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List of abbreviations	
AADs = antiarrhythmic drugs	LAVi = indexed left atrial volume
AF = atrial fibrillation	LVEF= left ventricular ejection fraction
AF-TR = atrial functional tricuspid regurgitation	MR = mitral regurgitation
AVVR = atrioventricular valve regurgitation	MRA = mineralocorticoid receptor antagonists
ACEi/ARB= angiotensin converting enzyme inhibitors/ angiotensin receptor blockers	NYHA = New York Heart Association
BB = beta blocker	PVI = pulmonary vein isolation
CI = confidence interval	RA/RAA= right atrium/ right atrial area
CKD = chronic kidney disease	RF = radiofrequency
ECG = electrocardiogram	RV = right ventricle
FTR = functional tricuspid regurgitation	RVSP = right ventricular systolic pressures
HR = hazard ratio	TA= tricuspid annulus
iTR = isolated tricuspid regurgitation	TAPSE= transannular plane systolic excursion
LA = left atrium	TTE= transthoracic echocardiography
LAD = left atrial diameter	TR= tricuspid regurgitation

2. Zusammenfassung

Einleitung: Vorhofflimmern ist weltweit die häufigste Herzrhythmusstörung und ist mit einer erhöhten Morbidität und Mortalität assoziiert. Unter den Risikofaktoren für die Entstehung und das Fortbeschreiten von Vorhofflimmern ist atrioventrikuläre Klappenerkrankung von großem Interesse. Insbesondere die atrioventrikuläre Klappeninsuffizienz führt zu einem ‘Remodeling‘ des Vorhofs durch Volumenüberlastung und ebnet so den Weg für ein Substrat für Vorhofflimmern. Andererseits kann Vorhofflimmern zu einer ringförmigen Erweiterung der Vorhöfe führen, was wiederum zu einer atrioventrikulären Klappeninsuffizienz führen oder diese verschlimmern könnte. Diese funktionelle Mitral- oder Trikuspidalklappeninsuffizienz atrialen Ursprungs tritt insbesondere bei Patienten mit Vorhofflimmern häufig auf. Während die Pathophysiologie der Mitralinsuffizienz bei Patienten mit Vorhofflimmern sowie ihre Rolle bei der Rhythmuskontrolle nach Katheterablation bereits beschrieben wurde, gilt dies nicht für die Trikuspidalinsuffizienz. Trikuspidalinsuffizienz kommt bei Vorhofflimmern häufiger als Mitralinsuffizienz vor und ist häufig mit einer hohen Rate an anhaltendem Vorhofflimmern sowie schlechteren kardiovaskulären Folgen verbunden.

Fragestellung: Das Ziel der vorliegenden Arbeit war zu untersuchen, ob das Vorliegen einer signifikanten atrioventrikulären Klappeninsuffizienz und insbesondere einer Trikuspidalklappeninsuffizienz das Wiederauftreten nach Pulmonalvenenisolation von Vorhofarrhythmien vorhersagen könnte. Darüber hinaus untersuchten wir, ob sich der Schweregrad der atrioventrikulären Klappeninsuffizienz nach dem Eingriff verbessern ließe. Schließlich untersuchten wir, ob die Ablation anderer Stellen, an denen der rechte Vorhof beteiligt ist, die Rezidivraten atrialer Arrhythmien bei Patienten mit Trikuspidalinsuffizienz beeinflussen könnte.

Methoden: In unsere Studie wurden Patienten aufgenommen, bei denen zwischen 2018 und 2021 zum ersten Mal eine Pulmonalvenenisolation aufgrund symptomatischen Vorhofflimmerns durchgeführt wurde. Insgesamt wurden 320 Patienten mit verfügbaren echokardiographischen Daten sowohl zu Studienbeginn als auch bei der Nachuntersuchung eingeschlossen. Die Patienten wurden für mindestens 6 Monate nachbeobachtet, inkl. der Durchführung einer Langzeit-EKG. Wir untersuchten, ob das Vorliegen einer signifikanten Trikuspidal- oder Mitralklappeninsuffizienz zu Studienbeginn und 6 Monate nach dem Eingriff das Wiederauftreten einer Vorhofarrhythmie vorhersagte. Als signifikant wurde eine mäßige bis schwere Insuffizienz definiert. Darüber hinaus, haben wir den Schweregrad der Trikuspidal- und Mitralinsuffizienz vor und 6 Monate nach dem Eingriff verglichen.

Ergebnisse: Zum Studienbeginn wurde bei 13,1% der Patienten eine signifikante Trikuspidalklappeninsuffizienz und bei 10,9% eine signifikante Mitralklappeninsuffizienz dokumentiert. Sechs Monate nach der Pulmonalvenenisolation verringerte sich der Anteil der Patienten mit signifikanter Trikuspidal- (13,1% auf 7,2%; p<0,001) und Mitralklappeninsuffizienz (10,9% auf 6,6%; p<0,001) deutlich. Bei Patienten ohne postinterventionelle Verbesserung der signifikanten Ausgangs-Trikuspidalklappeninsuffizienz, war die Dilatation des rechten Vorhofs zu Studienbeginn ausgeprägter (rechtsatriale Fläche 20,2 ± 4,4 vs. 26,6 ±8,3 cm^2; p=0,002). Das Vorhandensein einer signifikanten Trikuspidalklappeninsuffizienz, insbesondere ohne Verbesserung während der Nachbeobachtung erhöhte das Risiko von Vorhofarrhythmie-Rezidiven. Auch nach dem Propensity-Score-Matching blieb die Trikuspidalklappeninsuffizienz zu Studienbeginn ein unabhängiger Risikoprädiktor für wiederkehrende Vorhofarrhythmien (HR 2,2 [95%-KI, 1,1–4,9]; p = 0,045). Eine signifikante Mitralklappeninsuffizienz war nicht mit einem erhöhten Risiko für Vorhofarrhythmien verbunden.

Diskussion: Die vorliegende Analyse unterstützt die wachsende Menge an Literatur, indem sie einen Zusammenhang zwischen Trikuspidalinsuffizienz und anhaltendem Vorhofflimmern sowie einer Dilatation des rechten Vorhofs aufzeigt. Darüber hinaus wurde gezeigt, dass die Pulmonalvenenisolation bei Patienten mit symptomatischem Vorhofflimmern bei einem erheblichen Anteil zu einer Verbesserung des Grades der Mitral- und Trikuspidalinsuffizienz führen kann. Interessanterweise wurde dargestellt, dass der Schweregrad der Trikuspidalklappeninsuffizienz, insbesondere in Fällen ohne Verbesserung 6 Monate nach dem Eingriff, ein unabhängiger Risikoprädiktor für das Wiederauftreten einer Vorhofarrhythmie nach Katheterablation ist, der sich als weitaus bedeutsamer erwies als das Vorliegen einer Mitralklappeninsuffizienz. Weitere Studien sind erforderlich, um die Entwicklung und das Fortbestehen von Vorhofarrhythmien bei Patienten mit Trikuspidalinsuffizienz besser zu verstehen und möglicherweise individuelle Ablationsziele zu lokalisieren

3. Abstract

SEVERITY OF TRICUSPID REGURGITATION PREDICTS RISK OF ATRIAL FIBRILLATION RECURRENCE AFTER PULMONARY VEIN ISOLATION

Introduction: Atrial fibrillation is the most common cardiac arrhythmia worldwide, constituting a cause for increased morbidity and mortality. Among the risk factors for the development and persistence of atrial fibrillation, the role of atrioventricular valve disease is of great interest. In particular atrioventricular valve regurgitation causes atrial remodeling through volume overload and thus paves the way for a substrate for atrial fibrillation. On the other hand, atrial fibrillation can lead to annular dilatation of the atria, which could in turn develop or deteriorate atrioventricular regurgitation. This functional mitral or tricuspid regurgitation of atrial origin is quite common in patients with atrial fibrillation. However, while the pathophysiology of mitral regurgitation in patients with atrial fibrillation as well as its role in rhythm control after catheter ablation has already been investigated, the same does not apply for tricuspid regurgitation. Tricuspid regurgitation in the setting of atrial fibrillation is actually more common than mitral regurgitation and is frequently associated with high rates of persistent atrial fibrillation as well as worse cardiovascular outcomes.

Aims: Our aim was to investigate whether the presence of significant atrioventricular valve regurgitation and particularly tricuspid regurgitation could predict the recurrence of atrial arrhythmias. Moreover, we examined whether the degree of severity of atrioventricular valve regurgitation could be improved after pulmonary vein isolation. Finally, we studied if the ablation of other sites involving the right atrium could affect the recurrence rates of atrial arrhythmias in patients with tricuspid regurgitation.

Methods: Patients who underwent first-time pulmonary vein isolation due to symptomatic atrial fibrillation between 2018 and 2021 were enrolled in our study. A total of 320 patients with available echocardiographic data at baseline as well as at follow-up were included. All patients had a follow-up for at least 6 months, including a twenty-four-hour-Holter-ECG. We examined whether the presence of significant tricuspid or mitral valve regurgitation at baseline and 6 months after the procedure predicted the recurrence of atrial arrhythmia. Moderate to severe insufficiency was defined as significant. Moreover, we compared the severity of tricuspid and mitral regurgitation before and 6 months after the procedure.

Results: At baseline, significant tricuspid regurgitation was documented in 13.1% of patients and significant mitral regurgitation in 10.9%. Six months after pulmonary vein isolation, the

proportion of patients with moderate to severe tricuspid (13.1% to 7.2%; p<0.001) and mitral valve regurgitation (10.9% to 6.6%; p<0.001) decreased significantly. In patients without postinterventional improvement in significant baseline tricuspid regurgitation, baseline right atrial dilatation was more pronounced (right atrial area 20.2 ± 4.4 vs. 26.6 ± 8.3 cm^2; p = 0.002). The presence of significant tricuspid regurgitation, particularly in patients without improvement throughout the 6-month follow-up period, increased the risk of atrial arrhythmia recurrence. Even after propensity score matching, tricuspid valve regurgitation at baseline remained an independent risk predictor for recurrent atrial arrhythmias (HR 2.2 [95% CI, 1.1–4.9]; p = 0.045). Significant mitral regurgitation was not associated with an increased risk of atrial arrhythmias, neither at baseline nor at follow-up.

Discussion: The present analysis supports the growing amount of literature, by displaying a link between tricuspid regurgitation and persistent atrial fibrillation as well as right atrial enlargement. Furthermore, it was demonstrated that pulmonary isolation for patients with symptomatic atrial fibrillation could lead to an improvement of the grade of mitral and tricuspid regurgitation in a significant proportion of patients. Interestingly, it was shown that tricuspid regurgitation, particularly in patients without improvement throughout the follow-up, is an independent risk predictor for atrial arrhythmia recurrence after catheter ablation, which proved far more significant than the presence of mitral regurgitation. Further trials are needed in order to better understand the development and persistence of atrial arrhythmia in patients with tricuspid regurgitation as well as to possibly locate individualized ablation targets.

