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Clinical Research

Relationship Between Diuretic Dose and Outcome Following Transcatheter Tricuspid Valve Repair for Severe Tricuspid Regurgitation

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See editorial by Le Ruz et al., pages 658-660 of this issue.

ABSTRACT

Background: Severe tricuspid regurgitation (TR) leads to right heart volume overload and failure. Diuretic treatment is a cornerstone of medical therapy, being so far the only option in inoperable patients. Transcatheter tricuspid valve repair (TTVr) has become a viable treatment for these patients. In this study we evaluated the association between baseline loop diuretic dose and clinical outcomes after TTVr in patients with severe symptomatic TR.

Methods: In this retrospective, single-center study, symptomatic patients with severe TR treated between 2017 and 2022 with TTVr were analyzed for the combined endpoint of heart failure hospitalization (HFH) or death at 1-year follow-up, depending on loop diuretic dose.

Results: For the 225 patients (median age 80 years, 67% women) analyzed, the receiver-operating characteristic curve revealed an optimal cutoff of 95-mg furosemide-equivalent, stratifying into high-diuretic-dose (HDD) and low-diuretic-dose (LDD) groups. Intraprocedural success according to Tricuspid Valve Academic Research Consortium criteria was poorer in HDD patients (46% vs 68%, $P = 0.002$), as were outcomes (1-year mortality: 44% vs 11%, $P < 0.001$; HFH: 22% vs 10%, $P < 0.001$). HDD was independently associated with the combined endpoint (hazard ratio 2.498, 95% confidence interval 1.537-4.058, $P < 0.001$). New York Heart Association classification improved by 1 class or more in

RÉSUMÉ

Contexte : L'insuffisance tricuspidienne (IT) sévère entraîne une surcharge volémique et une défaillance du cœur droit. La prise de diurétiques est la pierre angulaire du traitement pharmacologique et à ce jour, la seule option envisageable chez les patients inopérables. La réparation de la valve tricuspide par cathéter (RVTC) est désormais un traitement viable pour ces patients. Cette étude visait à évaluer le lien entre la dose initiale de diurétique de l'anse et les résultats cliniques après une RVTC chez des patients présentant une IT symptomatique sévère.

Méthodologie : Cette étude rétrospective a été menée dans un seul centre auprès de patients présentant une IT sévère symptomatique qui s'étaient prêtés à une RVTC entre 2017 et 2022, analysés selon le critère d'évaluation combinant l'hospitalisation pour insuffisance cardiaque (IC) et le décès après 1 an de suivi, en fonction de la dose de diurétique de l'anse.

Résultats : Parmi les 225 patients analysés (âge médian de 80 ans; 67 % de femmes), la courbe RCO (*receiver operating characteristic*) a révélé que la valeur seuil optimale d'équivalent furosémide utilisée pour répartir les patients en groupes selon qu'ils recevaient une dose élevée ou une faible dose de diurétique (DED ou FDD) était de 95 mg. Le taux de succès intra-interventionnel selon les critères du TVARC (Tricuspid

Clinically relevant tricuspid regurgitation (TR) is known to lead to right heart volume overload and consecutively to dilation of the right atrium and right ventricle (RV), resulting in RV dysfunction and right heart failure.[1,2] About 4% of the population ≥ 75 years of age suffer from at least moderate TR, with the etiology being secondary in > 90%.[3] One-year mortality for moderate TR is around 20% but for severe TR it increases to 37%.[4] Due to frailty and comorbidities, most of these elderly patients are considered inoperable, and treatment for TR until recently consisted of medical therapy with diuretic drugs such as loop diuretics, thiazide diuretics, and mineral corticoid receptor antagonists (MRAs). Although

Keywords: loop diuretics; right heart failure; tricuspid regurgitation; transcatheter tricuspid valve repair; clinical outcomes

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68% of patients. Overall, the median diuretic dose at follow-up (median 388 days, interquartile range 362-537 days) remained stable.
Conclusions: Patients with HDD undergoing TTVr had worse procedural and clinical outcomes. However, they experienced symptom relief without diuretic escalation. Diuretic increases in patients with severe TR should be closely monitored and may indicate a need for prompt TTVr evaluation. This may prevent diuretic-related side effects and improve outcomes.

Valve Academic Research Consortium) était nettement inférieur chez les patients appartenant au groupe DED (46 % *vs* 68 %; $p = 0,002$), et les résultats étaient à l'avenant (mortalité à 1 an : 44 % *vs* 11 %; $p < 0,001$; hospitalisation pour IC : 22 % *vs* 10 %; $p < 0,001$). Un lien indépendant a été établi entre une dose élevée de diurétique et le critère d'évaluation combiné (rapport des risques instantanés : 2,498; intervalle de confiance à 95 % : 1,537 à 4,058; $p < 0,001$). La classification de la New York Heart Association s'est améliorée d'au moins une classe chez 68 % des patients. Dans l'ensemble, la dose médiane de diurétique au suivi (médiane de 388 jours; intervalle interquartile : 362 à 537 jours) est demeurée stable.
Conclusions : Les résultats cliniques et interventionnels ont été les moins bons chez les patients ayant reçu une dose élevée de diurétique qui se sont prêtés à une RVTC. Ils ont néanmoins bénéficié d'un soulagement symptomatique sans qu'il soit nécessaire d'augmenter la dose de diurétique. L'augmentation de la dose de diurétique chez les patients présentant une IT sévère doit faire l'objet d'une étroite surveillance et pourrait indiquer la nécessité d'envisager rapidement une RVTC. Cette stratégie pourrait permettre d'éviter les effets secondaires liés aux diurétiques et d'améliorer les résultats.

diuretics are relatively safe drugs, side effects can especially harm elderly patients. Hypokalemia can lead to cardiac arrhythmias and muscle weakness and hyponatremia can cause confusion and delirium. In addition, a positive correlation between diuretic dose and mortality was demonstrated in historic studies, caused by the consequences of hypovolemia, such as renal impairment and venous thromboembolism.[5,6] Furthermore, although diuretics provide immediate relief by intravascular volume reduction, they activate neurohormonal forces that are deleterious to both the heart and kidney.[7] The majority of patients with severe TR do not respond adequately to diuretics,[8] highlighting the need for alternative therapeutic options.

