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TRANSCATHETER INTERVENTIONS IN VALVOPATHIES: IMPACT ON CLINICAL OUTCOMES AND CARDIAC REMODELING - SYSTEMATIC REVIEW AND META-ANALYSIS

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ABSTRACT

Objective: To evaluate the effects of transcatheter interventions on clinical outcomes, safety, and cardiac remodeling in patients with aortic, mitral, and tricuspid valvular disease. **Methods:** A systematic review was conducted that included 45 publications, corresponding to 21 independent populations. Randomized clinical trials and prospective studies were considered that evaluated transcatheter aortic valve implantation or replacement, transcatheter edge-to-edge mitral repair, transcatheter edge-to-edge tricuspid repair, and transcatheter tricuspid valve replacement. Meta-analyses were performed only when the studies showed clinical and methodological comparability regarding population, intervention, comparator, outcome, and follow-up period. Random-effects models were used. Risk of bias was assessed using the RoB 2 tool, and the certainty of evidence was assessed using the GRADE system. **Results:** In aortic valve disease, the PARTNER 2A, SURTAVI, and PARTNER 3 meta-analysis showed no difference between TAVI/TAVR and surgical aortic valve replacement for all-cause death or disabling stroke over five years (HR=0.98; 95% CI 0.83–1.17; I^2=57.4%). The transcatheter approach was associated with a lower occurrence of bleeding, acute kidney injury, and atrial fibrillation; however, it carried a higher risk of vascular complications, pacemaker implantation, and residual aortic regurgitation. In secondary mitral regurgitation, the exploratory synthesis of MITRA-FR, COAPT, and RESHAPE-HF2 favored M-TEER, without statistical significance and with high heterogeneity (HR=0.72; 95% CI 0.49–1.06; I^2=72.6%). In tricuspid interventions, the most consistent benefits were observed in quality of life and functional status, without a statistically robust reduction in mortality or hospitalization for heart failure within one year. The remodeling findings suggested favorable hemodynamic and structural changes, but did not allow meta-analysis due to heterogeneity in the parameters and measurement methods. **Conclusion:** Transcatheter interventions showed clinical efficacy similar to surgery in aortic valve disease and relevant functional benefits in mitral and tricuspid valve diseases. Individualized patient selection remains essential, especially in secondary mitral regurgitation and tricuspid regurgitation. Studies with prolonged follow-up and standardized outcomes are needed to clarify durability, cardiac remodeling, and the impact on mortality and hospitalization.

Keywords: diseases of the heart valves; transcatheter aortic valve replacement; mitral valve regurgitation; tricuspid valve regurgitation.

INTRODUCTION

Valvular diseases are an important cause of morbidity, functional disability, hospitalization, and mortality cardi ovascular,

particularly in elderly populations and in individuals with multiple comorbidities. The increase in life expectancy, associated with a higher prevalence of degenerative cardiovascular diseases, has contributed to the progressive growth of calcific aortic stenosis and clinically significant mitral and tricuspid regurgitation. When not treated adequately, these conditions impose persistent hemodynamic overload on the heart chambers, favoring hypertrophy, ventricular dilation, myocardial dysfunction, pulmonary hypertension, heart failure, and a substantial worsening of survival.

For decades, cardiac surgery has represented the main therapeutic strategy for patients with severe valvular disease. However, a significant proportion of symptomatic individuals have a high or prohibitive surgical risk due to advanced age, frailty, ventricular dysfunction, disease renal,

pulmonary compromise, and other associated conditions. In this context, the development of transcatheter interventions has profoundly changed the treatment of valvular diseases, enabling less invasive approaches and expanding therapeutic possibilities for patients previously considered ineligible for intervention.

The transcatheter implantation of the aortic valve, also called TAVI or TAVR, was initially assessed in patients with severe aortic stenosis who were considered inoperable or at high surgical risk. The first randomized trials showed a reduction in mortality compared with conservative treatment and clinical outcomes comparable to surgical aortic valve replacement in high-risk patients (1,2,6) . Based on these findings, different clinical programs progressively expanded the indication for TAVI to individuals at intermediate risk and, subsequently, to populations at low surgical risk
(8- 10, 14, 19,23-25) .

The PARTNER 2A and SURTAVI trials showed that TAVI was not inferior to surgical replacement in patients at intermediate risk, considering outcomes as

mortality and disabling stroke (8,9) . Next, PARTNER 3, Evolut Low Risk, DEDICATE-DZHK6 and NOTION-2

expanded the investigation to lower-risk patients and, in some cases, younger patients, consolidating the transcatheter approach as an alternative to surgery in groups previously treated predominantly with conventional intervention (14, 19,23,25) . Prolonged follow-up from these trials also enabled assessment of late mortality, reintervention, structural deterioration of the bioprostheses, hemodynamic performance, and durability of the clinical results (3-5,7, 11- 13, 15, 16, 20-22,26) .

Despite the expansion of TAVI, the choice between transcatheter intervention and surgery remains complex. Aspects such as age, life expectancy, surgical risk, valvular anatomy, presence of a bicuspid valve, vascular access, need for concomitant revascularization, risk of pacemaker implantation, paravalvular regurgitation, and the possibility of future interventions must be considered. In addition, although transcatheter prostheses often present lower residual gradients and higher effective valve areas, certain platforms are associated with a greater need for pacemaker implantation and a higher occurrence of paravalvular regurgitation compared with surgery (12, 17-22) .

In the field of mitral regurgitation, transcatheter edge-to-edge repair, known as mitral transcatheter edge-to-edge repair, or M-TEER, has become one of the main strategies for patients at high surgical risk or with secondary mitral regurgitation associated with heart failure. The EVEREST II trial compared percutaneous repair with mitral surgery, showing less invasiveness and greater initial safety with the transcatheter approach, although with a higher frequency of residual mitral regurgitation and the need for subsequent intervention in certain patients (27-29) .

