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Clinical impact of elevated tricuspid valve inflow gradients after transcatheter edge-to-edge tricuspid valve repair

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Short running title: Tricuspid valve gradient after tricuspid valve repair

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Conflict of interest statement

Martin Orban has received speaker honoraria from SedanaMedical and AstraZeneca. D. Braun has received speaker honoraria from Abbott Vascular. N. Karam has received consultant fees from Abbott Vascular. M. Nabauer has received speaker honoraria from Abbott Vascular. J. Hausleiter has received speaker honoraria and research support from Abbott Vascular and Edwards Lifesciences. The other authors have no conflicts of interest to declare.

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Abstract

Aims: The aim of this study was to compare outcome of patients with a post-procedural tricuspid valve gradient (TVG) of >3 mmHg vs. ≤3 mmHg after transcatheter edge-to-edge tricuspid valve repair (TTVR).

Methods and results: Between March 2016 and October 2018 we treated 145 patients with severe tricuspid regurgitation (TR) with TTVR by placing 2.2±0.7 clips per patient. Device success (TR reduction ≥1° to at least moderate) was achieved in 125 patients (86.2%). TTVR resulted in an elevated TVG >3 mmHg in 25 (17.2%) patients. Device success (84% vs. 86.7%, p=0.9), number of clips implanted (2.3±0.7 vs. 2.2±0.7, p=0.33), clinical improvement including NYHA class (III/IV 24% vs. 28%, p=0.92) and increase in 6 minute walking test at 1 month (67 m [IQR 5-103 m] vs. 56 m [IQR 8-97 m], p=0.93), mortality (HR 1.07; 95% CI [0.43-2.65], $p_{logrank}$=0.88) and the combined endpoint mortality and hospitalization for heart failure at one year (HR 1.07; 95% CI [0.46-2.48], $p_{logrank}$=0.88) was similar between patients with a TVG >3 mmHg vs. patients with a TVG ≤3mmHg.

Conclusion: A small cohort of patients demonstrated with an elevated TVG higher than 3 mmHg at discharge. This elevation had no impact on clinical improvement, on mortality and hospitalization for heart failure.

Classification: Tricuspid disease, TTVR, Mitral Valve repair, Femoral, Transthoracic echocardiogram, Chronic heart failure

Abbreviations

MR: mitral regurgitation

MLHFQ: Minnesota Living With Heart Failure Questionnaire

NYHA: New York Heart Association functional class

RV: right ventricle, right ventricular

RVTG: right ventricular tricuspid pressure gradient

TR: tricuspid regurgitation

TTE : Trans-thoracic echocardiography

TTVR: transcatheter edge-to-edge tricuspid valve repair

TV: tricuspid valve

TVG: tricuspid valve gradient

Condensed Abstract

The clinical impact of an elevated tricuspid valve gradient (TVG) after transcatheter edge-to-edge tricuspid valve repair (TTVR) is unclear. TTVR resulted in an elevated TVG >3 mmHg in 25 (17.2%) out of 145 treated patients. Device success (84% vs. 86.7%), NYHA class (III/IV 24% vs. 28%) and increase in 6 minute walking test at 1 month (67 m vs. 56 m), mortality (HR 1.07; 95% CI [0.43-2.65], plogrank=0.88) and the combined endpoint mortality and hospitalization for heart failure at one year (HR 1.07; 95% CI [0.46-2.48], plogrank=0.88) was similar between patients with a TVG >3 mmHg vs. patients with a TVG ≤3mmHg.

Introduction

Severe tricuspid regurgitation (TR) causes right ventricular and tricuspid valve annular dilatation leading to right heart failure and is associated with poor outcomes [1]. Although tricuspid valve repair or replacement are recommended by European and American guidelines [2, 3] many patients are considered inoperable due to high morbidity and mortality risk. Transcatheter edge-to-edge tricuspid valve repair (TTVR) is a novel treatment approach in heart failure patients with severe tricuspid regurgitation (TR) at prohibitive surgical risk [4, 5]. Effective TR reduction and clinical improvement following TTVR with edge-to-edge devices has been demonstrated, including improvement in symptoms and in functional capacity [6, 7]. An edge-to-edge repair technique of atrio-ventricular valves narrows regurgitant orifice by approximating the leaflets and reducing valve diameter. Both mechanisms potentially increase trans-valvular inflow gradient. It has been shown in a single-center study that patients with a post-procedural mitral valve gradient > 5 mmHg after trans-catheter edge-to-edge mitral valve repair have a poorer long-term outcome including an increased all-cause mortality [8]. Indeed, pressure and flow conditions of mitral and tricuspid valve are different. The mitral valve consists only of two leaflets and is smaller[9] than the tricuspid valve which physically leads to a higher inflow velocity and higher pressure-gradient compared to the tricuspid valve. In contrast, the tricuspid valve – embedded within the right-sided low-pressure circulation - contains three, sometimes four leaflets and is considerably larger[10] than the mitral valve which leads to a lower inflow velocity and subsequently lower pressure gradient compared to the mitral valve. An arbitrarily defined tricuspid valve gradient (TVG) of ≤ 3 mmHg has been used in TTVR procedures by us and others in the past[4] due to lack of an evidence based interventional strategy which defines a TVG acceptable after TTVR.

The clinical relevance of a post-procedural elevated TVG on clinical outcome is unknown. Hence, the aim of this study was to investigate TVG after TTVR over time and compare patient characteristics and outcome of patients with a TVG at discharge of > 3 mmHg vs. ≤ 3 mmHg.

Methods

Study population and design

All patients who were treated in an off-label and compassionate use setting with TTVR between March 2016 and October 2018 at the university hospital of Munich were included in this analysis. All patients were symptomatic with signs of right-sided heart failure. Patients were deemed at prohibitive surgical risk by an interdisciplinary heart team and provided written informed consent. The local Ethics Committees approved the data analysis of patients treated with TTVR.

Procedure

The transcatheter edge-to-edge repair system (MitraClip®, Abbott, Santa Clara, California, United States of America) was used as described previously [6]. Image guidance was provided by two- and three-dimensional transesophageal and transthoracic echocardiography with additional fluoroscopy [11, 12]. Careful assessment of TVG was performed after every clip implantation with the aim to maintain a TVG ≤ 3 mmHg [4].

Outcomes

The primary outcome of this study was death and hospitalization for heart failure in the follow-up period. Further information is provided in supplementary material.

