MAURICIO FELIPPI DE SÁ MARCHI

Incidence, predictors and clinical impact of myocardial injury after transcatheter interventions for valve dysfunction

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Incidence, predictors and clinical impact of myocardial injury after transcatheter interventions for valve dysfunction

Incidência, preditores e impacto clínico da injúria miocárdica após o tratamento transcateter das disfunções valvares

Thesis presented to the Faculty of Medicine of the University of São Paulo to obtain the title of Doctor of Science.

Cardiology Program

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To my wife, Eduarda Raquel Przygoda Alves

To my daughter, Beatriz Alves de Sá Marchi

To my mother, Genésia Bezerra de Sá

To my father, Vanderley Luiz Marchi

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“The things that we love tell us what we are”.

St. Thomas Aquinas (1225-1274)

RESUMO

De Sá Marchi MF. Incidência, preditores e impacto clínico da injúria miocárdica após o tratamento transcateter das disfunções valvares [tese]. São Paulo: Faculdade de Medicina, Universidade de São Paulo; 2024.

O reparo e a substituição cirúrgica das válvulas cardíacas são geralmente considerados o padrão ouro para pacientes com disfunção valvar e permanecem como indicações indiscutíveis em situações como endocardite infecciosa e trombose valvar. Além disso, observa-se uma tendência crescente do uso de válvulas biológicas ao invés de válvulas mecânicas nas cirurgias de troca valvar. Por outro lado, devido ao aumento global da idade populacional várias opções transcateter têm sido amplamente utilizadas, incluindo o implante transcateter de válvula aórtica (TAVI), o implante transcateter de válvula mitral (TMVR) e o reparo transcateter mitral de borda-a-borda (TEER). Essas técnicas fornecem alternativas promissoras no tratamento das valvopatias aórticas e mitrais, tornando-se o tratamento de escolha para pacientes idosos (idade > 70 anos) e com anatomia favorável. No entanto, dados sobre a elevação de biomarcadores cardíacos denotando lesão miocárdica (CK-MB, troponina e BNP) e seu impacto prognóstico no contexto de intervenções valvares transcateter ainda precisam ser mais bem esclarecidos. Portanto, esta tese buscou avaliar a incidência, os preditores e o valor prognóstico da lesão miocárdica por meio da análise de biomarcadores e seu impacto nas intervenções transcateter, incluindo TAVI, TMVR e TEER.

Palavras-chave: Valva aórtica, Substituição da valva aórtica transcateter, Valva mitral, Estenose da valva mitral, Insuficiência da valva mitral, Biomarcadores.

ABSTRACT

De Sá Marchi MF. Incidence, predictors and clinical impact of myocardial injury after transcatheter interventions for valve dysfunction [thesis]. São Paulo: “Faculdade de Medicina, Universidade de São Paulo”; 2024.

Surgical repair and replacement of cardiac valves are generally considered the gold standard for valve dysfunctions and remains undisputed in indications such as infective endocarditis and valve thrombosis. Likewise, there has been an increasing frequency of patients receiving bioprosthetic valves rather than mechanical valves. Still, due to the global increasing age of the population, various transcatheter options have largely supplanted surgical interventions, including transcatheter aortic valve implantation (TAVI), transcatheter mitral valve replacement (TMVR), and transcatheter edge-to-edge repair (TEER). These techniques provide promising alternatives to the treatment of aortic and mitral valve diseases, becoming the treatment of choice for older patients (age > 70 years) with favorable anatomy. Yet, data on the elevation of cardiac biomarkers denoting myocardial injury (CK-MB, troponin and BNP) and their prognostic impact in the context of transcatheter valve interventions still need to be better clarified. Therefore, this thesis sought to assess the incidence, predictors, and prognostic value of myocardial injury through the analysis of biomarkers and their impact on transcatheter interventions, including TAVI, TMVR, and TEER.

Key words: Aortic valve, Transcatheter aortic valve replacement, Mitral valve, Mitral valve insufficiency, Mitral valve stenosis, Biomarkers.

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LIST OF ABBREVIATIONS

AUC	-	Area under the curve
BEV	-	Balloon-expandable valve
BMI	-	Body mass index
BP	-	Bioprosthetic
BVF	-	Bioprosthetic valve fracture
CABG	-	Coronary artery bypass graft
CI	-	Confidence interval
CKD	-	Chronic kidney disease
CK-MB	-	Creatine kinase myocardial band
COPD	-	Chronic obstructive pulmonary disease
cTn	-	Cardiac troponin
CV	-	Cardiovascular
eGFR	-	Estimated glomerular filtration rate
EuroSCORE II	-	European System for Cardiac Operative Risk Evaluation II
GDMT	-	Guideline-directed medical therapy
GRASP	-	Getting Reduction of MitrAl inSufficiency by Percutaneous clip implantation
HCFMUSP	-	Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo
HF	-	Heart failure
HR	-	Hazard ratio
ID	-	Internal diameter
InCor	-	Instituto do Coração (Heart Institute)
IPD	-	Individual patient data
IQR	-	Interquartile range
KM	-	Kaplan-Meier
KS	-	Kolmogorov-Smirnov
LV	-	Left ventricle
LVEF	-	Left ventricular ejection fraction
LVESD	-	Left ventricular end-systolic diameter
LVEDD	-	Left ventricular end-diastolic diameter
LVMI	-	Left ventricular mass index

LVOT	-	Left ventricular outflow tract
M-VARC	-	Mitral valve academic research consortium
MAP	-	Mean arterial pressure
MITRALITY	-	Mitral Transcatheter Edge-To-Edge Repair Assessment of Risk Prediction Models
MP	-	Mechanical prostheses
MR	-	Mitral regurgitation
NT-proBNP	-	N-terminal pro-brain natriuretic peptide
NYHA	-	New york heart association
OS	-	Overall survival
PASP	-	Pulmonary artery systolic pressure
PCI	-	Percutaneous coronary intervention
PMR	-	Primary mitral regurgitation
PRISMA	-	Preferred reporting items for systematic reviews and meta-analyses
ROBINS-I	-	Risk of bias in non-randomized studies of interventions
ROC	-	Receiver operating characteristic
RVPA	-	Right ventricle to pulmonary artery
SCAI	-	Society for Cardiovascular Angiography and Interventions
SEV	-	Self-expanding valves
SMR	-	Secondary mitral regurgitation
SMVR	-	Surgical mitral valve replacement
SMVR-REDO	-	Reintervention of a surgical mitral valve
STS	-	Society of Thoracic Surgeons
STS-PROM	-	Society of Thoracic Surgeons Predicted Risk of Mortality
TA	-	Transapical
TAPSE	-	Tricuspid annular plane systolic excursion
TAVI	-	Transcatheter aortic valve implantation
TEER	-	Transcatheter edge-to-edge repair
TF	-	Transfemoral
THV	-	Transcatheter heart valve
TMVR	-	Transcatheter mitral valve replacement
TS	-	Transseptal
ULN	-	Upper limit of normal
ViMAC	-	Valve-in-mitral annular calcification

ViR	-	Valve-in-ring
ViV	-	Valve-in-valve
VIVID	-	Valve-in-valve international data
YI	-	Youden index

SUMMARY

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1 INTRODUCTION

1.1 PREFACE

This Ph.D. project's research was initiated in the Interventional Cardiology Department of the Instituto do Coração (InCor) at the Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (HC-FMUSP) in São Paulo, Brazil, under the guidance of Dr. Henrique Barborsa Ribeiro. Additionally, the student served as an interexchange Ph.D. candidate at Thoraxcentrum, affiliated with Erasmus Universiteit Rotterdam, Rotterdam, the Netherlands, under the supervision of Prof. Dr. Nicolas Van Mieghem. Four scientific articles (chapters 3 to 6) resulting from this work have been published in peer-reviewed cardiovascular journals to this date.

Throughout the research project, the student received an interexchange Ph.D. grant, the *Programa de Doutorado-Sanduíche no Exterior* (PDSE) (88887.716769/2022-00), from "CNPq, Conselho Nacional de Desenvolvimento Científico e Tecnológico - Brasil," effective from 01-03-2023 until 31-08-2023.

The first article presented in this doctorate thesis is entitled “Impact of Periprocedural Myocardial Injury After Transcatheter Aortic Valve Implantation on Long-Term Mortality: A Meta-Analysis of Kaplan-Meier Derived Individual Patient Data”. It has been published in the “Frontiers in Cardiovascular Medicine”, with the candidate serving as the first author. It has also been presented at the SOLACI/SBHCI Congress in August 2023 (Rio de Janeiro, Brazil) as an oral presentation, where it was awarded first prize in the Best Structural Abstract Award Competition. In this study, a comprehensive pooled analysis of individual patient data, extracted from Kaplan-Meier survival curves from previously published papers, was undertaken to assess and compare survival outcomes between patients with and without periprocedural myocardial injury (PPMI) following transcatheter aortic valve implantation (TAVI). The prognostic value of PPMI was determined using flexible parametric models with B-splines, and landmark analyses were conducted to establish its significance. Subgroup analyses were carried out based on VARC-2 criteria, creatine kinase-MB (CK-MB), and troponin levels, which defined the occurrence of PPMI.

The second article presented in this doctorate thesis is entitled “Myocardial Injury After Transcatheter Mitral Valve Replacement Versus Surgical Reoperation”. It has been published in the “American Journal of Cardiology” and the student is the first author. This study aimed to assess the incidence and clinical implications of myocardial injury, identified by elevated cardiac biomarkers (CK-MB and troponin), in patients undergoing treatment for mitral bioprosthesis dysfunction, comparing transcatheter mitral valve replacement (TMVR) to

surgical mitral valve replacement reoperation (SMVR-REDO). The study included 310 patients with mitral bioprosthesis failure treated at InCor between 2014 and 2023. Multivariable analysis and propensity score matching were employed to account for intergroup differences in baseline characteristics. CK-MB and troponin levels were assessed at various time points post-intervention. Biomarker values were compared to reference values, and outcomes were evaluated according to Mitral Valve Academic Research Consortium Criteria (M-VARC).

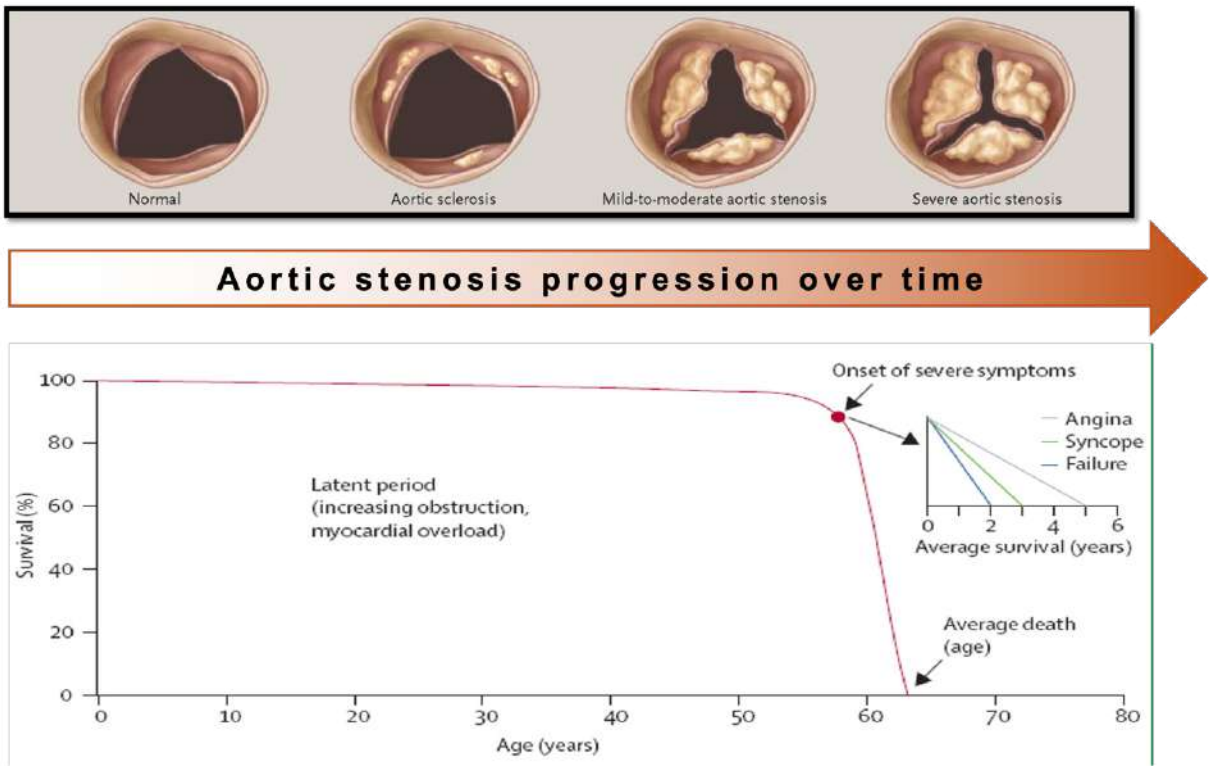
The third article presented in this doctorate thesis is entitled "Clinical and Hemodynamic Outcomes of Balloon-Expandable Mitral Valve-in-Valve Positioning and Asymmetric Deployment". It has been published in the "JACC: Cardiovascular Interventions" and the student and the supervisor are among the coauthors. This study included a worldwide collaboration network in TMVR that sought to assess the correlation between the depth of implantation and the asymmetry of a transcatheter heart valve relative to the bioprosthesis, aiming to elucidate their influence on clinical outcomes.

The fourth article presented in this thesis is "Comparative Analysis of Different Risk Prediction Tools After Mitral Transcatheter Edge-To-Edge Repair". This article has been published in the "International Journal of Cardiology" and the candidate is the first author. It has also been presented at the SOLACI/SBHCI Congress in August 2023 (Rio de Janeiro, Brazil) as an oral presentation, where it was awarded third prize in the Best Structural Abstract Award Competition. In this analysis, data from 206 patients undergoing treatment for mitral regurgitation (MR) at Erasmus Medical Center between 2011 and 2023 were studied. This paper aimed to assess the predictive accuracy of various mitral and surgical risk scores, including EuroSCORE II, GRASP, MITRALITY, MitraScore, TAPSE/PASP-MitraScore, and STS, in forecasting 1-year mortality and the composite outcome of 1-year mortality and/or heart failure hospitalization in patients with primary mitral regurgitation (PMR) and secondary mitral regurgitation (SMR). Additionally, a subanalysis focusing on SMR-only patients incorporated the COAPT Risk Score and baseline N-Terminal pro-Brain Natriuretic Peptide (NT-proBNP) was also performed.

1.2 VALVULAR HEART DISEASES AND TRANSCATHETER SOLUTIONS

Valvular heart diseases (VHD) represent a complex spectrum of pathologies with significant implications for patient morbidity and mortality. Among these, aortic stenosis (AS) stands out as the most prevalent primary valve dysfunction, particularly in Europe and North America. This condition is characterized by the narrowing and dysfunction of the aortic valve, which imposes a substantial hemodynamic burden on the heart, culminating in adverse cardiac remodeling and potentially catastrophic outcomes[1] (Figure 1). With the demographic shift towards an aging population, the incidence and prevalence of AS are rapidly escalating, mandating a comprehensive understanding of the diagnostic modalities, prognostic markers, and treatment strategies involved[2-4].

Figure 1 - Aortic stenosis progression over time

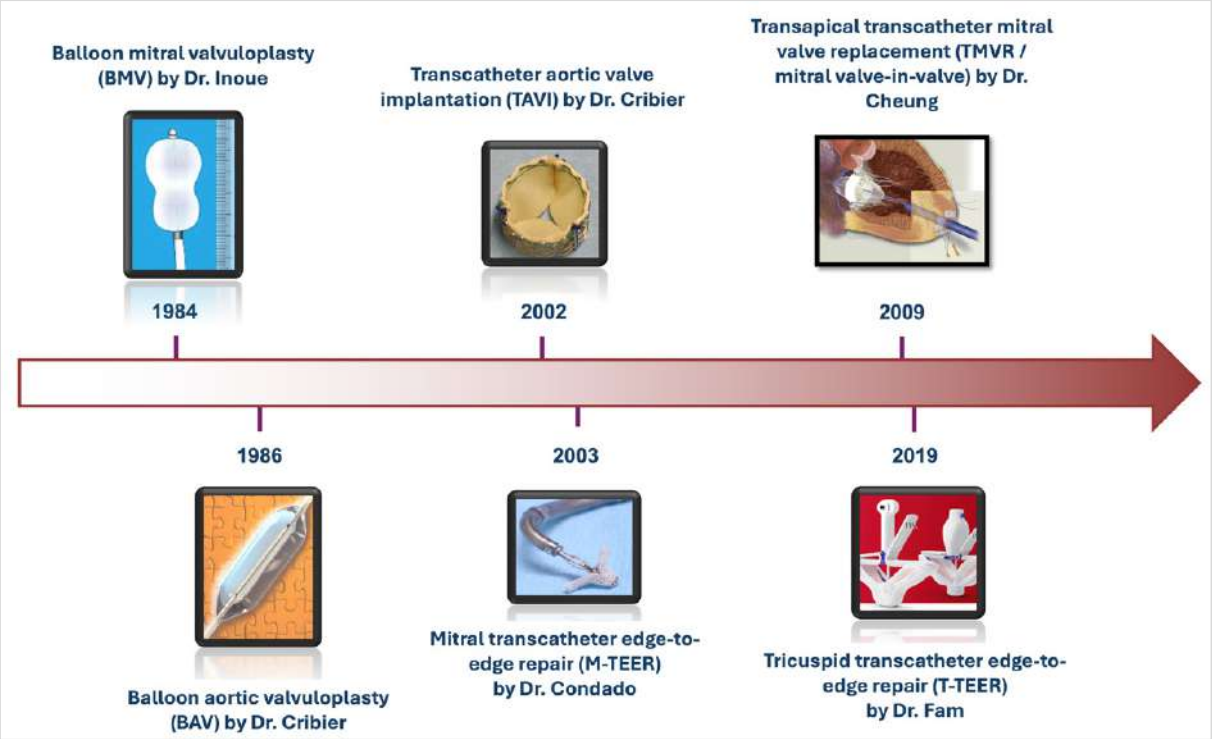


Adapted from Otto[5].

Furthermore, the complexity of clinical decision making warrants a wider approach, integrating parameters such as functional status, stroke volume, and valve calcification to tailor interventions more effectively[2,6,7]. Surgical aortic valve replacement (SAVR) is the treatment of choice for a large proportion of patients with AS, and despite persisting concerns regarding durability[8], biological prosthetic (BP) valves are progressively being favored over mechanical prostheses (MP) for SAVR in adult patients across all age groups[9]. Given the high burden of

comorbidities and older age, transcatheter aortic valve interventions (TAVI) emerged in 2002, evolving from a niche procedure to a widely accepted therapeutic approach[10,11]. Therefore, in the last two decades, TAVI has been posed as the treatment of choice for patients with favorable anatomy and age > 70 years, especially using the transfemoral approach[2]. Likewise, the development of TAVI has endorsed the development of structural heart interventions utilizing dedicated devices for mitral, tricuspid, and pulmonary becoming also viable options for VHD treatment[11-16] (Figure 2).

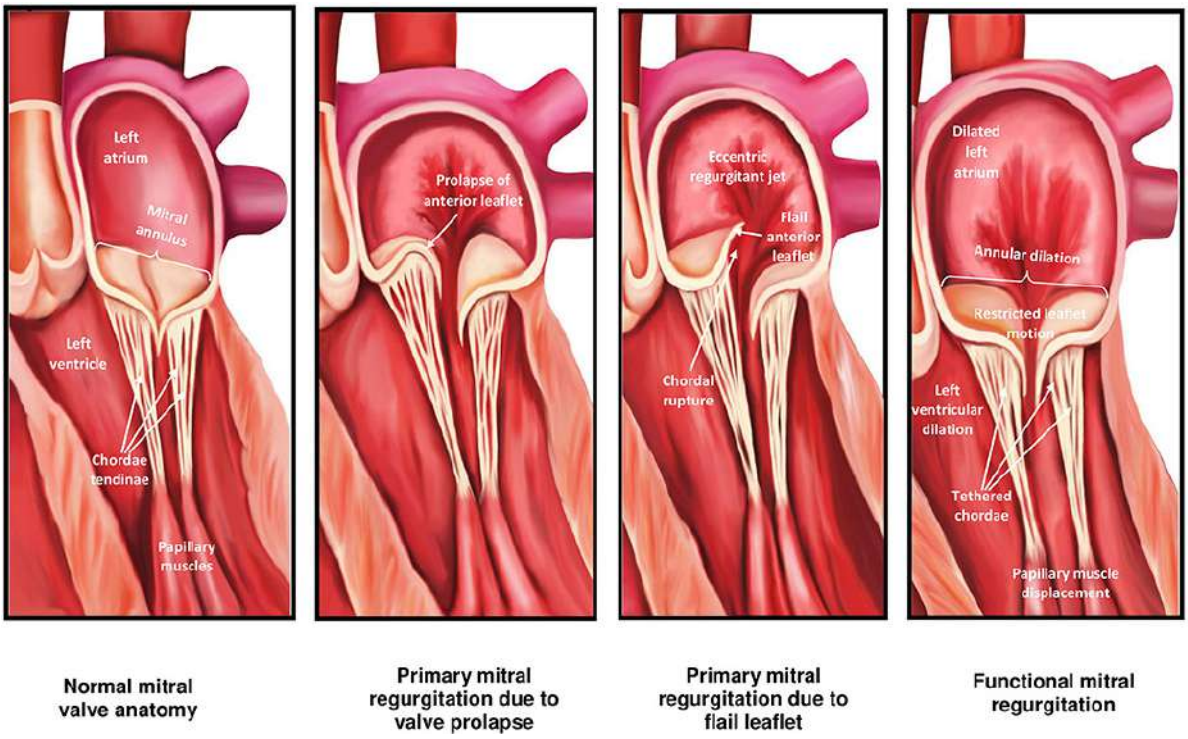
Figure 2 - Transcatheter therapies evolution in structural heart interventions



1984 - Balloon mitral valvuloplasty (BMV) by Dr. Inoue[12]; 1986 - Balloon aortic valvuloplasty (BAV) by Dr. Cribier[13]; 2002 - Transcatheter aortic valve implantation (TAVI) by Dr. Cribier[11]; 2003 – Mitral transcatheter edge-to-edge repair (M-TEER) using MitraClip by Dr. Condado[14]; 2009 - Transapical transcatheter mitral valve replacement (TMVR / mitral valve-in-valve) by Dr. Cheung[15]; 2019 – Tricuspid transcatheter edge-to-edge repair (T-TEER) using PASCAL by Dr. Fam[16].

Mitral valve disease is also highly common in developed nations, with mitral regurgitation (MR) ranking as the second most prevalent form of VHD in Europe[2,17]. MR can significantly impact quality of life and overall survival, as its management is intricately linked to the underlying cause[18]. MR is categorized as primary MR (PMR), stemming from structural or degenerative changes in the mitral leaflets, and secondary MR (SMR), occurring without primary mitral valve disease, often due to left ventricular or atrial dysfunction[19,20] (Figure 3). Distinguishing between PMR and SMR is pivotal, as it guides treatment selection and prognostication[21].

Figure 3 - Mitral valve apparatus and etiologies for mitral regurgitation



Adapted from Shah and Jorde[20].

Diagnostic precision relies on imaging techniques, notably echocardiography and cardiac magnetic resonance (CMR)[22,23]. While echocardiography remains the cornerstone for preliminary assessment and grading, CMR may aid in quantifying the regurgitant volume and assessing the ventricular function[22,23]. Moreover, three-dimensional echocardiography and CMR unveil intricate valvular anatomy, aiding surgical planning and prognostication[22,23].

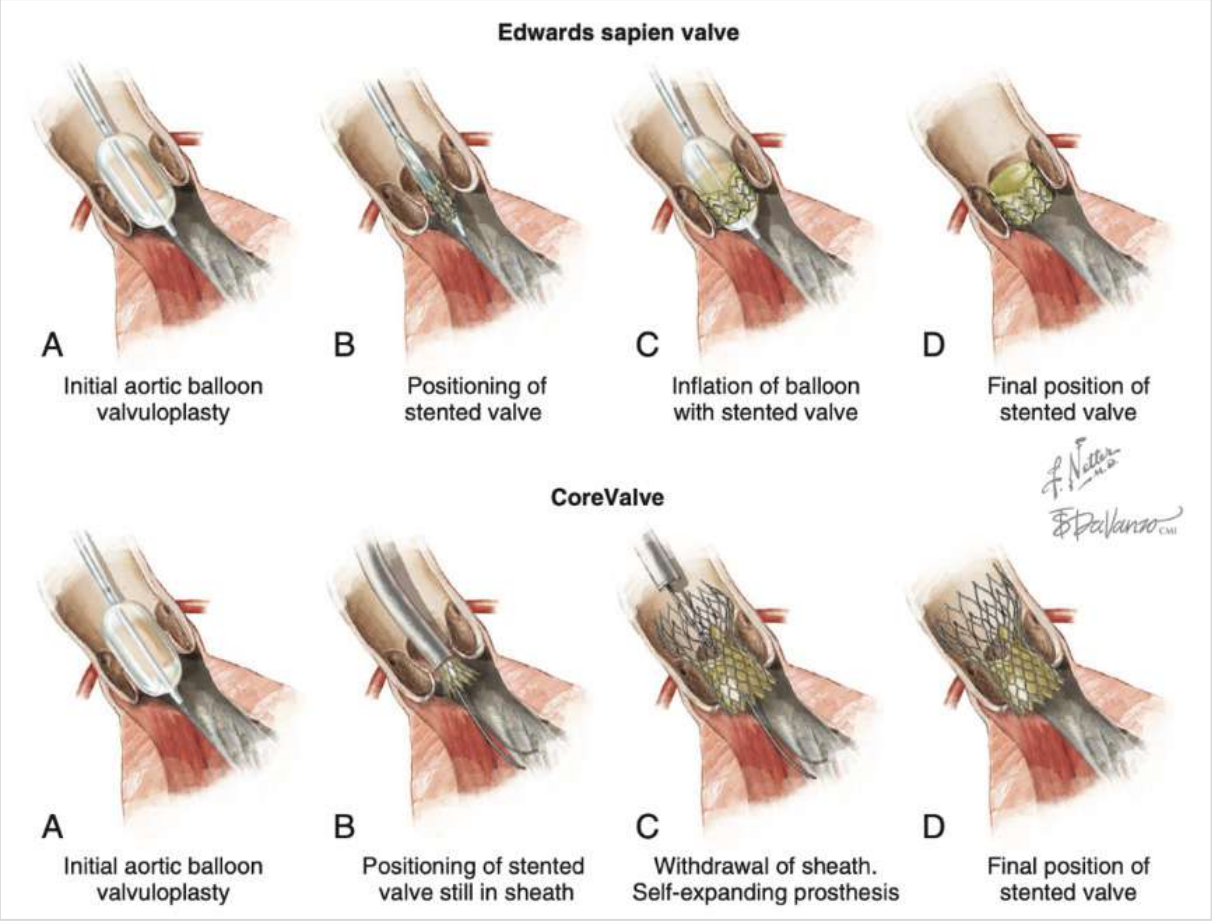
Surgical mitral valve replacement or repair (SMVR) is the preferred approach for the majority of primary mitral valve disease cases and is the third most common indication for cardiac surgery in worldwide registries[24]. The selection of the most appropriate timing for SMVR is essential to alleviate symptoms of heart failure (HF), prevent or reverse ventricular remodeling, and reduce mortality in patients with severe mitral valve disease[25,26]. Delayed referral for surgical intervention is associated with a decrease in overall survival[25,26]. While SMVR is the typical treatment for severe MR, its feasibility is limited for patients facing high surgical risks or comorbidities[27]. Hence the significant development in recent years of transcatheter options to bridge this treatment accessibility gap[7,15,28-31].

1.3 TRANSCATHETER AORTIC VALVE IMPLANTATION

Clinical trials underscore TAVI superiority over medical therapy in extreme-risk patients and its non-inferiority to surgical interventions across varied risk strata, including intermediate and low-risk cohorts[32-41]. The advent of this technology has signaled a paradigm shift, presenting a less invasive alternative capable of restoring hemodynamics and reducing patient morbidity and mortality as compared to SAVR[42].

TAVI background valve technology encompasses two principal categories: balloon-expandable valves (BEV) and self-expanding valves (SEV) (Figure 4). BEV offers precise placement and secure implantation, although with constraints such as limitations on its ability to be repositioned and potential for aortic trauma during deployment[43]. In contrast, SEV may present advantages such as supra-annular positioning and enhanced retrievability, albeit at the expense of heightened conduction disturbances[43].

Figure 4 - Transcatheter aortic valve (BEV and SEV) implantation



BEV: balloon-expandable valve; SEV: self-expanding valve.
Adapted from Arora and Vavalle[44].

Moreover, disparities persist in worldwide access to TAVI due to resource constraints and procedural costs[45,46]. Evolving evidence and real-world considerations taken, all recommendations underline the essential role of Heart Teams in individualizing treatment decisions, factoring in age, comorbidities, anatomical intricacies, and procedural nuances to optimize patient outcomes[2,6,7]. Nevertheless, through continuous innovation and collaboration, TAVI continues to redefine the landscape of AS treatment, enhancing outcomes and improving the patient's quality of life[47].