The use of M-TEER in secondary mitral regurgitation produced heterogeneous results across randomized trials. In MITRA-FR, transcatheter repair combined with medical treatment did not demonstrate a significant reduction in the composite endpoint of mortality or hospitalization for heart failure compared with isolated medical treatment (30,31). In contrast, COAPT showed a marked reduction in hospitalizations for heart failure and mortality in carefully

selected, with significant secondary mitral regurgitation despite optimized clinical treatment (32,33). More recently, the RESHAPE-HF2 trial added favorable evidence for the use of M-TEER in patients with heart failure and moderate-to-severe functional mitral regurgitation (35).

The differences between MITRA-FR, COAPT, and RESHAPE-HF2 indicate that the benefits of transcatheter mitral repair do not depend exclusively on reducing regurgitation. Characteristics such as left ventricular volume, ejection fraction, the proportional severity of mitral regurgitation, cardiomyopathy stage, pulmonary hypertension, right ventricular function, and adequacy of medical therapy can substantially influence the clinical response. In this scenario, assessing reverse ventricular remodeling after the intervention may provide additional information about the procedure's pathophysiological effectiveness and about patients' prognosis (30-35).

New mitral repair systems have also been developed with the aim of expanding anatomic possibilities and improving the reduction of residual regurgitation. The CLASP IID trial directly compared the PASCAL and MitraClip systems in patients with degenerative mitral regurgitation and prohibitive surgical risk, demonstrating favorable clinical and echocardiographic outcomes with both technologies (36,37). These advances highlight the rapid evolution of transcatheter platforms and reinforce the need to compare not only the procedure with conventional treatment, but also different repair devices and strategies.

Tricuspid regurgitation, historically undertreated, has also come to occupy a prominent position in the field of structural interventions. The disease is often associated with dilation of the right-sided chambers, atrial fibrillation, pulmonary hypertension, right ventricular dysfunction, systemic congestion, and high mortality. Isolated tricuspid surgery carries considerable risk in patients with advanced disease, which has driven the development of transcatheter repair and valve replacement techniques.

The TRILUMINATE studies showed that transcatheter edge-to-edge tricuspid repair can sustainably reduce the severity of regurgitation, improve functional class, and provide relevant gains in quality of life (39-43). The Tri.Fr trial

added evidence

randomized studies on the clinical benefit of transcatheter repair in patients with severe symptomatic tricuspid regurgitation (44). In parallel, TRISCEND II evaluated the transcatheter replacement of the tricuspid valve with the EVOQUE system, expanding the therapeutic spectrum to patients with anatomies or clinical features less favorable for edge-to-edge repair (45).

In addition of outcomes traditionally used in clinical trials, such as mortality, stroke, hospitalization, and complications related to the procedure, cardiac remodeling constitutes a relevant marker of response to valvular interventions. Correcting a valvular lesion abruptly changes the conditions of preload and afterload, which may promote regression of hypertrophy, reduction in ventricular volumes, improved myocardial function, and decreased pulmonary pressures. However, the magnitude and direction of these changes vary depending on the valve treated, the disease mechanism, the stage of cardiac dysfunction, and the presence of irreversible myocardial injury.

In aortic stenosis, the reduction in pressure overload after TAVI may favor regression of left ventricular mass and improved ventricular mechanics, although the presence of fibrosis, advanced hypertrophy, and myocardial dysfunction may limit reverse remodeling. The echocardiographic substudies of the NOTION and PARTNER 3 trials showed relevant changes in the hemodynamic performance of the prostheses, in transvalvular gradients, in the valve area, and in structural cardiac parameters during follow-up (12, 17, 18) .

In secondary mitral regurgitation, the reduction in volume overload after M-TEER may result in decreased ventricular and atrial volumes. However, interpreting these changes is complex, because reducing regurgitation also modifies the left ventricular ejection conditions and may produce apparent changes in ejection fraction. The COAPT echocardiographic substudy showed that the structural and functional evolution of the heart after mitral repair is closely related to the baseline features of the cardiomyopathy and to subsequent clinical outcomes (34) .

In tricuspid interventions, reduction of regurgitation modifies the volume overload of the right ventricle and right atrium. Imaging studies derived from TRILUMINATE identified remodeling of the right-sided chambers after an effective transcatheter repair, although improvement in right ventricular function may depend on the stage of the disease and the reversibility of myocardial dysfunction (43) . Analysis of right-sided remodeling is particularly relevant because abrupt reductions in regurgitation can increase the effective afterload of the right ventricle, requiring integrated assessment of volumes, systolic function, strain, and ventriculoarterial coupling.

Although different trials have demonstrated the efficacy and safety of transcatheter interventions, the literature remains marked by clinical and methodological heterogeneity. The studies cover different valves, disease mechanisms, risk profiles, device generations, anatomical criteria, comparators, definitions of outcomes, and follow-up periods. In addition, multiple publications derived from the same trial may represent follow-ups or subgroup analyses of the same population, creating a risk of double counting in quantitative syntheses conducted without adequate control of cohort overlap.

It can also be necessary to clarify to what extent the benefits observed on mortality,
hospitalizations and quality of life are accompanied by reverse cardiac remodeling and whether these structural changes show similar behavior in aortic, mitral, and tricuspid valvular diseases. Integrating these outcomes may provide a more comprehensive understanding of the effects of transcatheter therapies, going beyond an isolated assessment of technical success or the immediate reduction in the severity of valvular disease.

Given this context, the objective of this systematic review and meta-analysis was to evaluate the impact of transcatheter interventions in aortic, mitral, and tricuspid valvular diseases on clinical outcomes and cardiac remodeling. Evidence related to transcatheter aortic valve replacement, transcatheter mitral repair and transcatheter mitral replacement, and transcatheter repair and replacement strategies for the tricuspid valve was analyzed separately. The synthesis sought to compare mortality, hospitalization for heart failure, stroke, procedure-related complications, quality of life, valvular performance, and structural and functio-

nal changes of the chambers cardiac, respecting the differences between interventions, comparators, populations, and follow-up periods.

METHODOLOGY

A systematic review with meta-analysis was conducted to assess the effects of transcatheter interventions for aortic, mitral, and tricuspid valvular diseases on clinical outcomes and cardiac remodeling. The conduct and presentation of the review followed the recommendations of the *Preferred Reporting Items for Systematic Reviews and MetaAnalyses* PRISMA 2020 and the methodological guidance of the *Cochrane Handbook for Systematic Reviews ofInterventions*.

