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The strategy for bivalvular interventions in aortic stenosis and concomitant mitral regurgitation

Elena Golukhova[1], Inessa Slivneva[2], Karen Petrosyan[3], Magomedrasul Musaev[4], Yuliya Pirushkina[5], Mikhail Latyshev[6], Arslan Magammatov[7], Khadizha Patsoeva[8]

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Corresponding Author(s):

Inessa Slivneva
Bakulev National Medical Research Center for Cardiovascular Surgery, Moscow, Russian Federation. Email: slivneva@mail.ru

Abstract: Multivalvular heart disease represents a less explored domain within cardiovascular surgery. In patients with aortic stenosis (AS) undergoing surgical or transcatheter aortic valve replacement (TAVR), the prevalence of moderate to severe mitral regurgitation (MR) ranges from 8% to 33%. Among the most common presentations are patients with severe AS and clinically significant functional MR. In instances of moderate surgical risk, open-heart surgery is typically performed, sometimes involving combined valve correction procedures. However, for patients deemed to be at high surgical risk or deemed inoperable, an interventional approach may be considered if the anatomy of both the aortic and mitral valves is conducive to such intervention. Careful analysis of each patient is essential in determining the appropriate treatment strategy, whether it involves isolated TAVR or if a staged intervention targeting the aortic and mitral valves is warranted. In the article, we present a review of the literature devoted to the strategy for bivalvular interventions in patients of high surgical risk and also a clinical case of a successful step-by-step interventional approach in an 83-year-old patient of high surgical risk with hemodynamically significant aortic and mitral valve disease, along with an analysis of the chosen approach.

Keywords: Aortic stenosis; Concomitant mitral regurgitation; Bivalvular intervention; Transcatheter Aortic Valve Replacement; Transcatheter Edge-to-Edge Mitral Valve Repair; patients of high surgical risk.

1. Introduction

In patients with aortic stenosis (AS) undergoing surgical or transcatheter aortic valve replacement (TAVR), the prevalence of moderate to severe mitral regurgitation (MR) ranges from 8% to 33%. The current recommendation for low-surgical risk patients with severe AS and significant MR is bivalvular surgery. However, the optimal treatment strategy remains a matter of debate for patients with high surgical risk [1].

Catheter-based therapies for valvular heart disease are rapidly advancing globally. TAVR for severe AS and transcatheter mitral valve edge-to-edge repair (m-TEER) for severe MR have emerged as alternatives to surgical intervention. These procedures have consistently shown improvements in quality of life, shorter hospital stays, and reduced risk of postoperative complications [2]. The interventional approach allows for staged procedures, facilitating evaluation of the effect of transcatheter aortic intervention on MR severity, with the option to perform mitral valve (MV) repair if necessary.

The optimal treatment approach for patients presenting with severe AS and significant MR remains a subject of ongoing debate, with a lack of guideline-based recommendations [3]. Conventional surgery involving both aortic valve (AV) and MV interventions carries substantial surgical risks, with reported hospital mortality rates ranging from 5%-12.5% for combined interventions compared to 1%-3% for isolated AV intervention [4]. Moreover, isolated AV intervention may prove ineffective in cases where hemodynamically significant MR persists or progresses, potentially leading to unfavourable outcomes despite successful correction of the AV condition. The persistence of moderate or severe MR following TAVR is also linked with increased mortality, with observed hazard ratios (HR) ranging from 1.49 (95% confidence interval (CI): 1.04-2.11; p=0.027), and is reported in 17%-35% of patients post-AV intervention [5].

Contemporary interventional technologies present a viable alternative to conventional surgery, reshaping the landscape of clinical decision-making toward an interventional paradigm. However, this shift raises new inquiries for future exploration, including the optimal staging, sequence, and timing of procedures within a stepwise approach. Particular research interest lies in evaluating the likelihood of MR

[1,2,3,4,5,6,7,8] Bakulev National Medical Research Center for Cardiovascular Surgery, Moscow, Russian Federation. Email: egolukhova@bakulev.ru

regression after correcting AS, and understanding how uncorrected MR impacts clinical outcomes post-TAVR, and determining the necessity of treating persistent severe symptomatic MR. Additionally, the timing and sequence of procedures in bivalvular interventions are crucial, along with addressing the many unresolved questions that demand a detailed understanding of the mechanisms behind MR development.