1.4 TRANSCATHETER AND SURGICAL MITRAL VALVE REPLACEMENT

SMVR has shown significant growth in recent years, with an approximate annual volume of 30,000 surgeries in the United States in 2016[25]. Out of this total, 70.8% of patients received BP valves instead of MP, with a significant increase in this trend over time, similar to SAVR, as previously described[9,25]. This shift in trends is attributed to significant advantages of BP valves, such as not requiring lifelong anticoagulation with vitamin K antagonists (VKA) and enabling potential future transcatheter treatments[48-51]. These advantages are particularly important considering the growing number of elderly patients due to global population aging[48-51]. It is important to emphasize that, both in the Brazilian population and in other developing countries, rheumatic valve disease is a common cause of mitral valve dysfunction[52,53]. This often leads to interventions in younger patients and, consequently, a higher number of surgical reoperations throughout their lives[52,53].

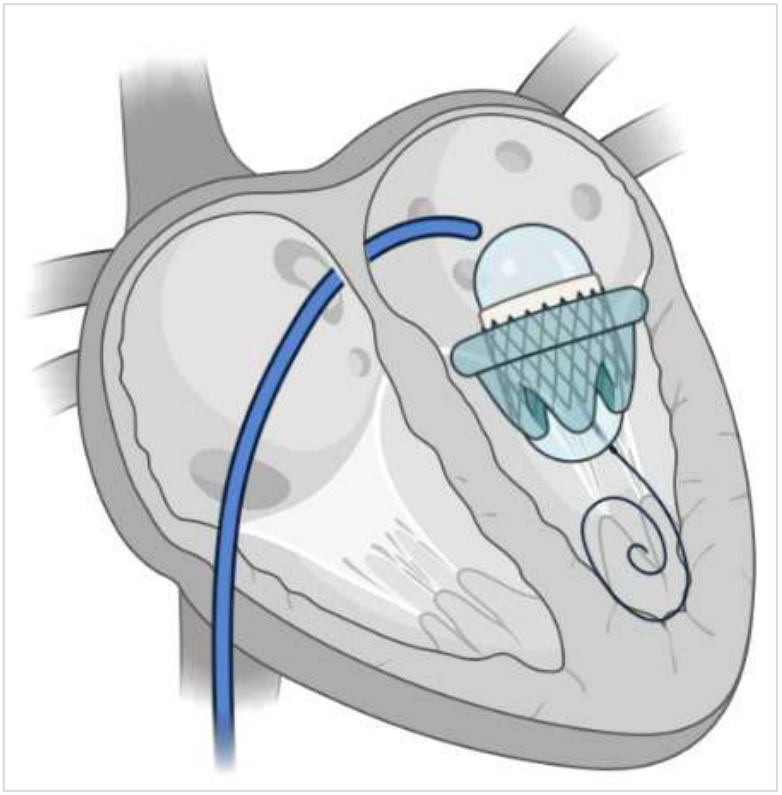
However, despite significant technical advances in recent decades, with the use of BP valves with modern anti-calcification treatments, a considerable proportion of patients undergoing mitral valve replacement will experience valve degeneration over time and require surgical mitral reinterventions (SMVR-REDO) during clinical follow-up[54-60]. Previous reports indicate that the median time to SMVR-REDO is approximately 8-10 years, with reoperation rates reaching up to 30% of patients at 15 yeas[51,56,61-63].

SMVR-REDO has long been regarded as the preferred treatment for patients experiencing dysfunction in bioprosthetic valves and is especially recommended in scenarios involving malfunction of the mitral prosthesis due to infective endocarditis and valve thrombosis[64]. However, the presence of comorbidities like pulmonary hypertension, atrial fibrillation, and ventricular dysfunction, combined with prior thoracotomies, significantly amplifies the morbidity and mortality risks for many of these patients considering this treatment option[65,66].

Moreover, intraoperative factors such as prolonged aortic clamping and cardioplegia time can contribute to higher rates of myocardial injury and short- and long-term morbidity and mortality in the follow-up of these patients[55,66,67]. Indeed, SMVR-REDO shows a progressive increase in mortality as the number of previous interventions rises, with studies indicating mortality rates of 5% for the first surgery, 8% for the second surgery, 18.8% for the third surgery, and up to 42% for the fourth mitral valve replacement surgery[68]. Other studies report perioperative mortality rates of up to 25%, even in the first reintervention, particularly in elderly, frail patients with multiple comorbidities[24,49,55,67,69-74].

It was in the context of patients with mitral BP valves dysfunction and high perioperative risk for SMVR-REDO that less invasive techniques, such as transcatheter mitral valve replacement (TMVR) first emerged in 2009, in which a transcatheter BEV was implanted in a dysfunctional mitral BP (valve-in-valve procedure)[15]. These devices, initially indicated for addressing dysfunction in native aortic valves and aortic BP valve dysfunction have also shown favorable clinical and hemodynamic outcomes in the short and mid-term follow-up for mitral BP valve dysfunction intervention, especially for high surgical risk and inoperable patients[50,63,71,73,75,76]. For most TMVR cases, a BEV is employed, "leveraging" the structure of the mitral bioprosthetic valve as support to anchor the transcatheter prosthesis[77-82] (Figure 5).

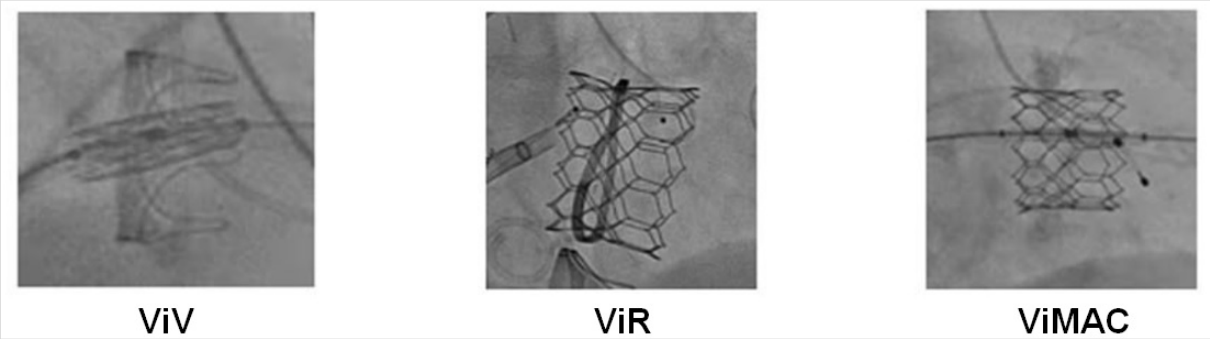
Figure 5 - Graphic representation of TMVR



TMVR: transcatheter mitral valve replacement

The same transcatheter implant technique is also used for cases of mitral ring dysfunction, known as valve-in-ring (ViR), and for mitral annular calcification, referred to as valve-in-mitral annular calcification (ViMAC)[83-85]. However, outcomes for these applications are inferior when compared to transcatheter implantation in surgically dysfunctional mitral valves, known as valve-in-valve (ViV), in a two-year follow-up[83-85] (Figure 6).

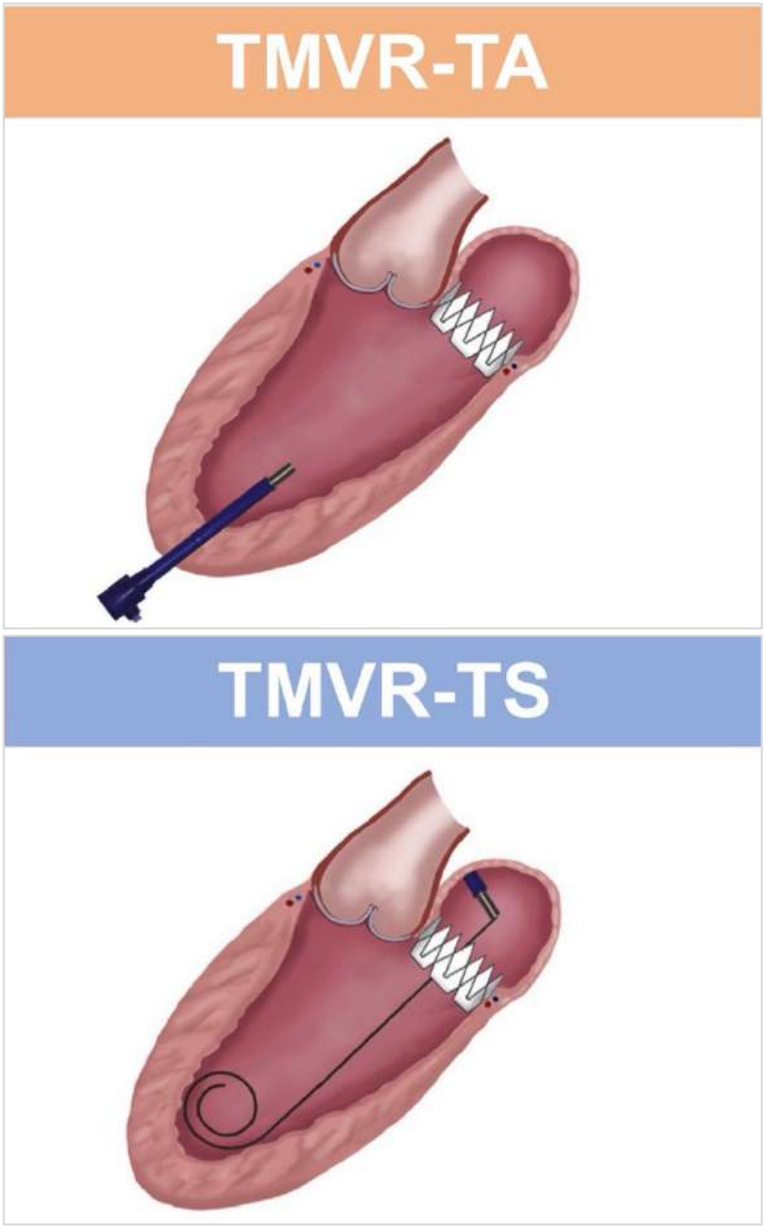
Figure 6 - Fluoroscopy of TMVR Procedures – ViV, ViR, and ViMAC



TMVR: transcatheter mitral valve replacement; ViV: *valve-in-valve*, ViR: *valve-in-ring*; ViMAC: *valve-in-mitral annular calcification.*
Adapted from Guerrero et al.[86].

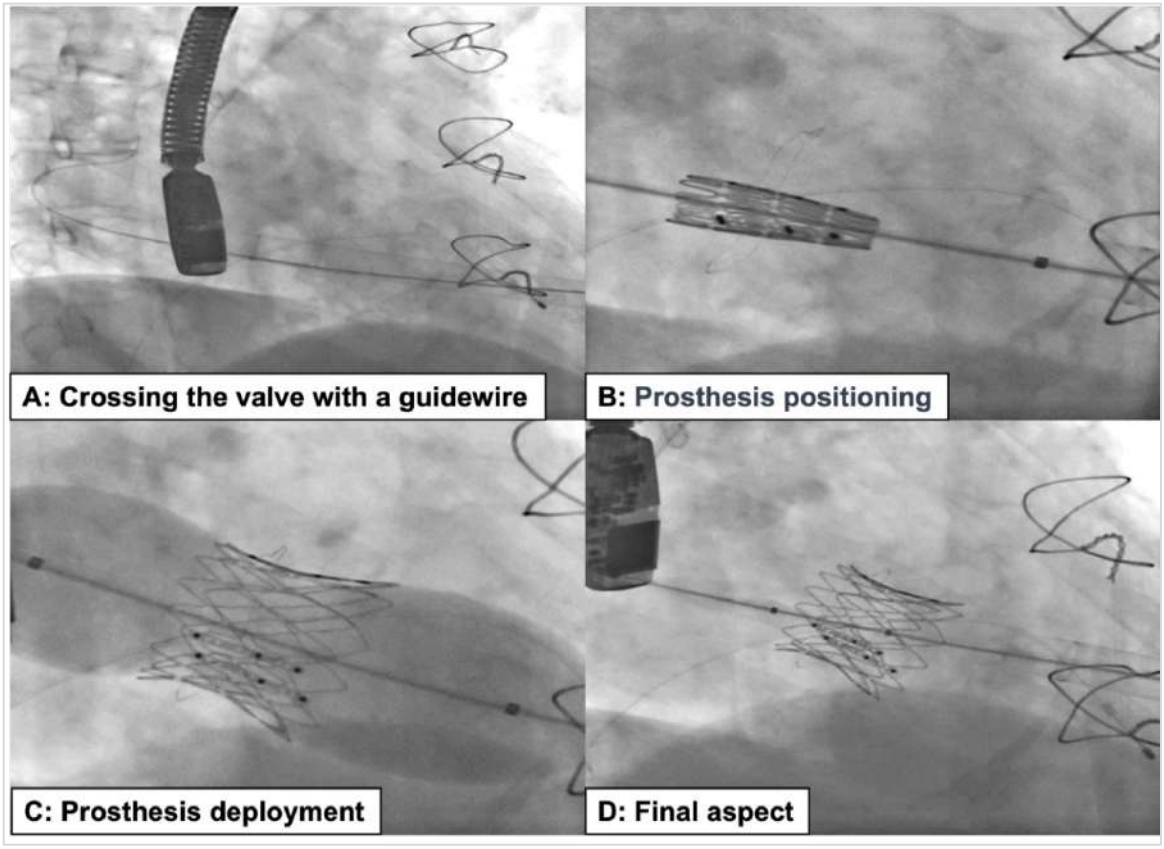
There are two possible access routes for TMVR. The first one is the transapical (TA) approach[65] (Figure 7). In the TA approach, the patient undergoes general anesthesia and a small anterolateral thoracotomy at the fifth or sixth intercostal space. Following the thoracotomy, a puncture is performed at the apex of the left ventricle under direct visualization, and the transcatheter heart valve (THV) delivery system is advanced under fluoroscopy and echocardiography to the mitral position. Once the ideal position is confirmed through fluoroscopy and echocardiography, the balloon is inflated under rapid pacing and the THV is expanded (Figure 8). Nonetheless, this approach has disadvantages, such as the need for surgical manipulation of the cardiac apex and pericardium, which may result in complications such as bleeding, myocardial injury, surgical wound infections, and more frequently new onset atrial fibrillation[87,88]. In this research, the TA-TMVR procedures were conducted using the Inovare® prosthesis, a balloon-expandable transcatheter valve with a cobalt-chromium framework developed by Braile Biomedical (São José do Rio Preto, Brazil), as described in a previously published article[81]. These valves are available in 6 sizes, ranging from 20 to 30 mm[81].

Figure 7 - Approaches for TMVR



TMVR: transcatheter mitral valve replacement; TA: transapical; TS: transseptal.
Adapted from Alperi et al.[89].

Figure 8 - Step-by-step fluoroscopic visualization of the TA TMVR procedure



The second developed access is the transseptal (TS) approach, through femoral venous puncture. Subsequently, a catheter is positioned in the right atrium, followed by TS puncture, guided by transesophageal echocardiography. After these steps, and the dilatation of the septum with a balloon, the transcatheter system is advanced through the left atrium to the mitral BP valve, and the THV is implanted[71,90,91]. The transfemoral TS approach avoids thoracotomy and apical puncture, making it considered a less traumatic strategy and potentially leading to less myocardial injury[84,86]. In general, the residual interatrial communication after TS puncture is small and does not have significant hemodynamic consequences, yet in rare cases, percutaneous closure with dedicated devices may be necessary[92]. The TS-TMVR procedures are generally performed using the Sapien 3® prosthesis, a balloon-expandable transcatheter valve developed by Edwards Lifesciences (Irvine, United States). The Sapien® valves come in 4 sizes, available in 20, 23, 26, and 29 mm.

To this date, studies did not show a clear survival benefit with the TS approach compared to the TA approach, nevertheless, it is believed that, with technical improvements in procedures and iterations of new generations of devices, less invasive procedures that avoid TA puncture may lead to lower mortality rates[93]. This is partly attributed to its capacity for causing less myocardial injury, particularly in patients with compromised ventricular function[93].

Indeed, recent studies with the introduction of third-generation devices, such as the SAPIEN 3 valve, have demonstrated favorable clinical outcomes with the TS approach, with a trend towards lower mortality rate when compared to the initially published studies[92,94]. These TS TMVR results in high-risk patients have been encouraging, with high technical success rates, low rates of periprocedural complications, and low mortality rates at 1-year follow-up[92].

Despite the absence of established guidelines for selecting the optimal therapeutic approach and the lack of randomized studies comparing TMVR vs. SMVR-REDO, the transcatheter approach, due to its lower invasiveness, expands the scope of evidence in the treatment of structural heart diseases, even in patients with a rheumatic etiology[65,81,82,95].

However, nuances persist in the implementation of TMVR, particularly concerning the relationship between hemodynamic and clinical factors and the final positioning of the THV within the surgical bioprosthesis[76,96].

Additionally, the potential impact of asymmetrical THV expansion, especially concerning implantation depth, which has shown promise in predicting reduced risk of left ventricular outflow tract (LVOT) obstruction, warrants attention[97,98]. Moreover, asymmetrical THV expansion has been independently associated with residual mitral stenosis, underscoring the importance of meticulous preprocedural planning to optimize coaxiality and minimize asymmetry during TMVR[96,99]. Symmetrical deployment in TMVR can be attained through careful planning and precise execution[96]. This meticulous approach aids in improving procedural outcomes, characterized by enhancements in echocardiographic parameters like residual mitral gradient, potentially resulting in reduced myocardial injury, which, in turn, may impact clinical endpoints such as overall mortality[96,99].

As the field of TMVR continues to advance, addressing these challenges comprehensively will be essential not only for enhancing patient care but also for further validating the efficacy and safety of this transcatheter approach in mitral valve interventions. These procedures are continuously emerging as less invasive alternatives to conventional surgical valve replacement for treating VHD, as they circumvent thoracotomy and the need for extracorporeal circulation mitigating further myocardial injury[32,34,36,38,40,71,100-106].

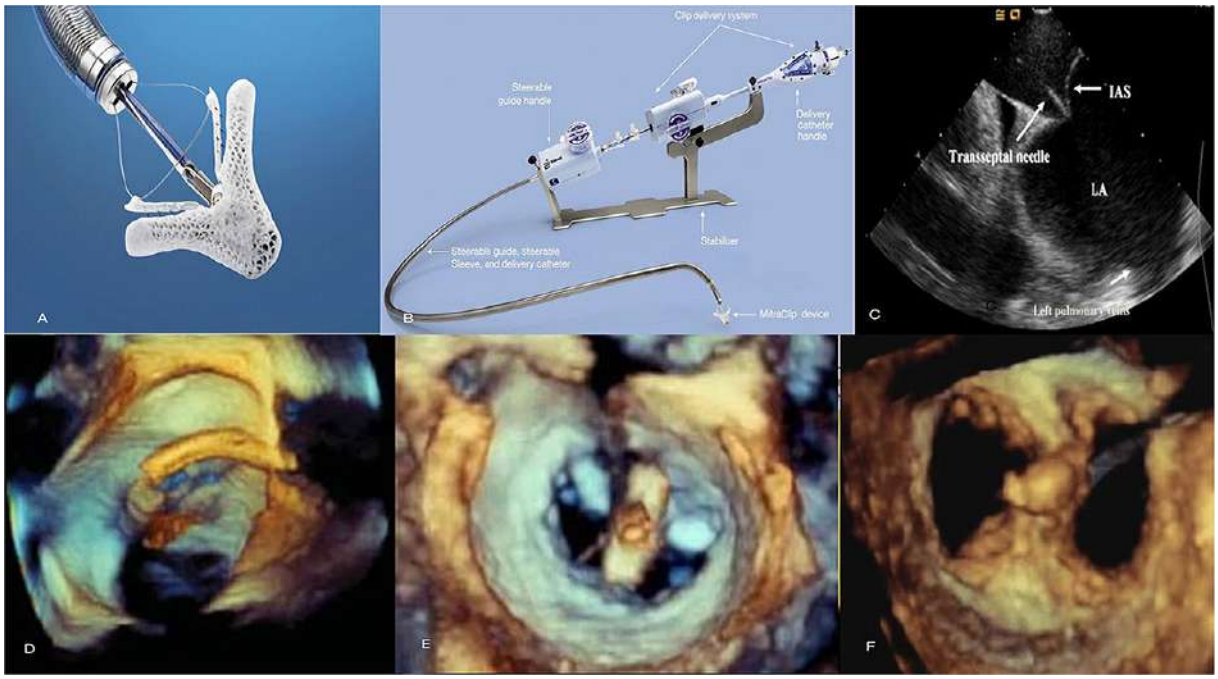
1.5 MITRAL TRANSCATHETER EDGE-TO-EDGE REPAIR

Percutaneous TS interventions have emerged as successful and minimally invasive procedures for MR, providing a viable option for these high-risk patients, defined as those with a Society of Thoracic Surgeons-predicted risk of mortality (STS-PROM) > 8%, or according to the evaluation of the Heart Team[27,107-110]. The broad spectrum of this technology signifies a transformative shift in valvular disease treatment, challenging the conventional paradigm with the advent of minimally invasive, catheter-based therapies[111]. Within this domain, transcatheter edge-to-edge repair (TEER) techniques have gained substantial interest in treating patients with MR who fulfill the eligibility echocardiographic criteria and are deemed inoperable or at high surgical risk by the Heart Team[7,112].

Through TEER, a clip is deployed to approximate the mitral valve leaflets, mimicking the Alfieri surgical procedure[113]. This approach effectively addresses severe MR whilst mitigating the inherent risks associated with traditional open-heart surgery. Notably, two cutting-edge devices, MitraClip (Abbott Vascular, Santa Clara, CA, USA) and PASCAL (Edwards Lifesciences, Irvine, CA, USA), have been developed as viable alternatives to conventional open surgical interventions, offering effective treatment options for selected patients with both PMR and SMR[18,31,114-116].

MitraClip is the pioneer FDA-approved TEER (Figures 9 and 10), and its efficacy has been rigorously evaluated through numerous randomized controlled trials, demonstrating not only minimal peri-procedural complications but also substantial improvements in patients' symptoms and overall quality of life[18,31,116]. In contrast, PASCAL represents a recent addition to mitral valve interventions, introducing innovations such as independent leaflet capture and a nitinol spacer between clasping arms[115,117-121] (Figure 11). This novel design aims to alleviate strain on leaflets and provides a potentially more user-friendly steering mechanism[115,121].

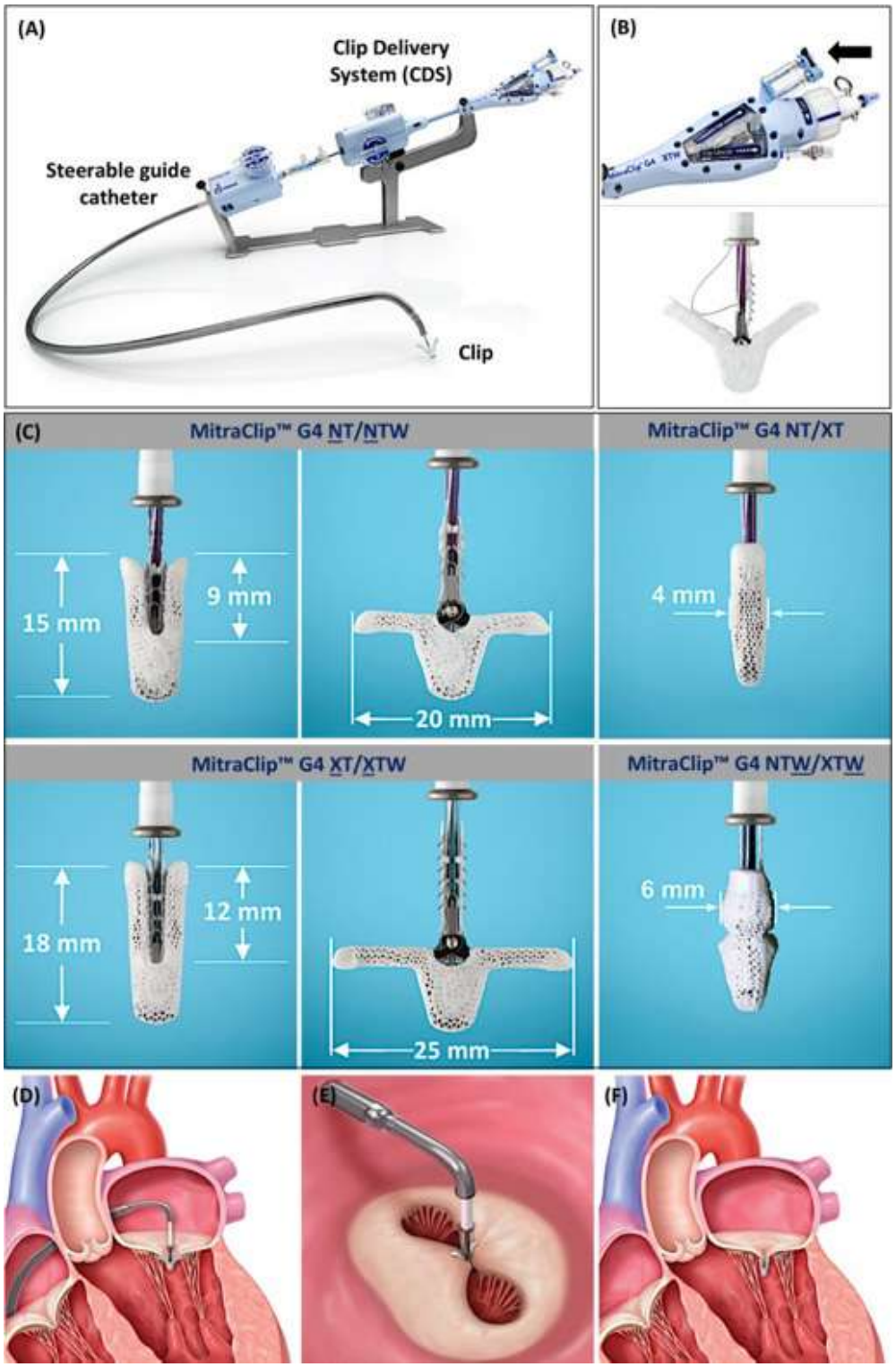
Figure 9 - Mitraclip system and echocardiographic images during the procedure



(A) MitraClip device has 2 arms and 2 grippers fabricated with metal alloys and polyester fabric. (B) The steerable guide catheter and clip delivery system. (C) Transseptal puncture using intracardiac echocardiography to enter the left atrium. (D, E) Stepwise positioning of the MitraClip perpendicular to the axis of the mitral valve adjacent to the A2-P2 scallops as seen on 3D TEE. (F) Post-MitraClip deployment double-orifice mitral valve seen on 3D TEE. TEE: transesophageal echocardiography.

Adapted from Shah and Jorde[20].

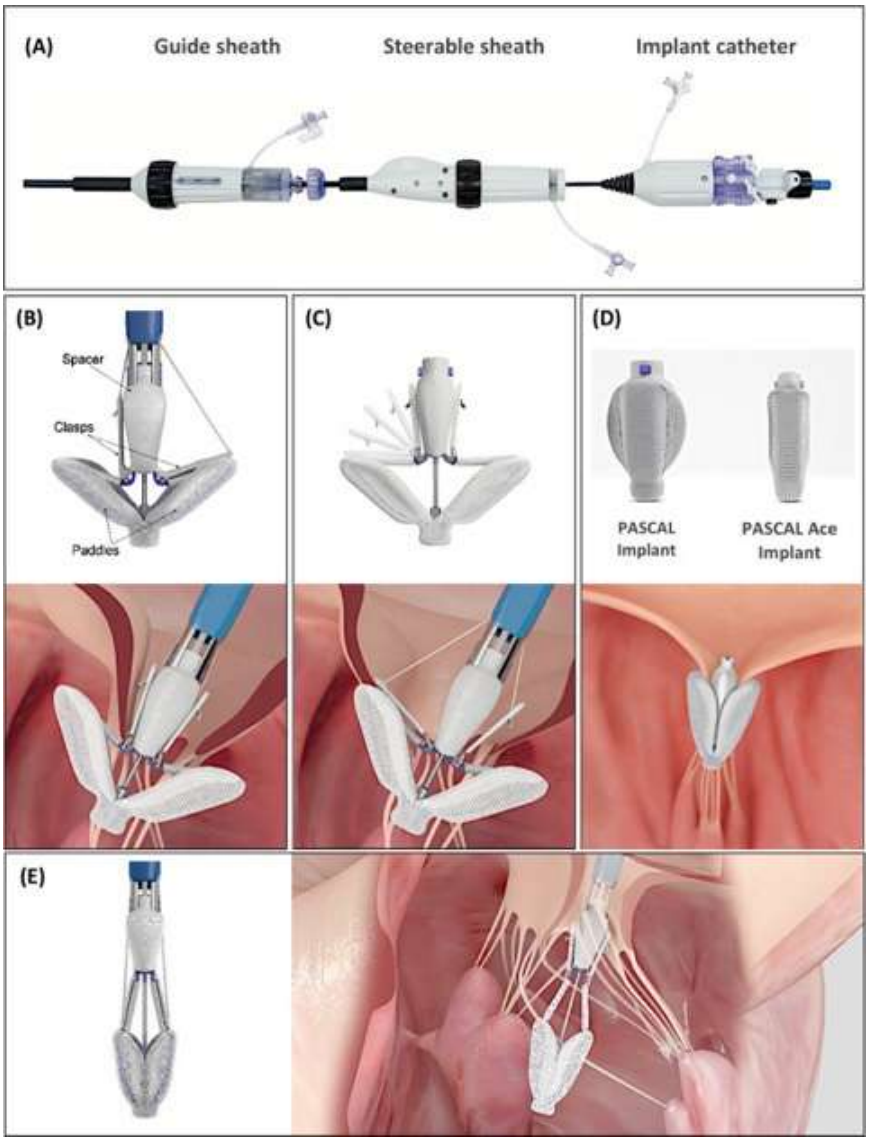
Figure 10 - MitraClip G4 System



(A) All components of the new-generation MitraClip G4 System. (B) Two independent gripper levers allow for independent grasping of the mitral leaflets. (C) The MitraClip G4 includes four clip sizes (NT, XT, NTW, and XTW) offering more options for patient-tailored mitral valve repair. (D) After steering the clip above the mitral valve and opening the clip arms, the clip is passed across the mitral leaflets into the left ventricle, the clip is gently pulled back and the leaflets are grasped by the grippers. (E) Next, the clip is closed, and a double orifice mitral valve opening can be seen by 3D-TEE surgeon's view. (F) Final result after MitraClip implantation with approximation of the anterior and posterior mitral leaflets and reduction of the mitral regurgitation.