Transcatheter tricuspid valve repair (TTVr) has become a valid therapy option for high-risk elderly or frail patients with severe TR over the last couple of years. In Europe, approved interventional repair methods include tricuspid valve transcatheter edge-to-edge repair (T-TEER) using TriClip (Abbott Cardiovascular) or PASCAL (Edwards Lifesciences) devices and annuloplasty with the Cardioband (Edwards Lifesciences) device. In addition to TTVr, transcatheter tricuspid valve replacement (TTVR) has recently emerged as another treatment option, with the CE-marked EVOQUE system (Edwards Lifesciences) already available in Europe and other devices under investigation, such as the LuX-Valve system (Jenscare). According to current guidelines on the management of valvular heart disease, diuretics are described as a useful treatment option in patients with TR and right heart failure.[9] Transcatheter treatment of secondary severe TR was given a IIa recommendation in the European Guidelines and thus should be considered in high-risk patients.[10] Lately, randomized, controlled, multicenter trials, such as the **Tri**al to Evaluate Cardiovasc**u**lar Outco**m**es **i**n P**a**tients **Tre**ated With the Tricuspid Valve Repair System (TRILUMINATE) and Transcatheter Edge-to-Edge Repair for Severe Isolated Tricuspid Regurgitation (Tri.Fr), have compared conservative therapy with T-TEER. Although there was a significant improvement in quality of life, no differences in death or hospitalization for heart failure (HFH) could be shown at 1 year.[11,12] However, recently published 2-year outcomes of TRILUMINATE Pivotal demonstrated a significantly lower rate of recurrent HFH in T-TEER compared with medical therapy alone (0.19 vs 0.26 event per patient-year, $P = 0.02$), suggesting the potential for favorable long-term outcomes after TTVr.[13]

We hypothesize that a significant reduction of TR after interventional valve repair can induce a steady state of the underlying disease and thereby lead to a reduction of diuretic dose or at least avoidance of an increase.

Our aim in this study was to determine whether high diuretic dose before TTVr is associated with a poorer outcome and whether the diuretic dose can be reduced after successful TTVr to prevent adverse outcomes.

Methods

Study design and patient population

We performed a retrospective analysis that included all consecutive patients undergoing TTVr between January 2017 and December 2022 at the Heart Center of the University Hospital of Cologne with available paired data about diuretic dose at baseline and follow-up. All patients presented with at least severe TR and were assessed by an interdisciplinary heart team and declared inoperable. Interventional reconstruction was done either by T-TEER using the PASCAL or TriClip or by annuloplasty via Cardioband implantation. Procedures were performed as described elsewhere.[14,15]

Data assessment

Patients were analyzed for the combined endpoint of HFH and death. Baseline demographic and clinical data were obtained before TTVr. Follow-up data were either obtained at follow-up appointments in our outpatient clinic or through records from treating physicians. The respective patients were contacted by phone to complete follow-up in cases of lack of documentation or missed appointments. Data assessment was

approved and overseen by the local ethics committee of the University of Cologne. All collected data were obtained through a prospective register and written consent was provided by all patients before intervention. N terminal pro—B-type natriuretic protein (NT-proBNP) was logarithmized to enable better discrimination in the regression analysis. For loop diuretics the dose was determined as furosemide-equivalent (furosemide:torasemide at a 2:1 ratio), in milligrams. For all patients the reported dose represented long-term oral maintenance therapy at baseline and follow-up, respectively. Any bolus intravenous dosing was not considered in this regard. The intake of sodium-glucose transport protein-2 inhibitors was evaluated since **E**uropean **M**edicines **A**gency (EMA) approval for dapagliflozin in November 2020. TR severity was graded according to Hahn and Zamorano's 5-grade classification based on echocardiographic assessment as mild (I), moderate (II), severe (III), massive (IV), or torrential (V).[16]

Statistical analysis

The study cohort was stratified into 2 groups receiving a high dose (HDD) or low dose (LDD) of diuretics. The optimal cutoff value of 95 mg was determined using receiver-operating characteristic curve analysis, with the Youden index applied to identify the threshold that maximized sensitivity and specificity. For comparison of diuretic dose, especially the delta at long-term follow-up, the cohort was compared based on intraprocedural success according to **T**ricuspid **V**alve **A**cademic **R**esearch **C**onsortium (TVARC) criteria.[1] For comparison of diuretic dose and especially the delta at long-term follow-up the cohort was compared based on intraprocedural success, defined as reduction of TR to at least moderate. Nominal and ordinal data are expressed as number and percentage. Categorical variables were analyzed using the χ^2 test, and the Fisher exact test was applied when expected cell counts were < 5. Continuous variables are reported as median with interquartile range (IQR) and were analyzed using either the independent t test or the Mann-Whitney U test, depending on distribution. Normality was assessed using the Shapiro-Wilk test. The Wilcoxon signed-rank test was used for paired continuous data and the McNemar test was used for paired nominal data. Kaplan-Meier survival curves were computed and group comparisons were performed using the log-rank test.

Uni- and multivariable Cox regression analyses were used to determine individual factors related to patient outcome and to identify independent prognostic factors, respectively. The TRI-SCORE and EuroSCORE II were not included in the multivariable analysis because they are composite scores already incorporating several of the variables. Collinearity diagnostics were conducted using tolerance and variance inflation factor (VIF) values to assess potential multicollinearity among covariates included in the multivariable Cox regression model. Multicollinearity was considered a concern if variance inflation factor was > 5 or tolerance was < 0.1. For sensitivity analysis, inverse probability of treatment weighting (IPTW) was performed using propensity scores derived from baseline covariates to confirm the robustness of the main findings.

A logistic regression analysis was conducted that included baseline demographic, clinical, and echocardiographic parameters, to identify predictors of postprocedural changes in loop diuretic dose. To account for baseline risk, a sensitivity analysis was performed, and patients were stratified according to the validated International Multisite Transcatheter **Tri**cuspid **Valve** Therapies Registry (TRIVALVE) score, a clinical risk model for TTVI patients that does not include diuretic dose as a component. Patients were classified into low- and high-risk groups using the recommended cutoff of 2.5 points.[17] Two-tailed $P < 0.05$ was considered statistically significant. Statistical analysis was performed using SPSS version 27.0.1.0 (IBM Corp, Armonk, NY, USA).