This clinical case illustrates the selection of a treatment strategy for a patient with severe AS and concurrent severe MR, along with an analysis of the chosen approach.

2. Clinical Case Description

An 83-year-old patient was admitted to the hospital with the following diagnosis: severe AS, severe MR, severe tricuspid regurgitation (TR), and high pulmonary hypertension. Additionally, the patient had atherosclerosis of the coronary arteries, coronary heart disease, stable exertional angina, II functional class. She had undergone aorto-coronary bypass surgery in 2015. Upon admission, the patient reported experiencing dyspnea during moderate physical activity, palpitations, and elevated blood pressure (130/80 mm Hg on antihypertensive therapy). Table 1 outlines the chronology of events leading up to hospitalization.

Table 1: Chronology of Events Before and During Hospitalization

Year	Event
2010	Acute cerebral circulation disorder with right-sided hemiparesis and subsequent regression of symptoms
2013	LV myocardial infarction of unknown age diagnosed based on electrocardiography data
2015	Chest pain and dyspnea on exercise; Multivessel coronary artery disease; CABG performed: left internal mammary artery graft to the left anterior descending coronary artery, saphenous vein grafts to posterior descending artery and left marginal artery
2022	Severe AS and moderate MR (TTE); Surgical treatment recommended
Jul-23	Bypass Graft Angiography was performed, shunts are patency
07.11.2023	Current hospitalization; Echocardiographic study revealed severe AS, severe MR and TR
08.11.2023	TAVR performed
15.11.2023	m-TEER procedure performed

Notes: LV - Left ventricle, CABG - Coronary Artery Bypass Grafting; PDA - Posterior Descending Artery; LCX - Left Circumflex Coronary Artery, AS - aortic stenosis, MR - mitral regurgitation, TTE – transthoracic echocardiography, TR - tricuspid regurgitation, TAVR - transcatheter aortic valve replacement, m-TEER - Mitral transcatheter edge-to-edge repair

Upon admission, the patient's anthropometric measurements were as follows: height 148 cm, weight 68 kg, body surface area 1.69 m², and body mass index 31.04 kg/m². The electrocardiogram demonstrated sinus rhythm with a heart rate of 68 beats per minute, with signs of cicatricial changes of the anterior and posterior walls of the left ventricle (LV). Additionally, single supraventricular extrasystoles were noted.

Transthoracic echocardiographic examination (TTE) revealed the following LV parameters: end-diastolic volume of 78 ml (end-diastolic index 46.1 ml/m²), end-systolic volume of 32 ml (end-systolic index 19 ml/m²), stroke volume of 46 ml (stroke index 27.2 ml/m²), and LV ejection fraction of 59%. The AV exhibited massive calcification of the leaflets, resulting in limited systolic opening. A maximum transvalvular aortic flow velocity of 4.8 m/s and a mean gradient of 53 mmHg. Quantitative assessment of MR revealed an effective regurgitation orifice area of 0.4 cm², regurgitation volume of 55 mL, and regurgitation fraction of 45%, classified as severe according to ESC 2021 criteria [1]. Severe TR was also observed. The calculated systolic pulmonary artery pressure was 65 mmHg. Cardiac surgical risk assessment indicated by the EuroSCORE II -10.03%.

Considering the severe AS, suitable anatomical conditions as determined by computed tomography, the patient's advanced age, previous CABG surgery, and the high surgical risk, TAVR was chosen as the initial treatment stage for this patient.

On November 8, 2023, the patient underwent TAVR under general anesthesia. The procedure involved the insertion of a 24.5 mm Myval (Meril, India) aortic prosthesis via transfemoral access following balloon valvuloplasty with a 20-40 mm balloon catheter. Control transesophageal echocardiography (TEE) and aortography confirmed the optimal positioning and satisfactory hemodynamic parameters with complete apposition of the implanted stent valve. The maximum transprosthetic flow velocity was 1 m/s and the mean transprosthetic pressure gradient was 7 mmHg. The procedure concluded without complications, and the puncture site was closed using Perclose (Abbott V., USA). Following the procedure, the postoperative course proceeded without complications.