Adapted from Ribeiro, Júnior and Abizaid[122].

Figure 11 - PASCAL Transcatheter Valve Repair System



(A) The three components of the PASCAL delivery system. (B) The PASCAL implant consists of two paddles, two clasps, and a central spacer. (C) Independent leaflet capture should enable operators to adjust leaflet insertion and capture leaflets in difficult pathologies. (D) The newest generation PASCAL Ace implant has 6 mm wide paddles and a smaller spacer that fills the regurgitant orifice and reduces the leaflet approximation distance. (E) Elongation of the PASCAL device facilitates retraction of the device from the left ventricle if needed, with a reduced risk of getting entangled in the chords.

Adapted from De Backer et al.[123].

The device selection highlights the evolving landscape of transcatheter interventions for MR, offering clinicians tailored options to address each patient's unique needs, as both PASCAL and MitraClip consistently indicate low short-term mortality, with no significant differences between the two devices[124]. The decision between MitraClip and PASCAL is personalized, requiring careful consideration of the distinctive morphological features of each device and the specific characteristics of the diseased valve, as well as the operator experience. In Brazil, PASCAL device is not yet available for commercial use.

Regardless of device, not all MR patients respond in the same way to TEER, as demonstrated in the COAPT and MITRA-FR trials[125,126]. In recent years, TEER-eligible patients presented with lower surgical risk scores, higher prevalence of NYHA III, and lower N-Terminal pro-Brain Natriuretic Peptide (NT-proBNP) baseline level when compared to patients in the first years of TEER experience[127]. This change indicates that TEER application is increasing among patients with longer life expectancy[128]. TEER has also been proven of used in the realm of acute MR, where urgent intervention is imperative to mitigate hemodynamic compromise and prevent adverse outcomes in this critical clinical entity[129].

In this context, the most important consideration is the selection of patients who would derive the greatest benefit from this strategy while simultaneously minimizing the predictability of mortality through an accurate risk stratification strategy. The validity of traditional surgical risk scores, such as STS and EuroSCORE II, in predicting outcomes post-TEER remains uncertain, with modest predictive accuracy for 1-year mortality[130]. Hence, a major effort has been made to improve accurate risk stratification scores in TEER patients. Multiple models have been developed for this purpose, including COAPT, GRASP, MITRALITY, and MitraScore[131-134]. Furthermore, novel models with additional echocardiographic data emerged to improve the accuracy of established scores, such as the addition of tricuspid annular plane systolic excursion (TAPSE) and pulmonary artery systolic pressure (PASP) ratio to MitraScore have also been propose[135]. Finally, NT-proBNP has also been shown to have valuable predictive ability for mortality and HF hospitalization after TEER and is a core variable in some risk score models[132,133]. Yet, the predictive accuracy these risk scores in forecasting 1-year mortality and the composite outcome of 1-year mortality and/or HF hospitalization remains limited.

1.6 MYOCARDIAL NECROSIS BIOMARKERS IN CARDIAC INTERVENTIONS

Over the past decades, there has been substantial refinement in the understanding of myocardial injury and its influence on clinical outcomes after cardiac procedures[136]. This progress is attributable to advancements in diagnostic techniques, evolving insights into the pathogenesis of such scenarios and encompasses a range of acute and chronic conditions arising from both cardiac and non-cardiac origins[137].

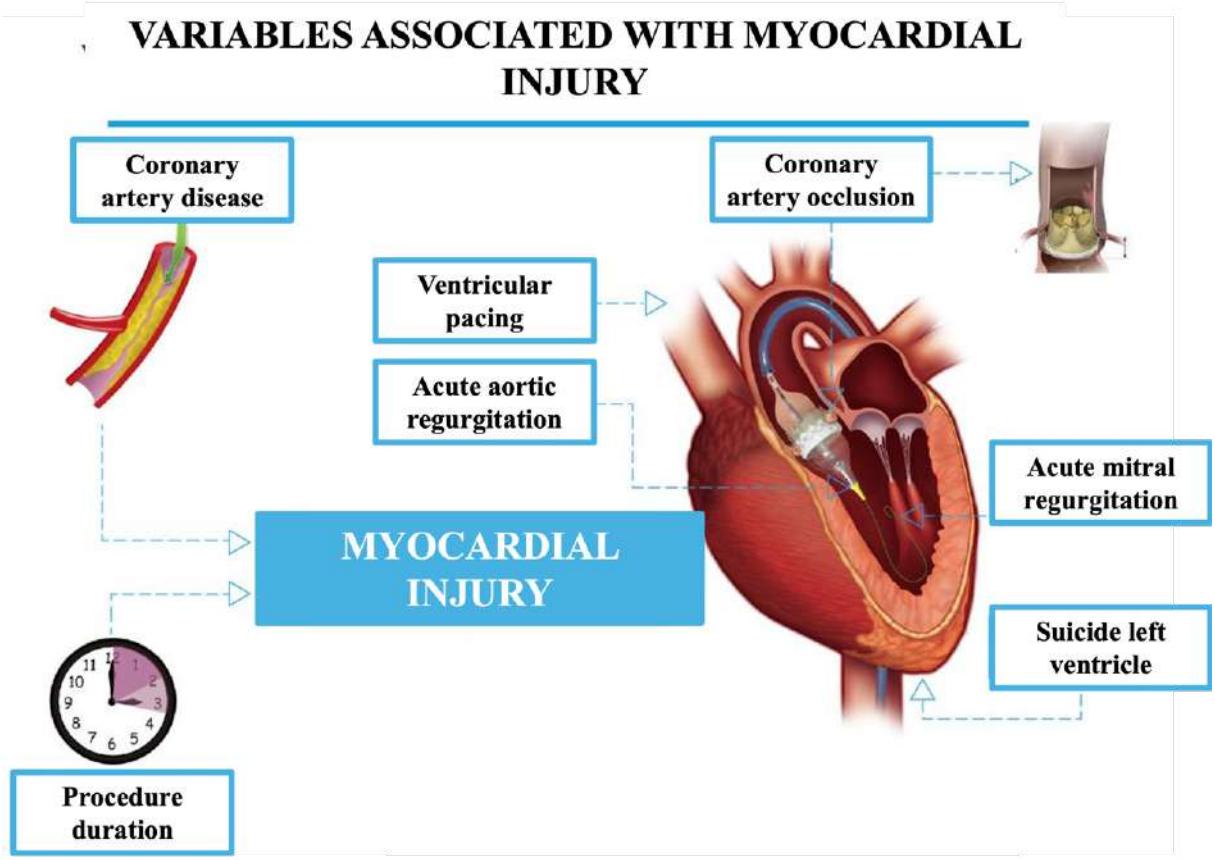
While myocardial infarction, defined by the presence of myocardial necrosis in a clinical context consistent with acute myocardial ischemia, specifically concerns ischemic necrosis within this spectrum, myocardial injury encompasses a broader array of pathophysiological mechanisms extending beyond ischemia[137-139]. At the core of this understanding lies the pivotal role played by cardiac biomarkers, such as Creatine Kinase-MB (CK-MB) and cardiac Troponins (cTn) elevation, regarded as the standard serum biomarkers for detecting myocardial necrosis[139-141]. Over time, the advent of high-sensitivity assays has transformed the detection of cTn, paving the way for heightened sensitivity and precision in the diagnosis of myocardial injury[142-144]. Cardiovascular biomarkers were also strongly linked to both fatal and nonfatal cardiovascular events and overall mortality in a recent publication by Neuman et al.[145]. While incorporating biomarkers into established risk factors only slightly improved risk prediction metrics for atherosclerotic cardiovascular disease, the enhancement was more significant for predicting heart failure and mortality[145].

A rise in CK-MB and cTn indicating myocardial necrosis have consistently been reported following cardiac interventions, especially after surgical procedures[146-149]. This rise in cardiac biomarkers among various cardiac interventions has a well-established negative prognostic impact in acute and mid-term follow-up[150-158].

New transcatheter devices, especially in TAVI, have shown a significant reduction in biomarker release compared to the surgical alternatives, due to the absence of aortic clamping and cardioplegia, among other factors[152,153]. However, even in the case of transcatheter device use, periprocedural myocardial injury (PPMI), denoted by increases in CK-MB and cTn levels, is associated with an increase in short- and long-term mortality. The Valve Academic Research Consortium 2 (VARC-2) characterizes PPMI as a periprocedural elevation in cardiac biomarkers, such as CK-MB or cTn, not meeting the criteria for myocardial infarction, with CK-MB and cTn threshold cutoff points set at 5× and 15× the upper limit of normal (ULN), respectively[144]. As cTn assays become more sensitive, the significance of PPMI warrants careful evaluation, especially with the revised cutoff points proposed in VARC-3[143]. Questions persist regarding the prognostic impact of PPMI and its long-term implications[143,159].

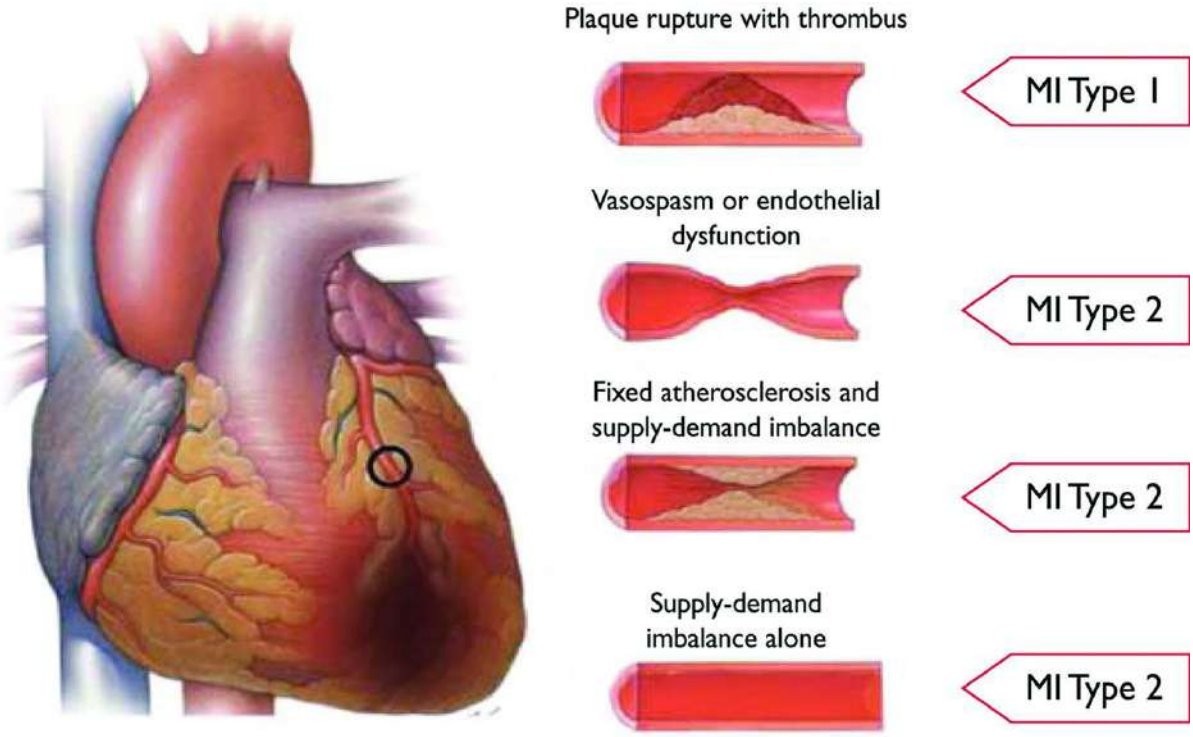
PPMI likely results from various factors, including transient hypotension during ventricular rapid pacing, microembolization during balloon dilatation, and mechanical compression of the left ventricular outflow[160-163] (Figure 12). Procedural predictors of PPMI include early experience, first-generation valves, and the TA approach[160,161]. SEV have been associated with a higher PPMI incidence compared to BEV, possibly due to procedural differences, that includes factors such as device and delivery system specificities[161-163].

Figure 12 - Variables associated with myocardial injury during TAVI



Hence, the ideal cutoff for PPMI remains controversial, especially with the increasing sensitivity of biomarker assays. Importantly, this heightened sensitivity may lead to the detection of even lower levels of myocardial injury, possibly inflating the reported incidence of PPMI and undermining its clinical significance[142]. Therefore, challenges remain in accurately distinguishing between different subtypes of myocardial injury, particularly in discerning type 2 myocardial infarction from myocardial injury without ischemia[136,138] (Figure 13). This challenge is further exacerbated by diverse overlapping clinical presentations and inconsistent management approaches[136].

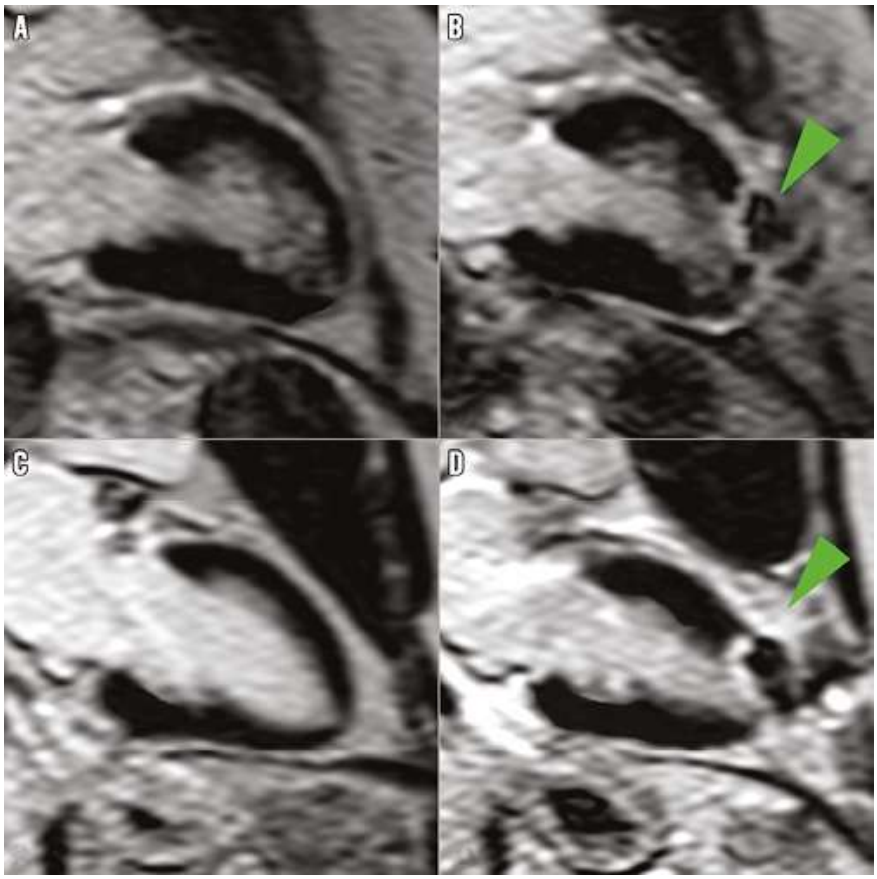
Figure 13 - Variables associated with myocardial injury during TAVI



Adapted from Thygesen et al.[164].

It is important to consider that most studies on this subject also included patients undergoing the transcatheter procedure through TA access, which is a known risk factor for increased myocardial necrosis biomarkers compared to other percutaneous routes. This is due to various factors, such as large-caliber catheters in the apical puncture, resulting in myocardial necrosis affecting approximately ~5% of the myocardium[140] (Figure 14). This injury can lead to a long-term reduction in the left ventricular ejection fraction and increased late mortality[140].

Figure 14 - Representative cardiovascular magnetic resonance image of two patients undergoing TAVI via TA access



A) & C) Before implantation; B) & D) After valve implantation. The arrows indicate typical late gadolinium enhancement at the apex of the left ventricle. TAVI: transcatheter aortic valve implantation; TA: transapical. Adapted from Ribeiro et al.[141].

Still, the optimal threshold to define clinically relevant myocardial injury following the treatment of mitral bioprosthesis dysfunction is undetermined. For instance, the Mitral Valve Academic Research Consortium (M-VARC) has recommended an increase of 10 times the ULN for CK-MB and 70 times the ULN for cTn. This recommendation is based on an adaptation of criteria from the Society for Cardiovascular Angiography and Interventions (SCAI) for clinically relevant perioperative Acute Myocardial Infarction (AMI) and the Third Universal Definition of Myocardial Infarction[164-167]. However, these cutoff points have not been adequately validated in this population. Furthermore, studies on surgical interventions have shown considerably higher cutoff points, around 500 times the ULN of cTn, for patients undergoing non-aortic interventions/non-coronary artery bypass graft surgery[148]. Thus, the ideal threshold to define clinically relevant myocardial injury after the treatment of mitral bioprosthesis dysfunction is not well-established in the literature. To date, no study has specifically compared the release of cardiac biomarkers in patients undergoing TMVR versus SMVR-REDO for the treatment of mitral bioprosthesis dysfunction.

In summary, existing evidence indicates that the elevation of myocardial injury biomarkers, including CK-MB and cTn, carries a negative prognostic impact in patients undergoing various transcatheter and surgical cardiac interventions[150-155]. However, specific studies assessing myocardial injury in patients undergoing TMVR versus SMVR-REDO procedures for the treatment of mitral bioprosthesis dysfunction, and their impact on clinical outcomes, are still lacking. Additionally, specific cutoff points to determine significant myocardial injury in the context of SMVR-REDO have not been defined, as the values suggested by M-VARC have not yet been validated in specific studies of patients treated with transcatheter mitral devices[166,167].

These data are of crucial importance, as myocardial injury is associated with increased length of hospitalization, morbidity, and mortality in patients undergoing cardiac interventions. Strategies that allow the identification of patients more prone to this type of complication could promote a more informed choice regarding the approach (TMVR or SMVR-REDO) and assist in the clinical management of these patients, aiming to reduce the morbidity and mortality of these interventions.

1.7 HYPOTHESIS

1.7.1 General hypothesis

Transcatheter interventions such as TAVI, TMVR, and TEER may result in lower incidences of myocardial injury compared to conventional cardiac surgery, as evidenced by reduced biomarker releases like CK-MB, cTn, and BNP. Additionally, certain predictors such as patient demographics, comorbidities, and procedural factors may significantly influence the incidence and prognostic value of myocardial injury across these transcatheter interventions.

1.7.2 Specific hypotheses

- Elevated levels of CK-MB and cTn following TAVI are associated with an increased risk of mortality, especially in shorter-term follow-up.
- CK-MB and cTn levels post-mitral interventions exhibit correlations with the approach used (TMVR or surgical), with higher increases relating to worse clinical outcomes.

- Refinements in TMVR deployment techniques, achieved through deployment analysis, may potentially reduce residual mitral gradient, leading to better in-hospital clinical outcomes, and ultimately impacting overall mortality rates.
- A comparative analysis of different risk scores for TEER including cardiac biomarkers may assist in identifying optimal patients for this strategy and determine the prognosis.

2 OBJECTIVES

2.1 GENERAL OBJECTIVE

The general objective of this thesis is to assess the incidence, predictors, and prognostic value of myocardial injury across various biomarkers (CK-MB, cTn and BNP) in the treatment of valve dysfunctions, with different transcatheter interventions (TAVI, TMVR, and TEER) and conventional cardiac surgery.

2.2 SPECIFIC OBJECTIVES

- Investigate the association between elevated CK-MB and cTn levels following TAVI and the risk of mortality, through a meta-analysis using pooled analysis of Kaplan-Meier estimated individual patient data.
- Examine the correlations between CK-MB and cTn levels post-mitral interventions comparing conventional cardiac surgery versus TMVR, as determined by the M-VARC[166].
- Evaluate the influence of the implantation depth and asymmetry index of TMVR on the overall mitral gradient and clinical outcomes post-procedure.
- Compare different risk scores and cardiac biomarkers for TEER to identify optimal patients for this strategy, improve patient selection and refine the risk assessment process for TEER interventions.

3 ARTICLE 1

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Impact of periprocedural myocardial injury after transcatheter aortic valve implantation on long-term mortality: a meta-analysis of Kaplan-Meier derived individual patient data

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Background: Periprocedural myocardial injury (PPMI) frequently occurs after transcatheter aortic valve implantation (TAVI), although its impact on long-term mortality is uncertain.

Methods: We performed a pooled analysis of Kaplan-Meier-derived individual patient data to compare survival in patients with and without PPMI after TAVI. Flexible parametric models with B-splines and landmark analyses were used to determine PPMI prognostic value. Subgroup analyses for VARC-2, troponin, and creatine kinase-MB (CK-MB)-defined PPMI were also performed.

Results: Eighteen observational studies comprising 10,094 subjects were included. PPMI was associated with lower overall survival (OS) after two years (HR = 1.46, 95% CI 1.30–1.65, $p < 0.01$). This was also observed when restricting the analysis to overall VARC-2-defined PPMI (HR = 1.23, 95% CI 1.07–1.40, $p < 0.01$). For VARC-2 PPMI criteria and VARC-2 troponin-only, higher mortality was restricted to the first 2 months after TAVI (HR = 1.64, 95% CI 1.31–2.07, $p < 0.01$; and HR = 1.32, 95% CI 1.05–1.67, $p = 0.02$, respectively), while for VARC-2 defined CK-MB-only the increase in mortality was confined to the first 30 days (HR = 7.44, 95% CI 4.76–11.66, $p < 0.01$).

Conclusion: PPMI following TAVI was associated with lower overall survival compared with patients without PPMI. PPMI prognostic impact is restricted to the initial months after the procedure. The analyses were consistent for VARC-2 criteria and for both biomarkers, yet CK-MB was a stronger prognostic marker of mortality than troponin.

KEYWORDS

aortic stenosis, transcatheter aortic valve implantation, transcatheter aortic valve replacement, periprocedural myocardial injury, biomarkers, valvular heart disease, structural heart disease

Introduction

Transcatheter aortic valve implantation (TAVI) is a well-established treatment for the management of severe aortic stenosis across the entire spectrum of surgical risk (1, 2).

Periprocedural myocardial injury (PPMI) is a common procedural complication, often evaluated by the release of cardiac biomarkers, as ischemic symptoms in the periprocedural setting are often misleading and confounding in nature (3).

The Valve Academic Research Consortium 2 (VARC-2) defines PPMI as a periprocedural cardiac biomarker, by either troponin or creatinine kinase-MB (CK-MB) elevation, not meeting the criteria for myocardial infarction, with threshold cutoff points of 15× the upper limit of normal (ULN) for troponin and 5× the ULN for CK-MB (4). As troponin assays progressively become more sensitive, the significance of PPMI should be carefully assessed. Notably, in the recently published VARC-3, the proposed cutoff points for both troponin (70× the ULN) and CK-MB (10× the ULN) were significantly higher (5). Therefore, questions remain regarding the prognostic impact of PPMI and its long-term impact.

Previously published meta-analyses on the prognostic relevance of PPMI after TAVI provided limited information on long-term mortality, as they aggregated data on heterogeneous fixed time points, which may result in overlooked patterns and outcome variability (6–8). Furthermore, their results should be viewed with caution, as central tenets of survival analysis are either not recognized or cannot be checked in traditional meta-analyses (9–11). Hence, to address these limitations, this study aimed to determine the prognostic significance of PPMI after TAVI using a pooled analysis of Kaplan-Meier (KM) estimated individual patient data (IPD) of VARC-2 studies or studies with comparable definitions, since, to the best of our knowledge, there is only one published study based on VARC-3 (12).

Methods

Eligibility criteria, databases and search strategy

This study followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline (13). Studies were included if the following criteria were fulfilled: (1) Population comprised patients who underwent TAVI; (2) Reported cardiac-specific biomarker elevation within 72 h; (3) Standardized thresholds cut-points for PPMI based on VARC-2 (peak troponin ≥15 × ULN or CK-MB ≥5 × ULN) or similarly comparable definitions (4); (4) KM curves of all-cause mortality; (5) Fully published status; and (6) Written in English.

PubMed, EMBASE, and Cochrane Center databases were systematically searched for articles that met our inclusion criteria and were published by February 25, 2023. Additionally, we reviewed the references of the included articles and previous reviews to identify relevant texts. We utilized the following search strategy: ("Myocardial injury" OR "PPMI" OR "Troponin" or "Troponin I [TnI]" or "Troponin T [TnT]" or "High-Sensitivity Troponin I [hsTnI]" or "High-Sensitivity Troponin T [hsTnT]" OR "CKMB" OR "CK-MB" OR "Creatine kinase" OR "Creatine phosphokinase" OR "CPK" OR "phosphocreatine kinase") AND ("Transcatheter aortic valve implantation" OR "TAVI" OR "Transapical aortic valve replacement" OR "TAVR").

The following steps were taken for study selection: (1) identification of titles of records through database search; (2) removal of duplicates; (3) screening and selection of abstracts; (4) assessment for eligibility through full-text papers; and (5) final inclusion in the study. Two independent reviewers (P.C. and M.M.G.) selected the studies. When there was disagreement, a third reviewer (M.F.S.M.) decided to include or exclude the study. Ethical approval was not applicable to this study as it consisted of a systematic review and meta-analysis.

VARC-2 standardized thresholds were utilized in 13 out of 18 studies (3, 12, 14–24). The other 5 studies utilized the following criteria: CK-MB and/or TnT rise > 5 ULN (25); hsTnT ≥ 166 pg/ml (26); CK-MB > 7 ng/ml (27); TnT increase > 3 ULN (28); and hsTnT rise ≥ 18.3 ULN (29).

Assessment of the risk of bias

The risk of bias was evaluated using the Risk of Bias In Non-randomized Studies of Interventions (ROBINS-I) (30). The studies and their characteristics were classified as having low, moderate, serious or critical risk of bias. Two independent reviewers (P.C. and M.M.G.) assessed risk of bias.

Statistical analysis

Time-to-event outcomes are not amenable to the standard statistical procedures. For meta-analyses, pooling the treatment effect over several studies must either use estimates of median survival and event rates assessed from survival estimates at given time points, or fall back on direct estimates of the hazard ratio. These approaches are unsatisfactory since they fail to consider the central principles of survival analysis, such as censoring and the proportional hazards assumption (11, 31). As a consequence, the "curve approach" has emerged as the current gold standard for meta-analysis of time-to-event data (32). This approach reconstructed individual patient data (IPD) based on published KM graphs from the included studies. In this meta-analysis, we used the R package "IPDfromKM" version 0.1.10 (33).

Raw data coordinates (time and survival probability) for each treatment arm were extracted from published KM survival curves using dedicated software. Subsequently, data coordinates were processed based on the raw data coordinates from the first stage in conjunction with the numbers at risk at given time points when available, and IPD was reconstructed using the IPDfromKM software.

Quality assessment of KM derived IPD data was performed graphically by comparing the derived KM curves with the original curves. The reconstructed IPD was then merged to create the study dataset.

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We visually assessed the outcomes of interest in both arms using KM estimates, next, hazard ratios (HRs) with 95% CIs for the difference between both arms were calculated using a Cox frailty model. The inclusion of a γ frailty term was used to account for heterogeneity between studies, with studies modelled as a random effect using random intercepts. The proportional hazards assumption of the Cox model was checked using the Grambsch-Therneau test and diagnostic plots based on Schoenfeld residuals (34).

To deal with proportional hazards assumption violations and assess how the prognostic value of post-TAVI PPMI changed over time, we performed two complementary techniques. First, we fitted a flexible parametric survival model with B-splines. The baseline hazard rate was modeled on a spline with four degrees of freedom. Interactions between the treatment arm and time were added by using a second spline function. We also added a γ frailty term to account for heterogeneity between studies. This technique allowed us to estimate time-varying hazard ratios for our analyses of interest. Finally, we performed landmark analyses to further discriminate short- and long-term PPMI prognostic values.

Subgroup analyses were performed for VARC-2-defined PPMI, and for the VARC-2 cutoff of both troponin and CK-MB-defined PPMI, to further assess the differences in mortality according to the different biomarkers and to investigate the effect of the VARC-2 cutoffs on mortality over the long-term follow-up.

All analyses were performed using R Statistical Software (version 4.2.2, Foundation for Statistical Computing, Vienna, Austria).

Results

Our systematic search identified 847 potential articles and one additional record was identified through other sources. There were 31 articles selected for further eligibility assessment after screening the abstracts. All articles were retrieved and reviewed at the full-text level for possible inclusion. The search strategy is shown in **Supplementary Figure S1**. After further revisions and exclusions, eighteen observational studies that met all eligibility criteria were included in our meta-analysis (3, 12, 14–29).

