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VENTRICULAR REMODELING AND CLINICAL OUTCOMES AFTER TRANSCATHETER THERAPIES IN VALVULAR HEART DISEASES: A SYSTEMATIC REVIEW AND META-ANALYSIS

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ABSTRACT

Cardiac valve diseases represent a significant cause of cardiovascular morbidity and mortality, especially in aging populations with multiple comorbidities. In recent decades, transcatheter therapies have profoundly modified the treatment of aortic stenosis, mitral regurgitation, and tricuspid regurgitation, expanding therapeutic possibilities for patients with high surgical risk or contraindications to conventional surgery. This systematic review with subgroup-structured meta-analysis aimed to evaluate the effects of transcatheter therapies for valve diseases on left and right ventricular remodeling, as well as their association with clinical outcomes. Thirty studies involving TAVI/TAVR, transcatheter edge-to-edge mitral repair, transcatheter mitral valve replacement, and transcatheter tricuspid interventions were included. Due to the clinical and methodological heterogeneity among valvulopathies, devices, and populations evaluated, the results were organized by therapeutic subgroups and analyzed through tabular quantitative synthesis.The findings indicated that TAVI/TAVR presented the most consolidated evidence, being associated with a reduction in pressure overload, reverse remodeling of the left ventricle, and improvement in clinical outcomes across different risk profiles. In mitral therapies, the benefit was more dependent on patient selection, the degree of baseline ventricular remodeling, and the proportionality of mitral regurgitation. In tricuspid interventions, an improvement in quality of life, a reduction in regurgitation, and potential remodeling of the right chambers were observed, although the effects on mortality still require further confirmation. It is concluded that ventricular remodeling constitutes a relevant marker of therapeutic response and prognosis after transcatheter valve therapies and should be incorporated into the clinical, echocardiographic, and methodological assessment of future studies.

Keywords:heart valve diseases; transcatheter procedures; ventricular remodeling; meta-analysis.

INTRODUCTION

Heart valve diseases represent one of the main causes of cardiovascular morbidity and mortality worldwide, especially in aging populations, where aortic stenosis, mitral regurgitation, and tricuspid regurgitation assume high clinical relevance. These conditions promote progressive hemodynamic changes, characterized by pressure or volume overload on the heart chambers, leading to structural and functional deterioration of the myocardium. When not properly treated, advanced valvulopathies can progress to heart failure, arrhythmias, pulmonary hypertension, decline in functional capacity, multiple hospitalizations, and a significant increase in the risk of cardiovascular death.

Historically, conventional surgical treatment was considered the therapeutic standard for most symptomatic severe valvulopathies. However, a significant portion of patients are of advanced age, frail, have multiple comorbidities, ventricular dysfunction, chronic kidney disease, pulmonary hypertension, or high surgical risk, factors that limit the indication for open surgery. In this scenario, transcatheter valve therapies profoundly modified the management of structural heart diseases, allowing the treatment of patients previously considered inoperable or at prohibitive risk. Transcatheter aortic valve implantation, initially evaluated in inoperable patients with severe aortic stenosis, demonstrated a significant reduction in mortality and readmissions when compared to isolated clinical treatment [1]. Subsequently, randomized studies confirmed the efficacy and safety of TAVI/TAVR in high-risk, intermediate-risk, and more recently, low surgical risk patients, progressively expanding their clinical indications [2-10].

In aortic stenosis, the chronic pressure overload imposed on the left ventricle initially leads to compensatory hypertrophy, increased ventricular mass, and alterations in myocardial compliance. With disease progression, this process can evolve into interstitial fibrosis, diastolic dysfunction, reduced contractile reserve, ventricular dilation, and heart failure. Correction of the valvular obstruction by TAVI/TAVR abruptly reduces the transvalvular gradient and ventricular afterload, creating conditions

favorable physiological conditions for reverse remodeling. Clinical studies have demonstrated that functional and structural recovery of the left ventricle after TAVR is associated with a better prognosis, suggesting that the reversibility of myocardial damage constitutes a relevant marker of therapeutic response [11]. Furthermore, recent investigations indicate that patients with predominant aortic stenosis or mixed aortic valve disease may exhibit regression of geometric and functional changes after transcatheter intervention, with a potential impact on clinical outcomes [12, 13].

Mitral regurgitation, in turn, represents a distinct pathophysiological model, in which chronic volume overload contributes to left ventricular dilation, increased systolic and diastolic volumes, atrial remodeling, pulmonary hypertension, and progressive worsening of heart failure. In patients with primary mitral regurgitation, the anatomical valve defect is the main determinant of regurgitation, whereas in secondary mitral regurgitation the alteration stems predominantly from ventricular remodeling and deformation of the subvalvular apparatus. This difference is essential, as the benefit of transcatheter therapies depends not only of the reduction of regurgitation, but also of the stage of ventricular impairment and the capacity for reverse remodeling after the intervention.

Transcatheter edge-to-edge mitral repair, initially represented by MitraClip, emerged as a less invasive alternative to surgery in selected patients with significant mitral regurgitation. The EVEREST II study demonstrated that percutaneous repair had a better initial safety profile when compared to surgery, although with a higher frequency of residual or recurrent mitral regurgitation [14]. The five-year follow-up confirmed the clinical durability of the procedure in selected subgroups, consolidating the role of transcatheter therapy as a viable alternative in patients with favorable anatomy and increased surgical risk [15]. However, it was in secondary mitral regurgitation associated with heart failure that the scientific discussion became more complex, especially in light of the divergent results between the COAPT and MITRA-FR studies.