Based on the ultrasound findings, severe MR persisted in the patient. As a result, the multidisciplinary team decided to consider m-TEER.

The TEE revealed severe MR of mixed origin. The MV exhibited thickened leaflets, primarily along the free edge, with retraction into the LV (tenting height 12 mm). The MR jet is primarily located in the central region with a slightly eccentric orientation towards the posterior wall of the left atrium. The dimensions of the mitral annulus were 34x35 mm, with an MV area of 4.2 cm². Mitral gradients were measured as peak - 6 mmHg and mean - 1 mmHg. No calcifications are observed in the region of presumed grasping, with minimal cleft-like indentations (3D beats 1). Flow reversal is noted in the left upper pulmonary vein. The transseptal distance to the coaptation zone of the MV leaflets measures 4.1 cm. The planned device is an XTW clip (MitraClip), with the procedure scenario involving the implantation of 1 clip in the central segments of the MV.

On November 15, 2023, the patient underwent m-TEER using the MitraClip device as the second stage of treatment. Antegrade catheterization of the inferior vena cava was performed using the Seldinger technique via left transfemoral access with a 6F introducer. Under fluoroscopy and TEE guidance, a transseptal puncture of the interatrial septum was made 4 cm above the plane of the MV annulus using a transseptal needle. A 0.035 guidewire was then advanced into the upper left pulmonary vein to facilitate safe catheter placement. Subsequently, the diagnostic guide was exchanged for an Amplatz SuperStiff guide, which was used to navigate the MitraClip G4 23F guided guidewire into the left atrium. The XTW clip was inserted and positioned in the left atrial cavity under echocardiographic and fluoroscopic guidance, followed by insertion into the LV. The MitraClip XTW clip was implanted in the central segments (A2-P2) resulting in the formation of two symmetrical orifices (Figures 1, 2). The peak transmitral pressure gradient was 8/10 mm Hg, and the mean pressure gradient was 3/4 mmHg. Residual MR was of insignificant degree. The LV parameters measured were as follows: end-diastolic volume - 90 ml, end-diastolic index - 53 ml/m^2, end-systolic volume - 45 ml, end-systolic index - 27 ml/m^2, stroke volume - 45 ml, stroke index - 27 ml/m², ejection fraction - 50%. A residual defect of the interatrial septum measuring 3x5 mm with left-to-right shunting was noted. Left atrial pressure was measured at 14 mmHg. Subsequently, the MitraClip delivery system was removed, and the procedure was completed without complications.

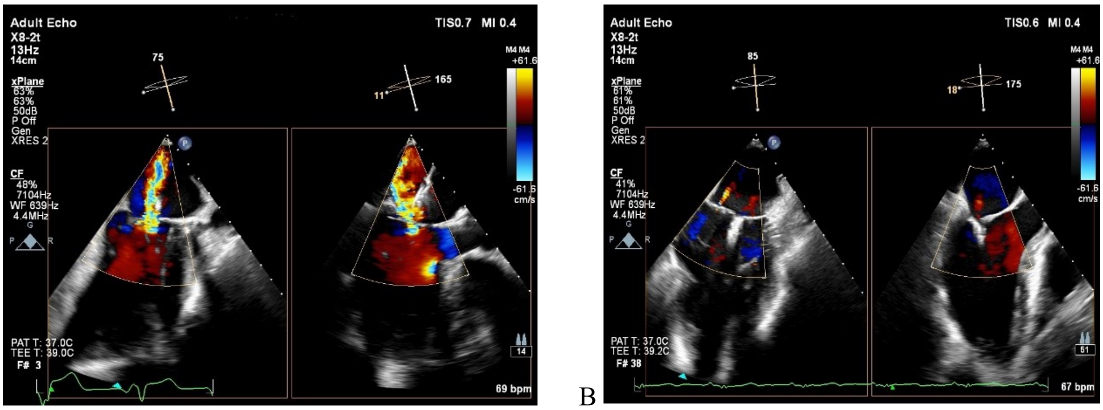

Figure 1: Transesophageal Echocardiography. Intercommissural View. A (before m-TEER) - Severe mitral regurgitation is observed with an eccentric jet along the left atrium free wall. B (after m-TEER) - Minor residual mitral regurgitation is observed.