A total of 10,094 patients were included, the main characteristics of the studies and their patients are presented in **Table 1**. The mean age was 81 years and 50% of the patients were men. Coronary artery disease and diabetes mellitus prevalence were 53% and 28%, respectively. Transfemoral (TF) approach was used in approximately 90% of all procedures. Valve type was similar between the PPMI and non-PPMI groups, with 50% of both groups using self-expandable valves (SEV) and 47% using balloon expandable valves (BEV). The median follow-up period of our reconstructed time-to-event population was 12 months (IQR: 6–16 months). The incidence of overall VARC-2 defined PPMI was 53%. The incidence of troponin-defined PPMI (61%) was almost sevenfold higher than CK-MB-defined PPMI (9%).

Quality assessment

The ROBINS-I tool identified ten studies as having a low risk of bias and eight studies as having a moderate risk of bias (**Supplementary Figure S2**). Quality assessment of KM-derived IPD data by visual comparison of the derived KM curves with the original curves did not show any relevant differences. This analysis, therefore, indicates the results derived from this meta-analysis are grounded on well-conducted observational studies and, therefore, should be regarded as more reliable compared with a scenario in which the aggregated studies were mostly at high-risk for bias.

Pooled analysis for overall survival

The pooled analysis for overall survival (OS) comparing patients who had PPMI with those who did not have PPMI after two years revealed that PPMI after TAVI associated with lower cumulative OS (HR = 1.46, 95% CI 1.30–1.65, $p < 0.01$). Likewise, when only VARC-2 criteria were considered, patients with PPMI also had a lower OS than those without PPMI (HR = 1.23, 95% CI 1.07–1.40, $p < 0.01$). To investigate the effects of different myocardial injury biomarkers on PPMI, we performed the same analysis with VARC-2 troponin-defined PPMI and VARC-2 CK-MB-defined PPMI. In both cases, OS at two years was lower in the PPMI group (HR = 1.16, 95% CI 1.01–1.33, $p = 0.04$, and HR = 1.59, 95% CI 1.20–2.09, $p < 0.01$, respectively), yet the association was much stronger with CK-MB than with troponin (**Figure 1**).

Landmark analyses and time-varying hazard ratio analyses

Using flexible parametric models with B-splines, we estimated time-varying HRs for VARC-2-defined PPMI, as well as for VARC-2-troponin and CK-MB-defined PPMI. This revealed that VARC-2 and troponin-PPMI were associated with lower OS in the initial two months (**Figures 2A, 3A**), whereas CK-MB-PPMI was associated with lower OS in the first month only (**Figure 3C**).

Furthermore, landmark analysis was performed using cutoff values determined by time-varying HRs. In the first two months (**Figure 2B**), VARC-2 PPMI was significantly associated with lower OS (HR = 1.64, 95% CI 1.31–2.07, $p < 0.01$). However, this was no longer observed after 2 months in the landmark analysis (HR = 0.98, 95% CI 0.83–1.14, $p = 0.75$). The same trend was observed in the subgroup of troponin-only defined PPMI (**Figure 3B**), and CK-MB only defined PPMI (**Figure 3D**). In the first two months, troponin-defined PPMI was significantly associated with lower OS (HR = 1.32 95% CI 1.05–1.67, $p = 0.02$), but no longer after the 2 month-landmark (HR = 1.00, 95% CI 0.85–1.17, $p = 0.98$). Finally, in the first month, CK-MB-defined PPMI was strongly associated with lower OS (HR = 7.44, 95% CI 4.76–11.66, $p < 0.01$), but this association was not statistically significant after 1 month (HR = 0.73, 95% CI 0.50–1.07, $p = 0.11$).

Discussion

In this systematic review and meta-analysis of 18 observational studies, the prognostic value of PPMI after TAVI for longer-term

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TABLE 1 Overview of the included studies with relevant characteristics.

Study	Population, n[a]	Troponin-defined PPMI/CK-MB-defined PPMI	Age, years[b], PPMI/No PPMI	Male, % PPMI/ No PPMI	HTN, % PPMI/ No PPMI	DM, % PPMI/ No PPMI	CAD, % PPMI/ No PPMI	Previous MI, % PPMI/No PPMI	AF, % PPMI/ No PPMI	SEV, % PPMI/ No PPMI	BEV, % PPMI/ No PPMI	Mean LVEF, % PPMI/ No PPMI	TF Approach, % PPMI/No PPMI	Follow-up, years[b]	Definition of PPMI
Alaoubd et al. (14)	805[c]	366/NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NI	1	hscTnT > 15 ULN
Barbash et al. (27)	103	NR/37	84/85	43/40	91/97	27/34	45/57	10/16	37/48	NR	NR	57/53	100/100	1	CK-MB > 7 ng/ml
ChorianopouLos et al. (26)	151	78/NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	100/100	1	hscTnT ≥ 166 pg/ml
Dagan et al. (15)	370	242/NR	83/82	50/62	76/69	23/42	39/41	NR	30/43	74/67	25/32	NR	94/99	5	cTnI > 15 ULN
De Marzo et al. (3)	596	471/NR	83/83	49/54	NR	25/37	41/56	16/23	33/37	35/22	57/77	55/55	92/96	1	cTnI ≥ 15 ULN
Hömena et al. (16)	106[d]	40/NR	82/81	10/39	35/61	13/31	NR	7/12	NR	30/16	36/24	51/46	NR	2	hsTnT > 15 ULN
Kohler et al. (17)	216	77/NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	2	hsTnT > 15 ULN
Kolfman et al. (18)	473	363/37	83/83	45/63	93/95	11/17	72/75	NR	NR	29/24	71/76	NR	100/100	1	cTn > 15 ULN or CK-MB > 5 ULN
Koskinas et al. (19)	577	338/NR	82/82	47/43	85/83	26/28	67/58	15/14	28/30	47/63	52/36	54/52	67/98	2	cTnT > 15 ULN
Nara et al. (20)	126	82/NR	85/83	14/38	79/65	22/36	7/15	8/15	26/20	22/11	78/89	62/54	96/95	1	cTnI ≥ 15 ULN
Rahhab et al. (21)	1,054	785/NR	85/83	47/60	NR	NR	NR	NR	NR	79/NR	76/NR	60/55	NR	30d	hsTnT > 15 ULN
Real et al. (12)	1,394	817/NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	1	Troponin > 15 ULN
Ribeiro et al. (22)	1,131	NR/108	81/80	45/51	NR	NR	56/53	NR	29/26	44/41	55/58	60/56	NR	2	CK-MB > 5 ULN
Schindler et al. (29)	1,331	322/NR	81/80	52/54	77/77	23/26	55/46	9/9	18/19	45/49	38/35	53/53	89/97	2	hs-cTnT ≥ 18.3 ULN
Sharma et al. (28)	510	376/NR	81/81	54/60	94/94	42/48	NR	NR	NR	NR	NR	NR	47/85	3	cTnT ≥ 3 ULN
Sinning et al. (23)	276	144/25[e]	81/80	50/59	NR	NR	69/59	15/14	36/39	89/79	10/20	53/44	92/97	1	cTnT ≥ 15 ULN or CK-MB ≥ 5 ULN
Staudi et al. (24)	756[d]	390/55	81/80	46/59	NR	26/30	61/60	7/13	39/46	58/64	14/25	57/49	96/97	5	hsTnT > 15 ULN or CK-MB > 5 ULN
Yong et al. (25)	119[d]	NR/28[e]	83/80	50/37	45/51	10/39	30/18	10/20	25/34	100/100	0/0	NR	100/100	1	cTnT > 5 ULN or CK-MB > 5 ULN

n, number, d, days.

[a]Data extracted from Kaplan-Meier curves at time 0, unless otherwise indicated. NR, not reported. ULN, upper limit of normal. PPMI, periprocedural myocardial injury.

[b]Mean or median years of follow-up, unless otherwise stated. HTN, hypertension. DM, diabetes mellitus. CAD, coronary artery disease. MI, myocardial infarction. AF, atrial fibrillation. SEV, self-expanding valves. BEV, balloon-expandable valves. LVEF, left ventricular ejection fraction. TF, transfemoral. hscTnT, high-sensitive cardiac troponin T. CK-MB, creatine kinase-myocardial band. cTnI, cardiac troponin I. cTnT, cardiac troponin T.

[c]Data extracted from 1 month mark in Kaplan-Meier curves

[d]Data extracted from Table 1, due to the Kaplan-Meier curve not presenting data at time 0

[e]Study reported number of CK-MB-defined PPMI, but did not report Kaplan-Meier curve for this subgroup.

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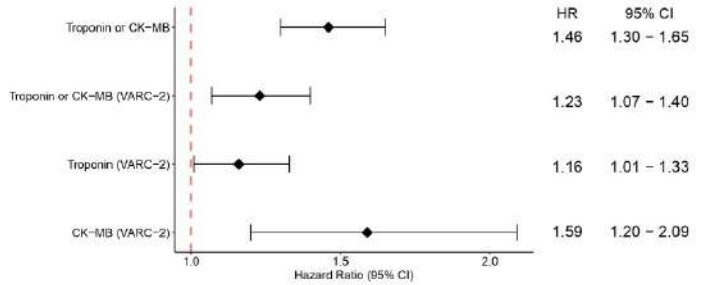

FIGURE 1
Pooled analysis showing the overall survival following TAVI for PPMI and no PPMI, and for subgroups of VARC-2, VARC-2 troponin-defined PPMI and VARC-2 CK-MB-defined PPMI. CI, confidence interval; HR, hazard ratio; PPMI, periprocedural myocardial injury; TAVI, transcatheter aortic valve implantation.

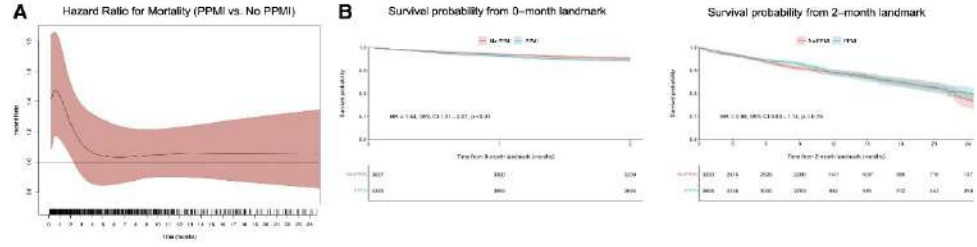

FIGURE 2
Time-varying HRs with 95% CI for all-cause mortality for patients with VARC-2-defined PPMI compared with no PPMI, at every given time during follow-up; these are derived from flexible parametric survival models with B-splines (A) and landmark analysis of overall survival in VARC-2-defined PPMI compared with no PPMI as defined by either troponin or CK-MB, designating 2 months of follow-up as the landmark time (B). Abbreviations as in Figure 1.

mortality was investigated. The main findings were as follows: (1) PPMI after TAVI was significantly associated with lower overall survival at 2 years; (2) the analysis remained consistent when performed in separate subgroups for VARC-2-defined PPMI and for both VARC-2 troponin- and CKMB-defined PPMI; (3) most deaths occurred within the first 2 months after the procedure; and (4) CK-MB defined VARC-2 criteria for PPMI was a much stronger mortality prognostic marker compared to troponin.

Incidence and predictors of PPMI

TAVI is a minimally invasive procedure that does not involve aortic cross clamping and cardioplegia, which are established factors for increased cardiac biomarkers release after valvular surgical procedures (35). Nevertheless, prior studies have demonstrated some degree of elevation of both CK-MB and troponin after the procedure in up to two-thirds of TAVI patients (22). Interestingly, PPMI incidence differs according to the cardiac injury biomarker analyzed and the cutoff point used; although troponin elevation > 15 ULN is of common occurrence during the first 72 h post-TAVI, only 10% of patients experience CK-MB elevation > 5 times the ULN (18). Our pooled analysis corroborates these findings, as the incidence of troponin PPMI was 61% vs. 9% for CK-MB defined PPMI, according to VARC-2 criteria of >5 times the ULN for CK-MB and >15 times the ULN for troponin. This difference in the incidence can be partially explained by the fact that CK-MB elevation requires a greater myocardial injury compared with troponin. For instance, as previously shown CK-MB VARC-2 cutoff threshold of >5 ULN displayed a better correlation with troponin levels of >75 ULN, which is much higher than the established VARC-2 recommendation of >15 times (4, 18). Therefore, the optimal PPMI cutoff point remains a matter of debate and, with the advent of ultra- and of high-sensitivity biomarkers assay kits even lower thresholds of myocardial injury can be measured, potentially overestimating the incidence of PPMI, ultimately jeopardizing its clinical relevance (36). Nonetheless, due to the new VARC-3 definition (≥70 times the ULN of troponin), we hypothesize that PPMI incidence will decrease in future studies while its prognostic significance will rise. This was recently demonstrated in a study by Real et al., in which PPMI incidence using troponin was 14% based on the VARC-3 criteria vs. 59% with VARC-2 (12).

PPMI is likely the result of several factors, such as transient hypotension during ventricular rapid pacing, distal microembolization of calcium particles during balloon dilatation and valve manipulation, mechanical compression of left

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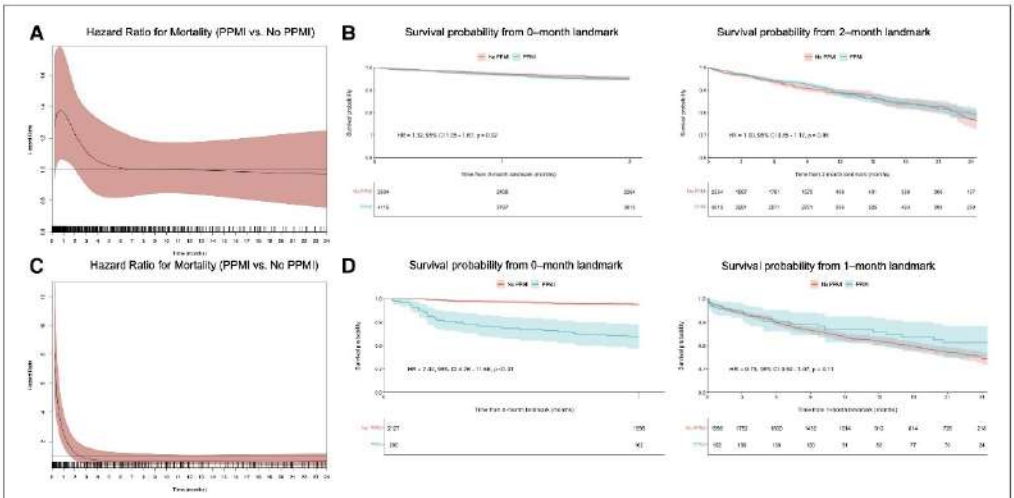

FIGURE 3
Time-varying HRs with 95% CI for all-cause mortality for patients with VARC-2 troponin-defined PPMI compared with no PPMI, at every given time during follow-up; these are derived from flexible parametric survival models with B-splines (A), landmark analysis of overall survival in VARC-2 troponin-defined PPMI compared with no PPMI, designating 2 months of follow-up as the landmark time (B), time-varying HRs with 95% CI for all-cause mortality for patients with VARC-2 CK-MB-defined PPMI compared with no PPMI, at every given time during follow-up (C) and landmark analysis of overall survival in VARC-2 CK-MB-defined PPMI compared with no PPMI, designating 1 month of follow-up as the landmark time (D). Abbreviations as in Figure 1.

ventricular outflow, subclinical ventricular trauma due to the wire, coronary artery disease that increases oxygen supply-demand mismatch, and coronary artery occlusion (3, 14, 29, 37). Several procedural predictors of post-TAVI PPMI are also known, such as early experience, first generation valves and transapical (TA) approach (5, 22). TA access is not only associated with PPMI, but is also a known factor for apical myocardial necrosis (38, 39). These findings further corroborate the use of alternatives accesses other than the TA, whenever TF access is not feasible (40). Regarding valve types and PPMI, self-expanding valves (SEV) were previously associated with a two-fold higher incidence of PPMI as compared with balloon-expandable valves (BEV), even after adjusting for several possible confounders (3, 21). This might be explained by various reasons, such as balloon pre-dilatation and after SEV deployment, which can lead small calcium particles to embolize to the coronary arteries, myocardial stunning triggered by more events of rapid pacing performed during the additional balloon dilations in comparison with BEV and perivalvular myocardial compression (41, 42).

Clinical impact of PPMI

Previously published meta-analyses found that PPMI was associated with an increased risk of early and late overall mortality (6–8). Our meta-analysis supports these findings and contributes to the existing literature by aggregating a significantly larger number of patients than previous analyses, indicating that most of the prognostic value of troponin-defined PPMI occurred within the first two months after TAVI, and even earlier for CK-MB-defined PPMI (first month). Furthermore, CK-MB was a better prognostic marker of short and 2-year mortality in comparison with troponin. Two important messages from these results are that first CK-MB using the VARC-2 definition of 5× the ULN is a valuable prognostic tool for mortality. Second, the VARC-2 definition for troponin-defined PPMI of 15× the ULN could overestimate the prevalence of PPMI and hinder its prognostic capacity. VARC-3 definition of 70× the ULN of troponin perhaps is a more suitable value and this is also corroborated by the recent publication of Real et al. which showed no association between VARC-2-troponin defined PPMI with the 1-year mortality (12). Yet, when the analysis was repeated using the VARC-3 cutoff, a statistically significant association was found (12). Importantly, whether the new cutoff is optimal remains uncertain and further studies with larger number of patients, using various assays, and with longer-term follow-up are required to confirm such findings. However, no study to date has specifically indicated potential measures which could improve PPMI patient's prognosis. Still, postprocedural cardiac biomarkers levels evaluation should be used to enhance early months risk assessment, indicating those in need for intensive postprocedural care such as a closer follow-up, possibly within a dedicated TAVI Heart Team, with intensive treatment of risk factors (8, 29).

Limitations

Our study has limitations that should be considered when interpreting the results. First, only observational studies were

included, which are prone to confounders and other biases. Second, this is a meta-analysis of KM derived IPD. We do not have access to patient-level data, which would allow us to minimize the risk of confounding effects through statistical techniques and to assess specific patient or procedural characteristics that could affect the clinical outcomes. Third, there is significant heterogeneity between studies, due to the different biomarker assay kits used and the evolution in the TAVI bioprostheses, technique and operator experience over time. Finally, some studies did not exclusively perform TF TAVI, which warrants special attention when considering PPMI rates and outcomes, as non-TF approaches are associated with higher PPMI rates and worse outcomes. Unfortunately, TA patients subgroup analysis was not possible in our study as TA approach effect on PPMI was not systematically described in the revised literature.

Conclusions

In this meta-analysis of 18 observational studies with 10,094 patients included, PPMI after TAVI was associated with lower OS as compared with no PPMI. This was consistent for both troponin-defined PPMI and CK-MB-defined PPMI. Time-varying hazard ratios and landmark analyses revealed that most of the prognostic power of the biomarkers, with respect to mortality, ensued in the first months after the procedure. Altogether, these results suggest that PPMI is an important prognostic marker in the acute phase following the procedure. Finally, given the more sensitive troponin assays currently in use, VARC-3 recommendations seem more suitable to determine clinically relevant PPMI than VARC-2, pending larger studies to confirm such findings.

Data availability statement

The original contributions presented in the study are included in the article/**Supplementary Materials**, further inquiries can be directed to the corresponding author.

Ethics statement

Ethical approval was not required for the study involving humans in accordance with the local legislation and institutional requirements. Written informed consent to participate in this study was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and the institutional requirements.

Author contributions

MS: methodology, formal analysis, investigation, writing – original draft. PC: methodology, formal analysis, investigation, writing. MG: formal analysis, investigation. GK: writing – review & editing. LR: writing – review & editing. CR: writing – review & editing. FT: review & editing. FB: review & editing. JR: review & editing, supervision. NV: review & editing, supervision. AA: review & editing, supervision. HR: conceptualization, writing – review & editing, supervision. All authors contributed to the article and approved the submitted version.

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Conflict of interest

FB is proctor for Edwards Lifesciences, Medtronic and Boston Scientific Scientific and received research grant from Medtronic. JR has received institutional research grants and speaker/consultant fees from Edwards Lifesciences and Medtronic. NV has received grants from Abbott, Boston Scientific, Biotronik, Edwards Lifesciences, Medtronic, Pulsecath BV, Abiomed, Daiichi Sankyo; consulting fees from: Jenavalve, Daiichi Sankyo, Abbott, Boston Scientific, Medtronic; payment or honoraria for lectures, presentations, speakers, manuscripts and educational events from Abiomed, Amgen and support for attending meetings and or travel from Jenavalve. AA is proctor for Boston Scientific and has received research grant from Medtronic. HR is proctor for Edwards Lifesciences, Medtronic and Boston Scientific and received research grant from Medtronic.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2023.1228305/full#supplementary-material

SUPPLEMENTARY FIGURE S1
PRISMA flow diagram of study screening and selection.

SUPPLEMENTARY FIGURE S2
Risk of bias summary- ROBINS-I tool with traffic lights (A) and summary plot (B).

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4 ARTICLE 2

Myocardial Injury After Transcatheter Mitral Valve Replacement Versus Surgical Reoperation

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This study aimed to evaluate the incidence and clinical implications of myocardial injury, as determined by cardiac biomarker increase, in patients who underwent mitral bioprosthesis dysfunction treatment with transcatheter mitral valve replacement (TMVR) versus surgical mitral valve replacement reoperation (SMVR-REDO). Between 2014 and 2023, 310 patients with mitral bioprosthesis failure were included (90 and 220 patients for TMVR and SMVR-REDO, respectively). Multivariable analysis and propensity score matching were performed to adjust for the intergroup differences in baseline characteristics. Creatinine kinase-MB (CK-MB) and cardiac troponin I (cTn) were collected at baseline and 6 to 12, 24, 48, and 72 hours after intervention. The cardiac biomarkers values were evaluated in relation to their reference values. The outcomes were determined according to the Mitral Valve Academic Research Consortium criteria. CK-MB and cTn increased above the reference level in almost all patients after SMVR-REDO and TMVR (100% vs 94%, respectively), with the peak occurring within 6 to 12 hours. SMVR-REDO was associated with a two- to threefold higher increase in cardiac biomarkers. After 30 days, the mortality rates were 13.3% in the TMVR and 16.8% in the SMVR-REDO groups. At a median follow-up of 19 months, the mortality rates were 21.1% in the TMVR and 17.7% in the SMVR-REDO groups. Left ventricular ejection fraction, estimated glomerular filtration rate, CK-MB, and cTn were predictors of mortality. In conclusion, some degree of myocardial injury occurred systematically after the treatment of mitral bioprosthetic degeneration, especially after SMVR, and higher CK-MB and cTn levels were associated with increased cumulative late mortality, regardless of the approach. **(Am J Cardiol 2024;214:8–17)**

Keywords: mitral, valve dysfunction, bioprosthetic valve degeneration, transcatheter mitral valve replacement, myocardial injury, transapical, transseptal, mitral valve surgery

Surgical mitral valve repair and replacement are frequently performed cardiac procedures. In the last decades, there has been an increased use of bioprosthetic (BP) valves implantation in favor of mechanical valves.[1] Surgical mitral valve replacement reoperation (SMVR-REDO) is the gold standard for BP dysfunction.[2] Still, this procedure poses a noteworthy myocardial injury risk, as determined by cardiac creatine kinase-MB (CK-MB) mass and cardiac troponin increase, likely because of the use of aortic cross-clamping and cardioplegia.[2,3] Hence, transcatheter mitral valve replacement (TMVR) has emerged as a minimally invasive alternative, yielding fewer periprocedural complications than SMVR-REDO.[4] Nonetheless, there is a lack of studies specifically evaluating myocardial injury in patients who underwent TMVR versus SMVR-REDO and their impact on the clinical outcomes. Furthermore, the proposed cut-off points used in the Mitral Valve Academic Research Consortium (M-VARC) to define significant myocardial injury are not clinically validated for neither TMVR nor SMVR-REDO.[5,6] The objectives of this study were to evaluate the incidence, predictors, and clinical outcomes of myocardial injury in patients with severe mitral BP valve dysfunction who underwent TMVR versus SMVR-REDO.

Methods

From January 2014 and March 2023, a total of 310 consecutive patients with severe mitral BP dysfunction were included, of whom 90 underwent TMVR (68 transapical [TA] and 22 transseptal [TS]) and 220 underwent SMVR-

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See page 16 for Declaration of Competing Interest.

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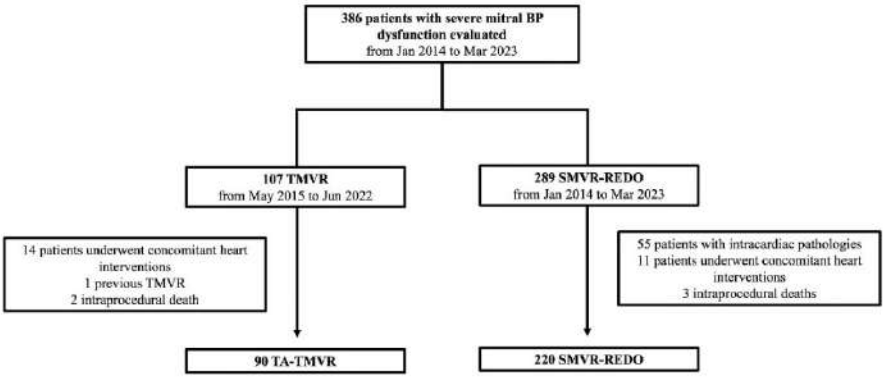

Figure 1. Study flowchart.

REDO. All TMVR and SMVR-REDO procedures were performed by the same heart team at a single center. Figure 1 shows the flow diagram of the study population. The exclusion criteria included the following: (1) patients with intracardiac pathologies that contraindicated transcatheter treatment, such as infective endocarditis or intracardiac thrombus, (2) concomitant heart interventions, (3) previous implant of a transcatheter mitral valve, (4) dysfunctional mitral ring and mitral annular calcification, and (5) transcatheter edge-to-edge repair. The study was approved by the ethics committee and the need for written informed consent from individual patients was waived because of the retrospective and anonymous nature of the study.

Patients who underwent TA and TS were grouped into a single category of patients who underwent TMVR. The baseline co-morbidities were defined according to the Society of Thoracic Surgeons (STS) criteria, and the clinical outcomes were defined according to the M-VARC criteria.[5,6] Clinical follow-up was carried out by clinical visits and/or through phone contact at 1 month, 6-to-12 months after transcatheter aortic valve replacement and yearly thereafter for both groups. Complete late clinical follow-up was available in all patients.

Blood samples were collected before intervention and between 6 to 12 hours, 12 to 24 hours, 24 to 48 hours, and 48 to 72 hours after mitral intervention. At least 1 measure of CK-MB and cardiac troponin I (cTn) was performed at each time point. cTn examinations between 2014 and February 2020 were performed with ADVIA Centaur XP Contemporary Sensitive Troponin I Assay, with a reference value of 0.04 ng/ml for both genders. After February 2020, cTn examinations were performed using ADVIA Centaur XP High Sensitivity Troponin I, with a reference value of 40 ng/L for women and 58 ng/L for men, respectively. The upper limits of normal (ULN) values were based on the ninety-ninth percentile in a healthy population and presented a coefficient of variation of <10%. Myocardial injury was defined as an increase in CK-MB and/or cTn above the ULN (up to 72 hours) after the intervention.[6,7] The degree of biomarkers increase was calculated by dividing CK-MB and/or cTn level by the ULN, and this was expressed as n-fold of increase.

Doppler echocardiographic examination was performed before mitral intervention, upon hospital discharge, and at late follow-up. The images were analyzed by 2 experienced cardiologists and BP dysfunction was defined according to the current guidelines.[8,9] Severe BP stenosis was defined as a calculated mitral prosthesis area ≤ 1.0 cm^2 or mean transmitral gradient ≥ 10 mm Hg, and mitral regurgitation was defined by integrating several doppler and quantitative findings.[10] Mitral regurgitation severity was classified according to the American Society of Echocardiography guideline as none/trace, mild, moderate, or severe.[11]

The Heart Team, which includes clinical cardiologists, interventional cardiologists, echocardiographers, and cardiac surgeons, evaluated each patient's needs and circumstances to determine the most appropriate treatment strategy. TA-TMVR was performed under general anesthesia through TA access with Braile Inovare (n = 68) (Braile Biomedical, São Paulo, Brazil) valves, as previously demonstrated.[12] Inovare is a balloon-expandable valve with a chromium-cobalt stent frame with 6 sizes, ranging from 20 to 30 mm.[12] All of the TS access were also performed under general anesthesia using the SAPIEN 3 (n = 21) and SAPIEN 3 Ultra (n = 1) valves. SMVR-REDO procedures were performed using traditional transatrial access under general anesthesia and extracorporeal circulation. The type and size of BP were chosen at the discretion of the operators.