Results

Study population

A total of 225 patients with paired data for diuretic dose at baseline and follow-up were included. Median age of the study population was 80 years; 67.3% were women. All patients presented with at least severe TR. Common comorbidities were atrial fibrillation (92%), arterial hypertension (83%), pulmonary hypertension (52%), and coronary artery disease (41%). About one fourth of the patients had diabetes mellitus (24%). A significant difference between LDD and HDD patients was shown for arterial hypertension and diabetes, both affecting more HDD patients (86.2% vs 72.9%, $P = 0.020$ and 33% vs 21%, $P = 0.046$, respectively). RV diameter was wider in HDD patients at 46 mm compared with 44 mm in LDD patients ($P = 0.008$), as was inferior vena cava diameter (27 vs 24 mm, $P < 0.001$). Most patients were highly symptomatic, with dyspnea, and were in **N**ew **Y**ork **H**eart **A**ssociation (NYHA) class III or IV (85%); 58% had peripheral edema the day before intervention despite decongestion therapy. All patients had heart failure: 81% with preserved ejection fraction (HFpEF) and 7% with reduced ejection fraction (HFrEF). NT-proBNP differed significantly between groups, with a median of 1959 ng/L in LDD patients and 2607 ng/L in HDD patients ($P = 0.027$). The median loop diuretic dose was 40 (IQR 20-100) mg. Median creatinine the day before the intervention was 1.27 mg/dL; patients in the HDD group had a significantly higher value of 1.78 mg/dL compared with 1.23 mg/dL in the LDD group ($P < 0.001$). Five patients in the HDD group and 1 patient in the LDD group had dialysis-dependent kidney disease (8.5% vs 0.6%, $P = 0.005$). The median EuroSCORE II was 4.1%, with LDD patients having a significantly lower score than HDD patients (3.7% vs 5.7%, $P = 0.019$). Median TRI-SCORE was 5 in LDD and 6 in HDD patients ($P < 0.001$). T-TEER was the most frequent intervention (60.2%). Detailed characteristics of both groups are shown in Table 1.

Outcomes

Median follow-up time was 388 (IQR 362-537) days. A reduction of TR to grade 2 or less was achieved in 62.8% of patients, with a significant difference between groups: 68.3% in the LDD group vs 47.5% in the HDD group ($P < 0.001$), as shown in Figure 1. Intraprocedural and clinical success (at 30 days) rates according to TVARC criteria were lower in the HDD group (68.3% vs 45.8%, $P = 0.002$ and 65.9% vs

44.1%, $P = 0.003$). For mortality, there were no patients lost to follow-up at 1 year, and 4 patients were missing with regard to the endpoint of HFH. Survival was poorer in the HDD group with a 1-year mortality of 44.1% compared with 10.8% in the LDD group ($P < 0.001$), as depicted in Supplemental Figure S1. HDD patients more frequently had a cardiac cause of death (50% vs 16.7%, $P = 0.014$). At 1-year follow-up, HDD patients were hospitalized more frequently due to heart failure decompensation (22% vs 9.6%, $P < 0.001$), as demonstrated in Supplemental Figure S2. In addition, the combined endpoint of death and HFH occurred significantly more frequently in the HDD group at 1-year follow-up (50.8% vs 16.3%, $P < 0.001$), as shown in Figure 2. Both the HDD and LDD groups showed a reduction in NYHA class of ≥ 1 (65% vs 69%, $P = 0.648$), as detailed in Figure 3. Clinical outcomes are summarized in Table 2. In the multivariable Cox regression analysis, the high diuretic dose of > 95 mg furosemide showed an independent association with the combined endpoint of death or HFH after 1 year (hazard ratio [HR] 2.498, 95% confidence interval [CI] 1.537-4.058, $P < 0.001$), as shown in Table 3. The observed association was not device specific.

Sensitivity analyses

In the sensitivity analysis, the TRIVALVE score was significantly associated with the combined endpoint in the univariable analysis. In a bivariable model including the TRIVALVE high-risk group and the HDD group, both variables remained independently associated with adverse outcomes (TRIVALVE high risk: HR 2.851, 95% CI 1.784-4.555, $P < 0.001$; HDD: HR 3.262, 95% CI 2.065-5.155, $P < 0.001$; Supplemental Table S1).

To confirm the robustness of the 95-mg cutoff, additional analyses using alternative furosemide-equivalent thresholds of 80, 100, and 125 mg were performed. The 80- and 100-mg thresholds remained significantly associated with the combined endpoint (see Supplemental Tables S2 and S3). Furthermore, analysis of the ratio between loop diuretic dose and glomerular filtration rate (furosemide [in milligrams] and glomerular filtration rate [in milliliters per minute]) demonstrated consistent results, with the log-transformed ratio remaining independently associated with the combined endpoint (Supplemental Table S4). In an additional sensitivity analysis including intraprocedural success, the association between diuretic dose and outcome remained unchanged, confirming that the results were independent of procedural success (see Supplemental Table S5). IPTW-weighted Cox regression confirmed the independent association between high diuretic dose and the combined endpoint, yielding consistent HRs compared with the unweighted model. After weighting, all baseline covariates were well balanced (see Supplemental Table S6). The association between high diuretic dose and adverse outcomes remained statistically significant in both IPTW models (without intraprocedural success: weighted HR 2.16, 95% CI 1.22-3.82, $P = 0.008$; with intraprocedural success: weighted HR 2.14, 95% CI 1.20-3.82, $P = 0.010$), reaffirming the independent prognostic impact of a high diuretic dose.

