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Dietz, M.F.; Goedemans, L.; Vo, N.M.; Prihadi, E.A.; Bijl, P. van der; Gersh, B.J.; ... ; Bax, J.J.

Prognostic Implications of Significant Isolated Tricuspid Regurgitation in Patients With Atrial Fibrillation Without Left-Sided Heart Disease or Pulmonary Hypertension

Marlieke F Dietz, MD[a], Laurien Goedemans, MD[a], N Mai Vo, MD[a], Edgard A Prihadi, MD[a,b], Pieter van der Bijl, MB,ChB, MMed[a], Bernard J Gersh, MB, ChB, DPhil[c], Nina Ajmone Marsan, MD[a], Victoria Delgado, MD[a], and Jeroen J Bax, MD[a,*]

The prognostic impact of isolated tricuspid regurgitation (TR) in patients with atrial fibrillation (AF) has not been investigated. The purpose of this study was to investigate the prognostic implications of significant isolated TR in AF patients without left-sided heart disease, pulmonary hypertension, or primary structural abnormalities of the tricuspid valve.

A total of 63 AF patients with moderate and severe TR were matched for age and gender to 116 AF patients without significant TR. Patients were followed for the occurrence of all-cause mortality, hospitalization for heart failure and stroke. Patients with significant isolated TR (mean age 71 ± 8 years, 57% men) more often had paroxysmal AF as compared with patients without TR (mean age 71 ± 7 years, 60% men) (60% vs 43%, p = 0.028). In addition, right atrial size and tricuspid annular diameter were significantly larger in patients with significant isolated TR compared with their counterparts. During follow-up (median 62 [34 to 95] months), 53 events for the combined endpoint occurred. One- and 5-year event-free survival rates for patients with significant isolated TR were 76% and 56%, compared with 92% and 85% for patients without significant TR, respectively (Log rank Chi-Square p <0.001). The presence of significant isolated TR was independently associated with the combined endpoint (hazard ratio, 2.853; 95% confidence interval, 1.458 to 5.584; p = 0.002). In conclusion, in the absence of left-sided heart disease and pulmonary hypertension, significant isolated TR is independently associated with worse event-free survival in patients with AF. **(Am J Cardiol 2020;135:84−90)**

Isolated tricuspid regurgitation (TR) is an increasingly recognized subtype of TR, which is defined by the absence of concomitant left-sided heart disease or pulmonary hypertension and which is frequently associated with the presence of atrial fibrillation (AF).[1] Isolated TR accounts for 6% to 10% of all patients with significant (moderate and severe) TR.[2,3] However, due to lack of outcome studies, the management of isolated TR is not clearly addressed in current guidelines.[4,5] Similar to atrial functional mitral regurgitation,[6] a significant proportion of patients with isolated TR have AF.[7] The prognostic implications of isolated significant TR in patients with AF have not been extensively studied. The aim of this study was therefore to assess the prognostic influence of isolated significant TR in patients with AF in the absence of left-sided heart disease, pulmonary hypertension or primary structural abnormalities of the tricuspid valve.

Methods

Of 1,604 patients with a diagnosis of significant (moderate or severe) TR in the departmental echocardiographic database at the Leiden University Medical Center (LUMC) between June 1995 and September 2016, patients with AF and isolated TR were selected. To identify those patients, a query was performed based on a history of AF. As per current guidelines,[8] AF was diagnosed either on 12-lead ECG or during 24-hour Holter ECG monitoring. Subsequently, patients with any of the following conditions which could lead to primary or secondary TR were excluded − structural abnormalities of the tricuspid valve leaflets, significant (moderate or severe) aortic and/or mitral valve disease, previous cardiac surgery, congenital heart disease, left ventricular (LV) ejection fraction <50%, systolic pulmonary artery pressure >40 mm Hg, pacemaker or implantable cardioverter defibrillator leads and new onset AF (defined as AF that has not been diagnosed before, irrespective of the duration).[8]

[a]Department of Cardiology, Leiden University Medical Center, Leiden, The Netherlands; [b]Department of Cardiology, ZNA Middelheim Hospital, Antwerp, Belgium; and [c]Department of Cardiovascular Medicine, Mayo Clinic College of Medicine, Rochester, Minnesota. Manuscript received July 6, 2020; revised manuscript received and accepted August 18, 2020.