4. Introduction

4.1. Epidemiology, burden and risk factors of atrial fibrillation

Atrial fibrillation (AF) is the most common cardiac arrhythmia and affects approximately 1-2% of the global population (3). In the United States, the estimated prevalence of AF ranges between 2.7 and 6.1 million and is projected to increase to 12 million by 2030, while similar numbers have been described in Europe (11,45). As its prevalence increases with age, it is estimated that, due to the improved life expectancy of the population, one in five adults will develop AF during their life (50). Hence, AF may be detected in up to 10-17% of patients aged 80 years or older (112).

Without preventive treatment, AF will recur in 90% of patients (85). Furthermore, epidemiological studies have established the link between AF and poor cardiovascular outcomes, including reduced survival and major comorbidities such as stroke and congestive heart failure (10, 13, 57). Guidelines recommend the use of antiarrhythmic drugs (AADs) as initial therapy for the maintenance of sinus rhythm in symptomatic patients (4, 33, 39), but lately catheter ablation with isolation of the pulmonary veins (PVI) has emerged as a cornerstone therapy for AF. In fact, recent trials propose PVI as the first line therapy to reduce the rates of recurrence of atrial arrhythmia and improve quality of life (5, 6, 44, 46, 106). However, despite recent technological and procedural advances, the success rate of PVI remains at roughly 60-70% (80, 87, 97, 99). Particularly in patients with persistent AF, AF recurrences after PVI are common.

Different risk factors for the onset and recurrence of AF have been described, with a longer duration of AF, the presence of non-paroxysmal AF, diastolic dysfunction and diabetes as well as a large left atrium diameter (LAD) being the most established ones (43). Among them, the interaction of atrioventricular valve disease with AF is of great interest. Recent research has focused mainly on the interaction between the mitral valve and AF and in particular the effect of mitral regurgitation (MR) on AF. However, some studies have investigated the pathophysiologic link between AF and the tricuspid valve, in addition to the role of tricuspid regurgitation (TR) as a risk factor for the persistence of AF. Atrioventricular valve regurgitation (AVVR) causes atrial remodeling by volume overload of the atria, promoting the formation of an atrial arrhythmogenic substrate, thus potentially reducing the efficacy of rhythm control. On the other hand, AF leads to annular dilatation, both of the right (RA) and left atrium (LA), which results in the development and/or progressive deterioration of TR and MR, respectively. In this vicious circle, the identification of the leading pathomechanism can be challenging. As a result, the optimal handling of AVVR in patients with AF is a subject of debate. Aim of this study was

to provide an extensive overview of the link between AVVR and AF, focusing especially on the role of the ‘forgotten’ tricuspid valve.

4.2. Definition and epidemiology of functional atrioventricular valve regurgitation

In order to describe the interaction between AVVR and AF as well as the changes brought to this interplay by rhythm control through PVI, a better understanding of the anatomical and electrophysiological substrate is needed. As previously mentioned, the correlation between AF and AVVR and in particular TR, is double-sided; the presence of primary or secondary AVVR promotes atrial remodeling and as a result the formation of an electrophysiologic substrate, giving rise to AF. On the other hand, AF may lead to annular dilatation of the atrioventricular valves, thus causing or deteriorating functional AVVR.

The concept of secondary or functional TR (FTR) i.e., that significant or even severe TR can occur in the setting of an anatomically normal tricuspid leaflet and chordae, has already been thoroughly described. This type of TR is thought to be much more common than primary TR, accounting for up to 90% of the total cases (77). The main causes are left-sided heart disease, pulmonary hypertension, right ventricular (RV) myocardial infarction as well as RV ventricular dysfunction due to a range of cardiomyopathies (1, 59, 63). Deformation of the tricuspid valve apparatus, in the form of dilatation and geometric alteration of the tricuspid annulus (TA) and/or tricuspid leaflet tethering in association with RV pressure or volume overload are proposed as pathophysiologic mechanisms of FTR (8, 58, 67, 102). In a similar sense, ‘isolated tricuspid regurgitation’ (iTR) is an increasingly recognized subtype of FTR, which is described to account for 6-10% of all patients with moderate to severe TR (21, 61, 94, 96). Isolated TR is defined by the absence of left sided heart disease or pulmonary hypertension and most often occurs in the setting of lone AF, thus also receiving the term ‘atrial functional TR’ (AF-TR) (15, 77, 84). Consequently, exclusion of other potential primary or secondary causes of TR is mandatory to accurately categorize iTR/AF-TR. However, as often noticed in clinical reality, a variety of pathophysiological mechanisms may be involved, so avoiding a label for FTR may be more sensible (31).

The presence of significant TR in patients with AF is quite common. The prevalence varies among studies, ranging from 5% to 37% (72, 78, 91, 101), but is most commonly described approximately between 15% and 20% (1, 64, 75), making TR more frequent than MR (64). Some degree of TR, including clinically insignificant grades, has been documented at up to 93% of all AF patients (38). The reported discrepancy among different studies could lie on

several factors, including the size and demographics of the study population, AF type and duration as well as different echocardiographic techniques, measurements and stratification. Naturally, according to its definition i.e., the absence of other diseases potentially causing FTR, the prevalence of the labeled 'AF-TR' is not so common. Severe AF-TR in a population of AF patients was described at 8% (103), while the development of significant TR in patients with new-onset AF and absence of left heart or pulmonary diseases was documented at 10% of the cases (74). Of note, patients who develop AF-TR tend to have more frequently moderate TR (54).

Conversely, a considerable amount (6%) of the total TR-cases (i.e., primary and functional TR) can be stratified as 'AF-TR' (94). These rates are similar (5-10%) when examining patients with clinically severe TR (16, 61, 69) and have also been confirmed by more advanced echocardiographic measurements, such as 3D-transesophageal echocardiography (101). However, as previously mentioned, sometimes it may be difficult to single out the exact cause of TR, as many different pathophysiological mechanisms may play a role. Interestingly, in a large cohort of patients with mild TR a total of 35% of them had AF (48), which could have a central role or possibly contribute to the persistence or deterioration of the disease. Overall, these rates from both sides of the spectrum are indicative of the strong pathophysiological link between TR and AF.

4.3. Pathophysiology of functional mitral and tricuspid regurgitation related to atrial fibrillation

In recent decades, more and more investigations, mainly echocardiographic studies, have been conducted in order to better understand the pathophysiological relationship between AF and AVVR. These investigations have mainly concerned MR. Atrial fibrillation induces MR due to the development of atrial remodeling (64), which is defined as a change in atrial structure or function, which can further promote atrial arrhythmias (66). The atrial remodeling in AF is associated with larger left atrial and mitral valve orifice areas, a finding that has been documented in large cohorts of patients with MR (28). In contrast to functional MR caused by left ventricular dysfunction, in MR associated with AF, the left ventricle shows normal dimension and function, leaving mitral annulus dilatation as the culprit mechanism leading to mitral leaflet malcoaptation. The diseased LA in turn paves the substrate for AF and thus this vicious cycle lowers the probability of recovering sinus rhythm (18). The exact underlying mechanism of atrial functional MR involves LA enlargement which displaces the posterior mitral annulus onto the crest of the left ventricular inlet. The displaced annulus tethers the

posterior mitral leaflet superiorly, while the contracting papillary muscles tether it inferiorly, reducing its ability for coaptation. This anatomical change is referred as atriogenic leaflet tethering, which combines both Carpentier type 1 and type 3b mechanisms of MR (20, 83). Moreover, loss of the atriogenic component of contraction of the mitral annulus due to AF can increase the degree of MR, by delaying the onset of leaflet coaptation (20, 56, 92). Another mechanism that has been proposed is the concept of insufficient leaflet remodeling, which leads to varying grades of MR severity despite similar annular areas (40). In accordance to these mechanisms, Gertz et al. demonstrated that patients with recurrent AF had a significantly larger LA volume and >3 higher rate of significant MR (26). Furthermore, patients with long-standing AF seem to have a higher prevalence of significant MR (56). The pathophysiological link established by those echocardiographic investigations is further reinforced by the following findings: research has also shown that rhythm control can promote atrial reverse remodeling (26), which is associated with decreased left atrial volume (82), effective regurgitant orifice area and vena contracta width (88), thus also leading to a reduction in severity of MR (26, 53).

While the relationship between MR and AF had been well described, up until recently, the effect of AF on TR had been largely neglected. In patients with AF, TR often develops concomitantly with MR (54, 64), but the prevalence of TR seems to be more common (64). This phenomenon seems to have different causes. It has been reported that in the setting of AF, the RA enlarges more easily than the left, owing to a less fibrous skeleton in TA than the mitral valve, both in terms of quantity and possibly histologic development (36, 111). More specifically, only 40% dilatation of the TA is required to result in significant regurgitation, in comparison to 75% for the mitral valve (86). Furthermore, although the right atrial myocardial wall is thinner than the left, it includes muscle structures like the crista terminalis, the pectinate muscles and the right atrial vestibule. Therefore, due to the complex anatomic structures and in contrast to the mitral annulus, the TA is in contact with the right atrial myocardium over the largest part of the circumference, which, along with the lower extent of its fibrotic tissue, could explain why it is more prone to dilate along with the remodeling of the RA (60).

Some small studies, dating back to the 1990s, had suggested that AF may be a risk factor for the development of TR, owing to the enlargement of the TA and RA (29, 37, 41). In this direction the interest of research is shifting lately towards the interaction between the tricuspid valve and AF, displaying that AF is an independent risk factor for the development and progression of TR (47, 48, 74). Indeed, many studies have already demonstrated that TR in AF patients is associated with a significant enlargement of the RA volumes (16, 31, 48, 54, 60, 63, 70, 73, 101, 103, 108). Some investigators documented a concomitant dilatation of the

LA in this set of patients (63, 73), however Utsunomiya et al. reported a higher RA/LA ratio in patients with AF-TR (101), while Najib et al. demonstrated an impressive doubling of the RA size in patients with AF and severe TR (63). Furthermore, the persistence of AF also seems to be associated with more pronounced anatomical changes: Zhao et al. demonstrated that patients with recurrent atrial arrhythmias had more severe TR and more pronounced RA enlargement (110).

The pathophysiologic mechanism most likely involves an interplay between RA enlargement and dilatation of the TA (9, 59, 60). As a matter of fact, a plethora of echocardiographic investigations have displayed a related to RA-volumes dilatation of the TA area, which highlights the fact that TR in AF patients is predominantly a disease of the atrium and annulus (16, 54, 60, 63, 73, 101). The exact way that the enlargement of the TA in AF causes TR involves increased TA tenting volumes which lead to a reduction of the coaptation height and subsequently loss of coaptation (31, 108). A total of 40% increase in TA can be tolerated before coaptation reserve is exhausted and regurgitation develops as the free margins of the tricuspid valve move apart (84). These concepts were reinforced by echocardiographic analyses in 3D; Utsunomiya et al. reported a more dilated, planar, circular and dysfunctional TA with less tethering of the leaflets and an expansion of the TA mostly along the posterior border in patients with AF (101), while Ortiz-Leon et al. confirmed the correlation of the TA area with RA volume, in addition to showing that TA dilatation in AF patients was more prominent in comparison to FTR due to left-sided heart disease (70). Of note the severity of TR with the same degree of RA- and TA- dilatation can be extremely variable, perhaps owing to the extent of the leaflet areas adaptation in response to the dilatation (20, 22, 96). Another proposed mechanism involves a reduced contraction of the TA in AF, which hinders the physiologic reduction of annular area (24). Finally, Gunturiz-Beltrán et al. used comprehensive magnetic resonance imaging to show that TR of at least moderate intensity in the setting of AF was associated with increased right atrial sphericity (30). In conclusion and in accordance with these data, RA volume (31) and mainly TA diameter (31, 73) seem to be independent determinants of TR severity in patients with AF.