Echocardiography

Trans-thoracic echocardiographic (TTE) assessment of TVG was performed pre-procedurally, at discharge, and after 1, 6, and 12 months. We followed current recommendations for the assessment of native valve regurgitation, chamber quantification and assessment of the right heart [13-16]. Evaluation of TR comprised vena contracta width (biplane), TR volume and effective regurgitant orifice area according to the proximal isovelocity surface area method. The synthesis of all parameters led to a grading of TR with four grades: mild (1+), moderate (2+), severe (3+) and massive/torrential (4+). We measured the diastolic mean TVG and the systolic right ventricular tricuspid pressure gradient (RVTG) using the simplified Bernoulli equation. Patients were advised to remain in resting expiratory position and gradients / velocity time integral (VTI) signals were measured in all patients in transthoracic examinations to secure comparable conditions usually applying the RV focused view as recommended by guidelines on echogardiografic assessment on valvular stenosis [17]. The septal-lateral diameter of TV was measured in the RV focused view.

Statistics

Information on Statistics is provided in supplementary material.

Results

Baseline characteristics

Between March 2016 and October 2018 we treated 145 consecutive patients with severe TR with TTVR. The baseline characteristics of all patients are shown in Table 1.

Procedural outcome

Patients were treated with TTVR for isolated severe TR (70 patients) or in combination with mitral valve repair for concomitant severe MR and TR with significant annulus dilatation (75 patients). Device success which was defined as TR reduction ≥ 1° to at least moderate was

achieved in 125 patients (86.2%, Figure 1 and supplementary Figure 1). Clip detachment occured in 4 patients. Of these, 1 clip detachment occured during the procedure, 2 detachments occured within 1 day and one was noticed during 1 month follow-up echocardiografic examination. Persistant iatrogenic atrial septum defect was detected in 22 patients (29%) at follow-up examinations and the residual mitral valve inflow-gradient was 3 mmHg [2-4] in patients receiving TTVR and mitral valve repair concomitantly. The procedural outcome of all patients is shown in Table 2. The median time interval from procedure to pre-discharge echo was 3 [2-5] days. The median follow-up time of patients was 6.0 [2-11] month.

The median baseline TVG was 1 mmHg [1.0-1.4 mmHg]. The TVG at discharge increased to 2 mmHg [1.6 – 3.0 mmHg], p<0.001, and remained stable at 6 (2.0 mmHg [1.0 – 2.5 mmHg], p=0.11) and 12 months (2 mmHg [1.0-2.0 mmHg], p=0.78) follow-up (see Figure 2, Panel A and supplementary Figure 2, Panel A). Of these, twenty-five patients showed an elevated TVG > 3 mmHg at discharge. The TVG at 30 days and 6 month remained significantly higher in the TVG > 3 mmHg group compared to TVG ≤ 3 mmHg group (p=0.0035 at 30 days and p=0.018 at 6 month). In patients with a pre-discharge TVG > 3 mmHg at least 10 patients (45%, measured in 22 patients) presented with an elevated TVG ≥ 3 mmHg at 30 days, 5 patients (56%, measured in 9 patients) at 6 month and 2 patients (100%, measured in 2 patients) at 12 month (see Figure 1, panel B and C and supplementary Figure 2, Panel B and C, Supplementary figure 3).

Characteristics and outcome of patients with a post-procedural TVG > 3 mmHg vs. ≤ 3 mmHg

Patients with TVG >3 mmHg were younger (73.1±11.0 vs. 77.5±9.2 years, p=0.038) and presented with lower levels of NT-proBNP at baseline (2276 ng/l [906-5150 ng/l] vs. 4182 ng/l [2310-8629 ng/l], p=0.008) compared to patients with TVG ≤ 3mmHg. Patients with a TVG >

3 mmHg – albeit not significant - were less frequent male (36 % vs. 53%), had a better glomerular filtration rate (55 ml/min vs. 46 ml/min) and underwent more often cardiac surgery (36% vs. 24%). All other baseline characteristics are shown in Table 1. The echocardiographic RV parameters including septal lateral annular end-diastolic diameter (46mm [43-51 mm] vs. 46mm [42-51 mm], p=0.683) and TAPSE (17.6 ± 4.8 mm vs. 17.0 ± 4.9 mm, p=0.58) did not differ between both groups whereas RVTG (29 mmHg [18-37 mmHg] vs. 34 mmHg [24-43 mmHg], p=0.08) was absolutely lower in patients with TVG >3 mmHg.

Device success (TR reduction of ≥1 grade to at least moderate in 84% vs. 86.7%, p=0.9) and number of clips implanted (2.3 ±0.7 vs. 2.2 ±0.7, p=0.33) was similar between groups. At 1-month follow-up, there was no difference in NYHA class (see Table 2). Both groups showed a similar increase of 6MWD (67 m [5-103 m] vs. 56 m [8-97 m], p=0.93). The improvement of quality of life (MLHFQ) was more pronounced in patients with a TVG > 3mmHg vs. ≤ 3mmHg (17.8 ± 16.7 vs. 9.9 ± 17.0, p=0.08, see Figure 3). Only 2 patients showed a TVG in excess of 5 mmHg with a heart rate of 111/min and 83/min, respectively at determination of TVG. Of these, the first patient was alive 9 month after the procedure and the second patient who was treated with TTVR was alive at 1-month follow-up in very good physical condition. The frequency of triple-orifice technique (vs. bicuspidalisation technique [18]) was significantly higher in patients with a TVG > 3mmHg (p<0.001). Moreover the median TVG at discharge was significantly higher in patients undergoing a bicuspidalization technique (2.0 [1.5-2.9] mmHg vs. 2.0 [2.0-3.4] mmHg, p=0.04) in the whole population.

The clinical endpoints 1-year mortality (HR 1.07; 95% CI [0.43-2.65], $p_{logrank}$=0.88, Figure 4) and the combined endpoint mortality and hospitalization for heart failure at one year (HR 1.07; 95% CI [0.46 - 2.48], $p_{logrank}$=0.88, Figure 5) did not differ between patients with a TVG > 3 mmHg vs. patients with a TVG ≤ 3mmHg.

Discussion

This prospective observational study investigates the mean TVG after TTVR using the edge-to-edge repair technique and compares patient characteristics and outcomes of patients with a TVG at discharge of > 3 mmHg vs. ≤ 3 mmHg. The main findings at long-term follow-up are, that 1) the mean TVG increased slightly after TTVR from 1 mmHg to 2 mmHg and remained stable up to 6 and 12 months, 2) a small proportion of patients presented with an elevated TVG > 3 mmHg, 3) improvement in NYHA class and 6MWD at 1-month after the procedure was similar between groups 4) this elevation in TVG did neither result in an increase of mortality nor in the combined endpoint mortality and hospitalization for heart failure.