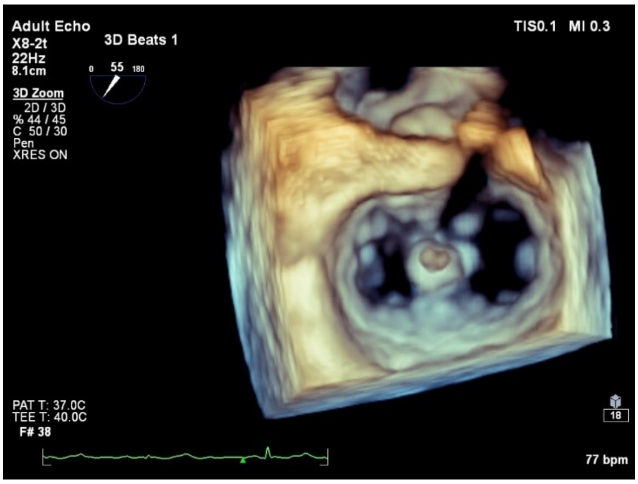

Figure 2: Transesophageal Echocardiography (3D beats 1). The central segments of the mitral valve leaflets were approximated with one clip (MitraClip XTW), resulting in the formation of two symmetrical orifices with a mean transmitral pressure gradient of 3.5 mm Hg.

The patient was discharged on the 5th day following the second procedure.

3. Discussion

3.1. Clinical outcomes in patients with severe MR after TAVR

The primary concern is the impact of MR on the early postoperative period after AV intervention. Whether postponing MV correction is viable considering its potential regression amidst LV reverse remodeling remains uncertain. Consequently, the question of prioritizing transcatheter intervention on the AV and MV is contentious.

The presence of moderate or severe MR in patients undergoing TAVR correlates with increased mortality and poorer clinical outcomes [6]. The PARTNER study indicates that moderate MR post-TAVR significantly elevates 30-day and long-term mortality rates in patients without concurrent MV intervention [7]. Moreover, the poorer outcomes in the absence of MV intervention for severe MR are highlighted in the meta-analysis by Nombela-Franco et al. (2015), revealing higher mortality rates at 30 days, 1 year, and 2 years following isolated TAVR [8].

According to data from the Swedish national registry, "The SWEDEHEART," patients experiencing progression or persistence of MR severity in a post-TAVR period face a twofold and 1.7-fold increase in mortality at the 5-year follow-up, respectively [9].

An 8-study meta-analysis involving 8,015 patients demonstrated elevated overall 30-day and 1-year mortality rates in patients with severe MR after TAVR compared to those without MR (OR 1.49, 95% CI 1.16 to 1.92; HR 1.32, 95% CI 1.12 to 1.55, respectively) [8]. Another meta-analysis encompassing 16 studies and 13,672 patients revealed a similar increase in both early all-cause mortality (a pooled analysis of 8 studies) and overall all-cause mortality (a pooled analysis of 14 studies), with respective 2.17-fold and 1.81-fold increments in patients with apparent relative to unapparent MR [10]. In a multicenter study by Cortes et al. involving 1,110 patients, a threefold increase in mortality was observed in patients with significant MR before TAVR at six months compared to those without significant MR (35.0% vs. 10.2%) [11]. The presented data suggest the influence of MR on the postoperative period, both immediately after TAVR and within a five-year timeframe. Ben-Assa et al. argues that the severity of post-procedural MR is associated with the lack of cardiac chamber remodeling, an increased incidence of adverse cardiac events, and fatal outcomes [12].