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*Corresponding author: Tel +31 71 526 2020; fax: + 31 71 526 6809
E-mail address: j.j.bax@lumc.nl (J.J. Bax).

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Patients with isolated significant TR were matched for age and gender in a 1:2 ratio by computer-generated frequency matching to patients who underwent echocardiographic evaluation for AF between June 1995 and September 2016, who did not show significant TR and in whom the same exclusion criteria as the significant TR group were applied.

Baseline data included demographic and clinical characteristics at the time of echocardiographic evaluation. Clinical data comprised cardiovascular risk factors, medication use, thyroid hormone levels, creatinine levels, New York Heart Association (NYHA) functional class and type of AF (paroxysmal AF vs persistent/permanent AF).[8] Coronary artery disease was defined as previous myocardial infarction or diagnosis of significant stenosis of an epicardial coronary artery (>70%) by invasive coronary angiography.

Data were analyzed retrospectively from the departmental Cardiology Information System (EPD-Vision; Leiden University Medical Center, Leiden, the Netherlands). The institutional review board of the Leiden University Medical Center authorized the study design and waived the need for patient written informed consent for retrospective analysis of anonymously handled data.

Transthoracic echocardiography was performed systematically according to institutional clinical protocols utilizing commercially available ultrasound systems (Vivid 7, E9 and E95 systems; GE-Vingmed, Horton, Norway). All images were digitally stored for offline analysis (EchoPAC version 113.0.3 and 202; GE-Vingmed, Horten, Norway). Parasternal, apical, and subcostal views were used to acquire M-mode and 2D images and color, continuous and pulsed wave Doppler data according to the current recommendations.[5,9–11] TR severity was classified using a multiparametric approach based on qualitative, semiquantitative, and quantitative assessment.[10] Patients were divided into 2 groups according to TR grade: nonsignificant (none to mild) TR versus significant (moderate to severe) TR. LV and left atrial volumes were measured on the apical 2- and 4-chamber views by the Simpson's biplane method. LV ejection fraction was calculated and expressed as percentage.[12] The peak velocity of the transmitral early diastolic flow (E) and late diastolic flow (A) in patients with sinus rhythm were measured and the E/A ratio calculated. The tricuspid annular diameter, right atrial (RA) dimensions, right ventricular (RV) dimensions and RV areas were measured on a focused RV apical view.[12] All left and right ventricular and atrial size measurements were indexed for body surface area.[12] To assess RV systolic function, tricuspid annular plane systolic excursion was measured on M-mode recordings of the lateral tricuspid annulus in a focused RV apical view. In addition, fractional area change (%) was derived from the RV end-systolic and end-diastolic areas traced on a focused RV apical view.[12] The systolic pulmonary artery pressure was estimated based on the TR jet velocity, adding 3, 8 or 15 mm Hg based on the inferior vena cava collapsibility.[9]

All-cause mortality data were ascertained from the Departmental Cardiology Information system, which is updated based on municipal civil registry data. All-cause mortality data were complete for all patients. Last follow-up date corresponded to the date of death or last recorded visit. The primary endpoint for this study was a composite of all-cause mortality, hospitalization for heart failure and stroke. Secondary end points were catheter ablation for AF and tricuspid valve surgery.