International guidelines consider mitral or tricuspid valve inflow gradients in excess of 5 mmHg as stenosis[2, 3]. In patients undergoing trans-catheter mitral valve repair it was demonstrated that a mitral valve gradient above 5 mmHg – which was reported in up to 25% of patients – is associated with an increase of a combination of all-cause mortality, left ventricular assist device implantation, mitral valve replacement, and recurrent procedure at long-term follow-up [8]. There is no data in this regard concerning TTVR. Edge-to-edge valve repair increases ventricular inflow valve gradients, but data on the clinical tolerability of increased diastolic gradients in the right-sided low-pressure circulation and its impact on outcome are unknown. In this regard, our analysis on TTVR shows that a TVG in excess of 5 mmHg is extremely rare and second that an elevated TVG in excess of 3 mmHg is not associated with impaired clinical improvement or prognosis. These findings might be explained by the difference in pressure and flow conditions between both atrio-ventricular valves. The bicuspid mitral valve - embedded within the left high pressure system - is smaller[9] than the tricuspid valve which physically leads to a higher inflow velocity, higher pressure gradient and increased susceptibility for mitral stenosis after an edge-to-edge repair technique. In contrast, the tricuspid valve – embedded

within the right-sided low-pressure circulation - contains three, sometimes four leaflets and is larger[10] than mitral valve which leads to a lower inflow velocity and subsequently lower pressure gradient compared to mitral valve. Although more clips are usually needed to reduce TR (2.2 ±0.7 tricuspid clips per patient in our cohort vs. 1.4 ±0.6 mitral clips per patient in the German transcatheter mitral valve interventions registry, TRAMI, n=828 patients[19]) due to larger valve area and the complex tricuspid anatomy – this fact does not lead to a higher inflow gradient in our analysis.

There is no evidence based interventional strategy which defines a TVG which is acceptable after TTVR. An arbitrarily defined TVG of ≤3 mmHg has been used in TTVR procedures and studies by us and others in the past[4]. Here we show that an elevated TVG in excess of 3 mmHg is not associated with an increase of clinical endpoints or a deterioration of functional capacity when compared to all other patients. In the study of Neuss et al. Kaplan Meier curves after TMTVR separated from the beginning of follow-up, whereas Kaplan Meier Curves in our study after TTVR did not separate up to 1 year. Our strategy of carefully monitoring the TVG during TTVR results in a small cohort of patients with TVG > 3 mmHg with only about 1 % of treated patients with TVG > 5 mmHg. Hence, in contrast to trans-catheter mitral valve repair a clinical relevant tricuspid stenosis after TTVR did not occur.

Limitations

This is a prospective, observational analysis of a single center investigating a rather small patient number in both groups but represents one of the largest patient cohorts undergoing TTVR. Echocardiografic parameters like effective regurgitant orrifice area and pressure half time were not available in all patients. Hence, our study focused on the significance of an isolated Doppler parameter rather than tricuspid valve stenosis which would require the integration of these multiple echocardiografic parameters. The transvalvular gradient cut-off 3

mmHg was arbitrary selected but has been used in TTVR procedures by us and others in the past. This analysis is based on a limited follow up due to the early nature of the TTVR field.

Conclusion

TTVR results in a small increase in the TVG, which remained stable at follow-up. A small cohort of patients shows an elevated TVG > 3 mmHg after the procedure. This elevation had no impact on the clinical improvement after TTVR as well as mortality and the need for hospitalization for heart failure.

Impact on daily practice

There is no evidence based interventional strategy which defines a TVG which is acceptable after TTVR – instead - an arbitrary defined TVG of ≤ 3 mmHg has been used in TTVR procedures by us and others in the past. Only a small cohort of patients shows an elevated TVG > 3 mmHg after the procedure which did not have had an impact on clinical improvement after TTVR as well as on mortality and the need for hospitalization for heart failure. Thus, an elevated TVG after TTVR might be an overestimated problem in the right-sided low-pressure circulation.

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Figures

Figure 1. The Figure shows TR grade at baseline and follow-up echocardiografic examinations in patients after TTVR.

Figure 2. The figure depicts the change of tricuspid valve gradient over time in all patients (Panel A) and according to study group (Panel B: TVG ≤ 3mmHg, Panel C: TVG > 3mmHg). Boxes represents interquarter range; whisker represents 5th ant 95th percentile, bold dark line represents median. Asterisks represent significant differences with p-value < 0.05.

Figure 3: The Figure shows improvement in 6-minute walking distance (6MWD, Panel A) and increase in quality of life according to the Minnesota Living with Heart Failure questionnaire (MLHFQ, Panel B) of patients 1 month after TTVR with TVG at discharge of ≤ 3 mmHg vs. > 3mmHg. Boxes represents interquarter range; whisker represents 5th ant 95Th percentile, bold dark line represents median in Panel A; whisker represents standard deviation in Panel B. dpmean, mean pressure gradient (d=delta, Δ).

Figure 4: The Figure shows the Kaplan-Meier 1-year survival estimates of patients after TTVR with post-procedural TVG ≤ 3 mmHg vs. > 3mmHg. Vertical markings within survival curves indicate last live contact.

Figure 5. The Figure shows 1-year estimates of the combined endpoint death and admission due to heart failure of patients after TTVR with post-procedural TVG ≤ 3 mmHg vs. > 3mmHg. Vertical markings within survival curves indicate last live contact.

