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Left ventricular ejection fraction and benefit of tricuspid valve interventions – insights from the international TRIGISTRY

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Aims

The impact of treatment for tricuspid regurgitation (TR) across different levels of left ventricular ejection fraction (LVEF) remains uncertain. This study aimed to compare the outcomes of surgical and transcatheter tricuspid valve interventions (TTVI) to conservative (medical) management across LVEF categories.

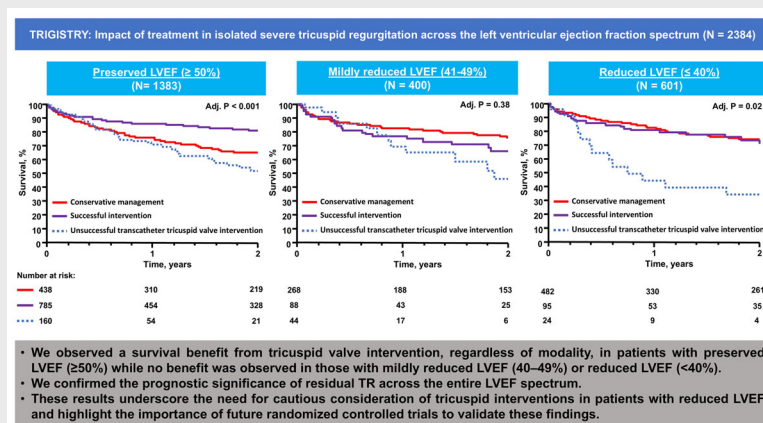
Methods and results

Patients with severe isolated TR from the TRIGISTRY, a multicentre international registry, were categorized based on LVEF (preserved ejection fraction [pEF]: $\geq 50\%$, mildly reduced ejection fraction [mrEF]: 41–49%, and reduced ejection fraction [rEF]: $\leq 40\%$). We assessed the impact of treatment modality and procedural success (mild-to-moderate or lower residual TR) on 2-year survival within each LVEF category. Among 2384 patients, 1383 had pEF, 400 had mrEF, and 601 had rEF. Compared to conservative management, surgery ($p < 0.0005$) and TTVI ($p < 0.0001$) were associated with a survival benefit in patients with pEF. No significant survival advantage was observed in patients with mrEF ($p = 0.28$ for both), nor in those with rEF ($p = 0.76$ and $p = 0.22$, respectively). Similar results were obtained when surgical and transcatheter interventions were grouped ($p < 0.0001$, $p = 0.17$ and $p = 0.29$ in patients with pEF, mrEF and rEF, respectively). Patients with residual TR after TTVI exhibited a trend toward worse survival compared to those managed conservatively across all LVEF categories ($p = 0.47$, $p = 0.33$ and $p = 0.008$ in pEF, mrEF and rEF, respectively).

Conclusions

Transcatheter tricuspid valve intervention, whether surgical or transcatheter-based, was associated with improved survival in patients with pEF but not in those with mrEF or rEF. Residual TR remained a significant prognostic factor across the entire LVEF spectrum. These findings highlight the need for careful patient selection when considering TTVI in individuals with rEF.

Graphical Abstract



Patients with isolated severe tricuspid regurgitation (TR) from TRIGISTRY were stratified by left ventricular ejection fraction (LVEF) into preserved ($\geq 50\%$), mildly reduced (41–49%) and reduced ($\leq 40\%$) groups and 2-year survival was evaluated. In patients with preserved LVEF, surgical or successful transcatheter-based treatment, resulted in favourable survival outcomes, while not in mildly reduced or reduced LVEF. Additionally, residual TR had prognostic implications across the entire LVEF spectrum.

Keywords

Tricuspid regurgitation • Transcatheter intervention • Procedural success • Futility

Introduction

The prevalence of tricuspid regurgitation (TR) is estimated at around 0.55% in the general population, similar to that of aortic stenosis, and it increases significantly with age.^{1–4} TR is even more common in patients with heart failure (HF), regardless of left ventricular ejection fraction (LVEF), affecting both those with HF and preserved (HFpEF) or reduced ejection fraction (HFrEF).^{3,4} TR is usually managed conservatively due to the misconception that surgery is intrinsically associated with prohibitively high mortality rates.^{5–7} Recently, TR treatment has gained significant interest with the development of less invasive transcatheter tricuspid valve (TV) therapies.^{8,9}

We and others have shown that clinical presentation and impact of TR on right ventricular (RV), kidney, and liver dysfunction are the main drivers of the observed poor survival after surgery but that excellent outcomes can be achieved when an intervention is performed early enough in the disease course, before the occurrence of end-organ consequences.^{6,10–12} The severity of the clinical presentation can be captured into the TRI-SCORE which accurately predicts surgical risk and in-hospital mortality.¹³ A survival benefit of either surgical or transcatheter intervention has been shown in patients with low and to a lower extent intermediate TRI-SCORE categories but not in patients with high TRI-SCORE.^{14,15} LVEF is one parameter integrated into the TRI-SCORE but presented as a dichotomic variable (above or below 60%) and its specific association with survival in patients with TR considered for a surgical or transcatheter intervention has not been specifically evaluated. This is critical as evidence clearly supports the importance of patient selection and timing of intervention to demonstrate the benefit of TV interventions.

