial results are encouraging, and the new data with much higher number of patients will be soon available.

## Conclusion

Percutaneous treatment of aortic stenosis with TAVI in patients over 75 years is challenging procedure and requires careful discussion and selection of the patients by the Heart team, detailed planning and preparation of the procedure taking into account all potential pitfalls, full engagement of the team performing the procedure, and careful observation of the in-hospital clinical course. Selection of the most appropriate mode of intervention should be considered in the light of comorbidities (including frailty and overall quality of life), anatomical and procedural characteristics, the relative risks of SAVR and TAVI, and long-term outcome.

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## *Sažetak*

## *Razvoj TAVI programa u Srbiji – desetogodišnje iskustvo*

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*Aortna stenoza (AS) je najčešće valvularno oboljenja koje zahteva hirurško (SAVR) ili transkatetersku intervenciju (TAVI). Prva TAVI urađena je 2002. godine kod hirurški inoperabilnog pacijenta, da bi u kratkom vremenskom periodu našla kliničku primenu tako da su inicijalne ESC preporuke ovu proceduru preporučivale kod pacijenata sa visokim rizikom za SAVR. Prema ESC preporukama za lečenje valvularnih mana iz 2021.godine odluku o modalitetu lečenja AS definiše Heart team, a SAVR se preporučuje kod mlađih pacijenata sa niskim rizikom od operacije (<75 godina STS-PROM/EuroScore II<4%), a TAVI se preporučuje kod starijih pacijenata ≥75 godina ili kod pacijenata sa visokim operativnim rizikom (STS-PROM/EuroScore II>8%) ili kod pacijenata koji nisu pogodni za operaciju. Sa druge strane velike randomizovane kliničke studije (PARTNER 3, Evolut Low Risk and NOTION studije) su pokazale da je TAVI bezbedna i ne-inferiorna u odnosu na SAVR i za pacijente sa niskim operativnim rizikom (STS-PROM/EuroScore II<4%)(UK TAVI trial). Prva TAVI procedura u Srbiji je urađena 22.04.2014. godine tokom BASIC 8+ kongresa. Od 2014-2023 godine u našoj zemlji je urađena 444 TAVI procedura sa eksponencijlanim rastom u poslednje 2 godine..*

***Ključne reči:*** *aortna stenoza, hirurška zamena aortne valvule (SAVR), transkateterska zamena aortne valvule (TAVI)*

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Review article

# Ten years from the first left atrial appendage closure in Serbia

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**Abstract** Atrial fibrillation (AF) is the most common arrhythmia, and stroke is the major complication of AF. Over 90% of thrombi associated with atrial fibrillation are located in the left atrial appendage (LAA). Oral anticoagulant therapy represents the first line of therapy as thromboembolic prophylaxis in patients with nonvalvular atrial fibrillation. As an alternative to anticoagulant therapy, in certain groups of patients with AF closure of the LAA with the Watchman occluder (LAAC) is used in thromboembolic prophylaxis. The efficacy and safety of LAAC was investigated in three randomized clinical trials and compared with standard anticoagulant therapy (PROTECT-AF, PREVAIL, and PRAGUE). The results of the studies indicate that LAAC represents a good alternative to anticoagulant therapy in certain groups of patients, but that additional studies are necessary.

**Kew words** atrial fibrillation, left atrial appendage occlude, Watchman device

## Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia and stroke is the most debilitating complication of AF.[1-4] AF-related strokes are more disabling, more likely to recur, and are associated with higher mortality rates than non-AF-associated strokes.[2] In AF, blood stagnates among left atrial appendage (LAA) pectinate muscles leading to thrombus and stroke[5] and LAA is source of at least 90% of AF-related thrombus. Oral anticoagulation remains an effective standard of care for the prevention of stroke in AF, but is associated with major and minor bleeding, challenging adherence, and drug interactions.[6] Trials comparing novel direct oral anticoagulants (DOACs) with warfarin for AF-associated stroke prevention provide comparative efficacy and safety data on both the DOACs as well as warfarin.[7,8] Despite advances in anticoagulation, the persistent risk of stroke, bleeding, patient compliance, and other major adverse cardiovascular events leaves relevant unmet clinical need for alternative AF-associated stroke prevention[4]. The series of Watchman (Boston Scientific, Natick, MA) trials demonstrated that Watchman device provides similar stroke prevention efficacy as warfarin.[4,9]