Table 1. Baseline characteristics

Parameter		All n=145	TVG≤3mmHg n=120	TVG>3mmHg n=25	p-value
Age, year ± SD		76.7±9.6	77.5±9.2	73.1±11.0	0.038
Male gender, n (%)		73 (50.3)	64 (53.3)	9 (36)	0.456
Body mass index, mean ± SD		25.7±1	25.8±5.2	24.8±4.6	0.356
Euro II SCORE, median [IQR]		5.7 [3.7-9.6]	5.7 [3.8-9.4]	5.4 [3.2-9.7]	0.74
STS-Score, median [IQR]		4 [2.3-7.2]	4.3 [2.5-7.5]	3.2 [1.9-6.1]	0.091
TR, aetiology, n (%)					
functional		134 (92.4)	111 (92.5)	22 (92)	1.0
TR, severity, n (%)					0.234
	2+	3 (2.1)	3 (2.5)	0 (0)	
	3+	76 (52.4)	66 (55)	10 (40)	
	4+	66 (45.5)	51 (42.5)	15 (60)	
NYHA functional class, n (%)					0.586
	II	4 (2.8)	3 (2.5)	1 (4)	
	III	94 (64.8)	76 (63.3)	18 (72)	
	IV	47 (32.4)	41 (34.2)	6 (24)	
MR, severity, n (%)					0.512
	≤1+	40 (29.0)	30 (26.3)	10 (42)	
	2+	28 (20.3)	22 (19.3)	6 (25)	
	3+	62 (42.8)	53 (44.2)	9 (36)	
	4+	15 (10.3)	15 (12.5)	0 (0)	
Concomittant TMVR		75 (51.7)	69 (57.5)	6 (24)	0.175
LV-EF, %, mean ± SD		49.9±13.4	49.5±13.6	51.9±12.6	0.410
TV septal lateral diam., mm		46 [42-51]	46 [42-51]	46 [43-51]	0.683
RV-midventricular diam., mm		40 [36-45]	40 [36-45]	38 [36-44]	0.387
RA area, median [IQR], cm²		35 [29-44]	36 [29-45]	34 [26-43]	0.423
VTI, median [IQR], mm		29 [24-37]	29 [23-34]	40 [30-46]	<0.001
Vena Cava width, mean ± SD, mm		27 ± 7	27 ± 7	28 ± 6	0.241
TAPSE, mm, mean ± SD		17.1 ± 4.8	17.0 ± 4.9	17.6 ± 4.8	0.579
RVTG, mmHg, median [IQR]		34 [23-41]	34[24-43]	29[18-37]	0.079
NT-proBNP, ng/l, median [IQR]		3831[1936-7652]	4182[2310-8629]	2276[906-5150]	0.008
Coronary artery disease, n (%)		76 (52.4)	63 (52.5)	13 (52)	0.871
Previous MI, n (%)		18 (7.3)	17 (14.2)	1 (4)	0.349
Atrial fibrillation, n (%)		123 (84.8)	102 (85)	21 (84)	0.900
GFR, ml/min, mean ± SD		47.7±23.6	46.2±23.4	55.1±24.0	0.085
Diabetes mellitus, n (%)		37 (25.5)	32 (26.7)	5 (20)	0.766
Hypertension, n (%)		121 (83.4)	101 (84.2)	20 (80)	0.992
COPD, n (%)		29 (20)	25 (20.8)	4 (16)	0.856
Previous cardiac surgery, n (%)		40 (27.6)	29 (24.2)	9 (36)	0.499
Previous stroke, n (%)		18 (12.4)	15 (12.5)	3 (12)	0.787
CRT, n (%)		8 (5.5)	6 (5)	2 (8)	0.933
Poor Mobility		37 (25.5)	32 (26.7)	5 (20)	0.766
6 MWT, m, mean ± SD		181.9±112.7	180.1±110.5	191.0±125.0	0.675

MLHFQ, mean ± SD	43.2±18.0	42.1±16.9	49.0±22.2	0.098
Medication on admission, n (%)				
Beta-blocker	128 (88.3)	106 (88.3)	22 (88)	0.882
ACE/AR inhibitors	79 (54.5)	61 (50.8)	18 (72)	0.407
Diuretics	136 (93.8)	112 (93.3)	24 (96)	0.946
Aldosteron antagonists	62 (42.8)	49 (40.8)	13 (52)	0.661
Loop Diuretics ED, median [IQR]	40 [20-100]	40 [20-100]	60 [20-120]	0.975
peripheral edema, n (%)	42 (29.0)	34 (28.3)	8 (32)	0.968

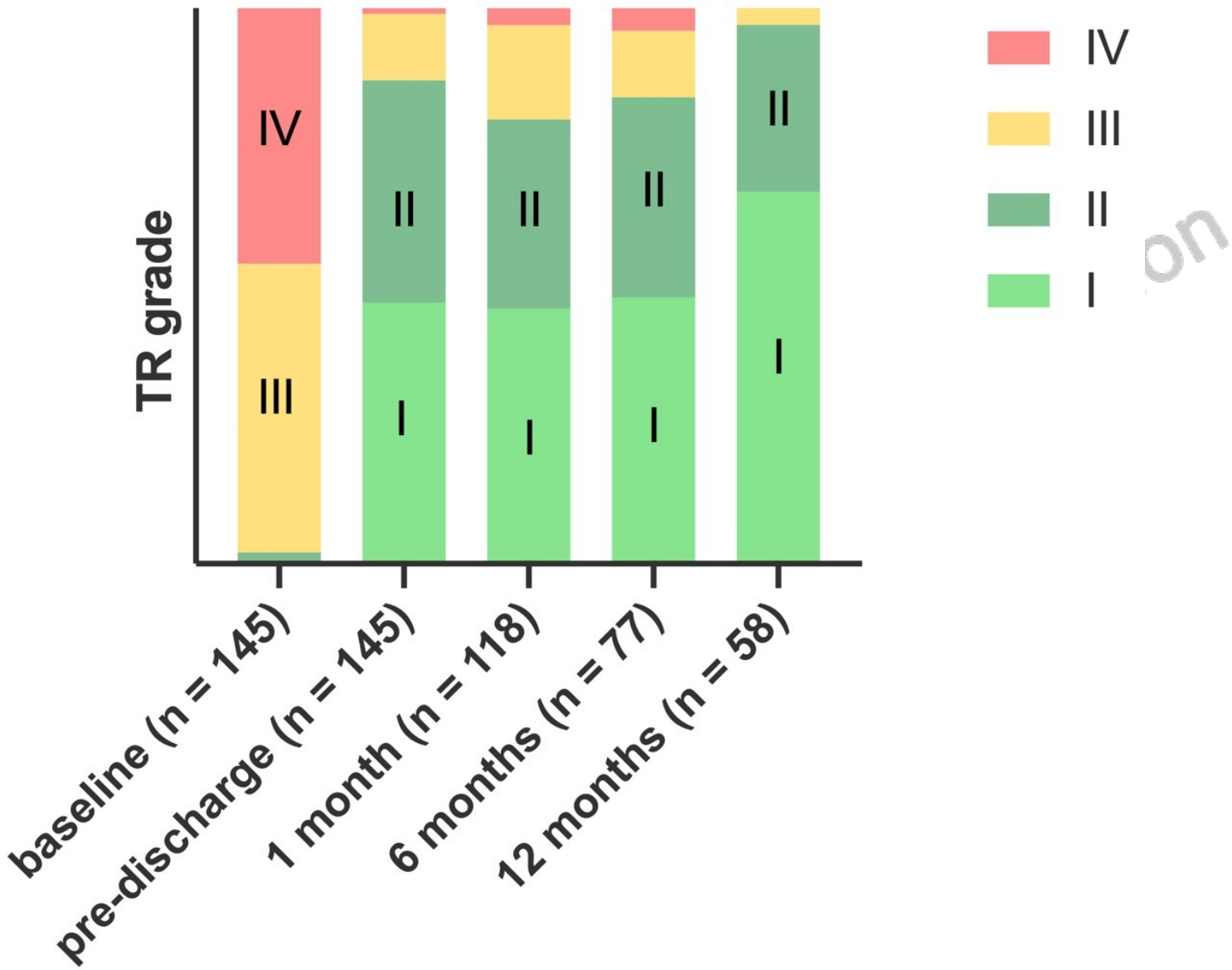
Legend to table 1: The table shows baseline characteristics of the study population. Data presented are means (± standard deviation [SD]), medians with inter quartile range (IQR) or numbers of patients (percentages). STS, Society of Thoracic Surgeons; TR, tricuspid regurgitation; NYHA, New York Heart Association functional class; MR, mitral regurgitation; LV-EF, left ventricular ejection fraction; TV, tricuspid valve; RV, right ventricular; RA, right atrium; VTI, velocity time integral; TAPSE, tricuspid annular plane systolic excursion; RVTG, right ventricular tricuspid pressure gradient; NT-proBNP, N-terminal pro-brain natriuretic peptide; MI, myocardial infarction; CRT, cardiac resynchronisation therapy; MWT, minute walking test; MLHFQ, Minnesota Living With Heart Failure questionnaire; ACE, angiotensinogen converting enzyme; AR, angiotensinogen receptor; ED, equivalent dose in mg furosemide.