Using data from TRIGISTRY, an international multicentre registry of patients with severe isolated TR treated either medically, surgically, or with transcatheter therapies, we aimed to assess whether the benefit of a TV intervention varies according to LVEF, accounting for the overall clinical presentation as assessed using the TRI-SCORE.

Methods

Study design

TRIGISTRY (ClinicalTrials.gov, NCT05825898) is an international, multicentre registry involving 33 centres across 10 countries (Austria, Canada, France, Germany, Israel, Italy, The Netherlands, Spain, Switzerland, and the USA). It enrolls consecutive adult patients with severe TR who are managed either conservatively (medically), with isolated TV surgery, or with transcatheter TV repair. Inclusion and exclusion criteria have been previously reported.^{14,15} Briefly, patients enrolled presented with severe functional (structurally normal TV), isolated (no moderate or greater concomitant left-sided valvular heart disease) TR on native valve. Patients who underwent an aortic or mitral valve intervention (either surgical or transcatheter) within 3 months prior to enrolment were also excluded. The surgical group only encompassed patients who underwent an isolated surgical TV repair or replacement (i.e. no concomitant intervention such as mitral or aortic valve surgery, or coronary artery bypass graft). All transcatheter TV repair techniques were included, while transcatheter TV replacements were not

considered. Data were stored anonymously in a centralized database at the University of Ottawa Heart Institute (UOHI) and analyses were performed by the UOHI Cardiovascular Research Methods Center. All the investigators were responsible for data collection and vouched for the completeness and accuracy of the data. All the authors reviewed and approved the manuscript. The study was conducted in accordance with local institutional policies and was approved by each local institutional review board. There was no dedicated funding for this study.

Baseline characteristics and primary endpoint

Clinical, laboratory, echocardiographic and outcome information were collected locally by each center. The TRI-SCORE was calculated for each patient (<https://www.tri-score.com/>).¹³ The TRI-SCORE derives from eight parameters (age ≥ 70 years, New York Heart Association functional class III–IV, right-sided HF signs, daily dose of furosemide ≥ 125 mg, glomerular filtration rate < 30 ml/min, elevated total bilirubin, LVEF $< 60\%$, moderate/severe RV dysfunction) and ranges from 0 to 12 points. Patients were divided into three subsets based on previously validated TRI-SCORE risk categories and predicted post-operative mortality (low risk: ≤ 3 points, intermediate risk: 4–5 points, and high risk: ≥ 6 points). Procedural success was defined as mild-to-moderate or lower residual TR after intervention. The primary endpoint was all-cause mortality at 2 years.

Echocardiographic evaluation

Echocardiographic parameters were provided by participating centres and no measurements were centrally performed in TRIGISTRY. Left and right ventricular and atrial dimensions were assessed locally according to recommended cut-offs.¹⁶ TR severity was graded using an integrative multiparametric approach as recommended.^{17,18} Residual TR after transcatheter or surgical intervention was semi-quantitatively graded using a 4-grade scheme (mild [1+], mild-to-moderate [2+], moderate-to-severe [3+], and severe [4+]) as previously reported.^{19,20} Procedural success was defined as mild-to-moderate or lower residual TR ($\leq 2+$) post-intervention. LVEF was calculated from the apical four- and two-chamber views according to Simpson's biplane method or was visually assessed. Patients were divided into three LVEF categories: preserved ejection fraction (pEF) ($\geq 50\%$), mildly reduced ejection fraction (mrEF) (41–49%), and reduced ejection fraction (rEF) ($\leq 40\%$).²¹

Statistical analysis

All categorical variables were expressed as count and percentage, while continuous variables were described as either mean $\pm$ standard deviation or median and interquartile range (25th–75th percentile) as required. Comparisons of baseline characteristics between groups were conducted using ANOVA, chi-square, Student's *t*-test or non-parametric Wilcoxon test as appropriate. Actuarial survival rates were calculated and presented using the Kaplan–Meier method. Due to violation of the proportional hazard assumption, the restricted mean survival time (RMST) was utilized as an alternative to compare survival between treatment groups (medical, surgical, and transcatheter) overall and in each LVEF category. The survival difference between groups was expressed using the RMST difference using 95% confidence intervals. Univariate and multivariate analyses (adjusted for age, sex, presence of atrial fibrillation [AF], diabetes, chronic lung disease, coronary artery disease, previous left heart valve intervention

and TRI-SCORE categories) were conducted. Two-by-two comparisons were also performed using the RMST method. All analyses were performed using a two-tailed level of $p < 0.05$. SAS statistical software version 9.4 (SAS Institute Inc, Cary, NC, USA) was utilized for all calculations.