The research question was structured according to the PICO strategy. The population included adults with moderate-severe or severe aortic, mitral, or tricuspid valvular disease. The interventions included transcatheter implantation or replacement of the aortic valve, transcatheter mitral repair or replacement, and transcatheter tricuspid repair or replacement. The comparators were surgical valve treatment, optimized medical treatment, another transcatheter device, or baseline values from the same group in the remodeling studies. The outcomes assessed included mortality, hospitalization for heart failure, stroke, complications related to the procedure, functional capacity, quality of life, valve performance, and structural and functional changes of the cardiac chambers.

Searches were conducted in the MEDLINE/PubMed, Embase, Cochrane Central Register of Controlled Trials, Scopus, and Web of Science databases, from the beginning of indexing through June 2026. The search was supplemented by consulting ClinicalTrials.gov and by analyzing the reference lists of eligible articles. Controlled descriptors and free-text terms related to TAVI, TAVR, M-TEER, TMVR, T-TEER, TTVR, MitraClip, PASCAL, TriClip, EVOQUE, aortic stenosis, mitral regurgitation, tricuspid regurgitation, mortality, heart failure, stroke, and cardiac remodeling were used. Boolean operators AND and OR were adapted to the syntax of each database.

Randomized clinical trials, prospective comparative studies, multicenter cohorts, and prospective single-arm studies were included to assess safety or cardiac remodeling. The studies should have included adult participants, evaluate a transcatheter valve intervention, and present numerical data for at least one outcome of interest. A minimum follow-up of 30 days was required for safety outcomes and six months for late clinical outcomes or remodeling. Case reports, reviews, meta-analyses, editorials, abstracts without full publication, experimental or pediatric studies, publications with no extractable data, and studies with unresolvable population overlap were excluded.

The retrieved records were organized in Zotero 7, used for reference management and the initial removal of duplicates. Screening was conducted on the Rayyan platform by reviewing titles, abstracts, and full texts. Two reviewers independently assessed the records, and disagreements were resolved by consensus. The reasons for exclusion after full-text reading were documented, and the selection process was presented in a PRISMA flow diagram.

The unit of analysis was the independent population, not each publication in isolation. Main articles, follow-up studies, and substudies originating from the same trial were grouped into a single family. Only one publication from each population was used for outcome and follow-up period. The imaging substudies were used exclusively in the analyses of remodeling and valvular performance, avoiding duplication of participants.

Data extraction was performed by two reviewers using a standardized form. Information was collected on design, sample size, participant characteristics, severity of the valvular disease, surgical risk, intervention, device, comparator, follow-up time, events per group, measures of effect, losses to follow-up, and funding. The numbers absolute denominators, relative risks, hazard ratios, means, standard deviations, and confidence intervals. Percentages derived from Kaplan–Meier curves were not converted into absolute numbers.

The primary outcomes were all-cause mortality,

mortality cardiovascular and hospitalization for heart failure. Secondary outcomes included stroke, major bleeding, acute kidney injury, vascular complications, pacemaker implantation, valve reintervention, functional class, quality of life, and exercise capacity. Cardiac remodeling was assessed using ejection fraction, ventricular volumes, left ventricular mass, atrial volumes, right ventricular function, TAPSE, strain, pulmonary artery pressure, transvalvular gradients, and residual regurgitation.

The quantitative syntheses were conducted separately according to the valve treated, the intervention modality, and the comparator. TAVI versus surgical aortic valve replacement, M-TEER versus medical treatment, M-TEER versus surgery, T-TEER versus medical treatment, and TTVR versus medical treatment were analyzed. Single-arm studies and pre- and post-intervention comparisons were analyzed
separately from the controlled trials.

For dichotomous outcomes, relative risks were calculated with 95% confidence intervals. Time-to-event outcomes were expressed as hazard ratios, while continuous outcomes were analyzed by mean difference or standardized mean difference. A random-effects model was used, with estimation of the variance between studies using the restricted maximum likelihood method. Heterogeneity was assessed using the statistics I 2 and τ 2 and by Cochran's Q test.

The risk of bias of randomized trials was assessed using the RoB 2 tool, and non-randomized studies were examined using ROBINS-I. The certainty of the evidence was rated using the GRADE system, considering risk of bias, inconsistency, imprecision, indirect evidence, and publication bias. The symmetry of the results was assessed using a funnel plot and Egger's test in analyses with at least ten comparable studies.

The statistical analyses were performed in R software, version 4.5.0, using the packages *meta* and *metafor*. A significance level of 5% was adopted, with two-sided tests and 95% confidence intervals.

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RESULTS

The review included 45 publications, corresponding to 21 independent populations. The main publications, follow-up analyses, durability studies and substudies

echocardiographic studies derived from the same population were grouped into families in order to avoid double counting of participants.

Of the 21 independent populations, ll investigated aortic interventions, six assessed mitral interventions, and four addressed tricuspid interventions. The aortic set included the PARTNER lB, PARTNER lA, CoreValve High Risk, PARTNER 2A, SURTAVI, NOTION, PARTNER 3, Evolut Low Risk,

DEDICATE-DZHK6, UK TAVI, and NOTION-2[1–26]. The mitral set included EVEREST II, MITRA-FR, COAPT, RESHAPE-HF2, CLASP IID, and EVEREST II High Risk/REALISM[27–38]. The tricuspid core consisted of TRILUMINATE single-arm, TRILUMINATE Pivotal, Tri.Fr and TRISCEND II[39–45].

The totals related to initial identification, duplicate removal, title and abstract screening, and full-text assessment were not reconstructed retrospectively, because the original export files from the bibliographic databases and the complete deduplication and screening reports were not available. Thus, only the confirmed counts of included publications and independent populations were considered in this phase.

General Characteristics of the Studies

The independent populations were organized according to the valve involved, the type of intervention, and the clinical or surgical comparator. To preserve concision in the presentation, Table l summarizes the main study groups, while the individual characteristics of each population may be presented in supplementary material.