Diuretic dose comparisons

Although there was no difference regarding the intake of thiazide diuretics or MRAs between the 2 groups at 1-year follow-up, more patients with an unsuccessful procedure took an sodium-glucose transport protein-2 inhibitor (44.4% vs 27.3%, $P = 0.023$). Within the group with an unsuccessful procedure (n = 84), a numerical reduction in MRA intake before and after the procedure was seen, but without statistical difference (60.7% vs 41.7%, $P = 0.637$). In both groups, we observed a numerically reduced intake of thiazide diuretics after TTVr (19.1% vs 14.2% for intraprocedural success and 22.6% vs 14.3% for unsuccessful procedure), also without statistical difference ($P = 0.197$ and $P = 1.000$, respectively). Patients with intraprocedural success had a significantly lower intake of loop diuretics before (30 mg vs 60 mg, $P < 0.001$) and after (30 mg vs 60 mg, $P = 0.004$) TTVr, as shown in Supplemental Table S7. There was no significant change in diuretic dose after the procedure within the groups, with a median delta of 0 mg ($P = 0.354$). On an individual level, 36.5% of patients required an increase, 30.5% a decrease, and 33.0% remained unchanged in loop diuretic dose after TTVr. In logistic regression analysis, none of the baseline parameters assessed were significantly associated with postprocedural dose escalation (see Supplemental Table S8).

Discussion

To the best of our knowledge, this study is the first to systematically investigate the role of loop diuretics with regard to outcomes of patients with severe TR undergoing TTVr. We have demonstrated the following:

1. Patients undergoing TTVr required a median of 40-mg furosemide-equivalent beforehand.
2. Diuretic dose remained stable after TTVr.
3. Stratifying the patients into HDD and LDD groups revealed a high-risk subgroup with more severe comorbidities and worse procedural and clinical outcomes.
4. There was an independent association of diuretic dose with clinical outcomes after adjustment for multiple risk factors, including intraprocedural success, possibly indicating need for TTVr in patients with escalating diuretic dose.

The key study findings are summarized graphically in the Central Illustration. The data from patients examined in this study were representative of existing real-world data on TR patients. Baseline characteristics and concomitant comorbidities were similar to those of patients included in large global registries and trials.[11,14] All patients in our study received medical therapy (ie, diuretic drugs), as suggested by the current ESC guidelines before intervention. Median loop diuretic dose was 40-mg furosemide-equivalent, similar to that in the cohort described by Sorajja et al. from the TRILUMINATE trial, which compared T-TEER to optimal medical therapy.[11] Similar doses at baseline were also described in the Tri.Fr, another randomized trial comparing optimal medical therapy to T-TEER, with daily administration of 40-125 mg furosemide.[18] Dreyfus et al. conducted the TRIGISTRY registry to compare conservative management of severe TR to isolated tricuspid valve surgery and TTVr. In their study, patients treated conservatively received a median

Table 1. Baseline characteristics

	Overall (n = 225)	LDD (n = 166)	HDD (n = 59)	*P* value
Age, years	80 (75-83)	80 (76-83)	78 (72-82)	0.023*
Women	152 (67.3%)	122 (73.1%)	30 (50.8%)	0.002*
Body mass index, kg/m^2	25.4 (22.3-29)	24.5 (22.1-28.3)	26.4 (22.7-30.5)	0.021*
Coronary artery disease	93 (41.2%)	66 (39.5%)	27 (45.8%)	0.402
Arterial hypertension	187 (82.7%)	144 (86.2%)	43 (72.9%)	0.020*
Pulmonary hypertension†	117 (51.8%)	89 (53.3%)	28 (47.5%)	0.441
Diabetes mellitus	55 (24.3%)	35 (21%)	20 (33.9%)	0.046*
CKD, n (%) = GFR < 60 mL/min	188 (83.5%)	135 (81.2%)	53 (89.8%)	0.112
eGFR, mL/min	41 (30-53)	43 (10-106)	33 (13-84)	< 0.001*
Creatinine, mg/dL	1.27 (0.95-1.81)	1.23 (0.9-1.6)	1.78 (1.23-2.26)	< 0.001*
On dialysis	6 (2.7%)	1 (0.6%)	5 (8.5%)	0.005*
Chronic obstructive pulmonary disease	36 (15.9%)	28 (16.8%)	8 (13.6%)	0.563
Atrial fibrillation	208 (92%)	154 (92.2%)	54 (91.5%)	1.000
Pacemaker/ICD/CRT	51 (22.6%)	33 (19.8%)	18 (30.5%)	0.090
Previous stroke	26 (11.5%)	14 (8.4%)	12 (20.3%)	0.013*
EuroSCORE II, %	4.1 (2.8-7.1)	3.7 (2.5-6.4)	5.7 (3.5-7.7)	0.019*
TRI-SCORE	5 (3-7)	5 (3-6)	6 (5-8)	< 0.001*
TR grade > 2	225 (100%)	166 (100%)	59 (100%)	1.0
RA area, cm^2	33.3 (27-41)	33.2 (27-40.4)	34 (25.6-44.2)	0.698
RV diameter basal, mm	44.6 (41-49)	44 (40-47.8)	46 (42.5-51)	0.008*
IVC, mm	25 (21-28)	24 (20.8-27)	27 (23-32.5)	< 0.001*
TAPSE, mm	17 (14-20)	17 (14-20)	17 (14-19)	0.786
Heart failure				0.852
HFpEF	182 (80.9%)	135 (81.3%)	47 (79.7%)	
HFmrEF	25 (11.1%)	18 (10.8%)	7 (11.9%)	
HFrEF	15 (6.7%)	11 (6.6%)	4 (6.8%)	
HFimpEF	1 (0.4%)	1 (0.6%)	0 (0%)	
NT-proBNP, ng/L	2093 (1343.75-4104)	1959 (1309.5-3977.5)	2607 (1534.75-5492)	0.027*
Edema at day of intervention	132 (58.4%)	91 (54.5%)	41 (69.5%)	0.044*
NYHA functional class				0.069
I	4 (1.8%)	3 (1.8%)	1 (1.7%)	
II	30 (13.3%)	24 (14.4%)	6 (10.2%)	
III	164 (72.6%)	125 (74.9%)	39 (66.1%)	
IV	28 (12.4%)	15 (9%)	13 (22%)	
HFH 12 months prior to intervention	132 (58.6%)	86 (51.8%)	46 (78%)	< 0.001*
Loop diuretics in furosemide-equivalent dose, mg	40 (20-100)	30 (0-90)	150 (100-800)	< 0.001*
Procedural data				
Transcatheter tricuspid valve repair				0.235
T-TEER	136 (61%)	105 (64%)	31 (52.5%)	
Cardioband	87 (39%)	59 (36%)	28 (47.5%)	
TR grade > 2	77 (34.2%)	48 (28.9%)	29 (49.2%)	0.004*
Intraprocedural success (TVARC)	141 (62.4%)	114 (68.3%)	27 (45.8%)	0.002*
Clinical success (TVARC) at 30 days	136 (60.2%)	110 (65.9%)	26 (44.1%)	0.003*

Nominal and ordinal data are expressed as number (percentage). Continuous variables are reported as median (interquartile range).