## Watchman trials

Up to date, 3 randomized controlled trials (RCTs) comparing LAAC to anticoagulation have been published.[10,11,12,13] The PROTECT-AF Trial[10] randomized 707 patients in a 2:1 ratio of Watchman vs. warfarin, with a primary combined endpoint of all stroke, systemic thromboembolism, and cardiovascular death. At initial analysis, the trial met its noninferiority primary efficacy endpoint with an incidence of all stroke, cardiovascular death, or systemic embolism of 3% with the device and 4.9% with warfarin therapy, a benefit which proved durable with longer-term follow up (the primary efficacy event rate was 3.0 per 100 patient-years (95% CI: 1.9-4.5) in the device group and 4.9 per 100 patient-years (2.8-7.1) in the control group (RR: 0.62, 95% CI: 0.35-1.25).[9] This study has been questioned for several reasons: device/procedure-associated adverse events, the inclusion of moderate risk (CHADS2 =1) patients, and a relatively short follow up).[4,9]

The PREVAIL trial[11] was designed to address the controversies of PROTECT-AF. Like PROTECT-AF, PREVAIL randomized 407 patients in a 2:1 ratio to Watchman and warfarin with a composite noninferiority endpoint. PREVAIL was designed to enroll a higher risk patient cohort than PROTECT-AF including significant participation of unexperienced operators. First co-primary efficacy endpoint (stroke, SE, and CV/unexplained death) event rate at 18 months was 6.4% in the device group vs 6.3% in the control group (RR 1.07 [95% CrI: 0.57-1.89].[11] Stroke was more common among patients randomized to the device than those to warfarin in the PREVAIL trial (2.5% vs. 2.0% (risk difference 0.5% [95% CI: 0.019 to 0.027]). Adverse events in this study was lower than PROTECT AF (4.2% vs 8.7%; p=0.004).

A patient-level meta-analysis of the PROTECT-AF and PREVAIL trials(12) aggregated the entire five year results of both studies. The primary composite endpoint was similar between groups. The ischemic stroke/SE rate was numerically higher with LAAC, but this difference did

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not reach statistical significance (HR: 1.71; p=0.080). However, differences in hemorrhagic stroke, disabling/fatal stroke, cardiovascular/unexplained death, all-cause death, and post-procedure bleeding all favored LAAC (HR: 0.20; p=0.0022; HR: 0.45; p=0.03; HR: 0.59; p=0.027; HR: 0.73; p=0.035; HR: 0.48; p = 0.0003, respectively).[12] PRAGUE trial[13] remains the only RCT to date that compared LAAC with direct oral anticoagulant (DOAC). The noninferiority of LAAC compared with DOAC was documented in the PRAGUE trial. The annualized rate of the primary composite outcome (stroke, TIA, SE, CV death, major or non-major clinically relevant bleeding, or procedure-/device-related complications) was 10.9% with LAAC and 13.4% with DOAC (sHR: 0.84; 95% CI: 0.53-1.31; p=0.44; p=0.004 for noninferiority). Major LAAC-related complications occurred in 9 (4.5%) patients[13] The main limitation of the trial is that the noninferiority of LAAC was only powered for a composite endpoint that combined ischemic and bleedings events as well as procedural complications. The study was, however, underpowered to assess the impact of LAAC on lowering ischemic events, which is the presumed mechanism of action of the LAAO procedure.[10]

In addition to the randomized trials, the nonrandomized studies continued access registries - Continued Access to PROTECT-AF (CAP) and Continued Access to PREVAIL (CAP2) included 566 and 578 Watchman implanted patients, respectively. Without a randomized comparison cohort, the CAP registries were compared to anticipated rates of stroke in the absence of oral anticoagulation based on validated stroke prediction scores. The rates of ischemic stroke were 78% and 69% lower than predicted in the absence of oral anticoagulation in the CAP and CAP2 registries, respectively.[14,15]

There is a few non-randomized trials for LAAC. The third-generation Watchman FLX was evaluated in the PINNACLE FLX Trial which included 400 patients.[16] The PINNACLE FLX primary safety endpoint of all-cause death, ischemic stroke, systemic embolism, or device/procedure-related adverse events requiring surgery or major endovascular intervention within seven days following the procedure was observed in 0.5% of patients. Implantation success was achieved in 98.8% of patients. The primary efficacy rate of effective LAAC, defined as any peri-device flow <5 mm demonstrated by TEE at 12 months, was achieved in all patients. Similar results were noticed in other nonrandomized trials as SUPRASS, CHAMPION-AF, etc.