Results

Study population

Out of the 2413 patients initially enrolled in TRIGISTRY, 29 were excluded due to missing LVEF numerical value, resulting in a final study population of 2384 patients. Among them, 1188 were treated medically, 551 underwent surgery, and 645 underwent a transcatheter intervention; 1383 patients presented with pEF, 400 patients with mrEF, and 601 patients with rEF. The rate of medically treated patients increased as LVEF decreased (32% in patients with pEF, 67% in patients with mrEF, and 80% in patients with rEF, $p < 0.0001$).

Compared to patients with mrEF and rEF, those with pEF were significantly older (74 ± 11 years, 72 ± 13 years and 70 ± 13 years, respectively, $p < 0.0001$), more frequently female (62%, 50% and 34%, respectively, $p < 0.0001$), had higher rates of prior left-sided intervention (32%, 21% and 18%, respectively, $p < 0.0001$), AF (73%, 62% and 54%, respectively, $p < 0.0001$) and RV dilatation (67%, 58% and 58%, respectively, $p < 0.0001$). Patients with rEF exhibited a higher rate of comorbidities such as coronary artery disease (51%, 43% and 31%, $p < 0.0001$), diabetes (31%, 24% and 24%, $p = 0.0028$) and more often had pacemakers (35%, 34% and 22%, $p < 0.0001$) in comparison to mrEF and pEF. Patients with rEF also showed more signs of end-organ dysfunction than mrEF and pEF (glomerular filtration rate < 30 ml/min: 14.5%, 10.3% and 9.7%, respectively, $p = 0.0065$; elevated bilirubin: 39%, 25% and 25%, respectively, $p < 0.0001$). Consequently, patients with rEF exhibited higher TRI-SCORE ($p < 0.0001$). Interestingly, functional status (New York Heart Association functional class III–IV) was not different between LVEF groups (pEF 65%, mrEF 64%, rEF 66%, $p = 0.82$). Comparisons of baseline characteristics according to LVEF category are presented in Table 1 and further comparisons according to treatment modalities within each LVEF category are detailed in online supplementary Tables S1–S3.

Impact of intervention across the left ventricular ejection fraction spectrum

Overall population

The impact of intervention in the overall population has been previously reported but briefly there was no difference in outcome according to treatment group in univariate analysis ($p = 0.11$) and after adjustment for age, sex, presence of AF, diabetes, chronic lung disease, coronary artery disease, previous left heart valve intervention and TRI-SCORE categories ($p = 0.10$).

Preserved ejection fraction

Out of the 1383 patients with pEF, 438 patients were medically treated, 469 patients underwent isolated TV surgery, and

476 patients underwent a transcatheter intervention (online supplementary Table S1). There was a significant survival difference according to treatment group in univariate ($p = 0.0002$) and multivariate analysis ($p < 0.0001$) with both the surgical ($p < 0.0005$) and the transcatheter groups experiencing higher survival rates compared with the medical group ($p < 0.0001$) (Figure 1A and Table 2).

Mildly reduced ejection fraction

No difference in survival according to treatment modality was observed in univariate ($p = 0.29$) and multivariate analyses ($p = 0.39$). The two-by-two comparisons did not show any survival difference between the surgical group or the transcatheter group and the medical group (both $p = 0.28$) (Figure 1B, Table 2 and online supplementary Table S2).

Reduced ejection fraction

No statistical difference in survival was observed between the three treatment groups in univariate ($p = 0.08$) and multivariate analyses ($p = 0.47$). The two-by-two comparisons did not show any survival difference between the medical and the surgical group ($p = 0.76$). In univariate analysis, the transcatheter group had significantly worse survival ($p = 0.03$), but this difference was no longer significant after adjustment ($p = 0.22$) (Figure 1C, Table 2 and online supplementary Table S3).

Intervention versus conservative management

Further analysis included the combination of the surgical and transcatheter groups ($n = 1196$) and comparison to the medical group ($n = 1188$). Consistent with the individual analysis of each treatment group, multivariate analysis showed a benefit of intervention in patients with pEF ($p < 0.0001$) (Figure 2A), but not in those with mrEF ($p = 0.17$) (Figure 2B) or rEF ($p = 0.29$) (Figure 2C).

Impact of procedural success across the left ventricular ejection fraction spectrum

According to the type of intervention

Among the 645 patients who underwent a transcatheter intervention, procedural success, defined as achieving mild-to-moderate residual TR ($\leq 2+$), was achieved in 411 patients (65%). The remaining 224 patients (35%) had moderate-to-severe residual TR ($\geq 3+$). In contrast, the procedural success rate for surgery was 97%. Patients who underwent surgery, successful transcatheter interventions, and unsuccessful transcatheter interventions were compared with those in the medical treatment group in each LVEF category (Figure 3). In patients with pEF, both in univariate and multivariate analyses, there were significant differences in survival between groups ($p < 0.0001$) with lower mortality rates in the surgical ($p = 0.0006$) and the successful transcatheter groups ($p < 0.0001$) (Figure 3A). In patients with mrEF, no difference in survival was observed between groups both in univariate ($p = 0.41$) and multivariate analysis ($p = 0.57$) (Figure 3B). Two-by-two comparisons

Table 1 Baseline characteristics of the total study population stratified by left ventricular ejection fraction