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Table 1 - Synthesis of the Characteristics of the Included Studies, According to Valve And Therapeutic Strategy

V lv mpa ção	P in ip is t d	D nh	Population of patients	S g im nt	D f h li dos
TAVI/TAVR versus clinical treatment	PARTNER 1B [1,5]	RCT	Aortic stenosis Severe; patients inoperable	Up to 5 years	Mortality, stroke, and hospitalization
TAVI/TAVR versus SAVR in high risk	PARTNER 1A and CoreValve High Risk[2–7]	RCTs	Aortic stenosis Severe; high risk Surgical	Up to 5 years	Mortality, stroke, reintervention, and safety
TAVI/TAVR versus SAVR in intermediate risk	PARTNER 2A and SURTAVI [8,9]	RCTs	Aortic stenosis Severe; risk intermediate	Up to 5 years	Death, stroke incapacitating and complications
TAVI/TAVR versus SAVR in low risk	NOTION, PARTNER 3, Evolut Low Risk, DEDICATE-DZHK6, UK TAVI, and NOTION-2[10–26]	RCTs	Low-risk patients or younger people	1–10 years	Mortality, stroke, durability, safety, and hemodynamics
M-TEER versus surgery or other device	EVEREST II and CL-ASP IID[27–29,36,37]	RCTs	Primary or degenerative mitral regurgitation; high surgical risk	Up to 5 years	Residual, reintervention, safety, and quality of life
M-TEER associated with clinical treatment versus clinical treatment	MITRA-FR, COAPT, and RESHAPE-HF2[30–35]	RCTs	Heart failure and secondary mitral regurgitation	2–5 years	Mortality, hospitalization for heart failure, and remodeling
T-TEER versus clinical treatment	TRILUMINATE Pivotal and Tri.Fr[41–44]	RCTs	Severe symptomatic tricuspid regurgitation	1 Year	KCCQ, mortality, hospitalization, and reduction of TR
Transcatheter tricuspid replacement versus medical therapy	TRISCEND II [45]	RCT	Severe symptomatic tricuspid regurgitation	1 year	Hierarchical clinical outcome, quality of life, and safety

Abbreviations:*stroke: cerebrovascular accident; HF: heart failure; MR: mitral regurgitation; TR: tricuspid regurgitation; KCCQ: Kansas City Cardiomyopathy Questionnaire; M-TEER: edge-to-edge transcatheter mitral repair; RCT: randomized clinical trial; SAVR: surgical aortic valve replacement; TAVI/TAVR: transcatheter aortic valve implantation or replacement; T-TEER: edge-to-edge transcatheter tricuspid repair.*

Transcatheter interventions in aortic valve disease - Death due to any cause or disabling stroke

The main meta-analysis included PARTNER 2A, SURTAVI, and PARTNER 3 because they provided estimates for the composite outcome of all-cause mortality or disabling stroke over a five-year horizon[8,9, 16].

The random-effects model, with heterogeneity estimated using the REML method, showed no statistically significant difference between TAVI/TAVR and SAVR: pooled HR=0.98; 95% CI 0.83–1. 17; I^2=57.4%; τ^2=0.013.

The point estimate remained close to 1, and the confidence interval included the null value. Heterogeneity was moderate, reflecting differences related to surgical risk, age, the device generation, and the clinical profile of the populations[8,9, 16].

All-Cause Mortality

Isolated mortality at five years was presented primarily as the cumulative incidence of Kaplan–Meier, without uniform availability of hazard ratios and standard errors.

In PARTNER 2A, five-year mortality was 46.0% after TAVR and 42. 1% after SAVR[8]. In PARTNER 3, the incidences were 10.0% and 8.2%, respectively[16]. In the Evolut Low Risk, the values were 13.5% after TAVR and 14.9% after SAVR[22].

These percentages were not converted into absolute counts because they corresponded to time-to-event estimates. Consequently, no specific meta-analysis of isolated mortality was performed.

Safety and Complications

In the UK TAVI, mortality at one year occurred in 21 of 456 patients in the TAVI group and in 30 of 457 in the SAVR group, corresponding to RR=0.70; 95% CI 0.41–1.20[24].

The risk of major bleeding was lower after TAVI, with HR=0.33; 95% CI 0.24–0.45. In contrast, TAVI was associated with a higher occurrence of vascular complications, with HR=4.42; 95% CI 2.54–7.71, and the greatest need for pacemaker, with HR=2.05; 95% CI 1.43–2.94[24].

In the Evolut Low Risk, at 30 days, TAVR was associated with a lower incidence of bleeding, acute kidney injury, and recently initiated atrial fibrillati-

on. The incidences were, respectively, 2.4% versus 7.5%, 0.9% versus 2.8%, and 7.7% versus 35.4%[19].

On the other hand, pacemaker implantation was more frequent after TAVR, at 17.4% versus 6.1%, as well as moderate or severe aortic regurgitation, at 3.5% versus 0.5%[8].

In PARTNER 2A, acute kidney injury occurred in 1.3% after TAVR and in 3.1% after SAVR <sp_1>[8]</sp_1>. These results were not pooled into a single estimate due to heterogeneity of the definitions, time windows, and effect measures.

Transcatheter interventions for mitral valve disease - M-TEER associated with clinical treatment versus isolated clinical treatment

MITRA-FR, COAPT, and RESHAPE-HF2 were the three independent randomized trials that assessed M-TEER in combination with clinical treatment compared with isolated clinical treatment in patients with secondary mitral regurgitation <sp_1>[30–35]</sp_1> .

The exploratory synthesis of all-cause death or first hospitalization for heart failure resulted in: combined HR= 0.72; CI95% 0.49–1.06; I^2=72.6%; τ^2= 0.088.

Although the direction of effect favored M-TEER, the confidence interval included the unit and heterogeneity was high. This estimate was considered exploratory because the studies differed with respect to the evaluation time, the severity of mitral insufficiency, the ventricular volumes, and the intensity of clinical treatment[30,31].

MITRA-FR Showed No Significant Benefit of M-TEER Over Death or Hospitalization <sp 1>[30,31]</sp 1>. In Contrast, COAPT Demonstrated Reduced Hospitalizations and Mortality in Selected Patients Under Optimized Clinical Therapy <sp 2>[32,33]</sp 2>. RESHAPEHF2 Added Evidence in a Population With Functional Mitral Regurgitation of a Less Extreme Profile <sp 2>[35]</sp 2>.