## Clinical guidelines

The 2019 American College of Cardiology Focused Update on the Management of Atrial Fibrillation assigns that left atrial appendage device occlusion, together with LAA surgical ligation/excision, received a class IIB recommendation, with the note that that LAA occlusion may be considered in patients with AF at increased risk of stroke who have contraindications to long-term anticoagulation.[6]

In our country, the first LAAC was implanted on April 24, 2014, during the BASIC 8+ congress (2 LAAC), and in 2015 year, one more LACC (BASIC 9+). Our initial results with Watchman LAAC are promising providing real alternative in patients with non-valvular AF and contraindication for long-term oral anticoagulation therapy and high bleeding risk.[17]

## Conslusion

LAAC represents a promising alternative to oral anticoagulation in selected patients with non-valvular AF who have contraindications for long-term anticoagulation.

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## *Sažetak*

## *Deset godina od prve ugradnje okludera u aurikulu leve pretkomore*

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*Atrijalna fibrilacija (AF) je najčešća aritmija, a moždani udar je najveća komplikacija AF. Preko 90% tromba povezanih sa atrijalnom fibrilacijom lokalizovano je u aurikuli leve pretkome (LAA). Oralna antikoagulatna terapija predstavlja prvu liniju terapije kao tromboembolijska profilaksa kod pacijenata sa nevalvularnom atrijalnom fibrilacijom. Kao alternativa antikoagulatne terapije kod pojedinih grupa pacijenata u tromboembolijskoj profilaksi AF primenju se zatvaranje aurikule leve pretkome Watchman okluderom. Efikasnost i bezbednost zatvaranja LAA praćena je u tri randomizovane studije i poređena sa antikoagulatnom terapijom (PROTECT-AF, PREVAIL i PRAGUE studije). Rezultati studija ukazuju da zatvaranje LAA predstavlja dobru alternativu antikoagulante terapije kod određenih grupa pacijenata, ali da su dodatna istraživanja neophodna.*

***Ključne reči**: atrijalna fibrilacija, okluder leve aurikule, Watchman uređaj*

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Review article

# Quality of life evaluation in peripartum cardiomyopathy patients: a focus on women's heart

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**Abstract**

**Introduction.** There is limited information available regarding the quality of life (QoL) in patients with Peripartum Cardiomyopathy (PPCM). We assessed how the disease impacted the day-to-day functioning of respondents, who were concerned about their QoL in the two weeks preceding the survey.
**Methods.** The study involved 24 subjects treated at the Institute for Cardiovascular Diseases of Vojvodina from January 2006 to December 2019. The Kansas City Cardiomyopathy Questionnaire (KCCQ) was used to assess their quality of life. The collected data were statistically processed.
**Results.** The mean age of the subjects was 37 ± 6.4 years, with an average time since initial diagnosis of 5.9 ± 3.4 years. Out of 24, thirteen participants completed the questionnaire, and a majority of respondents (53.8%) reported feeling sad or discouraged due to the effects of heart failure on their lives. Only 30.8% of respondents expressed complete satisfaction with the idea of living at their current level due to heart failure. Fatigue and weakness were reported by 76.9% of female participants. The initial left ventricle ejection fraction (EFLV) was predominantly severely impaired, while the currently measured EFLV averaged 55±10%. At follow-up, 38.4% showed no symptoms of heart failure. A majority (76.9%) were unable to engage in high-intensity physical activities.
**Conclusion.** Although most patients experience cardiac muscle recovery after the acute phase of PPCM, the disease continues to have long-term effects on their quality of life and mental well-being.