Categorical variables were reported as n (%). Continuous variables were expressed as mean SD or median (interquartile range), as appropriate. Group comparisons were made using Student's *t* test or Mann−Whitney *U* test for continuous variables and chi-square test for categorical variables. Propensity score matching (PSM) analysis using a 2-to-1 matching process was performed to adjust for the intergroup (TMVR versus SMVR-REDO) differences in baseline characteristics, using the algorithm of nearest-neighbor method matching by the R package MatchIt. The variables used for the matching process were age, hypertension, dyslipidemia, previous coronary artery bypass graft, atrial fibrillation,

estimated glomerular filtration rate (eGFR), EuroScore II, and STS. For the CK-MB and cTn analysis, normality assumption was verified using Anderson–Darling tests. The increase in values of CK-MB and cTn were logarithmically transformed to normalize distributions. Generalized linear model repeated measures analysis was used to evaluate variation of biomarkers, and the Tukey test was used for post hoc analyses. A linear regression analysis was conducted after standardizing cardiac biomarkers by assessing the n-fold increase (calculated by dividing the serum levels by the ULN for each kit) to identify the predictors of increased cardiac biomarker values. Continuous variables were checked for linearity assumption using distribution quartiles and fractional polynomials. Univariable and multivariable Cox proportional hazards models were used to determine predictors of cumulative 30-day and late overall mortality. Variables with a probability value <0.10 were candidates for construction of multivariable regression models. The mortality rates were presented using Kaplan–Meier estimates, and comparisons between groups were made using the logarithmic rank test. Younden index was used to identify the best accuracy point for 30-day and late mortality in the receiver operating characteristic analysis. The results were considered significant with $p < 0.05$. Analyses were made using SPSS 24 (IBM, Armonk, New York) and R Statistical Software 4.2.2 (Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline clinical, echocardiographic, and laboratory characteristics of the study population are listed in Table 1. Patients in the TMVR group were older than in the SMVR-REDO group ($p < 0.001$) and presented a greater burden of co-morbidities, such as higher rates of hypertension, dyslipidemia, atrial fibrillation, lower eGFR, and coronary artery bypass graft history (all with $p < 0.05$). Therefore, patients who underwent TMVR presented higher STS Predicted Risk of Mortality score (5.8 [3.8 to 9.5] vs 2.7 [1.7 to 5.0]%, respectively, $p < 0.001$) and EuroSCORE II (7.8 [4.6 to 11.5] vs 4.4 [3.0 to 6.7]%, respectively, $p < 0.001$). There were no differences in baseline echocardiographic variables, except for a higher left ventricular mass index in TMVR group than in the SMVR-REDO group (103 [90 to 132] g/m^2 vs 91 [71 to 106] g/m^2, respectively, $p < 0.001$). Baseline and procedural characteristics of the PSM population (TMVR and SMVR-REDO) are listed in Table 2 and were well balanced according to the major baseline characteristics.

The median peak values of CK-MB and cTn at each time point within 72 hours after mitral intervention, stratified according to approach (TMVR group vs SMVR-REDO), are shown in Figure 2. The levels of CK-MB and cTn increased in 94.4% of patients who underwent TMVR and in all SMVR-REDO cases, with a median increase of 7.72-fold (4.41 to 16.63) for CK-MB and 200.2-fold (115.50 to 398.75) for cTn, peaking at 6 to 12 hours after both procedures. This increase was significantly higher in the SMVR-REDO group than in the TMVR group, both for CK-MB (9.74 [6.55 to 14.71] vs 3.79 [2.34 to 4.89], respectively, $p < 0.001$) and cTn (258.97 [131.94 to 458.44] vs 118.25 [61.28 to 210], respectively, $p < 0.001$). The degree of increase in CK-MB and cTn according to the approach (TMVR group vs SMVR-REDO) expressed by folds-of-increase are depicted in Figure 3. The median peak values of CK-MB and cTn at each time point within 72 hours after mitral intervention and the degree of increase in CK-MB and cTn according to approach expressed by folds-of-increase stratified according to approach (TMVR group vs SMVR-REDO) in a PSM population are shown in Supplementary Figure 1 and according to a subanalysis of TMVR (TS-TMVR vs TA-TMVR groups) in Supplementary Figure 2. Importantly, TA-TMVR was related with a 2-fold higher increase in CK-MB and cTn with respect to TS-TMVR ($p < 0.05$).

The baseline and procedural variables associated with a higher degree of myocardial injury are listed in Supplementary Table 1. The multivariable analysis demonstrated that baseline left ventricular ejection fraction (LVEF) and SMVR-REDO were independent predictors of CK-MB increase ($p < 0.05$). Regarding cTn, SMVR-REDO was the only independent predictor of increase ($p < 0.05$). In patients who underwent SMVR-REDO, a multivariable subanalysis showed that the independent factors associated with greater increase in CK-MB levels were LVEF and duration of extracorporeal circulation ($p < 0.05$). Concerning cTn, a higher increase in cTn was only predicted by the duration of extracorporeal circulation ($p = 0.018$), as listed in Supplementary Table 2.

The procedural and 30-day outcomes of the overall study population and according to approach are listed in Table 3. Patients in the TMVR group had a shorter hospital stay, had lower rates of major bleeding, and required fewer blood transfusions than patients in the SMVR-REDO group. Yet, echocardiography at 30 days revealed that patients who underwent SMVR-REDO presented lower maximal and mean mitral gradients than those who underwent TMVR. There were no left ventricular outflow tract obstructions in the TMVR group.

The 30-day and late overall mortality did not differ between TMVR and SMVR-REDO groups. Within 30 days after mitral intervention, 48 patients (15%) died: 11 (12%) in TMVR group and 37 (17%) in the SMVR-REDO group ($p = 0.554$). The cumulative mortality rate was 19% in a median follow-up of 19.1 (3.1 to 37.9) months, 19 (21.1%) in the TMVR group and 39 (17.7%) in the SMVR-REDO group, with no difference between groups on long-term follow-up (hazard ratio [HR] 0.86, 95% confidence interval [CI] 0.49 to 1.49, $p = 0.59$). In the propensity-matched cohort, 9 patients (17%) in the TMVR group and 26 (26%) in the SMVR-REDO group died (HR 1.46, 95% CI 0.78 to 2.76, $p = 0.24$) (Figure 4).

Table 4 lists the univariable and multivariable analysis of predictors of 30-day and late cumulative mortality, with 2 models adjusted by CK-MB and cTn, respectively. In model 1, for 30-day mortality, a greater increase in CK-MB (HR 1.012, 95% CI 1.006 to 1.018, $p < 0.001$) and eGFR (HR 0.982, 95% CI 0.969 to 0.996, $p = 0.009$) were independent predictors of mortality. In model 2, a greater increase in cTn (HR 1.001, 95% CI 1.001 to 1.002, $p < 0.001$) and eGFR (HR 0.978, 95% CI 0.965 to 0.991, $p = 0.001$) were independent predictors of 30-day mortality.

Table 1
Baseline clinical and echocardiographic characteristics of the study population

	Overall (n = 310)	TMVR (n = 90)	SMVR-REDO (n = 220)	*p* value
Clinical variables				
Age, years	56.2 ± 13.9	67.3 ± 11.2	51.6 ± 12.2	< 0.001
Female sex	213 (68.7)	62 (68.9)	51 (68.6)	1.000
NYHA				0.839
Class I/II	38 (12.3)	10 (11.1)	28 (12.7)	
Class III/IV	272 (87.7)	80 (88.9)	192 (87.3)	
Angina	14 (4.5)	7 (7.9)	7 (3.2)	0.126
Etiology				0.131
Rheumatic	215 (70.7)	54 (63.5)	161 (73.5)	
Mitral valve prolapse	29 (9.5)	8 (9.4)	21 (9.6)	
Other	60 (19.7)	23 (27.1)	37 (16.9)	
Hypertension	135 (43.5)	50 (55.6)	85 (38.6)	0.009
Diabetes	36 (11.6)	15 (16.7)	21 (9.5)	0.114
Dyslipidemia	88 (28.4)	38 (42.2)	50 (22.7)	< 0.001
COPD	17 (5.5)	7 (7.8)	10 (4.5)	0.277
Atrial fibrillation	186 (60)	66 (73.3)	120 (54.5)	0.003
Cerebrovascular disease	48 (15.5)	17 (18.9)	31 (14.1)	0.375
eGFR < 60 mL/min/1.73 m^2	131 (42.3)	62 (68.9)	69 (31.4)	< 0.001
CABG	16 (5.2)	12 (13.3)	4 (1.8)	< 0.001
PCI	6 (1.9)	3 (3.3)	3 (1.4)	0.362
Pacemaker	19 (6.1)	9 (10)	10 (4.5)	0.120
Hospitalization in the last 30 days	83 (26.9)	22 (25)	61 (27.7)	0.730
Time since last surgery, years	11.7 ± 5.6	12.5 ± 5.4	11.4 ± 5.6	0.129
Number of previous surgeries	1 [1-2]	1 [1 - 2]	1 [1 - 2]	0.615
STS-PROM score, %	3.64 [1.99 − 5.81]	5.81 [3.79 − 9.52]	2.72 [1.69 − 4.97]	< 0.001
EuroSCORE II, %	4.95 [3.39 − 8.44]	7.84 [4.64 − 11.54]	4.36 [3 − 6.73]	< 0.001
Echocardiographic variables				
Left atrium diameter, mm	54 [48 − 61]	55 [48 − 63]	53 [48 − 60]	0.137
LVEF, %	61 [56 − 66]	60 [55 − 65]	62 [56.50 − 66]	0.181
LVESD, mm	33 [30 − 38]	33.5 [29.7 − 39]	33 [30 − 37]	0.622
LVEDD, mm	51 [46 − 55]	51 [45 − 56]	50.5 [46 − 55]	0.748
LVMI, g/m^2	96 [75 − 112]	103 [90 − 132]	91 [71 − 106]	< 0.001
Mitral valve area, cm^2	1.06 ± 0.43	1.07 ± 0.44	1.05 ± 0.43	0.129
Max mitral gradient, mmHg	25 [19 − 30]	24 [18 − 28]	25 [20 − 30]	0.130
Mean transmitral gradient, mmHg	10 [8 − 15]	10 [8 − 13]	11 [9 − 15]	0.129
Moderate/severe mitral regurgitation	121 (56)	51 (61)	70 (53)	0.363
PASP, mmHg	60.5 ± 21.6	60.7 ± 18.2	60.4 ± 23.0	0.935
Moderate/severe right ventricular dysfunction	71 (33)	33 (39)	38 (29)	0.157

Values are n (%), mean ± SD or median [IQR].

CABG = coronary artery bypass graft; COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration; EuroSCORE 2 = European System for Cardiac Operative Risk Evaluation predicted risk of in-hospital mortality; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; LVESD = left ventricular end-systolic diameter; LVMI = left ventricular mass index; NYHA = New York Heart Association; PASP = pulmonary artery systolic pressure; PCI = percutaneous coronary intervention; SMVR-REDO = surgical reoperation of the mitral valve; STS-PROM = Society of Thoracic Surgeons Predicted Risk of Mortality; TMVR = transcatheter mitral valve replacement.

Regarding late cumulative mortality, model 1 demonstrated that a greater increase in CK-MB (HR 1.013, 95% CI 1.007 to 1.019, p <0.001), eGFR (HR 0.984, 95% CI 0.972 to 0.997, p = 0.013), and LVEF (HR 0.975, 95% CI 0.951 to 1.000, p = 0.048) were independent predictors of mortality. In model 2, for late cumulative mortality, a greater increase in cTn (HR 1.001, 95% CI 1.001 to 1.002, p <0.001), eGFR (HR 0.982, 95% CI 0.970 to 0.994, p = 0.004), and LVEF (HR 0.040, 95% CI 0.951 to 0.999, p = 0.040) were variables related to greater mortality.

Using the Youden index, a 10-fold increase in CK-MB best predicted 30-day (area under the curve [AUC] 0.64, 95% CI 0.55 to 0.73, p = 0.046) and late cumulative mortality (AUC 0.58, 95% CI 0.49 to 0.67, p = 0.046), as shown in Supplementary Figure 3. Furthermore, a 500-fold increase in cTn best predicted 30-day (AUC 0.73. 95% CI 0.66 to 0.81, p = 0.040) and late cumulative mortality (AUC 0.69, 95% CI 0.61 to 0.77, p = 0.041).

A 10-fold increase of CK-MB and a 500-fold increase of cTn were associated with overall mortality, regardless of the approach, with an HR of 1.72 (95% CI 1.030 to 2.89, p = 0.04) and 3.87 (95% CI 2.31 to 6.48, p <0.001), respectively, as shown in Figure 5.

Compared with the immediate postmitral intervention measurements, the LVEF at late follow-up remained similar

Table 2
Baseline clinical and echocardiographic characteristics of the propensity-matched population

	Overall (n = 158)	TMVR (n = 53)	SMVR-REDO (n = 99)	*p* value
Clinical variables				
Age, years	60.6 ± 10.4	62.5 ± 11.2	59.5 ± 9.9	0.100
Female sex	103 (67.8)	39 (73.6)	64 (64.6)	0.346
NYHA				0.287
Class I/II	22 (10.5)	8 (15.1)	8 (8.1)	
Class III/IV	136 (89.5)	45 (84.9)	91 (91.9)	
Angina	10 (6.3)	7 (9.0)	3 (3.8)	0.317
Etiology				0.629
Rheumatic	105 (69.1)	36 (67.9)	69 (69.7)	
Mitral valve prolapse	15 (9.9)	4 (7.5)	11 (11.1)	
Other	32 (21.1)	13 (24.5)	19 (19.2)	
Hypertension	71 (46.7)	25 (47.2)	46 (46.5)	1.000
Diabetes	19 (12.5)	6 (11.3)	13 (13.1)	0.949
Dyslipidemia	50 (32.9)	19 (35.8)	31 (31.3)	0.699
COPD	11 (7.2)	3 (5.7)	8 (8.1)	0.826
PASP > 60 mmHg	61 (40.1)	20 (37.7)	41 (41.4)	0.789
Atrial fibrillation	107 (70.4)	41 (77.4)	66 (66.7)	0.234
Cerebrovascular disease	29 (19.1)	10 (18.9)	19 (19.2)	1.000
eGFR < 60 mL/min/1.73 m^2	84 (55.3)	31 (58.5)	53 (53.5)	0.679
CABG	7 (4.6)	3 (5.7)	4 (4)	0.962
PCI	5 (3.3)	2 (3.8)	3 (3)	1.000
Pacemaker	12 (7.9)	7 (13.2)	5 (5.1)	0.144
Hospitalization in the last 30 days	53 (35.1)	13 (25.0)	40 (40.4)	0.088
Time since last surgery, years	12.1 ± 5.7	11.6 ± 5.2	12.5 ± 6	0.364
Number of previous surgeries	2 [1 - 2]	2 [1 - 3]	1 [1 - 2]	0.016
STS-PROM score, %	4.38 [3.06 - 6.54]	4.56 [3.42 - 7.06]	4.29 [2.8 - 5.85]	0.144
EuroSCORE II, %	6.14 [4.06 - 9.21]	7.38 [4.48 - 10.46]	5.89 [3.71 - 8.6]	0.093
Echocardiographic variables				
Left atrium diameter, mm	54 [49 - 60]	54.5 [48.7 - 63]	53.5 [49 - 59]	0.232
LVEF, %	61 [55.5 - 66]	60 [55 - 65.2]	62 [56 - 66]	0.502
LVESD, mm	32 [30 - 37]	33.5 [30 - 38]	33 [30 - 36]	0.460
LVEDD, mm	50 [45 - 54]	49 [44 - 55]	50 [45 - 54]	0.927
LVMI, g/m^2	96 [75 - 111.5]	98 [83.5 - 114]	93 [70.5 - 108]	0.136
Mitral valve area, cm^2	1.02 ± 0.43	1.1 ± 0.5	1 ± 0.4	0.505
Max mitral gradient, mmHg	24 [19 - 29]	24 [19.7 - 29]	24 [19 - 29.7]	0.773
Mean transmitral gradient, mmHg	10 [9 - 14.7]	10 [9 - 13.2]	10 [9 - 15]	0.975
Moderate/severe mitral regurgitation	61 (58.7)	31 (60.8)	30 (56.6)	0.815
PASP, mmHg	61.4 ± 22.4	60.2 ± 18.3	62.1 ± 24.3	0.639
Moderate/severe right ventricular dysfunction	35 (33.7)	18 (35.3)	17 (32.1)	0.889

Values are n (%), mean ± SD or median [IQR].

in the TMVR and SMVR-REDO groups (59 [49.5 to 64] and 60 [52.5 to 65], respectively, p = 0.390). Notably, slightly higher values of mean transmitral gradients were observed in TMVR than in SMVR-REDO, 6 (5 to 7) versus 5 (4 to 7) mm Hg, respectively (p = 0.009).

Discussion

The main findings were as follows: (1) mitral reinterventions (TMVR and SMVR-REDO) were systematically associated with certain degree of myocardial injury, (2) SMVR-REDO and the duration of extracorporeal circulation were the main predictors of CK-MB and cTn increase, (3) greater levels of myocardial injury were independently correlated with higher mortality at 30-day and late follow-up, irrespective of the approach, and (4) CK-MB increase ≥10-fold and cTn ≥500-fold from baseline are relevant thresholds for defining clinically relevant myocardial injury.

Cardiac surgery systematically generates substantial increase in cardiac biomarkers, particularly, in combined procedures and valve reinterventions.[13,14] Minimally invasive interventions, such as transcatheter aortic valve implantation, have been shown to significantly reduce cardiac biomarkers release, most likely because of the avoidance of aortic cross-clamping and cardioplegia.[15,16] However, no study to date had specifically compared the release in cardiac biomarkers in patients who underwent TMVR versus SMVR-REDO. To the best of our knowledge, this study is the first to demonstrate that both approaches are related to a systematic increase in CK-MB and cTn, peaking at 6 to 12 hours, with SMVR-REDO presenting with a 2- to 3-fold higher fold of increase than TMVR.

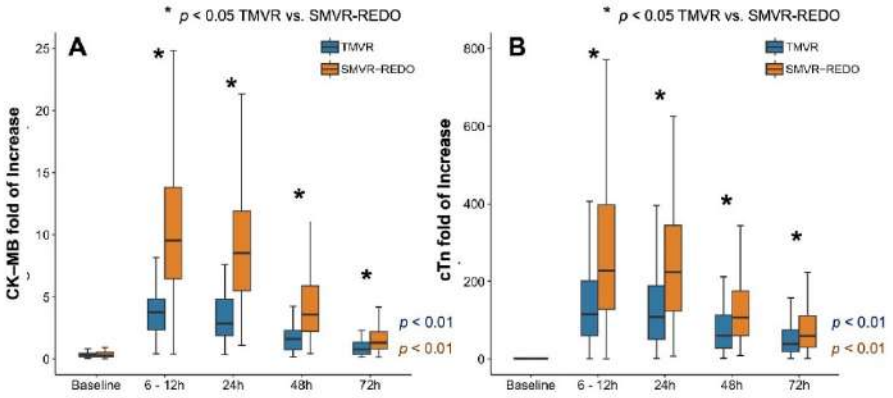

Figure 2. Cluster boxplot with the median changes in CK-MB (*A*) and cTn (*B*) levels after TMVR versus TMVR-REDO. Changes in CK-MB (*A*); and cTn (*B*); levels within the 72 hours after TMVR versus SMVR-REDO. Values are expressed as median (25th to 75th interquartile range) of fold of increase.

Baseline LVEF was significantly related to higher CK-MB and cTn increases, regardless of the approach, indicating the important role of ventricular dysfunction and myocardial compromise in the genesis of myocardial injury.[16,17] Likewise, the significant association of greater CK-MB release to the number of previous surgical interventions and hospitalization in the last 30 days further reinforces the extent of direct myocardial damage as a factor linked to myocardial injury.[18,19] In this study, most patients who underwent TMVR were treated using TA access, which is a known risk factor for myocardial injury.[20] This is likely because of the apex myocardial necrosis associated with large bore catheters.[7] TS approach for TMVR procedures has emerged as a less traumatic strategy, which precludes thoracotomy and apical puncture, potentially leading to less myocardial injury.[21,22] Despite the limited number of patients, this study demonstrated this reduction. However, larger studies are necessary to confirm such findings. Finally, in the surgical cohort, duration of extracorporeal circulation and aortic cross-clamping were factors associated with myocardial injury, underlining the importance of minimizing or even avoiding surgical procedures in patients with compromised ventricles, as previously described in previous studies in the transcatheter aortic valve implantation field.[16]

Myocardial injury has a detrimental prognostic impact in a variety of transcatheter and surgical cardiac interventions.[15,16,23] Accordingly, greater increases of CK-MB and cTn levels were associated with increased 30-day and long-term mortality, irrespective of the approach. The mortality rates were similar between TMVR and SMVR-REDO in the overall population and occurred predominantly in the acute phase, which is consistent with studies comparing these 2 strategies in high-risk patients who underwent mitral valve reintervention.[2,24] In the study population, patients in TMVR group were older and presented a higher burden of co-morbidities, yielding a 2-fold greater STS Predicted Risk of Mortality and EuroSCORE II, a finding consistent with previous reports.[24] The mortality rates were statistically similar between TMVR and SMVR-REDO, even after PSM for baseline characteristics was performed, which is consistent with a recently published meta-analysis comparing these 2 strategies.[24] However, the TMVR group experienced less periprocedural

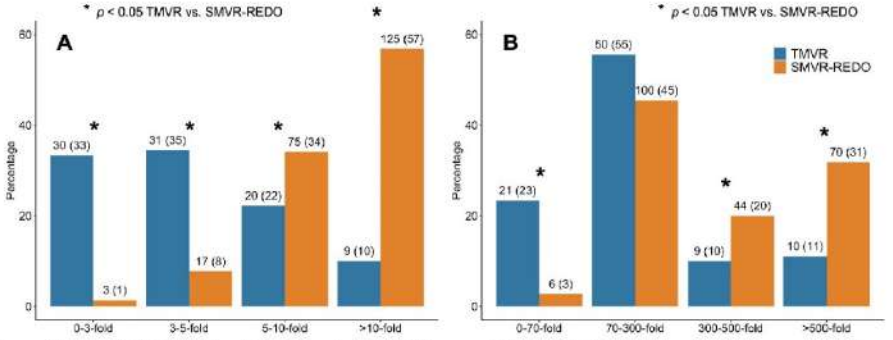

Figure 3. Degree of increase in CK-MB (*A*) and cTn (*B*) levels after TMVR versus SMVR-REDO. Cardiac biomarker changes are grouped according to the percent of patients in the TMVR versus SMVR-REDO according to fold of increase.

Table 3
Procedural and 30-day outcomes of the study population

	Overall (n = 310)	TMVR (n = 90)	SMVR-REDO (n = 220)	*p* value
Procedural outcomes				
Technical success*	261 (96)	81 (93.1)	180 (97.3)	0.111
Extracorporeal circulation, minutes	-	-	105.5 ± 25.6	-
Aortic cross-clamping, minutes	-	-	83.1 ± 20.9	-
Cardiac tamponade	3 (1)	1 (1.1)	2 (0.9)	1.000
Conversion to open surgery	4 (1.3)	4 (4.5)	-	-
Intrahospital mortality	48 (15.5)	11 (12.2)	37 (16.8)	0.400
Hospitalization ICU, days	8 [5 - 15]	9 [5 – 15.5]	8 [5 – 15]	0.974
Hospitalization total, days	11 [7 - 20]	9 [5.5 – 16.5]	12.5 [8 - 21]	< 0.001
30-day outcomes				
Mortality	49 (15.8)	12 (13.3)	37 (16.8)	0.554
NYHA functional class				1.000
Class I/II	236 (93.3)	71 (93.4)	165 (93.2)	
Class III/IV	17 (6.7)	5 (6.6)	12 (6.8)	
New onset atrial fibrillation	31 (10)	4 (4.4)	27 (12.3)	0.061
Cerebrovascular event	3 (1)	-	3 (1.4)	0.559
Acute Kidney Injury*	78 (25.2)	18 (20)	60 (27.3)	0.232
Infection	88 (28.4)	22 (24.4)	66 (30)	0.398
Reintubation	23 (7.4)	7 (7.8)	16 (7.3)	1.000
Endocarditis	2 (0.6)	-	2 (0.9)	1.000
Permanent pacemaker	15 (4.8)	1 (1.1)	14 (6.4)	0.076
Rehospitalization	17 (6.7)	7 (9.1)	10 (5.7)	0.469
eGFR, mL/min/1.73 m^2	64 ± 24.9	53 ± 24.0	70 ± 23.4	< 0.001
In-hospital echocardiographic variables				
Left atrium size, mm	52 [47 - 57]	53 [48 – 57.2]	52 [46 – 57.5]	0.262
LVEF, %	60 [52.5 - 64]	59 [52 - 64]	60 [52.7 - 64]	0.533
LVESD, mm	32 [29.7 - 37]	32 [30 - 37]	32 [29 - 37]	0.728
LVEDD, mm	49 [45 - 53]	49 [45 - 53]	49 [44.5 - 53]	0.826
LVMI, g/m^2	94 [74 - 109]	100 [78- 119]	88 [71.5 – 106]	0.006
Mitral valve size, cm^2	1.79 ± 0.66	1.66 ± 0.52	2 ± 0.80	0.061
Max mitral gradient, mmHg	13 [10 - 16]	15 [11 – 20]	12 [10 - 15]	< 0.001
Mean mitral gradient, mmHg	5.1 [4 - 7]	6 [5 – 9.9]	5 [4 - 7]	< 0.001
Moderate/severe mitral regurgitation	2 (0.9)	1 (1.2)	1 (0.8)	1.000
PASP, mmHg	44.8 ± 19.9	52.6 ± 16.9	41.4 ± 20.2	< 0.001
Moderate/severe right ventricle dysfunction	70 (32.7)	31 (37.3)	39 (29.8)	0.316
30-day laboratorial variables				
Hemoglobin, g/dL	10.1 ± 1.9	9.7 ± 2.2	10.2 ± 1.8	0.035
Creatinine, mg/dL	1 [0.8 - 1.2]	1.1 [0.9 - 1.5]	0.9 [0.8 - 1.2]	< 0.001
Platelets, mm^3	207000 [142500 - 294750]	138000 [113000 - 188000]	251000 [184000 - 351000]	< 0.001

Values are n (%), mean (± SD) or median [IQR]. Technical success, measured at exit from the catheterization laboratory, as: I. Absence of procedural mortality; II. Successful access, delivery, and retrieval of the device delivery system; III. Successful deployment and correct positioning of the first intended device; and IV. Freedom from emergency surgery or reintervention related to the device or access procedure.

ICU = intensive care unit; other abbreviations as in Table 1.

* Following M-VARC criteria:

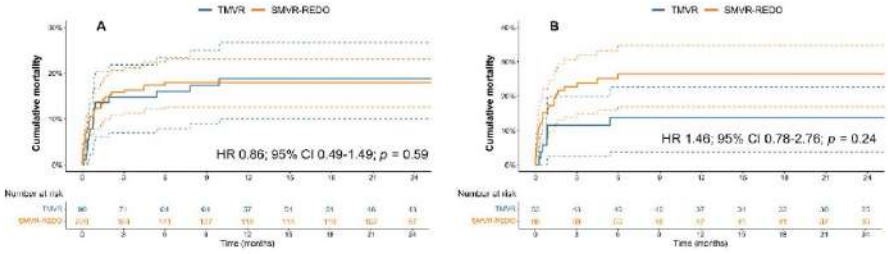

Figure 4. Long-term Kaplan–Meier cumulative mortality according to the approach TMVR versus SMVR-REDO for the overall population (*A*) and for the propensity-matched cohort (*B*).

Table 4
Univariable and multivariable analyses for 30-day and cumulative mortality

Variable	Univariable analysis		Multivariable Analysis	
	HR (95% CI)	*p* value	**HR** (95% CI)	*p* value
30-day mortality				
Model 1 - CK-MB				
Age	1.017 (0.996 - 1.038)	0.109	1.006 (0.982 - 1.029)	0.639
eGFR	0.983 (0.971 - 0.994)	0.003	0.982 (0.969 - 0.996)	0.009
Max fold CK-MB	1.009 (1.004 - 1.015)	0.001	1.012 (1.006 - 1.018)	<0.001
NYHA	1.584 (0.968 − 2.651)	0.073	1.616 (0.993 − 2.630)	0.054
Model 2 - cTn				
Age	1.017 (0.996 - 1.038)	0.109	1.007 (0.982 - 1.031)	0.600
eGFR	0.983 (0.971 - 0.994)	0.003	0.978 (0.965 - 0.991)	0.001
Max fold cTn	1.001 (1.000 - 1.001)	<0.001	1.001 (1.001 - 1.002)	<0.001
NYHA	1.584 (0.968 − 2.651)	0.073	1.615 (0.988 - 2.640)	0.056
Cumulative mortality				
Model 1-CK-MB				
Age	1.027 (1.008 - 1.047)	0.005	1.016 (0.993 - 1.040)	0.163
eGFR	0.981 (0.970 - 0.991)	<0.001	0.984 (0.972 − 0.997)	0.013
Max fold CK-MB	1.009 (1.003 - 1.014)	0.005	1.013 (1.007 - 1.019)	<0.001
LVEF	0.974 (0.951 - 0.997)	0.028	0.975 (0.951 − 1.000)	0.048
NYHA	1.562 (1.019 − 2.392)	0.041	1.540 (0.977 − 2.428)	0.063
COPD	2.604 (1.181 − 5.740)	0.018	1.590 (0.695 − 3.641)	0.272
Model 2 - cTn				
Age	1.027 (1.008 - 1.047)	0.005	1.019 (0.995 - 1.043)	0.131
eGFR	0.981 (0.970 - 0.991)	<0.001	0.982 (0.970 − 0.994)	0.004
Max fold cTn	1.001 (1.000 - 1.001)	<0.001	1.001 (1.001 - 1.002)	<0.001
LVEF	0.974 (0.951 - 0.997)	0.028	0.975 (0.951 - 0.999)	0.040
NYHA class	1.562 (1.019 − 2.392)	0.041	1.563 (0.987 − 2.475)	0.057
COPD	2.604 (1.181 − 5.740)	0.018	1.484 (0.654 − 3.367)	0.345

HR = hazard ratio; other abbreviations as in Table 1.

complications and a shorter hospital, a finding also observed in contemporary TMVR studies.[4]

Finally, the optimal threshold for defining clinically relevant myocardial injury after mitral BP dysfunction intervention is unsettled.[23] For instance, M-VARC recommends the cut-off value of 10-fold of increase in CK-MB and a 70-fold of increase in cTn, based on a modification of the Society for Cardiac Angiography and Interventions criteria for clinically relevant periprocedural myocardial infarction and the third universal definition of myocardial infarction.[6,25,26] However, these values have never been validated in the context of mitral reintervention. In the present study, a similar cutoff for CK-MB increase was observed, which provides evidence for M-VARC value. Nonetheless, the results showed a much higher cTn optimal cutoff than what was proposed in M-VARC.[5,6] M-VARC cTn cut-off point of 70-fold of increase is disputable, with reported values of approximately 500-fold in higher-risk patients who underwent nontranscatheter aortic valve replacement/noncoronary artery bypass graft operations.[14] This threshold has also been observed in this cohort, in which 500-fold of cTn increase best predicted the 30-day and late mortality. It is, however, important to consider that inconsistencies in studies involving cardiac biomarkers studies are attributable, at least in part, to the different assays used and the various patient populations. Further studies with more patients and

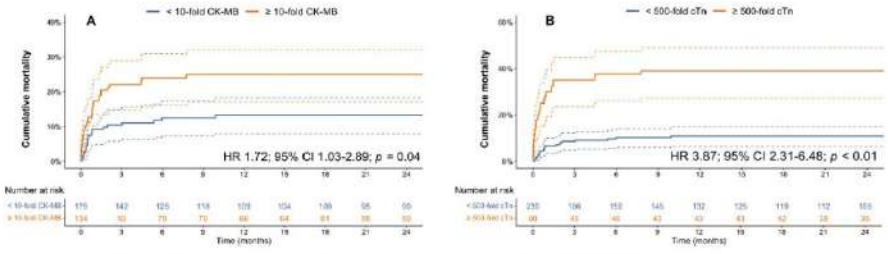

Figure 5. Long-term Kaplan–Meier cumulative mortality according to the percentiles of CK-MB (*A*) and cTn (*B*) increase after the procedure.

events also comparing the approaches of TMVR should further confirm such findings and determine the best cutoff in clinical practice.