M-TEER versus surgery EVEREST II compared MitraClip to mitral surgery <sp_1>[27–29]</sp_1>. Transcatheter repair showed less

Because the follow-up publications derived from the same randomized population, they were treated as a single study family.

Device Comparison

The CLASP IID compared PASCAL and MitraClip in patients with degenerative mitral regurgitation and high surgical risk[36,37]. The analysis remained separate due to the active comparator and the distinct etiologic profile in relation to secondary mitral regurgitation studies.

Transcatheter interventions for tricuspid valve disease - Mortality and hospitalization

The TRILUMINATE Pivotal and Tri. Fr trials compared T-TEER with clinical treatment in patients with severe symptomatic tricuspid regurgitation[41–44].

No pooled meta-analysis of mortality or hospitalization was conducted because TRILUMINATE showed freedom from events and annualized rates, while Tri.Fr provided simple counts.

In Tri.Fr, mortality occurred in 5 of 152 patients in the intervention group and 8 of 148 controls, corresponding to RR= 0.61; CI95% 0.20–1.82[44]. Hospitalization for heart failure occurred in 15 of 152 and 20 of 148 patients, respectively, with RR=0.73; CI95% 0.39–1.37[44].

Wide confidence intervals indicated imprecision and no statistically demonstrated difference at one year.

Quality of Life

In TRILUMINATE Pivotal, 52.3% of patients who underwent T-TEER showed an improvement of at least 15 points in the KCCQ, compared with 23.5% in the control group[41,42].

In Tri.Fr, the final KCCQ score was 69.9±25.5 in the T-TEER group and 55.4 ±28.8 in the control group, corresponding to a 14.5-point difference, with $p<0,001$ [44].

These results were not pooled because TRILUMINATE reported the proportion of responders and Tri.Fr reported final mean values.

Replacement tricuspid transcatheter

TRISCEND II assessed transcatheter tricuspid replacement using the EVOQUE system compared with clinical treatment [45]. As only one independent randomized population assessed this strategy, the

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Main quantitative results were presented individually.

Table 2 - Main Quantitative Effects of Transcatheter Interventions

Comparison of the ho	And everything or font	Measurement of the ito	Health and aging	Int p tion
TAVI/TAVR versus SAVR: death or disabling stroke at 5 years	PARTNER 2A, SURTAVI and PARTNER 3[8,9, 16]	HR 0,98; CI 95% 0,83– 1,17	I^2=57,4%; τ^2=0,013	No significant difference
TAVI versus SAVR: mortality at 1 year	UK TAVI [24]	RR 0,70; CI 95% 0,41– 1,20	Not applicable	No significant difference
TAVI versus SAVR: major bleeding	UK TAVI [24]	HR 0.33; CI 95% 0.24– 0.45	Not applicable	Lower risk after TAVI
TAVI versus SAVR: vascular complications	UK TAVI [24]	HR 4.42; CI 95% 2.54– 7.71	Not applicable	Higher risk after TAVI
TAVI versus SAVR: pacemaker implantation	UK TAVI [24]	HR 2.05; CI 95% 1.43– 2.94	Not applicable	Higher risk after TAVI
M-TEER + GDMT versus GDMT: death or first HFH	MITRA-FR, COAPT and RESHAPE-HF2[30–35]	HR 0.72; CI 95% 0.49– 1.06	I^2=72.6%; τ^2=0.088	Exploratory synthesis; not significant
T-TEER versus control: mortality at 1 year	Tri.Fr [44]	RR 0.61; CI 95% 0.20– 1.82	Not applicable	Inaccurate estimate
T-TEER versus control: Hospitalization for heart failure	Tri.Fr [44]	RR 0.73; 95% CI 0.39– 1.37	Not applicable	No significant difference
T-TEER versus control: KCCQ final	Tri.Fr [44]	Difference of 14.5 points	Not applicable	Clinically relevant benefit
T-TEER versus control: improvement of ≥15 points on the KCCQ	TRILUMINATE Pivotal [41,42]	52.3% versus 23.5%	Not applicable	Higher proportion of responders

Abbreviations:*stroke: cerebrovascular accident; GDMT: guideline-directed medical therapy; HFH: hospitalization for heart failure; HR: hazard ratio; KCCQ: Kansas City Cardiomyopathy Questionnaire; RR: relative risk.*

Cardiac remodeling and hemodynamic performance

The remodeling findings were presented as a narrative quantitative synthesis, since there were not at least two independent studies with comparable means, standard deviations, and evaluation times.

In the echocardiographic substudy of PARTNER 3, the mean transvalvular gradient at one year was 13.7±5.6 mmHg after TAVR and 11.6±5.0 mmHg after SAVR. The valve area was 1.72±0.37 cm ^{2} and 1.76±0.42 cm ^{2}, respectively[17].

Valvuloarterial impedance was lower after TAVR, with 3.7±0.8 versus 3.9 ±0.9 mmHg/mL/m ^{2}[17]. Left ventricular mass regression was similar between the groups. Right ventricular function remained stable after TAVR, whereas SAVR was associated with a reduction in TAPSE and an increase in tricuspid regurgitation[17].

In COAPT, ventricular volumes, ejection fraction, and the severity of mitral regurgitation were assessed longitudinally[34]. However, the results were not combined in a meta-analysis due to the lack of homogeneous change measures.

In TRILUMINATE, the imaging sub-study indicated favorable remodeling of the right chambers after reduction of tricuspid insufficiency[43]. The absence of another independent study with equivalent parameters prevented the calculation of a pooled effect.

Risk of Bias

PARTNER 2A, SURTAVI, and PARTNER 3 were classified as studies with **some global concerns** in RoB 2, mainly because of the open-label design, the possibility of crossovers, and losses to follow-up over the prolonged follow-up period[8,9,14–16].

The mortality and stroke measurement domain was considered to have low risk, since it involved objective and adjudicated outcomes.

MITRA-FR, COAPT, and RESHAPEHF2 also presented some concerns related to the lack of blinding, optimization of clinical treatment, and missing data [30–35].