CKD, chronic kidney disease; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate; HDD, high-diuretic-dose group; HFH, heart failure hospitalization; HFimpEF, heart failure with improved ejection fraction; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; ICD, implantable cardioverter-defibrillator; IVC, inferior vena cava; LDD, low-diuretic-dose group; NYHA, New York Heart Association; PASP, pulmonary artery systolic pressure; RA, right atrium; RV, right ventricle; TAPSE, tricuspid annular plain systolic excursion; T-TEER, tricuspid valve transcatheter edge-to-edge repair; TVARC, Tricuspid Valve Academic Research Consortium.

*Statistically significant at $P < 0.05$.

†PASP > 40 mm Hg, as measured by transthoracic echocardiography.

of 40 mg furosemide at baseline, whereas patients undergoing surgery or interventional treatment received 60 mg.[19]

Our analysis showed no significant decrease in diuretic dose after TTVr (furosemide-equivalent dose change of 0, $P = 0.862$). Similar to our study, the TRILUMINATE trial compared the daily furosemide-equivalent dose between patients undergoing T-TEER vs patients treated conservatively at baseline up to 1-year of follow-up. As mentioned earlier median furosemide dose was 40 mg in both the device group and the control group. At 1-year follow-up there was no change in median dose for both groups.[11] It seems to be a common finding that diuretic dose cannot be reduced after TTVr, which aligns with the understanding that TTVr primarily aims to halt or at least slow disease progression.[11,18,20] In our study there was likewise no need for a dose increase, which may facilitate prevention of side effects associated with diuretic intake, such as electrolyte derailment, hypovolemia, or progressive renal impairment. In fact, an increase in diuretic dose was observed in patients with untreated TR, among others, by Zancanaro et al. in a prospective study comparing TTVr to medical therapy optimization.[21] It is well known that long-term and progressive intake of diuretic drugs can lead to diuretic resistance, which is associated with worse prognosis in patients with TR.[22] Potential causes of developing resistance include poor absorption of diuretics due to gut edema, hypoalbuminemia,

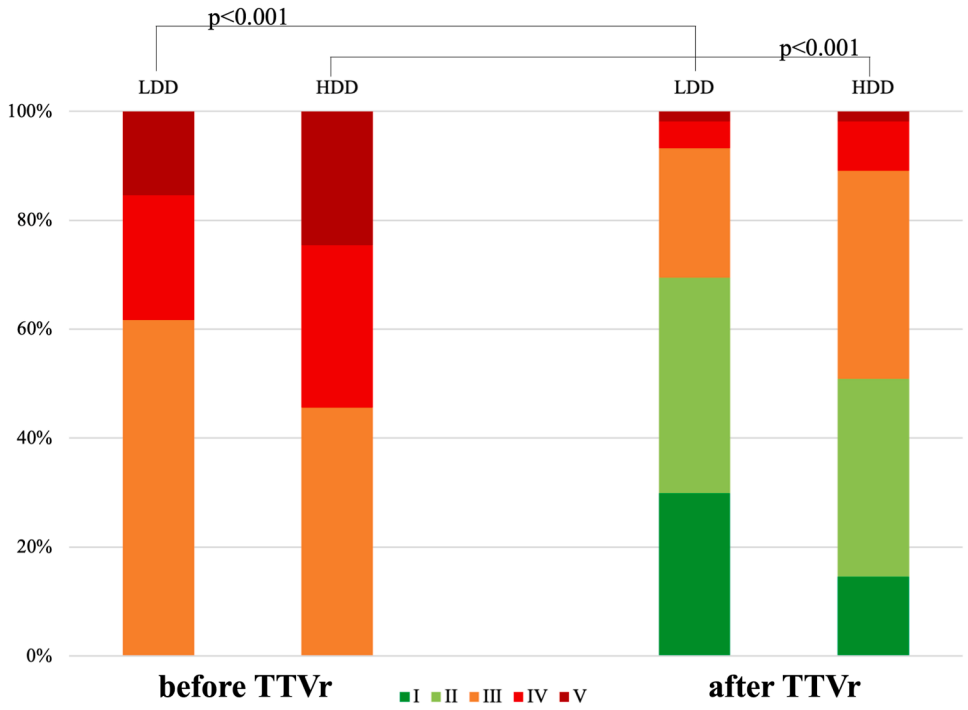


Figure 1. Tricuspid regurgitation (TR) grades before and after TTVr, stratified by diuretic dose group (HDD vs LDD). TR severity was classified according to the definition of Hahn and Zamorano.[1] Improvement is seen in TR grade in both groups after intervention. HDD, high diuretic dose; LDD, low diuretic dose; TTVr, transcatheter tricuspid valve repair; TR, tricuspid regurgitation.