In the COAPT study, transcatheter mitral repair associated with optimized clinical treatment reduced hospitalizations

for heart failure and mortality in carefully selected patients with moderate to severe or severe secondary mitral regurgitation [16]. In contrast, the MITRA-FR study did not demonstrate significant superiority of percutaneous repair over medical treatment alone in a population also with heart failure and secondary mitral regurgitation [17]. The subsequent follow-up of MITRA-FR maintained the absence of significant clinical benefit, reinforcing the hypothesis that the magnitude of baseline ventricular remodeling, the proportionality of mitral regurgitation relative to left ventricular size, and the anatomical selection of the patient directly influence outcomes [18]. The five-year follow-up of COAPT, on the other hand, confirmed sustained clinical benefit, suggesting that, in appropriately selected patients, transcatheter correction of mitral regurgitation can alter the natural trajectory of heart failure [19].

In this context, ventricular remodeling assumes a central position as an intermediate variable between technical success and clinical benefit. The simple reduction of valvular regurgitation may not be sufficient to improve survival or reduce hospitalizations when the myocardium already presents advanced and irreversible damage. On the other hand, the presence of reverse remodeling after the intervention may reflect effective hemodynamic recovery, reduction of parietal stress, improvement of contractile efficiency, and slower progression of heart failure. Analyses derived from COAPT demonstrated that ventricular remodeling after mitral TEER is associated with better clinical outcomes, reinforcing the relevance of echocardiographic and functional parameters as markers prognostic [20]. Multicenter studies also indicate that the etiology of mitral insufficiency and the pattern of cardiac remodeling influence outcomes after transcatheter repair, highlighting the need for individualized patient stratification [21].

In addition to mitral repair, transcatheter mitral valve replacement has been investigated as an emerging strategy for patients with severe mitral insufficiency, anatomy unfavorable for repair, or high surgical risk. Feasibility studies have demonstrated that transcatheter mitral valve replacement can significantly reduce regurgitation and improve symptoms in

selected patients, although there are still challenges related to anatomical selection, left ventricular outflow tract obstruction, valve thrombosis, prosthetic durability, and adverse events in high-complexity populations [22-24]. Despite being promising, this modality still requires greater consolidation of evidence,

especially regarding the impact on ventricular remodeling and long-term outcomes.

Tricuspid insufficiency, long underdiagnosed and undertreated, has received increasing scientific attention due to its association with worse prognosis, higher mortality, recurrent hospitalizations, and deterioration in quality of life. Significant tricuspid regurgitation promotes volume overload of the right ventricle, annular dilation, enlargement of the right chambers, right ventricular dysfunction, systemic congestion, and impairment of hepatorenal function.

Unlike the left ventricle, the right ventricle has greater sensitivity to changes in afterload and complex geometry, which makes its assessment more challenging. Thus, parameters such as TAPSE, fractional area shortening, right ventricular dimensions, right ventricular strain, and right atrial function are fundamental to understanding the response to transcatheter tricuspid therapies.

Transcatheter edge-to-edge tricuspid repair demonstrated reduction in tricuspid regurgitation severity, functional improvement, and gains in quality of life in selected symptomatic patients [25]. The TRILUMINATE Pivotal study represented an important milestone by demonstrating that transcatheter repair of tricuspid insufficiency improves patient-reported outcomes and reduces regurgitation severity, with an acceptable safety profile [26]. Subsequent follow-ups reinforced the partial durability of regurgitation reduction and clinical improvement in the medium term [27,28]. Recent studies also suggest that changes in right ventricular function and remodeling after tricuspid interventions may be related to clinical evolution, indicating that the right ventricle should be analyzed not only as a consequence of valvopathy, but as a central determinant of prognosis [29,30].

Despite significant advances in transcatheter therapies, there are still

relevant gaps in the literature. Many

studies prioritize clinical outcomes such as mortality, hospitalization, and procedural safety, while ventricular remodeling parameters are often assessed heterogeneously, with different imaging methods, follow-up times, and definitions of response. Furthermore, there is great variation among valvulopathies, devices, populations, disease severity, baseline ejection fraction, surgical risk, presence of pulmonary hypertension, and degree of preexisting ventricular dysfunction. This heterogeneity makes it difficult to interpret studies in isolation and reinforces the need for a systematic synthesis of the available evidence.

A meta-analysis becomes particularly relevant in this field because it allows for an aggregated estimation of the magnitude of structural and functional ventricular changes after transcatheter therapies, as well as their relationship with relevant clinical outcomes. By organizing studies by type of valvulopathy, intervention, and ventricle analyzed, it is possible to understand whether reverse remodeling constitutes merely an echocardiographic marker of response or whether it represents a prognostic mediator associated with reduced mortality, hospitalization for heart failure, and functional improvement. This approach may also contribute to identifying subgroups with greater benefit, refining patient selection criteria, and guiding future research in structural interventional cardiology.

Thus, this systematic review with meta-analysis aims to evaluate the impact of transcatheter therapies for valvular diseases on left and right ventricular remodeling, as well as to investigate its association with clinical outcomes in adult patients with aortic stenosis, mitral regurgitation, and tricuspid regurgitation. By integrating evidence from randomized clinical trials, multicenter registries, and observational studies, this study seeks to provide a critical and quantitative synthesis on the relevance of ventricular remodeling as a marker of therapeutic response and prognosis after transcatheter valve interventions.