In the tricuspid studies, the lack of blinding was especially relevant to quality of life and KCCQ, while mortality and hospitalization

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were considered less susceptible to this type of bias[41,42,44]

Certainty of the evidence

Table 3 - Summary of the Risk of Bias and Certainty of the Evidence

Compa action d f ho	I r o d ié	In onsi tên ia	Imp i ão	C t za d idê ia	Ju tifi ti a
TAVI/TAVR versus SAVR: death or disabling stroke at 5 years	Some Concerns	Moderate	Do not record	Moderate	RCTs with objective outcomes; downgrading due to I^2=57.4%
M-TEER + GDMT versus GDMT: death or first HFH	Some Concerns	Severe	Record	Not classified as primary	Differences in timing and in the outcome composition
T-TEER versus clinical treatment: quality of life	Some Concerns	Not severe	Do not record	Low	Lack of blinding and different KCCQ metrics
T-TEER versus clinical treatment: mortality and HFH	Some Concerns	Not severe	Record	Moderate	Few events and Wide intervals
Cardiac remodeling	Variable	Severe	Record	Lowering	Few comparable studies and heterogeneous measures

The certainty of evidence for death or disabling stroke five years after TAVI/TAVR versus SAVR was rated as moderate, with downgrading due to inconsistency.

The certainty regarding quality of life after T-TEER was considered low, mainly due to the absence of blinding and the use of different methods of measuring the KCCQ.

For mortality and hospitalization after T-TEER, certainty was classified as moderate, with downgrading due to imprecision.

Summary of Findings

Transcatheter aortic interventions produced results similar to surgery for death or disabling stroke at five years. TAVI/TAVR showed a lower incidence of bleeding, acute kidney injury, and atrial fibrillation, but a higher risk of vascular complications, pacemaker implantation, and residual aortic regurgitation [8, 19,24].

In secondary mitral insufficiency, the exploratory synthesis favored M-TEER, but did not show a statistically significant difference and presented high heterogeneity[30–35].

In tricuspid interventions, the most consistent benefits were observed in quality of life and functional status. No robust statistically significant reduction in mortality or hospitalization at one year was demonstrated[41,42,44,45].

The remodeling data suggested favorable hemodynamic and structural changes after transcatheter interventions; however, the heterogeneity of the parameters prevented the performance of specific meta-analyses[17,34,43].

DISCUSSION

This systematic review included 45 publications, corresponding to 21 independent populations, and showed that the impact of transcatheter interventions varies substantially depending on the affected valve, the patients' clinical profile, the comparator used, and the technological maturity stage of each procedure. The most consistent results were observed in aortic interventions, while the mitral and tricuspid evidence showed greater clinical and methodological heterogeneity.

Aortic Interventions and Equivalence long-term clinical

The main quantitative finding of this review was the absence of a significant difference between TAVI/TAVR and SAVR for the composite outcome of death from any cause or disabling stroke over five years. The pooled estimate, with an HR of 0.98 and a 95% CI of 0.83 to 1.17, suggests approximate clinical equivalence between the strategies in the long-term horizon, although the moderate heterogeneity of 57.4% should be considered.

This heterogeneity is clinically plausible. PARTNER 2A and SURTAVI predominantly included patients at intermediate surgical risk, whereas PARTNER 3 evaluated individuals at low risk [8,9, 14– 16]. In addition, the trials used different generations of devices, balloon-expandable and self-expanding platforms, distinct access strategies, and populations with different ages and anatomic profiles. Therefore, the combined effect should not

be interpreted as absolute uniformity across all patient categories.

The historical evolution of aortic trials demonstrates the progressive expansion of TAVI. Initially, PARTNER lB established benefit in patients inoperable [l,5]. Subsequently, PARTNER lA and CoreValve High Risk showed that the transcatheter approach could compete with surgery in high-risk patients[2–7]. PARTNER 2A and SURTAVI expanded this indication to intermediate risk[8,9], while PARTNER 3, Evolut Low Risk, NOTION, DEDICATE-DZHK6, and NOTION-2 extended the investigation to low-risk populations and younger patients [l0–26].

The absence of a significant difference at five years is particularly relevant because it reduces concern that the initial benefits of TAVI could be offset by higher mortality or stroke during prolonged follow-up. However, clinical equivalence does not mean equivalence in all components of treatment. The choice between TAVI and SAVR continues to require individualized assessment of age, life expectancy, valvular and vascular anatomy, the possibility of future coronary access, the presence of a bicuspid valve, the risk of pacemaker implantation, and the need for concomitant interventions.

Isolated mortality data also suggested results similar between TAVI/TAVR and SAVR in the main five-year studies[8,l6,22]. However, the inability to pool these estimates highlights a frequent limitation of long-term syntheses: many trials report Kaplan–Meier cumulative incidences without uniformly providing hazard ratios and standard errors. Converting these incidences into simple counts could ignore censoring and differences in follow-up time, producing potentially biased estimates.

Distinct Safety Profiles After TAVI/TAVR and SAVR

Safety outcomes showed that TAVI/TAVR and SAVR differ not only in the magnitude of risk, but also in the type of predominant complication. The transcatheter approach was associated with less bleeding, less acute kidney injury, and less new-onset atrial fibrillation[8,l9,24]. These findings are consistent with lower invasiveness, the absence of sternotomy,

reduced exposure to cardiopulmonary bypass, and faster recovery.

In contrast, TAVI/TAVR showed a higher incidence of vascular complications, need for a pacemaker, and residual or paravalvular aortic regurgitation[19, 24]. The need for a pacemaker remains one of the main limitations, especially with some self-expanding platforms. The close proximity between the prosthesis, the left ventricular outflow tract, and the conduction system can lead to persistent atrioventricular block.

The relevance of a pacemaker may be greater in younger patients or those at low risk, in whom exposure to the device will be prolonged. Although many patients do not show immediate clinical consequences, chronic ventricular pacing may be associated with dyssynchrony, reduced ventricular function, and future interventions related to the pacing system.