The data regarding the presence and effect of an enlarged RV or increased systolic pulmonary artery pressures (sPAP) on patients with AF and TR are conflicting in the literature (16, 23, 54, 63, 101, 103), perhaps owing to the varied patient-selection in the different investigations. In some investigations, increased RV pressures are reported. A possible explanation could be that patients with AF display a concomitant LA enlargement and subsequent increase in PAP, which indirectly leads to FTR (75).

4.4. Predictors, morbidity and mortality of tricuspid regurgitation in atrial fibrillation

According to the literature, among the predictors of significant TR in patients with AF belongs the age of the patients (63, 68, 103) as well as the female sex (63, 68, 74, 75). Of note and in accordance with pathophysiology, the most cited predicting factor remains the presence of persistent AF (31, 38, 64, 73, 74, 75, 103, 108) as well as its total duration (1, 63). The longer AF persists, especially without successful rhythm control (74), the more likely it is for the aforementioned anatomic changes to develop. Thus, persistent AF is associated with increased RA and TA dimensions (31, 38, 63, 73, 103, 108). Of note, significant TR, as well as MR, are rarely seen in patients with an AF duration of <1 year, while by 10 years one-fourth of the patients display relevant AVVR, a rate well above the documented total prevalence (1). Furthermore, chronic AF has been reported to even be an independent risk factor for the recurrence of TR after tricuspid annuloplasty (93).

In general, patients with TR and AF are more likely to have a higher burden of comorbidities, expressed by the CHA2DS2-VASc score (78, 103), such as higher systolic and diastolic blood pressure (101). These patients have more often NYHA functional class >2 heart failure symptoms (16), but reduced rates of coronary artery disease (16, 101). Finally, due to the higher prevalence of persistent AF, possibly exacerbated by the TR itself, it is reported that they are more likely to be on medical rhythm control (16).

It is important to note that the presence of significant TR in the setting of AF is associated with increased morbidity and mortality. TR is a valvular heart disease, which, despite medical treatment, has a poor prognosis, often progressing to end-stage right-heart failure with chronic liver injury (65, 95). In the setting of AF, which even after adjusting for other cardiovascular conditions portends an independent risk for mortality (78), TR may lead to RV dysfunction and thus increase mortality (63). Especially the combination of TR and MR secondary to AF is associated with worse prognosis (1). More specifically, studies have demonstrated that in patients with AF, the presence or worsening of significant TR was an independent risk for mortality (1, 16, 48, 74, 103), especially in older patients (57) with hypertension and renal insufficiency (109). As a result, quantified TR degree in iTR was strongly associated with decreased survival (95). Furthermore, TR in the setting of AF was associated with an increased number of hospitalizations for heart failure as well as poorer quality of life (1, 16, 25, 75), particularly in patients with higher CHA2DS2-VASc score (75). However, a more favorable prognosis of severe TR associated with AF in comparison to other TR types has also been reported (91).

The management of moderate to severe TR in the setting of AF is a subject of debate. Interestingly, a small analysis of 71 patients with severe TR and AF displayed that improvement in TR grade without performing surgical repair, through conservative means, can be relatively common (22.5%) (109). Nonetheless, a careful grading of AF-TR should be performed and the absence of RV enlargement should not be considered an exclusion criterion. In case of severe or torrential TR, different needs of clinical management as well choice of surgical intervention should be met, due to the distinct pathophysiological nature of AF-TR (22). As in other cases of symptomatic FTR, TTVI may be considered by the Heart-Team at experienced Heart Valve Centers (8), however echocardiographic findings indicate that severe AF-TR may be the most suitable sub-type of FTR for annuloplasty, due to its prominent annular dilatation without apparent tethering of the leaflets (101). Surgical ablation concomitant with the surgical repair could be the optimal treatment for patients with AF-caused moderate-to-severe TR, however this approach has not been comprehensively evaluated (105). Nevertheless, as FTR in association with left-sided heart disease or various cardiomyopathies may diminish or even disappear along with the improvement of the underlying causes (12), it would be mandatory to assess the risk of unnecessary valve surgery or intervention in patients with TR associated with AF. In accordance with this concept, another strategy along the lines of preventive medicine could be approached: maintaining sinus rhythm in these patients, early in the natural history of the disease, could prevent the cascade of changes in right-sided heart structures (31, 103). Considering that a proportion of these patients suffer from heart failure, catheter ablation could certainly reduce the occurrence of subsequent heart failure admission, irrespective of TR, according to the CASTLE-AF Trial (52). Indeed, it has been demonstrated that in patients with persistent AF and moderate to severe TR who underwent catheter ablation, patients with an improvement of TR grade had a higher incidence of major event-free survival (100).

4.5. Role of rhythm control for atrial fibrillation on reversing the severity of tricuspid regurgitation

Following this line of thought and while aiming to emulate similar studies for MR (26, 53), research has focused recently on the possible role of rhythm control for AF on reversing the severity of TR. Indeed, it has been demonstrated that pharmaceutical rhythm strategy can improve the RA-geometry and therefore the severity of AF-TR (103). Particularly regarding patients with sustained sinus rhythm through rhythm control, research has shown significant improvements in TR grade, which correlated with a regression of right cavity parameters such

as TA diameter, RA volume (88, 89). Furthermore, as catheter ablation has been proven to be an effective method for rhythm control (5, 6, 44, 46, 106), as well as for possibly improving MR related to AF (26), some studies investigated its impact on TR in patients with AF. Most of these studies are retrospective, observational investigations, nonetheless they demonstrated that catheter ablation can lead to an improvement of the TR grade (38, 51, 68, 100, 105) as well as of other parameters like the TR jet area, the RAA and the TA diameter (38, 68, 105). Of note, one investigation demonstrated an improvement of the TR grade without a significant decrease in TA diameter, raising questions about the mechanism by which a reversal of tricuspid regurgitation takes place after successfully restoring and maintaining sinus rhythm (51). Interestingly, these changes were even apparent in patients with persistent AF and presumably advanced remodeling of the RA (38, 100) as well as in AF patients with sinus rhythm at the time of the ablation (51). Age (100), the duration/type of AF (88) as well as the absence of AF-recurrence (51, 100) seem to be independent predictors of the improvement of TR after the catheter ablation. Of note, an analysis of the FASTRHAC database demonstrated that ablation within a year after the diagnosis of AF was significantly associated with reverse remodeling of the RA and LA (88). In conclusion, according to these findings, rhythm control both through conservative means and catheter ablation could possibly impact the severity of TR in patients with AF. To our knowledge, there is no investigation comparing catheter ablation with antiarrhythmic medical therapy on this matter. However, Wang et al. demonstrated that in patients with long standing persistent AF associated with moderate to severe TR, catheter ablation compared to surgical treatment had a similar risk of recurrence of AF as well as of worsening TR, thus potentially offering an alternative treatment even for patients with more advanced disease (105).

4.6. Mitral and tricuspid regurgitation as predictors for atrial arrhythmia recurrence after catheter ablation for atrial fibrillation

While the impact of AF on the severity of AVVR and in particular of TR is a topic that needs further investigation, a matter of equal or even greater importance is the role of TR as a risk factor for patients undergoing catheter ablation for AF. As already mentioned, AVVR causes volume overload of the atria and thus atrial remodeling, promoting the formation of an AF substrate, thus potentially reducing the efficacy of catheter ablation. So far, this concept has been better examined in the context of the mitral valve and the LA. Schill et al. managed to characterize atrial activation abnormalities using noninvasive electrocardiographic imaging in patients with MR referred to surgery. These abnormalities included prolonged left atrial conduction times and more complex conduction slowing with unidirectional conduction block, thus describing a potential substrate for AF (81). Accordingly, Gertz et al. demonstrated that

MR was associated with increased AF recurrence after catheter ablation, an impact mainly mediated by LA size (27). Moreover, Zhao et al. showed that in patients with long-standing AF, MR grade was an independent predictor for recurrent atrial arrhythmia (110).

While investigations of this scope have not yet been conducted in the context of the tricuspid valve, some smaller observational studies have hinted at a similar effect of TR on AF recurrence after catheter ablation. Zhao et al. also displayed an association between TR severity and recurrent atrial arrhythmia, indicating TR could also contribute to AF recurrence (110). Markman et al. demonstrated that patients who remained free from AF post-ablation were more likely to have experienced a concomitant reduction in TR severity (51), while Ukita et al. also showed that the absence of a late AF recurrence was independently associated with the improvement of TR after radiofrequency (RF) catheter ablation (100). Gunturiz-Beltrán demonstrated in an elegant magnetic-resonance study that right atrial sphericity induced by significant TR was a predictor of AF recurrence (30). Furthermore, Nakamura et al. examined 239 patients who underwent catheter ablation for symptomatic, drug-refractory non-paroxysmal AF. In a multivariate regression, significant FTR (HR 4.68, 95% CI 1.06 - 20.74, p=0.041) was a predictor of arrhythmia recurrence after ablation, especially in the concomitant presence of FMR. Of note, FMR alone yielded no significant differences during the 13 months of follow-up (64). However, another analysis of 102 patients with moderate or severe TR failed to demonstrate a significant difference between one-year recurrence of AF and TR severity at pre-ablation echocardiography (68), possibly implying a more complex pathophysiological relationship between TR and AF-recurrence. In accordance with the LA size, which is a well-established predictor for AF recurrence, right atrial structural remodeling has also been shown to pose a risk for AF-recurrences after catheter ablation (90), especially with concurrent LA enlargement (107), posing an interesting interplay between RA enlargement, TR severity and AF recurrence.

4.7. Ectopic sources of atrial arrhythmia and right atrial enlargement

Taking into consideration the particularities of patients with AF and FTR, it is tempting to hypothesize that a contrasting, underlying electrophysiological substrate revolving the RA may warrant tailored ablation strategies. A plethora of ectopic sources triggering atrial arrhythmia have been identified outside of the pulmonary veins, including for instance the vena cavae, the crista terminalis and the ostium of the coronary sinus in the RA (15). Santangeli et al. found that atrial arrhythmia triggers outside of the pulmonary veins were present in up to 11% of patients undergoing catheter ablation, with the crista terminalis, the eustachian ridge

region and the superior vena cava being among the most prevalent (79). Of note, in patients with atrial arrhythmia originating from non-pulmonary vein foci, rates of recurrence of atrial arrhythmia can be significantly higher, which can though be mitigated by ablation of the aforementioned triggers (32). Moreover, Hocini et al. demonstrated that an additional ablation of the RA substrate was required to achieve durable long-term results in patients without prolongation of AF cycle length after conventional PVI. Interestingly, these patients tended to have a larger RA diameter (35). Whether significant TR can produce the RA substrate required for atrial arrhythmia maintenance is up to debate and currently research data is sadly lacking. Hiram et al. showed in rat models that RA enlargement induced by pulmonary hypertension was associated with RA fibrosis and inducibility of atrial arrhythmia (34). It is intriguing to speculate that RA enlargement owing to TR related to AF could bring similar results in human atria.