Continuous variables are expressed as mean ± SD, or median (interquartile range) in case of Gaussian or non-Gaussian distributions, respectively. Categorical variables are presented as numbers and percentages. Differences between groups were evaluated by the unpaired *t*-test for normally distributed continuous variables, by the Mann-Whitney *U* test for continuous variables with skewed distribution and by the Chi-Square test for categorical variables. Event rates of the composite endpoint (all-cause mortality, hospital admission for heart failure and stroke) were estimated by the Kaplan-Meier method and compared between groups by the Log-rank test. Multivariable Cox proportional hazards regression analysis was performed to determine the clinical and echocardiographic factors that were independently associated with prognosis. The variables included in the multivariable analysis were selected based on the sample size and number of events at follow-up. Variables with a p-value <0.05 in univariable Cox regression analysis and considered of clinical significance were entered into the multivariable model. Odds ratios and 95% confidence intervals were calculated. All p-values were 2-sided and values <0.05 were considered of statistical significance. All statistical analyses were performed using SPSS for Windows, version 23 (SPSS Inc, Armonk, NY:IBM Corp).

Results

Of the 1,604 patients with significant TR evaluated within the study period, a total of 79 (4.9%)patients were classified as having isolated TR and AF. Sixty-three of these patients could be matched for age and gender by computer-generated frequency matching with 116 AF patients without significant TR, resulting in a total study population of 179 patients (mean age 71 ± 7 years, 59% male).

The baseline clinical characteristics of the overall population and for patients with versus without isolated significant TR are summarized in Table 1. Per design of the study, no significant differences in age and gender were observed between the 2 groups. The prevalence of hypertension in the overall population was high (84%) and 49% of the patients had hypercholesterolemia. Patients with isolated significant TR were more likely to be on rhythm control, as these patients had more often paroxysmal AF compared with patients without TR (60% vs 43%, p = 0.028). In addition, patients with isolated significant TR less frequently had coronary artery disease, but more often had NYHA functional class >2 heart failure symptoms. In terms of cardiovascular risk factors and medication use, no differences were observed between patients with and without significant TR. Hemoglobin levels were significantly lower and renal function was worse in patients with significant TR compared with patients without significant TR.

Table 2 shows the echocardiographic characteristics of the overall population with AF and the comparison between the 2 groups with vs without isolated significant TR. As per inclusion/exclusion criteria of the current study, LV ejection fraction was normal and subsequently did not differ

Table 1
Clinical characteristics of the total population with atrial fibrillation and according to tricuspid regurgitation severity

Variable	Overall	Tricuspid regurgitation		p Value
	(n = 179)	None/mild (n = 116)	Moderate/severe (n = 63)	
Age (years)	71 ± 7	71 ± 7	71 ± 8	0.940
Men	106 (59%)	70 (60%)	36 (57%)	0.677
Body surface area (m^2)	1.96 ± 0.23	1.98 ± 0.22	1.92 ± 0.25	0.081
Paroxysmal atrial fibrillation	88 (49%)	50 (43%)	38 (60%)	0.028
Coronary artery disease	51 (29%)	40 (35%)	11 (18%)	0.022
Obstructive pulmonary disease	21 (12%)	14 (12%)	7 (12%)	1.000
NYHA class >2	25 (14%)	7 (6%)	18 (31%)	<0.001
Hypertension	143 (84%)	96 (83%)	47 (86%)	0.656
Hypercholesterolemia	83 (49%)	60 (52%)	23 (42%)	0.226
Diabetes mellitus	25 (15%)	17 (15%)	8 (14%)	0.949
(Ex-)smoker	38 (22%)	28 (24%)	10 (18%)	0.352
Medications				
Anticoagulants	129 (76%)	87 (75%)	42 (78%)	0.693
Beta-blockers	114 (67%)	81 (70%)	33 (61%)	0.260
ACE-inhibitors	90 (53%)	58 (50%)	32 (59%)	0.260
Aldosterone antagonists	12 (7%)	6 (5%)	6 (11%)	0.159
Calcium channel antagonists	36 (21%)	24 (21%)	12 (22%)	0.820
Statins	78 (46%)	53 (46%)	25 (46%)	0.941
Diuretics	59 (34%)	37 (32%)	22 (37%)	0.525
Laboratory values				
Hemoglobin (mmol/L)	8.8 (8.0-9.5)	9.0 (8.4-9.2)	8.3 (6.1-9.2)	<0.001
Total cholesterol (mmol/L)	4.7 (4.1-5.8)	4.7 (4.2-5.7)	4.9 (3.6-6.4)	0.720
Total cholesterol (mg/dL)	85 (74-105)	85 (76-103)	88 (65-115)	0.720
TSH (mU/L)	1.8 (1.2-3.0)	1.8 (1.2-3.1)	1.8 (1.4-3.0)	0.931
T4 (pmol/L)	17 (15-19)	16 (15-19)	17 (15-21)	0.610
Creatinine (μmol/L)	85 (73-102)	81 (73-96)	95 (73-114)	0.030