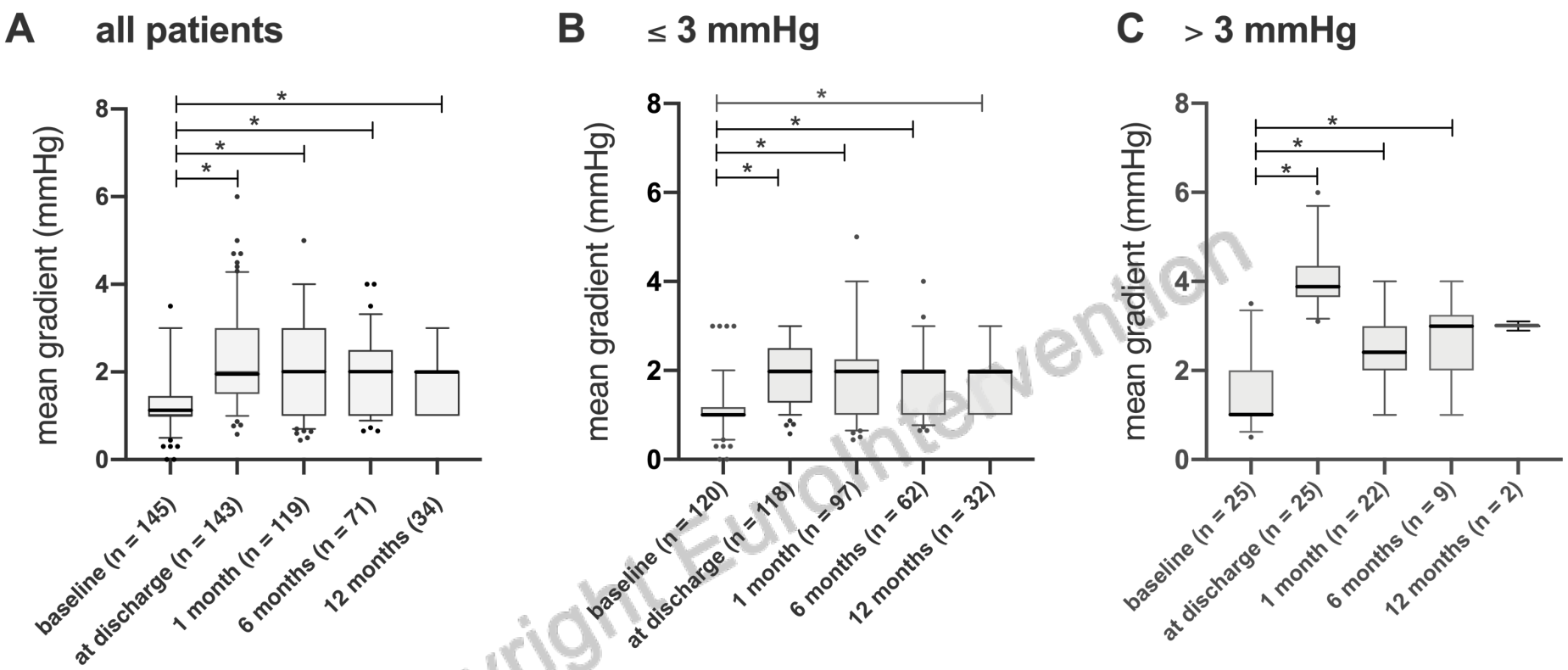
Table 2. Procedural outcome and follow-up

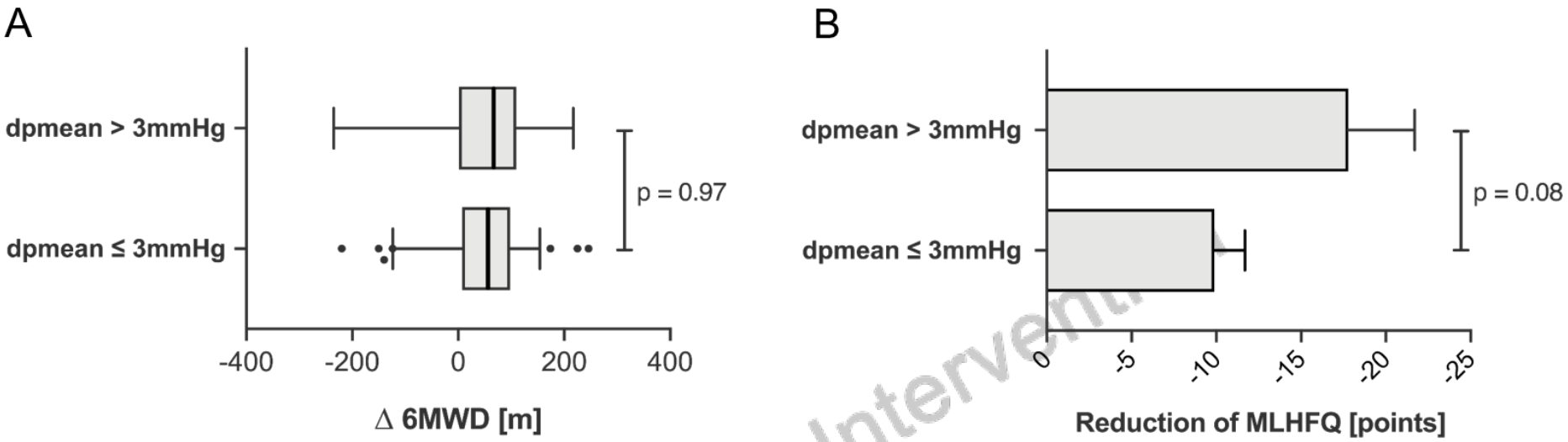
Procedural outcome and follow-up	all n=145	TVG≤3mmHg n=120	TVG>3mmHg n=25	P value
Successful Clip implantation, n (%)	144 (99.3)	119 (99.2)	25 (100)	0.898
Number of Clips, n (%)				0.697
1	17 (11.7)	15 (12.5)	2 (8)	
2	83 (57.2)	70 (58.3)	13 (52)	
3	40 (27.6)	31 (25.8)	9 (36)	
4	4 (2.8)	3 (2.5)	1 (4)	
Number of clips, mean ± SD	2.2±0.7	2.2±0.7	2.3±0.7	0.327
Device Success pre-discharge, n (%)	125 (86.2)	104 (86.7)	21 (84)	0.947
TR grade at discharge, n (%)				0.648
≤ 1+	67 (46.2)	55 (45.8)	12 (48)	
2+	58 (40)	49 (40.8)	9 (36)	
3+	18 (12.4)	15 (12.5)	3 (12)	
4+	2 (1.4)	1 (0.8)	1 (4)	
Concomitant TMVR	75 (51.7)	69 (57.5)	6 (24)	0.175
Heart rate discharge, median [IQR]	75 [65-85]	74 [64-83]	79 [66-91]	0.105
VTI, cm, median [IQR]	29 [24-37]	29 [23-34]	40 [30-46]	<0.001
Data on 1-month Follow-up				
NYHA class ≥ 3 at 1 month, n (%)	40 (27.6)	34 (28.3)	6 (24)	0.923
NYHA class at 1 month, n (%)				0.559
1+	6 (4.1)	5 (4.2)	1 (4)	
2+	74 (51.0)	60 (50)	14 (56)	
3+	38 (26.2)	33 (27.5)	5 (20)	
4+	2 (1.4)	1 (0.83)	1 (4)	
Reduction NYHA class, mean ± SD	1.0±0.7	1.0±0.6	0.9±0.7	0.471
NT-proBNP, ng/l, median [IQR]	3334 [1851-5631]	3520 [2033-5754]	2665 [1413-4938]	0.138
6 MWT, m, mean ± SD	251.3±116.3	250.5±111.7	255.5±140.6	0.872
MLHFQ, mean ± SD at 1 month	31.2±17.6	31.1±16.3	32.0±22.9	0.833