It is essential to evaluate the possibility of performing isolated TAVR with the aim of affecting both the aortic and mitral valves. Therefore, the next step is to assess the probability and potential for MR regression after AV correction. It is enough for the decrease in LV pressure post-TAVR to contribute to the reduction of MR, which is substantially dependent on afterload?

3.2. Natural Course of Mitral Regurgitation After TAVR

The coexistence of severe AS and clinically significant functional MR is relatively common. According to the PARTNER study, this combination occurs in approximately 20% of patients deemed at high surgical risk [7]. Relief of the obstruction in the AV area leads to a decrease in LV pressure, thereby reducing the overload on the MV and potentially contributing to a reduction in the severity of MR, particularly of functional aetiology.

Multiple processes can simultaneously influence the reduction of functional MR following TAVR. Immediately after AV intervention, hemodynamic changes play a predominant role over geometric changes in MR regression [13]. Subsequent MR changes are influenced by LV geometric remodeling, particularly the reverse remodeling often observed after TAVR [14]. However, persistence or even progression of MR severity has been observed in a subset of patients [15,16,17].

Predictors of persistent or worsening MR following transcatheter AV replacement include alterations in MV complex geometry resulting in significant leaflet malcoaptation [18], concurrent coronary artery disease, and sustained elevated LV pressure due to suboptimal aortic prosthesis positioning [19]. Massive calcification, particularly of the posterior annulus, severe tenting, or a combination of both, also contribute to the persistence of MR severity following TAVR [16]. Patients with baseline MR of grade 3 or higher, particularly of organic aetiology, also exhibit minimal MR regression or no response to aortic valve AV intervention. These patients have the lowest survival rates and the least symptom regression [5].

Other factors contributing to the progression of MR severity include deep valve implantation resulting in anterior mitral leaflet restriction [15], and paraprosthetic leak of severe or greater degree (odds ratio (OR) 8.104; 95% CI 1.78-36.87; $p = 0.007$) [18]. Paraprosthetic leaks are more commonly observed following the implantation of self-expanding prostheses [20], possibly due to incomplete apposition of the prosthesis and the shape of the LV outflow tract [21].

Additionally, several conditions associated with the progression of MR after TAVR include an initially low AV gradient, pulmonary hypertension, atrial fibrillation, a mitral annulus diameter exceeding 35.5 mm, calcification of the MV leaflets or annulus, organic MR, and a small LV volume [19]. These factors, beyond their individual significance, may act as cofactors in the development of MR, thereby amplifying their effects. Consequently, the prevalent yet underexplored coexistence of AS and MR exemplifies this clinical conundrum, the complexity of which is greater than the sum of its components [13].

3.3. Isolated or bivalvular treatment strategy

According to the 2021 ESC/EACTS guidelines, in high-risk or inoperable patients with severe AS and severe MR, simultaneous (or more often staged) TAVR and m-TEER may be considered, but there is insufficient experience to provide reliable recommendations. In patients with severe functional MR, a thorough clinical and echocardiographic reassessment should be conducted after TAVR to determine the necessity for further MV intervention [1].

The success of a combined approach involving transcatheter MV repair during TAVR has been documented in several studies [22, 23]. The initial case series presenting the performance of TAVR and m-TEER was introduced by Rudolph and colleagues (2013). Transcatheter treatment of high surgical risk patients with concurrent severe AS and severe MR was found to be technically feasible, thus marking a significant expansion of the therapeutic options available [22].

Kische et al. observed persistent severe MR after TAVR compared to baseline values. Subsequently, 12 patients underwent m-TEER with favorable long-term outcomes. The study concluded that in selected high-risk patients unsuitable for conventional surgery, symptomatic severe AS and concomitant MR can be managed using a transcatheter approach with a high safety profile [23].

In a study conducted by Elbadawi et al (2021), various approaches ranging from single-stage to separate interventions were examined, with m-TEER performed either before or after TAVR in different cases [24]. Compared to isolated TAVR, the performance of TAVR and m-TEER was associated with higher in-hospital mortality (10.8% vs. 1.9%). The observed increased mortality was correlated with a heightened risk of hemodynamic disturbances, bleeding events, and acute kidney injury. The authors propose that the elevated risk of in-hospital mortality is likely multifactorial and linked to the cumulative risk of the two procedures in elderly patients with a high comorbidity burden and a higher frequency of pre-existing hospitalizations.

