EuroIntervention 2019;15:e1057-e1064 published online September 2019 published online e-edition December 2019

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

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This paper also includes supplementary data published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-19-00237

KEYWORDS

- chronic heart failure
- femoral
- mitral valve repair
- transthoracic echocardiogram
- tricuspid disease
- TTVR

Abstract

Aims: The aim of this study was to compare the 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 six-minute walking test at one 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 hospitalisation for heart failure at one year (HR 1.07, 95% CI: 0.46-2.48, $p_{logrank}$=0.88) were similar between patients with a TVG >3 mmHg versus patients with a TVG ≤3 mmHg.

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

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SUBMITTED ON 04/03/2019 - REVISION RECEIVED ON 22/07/2019 - ACCEPTED ON 04/09/2019

DOI: 10.4244/EIJ-D-19-00237

Abbreviations

MLHFQ	Minnesota Living with Heart Failure Questionnaire
MR	mitral regurgitation
NYHA	New York Heart Association
RV	right ventricle, right ventricular
RVTG	right ventricular tricuspid pressure gradient
TR	tricuspid regurgitation
TTE	transthoracic echocardiography
TTVR	transcatheter edge-to-edge tricuspid valve repair
TV	tricuspid valve
TVG	tricuspid valve gradient

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 is 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 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 atrioventricular valves narrows the regurgitant orifice by approximating the leaflets and reducing the valve diameter. Both mechanisms potentially increase transvalvular inflow gradient. It has been shown in a single-centre study that patients with a post-procedural mitral valve gradient >5 mmHg after transcatheter edge-to-edge mitral valve repair have a poorer long-term outcome, including an increased all-cause mortality[8]. Indeed, the pressure and flow conditions of the mitral and tricuspid valve are different. The mitral valve consists of only 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 a 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 the lack of an evidence-based interventional strategy which defines a TVG as 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 versus ≤3 mmHg.

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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 Vascular, Santa Clara, CA, USA) was used as described previously[6]. Image guidance was provided by two- and three-dimensional transoesophageal and transthoracic echocardiography (TTE) with additional fluoroscopy[11,12]. Careful assessment of TVG was performed after every clip implantation with the aim of maintaining a TVG ≤3 mmHg[4].

OUTCOMES

The primary outcome of this study was death and hospitalisation for heart failure in the follow-up period. Further information is provided in **Supplementary Appendix 1**.

ECHOCARDIOGRAPHY

TTE assessment of TVG was performed preprocedurally, 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 into 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 the 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 echocardiographic assessment for valvular stenosis[17]). The septal-lateral diameter of the TV was measured in the RV focused view.

STATISTICAL ANALYSIS

Information on statistics is provided in **Supplementary Appendix 1.**

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

Table 1. Baseline characteristics.

Parameter		All n=145	TVG ≤3 mmHg n=120	TVG >3 mmHg n=25	*p*-value
Age, years±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
EuroSCORE II, 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 (%)	2+	3 (2.1)	3 (2.5)	0 (0)	0.234
	3+	76 (52.4)	66 (55)	10 (40)	
	4+	66 (45.5)	51 (42.5)	15 (60)	
NYHA functional class, n (%)	II	4 (2.8)	3 (2.5)	1 (4)	0.586
	III	94 (64.8)	76 (63.3)	18 (72)	
	IV	47 (32.4)	41 (34.2)	6 (24)	
MR severity, n (%)	≤1+	40 (29.0)	30 (26.3)	10 (42)	0.512
	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)	
Concomitant TMVR		75 (51.7)	69 (57.5)	6 (24)	0.175
LVEF, %, mean±SD		49.9±13.4	49.5±13.6	51.9±12.6	0.410
TV septal-lateral diameter, mm		46 [42-51]	46 [42-51]	46 [43-51]	0.683
RV mid-ventricular diameter, mm		40 [36-45]	40 [36-45]	38 [36-44]	0.387
RA area, cm^2, median [IQR]		35 [29-44]	36 [29-45]	34 [26-43]	0.423
VTI, mm, median [IQR]		29 [24-37]	29 [23-34]	40 [30-46]	<0.001
Vena cava width, mm, mean±SD		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]		3,831 [1,936-7,652]	4,182 [2,310-8,629]	2,276 [906-5,150]	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
6MWT, 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
	Aldosterone 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 oedema, n (%)		42 (29.0)	34 (28.3)	8 (32)	0.968