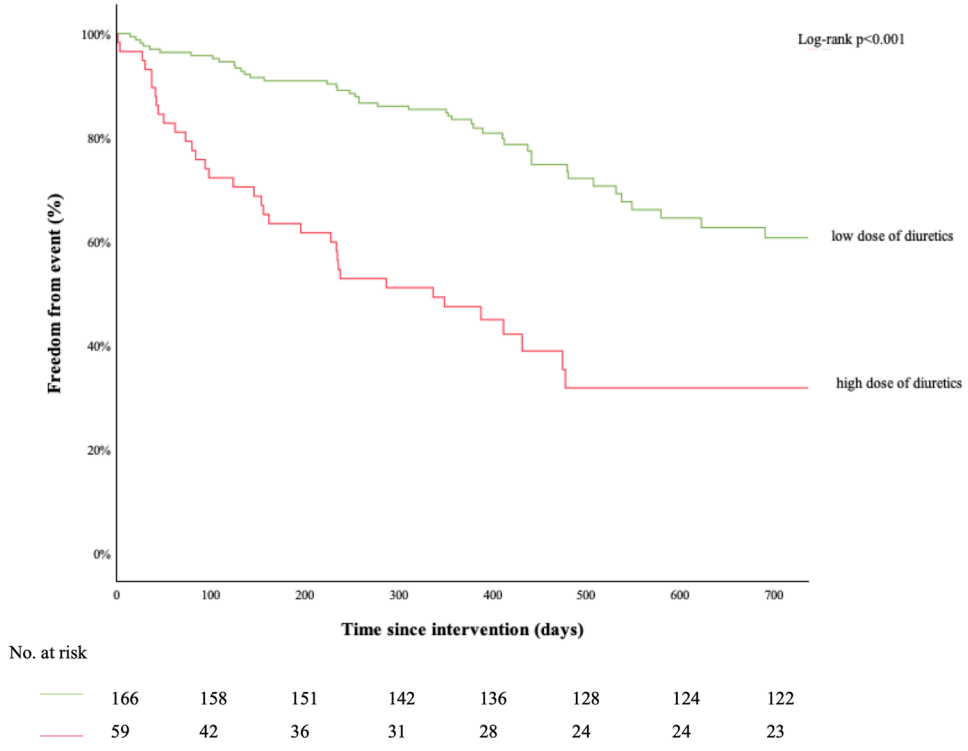


Figure 2. Kaplan-Meier analysis comparing freedom from the combined endpoint of death or heart failure hospitalization between patients with HDD and LDD. Groups were defined by a 95-mg furosemide-equivalent cutoff. The HDD group showed significantly reduced event-free survival ($P < 0.001$). HDD, high diuretic dose; LDD, low diuretic dose; TTVr, transcatheter tricuspid valve repair.

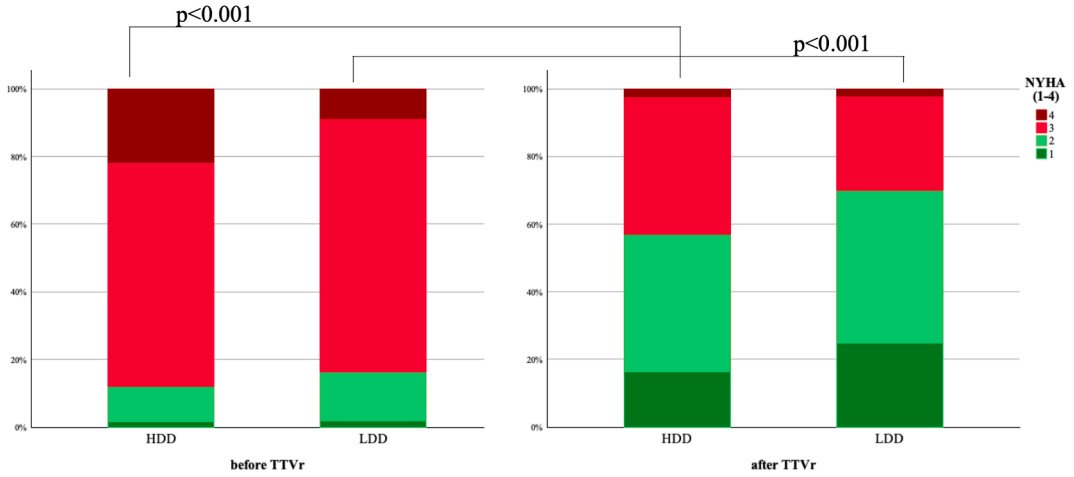


Figure 3. NYHA functional class distribution before and after TTVr, stratified by baseline diuretic dose (HDD vs LDD). Both groups showed significant symptomatic improvement at follow-up. NYHA classes I-IV are color-coded. HDD, high diuretic dose; LDD, low diuretic dose; NYHA, New York Heart Association; TTVr, transcatheter tricuspid valve repair.

progressive deterioration of glomerular filtration rate, or distal tubular remodeling from prolonged diuretic exposure.[23] Elderly patients undergoing TTVr show many of the noted symptoms associated with diuretic resistance; thus, aversion or delay of diuretic resistance by stabilizing the diuretic dose could be a beneficial secondary effect of this intervention. Furthermore, initiation of loop diuretics should already prompt consideration of transcatheter intervention in suitable patients who are not excessively frail, rather than deferring referral until further dose escalation, as our findings demonstrate that higher diuretic requirements are associated with worse outcomes.

Our results show that patients in the HDD group were at higher risk for a poor outcome according to EuroSCORE and TRI-SCORE, as a result of poorer kidney function and a higher rate of diabetes mellitus. Intraprocedural and clinical success rates as defined by the TVARC criteria were significantly lower in those patients at 45.8% and 44.1%, compared with 68.3% and 65.9%, respectively, in LDD patients. This association was confirmed in the univariable analysis and can be explained by more congestion and consecutively wider right heart dimensions (particularly the annulus) in HDD patients, as described elsewhere.[1,24] This is consistent with our results as HDD patients presented with a wider inferior vena cava (27 vs 24 mm, $P < 0.001$) and wider basal right ventricular diameter (46 vs 44 mm, $P = 0.008$). Right ventricular dilation was found to be marker of worse outcomes and subsequently led to reduced cardiac output and symptoms of backward failure.[25] In our analysis, HDD was significantly associated with the presence of edema the day before intervention and severe dyspnea (NYHA class III or IV), both symptoms of clinical deterioration due to right heart failure. NT-proBNP levels also reflected more congestion and worse right heart failure in HDD patients, being significantly higher in this group. Subsequently, there was a significant association of HDD with HFH 12 months before intervention. At 1-year follow-up, HDD patients had more often been hospitalized due to heart failure. The newest outcomes from TRILUMINATE Pivotal showed a significantly lower rate of recurrent HFH 2 years after intervention in previously conservatively treated patients, indicating a potential for favorable long-term outcomes after TTVr.[13]

Table 2. Clinical outcomes (1-year follow-up)

	Overall (n = 225)	LDD (n = 166)	HDD (n = 59)	*P* value
1-year mortality	44 (19.6%)	18 (10.8%)	26 (44.1%)	< 0.001*
Cardiac cause of death	16 (33.3%)	4 (16.7%)	12 (50%)	0.014*
1-year HFH	29 (12.9%)	16 (9.6%)	13 (22%)	< 0.001*
NYHA functional class (n = 178)				0.199
I	44 (24.7%)	38 (27%)	6 (16.2%)	
II	80 (44.9%)	65 (46.1%)	15 (40.5%)	
III	50 (28.1%)	35 (24.8%)	15 (40.5%)	
IV	4 (2.2%)	3 (2.1%)	1 (2.7%)	
Reduction of NYHA functional class ≥ 1	121 (68%)	97 (69%)	24 (65%)	0.648
Combined endpoint† at 1 year	57 (25.3%)	27 (16.3%)	30 (50.8%)	< 0.001*

Data expressed as number (percentage).