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METHODOLOGY

This systematic review with subgroup-structured meta-analysis was conducted according to the PRISMA 2020 statement recommendations, with the objective of evaluating the effects of transcatheter therapies in valvular heart diseases heart on the ventricular remodeling and clinical outcomes in adults. The guiding question was structured based on the PICO strategy: in adult patients with valvular heart diseases, were transcatheter therapies, when compared to optimized clinical treatment, conventional surgery, or the pre-procedure baseline state, associated with reverse ventricular remodeling and improvement in clinical outcomes?

Publications involving adult patients with aortic stenosis, mitral regurgitation, or tricuspid regurgitation undergoing transcatheter therapies were considered eligible, including TAVI/TAVR, transcatheter edge-to-edge mitral repair, transcatheter mitral valve replacement, transcatheter tricuspid repair, and transcatheter tricuspid valve replacement. Randomized clinical trials, prospective studies, multicenter registries, retrospective cohorts, and secondary analyses of major studies, provided they presented data related to left or right ventricular remodeling, ventricular function, mortality, hospitalization for heart failure, cardiovascular events, functional class, or quality of life.

The literature search was conducted in the PubMed/MEDLINE, Embase, Scopus, Web of Science, Cochrane Library, and ClinicalTrials.gov databases. Controlled and free terms related to valvular heart diseases, transcatheter interventions, ventricular remodeling, and clinical outcomes were used. The search strategy combined terms such as "valvular heart disease" " aortic , stenosis", "mitral regurgitation", "tricuspid regurgitation", "transcatheter aortic valve replacement", "TAVR", "TAVI", " transcatheter edge-to-edge repair", " TEER", "MitraClip", "TriClip", "PASCAL", "TMVR", "TTVR", "ventricular remodeling", "reverse remodeling", "left ventricular function", "right ventricular function", "mortality", "heart failure hospitalization", and "clinical outcomes". Isolated case reports, preclinical studies, editorials, letters to the editor, reviews

narratives and studies without extractable data related to the outcomes of interest.

The study selection was conducted in two stages. Initially, titles and abstracts were evaluated by two independent reviewers. Subsequently, potentially eligible articles were analyzed in full text. Disagreements were resolved by consensus or by a third evaluator. The identification, screening, eligibility, and inclusion process was organized according to the PRISMA logic, with the reasons for exclusion recorded at the full reading stage.

The extracted data included author, year, country or consortium, study design, sample size, clinical characteristics of the population, type of valvulopathy, intervention performed, comparator, follow-up time, ventricular remodeling parameters, and clinical outcomes. For left ventricular remodeling, data on ejection fraction, ventricular volumes, left ventricular mass, ventricular diameters, cardiac geometry, and global longitudinal strain were considered when available. For right ventricular remodeling, TAPSE, fractional area shortening, right ventricular volume, and basal dimension of the right ventricle, remodeling of the right chambers, and right ventricular strain, when available. The main clinical outcomes included all-cause mortality, cardiovascular mortality, hospitalization for heart failure, major cardiovascular events, valve reintervention, NYHA functional class, quality of life, reduction in valve regurgitation severity, and procedural safety.

The risk of bias was assessed according to the methodological design of the included studies. Randomized clinical trials were analyzed based on the domains of the Cochrane RoB 2 tool, while non-randomized intervention studies were evaluated according to the principles of ROBINS-I. Observational studies, registries, and cohorts were analyzed considering population selection criteria, comparability between groups, definition of outcomes, follow-up time, and clarity in the presentation of results. The overall certainty of the evidence was interpreted qualitatively, considering risk of bias, consistency of findings, clinical applicability, precision of results, and relevance of the outcomes evaluated.

The synthesis of the results was initially descriptive and later organized into a quantitative matrix by subgroups, considering the type of intervention, the treated valvulopathy, the predominantly analyzed ventricle, and the main clinical outcomes. Due to the high clinical and methodological heterogeneity among the evaluated transcatheter therapies, a single global estimate involving all studies was not performed. The analysis was conducted in a stratified manner, separately grouping studies on TAVI/TAVR, transcatheter edge-to-edge mitral repair, transcatheter mitral replacement, and transcatheter tricuspid interventions.

For data interpretation, the predominant direction of the effect, the consistency of findings among studies, the methodological profile of the publications, the type of comparator used, the follow-up time, and the presence of outcomes related to remodeling ventricular and clinical evolution were considered. The results were presented in summary tables, including study distribution, ventricular remodeling parameters, clinical outcomes, heterogeneity among subgroups, and strength of evidence. This strategy allowed preserving the clinical coherence of the analysis, avoiding the statistical combination of substantially distinct populations, devices, and valvulopathies.

Subgroup analyses were performed according to the type of intervention, type of valvulopathy, ventricle analyzed, follow-up time, surgical risk profile, baseline ejection fraction, and study design. The robustness assessment of the findings considered the consistency among studies, the presence of multicenter samples, the methodological design, the risk of bias, and the clinical applicability of the results. Publication bias was considered qualitatively, especially in subgroups with a smaller number of studies, in which the application of graphical or formal statistical methods would be limited.

This methodological approach was adopted to align the meta-analysis proposal with the heterogeneity of the transcatheter valve therapies field, allowing a quantitative tabular synthesis by subgroups without producing an artificial global estimate. In this way, we sought to more accurately assess the relationship between transcatheter intervention, ventricular remodeling, and clinical outcomes, respecting the

pathophysiological differences between aortic stenosis, mitral insufficiency and tricuspid insufficiency.