Paravalvular regurgitation also remains clinically important. Even with device evolution, improvements in sealing, and greater implant accuracy, the occurrence of moderate or severe reflux continues to be more frequent after TAVI in some trials[19]. In patients with long life expectancy, the cumulative impact of this finding on ventricular remodeling, symptoms, and survival should be monitored.

These results reinforce that the therapeutic choice should not be based solely on mortality. The decision should consider the balance between surgical and transcatheter complications, as well as the patient's preferences and the center's experience.

Prosthesis durability and expansion to younger patients

The inclusion of younger, low-risk patients made durability one of the main points of discussion. Follow-ups from NOTION, PARTNER 3, and Evolut Low Risk provided evidence of clinical and hemodynamic stability in the medium and long term[10–22]. NOTION showed follow-up of up to ten years, while PARTNER 3 and Evolut Low Risk reported five-year results.

Despite these favorable data, it is still necessary to distinguish hemodynamic performance from definitive structural durability. Low gradients and preserved valve area do not rule out the possibility of late structural deterioration, subclinical thrombosis, the need for reintervention, or

difficulty accessing the coronary arteries.

In elderly patients, the durability of the prosthesis may exceed life expectancy. In younger patients, however, lifecycle strategies should be considered, including TAVR-in-TAVR, surgery after TAVR, and future access to the coronary arteries. Thus, current good outcomes do not eliminate the need for follow-up beyond ten years.

Heterogeneity of Mitral Evidence

Mitral outcomes were less uniform than aortic outcomes. The exploratory synthesis of MITRA-FR, COAPT, and RESHAPE-HF2 showed a combined HR of 0.72 for death or the first hospitalization for heart failure, but with a 95% CI of 0.49 to 1.06 and heterogeneity of 72.6% [30–35].

The high heterogeneity likely reflects fundamental differences in patient selection. MITRA-FR included individuals with more dilated ventricles and mitral regurgitation proportional to the severity of cardiomyopathy[30,31]. In this situation, correcting regurgitation may not be sufficient to change the prognosis determined by advanced ventricular disease.

COAPT selected patients with relevant secondary mitral regurgitation, persistent symptoms, and rigorously optimized medical therapy[32–34]. The observed benefit suggests that M-TEER may be more effective when regurgitation contributes disproportionately to hemodynamic overload and when ventricular function still allows for clinical benefit.

RESHAPE-HF2 extended this discussion by evaluating a population with a profile partly intermediate between MITRA-FR and COAPT[35]. Taken together, the studies indicate that the efficacy of MTEER depends less on the isolated presence of secondary mitral regurgitation and more on the integration among regurgitation severity, ventricular size, ventricular function, pulmonary pressure, clinical therapy, and valvular anatomy.

For this reason, the combined estimate should not be interpreted as an average effect applicable to all patients. Heterogeneity is a clinically relevant finding, as it shows that selection is decisive for the benefit.

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Transcatheter Repair Versus Mitral Surgery

EVEREST II showed that transcatheter repair is less invasive, but it may result in greater residual mitral regurgitation and a higher need for reintervention compared with surgery[27–29]. These findings remain important even with technological evolution.

Surgery continues to offer a greater ability to achieve complete anatomic correction, especially in patients with complex degenerative disease and low operative risk. M-TEER has greater utility in patients with high surgical risk, advanced age, significant comorbidities, or favorable anatomy for percutaneous repair.

CLASP IID showed that the mitral field has evolved toward comparisons between transcatheter devices, and not only between intervention and surgery or clinical treatment[36,37]. This transition indicates increasing technological maturity and the need to evaluate differences between systems in terms of reducing regurgitation, safety, durability, and technical ease.

Tricuspid interventions and predominance of symptomatic benefit

In tricuspid interventions, the most consistent benefit was observed in quality of life, symptoms, and reduced severity of regurgitation[41–45]. TRILUMINATE Pivotal and Tri.Fr demonstrated clinically relevant improvement in KCCQ after T-TEER[41,42,44].

In TRILUMINATE, the proportion of patients with improvement of at least l5 points in KCCQ was substantially greater after T-TEER[41,42]. In Tri.Fr, the l4.5-point difference in the final score also exceeded thresholds usually considered clinically relevant[44].

However, the effects on mortality and hospitalization were less conclusive. In Tri.Fr, the relative risks for mortality and hospitalization favored numerically T-TEER, but showed wide and non-significant intervals[44]. This result may reflect low statistical power, short follow-up, few events, or predominance of functional benefit without immediate impact on hard outcomes.

Tricuspid regurgitation generally occurs in patients with advanced disease, right ventricular dysfunction, pulmonary hypertension, atrial fibrillation, and renal

or hepatic impairment. In these cases, valve correction can improve symptoms, but it does not necessarily reverse established systemic damage.

Early selection can be decisive. Intervening before irreversible right ventricular dysfunction and advanced systemic congestion may yield greater prognostic benefit. However, this hypothesis requires confirmation in longer follow-up studies.

TRISCEND II introduced a distinct approach to evaluating transcatheter tricuspid replacement[45]. TTVR may produce more complete elimination of regurgitation, but it can also increase
the risk of acute right ventricular overload after removal of the regurgitant discharge mechanism. Selection should consider right ventricular function, pulmonary vascular resistance, and the ability to adapt hemodynamically.

Cardiac Remodeling

The remodeling data suggested hemodynamic and structural benefits after transcatheter interventions, but did not allow for meta-analysis due to lack of uniformity[17,34,43].

In PARTNER 3, TAVR showed hemodynamic performance similar to surgery, lower valvuloarterial impedance and more favorable preservation of right ventricular function parameters <sp_ 1>[17]</ sp_ 1> . These findings may be related to the absence of extracorporeal circulation, less myocardial injury, and less geometric alteration caused by the procedure. valvuloarterial and more favorable preservation of right ventricular function parameters[17]. These findings may be related to the absence of extracorporeal circulation, less myocardial injury, and less geometric alteration caused by the procedure.

In COAPT, echocardiographic analyses showed that prognosis remained strongly related to the underlying ventricular disease, although M-TEER reduced mitral regurgitation[34]. This reinforces that valvular intervention does not replace treatment for cardiomyopathy.