This study has some limitations. First, it is an observational analysis with inherent selection bias and significant between-group differences that may not have been accounted, despite performing propensity match scoring and multivariable analysis. Yet, it is important to emphasize that the study population reflects clinical practice, in which patients referred for TMVR are generally older and at a higher operative risk than patients who underwent SMVR-REDO. In addition, patients with concomitant coronary artery disease interventions have been excluded from the analysis; therefore, a conclusion on the potential impact of its presence on cardiac biomarkers magnitude of increase cannot be established.

In conclusion, TMVR and SMVR-REDO resulted in increased CK-MB and cTn levels, with a **2- to 3-fold** higher increase in SMVR-REDO than in TMVR. Higher CK-MB and cTn levels were associated with increased late mortality, regardless of the choice of intervention. Lastly, this study demonstrated that a CK-MB increase ≥10-folds and cTn ≥500-fold from baseline appear to be the optimal thresholds to define clinically relevant myocardial injury after the procedure.

Declaration of competing interest

Dr. José Honório de Almeida Palma da Fonseca is proctor and has received research grant from Braile Biomédica. Dr. Van Mieghem is consultant and has received research grant from Edwards Lifesciences. Dr. Abizaid is proctor for Boston Scientific and has received research grant from Medtronic. Dr. de Brito Jr is proctor for Edwards Lifesciences, Medtronic, and Boston Scientific and received research grant from Medtronic. Dr. Ribeiro is proctor for Edwards Lifesciences, Medtronic, and Boston Scientific and received research grant from Medtronic. The remaining authors have no competing interest to declare.

CRediT authorship contribution statement

Mauricio Felippi de Sá Marchi: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Visualization, Writing – original draft, Writing – review & editing. **Vitor Emer Egypto Rosa:** Conceptualization, Methodology, Supervision, Writing – review & editing. **Pedro Felipe Gomes Nicz:** Data curation, Investigation, Writing – review & editing. **José Honório de Almeida Palma da Fonseca:** Resources, Writing – review & editing. **Pedro Calomeni:** Data curation, Formal analysis, Methodology, Writing – review & editing. **Fernando Chiodini:** Data curation, Investigation, Writing – review & editing. **Roney Orismar Sampaio:** Resources, Writing – review & editing. **Pablo Maria Alberto Pomerantzeff:** Resources, Writing – review & editing. **Marcelo de Campos Vieira:** Resources, Writing – review & editing. **Flávio Tarasoutchi:** Resources, Writing – review & editing. **Nicolas M. Van Mieghem:** Supervision, Writing – review & editing. **Alexandre Abizaid:** Supervision, Writing – review & editing. **Henrique Barbosa Ribeiro:** Conceptualization, Methodology, Project administration, Supervision, Writing – review & editing.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2023.12.009.

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5 ARTICLE 3

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NEW RESEARCH PAPER

STRUCTURAL

Clinical and Hemodynamic Outcomes of Balloon-Expandable Mitral Valve-in-Valve Positioning and Asymmetric Deployment

The VIVID Registry

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ABSTRACT

BACKGROUND Mitral valve-in-valve (ViV) is associated with suboptimal hemodynamics and rare left ventricular outflow tract (LVOT) obstruction.

OBJECTIVES This study aimed to determine whether device position and asymmetry are associated with these outcomes.

METHODS Patients undergoing SAPIEN 3 (Edwards Lifesciences) mitral ViV included in the VIVID (Valve-in-Valve International Data) Registry were studied. Clinical endpoints are reported according to Mitral Valve Academic Research Consortium definitions. Residual mitral valve stenosis was defined as mean gradient ≥5 mm Hg. Depth of implantation (percentage of transcatheter heart valve [THV] atrial to the bioprosthesis ring) and asymmetry (ratio of 2 measures of THV height) were evaluated.

RESULTS A total of 222 patients meeting the criteria for optimal core lab evaluation were studied (age 74 ± 11.6 years; 61.9% female; STS score = 8.3 ± 7.1). Mean asymmetry was 6.2% ± 4.4%. Mean depth of implantation was 19.0% ± 10.3% atrial. Residual stenosis was common (50%; mean gradient 5.0 ± 2.6 mm Hg). LVOT obstruction occurred in 7 cases (3.2%). Implantation depth was not a predictor of residual stenosis (OR: 1.19 [95% CI: 0.92-1.55]; $P = 0.184$), but more atrial implantation was protective against LVOT obstruction (0.7% vs 7.1%; $P = 0.009$; per 10% atrial, OR: 0.48 [95% CI: 0.24-0.98]; $P = 0.044$). Asymmetry was found to be an independent predictor of residual stenosis (per 10% increase, OR: 2.30 [95% CI: 1.10-4.82]; $P = 0.027$).

CONCLUSIONS Valve stenosis is common after mitral ViV. Asymmetry was associated with residual stenosis. Depth of implantation on its own was not associated with residual stenosis but was associated with LVOT obstruction. Technical considerations to reduce postdeployment THV asymmetry should be considered.
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ABBREVIATIONS AND ACRONYMS

BEV = balloon-expandable valve

BVF = bioprosthetic valve fracture

ID = internal diameter

LVOT = left ventricular outflow tract

STS = Society of Thoracic Surgeons

THV = transcatheter heart valve

ViV = valve-in-valve

Implantation of transcatheter heart valves (THV) in failed mitral bioprostheses, also known as mitral valve-in-valve (ViV), is a less invasive approach to patients with failed bioprosthetic valves. Two large analyses, one from the VIVID (Valve-in-Valve International Data) Registry[1] and another from the TVT (Transcatheter Valve Therapy) Registry,[2] have established the safety and effectiveness of transcatheter mitral ViV. These analyses have also demonstrated some adverse events, including residual valve stenosis and left ventricular outflow tract (LVOT) obstruction. Elevated postprocedural gradients are present in the majority of mitral ViV patients,[1] and in severe conditions, have been associated with worse outcomes.[3] LVOT obstruction is an uncommon adverse event observed in approximately 2% of contemporary mitral ViV cases[3] and is associated with high mortality.[2]

Previous data from aortic ViV experience have shown that THV position may affect hemodynamic results, with a more supra-annular implantation being associated with lower gradients.[4-6] The mechanism explaining this difference relates to constriction of the functional area of the THV by the surgical valve ring,[4] which suggests that incomplete or asymmetric expansion of the THV could also lead to worse hemodynamics. Theoretically, the same mechanism could apply to the mitral position. However, supra-annular (in the mitral case, more ventricular) implantation may potentially lead to LVOT obstruction. To our knowledge, there have been no studies assessing THV positioning and symmetric expansion in mitral ViV. Our objectives with the current analysis were the following: 1) to evaluate the relationship between THV position in relation to the surgical valve and residual stenosis; 2) to evaluate the relationship between THV position in relation to the surgical valve and LVOT obstruction; and 3) to evaluate whether asymmetric valve expansion affects hemodynamic results.

METHODS

DATA COLLECTION, INCLUSION, AND EXCLUSION CRITERIA. The VIVID Registry is an established international multicenter registry collecting cases of THV implantation in failed surgical valves.[7] Deidentified data were collected through the use of an electronic case report form. Cases were included in the registry after local institutional review board approval. The study was deemed exempt by the Yale University Institutional Review Board (2000034743). Inconsistencies and missing information in the dataset were resolved through direct contact with the participating investigators by the registry team. Among cases of mitral ViV, we selected cases performed with the SAPIEN 3 (Edwards Lifesciences) balloon-expandable valve (BEV) and excluded other THVs. Fluoroscopic still frames with good perpendicularity of the BEV in its final position were required for inclusion. Given the need for estimation of the depth of implantation, we excluded cases without fluoroscopic markers of the surgical valve ring (eg, Mosaic [Medtronic] and homografts) or cases requiring implantation of a second THV. We also excluded cases with missing follow-up or post-implantation hemodynamics.

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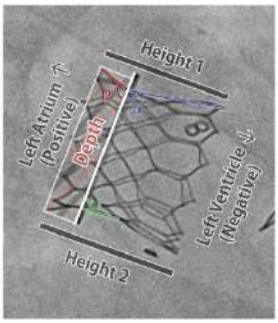
FIGURE 1 Depth of Implantation Was Assessed by Dividing the Depths by the Heights of the THV



Depth (%)

$$100\left(\frac{\text{Depth 1} + \text{Depth 2}}{\text{Height 1} + \text{Height 2}}\right)$$

Asymmetry index (%)

$$100\left(\frac{\text{Longer height}}{\text{Shorter height}} - 1\right)$$

Angles (°)

α: Angle between ring and top of THV

β: Angle between ring and bottom of THV

γ: Angle between ring and belly of THV

A more positive depth represents a more atrial implantation. The asymmetry index is assessed by dividing the longer height by the shorter height. Formulas for calculation of these parameters are also described in the figure. Three different angles were measured for all included cases: the angle between the ring and the top of the transcatheter heart valve (THV) (α), the angle between the ring and the bottom of the THV (β), and the angle between the ring and the belly (ie, area of greatest compression) of the THV (γ).

DEFINITIONS. Clinical endpoints are reported per MVARC (Mitral Valve Academic Research Consortium) criteria.[8] Residual stenosis was defined as final postprocedural mean gradient ≥5 mm Hg.[8] LVOT obstruction was defined as outflow mean gradient increase ≥10 mm Hg[8] or cardiogenic shock that was clinically related to the obstruction as reported by the submitting center.[1] The mechanism of bioprosthetic valve failure was defined according to European Association of Echocardiography and American Society of Echocardiography criteria.[9] The presence of at least moderate mitral regurgitation and mitral stenosis was defined as mixed failure. Surgical risk was estimated by the Society of Thoracic Surgeons (STS) score. Chronic kidney disease was defined as estimated glomerular filtration rate ≤60 mL/min/1.73 m^2 (ie, stage III and above). The true internal diameter (ID), type of leaflet, and height for each model and size of surgical valve was derived from prior publications[10] and from the Valve-in-Valve Digital Application (Dr Vinayak Bapat, Minneapolis Heart Institute Foundation, Minneapolis, Minnesota).

MEASUREMENT TECHNIQUE. A core lab measured all included pictures. The bottom of the surgical valve ring serves as the reference line for calculation of the depth. The shorter and longer heights of the THV were measured with image processing software (Photoshop 23.5.0, Adobe). THV height was defined as the distance between the upper and lower struts of the device on each of the 2 extremes of the "flattened" THV in the fluoroscopic still frame. In addition, as a secondary analysis, we measured 3 different angles between the THV and the surgical valve ring, again on the 2 extremes of the "flattened" THV. First, we measured the angle between the surgical valve ring and the top of the THV. Second, we measured the angle between the surgical valve ring and the bottom of the THV. Finally, we measured the angle between the surgical valve ring and the "belly" (ie, area of greatest compression) of the THV (Figure 1). The asymmetry index was defined as the ratio of the heights of the THV and refers to the symmetry of THV expansion.

$$Asymmetry\ index\ (\%) = 100\left(\frac{Longer\ height}{Shorter\ height} - 1\right)$$

An asymmetry index of 0% indicates that the THV is symmetrical. The depth technique employed in this analysis is similar to the technique previously employed for aortic ViV.[4-6] The depth (ie, the percent of the THV located atrial to the surgical valve ring) was measured on both sides of the THV (Figure 1). Heights and the depths are averaged.

$$Average\ depth\ (\%) = 100\left(\frac{Depth\,1 + Depth\,2}{Height\,1 + Height\,2}\right)$$

STATISTICAL ANALYSIS. Results are presented as mean ± SD or median (IQR) for continuous variables, and percentage for categorical data. Student's *t*-test was used to compare means of normally distributed continuous variables between 2 groups. The independent samples Mann-Whitney *U* test was used to

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TABLE 1 Baseline Characteristics Stratified by Degree of Asymmetry

	Total (N = 222)	Low Asymmetry (n = 180)	High Asymmetry (n = 42)	*P* Value
Male, %	38.1	38.4	36.6	0.828
Age, y	74.0 ± 11.6	73.8 ± 12.0	74.9 ± 9.6	0.581
Height, cm	165.7 ± 9.5	166.0 ± 9.7	164.8 ± 9.1	0.474
Weight, kg	71.6 ± 15.3	72.4 ± 15.5	68.5 ± 14.4	0.15
Body mass index, kg/m^2	26.2 ± 4.7	26.3 ± 4.8	25.5 ± 4.4	0.352
NYHA functional class				0.002
II	16.4	19.1	4.8	
III	57.7	59.6	50	
IV	25.9	21.3	45.2	
Mechanism of failure				0.311
Mixed failure	41	42.8	33.3	
Regurgitation	19.4	20	16.7	
Stenosis	39.6	37.2	50	
Label size, mm	28.7 ± 2.1	28.8 ± 2.1	28.4 ± 2.0	0.272
True internal diameter, mm	25.6 ± 1.9	25.6 ± 1.9	25.4 ± 1.8	0.586
Diabetes mellitus	19.4	18.6	22.5	0.577
Peripheral vascular disease	6.9	5.6	12.5	0.123
Chronic kidney disease	50.3	50.6	48.6	0.828
Atrial fibrillation	79.1	79.2	78.6	0.929
Cerebrovascular disease	16.7	17.7	12.5	0.426
Chronic lung disease	23.5	24.9	17.5	0.322
Permanent pacemaker	22.3	22.2	22.9	0.935
STS, %	8.3 ± 7.1	8.3 ± 7.0	8.7 ± 7.8	0.709
Baseline hemodynamics				
Left ventricular ejection fraction, %	55.0 ± 11.3	55.3 ± 11.0	53.5 ± 12.6	0.403
Mitral valve area, cm^2	1.36 ± 0.89	1.42 ± 0.94	1.09 ± 0.48	0.097
Maximum gradient, mm Hg	22.6 ± 11.1	22.1 ± 11.0	24.9 ± 11.5	0.314
Mean gradient, mm Hg	11.3 ± 5.8	11.3 ± 6.2	11.1 ± 4.2	0.78
Mitral regurgitation				0.23
None/trace	16.5	17.6	11.1	
Mild	21.8	18.8	36.1	
Moderate	14.1	14.2	13.9	
Moderate to severe	8.7	8.8	8.3	
Severe	38.8	40.6	30.6	

Values are % or mean ± SD.

compare nonparametric variables. Chi-square and Fisher exact tests were used to compare proportions of categorical variables, as appropriate. The Mantel-Haenszel test for trend was used for ordinal variables. The log-rank test was used to compare survival among different groups. Receiver-operating characteristic curves were built to establish cutoffs for the independent variables, selecting the cutoff with the highest combined sensitivity and specificity. Binary logistic regression was used to identify predictors of LVOT obstruction and elevated mean gradients. The following variables were planned for inclusion in the logistic regression models: depth of implantation, asymmetry index, age, sex, body mass index, pericardial valve (vs porcine), surgical valve height, label size, mitral true ID, chronic lung disease, cerebrovascular disease, atrial fibrillation, history of myocardial infarction, peripheral vascular disease, renal failure, diabetes mellitus, mechanism of failure, history of permanent pacemaker, STS score, baseline mean and maximum mitral gradient, baseline left ventricular ejection fraction, moderate or worse mitral regurgitation, and the THV diameter. Variables with a $P < 0.10$ on the univariable model are used to generate a forward stepwise model. ORs with a 95% CI are reported for these models. A 2-tailed *P* value <0.05 was considered statistically significant. Statistical analyses were performed with SPSS 24 software (IBM Corporation).

RESULTS

BASELINE CHARACTERISTICS. A total of 260 images were submitted for core lab evaluation. Of these, we excluded 38 cases (20 with missing follow-up or echocardiographic data, 6 with poor perpendicularity, 6 without visible surgical valve ring, 6 with poor quality). A final number of 222 BEV mitral ViV cases were included in the analysis. Baseline characteristics are described in Table 1. Patients were older (74.0 ± 11.6 years), predominantly female (61.9%), and highly symptomatic (83.6% had NYHA functional class III or IV symptoms). Most patients had either mixed failure (41%) or stenosis (39.6%) as the mechanism of failure. Significant comorbidities included atrial fibrillation (79.1%) and chronic kidney disease (50.3%). Baseline mean gradients were elevated (11.3 ± 5.8 mm Hg), and 61.6% of patients had moderate or worse mitral regurgitation.

PROCEDURAL CHARACTERISTICS, CLINICAL AND HEMODYNAMIC OUTCOMES. Procedural characteristics and outcomes are reported in Table 2. The THVs utilized in the included cases were in the upper range of the BEV sizes, with 61.3% of cases receiving a 29-mm valve. The majority of cases were treated with transseptal access (74.6%). Rates of technical success were high (96.4%), but device success was low (47.7%) due to high incidence of residual stenosis (mean gradient ≥5 mm Hg; 50%). The average post-procedural mean gradient was 5.0 ± 2.6 mm Hg. A total of 7 cases (3.2%) developed LVOT obstruction.

DEPTH OF IMPLANTATION, ASYMMETRY INDEX, AND OUTCOMES. The mean asymmetry index was 6.2% ± 4.4%, and the mean depth of implantation was 19.0% ± 10.3%. Receiver-operating characteristic curve analysis (Supplemental Figure 1) showed that the asymmetry index was specific for residual stenosis (cutoff 10.3%; sensitivity 24.3%, specificity 90.1%;

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TABLE 2 Procedural Outcomes Stratified by Degree of Asymmetry

	Total (N = 222)	Low Asymmetry (n = 180)	High Asymmetry (n = 42)	P Value
Transcatheter heart valve diameter, mm	27.8 ± 1.6	27.8 ± 1.6	27.8 ± 1.5	0.993
Access				0.572
Transseptal	74.6	73.2	81.1	
Transapical	24.9	26.2	18.9	
Other	0.5	0.6	0	
General anesthesia	95.2	94.7	97.2	0.53
Transesophageal echocardiography	97.4	97.4	97.2	0.951
Preinflation	14.6	13.9	17.6	0.577
Postinflation	7.8	9	2.4	0.158
Vascular complications				0.511
Minor	1.8	2.2	0	
Major	1.4	1.1	2.4	
Major bleeding complication	3.2	3.4	2.4	0.742
Major stroke	0.9	0.6	2.4	0.264
Acute kidney injury	4.6	4	7.1	0.378
Technical success	96.4	97.2	92.9	0.172
Device success	47.7	51.1	33.3	0.038
Left ventricular outflow tract obstruction	3.2	2.2	7.1	0.127
Hospital stay, d	8 (5-13)	8.5 (5-13)	7 (3-16.5)	0.601
Positioning details				
Average depth, %	19.0 ± 10.3	19.5 ± 10.5	17.0 ± 9.2	0.151
Asymmetry index, %	6.2 ± 4.4	4.5 ± 2.6	13.3 ± 3.0	<0.001
Maximum angle, top of THV and ring, °	98.5 ± 4.0	98.5 ± 3.8	98.4 ± 5.0	0.972
Maximum angle, bottom of THV and ring, °	105.5 ± 7.8	105.2 ± 7.8	107.0 ± 7.7	0.19
Maximum angle, belly of THV and ring, °	90.5 ± 6.1	90.5 ± 6.0	90.5 ± 6.7	0.974
Minimum angle, top of THV and ring, °	91.8 ± 4.2	92.0 ± 3.3	90.7 ± 6.8	0.212
Minimum angle, bottom of THV and ring, °	96.5 ± 6.3	96.3 ± 6.2	97.5 ± 6.6	0.274
Minimum angle, belly of THV and ring, °	82.9 ± 6.4	83.2 ± 6.5	81.8 ± 5.7	0.216
Average angle, top of THV and ring, °	95.1 ± 3.1	95.2 ± 2.7	94.5 ± 4.3	0.188
Average angle, bottom of THV and ring, °	101.0 ± 6.1	100.7 ± 6.1	102.2 ± 6.0	0.159
Average angle, belly of THV and ring, °	86.7 ± 5.2	86.8 ± 5.2	86.2 ± 5.1	0.458
Post-procedural hemodynamics				
Left ventricular ejection fraction, %	54.4 ± 11.4	54.4 ± 11.6	54.6 ± 10.7	0.931
Mitral valve area, cm^2	2.10 ± 0.70	2.15 ± 0.71	1.85 ± 0.66	0.137
Maximum gradient, mm Hg	10.9 ± 4.9	10.3 ± 4.4	13.7 ± 6.0	0.006
Mean gradient, mm Hg	5.0 ± 2.6	4.8 ± 2.7	5.6 ± 2.5	0.098
Mean gradient ≥5 mm Hg	50	46.7	64.3	0.04
Mitral regurgitation				0.604
None/trace	86.7	87.1	85	
Mild	11.5	11.2	12.5	
Moderate	0.9	0.6	2.5	
Moderate to severe	0	0	0	
Severe	0.9	1.1	0	

Values are mean ± SD, %, or median (Q1-Q3).
THV = transcatheter heart valve.

area under the curve 0.58; $P = 0.038$). Depth of implantation failed to classify patients for residual stenosis ($P = 0.14$) but was able to significantly discriminate cases with LVOT obstruction (cutoff 15.9%; sensitivity 63.7%, specificity 85.7%; area under the curve 0.74; $P = 0.032$).

Cases were further stratified according to the aforementioned cutoffs (asymmetry: <10% [low asymmetry] vs ≥10% [high asymmetry]; depth: <16% [more ventricular implantation] vs ≥16% [more atrial implantation]). Baseline characteristics are presented in Table 1 and Supplemental Table 1, respectively. The groups were well-matched. However, there were more patients with NYHA functional class IV symptoms in the high asymmetry group (45.2% vs 21.3%; $P = 0.002$) and baseline mean gradients were higher in the more ventricular implantation group (12.4 ± 6.1 mm Hg vs 10.6 ± 5.6 mm Hg; $P = 0.04$).

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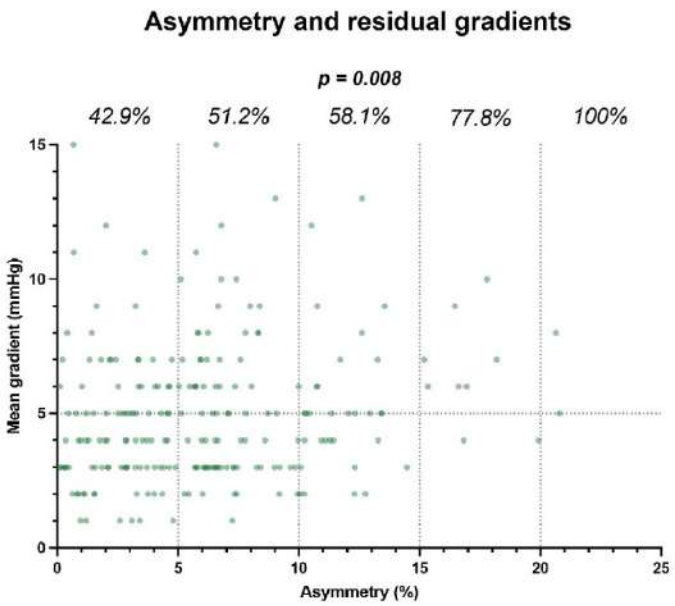
FIGURE 2 More Transcatheter Heart Valve Asymmetry Was Associated With Increased Incidence of Residual Stenosis



Cases with high asymmetry (≥10% asymmetry index) were associated with significantly higher rate of residual stenosis (64.3% vs 46.7%; $P = 0.04$) (Table 2). This difference was more pronounced when only cases with mitral true ID ≤24 mm were considered (87.5% vs 47.7%; $P = 0.04$). Increasing asymmetry levels were associated with increased incidence of residual stenosis (Figure 2). There were no differences in the measured angles of cases with high asymmetry vs cases with low asymmetry. Final maximum gradients were higher in the high asymmetry group (13.7 ± 6.0 mm Hg vs 10.3 ± 4.4 mm Hg; $P = 0.006$) with a trend towards higher mean gradients ($P = 0.098$) (Table 2). The rate of balloon postdilatation was numerically lower but not significantly different in the high asymmetry group (2.4% vs 9% low asymmetry; $P = 0.158$). There was no difference in the degree of asymmetry by access site (6.4 ± 4.3% transseptal vs 5.4% ± 4.3% transapical; $P = 0.159$).

There was no difference in the rate of residual stenosis among depth of implantation groups (44.7% vs 53.3%; $P = 0.21$) (Figure 3A). Cases with more ventricular position were associated with a significantly higher risk of LVOT obstruction (7.1% vs 0.7% low positioning; $P = 0.009$) (Figures 3B, Supplemental Table 2). Mean depth (percent atrial) in the LVOT obstruction cases was 11.3%, compared with 19.3% in the cases without obstruction ($P = 0.043$). Cases with more ventricular implantation were deployed with smaller (ie, less flared) angles than those with more atrial implantation (Supplemental Table 2). Regarding other outcomes, cases with more ventricular implantation were associated with lower final left ventricular ejection fraction (51.4% ± 12.5% vs 55.7% ± 10.7%; $P = 0.027$). Median duration of follow-up for survival was 371.5 [Q1-Q3: 36.0-765.5] days. There was no difference in survival between patients in different implantation groups ($P = 0.959$) nor between patients with more vs less asymmetry ($P = 0.397$).

We then divided our cohort into 4 groups based on the degree of asymmetry and depth of implantation: high asymmetry (asymmetry ≥10%) and more atrial implantation (depth ≥16%) (least optimal implantation); high asymmetry and more ventricular implantation (depth <16%); low asymmetry (asymmetry <10%) and more atrial implantation; and finally, low asymmetry and more ventricular

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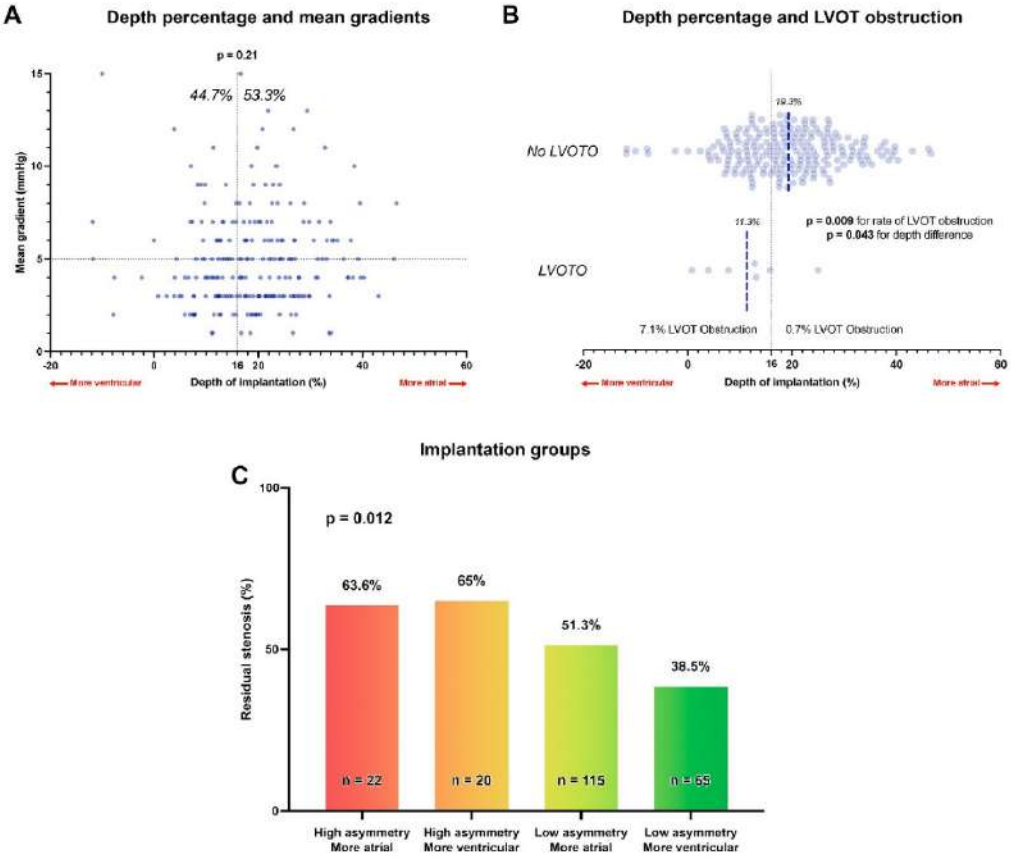
FIGURE 3 Scatter Plots for Depth and Residual Stenosis



There was no difference identified in the rate of residual stenosis by depth (A). Cases with left ventricular outflow tract (LVOT) obstruction were on average implanted in a more ventricular direction (B). Cases with less asymmetry and more ventricular positioning had lower incidence of residual stenosis when compared with those with more asymmetry and atrial positioning (C).

implantation (most optimal implantation, at least from a hemodynamic perspective). Cases in the least optimal group had a rate of residual stenosis of 63.6%, compared with 38.5% in the most optimal group ($P = 0.012$) (Figure 3C).