Characteristics	Left ventricular ejection fraction			p-value
	≥50% (n = 1383)	41–49% (n = 400)	≤40% (n = 601)	
Clinical				
Age, years	74 ± 11	72 ± 13	70 ± 13	<0.0001
Age ≥70 years, n (%) ^a	983 (71)	274 (69)	346 (58)	<0.0001
Female sex, n (%)	863 (62)	198 (50)	202 (34)	<0.0001
Diabetes mellitus, n (%)	329 (24)	96 (24)	186 (31)	0.0028
Chronic lung disease, n (%)	282 (20)	65 (16)	114 (19)	0.1733
Coronary artery disease, n (%)	422 (31)	172 (43)	304 (51)	<0.0001
Permanent pacemaker, n (%)	296 (22)	134 (34)	211 (35)	<0.0001
Prior left heart valve intervention, n (%)	441 (32)	82 (21)	110 (18)	<0.0001
New York Heart Association functional class III–IV, n (%) ^a	892 (65)	256 (64)	395 (66)	0.8245
Right-sided heart failure signs, n (%) ^a	840 (61)	221 (55)	355 (59)	0.1416
Daily dose of loop diuretics, mg	83 ± 111	68 ± 72	94 ± 133	0.0064
Daily dose of loop diuretics ≥125 mg, n (%) ^a	247 (18)	48 (12)	101 (17)	0.0211
Atrial fibrillation, n (%)	962 (73)	237 (62)	318 (54)	<0.0001
Laboratory				
Haemoglobin, g/dl	11.5 ± 2	11.8 ± 2	12.1 ± 2	<0.0001
Creatinine, μmol/L	118 ± 77	120 ± 64	141 ± 87	<0.0001
Glomerular filtration rate, ml/min	62 ± 33	63 ± 34	62 ± 34	0.6840
Glomerular filtration rate <30 ml/min, n (%) ^a	134 (9.7)	41 (10.3)	87 (14.5)	0.0065
Elevated total bilirubin, n (%) ^a	340 (25)	98 (25)	234 (39)	<0.0001
Echocardiographic				
Left ventricular ejection fraction, %	59 ± 6	45 ± 2	29 ± 8	<0.0001
Left ventricular ejection fraction <60%, n (%) ^a	695 (50)	400 (100)	601 (100)	<0.0001
Moderate/severe right ventricular dilatation, n (%)	893 (67)	225 (58)	342 (58)	<0.0001
Moderate/severe right ventricular dysfunction, n (%) ^a	406 (29)	183 (46)	389 (65)	<0.0001
Systolic pulmonary artery pressure, mmHg	48 ± 17	50 ± 21	50 ± 17	0.0100
TRI-SCORE				
≤3, n (%)	480 (35)	117 (29)	137 (23)	<0.0001
4–5, n (%)	500 (36)	140 (35)	162 (27)	<0.0001
≥6, n (%)	403 (29)	143 (36)	302 (50)	<0.0001

Values are n (%), mean ± standard deviation, or median [interquartile range].

^aThe eight parameters included in the TRI-SCORE.

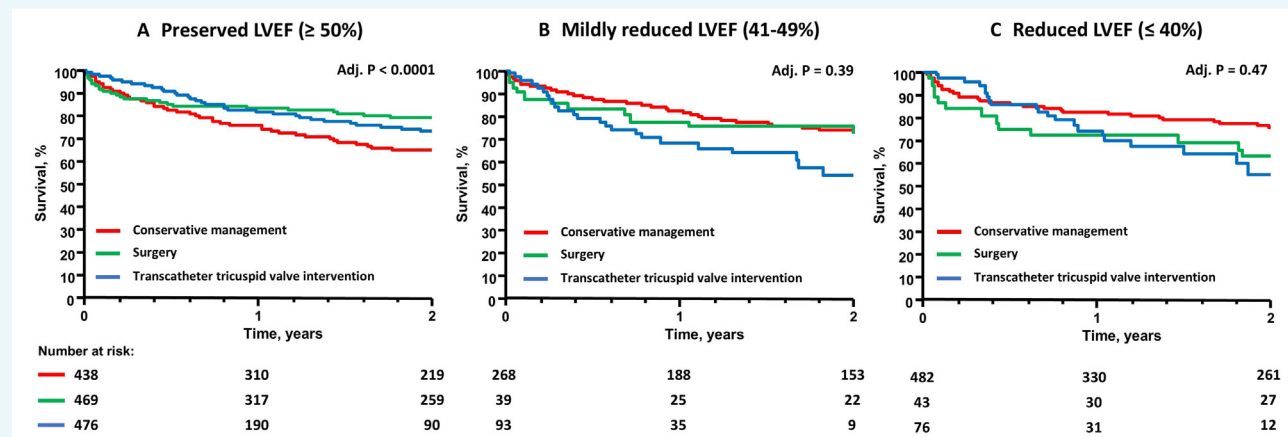


Figure 1 Survival of patients according to treatment modality across the left ventricular ejection fraction (LVEF) spectrum. Kaplan–Meier curves depicting the survival of patients according to the respective medical, surgical and transcatheter treatment groups. (A) Patients with preserved LVEF (≥50%), (B) patients with mildly reduced LVEF (41–49%), and (C) patients with reduced LVEF (≤40%).