In TRILUMINATE, the reduction in tricuspid regurgitation was associated with favorable remodeling of the right chambers[43]. However, interpretation should consider that immediate reductions in volume may reflect changes in loading conditions and not necessarily complete myocardial recovery.

The inability to pool these data resulted from the heterogeneity of the parameters used, including ventricular mass, volumes, ejection fraction, TAPSE, atrial dimensions, right ventricular function, and valvuloarterial impedance. Fut-

ure studies should standardize parameters, assessment time points, and imaging methods.

Risk of Bias and Certainty of the Evidence

The main aortic trials were classified as presenting some overall concerns, but mortality and stroke outcomes were considered low-risk for measurement. The open-label nature of the procedures is difficult to avoid, but it has less impact on objective and adjudicated events.

Moderate certainty for death or disabling stroke at five years supports the conclusion of no relevant difference between TAVI/TAVR and SAVR. The downgrading occurred mainly due to heterogeneity between studies.

In the mitral evidence, heterogeneity and non-uniformity of outcomes limited the certainty of the combined synthesis. The exploratory result should be interpreted as indicating the direction of effect, not as a definitive estimate.

In the tricuspid trials, the lack of blinding may influence patient-reported outcomes, such as KCCQ. However, the magnitude and consistency of the observed improvement across different studies suggest a real clinical benefit, even though the certainty remains limited.

Clinical Implications

The results support an approach based on shared decision-making and assessment by multidisciplinary teams.

In aortic stenosis, TAVI/TAVR should be considered a consolidated alternative to surgery across different risk profiles. The choice should consider not only operative risk, but also age, anatomy, vascular access, the need for revascularization, the presence of other valvular diseases, life expectancy, and the strategy for future interventions.

In secondary mitral regurgitation, M-TEER should be directed to carefully selected patients with significant regurgitation despite optimized medical therapy and suitable anatomy. The mere presence of mitral regurgitation is not enough to indicate benefit.

In tricuspid regurgitation, the main current benefit is related to quality of life and functional status. Indication should occur before irreversible deterioration of

the right ventricle and advanced systemic injury.

Review Limitations

This review presents limitations that should be considered. The first was clinical heterogeneity across populations, devices, comparators, and follow-up times. The second was incomplete availability of uniform measures for some outcomes, especially isolated mortality, safety, and remodeling.

Including publications derived from the same family required rigorous control to avoid double counting. Although the analyses were organized by independent populations, some long-term outcomes and substudies were used only in narrative syntheses.

The mitral meta-analysis was classified as exploratory because the trials differed in the composition of the outcome and the time horizon. Similarly, it was not possible to perform a tricuspid meta-analysis of mortality or hospitalization due to the incompatibility of the published metrics.

Another limitation was the inability to reconstruct all the numerical steps of the PRISMA flow retrospectively without the original search, deduplication, and screening files. This limitation did not change the final base analyzed, but it prevents presenting a complete flow diagram with auditable counts of the initial steps.

The small number of studies in some comparisons also made it impossible to reliably assess publication bias. Tests of asymmetry and funnel plots would not be appropriate in analyses with fewer than ten studies.

Future Prospects

Future trials should prioritize prolonged follow-up, standardization of outcomes, and publication of complete effect size measures. In aortic stenosis, data beyond ten years are needed on durability, reintervention, coronary access, and life-cycle strategies.

In mitral valve disease, studies should improve selection criteria and identify markers that distinguish patients with a higher likelihood of prognostic benefit. Integrating imaging, biomarkers, artificial intelligence, and hemodynamic assess-

ment can enhance selection.

For tricuspid valve disease, it is necessary to determine whether symptomatic improvement translates into reduced hospitalizations and mortality in the long term. Criteria must also be established for choosing between repair and transcatheter replacement.

Finally, remodeling studies should adopt standardized sets of echocardiographic and tomographic parameters, enabling future quantitative meta-analyses and a better understanding of the relationship between valve correction, ventricular recovery, and prognosis.

CONCLUSION

Transcatheter interventions have established themselves as relevant therapeutic strategies in the management of aortic, mitral, and tricuspid valve diseases, although the magnitude and nature of the benefits vary depending on the valve treated, the patients' clinical profile, and the comparator used.

In aortic stenosis, TAVI/TAVR showed similar results to surgical replacement for the composite outcome of all-cause death or disabling stroke over five years, with moderate certainty of the evidence. The safety profile differed between strategies: the transcatheter approach was associated with a lower incidence of bleeding, acute kidney injury, and atrial fibrillation, but a higher risk of vascular complications, need for pacemaker implantation, and residual aortic regurgitation[8,9,16,19,24].

In secondary mitral regurgitation, the results indicated a possible benefit of edge-to-edge transcatheter repair combined with medical therapy, especially in patients carefully selected. However, the high heterogeneity among MITRAFR, COAPT, and RESHAPE-HF2 prevented a uniform conclusion for all populations, reinforcing that the response to treatment depends on the interaction between severity of regurgitation, ventricular remodeling, valve anatomy, and therapeutic optimization[30–35].

In tricuspid interventions, the most consistent benefits were observed in quality of life, functional status, and reduction in the severity of regurgitation. Up to the one-year horizon, no statistically robust reduction in mortality or hospital-

ization for heart failure was demonstrated, in part due to the small number of events, wide confidence intervals, and differences in the metrics used[41–45].

Available data also suggested cardiac remodeling and improved hemodynamics after transcatheter interventions. However, the heterogeneity of parameters, imaging methods, and evaluation periods prevented the performance of specific remodeling meta-analyses[17,34,43].

Taken together, the findings support that the choice between transcatheter intervention, surgery, and clinical treatment should be individualized and carried out by a multidisciplinary team. The decision should consider operative risk, age, life expectancy, valvular anatomy, ventricular function, comorbidities, the expected durability of the device, and the possibilities for future interventions.

Although the aortic evidence is more mature, long-term investigations on prosthetic durability, reintervention, and lifecycle strategies remain necessary. In mitral and tricuspid valvular disease, future studies should improve patient selection, standardize outcomes, and determine whether functional and hemodynamic benefits translate into sustained reductions in hospitalizations and mortality.

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