4.8. Aims of the study

Taking this complex pathophysiological link between TR and AF into consideration, we hypothesized that TR severity is associated with recurrence of atrial arrhythmia after ablation. Thus, we examined the effect of TR, as well as of MR, on recurrence of atrial arrhythmia in patients undergoing PVI treatment for the first time due to symptomatic AF. Moreover, we investigated if rhythm control through PVI could possibly impact the severity of AVVR. Finally, we explored whether an ablation at additional sites involving the RA (e.g the cavotricuspid isthmus) could possibly have an effect on the rates of atrial arrhythmia recurrence in patients with significant TR.

5. Methods

5.1. Study subjects and design

This explorative, retrospective analysis enrolled patients with symptomatic AF treated with PVI for the first time at the Department of Internal Medicine III – Cardiology, Angiology, and Intensive Care Medicine of the University Hospital Saarland between 2018 and 2021. As patients with AF and severe MR are better suited for surgical repair and concomitant surgical ablation (14, 102), the PVI procedure was not performed in those cases (defined as MR stage 3 or higher according to ESC guidelines (49)), as well as in patients lacking consent. Furthermore, patients with history of prior ablation of the pulmonary veins were excluded from our analysis. At baseline, all patients were interviewed regarding symptoms, comorbidities, medication and medical history, particularly regarding type of AF. Moreover, all patients received a 12-lead-ECG and a transthoracic echocardiography (TTE). To exclude intracardiac thrombi prior to the PVI treatment, the patients underwent a transesophageal echocardiography or contrast enhanced computed tomography. After the PVI procedure, the use of AADs was personalized, according to the individual risk for atrial arrhythmia recurrence and was usually limited to 4 weeks. Moreover, patients were asked for follow-up visits in our outpatient clinic after 6 weeks and 6 months. During both visits, patients' symptoms and potential changes in medication were assessed. Furthermore, after 6 months, a follow-up TTE was performed to assess potential changes.

5.2. Pulmonary vein isolation procedure

The PVI was either performed with cryoablation or RF ablation, which was left at the physicians' discretion. Cryoablation was performed with the 28 mm diameter second-generation cryoballoon (Medtronic Inc., Dublin, Ireland) guided by a circular mapping catheter (Achieve mapping catheter, Medtronic Inc.). A minimum of one freeze lasting between 180 and 240 seconds was delivered at the ostium of each pulmonary vein. The PVI was confirmed by entrance and/or exit block. For RF ablation, a Smarttouch catheter (Biosense Webster, Irvine, CA, USA) was used with guidance from a CARTO 3-dimensional mapping system (Biosense Webster) using a double Lasso technique. The point-by-point RF ablation was performed with a power maximum of 30 W aiming an ablation index of 350-400, and the endpoint was a bidirectional conduction block between the LA and the pulmonary vein. Furthermore, in case of history of right atrial flutter, an additional ablation of the cavotricuspid isthmus was performed.

5.3. Echocardiography

All patients included in our study received at least one TTE at baseline and after a 6 months follow-up following the PVI treatment. All TTEs were performed at the echo lab of the University Hospital of Saarland. Analysis of TTE was performed blinded to the outcome of the PVI. The graduation of AVVR was in accordance with recently published guidelines by the European Society of Cardiology (49). We defined AVVR of at least moderate severity as significant, while mild or non-existent AVVR was defined as non-significant. The reasoning behind this decision was the following: AVVR of at least moderate severity (Grade 2+) can be more clearly stratified using TTE in comparison to mild AVVR (Grade 0-1). At the same time, patients with severe AVVR (Grade 3+) do not often undergo catheter ablation for AF in clinical practice. Thus, labeling AVVR of at least moderate severity as significant provided the best balance between accuracy and applicability. Moreover, we defined an improvement of the AVVR to at least mild grade after the intervention as relevant, to mirror the above stratification. Furthermore, we aimed to assess the cardiac function and to identify potential echocardiographic factors for atrial arrhythmia recurrence at both time points, including the systolic function of the left and right ventricle, the size of the LA and RA, the diastolic function of the heart as well as signs of pulmonary hypertension.

5.4. Detection of atrial arrhythmia recurrences

All patients were followed up for atrial arrhythmia recurrences in our outpatient clinic for a minimum of 6 months after the procedure. Any documented atrial tachycardia, atrial flutter or AF of at least 30 seconds after the PVI procedure, excluding a 3-month blanking period, was defined as recurrent atrial arrhythmia episode. All patients received a 12-lead ECG prior to discharge during the index hospital stay as well as 6 weeks and 6 months after the PVI treatment. Moreover, twenty-four-hour-Holter-ECG was performed 6 months after PVI, unless the patients already had a documented episode of atrial arrhythmia recurrence following the blanking period of 3 months.

5.5. Definition of endpoints

We hypothesized that TR severity is associated with recurrence of atrial arrhythmia after ablation, thus the primary endpoint of this study was the influence of TR severity on the probability of atrial arrhythmia recurrence following the PVI procedure. Moreover, we investigated the existence of other risk predictors for atrial arrhythmia recurrence, such as the

presence of significant mitral regurgitation. Furthermore, we studied if the catheter ablation could improve echocardiographic parameters 6 months after the procedure, mainly the grade of TR and MR severity. Finally, we explored the possible impact of the ablation at additional sites involving the RA (e.g., the cavotricuspid isthmus) on the rates of atrial arrhythmia recurrence in patients with significant TR.

5.6. Statistical analysis

Continuous variables were tested for normal distribution with the Kolmogorov Smirnov test. Normally distributed values are reported as mean ± standard deviation (SD), while non-normally distributed values are reported as median and first to third interquartile range (Q1-Q3). Continuous variables between 2 groups were compared with the Wilcoxon rank-sum test, while the Kruskal-Wallis-Test was used for comparing continuous variables between more than 2 groups. Comparisons for categorical variables were performed with the Pearson Chi-Square test. The survival curves of the patients were calculated by the Kaplan-Meier method and compared with the log-rank test. Stratified Cox proportional-hazards regression models were used to calculate hazards ratios (HRs) and associated 95% CI. Furthermore, we performed a secondary analysis that used propensity-score matching. In the propensity-score matching analysis, the nearest-neighbor method was applied to create a matched control sample. All analyses were performed with SPSS statistical software (version 29.0, IBM Inc., Chicago, IL, USA).

6. Results

6.1. Patient characteristics

From 2018 to 2021, a total of 745 patients underwent PVI due to symptomatic AF in our clinic. A total of 98 patients were excluded from the analysis because of history of previous PVI procedure, while 327 patients were excluded due to lacking echocardiographic data. As a result, a total of 320 consecutive patients with first time PVI and available echocardiographic data at baseline as well as 6 months after the procedure were included in the study **(Figure 1)**. Their mean age was 66.3 ± 10 years and 61.6% of them were male. Of note, a considerable number of patients had persistent AF (40%) at the time of the catheter ablation. In most cases (66.3%) the PVI procedure was performed with cryoablation. In 14.1% of the patients an additional ablation of the cavotricuspid isthmus was performed due to history of right atrial flutter. The primary symptoms of the patients were palpitations (72.8%), shortness of breath (53.1%) and dizziness (19.6%) while a small minority of them (2.8%) experienced a syncopal episode. Almost all patients (99.6%) received anticoagulation, usually non-vitamin K oral anticoagulants (NOAC). Concerning antiarrhythmic medications at baseline, 62 and 73 patients received class I or III drugs respectively, while the majority (86.3%) was taking a beta-blocking agent.

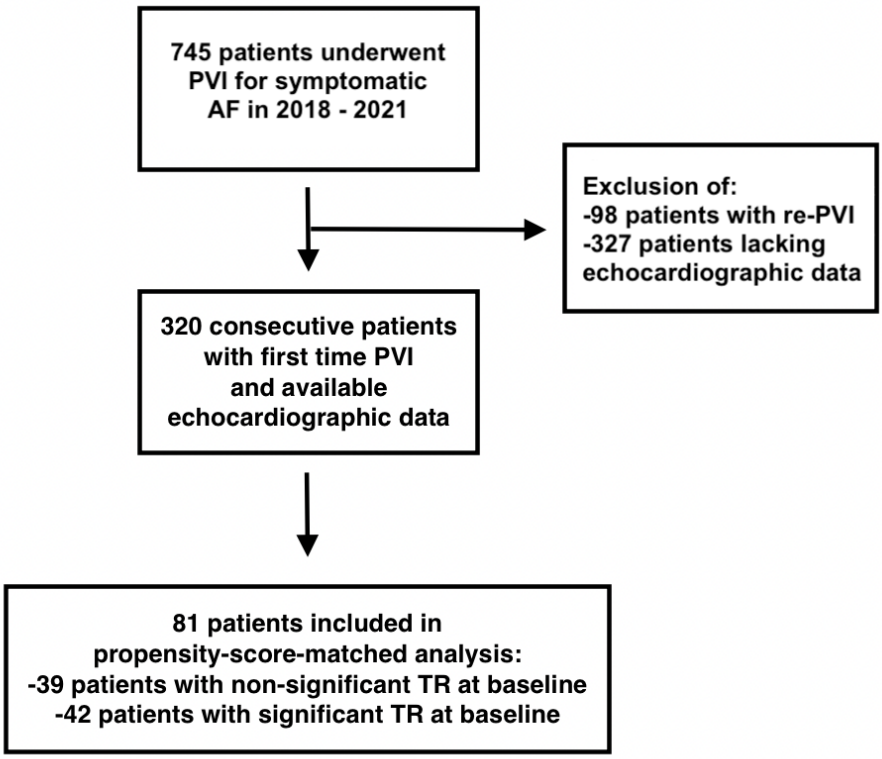


Figure 1: Study population and design

In accordance with the mean age of the patients as well as the presence of AF, the burden of comorbidities was high. Among the most frequent ones were arterial hypertension (79.3%), dyslipidemia (61.2%), coronary artery disease (27.5%) and hypo-/hyperthyroidism (24.3%). On the contrary, the prevalence of diseases like diabetes mellitus (11.3%), CKD (9.1%) and obstructive pulmonary diseases (7.5%) was modest. Moreover, 37.1% of the patients were treated for congestive heart failure. Of note, a catheter ablation for other non-left atrial arrhythmias (e.g., ablation for ventricular extrasystole) had already been performed in 6.3% of the patients (**Table 1**).