HDD, high-diuretic-dose group; HFH, heart failure hospitalization; LDD, low-diuretic-dose group; NYHA, New York Heart Association.

† Consisting of mortality and hospitalization for heart failure.

* Statistically significant at $P < 0.05$.

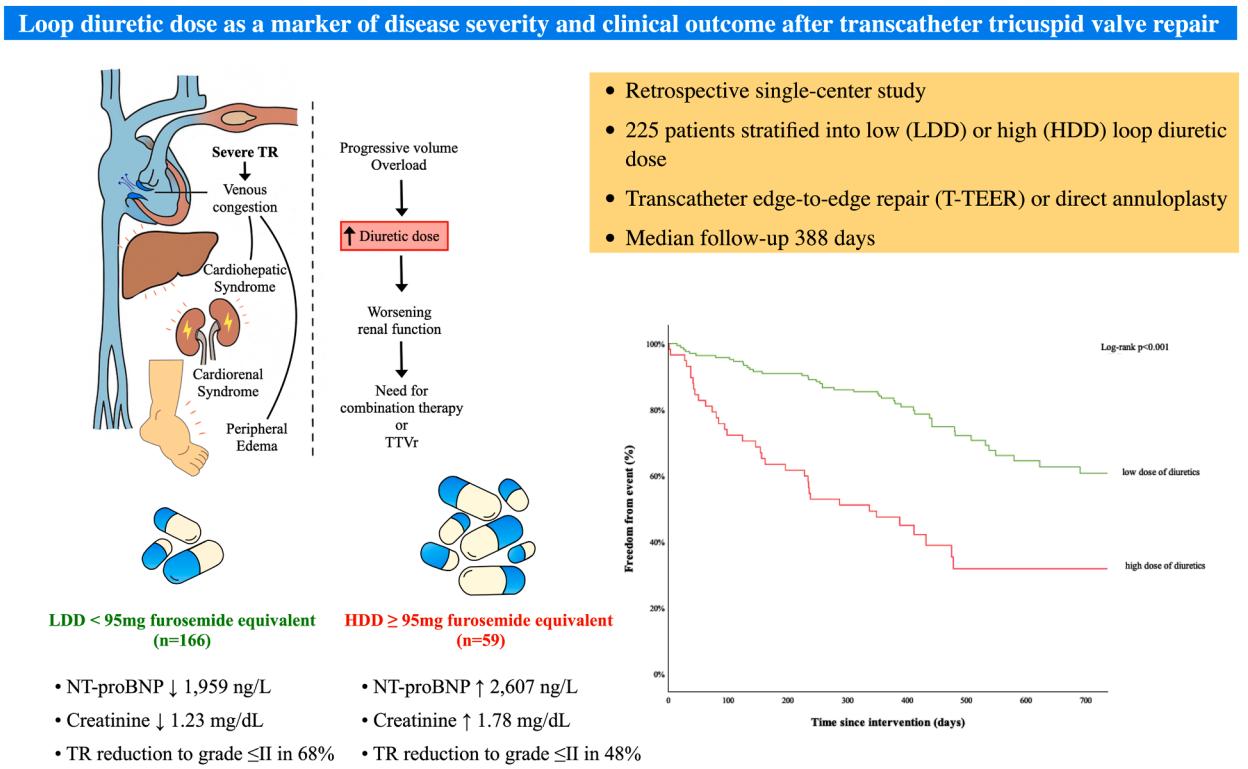
† Consisting of mortality and hospitalization for heart failure.

Table 3. Cox proportional hazards models for rate of death or hospitalization for heart failure at 1 year, estimated by diuretic dose

	Univariable analysis			Multivariable analysis		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Male	0.520	0.341-0.749	0.002*	0.757	0.467-1.228	0.259
High diuretic dose	3.286	2.126-5.079	< 0.001*	2.498	1.537-4.058	< 0.001*
Age	0.989	0.964-1.014	0.394			
GFR, mL/min	0.975	0.962-0.989	< 0.001*	0.992	0.976-1.008	0.336
PASP, mm Hg	0.999	0.985-1.013	0.911			
Edema on day before intervention	1.746	1.108-2.752	0.016*	1.045	0.630-1.732	0.865
TAPSE, mm	0.942	0.895-0.992	0.023*	0.962	0.905-1.023	0.219
RV-PA coupling	0.577	0.161-2.074	0.400			
PAPi	0.900	0.659-1.229	0.509			
Arterial hypertension	0.855	0.503-1.455	0.564			
Diabetes mellitus	1.569	0.999-2.465	0.051			
Coronary artery disease	1.427	0.936-2.175	0.098			
T-TEER	0.776	0.505-1.192	0.247			
LVEF ≤ 40% (HFrEF)	1.163	0.558-2.421	0.688			
logNT-proBNP	1.606	1.260-2.048	< 0.001*	1.226	0.922-1.631	0.160
Obesity (BMI > 25.0)	1.259	0.820-1.933	0.292			
HFH 12 months prior intervention	1.872	1.154-3.037	0.011*	1.418	0.826-2.434	0.206

BMI, body mass index; GFR, glomerular filtration rate; HFH, heart failure hospitalization; HFrEF, heart failure with reduced ejection fraction; HR, hazard ratio; LVEF, left ventricular ejection fraction; NT-proBNP, N terminal pro—B-type natriuretic protein; PAPi, pulmonary artery pulsatility index; PASP, pulmonary artery systolic pressure; RV-PA, right ventricle-pulmonary artery; TAPSE, tricuspid annular plane systolic excursion; T-TEER, tricuspid valve transcatheter edge-to-edge repair.

*Statistically significant at $P < 0.05$.