Zahid et al. (2023) reported extensive experience in treating this patient population, with a preference for m-TEER after TAVR in the majority of cases [25]. The authors observed no differences in in-hospital mortality rates based on the chosen treatment strategy; however, complication rates and prolonged hospital stays were notably higher in patients undergoing both procedures during a single hospitalization. Table 2 outlines the interventional treatment strategies–simultaneous or staged approaches–discussed in the aforementioned studies.

Table 2: Summary of studies on interventional treatment of aortic stenosis and concomitant mitral regurgitation

Study	Rudolph (2013)	Kische (2013)	Elbadawi (2021)	Sagheer (2022)	Zahid (2023)	Total
Participants, n	11	12	110	213	627	973
Transcatheter MV reconstruction after TAVR	7 (63.6%)	12 (100%)	29 (26.4%)	124 (58.2%)	453 (72.3%)	625 (64.25%)
Transcatheter MV reconstruction together with TAVR	3 (27.3%)	-	75 (68.2%)	89 (41.8%)	174 (27.7%)	341 (35.05%)
Transcatheter MV reconstruction before TAVR	1 (9.1%)	-	6 (5.5%)	-	-	7 (0.72%)
In-hospital mortality, %	9.1%	0%	10.8%	Not presented	6.1% (staged) /7.0% (concomitant)	Overall in-hospital mortality rate: 7.22%

Notes: TAVR – Transcatheter aortic valve replacement, MV – mitral valve.

The differences in mortality rates across the studies (Rudolph, Elbadawi, and Zahid) are not statistically significant ($p = 0.391$).

A less frequent scenario involves primary intervention on the MV followed by intervention on the AV. However, it is important to note that a sudden increase in afterload due to MR resolution may result in cardiac decompensation [13]. Therefore, this approach is more appropriate when MR predominates over AS severity hemodynamically, particularly in cases of moderate AS and severe MR.

Due to the lack of randomized comparisons between surgical and transcatheter bivalvular interventions versus medical management of MR after AV intervention, evidence-based recommendations on patient selection and optimal timing of interventions cannot be made [3]. Following the removal of valve obstruction, reverse LV remodelling can occur, potentially leading to a reduction in MR in some patients. Functional MR is more likely to regress after AV intervention, provided that the associated LV remodelling process, if present, is also reversible. If MR diminishes with optimal medical therapy, the likelihood of its progression decreases, and a strategy of observation at 2-3 months after TAVR becomes more justified [13].

The potential regression of MR subsequent to AS treatment advocates for a stepwise strategy, facilitating a reevaluation of concurrent MR following AS intervention intervention [13]. Therefore, in individuals with severe AS and secondary MR, initiating TAVR is recommended; should symptoms persist and MR severity remain significant, m-TEER may be considered if anatomical criteria for the procedure are met (ACC/AHA 2020 guidelines) [26].

In cases of severe MR of organic origin, the outcomes of a watchful waiting strategy are less promising [27]. For instance, in the study by Doldi et al. (2023) [5], the persistence of MR during follow-up correlated with increased mortality (HR 1.49, 95% CI: 1.04-2.11; p=0.027), predominantly in the primary MR subgroup of patients. The rate of MR reduction was 40.8% in primary MR (p<0.001), which was half that of atrial functional MR. This is logical, as in primary MR, the underlying defect causing the MR (such as MV prolapse or calcification) persists following TAVR [28]. Hence, identifying the aetiology and severity of MR is critical for evaluating the potential for regression after AVR and subsequently devising the treatment strategy [29].

Although AS and MR can arise independently or share a common mechanism of development, their synchronous occurrence or predominance of one over the other inevitably affects each other. Therefore, a meticulous evaluation of their hemodynamic significance and influence on cardiac function is essential to determine the indications for intervention type and staging. Selecting the optimal timing and method of intervention is a crucial aspect of decision-making, requiring consideration not only of the individual characteristics of each valve but also of their interplay.