RESULTS

This systematic review with subgroup-structured meta-analysis included 30 studies that evaluated transcatheter therapies applied to the treatment of heart valve diseases and their effects on ventricular remodeling and clinical outcomes. The selected studies covered three major groups of valvulopathies: aortic valve disease, mitral insufficiency, and tricuspid insufficiency. The analyzed interventions included transcatheter aortic valve implantation, transcatheter edge-to-edge mitral repair, transcatheter mitral valve replacement, and transcatheter tricuspid interventions.

Of the total included studies, 13 addressed transcatheter aortic interventions, 11 evaluated transcatheter mitral therapies, and 6 investigated transcatheter tricuspid interventions. Most studies presented a robust clinical design, including randomized clinical trials, multicenter registries, prospective studies, cohorts observational and secondary analyses of major studies. The main outcomes evaluated outcomes involved all-cause mortality, hospitalization for heart failure, major cardiovascular events, improvement in functional class, quality of life, reduction in valvular regurgitation severity, and parameters of left or right ventricular remodeling.

The analysis of the studies revealed high clinical and methodological heterogeneity across therapeutic areas, particularly regarding the type of valvulopathy, intervention performed, baseline patient profile, ventricle analyzed, imaging evaluation method, and follow-up time. For this reason, the results were organized by therapeutic and anatomical subgroups, avoiding the indiscriminate combination of populations and interventions that are substantially distinct. This structure allowed for the interpretation of the predominant direction of the effects of transcatheter therapies on ventricular remodeling and clinical outcomes, preserving the pathophysiological coherence among the evaluated valvular diseases.

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Table 1 - Distribution of included studies by therapeutic axis and transcatheter intervention

Therapeutic axis	Type of intervention	Included studies	Study proportion	Predominant valvulopathy	Predominantly ventricular Applied
Aortic valve disease	TAVI/TAVR	13	43,3%	Severe aortic stenosis and mixed aortic valve disease	Left ventricle
Mitral valve disease	Mitral TEER/MitraClip	8	26,7%	Primary and secondary mitral regurgitation	Left ventricle
Mitral valve disease	TMVR	3	10,0%	Severe mitral regurgitation in high-risk patients	Left ventricle
Tricuspid valve disease	T-TEER/TTVR	6	20,0%	Significant tricuspid regurgitation	Right ventricle
Total	Therapies transcatheter valve	30	100%	Heart valve diseases	Left and right ventricle

Regarding aortic interventions, studies have shown that TAVI/TAVR was associated with hemodynamic improvement in patients with severe aortic stenosis, primarily by reducing the pressure overload imposed on the left ventricle. The PARTNER, SURTAVI, and other related investigations supported progressive clinical benefit of TAVI/TAVR in different surgical risk profiles, including inoperable, high-risk, intermediate-risk, and low-risk patients [1-10].

Specific studies also indicated that the reversibility of ventricular function and the regression of structural changes after TAVR were associated with a better prognosis, reinforcing left ventricular remodeling as a relevant marker of therapeutic response [11-13].

In transcatheter mitral therapies, greater heterogeneity of results was observed. Edge-to-edge transcatheter mitral repair presented a profile of

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favorable safety compared to surgery in the EVEREST II study, although with a higher frequency of residual regurgitation in certain groups [14,15]. In patients with secondary mitral regurgitation and heart failure, the COAPT and MITRA-FR studies showed divergent results. While COAPT demonstrated clinical benefit in carefully selected patients [16,19], MITRA-FR did not show relevant clinical superiority compared to medical treatment alone [17,18]. This divergence indicated that the degree of baseline ventricular remodeling, the proportionality of mitral regurgitation, and the anatomical selection of patients directly influenced the clinical response after TEER.

In tricuspid interventions, the included studies demonstrated that transcatheter tricuspid repair was associated with a reduction in the severity of tricuspid regurgitation, improvement in functional class, and gains in quality of life in selected patients [25-28]. More recent studies indicated that changes in right ventricular function after T-TEER were related to clinical outcomes, highlighting the importance of right ventricular assessment as a prognostic marker in patients with significant tricuspid regurgitation [29,30].

Table 2 - Tabular quantitative synthesis by therapeutic subgroup and predominant outcomes

Analyzed subgroup	Included studies	Predominant outcomes evaluated	Predominant direction of effect	Clinical and methodological heterogeneity	Clinical interpretation
TAVI/TAVR	13	Mortality, stroke, hospitalization, major cardiovascular events and LV remodeling	Favorable to TAVI/TAVR in the most robust studies	Moderate	Most consolidated evidence among the analyzed therapies, with clinical improvement and remodeling reverse of the LV in different risk profiles.
Mitral TEER	8	Hospitalization for heart failure, mortality, functional class,	Favorable in selected patients, especially in profile	High	Benefit dependent on anatomical selection, severity of regurgitation and

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Analyzed subgroup	Included studies	Predominant outcomes assessed	Predominant direction of effect	Clinical and methodological heterogeneity	Clinical interpretation
		quality of life and LV remodeling	similar to COAPT		baseline degree of ventricular remodeling.
TMVR	3	Safety, reduction of mitral regurgitation, symptomatic improvement, mortality, and adverse events	Favorable for technical feasibility and symptomatic improvement	High	Promising technology, but with less consolidated evidence and a need for longer follow-up.
TTEER/TTVI	6	Reduction of tricuspid regurgitation, functional class, quality of life, RV function, and safety	Favorable for symptoms, quality of life, and reduction of regurgitation	Moderate to high	Growing evidence for functional improvement, with effects on mortality and hospitalization still under consolidation.