Table 2 Crude and adjusted survival in patients according to treatment modality across the left ventricular ejection fraction spectrum

Left ventricular ejection fraction	Treatment group	Crude			Adjusted ^a		
		Estimate	95% confidence interval	p-value	Estimate	95% confidence interval	p-value
Preserved	Surgery	0.19	0.1–0.29	0.0001	0.18	0.08–0.28	0.0005
	Transcatheter tricuspid valve intervention	0.17	0.08–0.26	0.0003	0.23	0.14–0.33	<0.0001
Mildly reduced	Surgery	–0.19	–0.47 to 0.09	0.18	–0.16	–0.46 to 0.13	0.28
	Transcatheter tricuspid valve intervention	–0.08	–0.24 to 0.07	0.29	–0.10	–0.3 to 0.08	0.28
Reduced	Surgery	–0.07	–0.31 to 0.17	0.56	–0.03	–0.28 to 0.20	0.76
	Transcatheter tricuspid valve intervention	–0.20	–0.39 to –0.02	0.03	–0.11	–0.3 to 0.07	0.22

Patients with conservative management were considered as the reference group. Restricted mean survival time difference analyses are presented for crude and adjusted models. The restricted mean survival time difference represents the average event-free time until the 2-year endpoint of treatment groups in comparison to conservatively managed patients.

^aAdjusted for age, gender, diabetes mellitus, chronic lung disease, coronary artery disease, previous left heart surgery, atrial fibrillation and TRI-SCORE category.

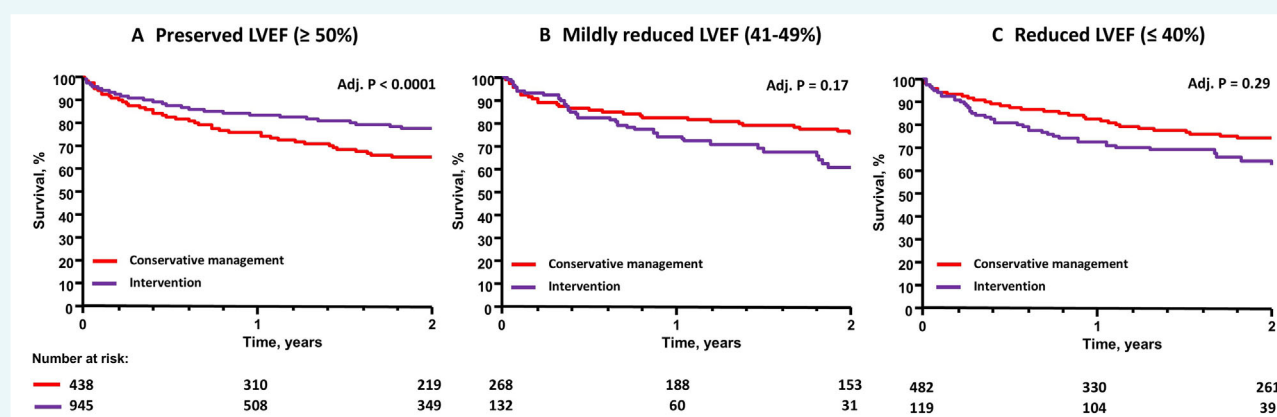


Figure 2 Survival of patients who underwent surgical or transcatheter intervention compared to the medical group across the left ventricular ejection fraction (LVEF) spectrum. Kaplan–Meier curves depicting the survival of patients who underwent an isolated tricuspid valve intervention (surgery or a transcatheter) versus those who were conservatively managed (medical group). (A) Patients with preserved LVEF ($\geq 50\%$), (B) patients with mildly reduced LVEF (41–49%), and (C) patients with reduced LVEF ($\leq 40\%$).

also did not show any differences. In patients with rEF, there was a significant difference in survival between groups in univariate analysis ($p = 0.0006$) which was of borderline statistical significance in multivariate analysis ($p = 0.06$) mostly driven by a worse survival in patients with unsuccessful intervention ($p = 0.0008$ vs. medical group) (Figure 3C).