Comorbidity	n (%)
Arterial Hypertension	254 (79.3%)
Dyslipidemia	196 (61.2%)
Congestive Heart Failure	119 (37.1%)
Coronary Artery Disease	88 (27.5%)
Hypo/Hyperthyroidism	78 (24.3%)
Diabetes Mellitus	36 (11.3%)
Chronic Kidney Disease	29 (9.1%)
Aortic Valvular Disease	27 (8.4%)
Sleep Apnea Syndrome	25 (7.8%)
Obstructive Pulmonary Disease	24 (7.5%)
Non-Ischemic Cardiomyopathy	22 (6.8%)
Stroke/Transient Ischemic Attack	21 (6.5%)
Pacemaker/Implantable Defibrillator	19 (5.9%)
Peripheric Artery Disease	16 (5.0%)
Patent Foramen Ovale/Atrial Septal Defect	14 (4.3%)
Pulmonary Embolism	8 (2.5%)

Table 1: Burden of comorbidities in the population

At baseline, most patients exhibited a preserved LVEF (mean LVEF 55.3 ± 8.2%), while only 20.3% of the population had a reduced or mildly reduced ejection fraction. Moreover, most patients had a dilated right (mean right atrial area (RAA) 19.8 ± 5.6 cm²) and left atrium (mean left atrial systolic volume index (LAVi) 43.6 ± 13.2 ml/m²) as well as a normal diastolic function (mean E/E' 10.8 ± 5) and RV longitudinal function (mean TAPSE 23.4 ± 5.0 mm). Furthermore, RV systolic pressure was slightly elevated (mean RVSP 27.5 ± 8.7 mmHg). Significant MR was observed in 35 patients (10.9%), while significant TR was documented in 42 patients (13.2%). Finally, a small minority of the patients at baseline (4.4%) had a combination of clinically relevant MR and TR.

Before propensity-score matching, different characteristics between patients with and without relevant TR at baseline were observed. Patients with significant TR at baseline were older (71.9 ± 7.6 vs. 65.4 ± 10.1 years; p<0.001) and more often female (57.1% vs. 35.6%; p=0.007) than patients without significant TR (**Table 2**). Additionally, the presence of persistent AF was more frequent among patients with relevant TR (57.1% vs. 37.4%; p=0.015). Moreover, diabetes mellitus (21.4% vs. 9.7%; p=0.025), obstructive pulmonary disease (14.3% vs 6.5%; p=0.074) as well as a concomitant significant MR (33.3% vs 7.6%; p<0.001) were also more common. Patients with clinically relevant TR had a dilated RA (RAA 23.5 ± 7.3 vs. 19.2 ± 4.9 cm², p<0.001) in comparison to patients without significant TR. Furthermore, signs of mild pulmonary hypertension (RVSP 34.2 ± 10.6 vs. 26.4 ± 7.9 mmHg, p<0.001) were observed. On the contrary, no significant differences existed regarding LVEF (54.5 ± 8.2% vs. 55.5 ± 8.3%; p=0.485) and the size of the LA (LAVi 46.4 ± 12.4 vs. 43.2 ± 13.3 mL/m²; p=0.161). Furthermore, the percentage of patients treated with a class Ic or III antiarrhythmic agent was independent of TR significance (45.2% vs. 42.1%; p=0.701). Lastly, no notable differences existed regarding the technique of PVI (cryoablation in 57.1% vs. 67.6%; p=0.182). However, an additional isolation of the cavotricuspid isthmus due to history of right atrial flutter was performed more frequently among patients with significant TR (26.2% vs. 12.2%; p=0.015).

	All patients (n=320)	Patients with non-significant TR (n=278)	Patients with significant TR (n=42)	p
Age (years)	66.3 ± 10	65.4 ± 10.1	71.9 ± 7.6	**<0.001**
male sex	197 (61.6%)	179 (64.4%)	18 (42.9%)	**0.007**
Persistent AF	128 (40%)	104 (37.4%)	24 (57.1%)	**0.015**
Cryoablation	212 (66.3%)	188 (67.6%)	24 (57.1%)	0.182
Ablation of the cavotricuspid isthmus	45 (14.1%)	34 (12.2%)	11 (26.2%)	**0.015**
Arterial hypertension	254 (79.4%)	221 (79.5%)	33 (78.6%)	0.891
Diabetes Mellitus	36 (11.3%)	27 (9.7%)	9 (21.4%)	0.025
Chronic kidney disease	29 (9.1%)	23 (8.3%)	6 (21.4%)	0.207
Coronary artery disease	88 (27.5%)	77 (27.7%)	11 (26.2%)	0.839
Obstructive pulmonary disease	24 (7.5%)	18 (6.5%)	6 (14.3%)	0.074
Hypo-/Hyperthyroidism	78 (24.4%)	66 (23.7%)	8 (28.6%)	0.498
ACEi/ARB	204 (63.7%)	176 (63.3%)	28 (66.6%)	0.674
MRA	63 (19.7%)	51 (18.3%)	12 (28.6%)	0.121
BB	276 (86.3%)	241 (86.6%)	35 (83.3%)	0.557
AAD	136 (42.5%)	117 (42.1%)	19 (45.2%)	0.701
LAD (mm)	44.6 ± 6	44.5 ± 5.9	44.9 ± 6.6	0.642
LAVi (ml/m²)	43.6 ± 13.3	43.2 ± 13.3	46.4 ± 12.7	0.161
EF (%)	55.4 ± 8.3	55.5 ± 8.3	54.5 ± 8.2	0.485
Mitral E/E ratio’	10.8 ± 5	10.7 ± 4.9	12.0 ± 5.5	0.141
TAPSE (mm)	23.5 ± 5	23.6 ± 5.0	22.3 ± 4.9	0.106
RA Area (cm²)	19.9 ± 5.6	19.2 ± 4.9	23.5 ± 7.3	**<0.001**
RVSP (mmHg)	27.5 ± 8.8	26.4 ± 7.9	34.2 ± 10.6	**<0.001**
Significant MR	35 (10.9%)	21 (7.6%)	14 (33.3%)	**<0.001**
Sinus rhythm at follow-up (6 months)	284 (88.8%)	251 (90.3%)	33 (78.6%)	**0.025**

Table 2: Patient characteristics at baseline in relation to the degree of TR

Similarly, patients with significant MR at baseline had more often a dilated LA (LAVi 51.2 ± 14.8 vs. 42.7 ± 12.8 mL/m²; p<0.001) as well signs of mild pulmonary hypertension (RVSP 30.6 ± 10.4 vs. 27.1 ± 8.5 mmHg, p=0.026) than patients without significant MR (**Table 3**). Furthermore, concomitant significant TR (40.0% vs 9.8%; p<0.001) as well as diabetes

mellitus (25.7% vs 9.5%; p=0.004) were observed more frequently. No other differences were detected between the two groups, including the rates of persistent AF (45.7% vs 39.3%; p=0.466). Like patients with significant TR, an additional ablation of the cavotricuspid isthmus was performed more frequently in this group of patients (25.7% vs. 12.6%; p=0.036).

	All patients (n=320)	Patients with non-significant MR (n=285)	Patients with significant MR (n=35)	p
Age (years)	66.3 ± 10	66.0 ± 10.0	68.4 ± 9.8	0.181
male sex	197 (61.6%)	179 (62.8%)	18 (51.4%)	0.193
Persistent AF	128 (40%)	112 (39.3%)	16 (45.7%)	0.466
Cryoablation	212 (66.3%)	190 (66.6%)	22 (62.8%)	0.654
Ablation of the cavotricuspid isthmus	45 (14.1%)	36 (12.6%)	9 (25.7%)	**0.036**
Arterial hypertension	254 (79.4%)	226 (79.3%)	28 (80.0%)	0.923
Diabetes Mellitus	36 (11.3%)	27 (9.5%)	9 (25.7%)	**0.004**
Chronic kidney disease	29 (9.1%)	27 (9.5%)	2 (5.7%)	0.466
Coronary artery disease	88 (27.5%)	78 (27.4%)	10 (28.6%)	0.881
Obstructive pulmonary disease	24 (7.5%)	22 (7.7%)	2 (5.7%)	0.672
Hypo-/Hyperthyroidism	78 (24.4%)	69 (24.2%)	9 (25.7%)	0.846
ACEi/ARB	204 (63.7%)	181 (63.5%)	23 (65.7%)	0.799
MRA	63 (19.7%)	56 (19.6%)	7 (20.0%)	0.961
BB	276 (86.3%)	246 (86.3%)	30 (85.7%)	0.923
AAD	136 (42.5%)	122 (42.8%)	14 (40.0%)	0.752
LAD (mm)	44.6 ± 6	44.4 ± 5.9	46.2 ± 6.2	0.094
LAVi (ml/m²)	43.6 ± 13.3	42.7 ± 12.8	51.2 ± 14.8	**<0.001**
EF (%)	55.4 ± 8.3	55.5 ± 8.3	54.2 ± 7.9	0.382
Mitral E/E ratio’	10.8 ± 5	10.8 ± 5.2	11.3 ± 3.6	0.579
TAPSE (mm)	23.5 ± 5	23.6 ± 5.2	22.7 ± 3.9	0.342
RA Area (cm²)	19.9 ± 5.6	19.6 ± 5.4	21.3 ± 6.7	0.144
RVSP (mmHg)	27.5 ± 8.8	27.1 ± 8.5	30.6 ± 10.4	**0.026**
Significant TR	42 (13.1%)	28 (9.8%)	14 (40.0%)	**<0.001**
Sinus rhythm at follow-up (6 months)	284 (88.8%)	257 (90.3%)	27 (78.6%)	**0.025**

Table 3: Patient characteristics at baseline in relation to the degree of MR

When comparing patients at baseline with exclusively significant MR and exclusively significant TR, few relevant differences were observed, which were limited to the systolic pressure of the right ventricle (RVSP 25.7 ± 6.2 vs. 32.4 ± 9.8 mmHg, p=0.028). Patients with AVVR often presented different characteristics in comparison to patients without, in accordance with the previously described variations. Compared to patients without any significant AVVR, patients with exclusively significant TR were older, had larger RA, and higher right ventricular systolic pressure (RVSP) values. Moreover, patients with exclusively significant MR presented with pronounced dilatation of the LA (**Table 4a and 4b**).