The subgroup synthesis demonstrated that producing a single global estimate for all transcatheter therapies would not be methodologically appropriate, considering the differences between valve diseases, devices, populations, analyzed ventricular chambers, and follow-up times. Thus, the analysis was structured tabularly according to the therapeutic axis and the predominantly affected ventricle, allowing for a more consistent interpretation of the effects of TAVI/TAVR on the left ventricle, mitral therapies on left ventricular volume overload, and tricuspid interventions on the remodeling of the right chambers.

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Table 3 - Ventricular remodeling parameters evaluated in the included studies

Remodeling parameters	Ventricular remodeling	Myocardial interactions	Predominant direction b d	Linear relationship
Left ventricular ejection fraction	LV	TAVI/TAVR, TEER mitral, TMVR	Improvement or stabilization in selected subgroups	Indicator of functional recovery or stabilization of ventricular dysfunction.
Left ventricular mass	LV	TAVI/TAVR	Reduction after relief of pressure overload	Marker of left ventricular hypertrophy regression.
Left ventricular end-diastolic volume	LV	Mitral TEER, TMVR	Reduction or stabilization in responsive patients	Reflects reduction of volumetric overload and reverse remodeling.
Left ventricular end-systolic volume	LV	Mitral TEER, TAVI/TAVR	Reduction or Stabilization	Related to improvement in contractile efficiency and slower progression of heart failure.
Cardiac geometry	LV/RV	TAVI/TAVR, T TEER/TTVI	Variable improvement according to disease stage	Indicates structural reversibility after valve correction.
TAPSE	RV	T-TEER/TTVI	Stabilization or change dependent on loading conditions	Relevant parameter of right ventricular longitudinal function.
Right ventricular dimensions	RV	T-TEER/TTVI	Reduction or stabilization in patients with favorable response	Suggests reverse remodeling of the right chambers.
Ventricular strain	LV/RV	TAVI/TAVR, mitral TEER, TTEER/TTVI	Improvement in studies with advanced imaging assessment	Sensitive marker of subclinical myocardial function.

The analysis of structural parameters demonstrated that reverse ventricular remodeling was described most consistently in studies involving TAVI/TAVR, especially due to the reduction of pressure overload after

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correction of aortic stenosis [1-13]. In mitral studies, the ventricular response was more variable, depending on the baseline severity of ventricular dysfunction, the intensity of mitral regurgitation, anatomical selection, and the optimization of clinical treatment [14-21]. In interventions tricuspid, the remodeling of the right chambers showed an association with functional improvement and quality of life, although data on mortality and hospitalization have still been less conclusive [25-30].

Table 4 - Summary of clinical outcomes according to type of transcatheter intervention

I t ntion	Mortality	Hospitalization p i s fi iên i a day	Class Linear function Data quality	Follow-up Fundamental	Synthesis Interpretation
TAVI/TAVR	Reduction or non-inferiority compared to surgery, according to risk profile	Reduction in subgroups with greater benefit	Improvement functional progressive	Consolidated safety profile, with attention to stroke, vascular complications, and need for Pacemaker	Evidence clinical more robust among the therapies analyzed.
Mitral TEER	Benefit in selected patients, especially in COAPT	Significant reduction in patients with secondary mitral insufficiency and favorable anatomical-functional profile	Symptom and quality of life improvement	Less invasive than surgery, with possibility of residual regurgitation	Benefit strongly dependent on patient selection.
TMVR	Data still limited for definitive conclusion	Insufficient evidence for robust conclusion	Symptomatic improvement in studies of feasibility	Risk associated with anatomical complexity and specific adverse events	Promising technology, but still with a lower level of evidence.
TTEER/TTVI	Effect on mortality Not yet Fully defined	Data still being consolidated	Improvement consistent Of symptoms, class functional and quality of Life	Favorable initial profile in selected patients	Intervention emerging with impact functional relevant.

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Clinical results indicated that transcatheter therapies had a more robust impact on mortality and hospitalization in aortic studies and in carefully selected mitral subgroups. In interventions tricuspid, the most consistent effects occurred on quality of life, functional class and reduction of regurgitation, while the effects on mortality and hospitalization still depended on longer follow-up time and studies with greater statistical power.

Table 5 - Clinical and methodological heterogeneity among the analyzed subgroups

Font d h t g n idad	Imp t Under the The analysis	Co s q ê ia pa a sí t s d left d s	And the strategy of the
Type of valve disease	High	Prevented a single global analysis involving all interventions	Organization by aortic, mitral and tricuspid subgroups.
Type of device	Moderate to High	Influenced technical success, safety and remodeling	Separate analysis by TAVI/ TAVR, mitral TEER, TMVR, and T-TEER/TTVI.
Baseline patient profile	Elevated	Modified mortality, hospitalization, and ventricular response	Consideration of surgical risk, baseline LVEF, and disease severity.
Follow-up time	Moderate	Changed the magnitude of clinical and structural effects	Separate interpretation according to short, medium, or long-term follow-up.
Imaging parameters	High	Made direct comparison between remodeling measures difficult	Grouping by similar variable and ventricle analyzed.
Study design	Moderate	Clinical trials, registries, and cohorts showed different risks of bias	Interpretation according to methodological robustness and consistency of findings.

The observed heterogeneity reinforced the need to interpret the findings with caution. The combination indiscriminate statistical pooling of studies on different valve diseases could overestimate or underestimate the effect of transcatheter therapies. Therefore, subgroup synthesis represented the strategy

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most appropriate methodological approach to preserve the clinical validity of the findings.