Values are mean ±SD, median (IQR) or n (%). p-value by unpaired *t* test or Mann-Whitney *U* test for Gaussian and non-Gaussian distributed continuous variables, respectively. p-value by Chi-Square for categorical variables. ACE = angiotensin-converting enzyme; IQR = interquartile range; NYHA = New York Heart Association; SD = standard deviation; TSH = thyroid-stimulating hormone; TR = tricuspid regurgitation.

Table 2
Echocardiographic characteristics of the total population with atrial fibrillation and according to tricuspid regurgitation severity

Variable	Overall	Tricuspid regurgitation		p Value
	(n = 179)	None/mild (n = 116)	Moderate/severe (n = 63)	
Heart rate (bpm)	72 (61-85)	69 (59-82)	75 (65-90)	0.020
LV end-diastolic volume (ml/m^2)	48 ± 14	48 ± 13	48 ± 16	0.967
LV end-systolic volume (ml/m^2)	20 ± 7	20 ± 6	20 ± 8	0.597
LVEF (%)	58 (54-63)	58 (55-64)	57 (54-62)	0.335
E/A ratio	1.1 (0.8-1.5)	1.0 (0.8-1.3)	1.5 (1.0-2.6)	<0.001
LA maximum volume (ml/m^2)	42 (30-56)	41 (31-50)	48 (29-60)	0.145
Tricuspid annular diameter (mm)	38 ± 8	35 ± 5	43 ± 9	<0.001
RV basal dimension (mm/m^2)	23 ± 4	22 ± 3	24 ± 4	<0.001
RV mid dimension (mm/m^2)	18 ± 3	17 ± 3	19 ± 4	<0.001
RV longitudinal dimension (mm/m^2)	38 ± 5	38 ± 5	37 ± 6	0.065
RV end-diastolic area (cm^2/m^2)	12 (10-14)	12 (10-14)	12 (10-14)	0.642
RV end-systolic area (cm^2/m^2)	7 (6-8)	7 (6-8)	7 (6-9)	0.608
RV fractional area change (%)	39 ± 12	38 ± 11	39 ± 13	0.535
TAPSE (mm)	20 ± 6	21 ± 6	17 ± 5	<0.001
Systolic pulmonary artery pressure (mmHg)	30 (25-35)	32 (27-36)	27 (24-33)	0.001
RA maximum area (cm^2/m^2)	11 (9-15)	10 (9-11)	16 (13-19)	<0.001
RA long-axis dimension (mm/m^2)	29 (26-33)	27 (25-31)	34 (30-38)	<0.001
RA short-axis dimension (mm/m^2)	23 (21-27)	22 (19-24)	28 (25-32)	<0.001

Values are mean ±SD, median (IQR) or n (%). p-value by unpaired *t* test or Mann-Whitney *U* test for non-Gaussian and Gaussian distributed continuous variables, respectively. p-value by Chi-Square test for categorical variables. AF = atrial fibrillation; E/A = ratio of mitral inflow peak early diastolic flow-velocity to atrial contraction peak-velocity; IQR = interquartile range; LA = left atrium; LV = left ventricular; RA = right atrial; RV = right ventricular; SD = standard deviation; TAPSE = tricuspid annular plane systolic excursion; TR = tricuspid regurgitation.