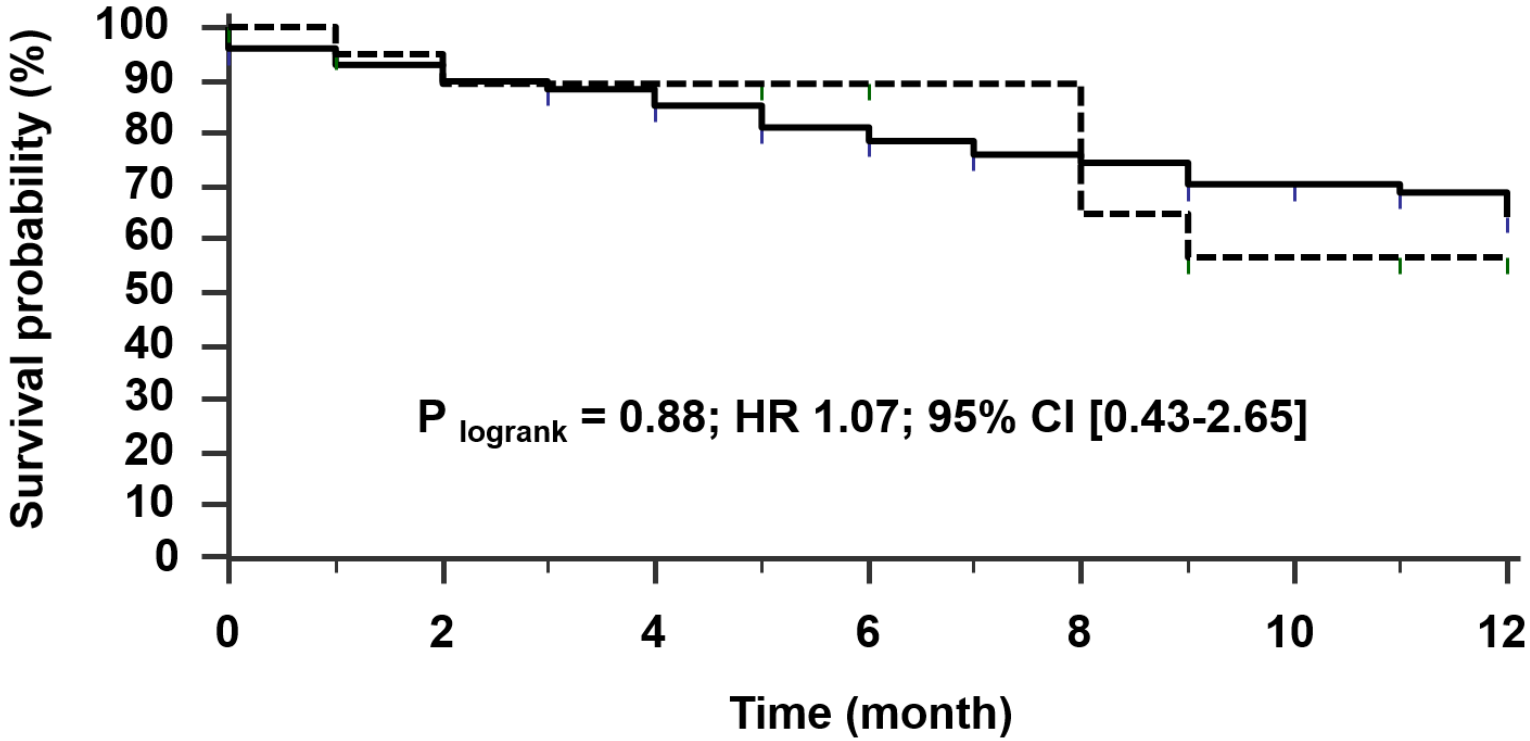
Legend to table 2: The table shows the procedural outcome of TTVR in the study population and in patients with a post-procedural TVG ≤ 3 mmHg vs. patients with a TVG > 3mmHg. Data presented are means (± standard deviation [SD]), medians with inter quartile range (IQR) or numbers of patients (percentages). TR, tricuspid regurgitation; TMVR, trans-catheter mitral valve repair; VTI, velocity time integral; NYHA, New York Heart Association functional class;

NT-proBNP, N-terminal pro-brain natriuretic peptide; MWT, minute walking test; MLHF, Minnesota Living With Heart Failure questionnaire.