Table 6 - Strength of evidence according to the evaluated domain

Domínio avaliado	Força da evidência	Principais achados	Implicações clínicas
Reverse remodeling of the LV after TAVI/TAVR	High	Reduction of pressure overload and structural improvement of the LV	TAVI/TAVR showed consistent evidence for favorable ventricular remodeling.
Clinical outcomes after TAVI/TAVR	High	Clinical benefit or non-inferiority in mortality and major events, according to risk profile	Consolidated therapy in different surgical risk strata.
LV remodeling after mitral TEER	Moderate	Response dependent on patient selection and degree of baseline remodeling	The benefit was greater when the intervention occurred before irreversible ventricular damage.
Clinical outcomes after mitral TEER	Moderate	Reduction in hospitalization and mortality in selected subgroups	Anatomical and functional selection was crucial for the success.
TMVR and ventricular remodeling	Low to moderate	Promising but still limited evidence	Need for randomized studies and extended follow-up.
RV remodeling after T-TEER/TTVI	Moderate	Reduction of tricuspid regurgitation and functional improvement	The RV should be considered a central marker of response.
Mortality after tricuspid interventions	Low to moderate	Benefit not yet fully defined	Need for studies with greater statistical power and long-term follow-up.

Overall, the results indicated that transcatheter therapies in valvular diseases were associated with cardiac structural and functional improvement, with variable clinical impact depending on the treated valvopathy. In aortic diseases, ventricular reverse remodeling occurred mainly through the reduction of pressure overload after correction of stenosis. In mitral diseases, the response depended on the reduction of volume overload and the degree of

previous ventricular compromise. In tricuspid diseases, the benefit was related to the reduction of regurgitation, improvement of systemic congestion, and partial recovery of right ventricular function.

Integrated analysis demonstrated that ventricular remodeling should not be interpreted merely as a secondary echocardiographic finding, but as an intermediate marker of therapeutic response. Patients who presented

regression of hypertrophy, reduction of ventricular volumes, improvement of systolic function, or stabilization of cardiac geometry tended to have a more favorable clinical evolution, with lower symptomatic burden and reduction of heart failure-related events [11,20,29,30].

Another relevant finding was the importance of adequate patient selection. The divergent results between COAPT and MITRA-FR demonstrated that the presence of secondary mitral insufficiency alone does not guarantee clinical benefit after TEER. The stage of ventricular remodeling, the extent of LV dilation, the effective severity of regurgitation and the optimization of clinical treatment were fundamental factors in determining the response to intervention [16-19]. This same principle applied to tricuspid interventions, in which advanced right ventricular dysfunction may limit the degree of clinical recovery, even when there is a significant reduction in regurgitation [25-30].

Thus, the findings of this systematic review with meta-analysis structured by subgroups demonstrated that transcatheter therapies in valvular diseases are associated with favorable ventricular remodeling and improvement of clinical outcomes, particularly when indicated in carefully selected patients. The magnitude of benefit varied according to the type of valvulopathy, the stage of ventricular remodeling, baseline myocardial function, anatomical selection, the device used, and the follow-up time. These results reinforce the need to consider ventricular remodeling as a central variable in the assessment of the effectiveness of transcatheter therapies, especially in high-risk populations and those with advanced heart failure.

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DISCUSSION

The findings of this systematic review with subgroup-structured meta-analysis indicate that transcatheter therapies in valvular heart diseases are associated with relevant clinical and structural benefits, although the magnitude of the response varies according to the treated valvulopathy, the type of intervention, the predominantly affected ventricle, and the baseline stage of the disease. The tabular synthesis demonstrated that a single global analysis of all transcatheter therapies would not be methodologically adequate, considering the heterogeneity between aortic stenosis, mitral regurgitation, and tricuspid regurgitation, as well as the pathophysiological differences between pressure overload, left volume overload, and right volume overload.

The organization of results by subgroups allowed for a more coherent interpretation of therapeutic effects. In the aortic axis, studies involving TAVI/TAVR presented the most consolidated evidence, with consistent clinical benefit in different surgical risk profiles and association with reverse remodeling of the left ventricle [1-13]. In the mitral axis, the results were more heterogeneous, especially in secondary mitral insufficiency, where the response to transcatheter repair depended heavily on patient selection, valvular anatomy, the extent of ventricular remodeling, and the proportionality of regurgitation [14-21]. In the tricuspid axis, data demonstrated functional and quality-of-life improvement after transcatheter interventions, although the effects on mortality and hospitalization remain less defined [25-30].

In severe aortic stenosis, TAVI/TAVR represents the most mature field among the evaluated transcatheter therapies. Randomized clinical trials and their follow-ups have demonstrated that transcatheter intervention can achieve outcomes comparable or superior to conventional surgery in different risk strata, from inoperable patients to individuals with low surgical risk [1-10]. These findings reflect not only the technical success of valve replacement but also the intervention's ability to modify the hemodynamic burden imposed on the left ventricle.

From a pathophysiological standpoint, aortic stenosis imposes an overload

progressive pressure overload on the left ventricle, leading to ventricular hypertrophy, increased myocardial mass, diastolic dysfunction and, in advanced stages, systolic impairment. Correction of the valvular obstruction by TAVI/TAVR reduces ventricular afterload, favoring regression of hypertrophy and improvement of cardiac geometry. Specific studies included in this review indicated that the reversibility of cardiac function and reverse remodeling after TAVR were associated with better clinical outcomes, reinforcing the prognostic value of ventricular parameters [11-13].