The Table shows the baseline characteristics of the study population. Data presented are means (±standard deviation [SD]), medians with interquartile range or numbers of patients (percentages). 6MWT: six-minute walking test; ACE: angiotensin-converting enzyme; AR: angiotensin receptor; CRT: cardiac resynchronisation therapy; ED: equivalent dose in mg furosemide; IQR: interquartile range; LVEF: left ventricular ejection fraction; MI: myocardial infarction; MLHFQ: Minnesota Living with Heart Failure Questionnaire; MR: mitral regurgitation; NT-proBNP: N-terminal pro-brain natriuretic peptide; NYHA: New York Heart Association; RA: right atrium; RV: right ventricular; RVTG: right ventricular tricuspid pressure gradient; STS: Society of Thoracic Surgeons; TAPSE: tricuspid annular plane systolic excursion; TR: tricuspid regurgitation; TV: tricuspid valve; VTI: velocity time integral

(75 patients). Device success, which was defined as TR reduction ≥1° to at least moderate, was achieved in 125 patients (86.2%) **(Figure 1, Supplementary Figure 1)**. Clip detachment occurred in four patients. Of these, one clip detachment occurred during the procedure, two detachments occurred within one day and one was noticed during echocardiographic examination at one-month follow-up. Persistent 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 (2-11) months.

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 six-month (2.0 mmHg [1.0-2.5 mmHg], p=0.11) and 12-month (2 mmHg [1.0-2.0 mmHg], p=0.78) follow-up **(Figure 2A, Supplementary Figure 2A)**. Of these, twenty-five patients showed an elevated TVG >3 mmHg at discharge. The TVG at 30 days and six months remained significantly higher in the TVG >3 mmHg group compared to the TVG ≤3 mmHg group (p=0.0035 at 30 days and p=0.018 at six months). 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 six months and 2 patients (100%, measured in 2 patients) at 12 months **(Figure 2B, Figure 2C, Supplementary Figure 2B, Supplementary Figure 2C)**.

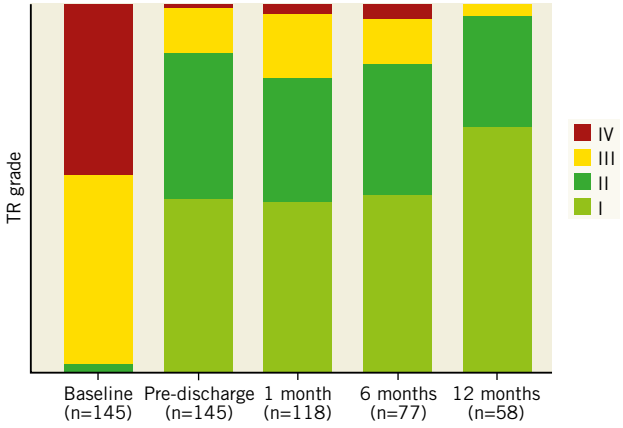

Figure 1. *TR grade at baseline and follow-up echocardiographic examinations in patients after TTVR.*

CHARACTERISTICS AND OUTCOME OF PATIENTS WITH A POST-PROCEDURAL TVG >3 mmHg VERSUS ≤3 mmHg

Patients with a 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 (2,276 ng/l [906-5,150 ng/l] vs 4,182 ng/l [2,310-8,629 ng/l], p=0.008) compared to patients with a TVG ≤3 mmHg. Patients with a TVG >3 mmHg – albeit not significant – were less frequently male (36% vs 53%), had a better glomerular filtration rate (55 ml/min vs 46 ml/min) and more often underwent 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 (46 mm [43-51 mm] vs 46 mm [42-51 mm], p=0.683) and tricuspid annular plane systolic excursion (TAPSE) (17.6±4.8 mm vs 17.0±4.9 mm, p=0.58) did not differ between the groups, whereas RVTG (29 mmHg [18-37 mmHg] vs 34 mmHg [24-43 mmHg], p=0.08) was absolutely lower in patients with a 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) were similar between the groups. At one-month