REGRESSION ANALYSES. Predictors of residual stenosis in univariable analysis were greater asymmetry, smaller THV diameter, mitral true ID, STS score, history of permanent pacemaker, and atrial fibrillation. In the multivariable analysis, greater asymmetry was independently associated with residual stenosis (per 10% increase OR: 2.30; 95% CI: 1.10-4.82; $P = 0.027$) and THV size (per 1-mm increase OR: 0.81; 95% CI: 0.66-0.99; $P = 0.039$) (Figure 4A, Supplemental Table 3). More atrial implantation was associated with reduced risk of LVOT obstruction (per 10% atrial OR: 0.48; 95% CI: 0.24-0.98; $P = 0.044$) (Figure 4B, Supplemental Table 4). There were no other identified predictors of LVOT obstruction.

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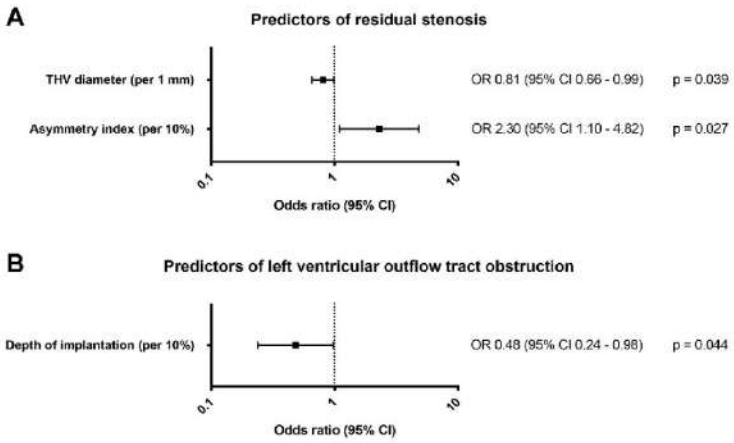
FIGURE 4 Predictors of Residual Stenosis and LVOT Obstruction



Predictors for residual stenosis in multivariable analysis (A) were increase in the asymmetry index, as well as decreasing THV diameter. Depth of implantation was a predictor for LVOT obstruction (B). There were no other predictors identified for LVOT obstruction in the current dataset. Abbreviations as in Figures 1 and 3.

DISCUSSION

In this multicenter analysis from the VIVID Registry, we performed a core lab evaluation of the association between BEV position and expansion in mitral ViV with clinical and hemodynamic outcomes. Main findings (**Central Illustration**) include: 1) more ventricular implantation of the BEV in mitral ViV is associated with an increased risk of LVOT obstruction with no evidence of improved transvalvular diastolic mitral gradients; and 2) asymmetrical expansion of the BEV was strongly associated with elevated postprocedural gradients with a cutoff of asymmetry index ≤10% for optimal valve function.

Mitral ViV is a well-established, less invasive procedure supported by a large body of literature, demonstrating relatively low mortality compared with what would be expected with surgery, rapid recovery, and a low rate of major complications.[1,2,11–15] Limitations include a high incidence of residual stenosis and potentially deadly LVOT obstruction. Data from the VIVID Registry have shown a rate close to 60% of elevated mean gradients.[1] This has been reproduced in multiple other analyses,[11–13,15] with relevant clinical consequences. It has been previously shown that postprocedural mean gradients ≥10 mm Hg are associated with over 4-fold risk of mitral valve reintervention and persistent symptoms.[1] Another group described worse mortality and higher gradients at 1 year in patients treated with small BEVs (≤23 mm),[2] which highlights the importance of prosthesis–patient mismatch.

Therefore, strategies to reduce the risk of residual gradients are needed. We have described a novel and clinically relevant parameter for mitral ViV operators. The asymmetry index is a simple measure that can be easily assessed in the catheterization laboratory after implantation. Asymmetry was found to be an independent predictor of elevated mean gradients for mitral ViV, controlling for THV size and true ID, among other variables (**Figure 5**). Asymmetric implantation was common in the current analysis, with almost 20% of cases showing significant (ie, ≥10%) asymmetry. Asymmetry seems to behave separately from the angular relationship between the surgical valve ring and the THV. Asymmetry may lead to poor leaflet opening and coaptation, contributing to higher gradients. This mechanism could have even greater implications for mitral ViV. For example, it is possible that asymmetry would lead to more structural valve degeneration. Evidence from computational finite element analysis suggests that poor THV expansion creates high-stress regions in the commissures and THV leaflets, potentially reducing durability.[17]

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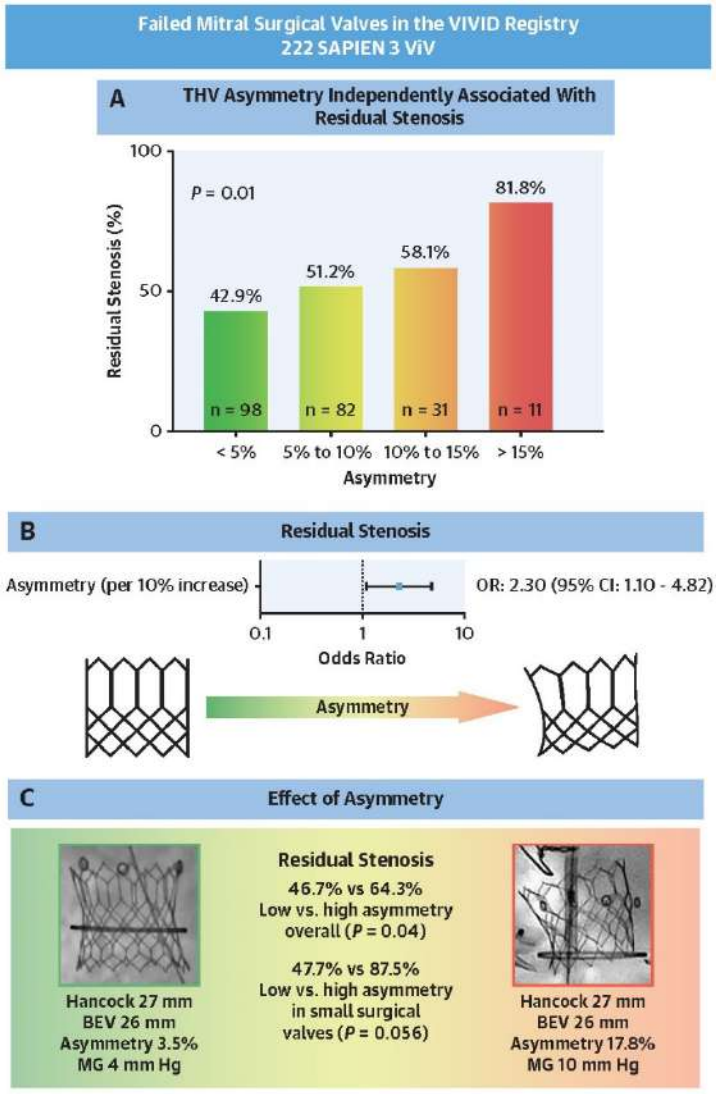
CENTRAL ILLUSTRATION **Transcatheter Heart Valve Asymmetry and Outcomes for Mitral Valve-in-Valve Cases**



Simonato M, et al. J Am Coll Cardiol Intv. 2023;16(21):2615-2627.

(A) Controlling for transcatheter heart valve (THV) size and valve true internal diameter, the extent of THV asymmetry was significantly associated with residual stenosis. (B) A 10% increase in THV asymmetry was associated with a twofold increase in the odds of residual stenosis. (C) The effect of asymmetry was sharper in patients with small (true internal diameter ≤23 mm) surgical valves.
BEV = balloon-expandable valve; MG = mean gradient; ViV = valve-in-valve.

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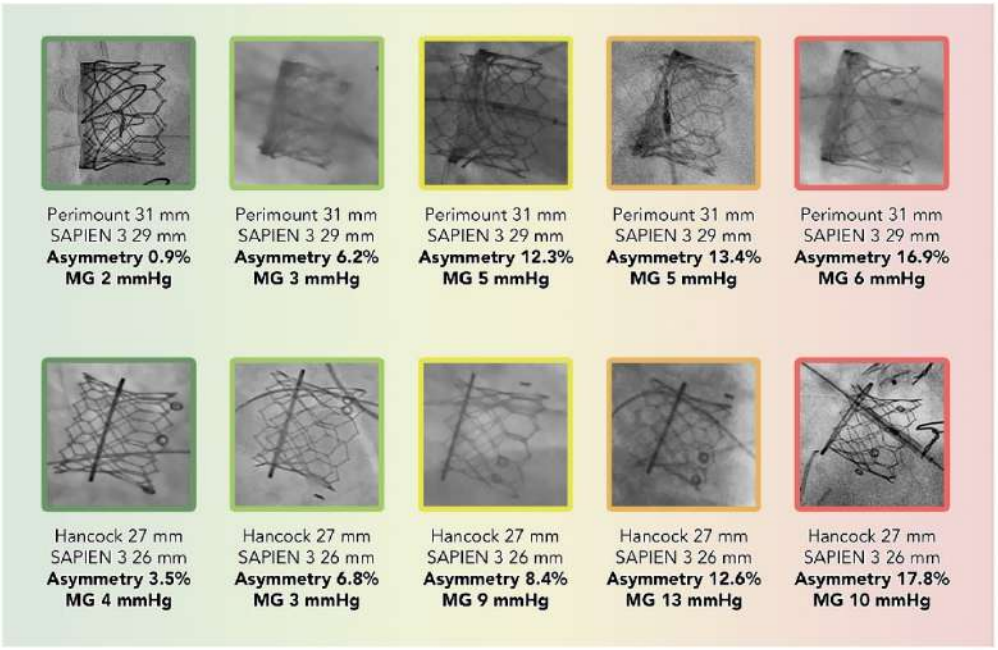
FIGURE 5 Selected Cases Demonstrating Gradually Increasing Asymmetries in 2 Different Surgical Valve Models



Note the higher gradients reached in asymmetric transcatheter heart valves implanted in a small surgical valve (lower row; Hancock 27 mm has a true internal diameter of 22 mm). MG = mean gradient.

In addition, asymmetry could lead to increased thrombosis. In 1 study, the rate of thrombosis after transcatheter mitral valve replacement ranged from 1% to 6%, depending on the use of anticoagulation, and was most frequent after mitral ViV.[11] In vitro data indicate underexpansion of the BEV may lead to increased blood stasis, thereby increasing the risk of THV thrombosis.[18] The relationship of incomplete expansion and thrombosis has been documented in the aortic field.[19] Further study would be necessary to correlate the asymmetry index to these outcomes.

Asymmetry may be minimized through optimal deployment techniques. Preprocedural imaging may help optimize transseptal access,[20,21] because a suboptimal puncture site could lead to poor coaxiality with the mitral surgical apparatus and asymmetric expansion. Wire selection, such as favoring a stiffer wire, may also improve coaxiality. Adjunctive techniques such as bioprosthetic valve fracture (BVF) may also be relevant. BVF will allow for more complete expansion of the THV, although this should probably be reserved for more extreme cases because data for mitral BVF are currently limited to case reports.[22] The use of a smaller THV device (perhaps with an overfilled balloon) may also allow for symmetric valve expansion when dealing with excessive constraint by the failed bioprosthesis, but this may also result in a smaller effective orifice area. Balloon postdilation could also improve asymmetry, but in the current analysis, no significant difference was seen in its rate among asymmetry groups. Finally, future iterations of THV delivery systems may allow for greater THV maneuverability with coaxial delivery and symmetrical expansion.

Depth of implantation has been shown in aortic ViV to be associated with lower gradients. In 1 study of 113 aortic ViV cases, supra-annular implantation was associated with a rate of elevated gradients of 3.6%, compared with 25% of cases with deep implantation.[6] Pulse duplicator models also for the aortic position

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have demonstrated the linear relationship between depth of implantation, effective orifice area, and mean gradient, showing that deep implantation leads to poor THV expansion and leaflet coaptation.[4] In the current analysis, we were unable to identify a clear association between depth of implantation and elevated gradients. There are a few explanations for this. First, mitral surgical valves are on average larger than their aortic counterparts, which may obviate some of the impact of depth of implantation. Second, the ventricular implantation group had worse stenosis at baseline, which may have contributed to no difference being found. However, although the baseline mean gradient was higher in the ventricular implantation group, the actual true ID was, even if only slightly, larger. Nevertheless, we did identify that the combination of low asymmetry and more ventricular positioning may be protective against residual stenosis, but positioning did not appear to influence hemodynamic outcomes if the degree of asymmetry was elevated.

The other major clinical issue in mitral ViV is LVOT obstruction. The rate of LVOT obstruction in mitral ViV ranges from 0.9% to 1.8% in large registries.[1,2] LVOT obstruction is a potentially deadly complication, with as much as 20% 30-day mortality.[2] In the current analysis, we have shown that cases with more ventricular implantation can have a rate of LVOT obstruction 10 times higher than cases with more atrial implantation. Additionally, depth of implantation was the only predictor of LVOT obstruction in the current analysis. Mechanistically, a valve implanted in a more ventricular direction will displace the surgical valve leaflets more and lead to the complication. It is possible to predict the risk of developing LVOT obstruction, with sensitivity and specificity ranging from 90% to 100%, through computed tomography measures such as the neo-LVOT and the skirt neo-LVOT.[23-25] Once a case at high risk is identified, operators should make every effort to position the valve in a more atrial direction, especially since gradients do not seem to be severely impacted. Techniques such as LAMPOON, ShortCut (Pi-Cardia), or ventricular septal ablation can also be employed as part of the arsenal to prevent this complication.[26,27]

STUDY LIMITATIONS. There were insufficient cases of mean gradient ≥10 mm Hg to evaluate the association of asymmetry with more severe gradient elevations. Computed tomography–derived measures, including neo-LVOT, were not consistently available to better stratify cases at risk for LVOT obstruction and evaluate the association of depth of implantation in a more selected population. There was also insufficient data to evaluate other parameters such as annular calcification and anatomic relationships between the mitral and aortic valve. We did not systematically evaluate THV thrombosis in the current data. Longer term clinical and echocardiographic follow-up would be necessary to evaluate the effects of depth and asymmetry on durability.

CONCLUSIONS

Mitral ViV with BEV may be complicated by elevated mean gradients and LVOT obstruction. Asymmetric implantation was associated with higher incidence of residual stenosis. Atrial BEV implantation on its own did not increase the risk of residual stenosis but was protective against LVOT obstruction. Nevertheless, the combination of depth of implantation and asymmetry may be hemodynamically significant. Implementing these findings may reduce complications and potentially improve long-term durability of the procedure.

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Dr Whisenant is a consultant for Edwards Lifesciences. Dr Unbehaun is a proctor for Edwards Lifesciences. Dr Erlebach has received speaker honoraria from Medtronic and Abbott; and is a proctor for Abbott. Dr Guerrero has received institutional research grant support from Edwards Lifesciences. Dr Bruschi is a consultant for Abbott. Dr Rudolph has received speaker honoraria from Edwards Lifesciences; and is a proctor for Edwards Lifesciences. Dr Andreas is a consultant for Edwards Lifesciences, Abbott, Medtronic, Boston Scientific, Zoll, and AbbVie; and has received institutional research grants from Edwards Lifesciences, Abbott, Medtronic, and LSI. Dr Dvir is a consultant for Edwards Lifesciences. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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PERSPECTIVES

WHAT IS KNOWN? Mitral ViV implantation is safe and effective but may be complicated by residual gradients and LVOT obstruction. The effect of THV position and symmetry on clinical and hemodynamic outcomes is unknown.

WHAT IS NEW? In a core lab analysis of 222 balloon-expandable mitral ViV implants, we have found that asymmetric THV expansion predicts post-procedural residual stenosis independent of the mitral valve true internal diameter and THV size. Depth of implantation was not associated with post-procedural gradients, but more ventricular THV implantation was associated with an increased incidence of LVOT obstruction.

WHAT IS NEXT? Operators should aim for THV symmetry and complete expansion in mitral ViV. Improvements in transseptal access and delivery systems, and also the use of adjunct procedures such as bioprosthetic valve fracture may facilitate symmetric expansion. Operators should also avoid excessively ventricular THV deployment especially in cases at higher risk of LVOT obstruction, considering there is possibly no hemodynamic benefit of a more ventricular implantation.

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KEY WORDS depth of implantation, left ventricular outflow tract obstruction, mitral valve-in-valve, positioning, residual stenosis, SAPIEN 3

APPENDIX For a supplemental figure and tables, please see the online version of this paper.

6 ARTICLE 4

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Comparative analysis of different risk prediction tools after mitral Transcatheter edge-to-edge repair

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ABSTRACT

Background: Transcatheter edge-to-edge repair (TEER) has become an established treatment for primary and secondary mitral regurgitation (PMR and SMR). The objective of this study was to compare the accuracy of different risk scores for predicting 1-year mortality and the composite endpoint of 1-year mortality and/or heart failure (HF) hospitalization after TEER.

Methods: We analyzed data from 206 patients treated for MR at a tertiary European center between 2011 and 2023 and compared the accuracy of different mitral and surgical risk scores: EuroSCORE II, GRASP, MITRALITY, MitraScore, TAPSE/PASP-MitraScore, and STS for predicting 1-year mortality and the composite of 1-year mortality and/or HF hospitalization in PMR and SMR. A subanalysis of SMR-only patients with the addition of COAPT Risk Score and baseline N-Terminal pro-Brain Natriuretic Peptide (NT-proBNP) list was also performed.

Results: MITRALITY had the best discriminative ability for 1-year mortality and the composite endpoint of 1-year mortality and/or HF hospitalization, with an area under the curve (AUC) of 0.74 and 0.74, respectively, in a composed group of PMR and SMR. In a SMR-only population, MITRALITY also presented the best AUC for 1-year mortality and the composite endpoint of 1-year mortality and/or HF hospitalization, with values of 0.72 and 0.72, respectively.

Conclusion: MITRALITY was the best mitral TEER risk model for both 1-year mortality and the composite endpoint of 1-year mortality and/or HF hospitalization in a population of PMR and SMR patients, as well as in SMR patients only. Surgical risk scores, MitraScore, TAPSE/PASP-MitraScore and NT-proBNP alone showed poor predictive values.

1. Introduction

Mitral regurgitation (MR) is a common heart valvular disorder with impaired quality of life and overall survival. [1,2] MR is classified as primary (PMR), when its etiology is attributable to a structural or degenerative change in the mitral leaflets; and secondary (SMR), when MR occurs in the absence of primary mitral valve disease, usually as a consequence of left ventricular or atrial dysfunction [3]. Transcatheter edge-to-edge repair (TEER) is a minimally invasive procedure that has emerged as an effective treatment option for selected patients with PMR and SMR [4,5].

However, not all MR patients respond in the same way to TEER [6,7]. The validity of traditional surgical risk scores, such as STS and EuroSCORE II, in predicting outcomes post-TEER remains uncertain, with modest predictive accuracy for 1-year mortality [8]. Hence, a major effort has been made to develop accurate risk stratification scores to improve TEER patient selection. Multiple models have been developed for this purpose, including COAPT, GRASP, MITRALITY, and MitraScore [9–12]. Furthermore, novel models with additional echocardiographic data emerged to improve the accuracy of established scores, such as the

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addition of tricuspid annular plane systolic excursion (TAPSE) and pulmonary artery systolic pressure (PASP) ratio to MitraScore [13]. Finally, N-Terminal pro-Brain Natriuretic Peptide (NT-proBNP) has also been shown to have valuable predictive ability for mortality and heart failure (HF) hospitalization after TEER and is a core variable in some risk score models [10,11].

The objective of this study was to compare the accuracy of different risk prediction tools for 1-year mortality and the composite endpoint of 1-year mortality and/or heart failure (HF) hospitalization in patients after TEER for MR at a European tertiary center.

2. Methods

2.1. Study population and protocol

This single-center retrospective study included consecutive patients treated for MR at Erasmus University Medical Center between 2011 and 2023. Indications for TEER included PMR and SMR. The choice of device (MitraClip and PASCAL), and strategy was left at the discretion of the operators. All procedures were executed by the same first operator (N.M. V.M.). Details regarding MitraClip and PASCAL generations are available in **Supplemental Table 1**. Exclusion criteria for the present study were as follows: (1) previous surgical mitral valve repair or replacement, (2) prior mitral TEER, (3) age < 18 years, (4) mixed MR etiology and (5) no information on MR etiology. The study was approved by the Medical

Table 1
Mitral transcatheter edge-to-edge repair risk scores analyzed.

Risk score	Authors	Population	Outcome and AUC	Variables
Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation (COAPT) risk score, *JACC Cardiovascular Interventions*, 2022 [9]	Shah N, Madhavan MV, Gray WA, Brener SJ, Ahmad Y, Lindenfeld J, et al	Secondary MR patients	2-year mortality and/or HF hospitalization AUC: 0.74	- Chronic kidney disease (CKD): estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73m^2 or lower - New York Heart Association (NYHA) class III or higher - Chronic obstructive pulmonary disease (COPD) - Atrial fibrillation or flutter history - Right ventricular systolic pressure (RVSP) > 45 mmHg or higher - Left ventricle ejection fraction (LVEF): if <35% or lower - Left ventricular end-systolic diameter (LVESD) > 5.5 cm or higher - Tricuspid regurgitation (TR) > mild or greater Guideline-directed medical therapy (GDMT) alone
Getting Reduction of mitrAl inSufficiency by Percutaneous clip implantation (GRASP) Risk Score, *American Journal of Cardiology*, 2017 [10]	Buccheri S, Capodanno D, Barbanti M, Popolo Rubbio A, Di Salvo ME, Scandura S, et al	Primary and secondary MR	1-year mortality AUC: 0.78	- N-terminal pro–brain natriuretic peptide (NT-proBNP) - Mean arterial pressure (MAP) - NYHA class IV - Hemoglobin
MITRALITY score, *JACC Cardiovascular Interventions*, 2021 [11]	Zweck E, Spieker M, Horn P, Iliadis C, Metze C, Kavsur R, et al	Primary and secondary MR	1-year mortality AUC: 0.78	- Blood urea nitrogen (BUN) - Body mass index (BMI) - Hemoglobin - NT-proBNP - Creatinine
MitraScore, *Journal of the American College of Cardiology*, 2022 [12]	Raposeiras-Roubin S, Adamo M, Freixa X, Arzamendi D, Benito-González T, Montefusco A, et al	Primary and secondary MR	1-year mortality AUC All MR: 0.70 AUC Functional MR: 0.69 1-year mortality and/or HF hospitalization AUC All MR: 0.67 AUC Functional MR: 0.65	- Age > 75 years or older - LVEF <40% - Anemia - CKD: if eGFR <60 mL/min/1.73m^2 or lower - Peripheral artery disease - COPD - High dose of diuretic: if >80 mg of furosemide/daily or use of >2 diuretic agents excluding antialdosteronic drugs - No therapy with renin-angiotensin system (RAS) drugs
TAPSE/PASP-MitraScore, *Journal of the American Society of Echocardiography*, 2023 [13]	Sheehter A, Vaturi M, Kaewkes D, Koren O, Koseki K, Solanki A, et al	Primary and secondary MR	1-year mortality and/or HF hospitalization AUC All MR: 0.71 AUC Functional MR: 0.69 1-year mortality AUC All MR: 0.70 AUC Functional MR: 0.67	- TAPSE/PASP ratio of 0.37 added to MitraScore

COAPT Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation; CKD chronic kidney disease; eGFR estimated glomerular filtration rate; COPD chronic obstructive pulmonary disease; RVSP right ventricular systolic pressure; LVEF left ventricle ejection fraction; LVESD left ventricular end-systolic; TR tricuspid regurgitation;
GDMT guideline-directed medical therapy; GRASP Getting Reduction of mitrAl inSufficiency by Percutaneous clip implantation; NT-proBNP N-terminal pro–brain natriuretic peptide; MAP mean arterial pressure; BUN blood urea nitrogen; BMI body mass index; RAS renin-angiotensin system.

Ethics Committee of the Erasmus University Medical Center and the need for individual informed consent was waived due to the retrospective and anonymous nature of the study. The following dedicated scores for mitral TEER were evaluated: COAPT Risk Score [9], GRASP [10], MITRALITY [11], MitraScore [12] and TAPSE/PASP-MitraScore [13], as summarized in Table 1. Two general surgical risk scores were examined: EuroSCORE II and STS [14–16]. Pre-intervention NT-proBNP was analyzed by electrochemical luminescent immunoassay (Cobas 8000; Roche Diagnostics GmbH, Mannheim, Germany). The endpoints of interest were 1-year mortality and the composite endpoint of 1-year mortality and/or HF hospitalization. Clinical outcomes were defined according to M-VARC criteria [17,18]. HF hospitalization was defined by the Universal Definition of HF [19]. Data was obtained from hospital and administrative records from the Dutch National Register of Deceased Persons. Clinical follow-up was assessed at 1 year.

2.2. Doppler echocardiographic measurements

Transthoracic echocardiographic (TTE) examination was performed before mitral intervention and upon hospital discharge. All patients had at least one pre-intervention TTE showing moderate-to-severe or severe MR. Echocardiographic parameters were measured using the methods recommended by the American Society of Echocardiography guidelines [20,21]. MR severity was assessed by TTE using a combination of both qualitative and quantitative parameters, such as effective regurgitant orifice area (EROA), regurgitant volume (RVol), and regurgitant fraction (RF) [22,23].

2.3. Statistical analysis

Categorical variables are reported as n (%). Continuous variables are expressed as mean and standard deviation or median and 25th - 75th percentiles, depending on distribution normality, which was assessed by Kolmogorov-Smirnov test and kernel density plots. All mitral TEER risk scores were reconstructed from baseline variables, based on their description in the original reports [9–16]. To assess the discriminative abilities of the analyzed risk scores and cardiac biomarkers, area under the curves (AUC) were calculated using the R package "pROC" version 1.18.0. All analyzes were performed using R Statistical Software (version 4.3.0, Foundation for Statistical Computing, Vienna, Austria).

3. Results

A total of 237 consecutive patients who received mitral TEER in our center between 2011 and 2023 were evaluated for inclusion. 31 patients were excluded, of which 10 had previous surgical mitral valve repair or replacement, another 10 had undergone prior mitral TEER, 10 had mixed MR, and 1 was under 18 years old. The study population consisted of the remaining 206 patients. Clinical, echocardiographic, procedural characteristics and outcomes of the overall study population and the SMR-only population are shown in Table 2. MitraClip was used in 188 (91%) cases and PASCAL in 18 (9%). PMR was present in 60 (29%) patients and SMR in 146 (71%).

3.1. Clinical outcomes and predictive accuracy of risk prediction tools

After 1 year, 45 patients (22%) in the overall population died. The cumulative endpoint of 1-year mortality and/or HF hospitalization occurred in 69 (33.5%) of the available patients. In the SMR-only population, there were 34 (23%) deaths after 1 year. The composite endpoint of 1-year mortality and/or HF hospitalization occurred in 54 (37%) of the available patients.

ROC curves of the analyzed risk scores for 1-year mortality and the composite endpoint of 1-year mortality and/or HF hospitalization are shown in Fig. 1.**A** and Fig. 1.**B**, respectively. EuroSCORE II score displayed an area under the curve (AUC) value of 0.61 (95% CI: 0.51–0.71)

Table 2
Clinical, echocardiographic, and procedural characteristics of the study population.