However, the ventricular response after TAVI/TAVR should not be interpreted as a uniform phenomenon. Patients with advanced myocardial fibrosis, significant ventricular dysfunction, pulmonary hypertension, chronic kidney disease, or a long time of exposure to pressure overload may present incomplete remodeling, even after adequate valve correction. This suggests that the timing of the intervention is decisive. The earlier the correction is performed in relation to the stage of irreversible myocardial damage, the greater the likelihood of favorable remodeling and better clinical response.

In mitral diseases, the interpretation of results requires greater caution. Mitral insufficiency, especially when secondary, does not represent just an isolated valvular alteration, but often a consequence of left ventricular remodeling. In these cases, mitral regurgitation results from ventricular dilation, displacement of the papillary muscles, and alteration of the mitral apparatus geometry. Thus, transcatheter intervention acts on a functional manifestation of cardiomyopathy, and not necessarily on its primary cause.

This characteristic largely explains the divergent results between COAPT and MITRA-FR [16-19]. COAPT demonstrated significant clinical benefit of mitral TEER in carefully selected patients with mitral mitral secondary significant insufficiency, optimized clinical treatment, and adequate anatomical profile [16, 19]. In contrast, MITRA-FR did not demonstrate relevant superiority of transcatheter repair compared to isolated clinical treatment [17, 18]. This divergence suggests that patient selection is decisive for the success of mitral TEER.

The critical analysis of these studies reinforces the concept that the benefit of transcatheter mitral repair depends on the relationship between the severity of regurgitation and the degree of ventricular dilation. When mitral insufficiency is disproportionate to the size of the ventricle, its correction can significantly reduce the volumetric overload and improve outcomes. On the other hand, when regurgitation is merely an expression of a widely dilated and functionally compromised ventricle, valve repair may have a limited effect on mortality, hospitalization and reverse remodeling. Thus, mitral TEER should be interpreted as a therapy highly dependent on clinical, anatomical, and ventricular phenotype.

Studies related to remodeling after mitral TEER indicated that the structural and functional improvement of the left ventricle is associated with better clinical evolution [20,21]. This finding is relevant because it shifts the focus of the procedure's evaluation beyond the immediate reduction of regurgitation. The ventricular response after the intervention becomes an intermediate marker of therapeutic effectiveness. In practical terms, patients who present a reduction in ventricular volumes, stabilization of the ejection fraction, symptomatic improvement, and lower recurrence of mitral insufficiency tend to represent the group with the greatest clinical benefit.

Transcatheter mitral valve replacement has shown more limited evidence when compared to TAVI/TAVR and mitral TEER [22-24]. The included studies demonstrated technical feasibility, reduction in regurgitation, and symptomatic improvement in high-risk patients, but there are still significant limitations related to sample size, follow-up, anatomical selection, and long-term safety. Furthermore, the impact of TMVR on ventricular remodeling is not yet as well established as in aortic therapies. Therefore, although promising, this modality remains in the scientific consolidation phase.

In the tricuspid axis, the results demonstrated that transcatheter interventions represent a relevant alternative for a historically undertreated population. Significant tricuspid insufficiency is associated with systemic congestion, right ventricular dysfunction, worsening functional capacity, and reduced quality of life. The included studies showed that transcatheter tricuspid repair can

reduce the severity of regurgitation, improve functional class, and promote patient-perceived gains [25-28].

The assessment of right ventricular remodeling, however, is more complex than the assessment of the left ventricle. The right ventricle has an irregular geometry, high dependence on loading conditions, and great sensitivity to pulmonary hypertension. After the reduction of tricuspid insufficiency, changes in parameters such as TAPSE, right ventricular dimensions, and strain may reflect both structural improvement and hemodynamic changes related to the new loading condition. Therefore, the interpretation of right ventricular function after T-TEER requires multiparametric and contextualized analysis.

The most recent studies suggested that changes in the right ventricle after tricuspid interventions are associated with clinical evolution [29,30]. This finding is particularly important because it indicates that the benefit of the intervention does not depend solely on the reduction of regurgitation, but also on the right ventricle's ability to respond to the new hemodynamic state. Patients with advanced right ventricular dysfunction, severe pulmonary hypertension, or patients with prolonged systemic congestion may show symptomatic improvement, but a lower likelihood of broad structural recovery. Thus, as occurs in mitral valve diseases, the timing of intervention appears to be decisive.

Subgroup synthesis also revealed important differences in the strength of evidence among interventions. TAVI/TAVR presented the most robust set of studies, with a greater presence of randomized trials, prolonged follow-ups, and consistent results. Mitral TEER presented moderate evidence, strongly influenced by patient selection and anatomical and functional criteria. TMVR presented low to moderate evidence, as it is a technology still in maturation. Tricuspid therapies demonstrated growing evidence, especially for functional improvement and quality of life, but still requiring greater confirmation for hard outcomes.

This pattern of evidence has direct implications for clinical practice. In aortic valve diseases, the therapeutic decision can already be strongly supported by consolidated evidence in different risk profiles. In mitral diseases, the decision must be more

selective, requiring integration between regurgitation severity, ventricular dimensions, ejection fraction, valvular anatomy, response to clinical treatment, and surgical risk. In tricuspid diseases, the decision should consider not only the severity of the regurgitation but also the functional reserve of the right ventricle, the presence of pulmonary hypertension, the degree of systemic congestion, and the expectation of functional improvement.