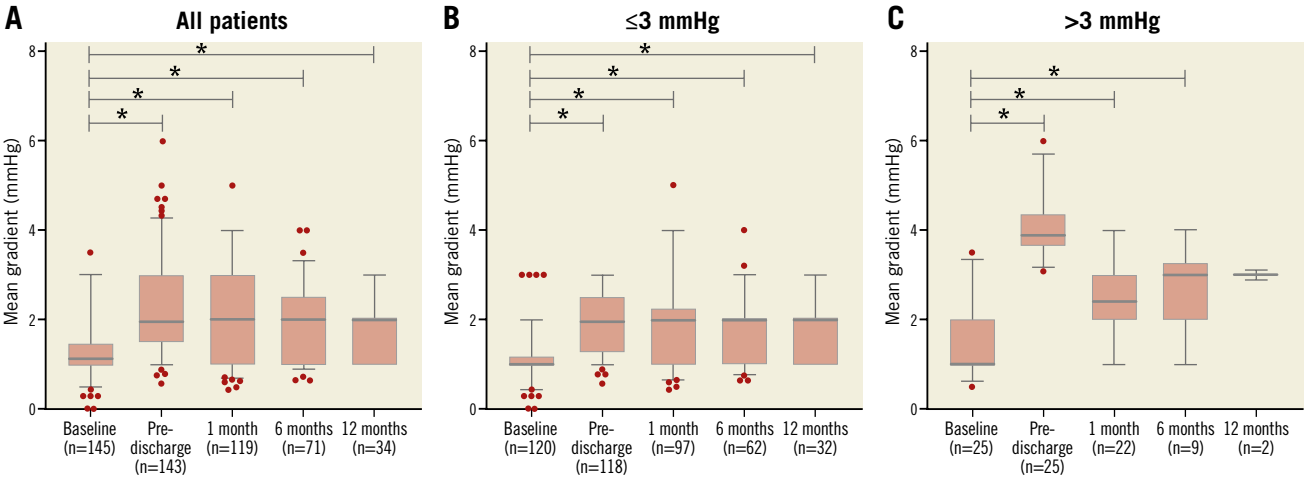

Figure 2. *Changes in tricuspid valve gradient over time. Changes in all patients (A) and according to study group (B: TVG ≤3 mmHg, C: TVG >3 mmHg). Boxes represent interquartile range; whisker represents 5th and 95th percentile, bold dark line represents median. Asterisks represent significant differences with a p-value <0.05.*

follow-up, there was no difference in NYHA class **(Table 2)**. More information on patients undergoing concomitant TMVR is shown in **Supplementary Appendix 2** and **Supplementary Figure 3**. Both groups showed a similar increase in 6-minute walking distance (6MWD) (67 m [5-103 m] vs 56 m [8-97 m], p=0.93). The improvement of quality of life (Minnesota Living with Heart Failure Questionnaire [MLHFQ]) was more pronounced in patients with a TVG >3 mmHg versus ≤3 mmHg (17.8±16.7 vs 9.9±17.0, p=0.08) **(Figure 3)**. Only two patients showed a TVG in excess of 5 mmHg with a heart rate of 111/min and 83/min, respectively, at the determination of TVG. Of these, the first patient was alive nine months after the procedure and the second patient who was treated with TTVR was alive at one-month follow-up in very good physical condition. The frequency of the triple-orifice technique

Table 2. Procedural outcome and follow-up.

Procedural outcome and follow-up			All n=145	TVG ≤3 mmHg n=120	TVG >3 mmHg n=25	*p*-value
Successful clip implantation, n (%)			144 (99.3)	119 (99.2)	25 (100)	0.898
Number of clips, n (%)		1	17 (11.7)	15 (12.5)	2 (8)	0.697
		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 (%)		≤1+	67 (46.2)	55 (45.8)	12 (48)	0.648
		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 at 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 ≥III at 1 month, n (%)		40 (27.6)	34 (28.3)	6 (24)	0.923
	NYHA class at 1 month, n (%)	I+	6 (4.1)	5 (4.2)	1 (4)	0.559
		II+	74 (51.0)	60 (50)	14 (56)	
		III+	38 (26.2)	33 (27.5)	5 (20)	
		IV+	2 (1.4)	1 (0.83)	1 (4)	
Reduction in NYHA class, mean±SD			1.0±0.7	1.0±0.6	0.9±0.7	0.471
NT-proBNP, ng/l, median [IQR]			3,334 [1,851-5,631]	3,520 [2,033-5,754]	2,665 [1,413-4,938]	0.138
6MWT, 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