Central Illustration. High-dose loop diuretic (≥ 95 mg) was associated with significantly worse 1-year outcomes in 225 patients with severe tricuspid regurgitation undergoing TTVr,. CI, confidence interval; HDD, high-diuretic-dose group; HR, hazard ratio; LDD, low-diuretic-dose group; RA, right atrium; RV, right ventricle; TR, tricuspid regurgitation; T-TEER, tricuspid valve transcatheter edge-to-edge repair; TTVr, transcatheter tricuspid valve repair.

Although 1-year mortality in this study was 19.6% overall, which compares with real-life but early data from the **Tri**-catheter Tricuspid **Valve** Therapies (TriValve) registry where 1-year mortality was 23%,[26] HDD patients had a significantly higher mortality of 44.1% vs 10.8% in LDD patients. This difference may reflect a higher degree of congestion in HDD patients and aligns with the observations of Rommel et al., who analyzed a multicenter, international transcatheter tricuspid valve intervention (TTVI) registry and demonstrated that patients with right-sided congestion had increased mortality after TTVI.[24] These findings further support the concept that transcatheter intervention should ideally be discussed upon initiation of diuretic therapy, before congestion leads to advancement of heart failure stages. Similarly, Schlotter et al. demonstrated that patients in intermediate stages of TR had the greatest survival benefit from T-TEER as compared with conservative therapy. This finding further underscores the importance of timely referral before progression to advanced disease.[27]

We were able to show that most patients undergoing TTVr had symptom relief. This was reflected in the reduction of NYHA functional class of 1 or more, which was achieved in 68% of patients overall. This coincides with previous studies such as the multicenter study by Nickenig et al., who showed an improvement of at least 1 NYHA class in 76% of treated patients,[14] and the study by Besler et al., who also had a 76% improvement on this measure.[28] Notably, the symptomatic benefit was not different among the HDD and LDD groups, which supports that HDD patients should not be precluded from TTVr. Both groups benefited from the procedure, which demonstrates its safety and efficacy. It is important to recognize that the patients in the HDD group were treated at very advanced stages of disease, making their outcomes not directly comparable to those in the TRILUMINATE trial, where the 1-year mortality rate was around 10%. In contrast, the 44% mortality observed in HDD patients in our study is notably high, reflecting the real-world context of an expert center treating patients with severe comorbidities who may have been excluded from other treatment options. This underscores the unique challenges of managing such critically ill patients.

One of the most important findings of our study is the independent association of HDD with the occurrence of death or HFH after intervention in the multivariable analysis. More likely this indicates an advanced disease than a direct cause of worse outcomes. This fact may serve as a sign of need for tricuspid intervention and suggests considering diuretic dose as a simple marker for identifying patients at risk of undergoing TTVr. One possible conclusion is that an incremental diuretic dose may reflect the progression of TR. Persistent venous congestion due to untreated TR causes diuretic resistance in up to 30% of patients with heart failure, ultimately leading to refractory TR.[26] One marker for diuretic resistance in congestive nephropathy is the persistently low fractional excretion of sodium in urine, as sodium output of < 50 mmol/L in spot urine 1-2 hours after loop diuretic intake indicates inadequate natriuresis.[29,30] This may be examined in patients with TR to identify those patients with diuretic resistance, although this is logistically challenging in daily clinical practice. We suggest that patients with severe TR and an increased diuretic dose be evaluated for TTVr and promptly treated. Diuretic dose is an easy parameter to monitor, especially in an outpatient setting, and it can be used by treating primary care physicians to detect patients who should be referred to a heart valve center for evaluation of TTVr. However, more studies are needed with regard to optimal timing of transcatheter treatment of TR. It can only be assumed that diuretic resistance played at least a partial role in the development of high diuretic dose in the patients assessed in our study. To verify whether diuretic resistance affects these patients and thus puts them at risk for an unsuccessful procedure, standardized laboratory parameters, such as sodium excretion in spot urine, should be included in the patient's work-up before intervention.

Limitations

This work is a retrospective, single-center, observational study and therefore has limitations that should be taken into consideration. First, no causal inferences can be drawn and findings should be interpreted as exploratory in the context of an experienced tertiary care center. Second, our study included a population treated with either T-TEER or annuloplasty, representing different interventional techniques. However, the association observed applied for both techniques. Third, data on sodium excretion in urine were not available for our patients; however, this is not standard practice in patients undergoing TTVr in the clinical routine. Fourth, the study lacked a comparator arm of conservatively managed patients, which limited the ability to assess the effect of the intervention in comparison to natural disease progression.

Conclusions

TTVr procedures, such as T-TEER and direct annuloplasty, have been shown to be feasible treatment options for severe TR in patients with high surgical risk. Nevertheless, the intake of diuretic agents remains an important pillar of treatment in terms of managing common symptoms such as peripheral edema, ascites, dyspnea, and exercise intolerance. Considering potential side effects of diuretics as well as the development of diuretic resistance, the fact that an increase in dose could be avoided after TTVr is promising. This was underlined by the association between high loop diuretic dose and mortality. Assuming a high diuretic dose is an expression of late stage disease, early intervention of TR should be considered to positively affect outcome. We suggest an increase in diuretic dose as a simple parameter for primary care physicians to consider referral to a specialized heart valve unit. Further research is needed to identify the optimal time for treatment of TR.

Ethics Statement

Data assessment was approved and overseen by the local ethics committee of the University of Cologne.

Patient Consent

Patient consent is not applicable to this article. This is a retrospective study using de-identified data; therefore, the institutional review board did not require patient consent.

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Disclosures

Dr J. von Stein has received lecture fees from Edwards Lifesciences. Dr Körber has received travel support by JenaValve and lecture fees from Edwards Lifesciences and Abbott. Dr Baldus has received honoraria for consultation from Abbott and Edwards Lifesciences. Dr Pfister has received speaker fees from Edwards Lifesciences and Abbott. Dr Iliadis has received travel expenses and consultant honoraria from Abbott and Edwards Lifesciences. The remaining authors have no conflicts of interest to disclose.

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Supplementary Material

To access the supplementary material accompanying this article, visit the online version of the *Canadian Journal of Cardiology* at www.onlinecjc.ca and at https://doi.org/10.1016/j.cjca.2025.12.014