Table 3
Follow-up variables for the overall population with atrial fibrillation and according to tricuspid regurgitation severity

Variable	Overall	Tricuspid regurgitation		p Value
	(n = 179)	None/mild (n = 116)	Moderate/severe (n = 63)	
All-cause mortality	37 (21%)	14 (12%)	23 (37%)	<0.001
Stroke	16 (10%)	7 (7%)	9 (15%)	0.085
Hospital admission for heart failure	19 (11%)	5 (4%)	8 (13%)	0.039
Catheter ablation	47 (27%)	30 (26%)	17 (28%)	0.774
TR surgery	6 (3%)	0 (0%)	6 (10%)	0.001

TR = tricuspid regurgitation.

significantly between groups (none/mild TR: 58% [55 to 64] vs moderate/severe TR: 57% [54 to 62], p = 0.335). RA maximum dimensions were significantly larger in patients with isolated significant TR compared with patients without significant TR. As expected, the tricuspid annular diameter was more dilated in patients with isolated significant TR. Interestingly, RV basal and midventricular dimensions were significantly larger in patients with TR, while no significant differences in RV areas and fractional area change were observed between groups. However, RV function measured with tricuspid annular plane systolic excursion was significantly less in patients with significant TR.

During a median follow-up of 62 (34 to 95) months, 53 adverse events for the combined endpoint occurred. Of the overall population, 19 (11%) patients were hospitalized for heart failure, 16 (10%) had a stroke and 37 (21%) patients died. All-cause mortality and the amount of hospitalizations for heart failure during follow-up were significantly higher in patients with isolated significant TR compared with patients without significant TR. During follow-up, 47 patients (27%) underwent catheter ablation and 6 patients with isolated significant TR received tricuspid valve annuloplasty (Table 3). In the overall population, the cumulative event-free survival for the combined endpoint at 1 year and 5 years was 87% and 75%, respectively. Figure 1 shows the Kaplan-Meier curves for event-free survival of the combined endpoint according to the presence or absence of isolated significant TR. At long-term follow-up, the clinical outcome was significantly worse in patients with TR (Log rank Chi-Square: 18.694; p <0.001). One- and 5-year event-free survival rates for patients with isolated significant TR were 76% and 56%, compared with 92% and 85% in patients without significant TR, respectively.

In the multivariable Cox proportional hazard model adjusted for age, gender, NYHA functional class >2, renal function and RV function, the presence of isolated significant TR was independently associated with the combined endpoint of all-cause mortality, hospitalization for heart failure and stroke (Table 4). In addition, older age, NYHA functional class >2 and worse renal function were significantly associated with the combined endpoint.

Discussion

TR is a heterogeneous disease with diverse characteristics due to various underlying mechanisms. Isolated TR is a morphologic type of TR characterized by the absence of primary tricuspid valve abnormality, left-sided heart disease and pulmonary hypertension.[1] Compared to left-sided heart disease-related TR, isolated TR is associated with older age, female sex and a high prevalence of AF.[7,13] Because longstanding AF leads to RA enlargement and subsequent tricuspid annular dilation, various studies have suggested AF to be a major cause of isolated TR.[6,14,15] Park et al.[15] demonstrated in 89 patients with lone AF that persistent AF was independently associated with greater TR