The Table shows the procedural outcome of TTVR in the study population and in patients with a post-procedural TVG ≤3 mmHg versus patients with a TVG >3 mmHg. Data presented are means (±standard deviation [SD]), medians with interquartile range or numbers of patients (percentages). 6MWT: six-minute walking test; MLHFQ: Minnesota Living with Heart Failure Questionnaire; NT-proBNP: N-terminal pro-brain natriuretic peptide; NYHA: New York Heart Association; TMVR: transcatheter mitral valve repair; TR: tricuspid regurgitation; VTI: velocity time integral

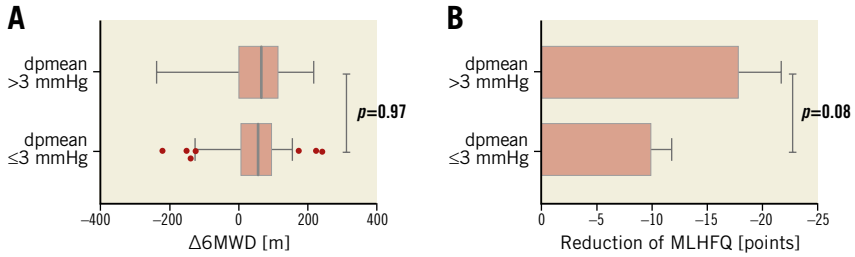

Figure 3. *Improvement in 6MWD and increase in quality of life at one month after TTVR with TVG at discharge of ≤3 mmHg versus >3 mmHg. Improvement in 6MWD (A) and increase in quality of life according to the MLHFQ (B). Boxes represent interquartile range; whisker represents 5th and 95th percentile, bold dark line represents median in panel A; whisker represents standard deviation in panel B. 6MWD: six-minute walking distance; dpmean: mean pressure gradient (d: delta, Δ); MLHFQ: Minnesota Living with Heart Failure Questionnaire*

(versus the bicuspidalisation technique[18]) was significantly higher in patients with a TVG >3 mmHg (p<0.001). Moreover, the median TVG at discharge was significantly higher in patients undergoing a bicuspidalisation 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 one-year mortality (HR 1.07, 95% CI: 0.43-2.65; $p_{logrank}$=0.88) **(Figure 4)** and the combined endpoint mortality and hospitalisation 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 versus patients with a TVG ≤3 mmHg.

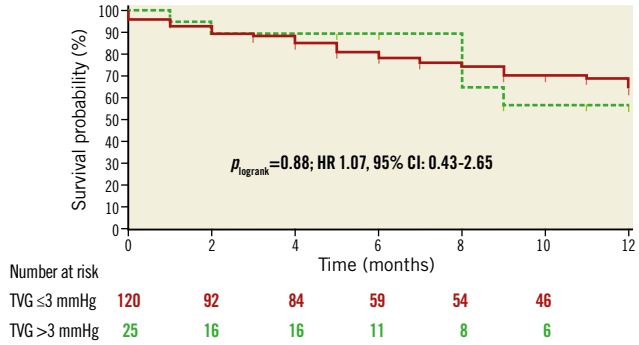

Figure 4. *Kaplan-Meier one-year survival estimates of patients after TTVR with post-procedural TVG ≤3 mmHg versus >3 mmHg. Vertical markings within survival curves indicate last live contact.*

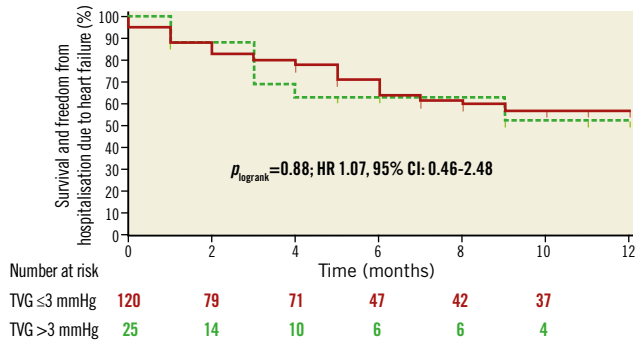

Figure 5. *One-year estimates of the combined endpoint death and admission due to heart failure of patients after TTVR with post-procedural TVG ≤3 mmHg versus >3 mmHg. Vertical markings within survival curves indicate last live contact.*