In conclusion, selecting the timing and preferred intervention method in the context of AS and MR requires a comprehensive approach tailored to individual patients.

4. Conclusion

The optimal approach in cardiac surgery, whether correction of the leading AV malformation or bivalvular surgery, is still under investigation. Despite the numerous advantages of conventional surgery, m-TEER remains a viable option for patients at high risk of complications with preserved reconstructive potential of the MV. Moreover, the clinic's expertise allows for the expansion of the technology's application beyond its initial criteria, enabling interventional interventions across a broad spectrum of MV pathologies.

The advantages of the chosen transcatheter approach are evident in risk reduction compared to conventional surgery, utilization of interventional valve treatment technologies with established efficacy (TAVR, m-TEER), ability to reassess MR severity post-TAVR to decide on the need for further intervention, establishment of individualized timing between stages, and achievement of optimal hemodynamic outcomes post-procedure.

In high-risk patients with persistent severe symptomatic MR after TAVR, the m-TEER procedure is the preferred method. Although the timing and sequence of these procedures have not been clearly defined, determining the staging of interventions requires comparison of factors influencing effective reverse LV remodeling and the potential for MR reduction, along with an analysis of the dominant mechanism of MR progression/persistence and the prospects for its interruption.

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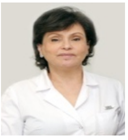
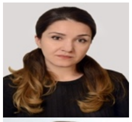
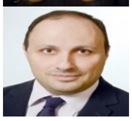
About the Author



Elena Golukhova, Doctor of Medical Sciences, Professor, Academician of the RAS, Honored Scientist of the RF, Director of A.N. Bakulev National Medical Research Center for Cardiovascular Surgery of the Russian Ministry of Health, Chief Consultant Arrhythmologist of the Russian Ministry of Health, Head of Department of Non-Invasive Arrhythmology and Combined Pathology Surgical Treatment.Elena Golukhova is a member of the Department of Medical Sciences Bureau of the RAS, member of the Thesis Board for cardiology speciality at A.N. Bakulev National medical research center for cardiovascular surgery of the Russian Ministry of Health, Chairman of the Expert Council of the HAC for therapeutic sciences, Chairman of “Cardiology and visualization in cardiology” panel at the Russian Association of cardiovascular surgeons, board member of the Russian Society of Cardiology, an active member of the European Society of Cardiology, member of Commission on Pseudoscience, deputy chief editor of the journal “Creative Cardiology”, member of the editorial boards of a number of journals.

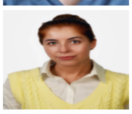


Inessa Slivneva, Candidate of Sciences, Ultrasound Diagnostics Specialist, Head of the Group of the Cardiac Imaging and Innovative Technologies, Associate Professor of the Department of Cardiology, Functional and Ultrasound Diagnostics with a Course of Pediatric Cardiology.



Karen Petrosyan, Doctor of Medical Sciences, Professor, Endovascular surgeon, Head of the Department of X-ray Surgical Methods of Heart and Vessels Examination and Treatment, Head of Chair of X-ray Endovascular Methods of Diagnostics and Treatment at the Institute of Higher Qualification Personnel Training and Professional Development of «A.N. Bakulev NMRC for cardiovascular surgery» Russian Ministry of Health

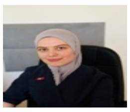
Magomedrasul Musaev, Endovascular surgeon, Head of Department of Radiosurgical, Electrophysiological Methods of Examination, Treatment and Practical Evaluation of the New Technologies.



Yuliya Pirushkina, Functional Diagnostics Specialist, Junior Researcher at Cardiac Surgery Unit.

Mikhail Latyshev, Candidate of Sciences, Cardiovascular Surgeon and Senior Researcher at the Department of Cardiac Surgery.

Arslan Magammatov, Endovascular surgeon, Department of Radiosurgical, Electrophysiological Methods of Examination, Treatment and Practical Evaluation of the New Technologies.



Khadija Patsoyeva, Functional Diagnostics Specialist, Postgraduate Student in Cardiology.