	All patients (n=320)	Patients without significant AVVR (n=257)	Patients with isolated significant TR (n=28)	p vs. no AVVR	p vs. MR	p vs. TR and MR
Age (years)	66.3 ± 10	65.4 ± 10.1	71.3 ± 8.1	**0.016**	0.162	0.951
male sex	197 (61.6%)	165 (64.2%)	14 (50 %)	0.839	0.999	0.999
Persistent AF	128 (40%)	97 (37.7%)	15 (53.5%)	0.621	0.952	0.999
Cryoablation	212 (66.3%)	173 (67.3%)	20 (71.4%)	0.999	0.999	0.999
Ablation of the cavotricuspid isthmus	45 (14.1%)	29 (11.3%)	7 (23.8%)	0.228	0.999	0.999
Arterial hypertension	254 (79.4%)	203 (78.9%)	23 (82.1%)	0.999	0.999	0.999
Diabetes Mellitus	36 (11.3%)	22 (8.6%)	5 (17.8%)	0.664	0.999	0.999
Chronic kidney disease	29 (9.1%)	22 (8.6%)	5 (17.8%)	0.664	0.998	0.999
Coronary artery disease	88 (27.5%)	69 (26.8%)	9 (32.1%)	0.999	0.999	0.999
Obstructive pulmonary disease	24 (7.5%)	18 (7.0%)	4 (14.3%)	0.511	-	0.999
Hypo-/Hyperthyroidism	78 (24.4%)	61 (23.7%)	8 (28.6%)	0.999	0.999	0.999
ACEi/ARB	204 (63.7%)	162 (63.0%)	19 (67.9%)	0.999	0.999	0.999
MRA	63 (19.7%)	46 (17.9%)	7 (23.8%)	0.999	0.999	0.999
BB	276 (86.3%)	224 (87.2%)	22 (80.9%)	0.999	0.999	0.999
AAD	136 (42.5%)	107 (41.6%)	13 (47.6%)	0.999	0.999	0.749
LAD (mm)	44.6 ± 6	44.3 ± 5.8	44.9 ± 6.9	0.947	0.675	0.999
LAVi (ml/m²)	43.6 ± 13.3	42.5 ± 12.8	44.8 ± 6.9	0.828	0.187	0.712
EF (%)	55.4 ± 8.3	55.7 ± 8.3	54.1 ± 8.5	0.783	0.993	0.965
Mitral E/E ratio’	10.8 ± 5	10.6 ± 5.0	12.6 ± 6.6	0.311	0.872	0.834
TAPSE (mm)	23.5 ± 5	23.7 ± 5.1	22.3 ± 5.4	0.527	0.964	0.999

RA Area (cm²)	19.9 ± 5.6	19.1 ± 4.9	23.9 ± 7.2	**0.001**	0.137	0.953
RVSP (mmHg)	27.5 ± 8.8	26.4 ± 8.1	32.4 ± 9.8	**0.002**	**0.028**	0.191
Sinus rhythm at follow-up (6 months)	284 (88.8%)	230 (89.5%)	21 (75.0%)	0.074	0.999	0.999

	All patients (n=320)	Patients with isolated significant MR (n=21)	p vs. no AVVR	p vs. significant TR and MR	Patients with significant MR and TR (n=14)	p vs no AVVR
Age (years)	66.3 ± 10	65.4 ± 10.5	0.999	0.113	73.0 ± 6.6	**0.028**
male sex	197 (61.6%)	14 (66.6%)	0.999	0.163	4 (28.5%)	**0.044**
Persistent AF	128 (40%)	7 (33.3%)	0.999	0.430	9 (64.2%)	0.285
Cryoablation	212 (66.3%)	13 (60.7%)	0.999	0.999	7 (50.0%)	0.999
Ablation of the cavotricuspid isthmus	45 (14.1%)	5 (23.8%)	0.553	0.999	4 (28.5%)	0.324
Arterial hypertension	254 (79.4%)	18 (85.7%)	0.999	0.999	10 (71.4%)	0.999
Diabetes Mellitus	36 (11.3%)	5 (23.8%)	0.140	0.999	4 (28.5%)	0.080
Chronic kidney disease	29 (9.1%)	1 (4.7%)	0.999	0.999	1 (7.1%)	0.999
Coronary artery disease	88 (27.5%)	8 (38.1%)	0.999	0.760	2 (14.3%)	0.999
Obstructive pulmonary disease	24 (7.5%)	0 (0%)	-	-	2 (14.3%)	0.931
Hypo-/Hyperthyroidism	78 (24.4%)	5 (23.8%)	0.999	0.999	4 (28.6%)	0.999
ACEi/ARB	204 (63.7%)	14 (66.6%)	0.999	0.999	9 (64.2%)	0.999
MRA	63 (19.7%)	7 (33.3%)	0.146	0.884	2 (14.3%)	0.999
BB	276 (86.3%)	16 (78.6%)	0.999	0.999	13 (92.8%)	0.999
AAD	136 (42.5%)	11 (53.6%)	0.999	0.999	4 (28.5%)	0.999
LAD (mm)	44.6 ± 6	46.9 ± 6.4	0.220	0.806	45.0 ± 6.2	0.977
LAVi (ml/m²)	43.6 ± 13.3	52.6 ± 15.5	**0.005**	0.896	49.4 ± 14.1	0.220
EF (%)	55.4 ± 8.3	53.4 ± 8.0	0.638	0.906	55.4 ± 7.9	0.999
Mitral E/E ratio’	10.8 ± 5	11.4 ± 3.9	0.910	0.999	11.1 ± 3.1	0.984
TAPSE (mm)	23.5 ± 5	23.0 ± 3.8	0.933	0.964	22.2 ± 3.9	0.711
RA Area (cm²)	19.9 ± 5.6	19.9 ± 5.6	0.945	0.466	22.9 ± 7.8	0.074
RVSP (mmHg)	27.5 ± 8.8	25.7 ± 6.2	0.983	**<0.001**	37.9 ± 11.2	**<0.001**
Sinus rhythm at follow-up (6 months)	284 (88.8%)	21 (100 %)	0.999	0.999	12 (85.7%)	0.999

Tables 4a and 4b: Patient characteristics at baseline in relation to the degree of AVVR.

6.2. Echocardiographic changes after the pulmonary vein isolation

All patients included in our study received at least one TTE after a 6 months follow-up following the PVI treatment. Here, a significant improvement of some echocardiographic characteristics was documented, including the LVEF (mean LVEF 55.3 ± 8.2% vs. 57 ± 6.9%; p<0.001), as well as the size of the LA (mean LAVi 43.6 ± 13.2 mL/m² vs. 39.9 ± 12.1; p<0.001) and the RA (mean RAA 19.8 ± 5.6 cm² vs. 18.7 ± 5.6; p<0.001) (**Table 5**). Interestingly, the rate of significant TR (13.2% vs. 7.2%; p<0.001) as well as MR (10.9% vs. 6.6%; p<0.001) also improved significantly after the PVI treatment (**Figure 2).**

	Baseline	Follow-up	p
Significant TR	42 (13.1%)	23 (7.2%)	**<0.001**
Significant MR	35 (10.9%)	21 (6.6%)	**<0.001**
LAD (mm)	44.5 ± 5.9	43.8 ± 7.1	**0.011**
LAVi (ml/m²)	43.6 ± 13.2	39.9 ± 12.1	**<0.001**
EF (%)	55.3 ± 8.2	57 ± 6.9	**<0.001**
Mitral E/E ratio'	10.8 ± 5	10.8 ± 5.1	0.845
TAPSE (mm)	23.4 ± 5.0	23.6 ± 4.5	0.490
RA Area (cm²)	19.8 ± 5.6	18.7 ± 5.6	**<0.001**
RVSP (mmHg)	27.5 ± 8.7	26.1 ± 7.9	**0.010**

Table 5: Echocardiographic parameters at baseline in comparison to 6 months following the PVI procedure

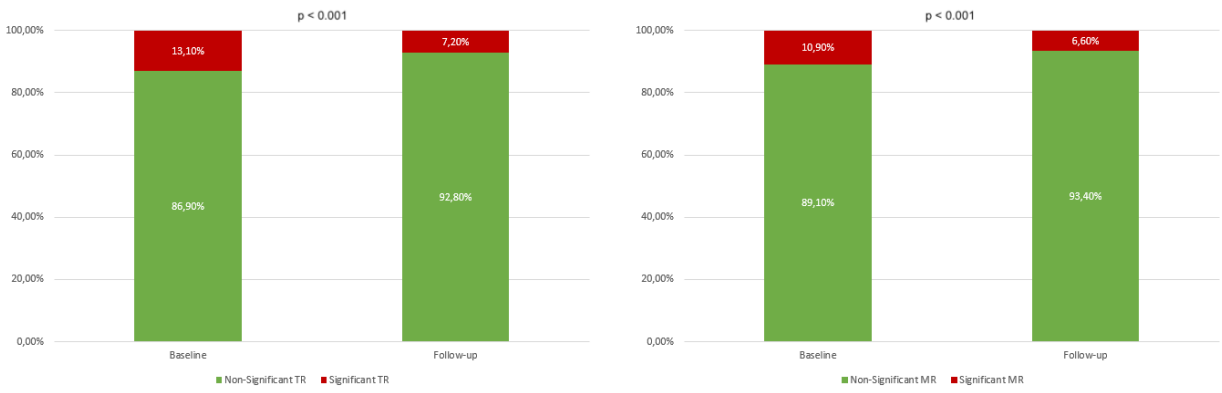
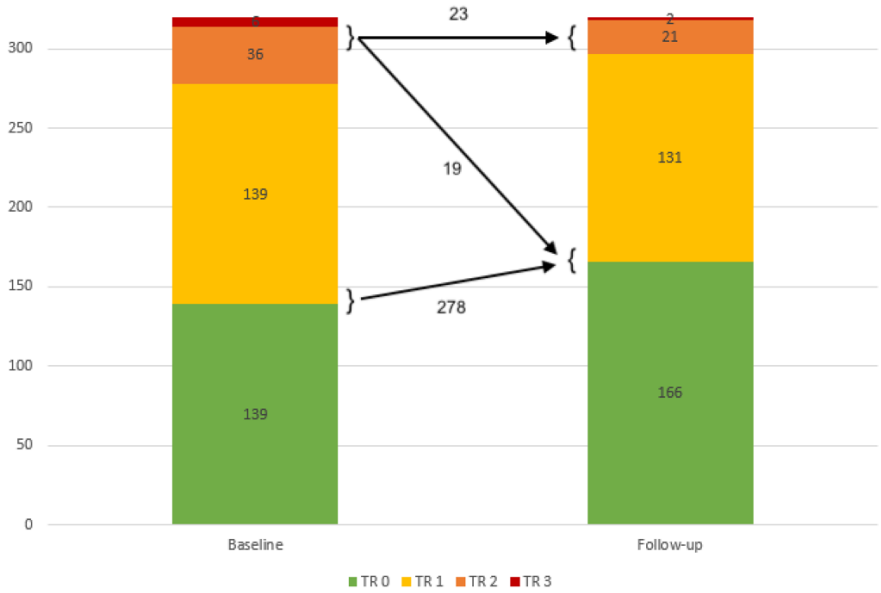
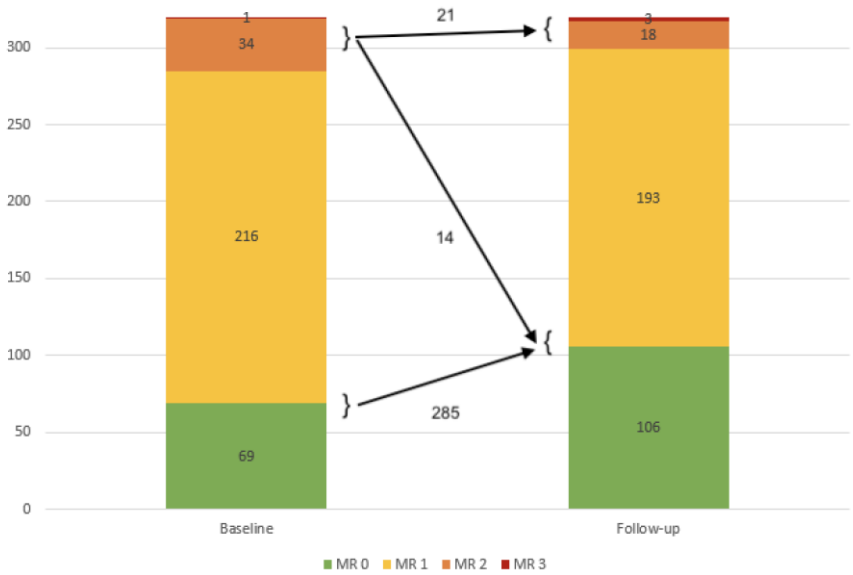


Figure 2: Proportion of patients with significant TR (left) and MR (right) at baseline and follow-up





Figures 3a and 3b: Changes in the degree of TR and MR throughout the follow-up

Out of 42 Patients with a significant TR at baseline, a relevant improvement in TR grade was documented in 19 patients (45.2%) **(Figure 3a)**. These patients were more likely to have a smaller RA at baseline in comparison to those with persistent relevant TR (RAA 20.2 ± 4.4 vs. 26.6 ± 8.3 cm²; p=0.002). Moreover, the frequency of concomitant significant MR was comparable between patients with and without an improvement in TR severity after the PVI procedure (30.4% in patients with persistent significant TR vs. 36.8% in patients with improved significant TR; p=0.999), while the same applied to the rates of persistent AF (69.6% vs. 42.1%; p=0.220) (**Tables 6a and 6b**).