	Overall population ($n = 206$)	**SMR-only ($n = 146$)**
Clinical variables		
Age, years	74.5 [67–81.3]	72.9 [65.1–77.6]
Male	134 (65)	96 (66)
Mitral dysfunction etiology		
Primary	60 (29)	
Secondary	146 (71)	146 (100)
NYHA functional class		
II	41 (20)	30 (21)
III-IV	165 (80)	116 (80)
Diabetes mellitus	47 (23)	39 (27)
Hypertension	142 (69)	100 (68)
Prior percutaneous coronary intervention	80 (39)	62 (42)
Prior coronary artery bypass graft	45 (22)	37 (25)
Atrial fibrillation	125 (60)	88 (60)
Cerebrovascular disease	14 (7)	7 (5)
Peripheral vascular disease	26 (13)	20 (14)
Chronic obstructive pulmonary disease	33 (16)	24 (17)
eGFR, mL/min	45 [32–59]	44 [30–57]
Clinical Frailty	85 (41)	55 (38)
STS-PROM score, %	2.8 [1.8–5.5]	2.8 [1.7–5.7]
EuroSCORE II, %	4.8 [2.9–8.3]	5.7 [3.1–9.9]
Hemoglobin (g/dl)	12.7 ± 1.9	12.7 ± 1.8
N-terminal B-type natriuretic peptide (pg/ml)	358 [192–684]	449.3 [240–807]
Echocardiographic variables pre-procedure		
Left atrium size, cm	5.1 [4.7–5.7]	5.1 [4.7–5.7]
Left atrium volume, mm^2	137 [111.9–175.2]	137 [112.5–176.5]
LVEF, %	37 [27–55]	32 [24.2–44.7]
LVESD, cm	5.2 [4.2–6.3]	5.6 [4.7–6.5]
LVEDD, cm	6.2 [5.5–7]	6.4 [5.7–7.2]
LVESV, mL	130 [85–177]	135 [101–194]
LVEDV, mL	189 [146–242]	205 [165–247]
PASP >55, mmHg	32 (19)	25 (21)
TAPSE	18 [14–21]	18 [14–20]
Right ventricle systolic pressure, mmHg	43 [32–58]	41 [32.7–56]
RVPA coupling, ratio	0.41 [0.28–0.57]	0.38 [0.27–0.55]
Procedural characteristics and outcomes*		
Device		
MitraClip	188 (91)	133 (91)
PASCAL	18 (9)	13 (9)
Technical success	192 (93)	137 (94)
Moderate or less mitral regurgitation at discharge	181 (88)	124 (85)
Periprocedural death	10 (5)	5 (3)
Acute Kidney Injury		
Stage 1	16 (8)	9 (6)
Stage 2	4 (2)	3 (2)
New atrial fibrillation	6 (3)	4 (3)
Vascular Complications		
Major	6 (3)	2 (1)
Minor	3 (2)	2 (1)
Stroke	1 (1)	1 (1)

Values are n (%), mean ± SD or median [IQR].
SMR secondary mitral regurgitation; STS-PROM Society of Thoracic Surgeons Predicted Risk of Mortality; EuroSCORE II European System for Cardiac Operative Risk Evaluation predicted risk of in-hospital mortality; LVEDD left ventricular end-diastolic diameter; LVESV left ventricular end-systolic volume; LVEDV left ventricular end-diastolic volume; PASP pulmonary artery systolic pressure; TAPSE tricuspid annular plane systolic excursion; RVPA right ventricle to pulmonary artery. Other abbreviations as in Table 1.
* Following M-VARC criteria [17,18].

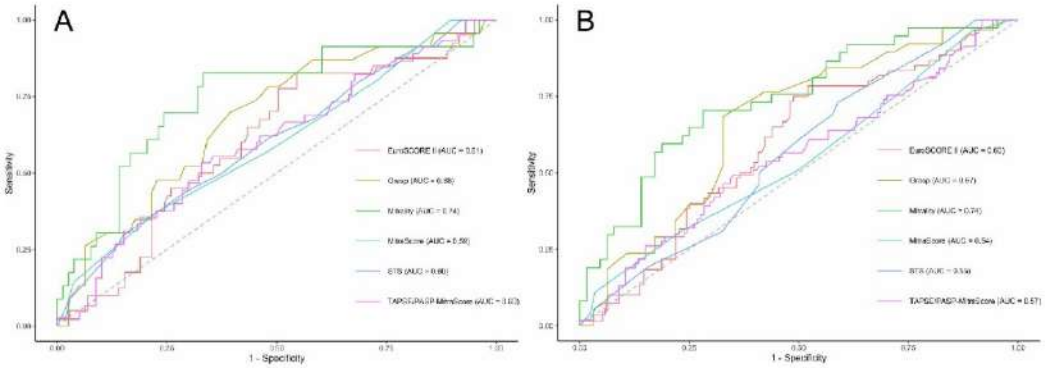

Fig. 1. ROC curves of different risk models for 1-year mortality (A) and for the composite endpoint of 1-year mortality and/or HF hospitalization (B).
Confidence interval (CI); area under the curve (AUC).

for 1-year mortality and 0.60 (95% CI: 0.51–0.69) for the composite endpoint of 1-year mortality and/or HF hospitalization. GRASP presented an AUC value of 0.68 (95% CI: 0.56–0.81) and 0.67 (95% CI: 0.56–0.78), respectively. MITRALITY showed an AUC value of 0.74 (95% CI: 0.62–0.87) and 0.74 (95% CI: 0.64–0.84), respectively. MitraScore had an AUC value of 0.59 (95% CI: 0.49–0.71) and 0.54 (95% CI: 0.45–0.64), respectively. TAPSE/PASP-MitraScore had an AUC value of 0.60 (95% CI: 0.50–0.72) and 0.57 (95% CI: 0.47–0.67), respectively. Finally, STS showed an AUC value of 0.60 (95% CI: 0.51–0.69) and 0.55 (95% CI: 0.47–0.64), respectively.

Analyses of 1-year mortality and the composite endpoint of 1-year mortality and/or HF hospitalization for SMR after TEER, with additional inclusion of the COAPT Risk Score and baseline NT-proBNP, are shown in Fig. 2.**A and 2.B**, respectively. COAPT Risk Score showed an AUC value of 0.59 (95% CI: 0.47–0.72) for 1-year mortality and 0.66 (95% CI: 0.56–0.76) for the composite endpoint of 1-year mortality and/or HF hospitalization. EuroSCORE II score displayed an AUC value of 0.62 (95% CI: 0.52–0.73) and 0.61 (95% CI: 0.52–0.72), respectively. GRASP presented an AUC value of 0.65 (95% CI: 0.51–0.79) and 0.63 (95% CI: 0.51–0.76), respectively. MITRALITY showed an AUC value of 0.72 (95% CI: 0.58–0.86) and 0.72 (95% CI: 0.61–0.84), respectively. MitraScore had an AUC value of 0.53 (95% CI: 0.45–0.68) and 0.52 (95% CI: 0.42–0.63), respectively. TAPSE/PASP-MitraScore had an AUC value of 0.56 (95% CI: 0.45–0.70) and 0.54 (95% CI: 0.43–0.64), respectively. Baseline NT-proBNP presented an AUC value of 0.59 (95% CI: 0.45–0.73) and 0.58 (95% CI: 0.45–0.70) for both 1-year mortality and the composite endpoint of 1-year mortality and/or HF hospitalization in SMR. Finally, STS displayed an AUC value of 0.64 (95% CI: 0.54–0.74) and 0.59 (95% CI: 0.49–0.68), respectively.

4. Discussion

The present study evaluated the discriminative ability of multiple risk scores for TEER in patients with MR. The main findings were as follows: (1) the MITRALITY model showed the best accuracy for mortality or the composite of 1-year mortality and/or HF hospitalization in a composed population of PMR and SMR; (2) in a SMR-only population, MITRALITY remained the best predictive models for 1-year mortality or the composite of 1-year mortality and/or HF hospitalization; and (3) surgical risk scores, MitraScore, TAPSE/PASP-MitraScore and NT-proBNP alone showed poor discriminative ability for both 1-year mortality and the composite of 1-year mortality and/or HF hospitalization in a composed population of PMR and SMR.

TEER is an established option for symptomatic patients with MR who

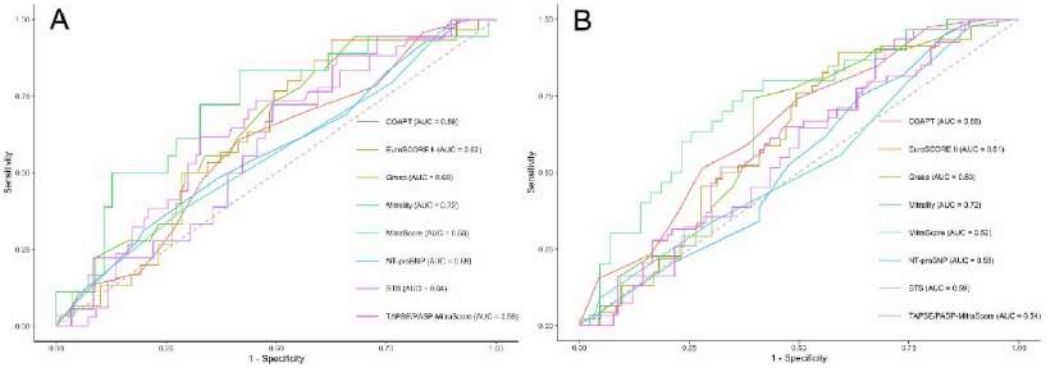

Fig. 2. ROC curves of different risk models for secondary MR for 1-year mortality (A) and for the composite endpoint of 1-year mortality and/or HF hospitalization (B).
N-terminal pro-Brain Natriuretic Peptide (NT-proBNP). Other abbreviations as in Fig. 1.

fulfill the eligibility echocardiographic criteria, and are deemed inoperable or at high surgical risk by the Heart Team [5]. Recent data have found TEER to be safe and result in lower hospitalization for HF rates and decreased mortality compared with medical therapy alone over a 5-year follow-up period [24]. In recent years, TEER eligible patients presented with lower surgical risk scores, higher prevalence of NYHA III, and lower NT-pro-BNP baseline level when compared to patients in the first years of TEER experience [25]. This shift indicates TEER uptake is expanding towards patients with longer life expectancy [26]. Therefore, accurate risk stratification is important to ensure proper patient selection.

4.1. Risks scores for overall TEER

We compared the accuracy of different baseline risk stratification tools in our cohort of 206 mitral TEER patients. The MITRALITY score displayed the best discriminative capability for both 1-year mortality and the composite endpoint of 1-year mortality and/or HF hospitalization, with acceptable AUC values of 0.74 and 0.74, respectively. In its original paper MITRALITY likewise outperformed other compared scores, with a 1-year mortality AUC of 0.78 [11]. This risk score also performed best in an external validation article [27]. In the original MITRALITY paper, machine-learning was applied to create a 1-year mortality score based on six variables derived from univariable analysis: baseline levels of hemoglobin, urea, creatinine, NT-proBNP, body mass index (BMI) and mean arterial pressure (MAP) [11]. The GRASP model for 1-year mortality was the second best model in our cohort, and displayed an AUC value of 0.68 as compared with 0.78 in its original publication [10]. The same AUC value of 0.68 for 1-mortality has also been reported in an external validation paper [27]. GRASP is based on four variables: NT-proBNP, MAP, NYHA class IV and hemoglobin [10].

Although MitraScore is simple to calculate, it exhibited no statistically significant discriminative value in our population, with an AUC value of 0.59 for 1-year mortality and 0.54 for 1-year mortality and/or HF hospitalization. These findings are lower than the 0.70 and 0.67 in the original study [12]. It is important to note the different risk profile in the MitraScore paper, yielding higher mortality rates of 31.9% after 1.6 years of follow-up in the original paper, as compared to 22% at 1-year in the present study. The addition of right ventricular-pulmonary artery coupling through the ratio of TAPSE and PASP only slightly improved the model's performance, to an AUC of 0.60 for 1-year mortality and 0.57 for 1-year mortality and/or HF hospitalization, as opposed to an AUC of 0.71 for 1-year mortality and/or HF hospitalization in its original publication [13]. It is important to consider that these scores were derived from both PMR and SMR cohorts, which are known to have heterogenous clinical outcomes [2]. Conventional surgical risk scores such as EuroSCORE II and STS have never been well validated for 1-year mortality prediction and showed an AUC of 0.61 and 0.60, respectively. This is similar to other studies published in the literature, with AUC values of 0.67 for EuroSCORE II and 0.61 for STS [8].

4.2. Risks scores for SMR

In our cohort of SMR only, MITRALITY outperformed the other scores, with an AUC of 0.72 for 1-year mortality and 0.72 for 1-year mortality or HF hospitalization. GRASP was the second-best model for 1-year mortality, but presented a lower AUC for the composed endpoint of 1-year mortality or HF hospitalization. COAPT Risk Score, which was derived from a strictly SMR population, has a reported AUC value of 0.74 for 2-year mortality or HF hospitalization [9]. In an external validation paper, *Adamo* et al. found a lower AUC value of 0.62 for the composite endpoint of 2-year mortality or HF hospitalization [28]. In our cohort, we found an AUC value of 0.59 for 1-year mortality and of 0.66 for 1-year mortality or HF hospitalization in SMR patients using COAPT Risk Score. A possible explanation for COAPT's underperformance is that HF hospitalizations can be underreported in real-life registries [28]. Finally, the COAPT Risk Score was designed for a 2-year follow-up; and, as our analysis was restricted to 1-year follow-up, this might have underestimated the score's predictive ability. MitraScore also had poor AUC in SMR-only, with values of 0.53 and 0.52 for 1-year mortality and for 1-year mortality or HF hospitalization, respectively.

TAPSE/PASP-MitraScore displayed a slight improvement, with AUC values of 0.56 and 0.54 for 1-year mortality and for 1-year mortality or HF hospitalization. The original validation paper reported an AUC value of 0.69 for 1-year mortality or HF hospitalization in SMR [13]. The lower AUC value in our population may be explained by different patient populations in both studies. EuroSCORE II showed an AUC of 0.63 and 0.61 for 1-year mortality and for 1-year mortality or HF hospitalization, respectively, performing better than some dedicated TEER scores in our analysis for SMR. STS demonstrated a similar performance in a SMR-only population, with AUC values of 0.64 and 0.59 for 1-year mortality and for 1-year mortality or HF hospitalization, respectively.

4.3. NT-proBNP for predicting outcomes

NT-proBNP correlated well with mortality in several publications [10,11,29,30]. Interestingly, despite successful TEER, NT-proBNP has been shown to remain fairly unchanged during follow-up and changes in NT-proBNP levels appeared poor predictors of functional improvement or clinical outcomes after MitraClip treatment [31]. In our cohort, we found an AUC of 0.59 for 1 year mortality and an AUC of 0.58 for 1-year mortality and/or HF hospitalization using baseline NT-proBNP, which corroborates NT-proBNP as a poor predictor for clinical outcomes after TEER.

5. Limitations

Our study has limitations. First, it is a single-center observational analysis with inherent selection bias and a relatively small sample size. Nevertheless, it is important to emphasize that the study population reflects contemporary clinical practice, with similar outcomes to those reported in the literature. Second, both the analyzed clinical outcomes and the echocardiographic measures were not adjudicated by a central committee and a core laboratory. Third, our analysis was limited to 1-year of follow-up, which is shorter than the 2-year follow-up time frame of some of the risk scores. Finally, HF hospitalizations may have been underreported whereas mortality checks were derived from and confirmed in the Dutch civil registry. Nonetheless, this limitation is commonly encountered in real-life research.

6. Conclusion

MITRALITY was the best mitral TEER risk model for both 1-year mortality and the composite endpoint of 1-year mortality and/or HF hospitalization in a population of PMR and SMR patients as well as SMR patients only.

Disclosures

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All other authors have reported that they have no relationship relevant to the content of this paper to disclose.

CRediT authorship contribution statement

Mauricio Felippi de Sá Marchi: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Visualization, Writing – original draft, Writing – review & editing. **Mark van den Dorpel:** Data curation, Investigation, Writing – original draft. **Pedro Calomeni:** Formal analysis, Writing – review & editing. **Sraman Chatterjee:** Data curation, Writing – review & editing. **Rik Adrichem:** Data curation, Writing – review & editing. **Sarah Verhemel:** Data curation, Writing – review & editing. **Antoon J.M. Van Den Enden:** Data curation, Writing – review & editing. **Joost Daemen:** Resources, Writing – review & editing. **Isabella Kardys:** Formal analysis, Methodology, Writing – review & editing. **Henrique Barbosa Ribeiro:** Supervision, Writing – review & editing. **Nicolas M. Van Mieghem:** Conceptualization, Project administration, Resources, Supervision, Writing – review & editing.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2024.131768.

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7 DISCUSSION

This thesis examined the occurrence, determinants, and predictive significance of myocardial injury using different cardiac biomarkers (CK-MB, cTn, and BNP) in the management of valve disorders. The presented research includes various transcatheter interventions such as TAVI, TMVR, and TEER, as well as traditional cardiac surgery. Furthermore, it explores the impact of enhancements in procedural execution, particularly focusing on valve coaxial deployment and height of implantation, to achieve better TMVR outcomes. The main findings were as follows:

(1) Post-TAVI PPMI was significantly linked to reduced overall survival at 2 years, with consistent trends observed across various subgroups defined by VARC-2 criteria. Most events occurred within the initial 2 months after the procedure, and CK-MB-based VARC-2 criteria for PPMI emerged as a stronger predictor of mortality as compared to cTn. Additionally, given the more sensitive cTn assays currently in use, VARC-3 recommendations seem more suitable to determine clinically relevant PPMI than VARC-2 definitions.

(2) Mitral reinterventions, including TMVR and SMVR-REDO, are consistently associated with myocardial injury. In SMVR-REDO cases, the duration of extracorporeal circulation emerged as a significant predictor of CK-MB and cTn elevation. Elevated levels of myocardial injury were independently linked to increased mortality at both 30-day and late follow-up, regardless of the approach used. Clinically relevant thresholds for defining myocardial injury in mitral reinterventions were identified as CK-MB increase ≥10-fold and cTn increase ≥500-fold from baseline. Although both TMVR and SMVR-REDO resulted in elevated CK-MB and cTn levels, SMVR-REDO demonstrated a 2- to 3-fold greater increase in cardiac biomarkers compared to TMVR. Both CK-MB and cTn levels were associated with higher late mortality, regardless of the intervention chosen.

(3) Refinements in TMVR deployment techniques yield a significant influence on both clinical outcomes as well as hemodynamic parameters. More ventricular implantation of the THV during TMVR poses a significantly higher risk of LVOT obstruction and this amplified risk has the potential to precipitate myocardial injury, ultimately contributing to increased mortality rates. Furthermore, our findings revealed that asymmetrical expansion of the THV strongly correlates with elevated mitral post-procedural gradients, with a delineated threshold of ≤ 10% indicating optimal valve performance. These insights shed light on the complexities inherent to TMVR procedures, aiming to mitigate unfavorable clinical and echocardiographic outcomes.

(4) Multiple risk scores have been developed for assessing TEER risk in MR patients. Our findings revealed that the MITRALITY risk model showed the highest accuracy in predicting mortality or a composite of 1-year mortality and/or HF hospitalization. Conventional surgical risk scores like MitraScore, TAPSE/PASP-MitraScore, and NT-proBNP exhibited poor discriminative ability for both 1-year mortality and the composite endpoint across PMR and SMR populations.

Transcatheter procedures embody a range of minimally invasive strategies that avoid aortic cross-clamping and cardioplegia, both of which are recognized factors contributing to the heightened release of cardiac biomarkers following valvular surgical procedures[150]. Nevertheless, studies have demonstrated some degree of elevation of both CK-MB and cTn after transcatheter interventions, such as TAVI[152]. The elevation in cardiac biomarkers is likely attributed to various factors, including transient hypotension during ventricular rapid pacing, distal microembolization of calcium particles during balloon dilatation and valve manipulation, mechanical compression of the left ventricular outflow tract, subclinical ventricular trauma caused by the wire, coronary artery disease exacerbating oxygen supply-demand mismatch, and coronary artery occlusion[160-163].

Interestingly, the established thresholds for relevant myocardial injury incidence vary depending on the cardiac injury biomarker analyzed and the used cutoff point. For instance, while cTn elevation >15 times the ULN is commonly observed during the initial 72 hours post-TAVI, only 10% of patients experience CK-MB elevation >5 times the ULN[168]. This observation was confirmed by our meta-analysis, where the incidence of cTn-defined myocardial injury was 61%, compared to 9% for CK-MB-defined myocardial injury, according to VARC-2 criteria (>5 times the ULN for CK-MB and >15 times the ULN for cTn)[139]. Therefore, the optimal PPMI cutoff point remains a matter of debate and as biomarker assay kits become ever more sensitive, even lower thresholds of myocardial injury can be measured, potentially overestimating the incidence of PPMI, jeopardizing its clinical relevance[142]. Nonetheless, due to the new VARC-3 definition (≥ 70 times the ULN of cTn), we hypothesize that PPMI incidence will decrease in future studies while its prognostic significance will rise[139]. This was recently demonstrated in a study by Real et al., in which PPMI incidence using cTn was 14% based on the VARC-3 criteria vs. 59% with VARC-2[169].

Our research supports the prevailing understanding of myocardial injury correlating with heightened risks of both early and late overall mortality[139,153,155,170]. It also contributes to the existing literature by consolidating data from a substantially larger patient cohort compared to prior analyses and suggesting that the majority of prognostic significance associated with cTn-defined myocardial injury manifests within the initial two months post-TAVI, with even earlier implications for CK-MB-defined myocardial injury (within the first month)[139].

Despite numerous studies on myocardial injury in aortic valve interventions, none have directly compared the release of cardiac biomarkers between patients undergoing TMVR and SMVR-REDO. Our study on this subject was the first to show that both approaches lead to a systematic elevation in CK-MB and cTn, with SMVR-REDO exhibiting a 2- to 3-fold higher elevation compared to TMVR[171].

In our study, increased elevations of CK-MB and cTn levels were both associated with increased 30-day and long-term mortality, irrespective of approach[171]. Mortality rates were similar between TMVR vs. SMVR-REDO in the overall population and occurred predominantly in the early phase, which is consistent with studies comparing these two approaches in high-risk patients undergoing mitral valve reintervention[29,66,171]. However, the TMVR group experienced fewer periprocedural complications and a shorter hospital stay length, a finding also observed in current TMVR studies[84].

Finally, the optimal threshold for defining clinically relevant myocardial injury after mitral BP dysfunction intervention is unsettled[150]. M-VARC recommends the cutoff value of 10-fold of increase in CK-MB and a 70-fold of increase in cTn, based on a modification of the Society for Cardiac Angiography and Interventions criteria for clinically relevant periprocedural MI and the Third Universal Definition of Myocardial Infarction[164,167,172]. However, these values have never been validated in the context of mitral reintervention. In the present thesis, we were able to demonstrate a similar cutoff for CK-MB elevation, providing evidence for the M-VARC suggested value. Nonetheless, our results demonstrated a much higher optimal cutoff for cTn than the one proposed in the M-VARC[166,167]. For instance, in the M-VARC the proposed cutoff for cTn was 70-fold, yet in our study we have determined a much higher threshold of ~500-fold, which is more aligned with recent literature of higher-risk patients who underwent non-aortic valve replacement (AVR) / non-coronary artery bypass graft (CABG) operations[148]. Importantly, this 500-fold of increase in cTn was the best cutoff for predicting both 30-day and late mortality. It is important to acknowledge that discrepancies in studies investigating cardiac biomarkers are, at least in part, due to the use of different assays and inherent statistical variances among patient populations.

Despite the described advantages of TMVR, previously published data has indicated high rates of elevated mean gradients (≥ 10 mmHg) with this approach[173-176]. The presence of elevated mean gradients after TMVR is associated with a more than 4-fold risk of mitral valve reintervention and persistent symptoms[177]. Therefore, there is a significant need for strategies aimed at reducing the risk of elevated mean mitral gradient following TMVR.

In our paper, we proposed the asymmetry index, which provides a straightforward measure that can be readily evaluated in the catheterization laboratory post-valve implantation[96]. Whenever significant asymmetry is present, it can impede leaflet opening and coaptation, thereby increasing gradients, potentially exacerbating structural valve degeneration and compromising the device's durability[96].

Another major clinical issue in TMVR is LVOT obstruction, which ranges from 0.9 to 1.8% in large registries and is a potentially deadly complication, increasing 30-day mortality in ~20%[177,178]. In our current analysis, we've demonstrated that cases with deeper ventricular implantation exhibit LVOT obstruction rates 10-times higher than those with more atrial implantation[96]. Furthermore, the depth of implantation emerged as the sole predictor of LVOT obstruction in our analysis[96]. Mechanistically, we can speculate that a valve implanted in a more ventricular direction leads to a higher displacement of the surgical valve leaflets, causing this complication[179-181].

Another significant domain witnessing rapid evolution in transcatheter interventions is mitral TEER. This technology is recognized as a feasible choice for symptomatic patients with MR who fulfill the echocardiographic eligibility criteria and are deemed inoperable or at high surgical risk for mitral valve repair or replacement, as determined by the Heart Team[7]. The study presented in this thesis evaluated the discriminative ability of multiple risk scores and cardiac biomarkers for TEER in patients with MR.

In our study, the MITRALITY score displayed the best discriminative capability for both 1-year mortality and the composite endpoint of 1-year mortality and/or HF hospitalization, with acceptable AUC values of 0.74 and 0.74, respectively. In its original paper, MITRALITY likewise outperformed other compared scores, with a 1-year mortality AUC of 0.78[133]. This model was also the best-performing risk score in an external validation article[182]. In the original MITRALITY paper, machine learning was applied to create a 1-year mortality score based on six variables derived from the univariable analysis: baseline levels of hemoglobin, urea, creatinine, NT-proBNP, body mass index (BMI) and mean arterial pressure (MAP)[133]. The GRASP model for 1-year mortality was the second-best model in our cohort and displayed an AUC value of 0.68 as compared with 0.78 in its original publication[132]. The same AUC value of 0.68 for 1-mortality has also been reported in an external validation paper[182]. GRASP is based on four variables: NT-proBNP, MAP, NYHA class IV and hemoglobin[132].

Although MitraScore is simple to calculate, it exhibited no statistically significant discriminative value in our population, with an AUC value of 0.59 for 1-year mortality and 0.54 for 1-year mortality and/or HF hospitalization. These findings are lower than the 0.70 and 0.67

published in the original study[134]. However, it is important to consider the diverse patient risk profiles outlined in the MitraScore paper, yielding higher mortality rates of 31.9% after 1.6 years of follow-up in the original paper, as compared to 22% at 1-year in the present study. The addition of right ventricular-pulmonary artery coupling through the ratio of TAPSE and PASP only slightly improved the model's performance, to an AUC of 0.60 for 1-year mortality and 0.57 for 1-year mortality and/or HF hospitalization, as opposed to an AUC of 0.71 for 1-year mortality and/or HF hospitalization in its original publication[135]. It is important to take into account that these scores originated from both PMR and SMR cohorts, which are known to have diverse outcomes[183]. Conventional surgical risk scores such as EuroSCORE II and STS have never been well validated for 1-year mortality prediction and showed an AUC of 0.61 and 0.60, respectively. This is similar to other studies published in the literature, with AUC values of 0.67 for EuroSCORE II and 0.61 for STS[130].

NT-proBNP correlated well with mortality in several publications[132,133,184,185]. Remarkably, despite successful TEER, NT-proBNP levels remain unchanged during follow-up, and variations in NT-proBNP levels were poor predictors of functional improvement or clinical outcomes after MitraClip treatment[186]. In our cohort, we found an AUC of 0.59 for 1-year mortality and an AUC of 0.58 for 1-year mortality and/or HF hospitalization using baseline NT-proBNP, which supports the notion that the isolated measure of NT-proBNP is a weak predictor for clinical outcomes following TEER.

8 CONCLUSIONS

This thesis investigated the occurrence, determinants, and predictive significance of myocardial injury utilizing various biomarkers (CK-MB, cTn, and BNP) in the context of the transcatheter treatment of different valve disorders. The research encompassed both transcatheter interventions (TAVI, TMVR, and TEER) and traditional cardiac surgery, shedding light on crucial aspects of myocardial injury in these treatment modalities.

In the first paper, a comprehensive meta-analysis of 18 observational studies involving 10,094 patients was conducted to examine post-procedural myocardial injury (PPMI) following TAVI. The findings underscored the association between PPMI and lower overall survival, irrespective of whether it was CK-MB or cTn defined. Notably, the prognostic significance of PPMI was most prominent in the initial months post-procedure, indicating its importance as an acute phase prognostic marker. Furthermore, the study suggested that VARC-3 recommendations might offer a more suitable approach for identifying clinically relevant PPMI compared to VARC-2.

The second paper investigated myocardial injury following TMVR and SMVR-REDO, revealing a notable elevation in both CK-MB and cTn levels, particularly evident in SMVR-REDO cases. These elevated biomarker levels were associated with increased late mortality, regardless of the treatment strategy. The study proposed optimal thresholds for defining clinically significant myocardial injury post-procedure, providing valuable insights for clinical practice.

The third paper highlights the risk of elevated mean gradients and LVOT obstruction after TMVR procedures. Asymmetric implantation was linked to a higher incidence of residual stenosis, while atrial implantation appeared protective against LVOT obstruction. However, the combination of depth of implantation and asymmetry emerged as a potentially significant hemodynamic factor, offering insights to mitigate complications and enhance procedural durability.

In the final paper, we assessed various risk scores and biomarkers to evaluate preprocedural mitral TEER intervention's ability to predict 1-year mortality and the combined endpoint of 1-year mortality and/ HF. The MITRALITY risk model emerged as the superior predictor for both 1-year mortality and the composite endpoint of 1-year mortality and/or HF hospitalization in patients undergoing mitral TEER. This model demonstrated robust predictive ability across populations with primary and secondary mitral regurgitation, emphasizing its utility in guiding clinical decision-making.

Collectively, these findings contribute to a deeper understanding of myocardial injury in transcatheter and surgical interventions for both the aortic and mitral valves, offering valuable insights to optimize patient outcomes and further refine risk prediction models in clinical practice. Also, ongoing advancements in transcatheter and surgical techniques, along with enhancements in medical devices, refined patient selection criteria, and procedural optimization, hold the promise of further improving clinical outcomes for patients with VHD.

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