Another relevant point is that ventricular remodeling emerges as a central variable for the evaluation of transcatheter therapies. In cardiovascular studies, outcomes such as mortality and hospitalization are fundamental but do not always capture the structural response to treatment early. Ventricular remodeling allows us to understand whether valvular correction resulted in effective physiological improvement, stabilization of disease progression, or merely anatomical correction without significant functional repercussion. Thus, the systematic incorporation of parameters such as ejection fraction, ventricular volumes, ventricular mass, TAPSE, strain, and cardiac chamber dimensions can enhance the assessment of response and prognosis.

The heterogeneity observed among the studies also reinforces the importance of avoiding generalized conclusions. Combine indiscriminately TAVI/TAVR, TEER mitral, TMVR, and TTEER in a single global estimate could produce artificial interpretation, as each intervention acts on a distinct pathophysiology. Aortic stenosis predominantly involves pressure overload of the left ventricle. Mitral regurgitation involves volume overload and complex interaction between the ventricle and valvular apparatus. Tricuspid regurgitation involves the right ventricle, pulmonary circulation, and systemic congestion. Therefore, subgroup synthesis was the most appropriate strategy to preserve the clinical validity of the findings.

Among the limitations of the analyzed evidence, the variability of methodological designs, follow-up times, devices used, and reported imaging parameters stands out. Many studies prioritized safety, mortality, hospitalization, or quality of life, while ventricular remodeling parameters were assessed heterogeneously. This limitation makes direct comparisons between studies difficult and reduces the possibility of a global quantitative estimate.

uniform. Furthermore, part of the evidence on TMVR and tricuspid interventions still derives from feasibility studies, registries, or cohorts with lower statistical power.

Despite these limitations, the present synthesis demonstrates that transcatheter therapies have substantially modified the treatment of valvular diseases. Their effects go beyond the anatomical correction of the valvular lesion, involving relief of hemodynamic overload, improvement of ventricle-valve interaction, potential reverse remodeling and impact on symptoms, hospitalizations, and quality of life. The magnitude of this benefit, however, depends on adequate patient selection, timely intervention, and myocardial recovery capacity.

Thus, the results of this review support that ventricular remodeling should be considered an essential marker of therapeutic response after transcatheter valvular interventions. The integrated assessment of clinical outcomes and structural parameters can contribute to better risk stratification, post-procedure follow-up, and definition of ideal candidates for each therapeutic modality. Future research should prioritize standardization of imaging outcomes, prolonged follow-up, comparative analysis between devices, and identification of objective thresholds for reverse remodeling associated with sustained clinical benefit.

CONCLUSION

This systematic review with subgroup-structured meta-analysis demonstrated that transcatheter therapies in cardiac valve diseases are associated with relevant clinical and structural benefits, especially when analyzed according to the type of valvulopathy, intervention performed, and predominantly affected ventricle. The tabular quantitative synthesis allowed organizing the available evidence in a stratified manner, preserving pathophysiological coherence between aortic stenosis, mitral regurgitation, and tricuspid regurgitation, without producing a single global estimate that could be methodologically inadequate given the high heterogeneity of the studies.

In the studies involving TAVI/TAVR, evidence was observed

most consolidated among the evaluated therapies. Transcatheter correction of aortic stenosis was associated with reduced pressure overload, improved hemodynamics, and reverse remodeling of the left ventricle, with consistent clinical benefits across different surgical risk profiles. These findings reinforce TAVI/TAVR as a robust and consolidated therapeutic strategy in the treatment of severe aortic valve disease.

In transcatheter mitral therapies, especially in edge-to-edge mitral repair, the results indicated a benefit more dependent on adequate patient selection. The clinical response was related to the degree of baseline ventricular remodeling, the proportionality of mitral regurgitation, valve anatomy, and the optimization of clinical treatment. Thus, left ventricular remodeling proved to be a central variable for understanding the effectiveness of mitral TEER, especially in patients with secondary mitral regurgitation and heart failure.

Transcatheter mitral replacement showed promising results, mainly regarding technical feasibility, reduction of regurgitation, and symptomatic improvement in high-risk patients. However, the evidence was still less consolidated, requiring comparative studies with a larger number of patients, prolonged follow-up, and standardized assessment of ventricular remodeling and clinical outcomes.

In transcatheter tricuspid interventions, findings demonstrated improvement in regurgitation, functional class, and quality of life in selected patients. Remodeling of the right ventricle and right chambers emerged as an essential component in interpreting the therapeutic response. However, the effects of these interventions on mortality and hospitalization are still being consolidated, requiring studies with greater statistical power and long-term follow-up.

Overall, the results of this review reinforce that ventricular remodeling should be interpreted as a central marker of therapeutic response after transcatheter valve interventions. The regression of ventricular hypertrophy, the reduction or stabilization of ventricular volumes, the improvement of systolic function, the functional recovery of the right ventricle, and the improvement of cardiac geometry may indicate greater

probability of sustained clinical benefit.

It is concluded that transcatheter therapies in valvular diseases have a favorable impact on ventricular remodeling and clinical outcomes in selected subgroups of patients. The magnitude of this benefit varies according to the valvulopathy, the type of device, the stage of the disease, baseline myocardial function, the timing of intervention, and ventricular functional reserve. Subgroup analysis proved to be the most appropriate strategy to interpret this evidence, especially in the face of the diversity pathophysiological and methodological diversity of the available studies.

Future research should prioritize the standardization of imaging parameters, the definition of objective thresholds for reverse remodeling, long-term follow-up, comparison between devices, and the systematic incorporation of structural and clinical outcomes. This approach may improve patient selection, guide post-procedure follow-up, and strengthen evidence-based decision-making in structural interventional cardiology.

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