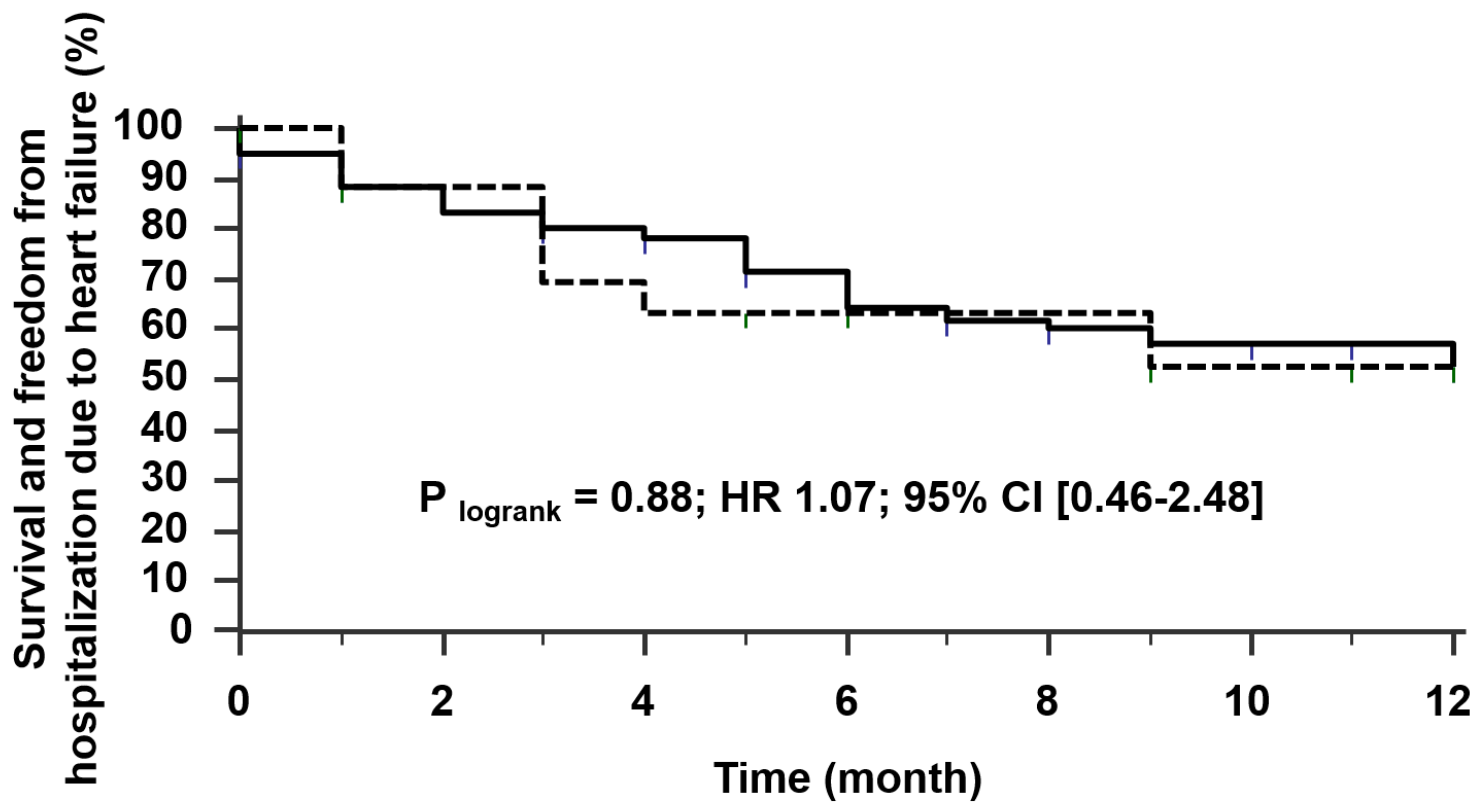






Number at risk

TVG ≤ 3 mmHG	———					
	120	92	84	59	54	46
TVG > 3mmHg	- - - - -					
	25	16	16	11	8	6



Number at risk

TVG ≤ 3 mmHG ———					
120	79	71	47	42	37
TVG > 3mmHg -----					
25	14	10	6	6	4

Supplementary Material

Methods

Outcomes

Heart failure admission was defined as any hospital admission with left- or right-sided heart failure and was confirmed through electronic medical records and clinic follow up notes. The follow-up period was 1 year. Furthermore, 6-minute walking distance (6MWD), the Minnesota Living With Heart Failure questionnaire (MLHFQ), and NYHA class were assessed pre-procedurally, and after 1, 6 and 12 months. We assessed diuretic dose of furosemide equivalent (10mg torasemide was considered equivalent to 20mg furosemide) at baseline.

Statistics

Continuous variables are presented as means ± standard deviations, if the D´Agostino-Pearson test for normal distribution has been passed, or median with interquartile range [IQR]. We applied Fisher's exact test or chi^2 test where appropriate to compare categorical variables. For continuous variables, statistical testing was done with either the t-test (normal distribution, paired or unpaired), the Wilcoxon test (no normal distribution, paired) or the Mann-Whitney test (no normal distribution, unpaired). Patient´s long-term survival was assessed using Kaplan-Meier estimates. A two-tailed P-value < 0.05 was regarded statistically significant. All analyses were performed using MedCalc software (MedCalc Software Version 12.4.0 and 18.11.3, Ostend, Belgium).