**Kew words** peripartum cardiomyopathy; QoL; KCCQ; quality of life evaluation

## Introduction

Cardiovascular diseases (CVDs) are a significant cause of morbidity and mortality in pregnancy, in which peripartum cardiomyopathy (PPCM), as a specific entity, is being increasingly recognized. In general, cardiomyopathy is defined as a myocardial disorder in which the heart muscle is structurally and functionally abnormal, in the absence of coronary artery disease (CAD), hypertension, valvular disease, and congenital heart disease (CHD) sufficient to cause the observed myocardial abnormality[1]. Therefore, PPCM is defined as an idiopathic form of heart failure (HF) that is developed during late pregnancy or after childbirth, in previously healthy, young women[2]. Globally, the incidence of PPCM varies, with reported rates ranging from 1 in 1421 to 1 in 9861 births[3].

The precise etiology of PPCM has not yet been established. However, various factors including inflammatory, immunological, hormonal, environmental, as well as genetic factors have been recognized to play a pivotal role in the progression of this disease. Additionally, some commonly known risk factors, such as age, obesity, smoking, alcohol abuse, diabetes mellitus, and chronic hypertension, alongside multiparity, and hypertensive disorders in pregnancy, have also been described to contribute to PPCM development[4-6]. Despite the exact pathophysiological mechanism of PPCM being understudied, one potential theory for the occurrence of this condition could be excessive exhaustion of the heart muscle during the adaptive period[7].

The disease presents itself with widely recognized symptoms of heart failure such as dyspnea, lack of stamina, cough, and orthopnea, which can sometimes be accompanied by abdominal discomfort, chest pain, and palpitations, as non-specific symptoms. Most of the patients, based on the New York Heart Association (NYHA) functional status, are classified as NYHA 3 and 4, but the class itself did not show a predictive value[8,9].

The diagnostic criteria for PPCM entail the onset of HF within the last month of pregnancy or up to five months post-delivery, with no prior diagnosis of heart disease until the final month of pregnancy. Additionally, there should be no other identifiable cause of HF present. Suspecting PPCM based on clinical evaluation alone can be challenging due to the overlapping of symptoms of normal pregnancy and HF[10,11]. In addition to the previously mentioned clinical criteria, an echocardiographic assessment is necessary to confirm the diagnosis, since PPCM can be described as left ventricular systolic dys-

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function with ejection fraction (EF) values below 45%, with an impaired fractional shortening of the left ventricle[12]. Since PPCM is present as HF, a therapeutic approach includes standard HF treatment[2].
The most commonly described outcome is a spontaneous recovery of cardiac function. However, in a smaller percentage of patients, HF may persist, or it can lead to death. Although the course of PPCM can vary, a complete recovery of the left ventricle systolic function can be expected in 6 to 12 months after the diagnosis[13]. Compared to other cardiomyopathies with reduced systolic function, PPCM objectively shows a more favorable prognosis[14]. Regardless of the most favorable outcome, the disease itself leaves a psychological and emotional burden, in the form of depressed moods, along with feelings of fear and hopelessness[15,16].
The aim of this research was to assess the impact of PPCM on the patient's quality of life, as well as their mental status.

## Methods

### Analyzed sample

This retrospective, single-center study included 24 participants who were diagnosed with peripartum cardiomyopathy during a 14-year period (January 2006-December 2019). Clinical data were collected from the Hospital Information System of the Institute for Cardiovascular Diseases of Vojvodina (Sremska Kamenica, Serbia).

### Clinical Data, Quality of Life (QoL) and Left Ventricular Ejection Fraction (EFLV) assessment

The diagnosis of PPCM was the main requirement for the inclusion in the study, and out of primarily 24 patients, quality of life (QoL) was assessed for 13, while the rest of the participants were not included due to lethal outcomes (n = 4), refusal of participation (n = 1), or other non-specified reasons (n = 6). Required data consisted of patient age, date of delivery, admission, and discharge, present comorbidities (e.g. hypertension, preeclampsia), harmful habits (e.g. smoking, alcohol consumption), performed diagnostic and therapeutic approaches, and echocardiographic findings.
The QoL was assessed using a specific Kansas City Cardiomyopathy Questionnaire (KCCQ), which was developed to provide a better insight into the quality of life of HF patients[17]. Using the questionnaire, the following clinically relevant domains were assessed: physical limitations (question 1), frequency of symptoms (questions 3, 5, 7, and 9), their severity (questions 4, 6, and 8), and fluctuation over time (question 2), level of independence and knowledge about the disease (questions 10-12), as well as quality of life (questions 13-15). We established contact with the interviewees through telephone conversations, during which they were provided access to relevant research materials. The survey questions, derived from a questionnaire, were then verbally presented to the respondents. On average, the data collection process, encompassing the entire interview, lasted approximately 15 minutes.
Measurements of the left ventricular ejection fraction (EFLV) were divided into three groups: (I) the initial value, (II) the value measured during a follow-up, and (III) a current EFLV value.