	Patients with stable non-significant TR (n=278)	Patients with improvement of significant TR (n=19)	p vs TR0
Age (years)	65.4 ± 10.1	70.8 ± 8.3	0.058
male sex	179 (64.4%)	7 (36.8%)	**0.049**
Persistent AF	104 (37.4%)	8 (42.1%)	0.999
Cryoablation	188 (67.6%)	11 (57.9%)	0.999
Ablation of the cavotricuspid isthmus	34 (12.2%)	2 (10.5%)	0.999
Arterial hypertension	221 (79.5%)	13 (68.4%)	0.760
Diabetes Mellitus	27 (9.7%)	4 (21.1%)	0.353
Chronic kidney disease	23 (8.3%)	1 (5.3%)	0.999
Coronary artery disease	77 (27.7%)	4 (21.1%)	0.999
Obstructive pulmonary disease	18 (6.5%)	3 (15.7%)	0.376
Hypo-/Hyperthyroidism	66 (23.7%)	5 (26.3%)	0.999
ACEi/ARB	176 (63.3%)	12 (63.2%)	0.999
MRA	51 (18.3%)	3 (15.7%)	0.999
BB	241 (86.6%)	14 (73.7%)	0.346
AAD	117 (42.1%)	9 (47.3%)	0.999
LAD (mm)	44.5 ± 5.9	44.7 ± 7.4	0.989
LAVi (ml/m²)	43.2 ± 13.3	43.7 ± 12.1	0.986
EF (%)	55.5 ± 8.3	55.2 ± 8.3	0.985
Mitral E/E ratio’	10.7 ± 4.9	11.5 ± 3.6	0.820
TAPSE (mm)	23.6 ± 5.0	23.2 ± 5.8	0.924
RA Area (cm²)	19.2 ± 4.9	20.2 ± 4.4	0.729
RVSP (mmHg)	26.4 ± 7.9	36.2 ± 10.7	**<0.001**
Significant MR	21 (7.6%)	7 (36.8%)	**<0.001**
Sinus rhythm at follow-up (6 months)	251 (90.3%)	17 (89.5%)	0.999

	Patients with stable non-significant TR (n=278)	Patients with persistent significant TR (n=23)	p vs TR0	p vs TRi
Age (years)	65.4 ± 10.1	72.8 ± 7.0	**0.002**	0.798
male sex	179 (64.4%)	11 (47.8%)	0.341	0.999

Persistent AF	104 (37.4%)	16 (69.6%)	**0.007**	0.220
Cryoablation	188 (67.6%)	13 (56.5%)	0.832	0.999
Ablation of the cavotricuspid isthmus	34 (12.2%)	9 (39.1%)	**0.001**	0.108
Arterial hypertension	221 (79.5%)	20 (86.9%)	0.999	0.435
Diabetes Mellitus	27 (9.7%)	5 (21.7%)	0.216	0.999
Chronic kidney disease	23 (8.3%)	5 (21.7%)	0.098	0.386
Coronary artery disease	77 (27.7%)	7 (30.4%)	0.999	0.999
Obstructive pulmonary disease	18 (6.5%)	3 (13.0%)	0.704	0.999
Hypo-/Hyperthyroidism	66 (23.7%)	7 (30.4%)	0.999	0.999
ACEi/ARB	176 (63.3%)	16 (69.6%)	0.999	0.999
MRA	51 (18.3%)	9 (39.1%)	0.049	0.287
BB	241 (86.6%)	21 (91.3%)	0.999	0.382
AAD	117 (42.1%)	10 (43.4%)	0.999	0.999
LAD (mm)	44.5 ± 5.9	45.2 ± 6.2	0.864	0.966
LAVi (ml/m²)	43.2 ± 13.3	48.8 ± 12.9	0.156	0.454
EF (%)	55.5 ± 8.3	53.9 ± 8.3	0.684	0.888
Mitral E/E ratio’	10.7 ± 4.9	12.5 ± 6.7	0.291	0.824
TAPSE (mm)	23.6 ± 5.0	21.5 ± 4.0	0.137	0.551
RA Area (cm²)	19.2 ± 4.9	26.6 ± 8.3	**<0.001**	**0.002**
RVSP (mmHg)	26.4 ± 7.9	32.7 ± 10.4	**0.002**	0.364
Significant MR	21 (7.6%)	7 (30.4%)	**0.001**	0.999
Sinus rhythm at follow-up (6 months)	251 (90.3%)	16 (69.6%)	**0.008**	0.353

Tables 6a and 6b: Patient characteristics at baseline in relation to the post-interventional change in the degree of TR. (TR0= no significant TR at baseline and follow-up, TRi= significant TR at baseline but with improvement at follow-up)

As a result, during the follow-up, significant TR was documented in 23 patients (7.2%) **(Figure 3a)**. These patients, in comparison to those without significant TR at the follow-up appointment, were at baseline older (72.7 ± 7.0 vs. 65.7 ± 10.0 years; p<0.001) and had more frequently persistent AF (69.6% vs. 37.7%; p=0.003) as well as CKD (21.7% vs. 8.1%; p=0.028) and diabetes mellitus (21.7% vs. 10.4%; p=0.099). Moreover, they presented at baseline a dilated RA (RAA 26.6 ± 8.3 vs. 19.3 ± 4.9 cm², p<0.001) and LA (LAVi 48.4 ± 12.9 vs. 43.3 ± 13.2 mL/m²; p=0.066), as well as signs of pulmonary hypertension (RVSP 32.7 ±

10.4 vs. 27.0 ± 8.5 mmHg; p =0.003). Additionally, the rates of significant MR (30.4% vs. 9.4%; p=0.002) at baseline were also higher. Of note, this group of patients also received much more frequently an additional ablation of the cavotricuspid isthmus at the time of the procedure (39,1% vs. 12.1%; p<0.001) due to the presence of right atrial flutter (**Table 7**).

	All patients (n=320)	Patients with non-significant TR at follow-up (n=297)	Patients with significant TR at follow-up (n=23)	p
Age (years)	66.3 ± 10	65.7 ± 10.0	72.8 ± 7.0	**<0.001**
male sex	197 (61.6%)	168 (62.6%)	11 (47.8%)	0.161
Persistent AF	128 (40%)	88 (37.7%)	16 (69.6%)	**0.003**
Cryoablation	212 (66.3%)	175 (67%)	13 (56.5%)	0.307
Ablation of the cavotricuspid isthmus	45 (14.1%)	25 (12.1%)	9 (39.1%)	**<0.001**
Arterial hypertension	254 (79.4%)	201 (78.8%)	20 (86.9%)	0.549
Diabetes Mellitus	36 (11.3%)	22 (10.4%)	5 (21.7%)	0.099
Chronic kidney disease	29 (9.1%)	18 (8.1%)	5 (21.7%)	**0.028**
Coronary artery disease	88 (27.5%)	70 (27.3%)	7 (30.4%)	0.744
Obstructive pulmonary disease	24 (7.5%)	15 (7.1%)	3 (13.0%)	0.296
Hypo-/Hyperthyroidism	78 (24.4%)	59 (23.9%)	7 (30.4%)	0.484
ACEi/ARB	204 (63.7%)	160 (63.3%)	16 (69.6%)	0.549
MRA	63 (19.7%)	42 (18.2%)	9 (39.1%)	**0.015**
BB	276 (86.3%)	220 (85.9%)	21 (91.3%)	0.467
AAD	136 (42.5%)	107 (42.4%)	10 (43.4%)	0.922
LAD (mm)	44.6 ± 6	44.5 ± 5.9	45.2 ± 6.2	0.612
LAVi (ml/m²)	43.6 ± 13.3	43.3 ± 13.2	48.8 ± 12.9	0.066
EF (%)	55.4 ± 8.3	55.5 ± 8.3	53.9 ± 8.3	0.411
Mitral E/E ratio’	10.8 ± 5	10.7 ± 4.9	12.5 ± 6.7	0.142
TAPSE (mm)	23.5 ± 5	23.6 ± 5.1	21.5 ± 4.0	0.059
RA Area (cm²)	19.9 ± 5.6	19.3 ± 4.9	26.6 ± 8.3	**<0.001**
RVSP (mmHg)	27.5 ± 8.8	27.0 ± 8.5	32.7 ± 10.4	**0.003**
Significant MR	35 (10.9%)	14 (9.4%)	7 (30.4%)	**0.002**
Sinus rhythm at follow-up (6 months)	284 (88.8%)	235 (90.2%)	16 (69.6%)	**0.002**

Table 7: Patient characteristics at baseline in relation to the degree of TR at follow-up

In a similar manner, out of 35 Patients with a significant MR at baseline, a relevant improvement in MR grade was documented in 14 patients (40%) **(Figure 3b)**. Patients with persistent significant MR throughout the follow-up were more likely to have a larger LA, concomitant TR as well as diabetes mellitus compared with those with stable non-significant MR. However, no parameter could predict the improvement of the MR grade after the ablation (**Tables 8a and 8b**).