Results

Cox regression analysis with TVG as contious variable

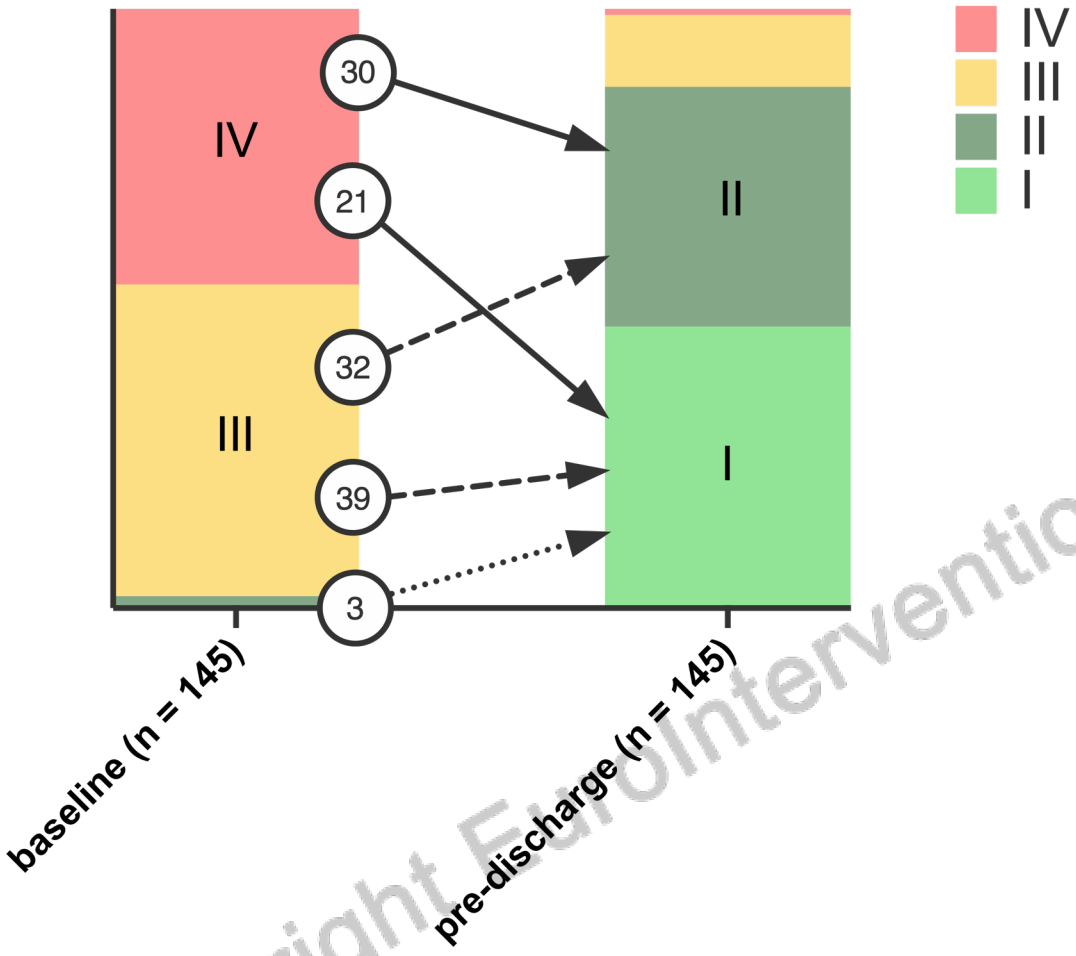
We performed a Cox regression analysis with TVG as contious variable. The TVG as continous variable (per 1 mmHg) was not identified as univariate predictor of outcome (neiter for death nor combined endpoint death and hospitalization due to heart failure) with HR 1.14 95% CI [0.84-1.54], p = 0.4 and HR 1.17 95% CI [0.90-1.52], p = 0.23, respectively.

Patients undergoing concomitant mitral valve repair

In patients undergoing concomitant mitral valve repair device success (measured post-procedurally in hospital) was achieved in 70 out of 75 patients (93%) and change of MR grade from baseline to pre-discharge is displayed in supplementary Figure 3. Patients treated with concomitant trans-catheter mitral valve repair had lower post-procedural TVG compared to patients undergoing isolated TTVR (2.0 mmHg [1.2-3.0 mmHg] vs. 2.4 mmHg [2-3.3 mmHg], p=0.012).

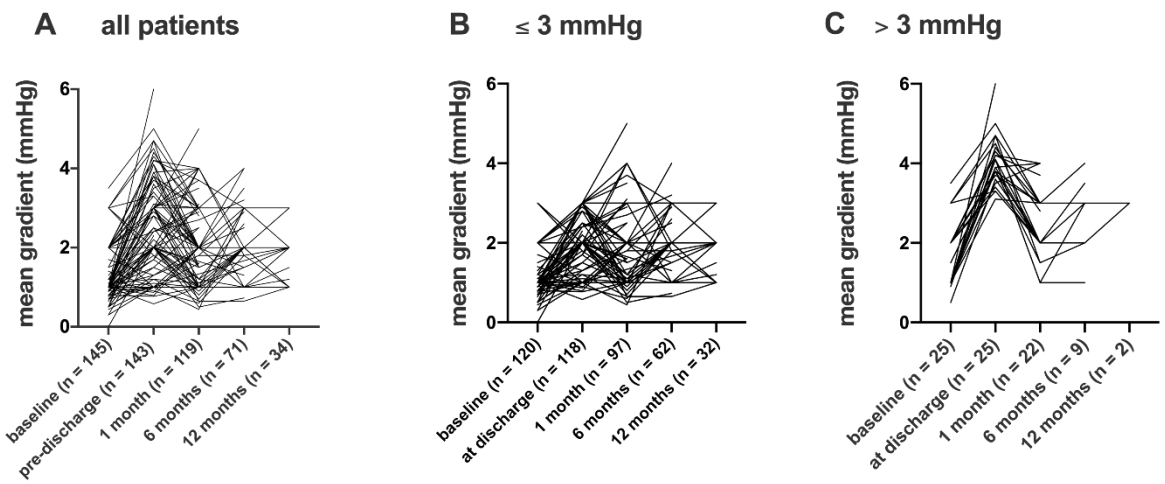
Supplementary Figures

Supplementary Figure 1. Change of TR grade on a class level after TTVR



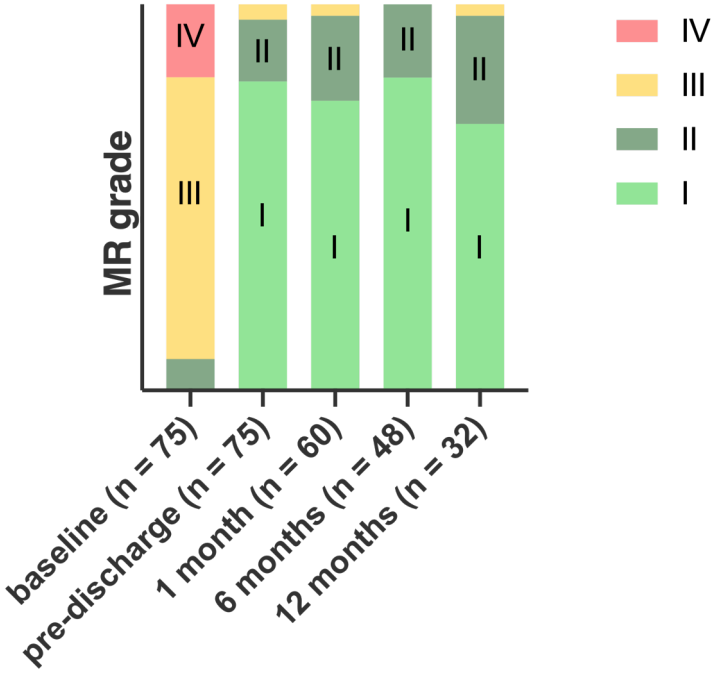
Legend to supplementary Figure 1: The Figure displays the change of TR grade from baseline to pre-discharge in patients undergoing TTVR on a class level.

Supplementary Figure 2. Change in TVG on a patient-level and according to study group



Legend to supplementary Figure 2: The Figure displays the change in TVG on a patient-level from baseline to 1-year in patients undergoing TTVR.

Supplementary Figure 3. Change of MR grade after mitral and tricuspid valve repair.



Legend to supplementary Figure 3: The Figure displays the change of MR grade from baseline to pre-discharge in patients undergoing concomittant mitral and tricuspid valve repair.