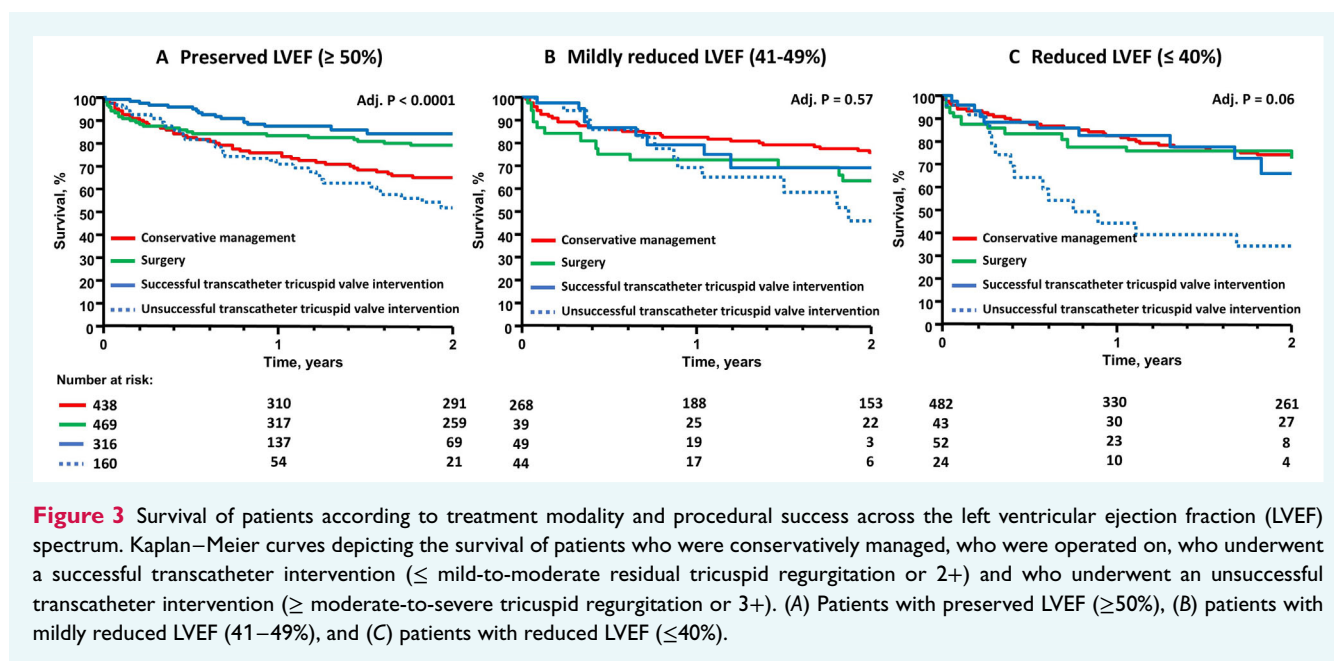
Intervention versus conservative management

Similar results were observed when the surgical and the successful transcatheter groups were combined. Significant differences in survival were noted between groups in patients with pEF ($p < 0.001$), no difference in patients with mrEF ($p = 0.38$), and significant differences in those with rEF ($p = 0.02$) (Graphical Abstract). In patients with pEF, those successfully treated had higher survival rates than

those medically treated ($p < 0.0001$), while the survival of patients with unsuccessful results was similar to that of the medical group ($p = 0.50$). In patients with mrEF, the survival rates of both successfully and unsuccessfully treated groups were not significantly different from those of the medical group ($p = 0.23$ and $p = 0.32$, respectively). In patients with rEF, differences in survival were again mainly driven by lower survival in patients with unsuccessful results ($p = 0.008$).

Discussion

In this large international registry of patients with severe isolated secondary TR, we assessed the 2-year survival impact of TV surgery and transcatheter repair versus medical therapy



across the LVEF spectrum. Intervention was associated with higher survival in patients with preserved LVEF but offered no benefit in those with mildly reduced or reduced LVEF compared to conservative management. These findings remained consistent even when accounting for procedural outcomes and residual TR, a key prognostic factor across all LVEF categories. Our results highlight the need for careful patient selection and emphasize the importance of procedural success in tricuspid interventions.

Tricuspid regurgitation has consistently been linked to increased mortality in various settings, including among patients with mitral regurgitation and HF.^{3,4,22} In a large administrative database of nearly half a million individuals with HF, TR was found to have a detrimental impact across all subsets, including age, sex, comorbidities, clinical presentation, presence of mitral regurgitation, and LVEF (both HFrEF and HFpEF). The severity of TR was directly correlated with worse outcomes, suggesting a dose–response effect and a potential causal relationship.⁴ However, definitive proof that correcting TR improves survival is still lacking. Three recent randomized controlled trials – TRILUMINATE, Tri.Fr, and TRISCEND II – compared transcatheter TV intervention (TTVI) (either repair or replacement) to medical therapy alone (primarily diuretics).^{8,23,24} These trials consistently demonstrated improvements in quality of life and functional status but failed to show any effect on survival or HF admissions at 1 year. Several explanations have been proposed for these discordant findings, including the low number of patients enrolled, procedural results, complication rates especially with transcatheter replacement, short follow-up duration, and the clinical presentation and stage of the disease. The severity of the clinical presentation is particularly significant and has been identified as a major predictor of outcomes.^{6,11,13} This severity is also the main reason for the high surgical mortality observed after isolated TV surgeries in most

series. The TRI-SCORE captures the disease stage and end-organ consequences, and it has been shown that the benefit of an intervention on survival was more likely in patients with low and, to a lesser extent, intermediate TRI-SCORE, while no benefit was seen in those with high TRI-SCORE.^{14,15} Other grading systems have been proposed although less comprehensive.¹² These results suggest that a holistic and multiparametric approach in severe TR in addition to careful patient selection is crucial to demonstrating the benefit of TV interventions.