Discussion

This prospective observational study investigated the mean TVG after TTVR using the edge-to-edge repair technique and compared patient characteristics and outcomes of patients with a TVG at discharge of >3 mmHg versus ≤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 six and 12 months, 2) a small proportion of patients presented with an elevated TVG >3 mmHg, 3) improvement in NYHA class and 6MWD at one month after the procedure was similar between groups, and 4) this elevation in TVG did not result in an increase either in mortality or in the combined endpoint of mortality and hospitalisation for heart failure.

International guidelines consider mitral or tricuspid valve inflow gradients in excess of 5 mmHg as stenosis[2,3]. In patients undergoing transcatheter 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 in a combination of all-cause mortality, left ventricular assist device implantation, mitral valve replacement, and recurrent procedure at long-term follow-up[8]. There are 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 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 atrioventricular 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. In contrast, the tricuspid valve – embedded within the right-sided low-pressure circulation – contains three, sometimes four leaflets and is larger[10] than the mitral valve, which leads to a lower inflow velocity and subsequently lower pressure gradient compared to the 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 did 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 in 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 TMVR separated from the beginning of follow-up, whereas Kaplan-Meier curves in our study after TTVR did not separate up to one year. Our strategy of carefully monitoring the TVG during TTVR resulted in a small cohort of patients with a TVG >3 mmHg, with only about 1% of treated patients with a TVG >5 mmHg. Hence, in contrast to transcatheter mitral valve repair, a clinically relevant tricuspid stenosis after TTVR did not occur.

Limitations

This was a prospective, observational analysis at a single centre investigating a rather small number of patients in both groups; however, it represents one of the largest patient cohorts undergoing

TTVR. Echocardiographic parameters such as effective regurgitant orifice 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 echocardiographic parameters. The transvalvular gradient cut-off of 3 mmHg was arbitrarily 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.

Conclusions

TTVR resulted in a small increase in the TVG, which remained stable at follow-up. A small cohort of patients showed an elevated TVG >3 mmHg after the procedure. This elevation had no impact on the clinical improvement after TTVR or on mortality and the need for hospitalisation 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 arbitrarily defined TVG of ≤3 mmHg has been used in TTVR procedures by us and others in the past. Only a small cohort of patients showed an elevated TVG >3 mmHg after the procedure which did not have an impact on clinical improvement after TTVR or on mortality and the need for hospitalisation for heart failure. Thus, an elevated TVG after TTVR might be an overestimated problem in the right-sided low-pressure circulation.

Conflict of interest statement

M. Orban has received speaker honoraria from Sedana Medical 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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Supplementary data

Supplementary Appendix 1. Methods.

Supplementary Appendix 2. Results.

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

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

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

The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-19-00237

Supplementary data

Supplementary Appendix 1. 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 one year. Furthermore, six-minute walking distance (6MWD), the Minnesota Living with Heart Failure Questionnaire (MLHFQ), and NYHA class were assessed preprocedurally, and after 1, 6 and 12 months. We assessed the diuretic dose of furosemide equivalent (10 mg torasemide was considered equivalent to 20 mg furosemide) at baseline.

Statistical analysis

Continuous variables are presented as means±standard deviations, if the D´Agostino-Pearson test for normal distribution was passed, or median with interquartile range [IQR]. We applied Fisher's exact test or chi² test where appropriate to compare categorical variables. For continuous variables, statistical testing was carried out 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). The long-term survival of patients was assessed using Kaplan-Meier estimates. A two-tailed p-value <0.05 was regarded as statistically significant. All analyses were performed using MedCalc software, Version 12.4.0 and Version 18.11.3 (MedCalc Software, Ostend, Belgium).