### Statistical analysis

The data were analyzed using the IBM SPSS Statistics, Version 28.0 (IBM Corp, Armonk, NY, USA). Continuous variables were expressed with their mean values, along with the associated standard deviations, while categorical variables were presented as numbers (percentages). The paired T-test was used to determine whether there was statistical evidence that the analyzed groups' means were significantly different, and the statistical significance was observed at a level of $p<0.05$.

## Results

### Analyzed sample

The average age of diagnosis was 31±5.6 years, with the average time frame from birth to the disease onset of 35.8±47 days. More than half of the participants were multiparous (54.2%), 8.3% were twin pregnancies, and 41.7% of the pregnancies ended with a cesarean delivery. None of the participants had subsequent deliveries after the diagnosis of PPCM. Almost half of the participants (45.8%) had some other comorbidity present. Data obtained about patients' medical history, physical examination, echocardiography, therapeutic approach, as well as the frequency of death, are shown in Tables 1 and 2.

**Table 1**. Data of the entire sample

| Variable | n=24 |
|---|---|
| Age at diagnosis<br>Mean ± SD | 31 ± 5,6 |
| Days from delivery to diagnosis<br>Mean ± SD | 35,8 ± 47 |
| Parity (%, n)<br>primiparous<br>multiparous | <br>45,8 (11)<br>54,2 (13) |
| Multiple pregnancy (%, n)<br>yes<br>no | <br>8,3 (2)<br>91,7 (22) |
| Type of delivery:<br>vaginal delivery<br>cesarean section | <br>58,3 (14)<br>41,7 (10) |
| Arterial hypertension (%, n)<br>yes<br>no<br>unknown | <br>20,8 (5)<br>75 (18)<br>4,2 (1) |
| Preeclampsia (%, n)<br>yes<br>no | <br>8,3 (2)<br>91,7 (22) |
| Tobacco use<br>yes<br>no | <br>58,3 (14)<br>41,7 (10) |

SD - Standard Deviation

**Table 2.** Clinical data of the participants

| Variable | n=24 |
|---|---|
| EFLV initial mean value ± SD | 30,5 ±6,3 (24) |
| NYHA class (%, n)<br>II<br>III<br>IV | <br>12,5 (3)<br>62,5 (15)<br>25 (6) |
| Treatment option<br>ACE inhibitors<br>ARBs<br>Beta-blockers<br>Diuretics | <br>79,2 (19)<br>4,2 (1)<br>83,3 (20)<br>95,8 (23) |
| Fatal events | 16,8 (4) |

EFLV- left ventricle ejection fraction; NYHA class- New York Heart Association Classification; ACE inhibitors- Angiotensin-converting enzyme inhibitors; ARBs- Angiotensin II Receptor Blockers

## Quality of Life (QoL) assessment

The average age was 37±6.4 years (Table 3), 92.3% were married, and 61.5% had higher education. The time that has passed from an initial diagnosis was 5.96±3.44 years. More than half of the respondents pointed out that they fully understand the necessity of compliance with the regime of secondary prevention (61.5%), and that HF did not diminish their life satisfaction in the last two weeks (53.8%). Furthermore, 38.5% of the patients are certain about the steps that should be taken in case of worsening HF symptoms, while the majority are somewhat sure. Analysis including the impact of HF on the lifestyle is shown in Table 4, while the physical limitations due to HF are present in Table 5.