Left ventricular ejection fraction is a crucial prognostic factor in left-sided valvular disease²⁵ and is also included in the TRI-SCORE but as a dichotomic parameter (above or below 60%) and its association with the benefits of TV interventions has not been specifically evaluated. In this study, we compared the survival rates of patients who underwent TV interventions to those who received medical treatment across the entire LVEF spectrum. We found that a TV intervention was associated with a higher survival rate than conservative management in patients with preserved LVEF but there was no apparent benefit for those with mildly reduced or reduced LVEF. Importantly, our results were supported by both univariate and multivariate analyses after adjustment for the main known prognostic factors including the TRI-SCORE and were consistent regardless of the type of intervention, whether considered individually or combined, and when the analysis was limited to patients with good procedural outcomes with mild-to-moderate or lower residual TR. Mechanistic insight into differences of impact to TTVI according to left ventricular systolic function deserves discussion. HF subtypes present as different phenotypes and baseline characteristics varied significantly across the three LVEF categories. Patients with preserved LVEF were generally older, more often female, and predominantly included those with atrial secondary TR, which has been linked to better outcomes compared to ventricular secondary TR in several observational studies.^{26,27}

However, the subset with preserved LVEF was not exclusively composed of patients with atrial secondary TR. Approximately one-third had undergone prior left-sided valve interventions, and 20% had a pacemaker. The benefit of intervention was observed across the entire subset, although no specific analysis by aetiology could be performed. It is also possible that in the setting of left ventricular systolic dysfunction, prognosis is primarily driven by left-sided disease, with TR serving more as a marker of poor outcome rather than a direct contributor, in contrast to patients with preserved LVEF, in whom TR may play a more causative role. Additionally, HF subtypes not only present with distinct clinical phenotypes but also differ in the degree of sympathetic nervous system and renin–angiotensin–aldosterone system activation, as well as myocardial fibrosis, all of which contribute to varying responses to pharmacological therapy. Regardless of the underlying mechanisms, the pathophysiological interaction between TR and LVEF is highly relevant and remains a key focus of ongoing research. We and others have shown that residual TR was a major prognostic factor,^{15,28,29} and that a more granular 4-grade scheme compared to the currently recommended 3-grade scheme provided more discriminative value.^{19,20} Our findings build on existing literature regarding the impact of residual TR, highlighting a neutral effect of unsuccessful procedures across the LVEF spectrum and a potentially detrimental impact of residual TR in patients with reduced LVEF. Overall, our results suggest that patients with preserved LVEF are more likely to benefit from TV interventions, especially when performed early in the disease course, while those with reduced LVEF may see minimal or no benefit. These observational and hypothesis-generating results should inform the design and enrolment criteria of future randomized controlled trials. Notably, the proportion of patients with reduced LVEF was 12% in TRILUMINATE and 25% in Tri.Fr, while nearly all patients in TRISCEND II had preserved LVEF. Whether left ventricular strain analysis can further discriminate patients with preserved LVEF who benefit most from TTVI remains to be demonstrated. Therefore, our findings provide new insights into a subset that has previously been relatively underexplored.

Strengths and limitations

The present study deserves several comments. Firstly, the retrospective design may introduce inherent bias, necessitating cautious interpretation of the results. However, the TRIGISTRY population was derived from the consecutive collection of patients with severe TR across participating centres, which strengthens the validity of the dataset. Secondly, this study was observational and included significant differences between groups. However, our findings remained consistent in both univariate and multivariate analyses adjusting for common clinical confounders and TRI-SCORE. Our results were also independent of the intervention modality, and persisted after excluding patients with significant residual TR. Nevertheless, the possibility of unmeasured confounders influencing survival in the subgroups cannot be ruled out, underscoring the need for future randomized controlled trials to validate these findings. Thirdly, several subgroups had small sample sizes, raising the possibility that the benefit of intervention may have been

missed due to limited statistical power. However, as noted earlier, the results remained consistent when surgical and transcatheter interventions were analysed together. Fourthly, there was no centralized echocardiographic evaluation (core lab). TR severity at baseline and residual TR post-intervention were assessed locally by each centre. While this could introduce variability, the evaluations were conducted by experienced cardiologists, and the inclusion of multiple international centres helps mitigate potential local systematic bias. Similarly, RV function was also graded by each centre locally. Quantitative assessment of RV function may add incremental prognostic value but was not available in this study. Fifthly, LVEF is included in the TRI-SCORE as a binary and simplified parameter ($\leq 60\%$ or $> 60\%$). In this study, we utilized more detailed LVEF categories, which should not be viewed as redundant and warranted adjustment for TRI-SCORE in the multivariate analysis. In addition, no follow-up echocardiograms were collected and whether changes in LVEF occurred during follow-up cannot be excluded. Sixthly, In TRIGISTRY, only baseline information on diuretic use and dose was collected, while data on HF medications and treatment changes over time were not available, although such information could provide valuable insights. Seventhly, the study focused solely on all-cause mortality. Although widely used, this endpoint does not capture other relevant outcomes, such as HF hospitalizations, which could provide additional valuable insights but were not collected. Eighthly, the survival rate of medically treated patients was higher in those with reduced LVEF compared to those with preserved or mildly reduced LVEF. However, patients with reduced LVEF were younger, whereas those treated presented with more advanced disease stage. We performed within-LVEF category adjustments and comparisons of survival across LVEF categories should be interpreted with caution, as they are unadjusted. Additionally, even if the observed survival of medically treated patients with mildly reduced or reduced LVEF was markedly lower, it is very unlikely that a treatment benefit would have been observed. Lastly, the success of TTVI partially depends on the operator's experience and patient selection, which may influence procedural outcomes. However, the variability in operator success rates in TRIGISTRY reflects real-world application and provides a more representative depiction of TTVI outcomes.