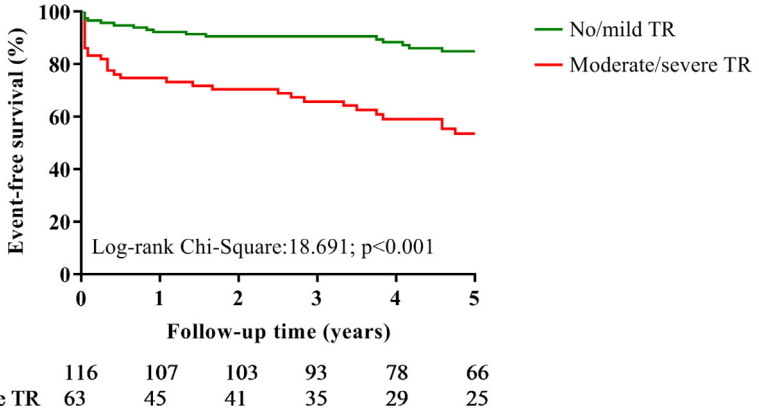

Figure 1. Kaplan-Meier curves for freedom of adverse events (death, hospital admission for heart failure, stroke) in atrial fibrillation patients with versus without significant isolated tricuspid regurgitation. In 179 age and gender matched atrial fibrillation patients without left-sided heart disease, pulmonary hypertension, or primary structural abnormalities of the tricuspid valve, isolated moderate and severe TR was associated with worse long-term prognosis in terms of mortality, hospitalization for heart failure and stroke compared to patients without isolated significant TR. AE = adverse events; TR = tricuspid regurgitation.

Table 4
Univariable and multivariable Cox proportional hazard models for freedom of adverse events (death, hospital admission for heart failure, stroke) for patients with atrial fibrillation

Variable	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	p Value	Hazard ratio (95% CI)	p Value
Age	1.053 (1.012-1.095)	0.012	1.061 (1.012-1.113)	0.015
Male gender	0.959 (0.552-1.663)	0.881	0.676 (0.352-1.297)	0.239
BSA (m^2)	0.563 (0.160-1.990)	0.373		
Paroxysmal atrial fibrillation	1.431 (0.823-2.486)	0.204		
Coronary artery disease	1.142 (0.646-2.020)	0.647		
NYHA class >2	3.069 (1.685-5.589)	<0.001	2.179 (1.089-4.357)	0.028
Hemoglobin	0.698 (0.575-0.847)	<0.001		
Creatinine	1.007 (1.004-1.009)	<0.001	1.006 (1.003-1.010)	<0.001
Heart rate	1.009 (0.996-1.022)	0.181		
LVEF	1.003 (0.958-1.050)	0.902		
E/A ratio	1.275 (0.937-1.735)	0.122		
TAPSE	0.940 (0.898-0.985)	0.010	1.023 (0.968-1.081)	0.427
Systolic pulmonary artery pressure	0.975 (0.936-1.015)	0.213		
RA maximum area, indexed	1.048 (0.994-1.104)	0.080		
Tricuspid annulus diameter	1.049 (1.015-1.081)	0.004		
Significant TR	3.130 (1.810-5.415)	<0.001	2.853 (1.458-5.584)	0.002

BSA = body surface area; CI = confidence interval; E/A = ratio of mitral inflow peak early diastolic flow-velocity to atrial contraction peak-velocity; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; RA = right atrial; RV = right ventricular; TAPSE = tricuspid annular plane systolic excursion; TR = tricuspid regurgitation.

severity compared to paroxysmal AF. Interestingly, in the present study, patients with isolated significant TR more often had paroxysmal AF compared with patients without significant TR. However, duration and burden of AF was not taken into account in the present study, which could be of influence on TR severity.

The strong association between AF and isolated significant TR is confirmed in the present study. Nevertheless, AF and isolated significant TR do not always coexist and other mechanisms such as a fibrous skeleton of the tricuspid annulus with less structural integrity or senescent annular degeneration may contribute to the development of isolated TR.[13,16]

Compared with other morphologic types of TR, prognosis in patients with isolated TR is relatively good.[1,2] It has been suggested that TR, in the context of other cardiac diseases, is not the cause of worse prognosis, but a surrogate for the associated comorbidities.[17] The absence of cardiac comorbidities such as pulmonary hypertension, left-sided valvular disease or LV systolic dysfunction, suggests isolated TR to be the ideal etiology to investigate the prognostic implications of TR itself. However, previous studies investigating the prognostic impact of isolated TR are scarce and significant variation in the definition of isolated TR challenge the interpretation of discrepant results.[14,18,19] The inclusion and exclusion criteria used by Topilsky et al[20] are most congruent with the definition of isolated TR as described by Prihadi et al[1] and therefore the most comparable to our study. In that study, AF patients with and without isolated significant TR were compared (similar to the present study), and the results confirmed that isolated TR has a significant influence on mortality and cardiac events in patients with AF, independent of RV size and function.[20] A more recent study compared 89 patients with moderate-to-severe isolated TR (assessed qualitatively) to a group of healthy individuals matched for age, sex, LV ejection fraction, systolic pulmonary artery pressure, and comorbidity index in a subanalysis and demonstrated that isolated significant TR was associated with increased mortality after adjustment for AF.[2] Interestingly, only 68% of patients with isolated significant TR had AF.