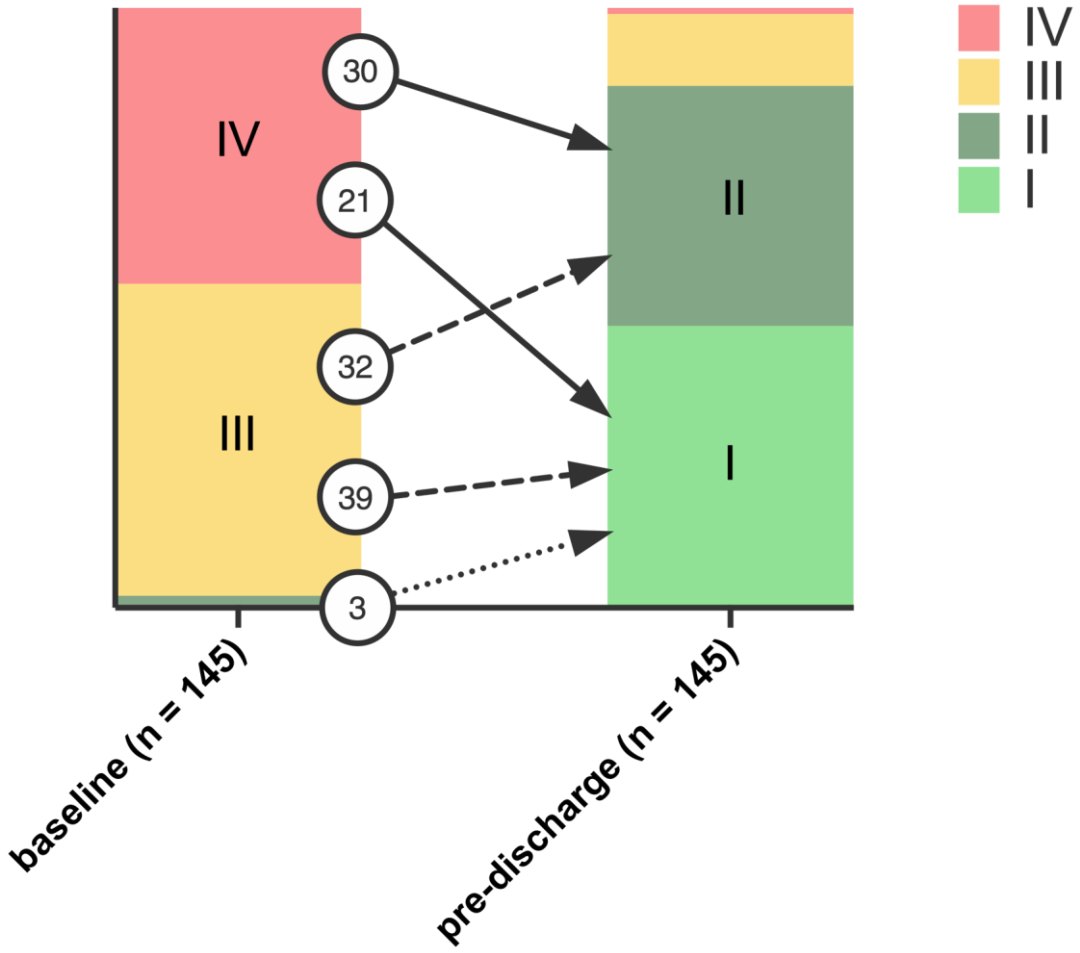
Supplementary Appendix 2. Results

Cox regression analysis with TVG as continuous variable

We performed a Cox regression analysis with TVG as continuous variable. The TVG as continuous variable (per 1 mmHg) was not identified as an univariate predictor of outcome (either for death or for the combined endpoint of death and hospitalisation due to heart failure) with an 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.