## Left Ventricle Ejection Fraction analysis

In the majority of patients (68.5%) the initial EFLV was seriously impaired (38.5%, EFLV = 25- 30%; 30.8%, EFLV = 30-35%). The average time that has passed from an initial diagnosis to the control echocardiography was 1.3±1.8 years, and it revealed that 69.2% of participants had satisfactory EFLV (>50%), with the highest percentage of recovery in the first year. The mean value of the initial EFLV was 31.7±6.5%, while the control EFLV was 49.6±11.1% (Table 6), and a statistically significant difference was observed between the compared measurements ($p<0.05$). The mean value of current EFLV measurements was 55±9.6%, and out of thirteen, only two participants (15.4%) did not reach satisfactory values. Statistically significant differences between the first and third measurements of EFLV ($p<0.05$) were observed, but there was no statistically significant difference between the control and current EFLV values.

**Table 3.** Demographic data of the QoL survey participants

| Variable | n=13 |
|---|---|
| Age (mean value ± SD) | 37±6,4 |
| Caucasian | 100% (13) |
| Years since initial diagnosis (mean value ± SD)<br>1 month to 1 year<br>1 to 3 years<br>over 3 years | 5,9± 3,4<br><br>7,7% (1)<br>23,1% (3)<br>69,2%(9) |
| Marital status<br>married<br>divorced | <br>92,3% (12)<br>7,7% (1) |
| Education<br>primary school<br>high school<br>faculty | <br>15,4% (2)<br>61,5% (8)<br>23,1% (3) |
| Later pregnancy | 0% (0) |

SD - Standard Deviation

**Table 4.** Quality of life among surveyed respondents

| | |
|---|---|
| How would you feel if you had to spend the rest of your life with the quality you currently have due to heart failure? | |
| unsatisfied | 15,4% (2) |
| somewhat satisfied | 23,1% (3) |
| mostly satisfied | 30,8% (4) |
| completely satisfied | 30,8% (4) |
| In the past 2 weeks, how often have you felt discouraged or sad because of the effect of heart failure on your life? | |
| constantly | 7,7% (1) |
| most of the time | 7,7% (1) |
| periodically | 38,4% (5) |
| infrequently | 23,1% (3) |
| never | 23,1% (3) |
| On average, in the last 2 weeks, how much did fatigue limit you from doing what you want? | |
| at least 1 per day | 15,4% (2) |
| >3 times a week | 7,7% (1) |
| 1-2 times a week | 15,4% (2) |
| <1 per week | 38,5% (5) |
| non even once | 23,1% (3) |
| How much does heart failure change your lifestyle when it comes to your employment or household chores? | |
| quite a lot | 7,7% (1) |
| moderately | 23,1% (3) |
| a little bit | 23,1% (3) |
| does not change | 46,2% (6) |

## Discussion

Quality of life involves multiple dimensions that consist of mental and physical health, social functioning, and psychological and general well-being[18], and its assessment is of great importance. Nevertheless, QoL in women who are faced with this disease still represents an understudied research objective. Therefore, we assessed how the disease affected the daily functioning of the participants who were concerned about their quality of life in the two weeks prior to joining the survey. Our study, in alignment with previous research, affirms that PPCM is more prevalent among women over the age of 30, particularly among those who have given birth multiple times as opposed to first-time mothers[13]. Addition-

**Table 5.** Physical limitations of the interviewed respondents

| Please indicate how short of breath or fatigue limited you in performing the following activities during the last 2 weeks. | n=13 |
|---|---|
| ACTIVITIES OF MODERATE INTENSITY | |
| - Working in the house, yard or carrying groceries | |
| very much | 15,4% (2) |
| moderately | 23,1% (3) |
| few | 38,5% (5) |
| no limits | 23,1% (3) |
| - A walk lasting 30 minutes | |
| a little | 30,8% (4) |
| no limits | 53,8% (7) |
| I didn't do that | 15,4% (2) |
| HIGH-INTENSITY ACTIVITIES | |
| - Climbing the stairs without stopping | |
| very | 23,1% (3) |
| moderately | 7,7% (1) |
| few | 7,7% (1) |
| no limits | 38,5% (5) |
| I didn't do that | 23,1% (3) |
| - Running | |
| very much | 7,7% (1) |
| moderately | 7,7% (1) |
| no limits | 7,7% (1) |
| I didn't do that | 76,9% (10) |

**Table 6.** Left ventricle ejection fraction analysis results

| n=13 | n=13 | n=13 | |
|---|---|---|---|
| EFLV initial mean value ± SD | EF control mean value ± SD | EF current Mean value ± SD | p-value |
| 31,6± 6,5 | 49,6± 11,1 | 55± 9,6 | *p*1<0,05<br>*p*2<0,05<br>*p*3>0,05 |