Tricuspid valve surgery for isolated TR is associated with high in-hospital mortality and morbidity due to complications, like right-sided heart failure.[21] However, recent studies have shown that an acceptable mortality rate can be reached in patients without RV dysfunction or pulmonary hypertension.[22] AF patients with isolated TR may be the best candidates for tricuspid valve annuloplasty, since TR in these patients is mainly caused by annular dilation whereas other cardiac comorbidities are absent.[16] Nevertheless, clinical decision making remains challenging with the limited data on prognosis in isolated TR at our disposal, leading to low referral rates for surgical treatment, which increase only after the onset of right heart failure. In the retrospective cohort described by Axtell et al,[23] 72% of patients had evidence of right heart failure at the time of diagnosis, but more than a quarter experienced a delay of more than a year before surgical referral. Prospective studies are needed to assess optimal timing for surgery in this particular group of patients. A clinical risk score for isolated tricuspid valve surgery as proposed by LaPar et al could be useful but needs validation.[24]

The present study is subject to the limitations inherent to a single-center retrospective cohort study. Assessing the stability of TR over time would have been subject to bias as follow-up echocardiography was not performed at fixed timepoints. Due to the strict definition of isolated TR, the final study population was limited to 179 patients. However, these exclusion criteria are necessary to minimize heterogeneity between patients and assess the true impact of TR on prognosis. The use of cut-off values for reduced LV systolic function and pulmonary hypertension are based on

current guidelines.[9,12] However, they may have led to over- or underestimation of the total population of patients with isolated TR, since not all patients with a LV ejection fraction <50% or systolic pulmonary artery pressure >40 mm Hg develop significant TR. The inevitable small number of events has led to a multivariable analysis with few variables to prevent overfitting of the model. The main challenge of a case-control study is the identification of an appropriate control group. In the present study, we have chosen controls with AF without significant TR instead of healthy individuals to be able to demonstrate the added prognostic impact of TR and eliminate the confounding factor of AF. As AF may be asymptomatic, the duration of diagnosis is often difficult to determine, which is why we did not take AF duration into account in the current study.

In conclusion, AF patients with isolated moderate and severe TR showed more RA dilation and RV conical remodeling than patients with AF without TR. Furthermore, isolated significant TR was independently associated with worse long-term prognosis in terms of mortality, hospitalization for heart failure, and stroke compared with patients without isolated significant TR. These results emphasize the need for prospective studies investigating the effect of early intervention in patients with AF and isolated significant TR.

Author Contributions

Marlieke F. Dietz: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Resources; Validation; Visualization; Writing - original draft. Laurien Goedemans: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Resources; Validation; Writing - review & editing. N. Mai Vo: Conceptualization; Data curation; Methodology; Resources; Validation; Writing - review & editing. Edgard A. Prihadi: Conceptualization; Data curation; Methodology; Resources; Validation; Writing - review & editing. Pieter van der Bijl: Conceptualization; Data curation; Methodology; Resources; Validation; Writing - review & editing. Bernard J. Gersh: Conceptualization; Methodology; Supervision; Validation; Writing - review & editing. Nina Ajmone Marsan: Conceptualization; Funding acquisition; Methodology; Project administration; Supervision; Validation; Writing - review & editing. Victoria Delgado: Conceptualization; Data curation; Funding acquisition; Methodology; Project administration; Resources; Supervision; Validation; Writing - review & editing. Jeroen J. Bax: Conceptualization; Data curation; Funding acquisition; Methodology; Project administration; Resources; Supervision; Validation; Writing - review & editing.

Disclosures

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