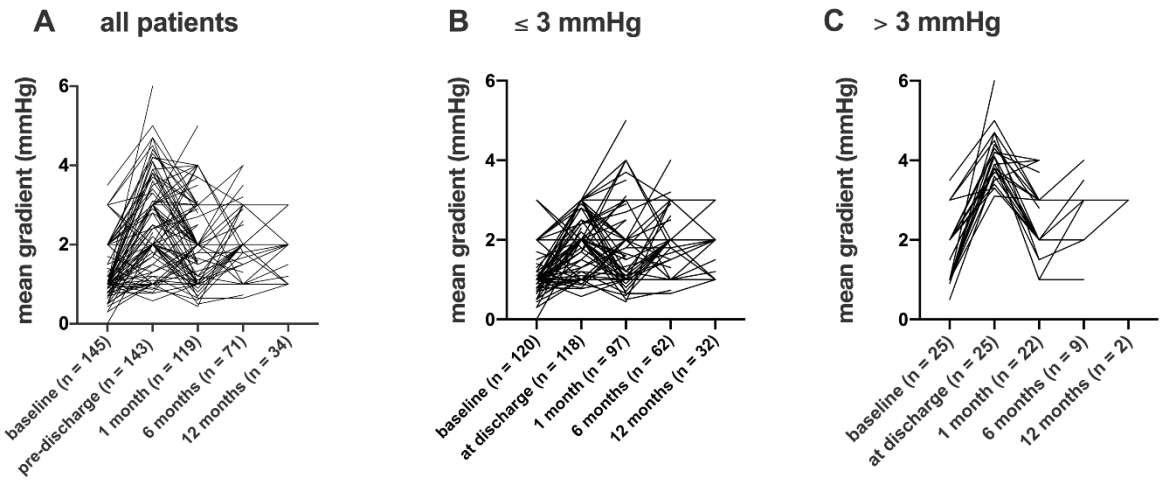
Patients undergoing concomitant mitral valve repair

In patients undergoing concomitant mitral valve repair, device success (measured post-procedurally in hospital) was achieved in 70 out of 75 patients (93%); change of MR grade from baseline to pre-discharge is displayed in **Supplementary Figure 3**. Patients treated with concomitant transcatheter 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).



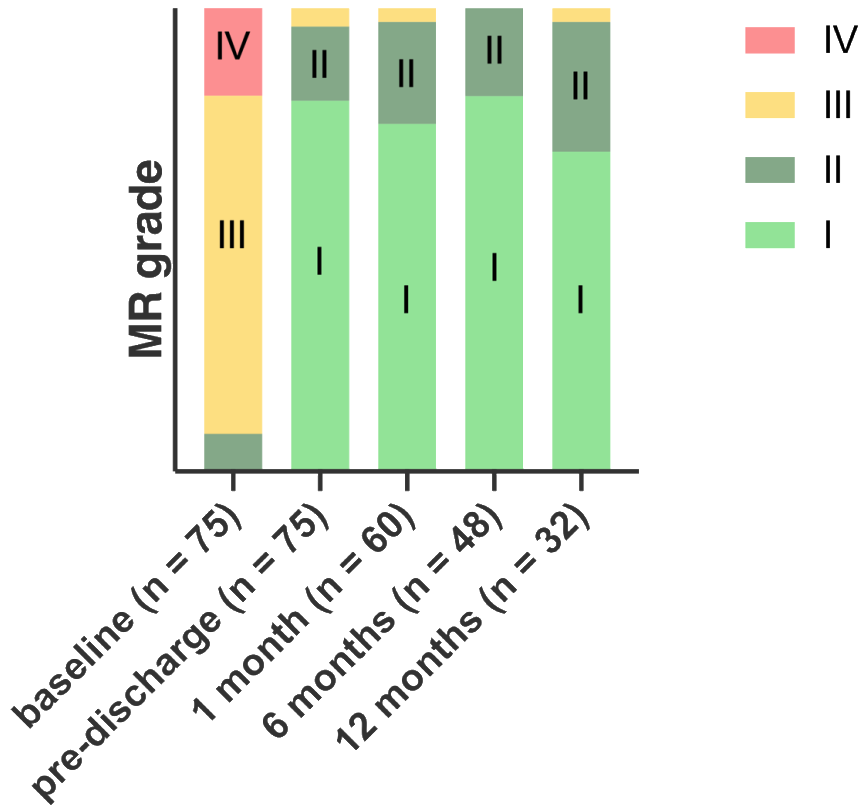
Supplementary Figure 1. Change in TR grade on a class level after TTVR.

Change in 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.

Change in TVG on a patient level from baseline to one year in patients undergoing TTVR.



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

Change in MR grade from baseline to pre-discharge in patients undergoing concomitant mitral and tricuspid valve repair.