EFLV- ejection fraction; SD- Standard Deviation
*p*1- EF initial and control, *p*2- EF initial and current, *p*3- EF control and current

ally, it suggests a relatively swift recovery of cardiac function in this demographic. While various studies[4-6] corroborate the higher incidence of PPCM in cases of multiple gestations and in pregnant or postpartum women with preeclampsia, our study diverges in this regard, as our dataset shows a notably smaller proportion of such patients. Research indicates that women of African descent are more susceptible to developing PPCM[9,19]. The highest recorded incidence of PPCM is in Nigeria, affecting 1 in every 102 births. Similarly, elevated incidences have been observed in South Africa and Haiti[20]. In our specific demographic, the majority of the population is of white racial background, and consequently, our study did not include any respondents of African descent.

Most of our respondents were married, had more than two children, and bore the responsibility of caring for a multi-member family. Among the reported symptoms, fatigue was the most experienced. These women, who are primarily mothers, are tasked with the care and well-being of their families. A significant portion of them expressed occasional feelings of sadness and discouragement, which can be attributed to the impact of heart failure on their lives[17]. At the moment of bringing a newborn into the world, rather than being able to attend to their child, they found themselves grappling with acute heart failure[15]. The respondents exhibit a strong awareness of the severity of this disease, especially concerning its long-term management, secondary prevention, and the reduction of relapses. It is recognized that subsequent pregnancies and childbirth can potentially represent a trigger[21], which would explain the fact that none of the patients reported subsequent pregnancies. A study assessing the quality of life may involve anywhere from one to several thousand patients[22]. In our region, epidemiological data on PPCM is limited. One of the challenges we encountered was the difficulty in identifying a larger number of women to form a representative sample, as this is a common issue faced by researchers studying rare diseases, and PPCM serves as a tangible example[16]. At the institution where the research was conducted, a total of twenty-four patients were treated over a fourteen-year period, and since only 13 of these patients were included in the survey, it is conceivable that the quality-of-life assessments could have yielded different results with a larger sample size.

According to the NYHA classification, during the initial hospitalization and the first presentation of the disease, individuals in class III and IV (representing 87.5% of cases) - signifying a severe degree of heart failure - were predominant. These findings align with the data reported by Shah T et al[9]. It has long been recognized that parameters of cardiac function, such as left ventricle ejection fraction and cardiac output, show only weak correlations with a patient's exercise capacity[23]. This observation is evident in our example, where a notable number of women with a high and stable ejection fraction are unable to engage in strenuous physical activity. Previous research has indicated that the presence of gestational hypertension, the onset of the disease after childbirth, as well as initial EFLV values above 35%, are associated with a favorable prognosis and the recovery of systolic function[24]. Conventionally, a patient is considered to have 'recovered' if the EFLV values are 50% or higher[25]. Patients with all cardiomyopathies should have access to multidisciplinary team with expertise in the management of cardiomyopathies. Recommendations for reproductive issues in patients who had PCMP are to be counseled for safe and effective contraception and pre-pregnancy risk assessment which is a class I recommendation according the Guidelines on Cardiomyopathies. It is also recommended that genetic testing and physiological support by a trained health professional should be offered to all individuals with cardiomyopathy[26].

## Conclusion

By applying the KCCQ we assessed the quality of life in patients with PPCM. Even though cardiac function recovers after the acute phase of the disease, long-term

consequences on quality of life and mental status could have been observed. It's necessary to search for aiding factors that contribute to the lowering of the quality of life so that their impact can be reduced or eliminated.