Conclusion

This analysis, based on TRIGISTRY, a large international multicentre registry of patients with severe isolated secondary TR, evaluated the 2-year survival impact of isolated TV surgery and transcatheter TV repair compared to medical therapy across the LVEF spectrum. Our findings revealed a survival benefit from TV intervention, regardless of modality, in patients with preserved LVEF ($\geq 50\%$) while no benefit was observed in those with mildly reduced LVEF (40–49%) or reduced LVEF ($< 40\%$). Furthermore, we confirmed the prognostic significance of residual TR across the entire LVEF spectrum. These results underscore the need for cautious consideration of tricuspid interventions in patients with reduced LVEF and highlight the importance of future randomized controlled trials to validate these findings.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Conflict of interest: J.D. reports speaker or proctoring fees from Abbott Vascular. V.D. received speaker and proctoring fees from Abbott Vascular and Edwards Lifesciences. N.A.M. received speaker fees from GE Healthcare, Philips Ultrasound, Abbott Vascular and Edwards Lifesciences and research grants from Alnylam, Pfizer, Pie Medical, Edwards Lifesciences and AstraZeneca. M.T. received consulting or speaker fees from Abbott Vascular, Edwards Lifesciences, Boston Scientific, Medtronic, Shenqi Medical, PiCardia, CardioValve, Coremedic, ReCross, CorQuest, VentriMend and Simulands. C.I. received consulting fees from Abbott Vascular and Edwards Lifesciences. L.N.F. received consulting or speaker fees from Abbott Vascular, Edwards Lifesciences and Products and Features. J.F.O. received consulting or speaker fees from Abbott, Delacroix Chevalier and Medtronic. R.E.L. received consulting or speaker fees from Abbott Vascular, Edwards Lifesciences, Boston Scientific, Jensacare, Valgen and Venus Medtech. Y.L.B. received proctoring fees from Abbott Vascular and speaker fees from Abbott Vascular, GE Healthcare, Edwards Lifesciences and Siemens. J.H. received grant and consulting fees from Edwards Lifesciences. A.C. received proctoring fees from Abbott Vascular and speaker fees from Abbott Vascular, Bristol Myers Squibb, Edwards Lifesciences, GE Healthcare, MSD and Pfizer. T.M. received speaker or consulting fees from Abbott, Edwards Lifesciences, Medtronic, Microport and GE. J.L.Z. received consulting or speaker fees from Novartis, Novo Nordisk, Bayer, Pfizer, Daiichi and Medtronic. R.S.v.B. received consulting or speaker fees from Abbott Vascular, Edwards Lifesciences, Medtronic, Philips and Siemens. R.T.H. reports speaker fees from Abbott Structural, Baylis Medical, Edwards Lifesciences and Philips Healthcare; she has institutional consulting contracts for which she receives no direct compensation with Abbott Structural, Anteris, Boston Scientific, Edwards Lifesciences, Medtronic, Novartis and Philips Healthcare; she is Chief Scientific Officer for the Echocardiography Core Laboratory at the Cardiovascular Research Foundation for multiple industry-sponsored valve trials, for which she receives no direct industry compensation. M.A. received speaker honoraria from Abbott Vascular and Edwards Lifesciences. M.N. received proctoring fees from Abbott Vascular. M.C.A. received consulting fees from Edwards Lifesciences, and for lectures and proctoring from Abbott Vascular and Atricure. V.R. received consulting fees and research grant (to institution) by Abbott Vascular and Edwards Lifesciences. J.C. received consulting fees from Medtronic. F.M. received grant and/or research institutional support from Abbott, Medtronic, Edwards Lifesciences, Biotronik, Boston Scientific Corporation, NVT, Terumo, Venus, and consulting fees, honoraria personal and institutional from Abbott, Medtronic, Edwards Lifesciences, Xeltis, Cardiovalve, Occlufit, Simulands, Mtex, Venus, Squadra, royalty income/IP rights from Edwards Lifesciences and is shareholder (including share options) of Cardiogard, Cardiovalve, Magenta, SwissVortex, Transseptalsolutions, 4Tech and Perifect. P.B. received proctoring fees for Abbott Vascular, speaker fees and is an advisory board member for Edwards Lifesciences. D.M.Z. received research grants from Edwards Lifesciences. All other authors have nothing to disclose.

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