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## *Sažetak*

## *Procena kvaliteta života kod pacijentkinja sa peripartalnom miokardiopatijom: Fokus na žensko srce*


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*Uvod. Dostupne su ograničene informacije o kvalitetu života pacijentkinja sa peripartalnom kardiomiopatijom (PPCM). Cilja rada je bio da se proceni uticaj bolesti na kvalitet života u dve nedelje koje su prethodile anketi.*
*Metode. Studija je obuhvatila 24 ispitanice lečenih u Institutu za kardiovaskularne bolesti Vojvodina od januara 2006. do decembra 2019. Upitnik za kardiomiopatiju Kanzas Siti (KCCK) je korišćen za procenu kvaliteta njihovog života. Prikupljeni podaci su statistički obrađeni.*
*Rezultati. Prosečna starost ispitanica bila je 37.0 ± 6.4 godine, sa prosečnim vremenom od inicijalne dijagnoze od 5.9 ± 3.4 godine. Od 24, trinaest učesnica (53,8%) je izjavilo je da se osećaju tužno ili obeshrabreno zbog uticaja simptoma srčane insuficijencije na njihov život. Samo 30,8% ispitanica je izrazilo potpuno zadovoljstvo sa aktuenim stanjem. Umor i slabost je imalo 76,9% žena. Početna ejekciona frakcija leve komore (EFLV) bila je smanjena, dok je trenutno izmerena EFLV bila 55±10%. Tokom praćenja, 38,4% nije pokazalo simptome srčane insuficijencije. Većina (76,9%) nije bila u stanju da se bavi fizičkim aktivnostima visokog intenziteta.*
*Zaključak: Iako većina pacijenatkinja doživljava oporavak srčanog mišića nakon akutne faze PPCM, bolest nastavlja da ima dugoročne efekte na njihov kvalitet života i mentalno blagostanje.*



***Ključne reči:*** *peripartalna kardiomiopatija; kvalitet života; KCCK*


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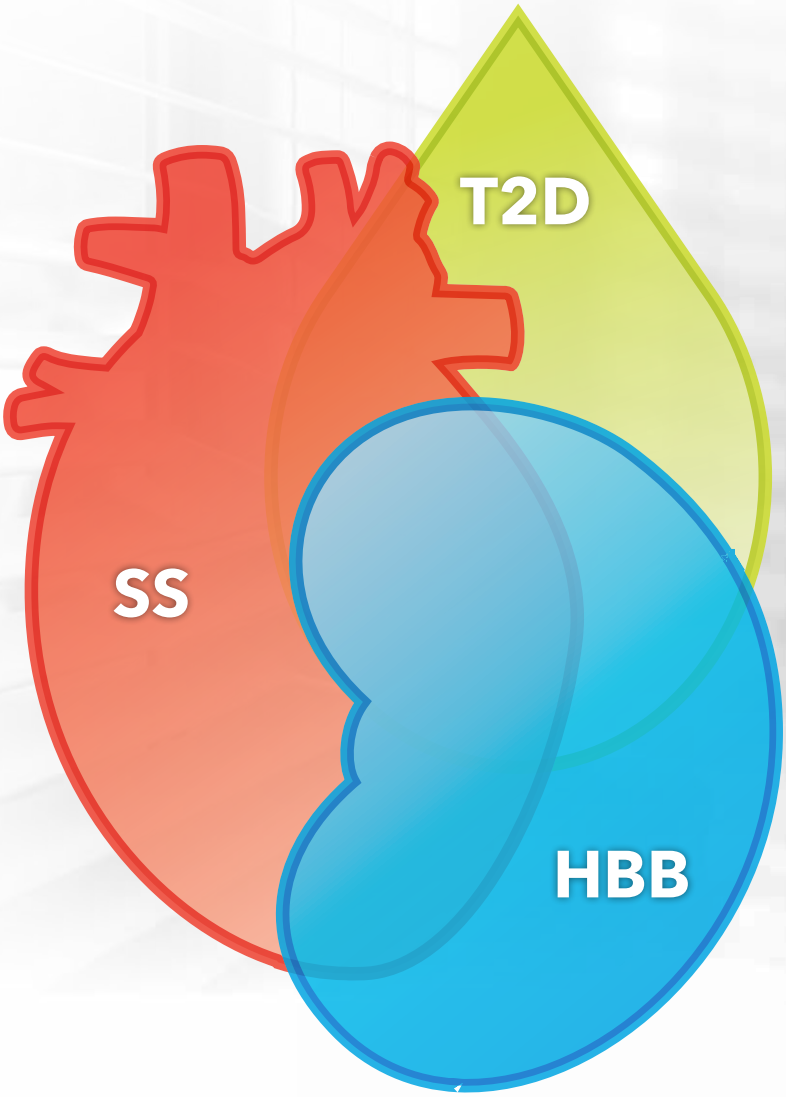


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