	Patients with stable non-significant MR (n=285)	Patients with improvement of significant MR (n=14)	p vs MR0
Age (years)	66.0 ± 10.0	70.6 ± 7.0	0.223
male sex	179 (62.8%)	7 (50.0%)	0.999
Persistent AF	112 (39.3%)	6 (42.9%)	0.999
Cryoablation	190 (66.6%)	10 (71.4%)	0.999
Ablation of the cavotricuspid isthmus	36 (12.6%)	4 (28.6%)	0.262
Arterial hypertension	226 (79.3%)	9 (64.3%)	0.544
Diabetes Mellitus	27 (9.5%)	3 (21.4%)	0.438
Chronic kidney disease	27 (9.5%)	0 (0%)	-
Coronary artery disease	78 (27.4%)	5 (35.7%)	0.999
Obstructive pulmonary disease	22 (7.7%)	1 (7.1%)	0.999
Hypo-/Hyperthyroidism	69 (24.2%)	6 (42.9%)	0.348
ACEi/ARB	181 (63.5%)	8 (57.1%)	0.999
MRA	56 (19.6%)	2 (14.3%)	0.999
BB	246 (86.3%)	12 (85.7%)	0.999
AAD	122 (42.8%)	8 (57.1%)	0.872
LAD (mm)	44.4 ± 5.9	46.2 ± 5.9	0.536
LAVi (ml/m²)	42.7 ± 12.8	50.6 ± 15.2	0.068
EF (%)	55.5 ± 8.3	54.6 ± 7.5	0.925
Mitral E/E ratio’	10.8 ± 5.2	11.7 ± 1.9	0.797
TAPSE (mm)	23.6 ± 5.2	22.5 ± 3.8	0.761
RA Area (cm²)	19.6 ± 5.4	20.2 ± 5.0	0.924
RVSP (mmHg)	27.1 ± 8.5	32.4 ± 9.5	0.070
Significant TR	28 (9.8%)	8 (57.1%)	**0.001**
Sinus rhythm at follow-up (6 months)	257 (90.3%)	13 (92.9%)	0.999

	Patients with stable non-significant MR (n=285)	Patients with persistent significant MR (n=21)	p vs MR0	p vs MRi
Age (years)	66.0 ± 10.0	67.0 ± 11.2	0.903	0.556
male sex	179 (62.8%)	11 (52.4%)	0.999	0.999
Persistent AF	112 (39.3%)	10 (47.6%)	0.999	0.999
Cryoablation	190 (66.6%)	12 (57.1%)	0.999	0.999
Ablation of the cavotricuspid isthmus	36 (12.6%)	5 (23.8%)	0.440	0.999
Arterial hypertension	226 (79.3%)	19 (90.5%)	0.648	0.173
Diabetes Mellitus	27 (9.5%)	6 (28.6%)	**0.019**	0.999
Chronic kidney disease	27 (9.5%)	2 (9.5%)	0.994	-
Coronary artery disease	78 (27.4%)	5 (23.8%)	0.999	0.999
Obstructive pulmonary disease	22 (7.7%)	1 (4.8%)	0.999	0.999
Hypo-/Hyperthyroidism	69 (24.2%)	3 (14.3%)	0.902	0.174
ACEi/ARB	181 (63.5%)	15 (71.4%)	0.999	0.999
MRA	56 (19.6%)	5 (23.8%)	0.999	0.999
BB	246 (86.3%)	18 (85.7%)	0.999	0.999
AAD	122 (42.8%)	6 (28.6%)	0.606	0.273
LAD (mm)	44.4 ± 5.9	46.3 ± 6.6	0.367	0.999
LAVi (ml/m²)	42.7 ± 12.8	51.7 ± 14.9	**0.009**	0.973
EF (%)	55.5 ± 8.3	53.9 ± 8.4	0.672	0.964
Mitral E/E ratio’	10.8 ± 5.2	11.0 ± 4.4	0.976	0.928
TAPSE (mm)	23.6 ± 5.2	22.8 ± 3.9	0.771	0.991
RA Area (cm²)	19.6 ± 5.4	22.2 ± 8.0	0.202	0.622
RVSP (mmHg)	27.1 ± 8.5	29.4 ± 10.9	0.471	0.584
Significant TR	28 (9.8%)	6 (28.6%)	**0.025**	0.273
Sinus rhythm at follow-up (6 months)	257 (90.3%)	20 (95.2%)	0.958	0.999

Tables 8a and 8b: Patient characteristics at baseline in relation to the post-interventional change in the degree of MR. (MR0= no significant MR at baseline and follow-up, MRi= significant MR at baseline but improvement at follow-up

6.3. Recurrence of atrial arrhythmia after PVI

The patients were followed-up for potential recurrences of atrial arrhythmias after the catheter ablation for a mean time-length of 349 days (median time length 210 days). At the time of the echocardiographic follow-up appointment 6 months after the procedure, a total of 284 patients (88.8%) were free of atrial arrhythmia episodes, while for the total length of the follow-up after PVI, recurrent atrial arrhythmia was documented in 104 patients (32.5%) **(Figure 4)**. In 32 of those patients, a second PVI had to be performed over time to achieve complete isolation of the pulmonary veins. Patients with recurrence of atrial arrhythmia during the follow-up period were more likely to have CKD (14.4% vs. 6.5%; p=0.020), persistent AF (51% vs. 34.7%; p=0.005) as well as an enlarged RA (23.0 ± 4.9 vs. 19.3 ± 5.3 cm²; p=0.061) and significant TR at baseline (21.2% vs. 9.3%; p=0.003) **(Table 9)**.

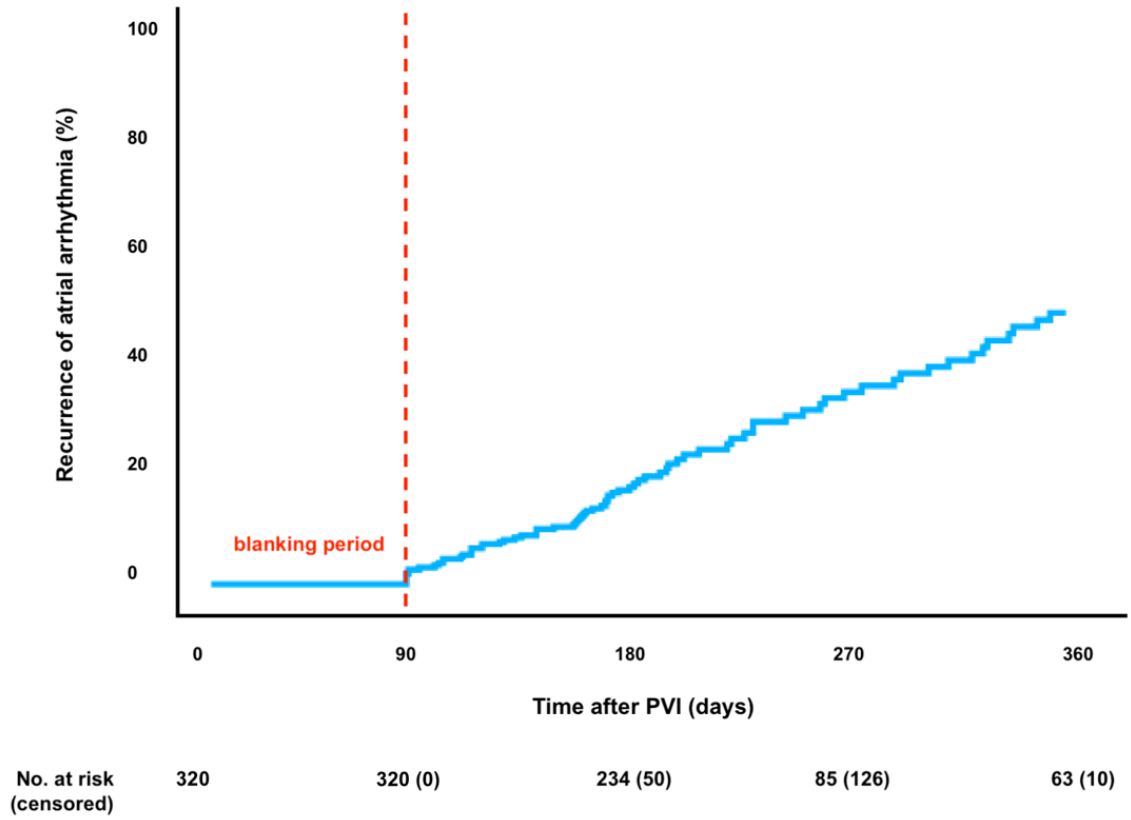


Figure 4: Kaplan-Meier curve of recurrence of atrial arrhythmia after PVI

	All patients (n=320)	Patients without a recurrence of atrial arrhythmia (n=216)	Patients with a recurrence of atrial arrhythmia (n=104)	p
Age (years)	66.3 ± 10	65.8 ± 9.9	67.2 ± 10.1	0.225
male sex	197 (61.6%)	136 (63%)	61 (58.7%)	0.460
Persistent AF	128 (40%)	75 (34.7%)	53 (51%)	**0.005**
Cryoablation	212 (66.3%)	149 (69%)	63 (60.6%)	0.137
Ablation of the cavotricuspid isthmus	45 (14.1%)	30 (13.9%)	15 (14.4%)	0.898
Arterial hypertension	254 (79.4%)	172 (79.6%)	82 (78.8%)	0.872
Diabetes Mellitus	36 (11.3%)	22 (10.2%)	14 (13.5%)	0.387
Chronic kidney disease	29 (9.1%)	14 (6.5%)	15 (14.4%)	**0.020**
Coronary artery disease	88 (27.5%)	60 (27.8%)	28 (26.9%)	0.873
Obstructive pulmonary disease	24 (7.5%)	19 (8.8%)	5 (4.8%)	0.206
Hypo-/Hyperthyroidism	78 (24.4%)	47 (21.8%)	31 (29.8%)	0.117
ACEi/ARB	204 (63.7%)	141 (64.4%)	63 (62.5%)	0.748
MRA	63 (19.7%)	37 (17.1%)	26 (25%)	0.098
BB	276 (86.3%)	187 (86.6%)	89 (85.6%)	0.809
AAD	136 (42.5%)	88 (40.7%)	48 (46.2%)	0.360
LAD (mm)	44.6 ± 6	44.3 ± 5.8	45.0 ± 6.1	0.362
LAVi (ml/m²)	43.6 ± 13.3	42.9 ± 13.2	45.2 ± 13.3	0.159
EF (%)	55.4 ± 8.3	55.2 ± 8.8	55.6 ± 7.1	0.695
Mitral E/E ratio’	10.8 ± 5	10.5 ± 4.5	11.5 ± 5.9	0.106
TAPSE (mm)	23.5 ± 5	23.6 ± 5.1	11.5 ± 5.9	0.341
RA Area (cm²)	19.9 ± 5.6	19.3 ± 5.3	23.0 ± 4.9	0.061
RVSP (mmHg)	27.5 ± 8.8	27.2 ± 8.6	28.1 ± 9.0	0.404
Significant MR	35 (10.9%)	26 (12.0%)	9 (8.7%)	0.365
Significant TR	42 (13.1%)	20 (9.3%)	22 (21.2%)	**0.003**

Table 9: Patient characteristics at baseline in relation to the recurrence of atrial arrhythmia during the follow-up

Furthermore, when examining patients with and without a recurrence of atrial arrhythmia, freedom of atrial arrhythmia was more likely to coincide with a relevant improvement of the TR grade after the ablation (60% vs. 31.8%, p=0.070). However, the same observation could not be made for MR (42.3% vs. 33.3%, p=0.648) The only other echocardiographic parameter which improved significantly more in patients without a recurrence throughout the 6 months of follow-up was the left ventricular systolic function (**Table 10**).

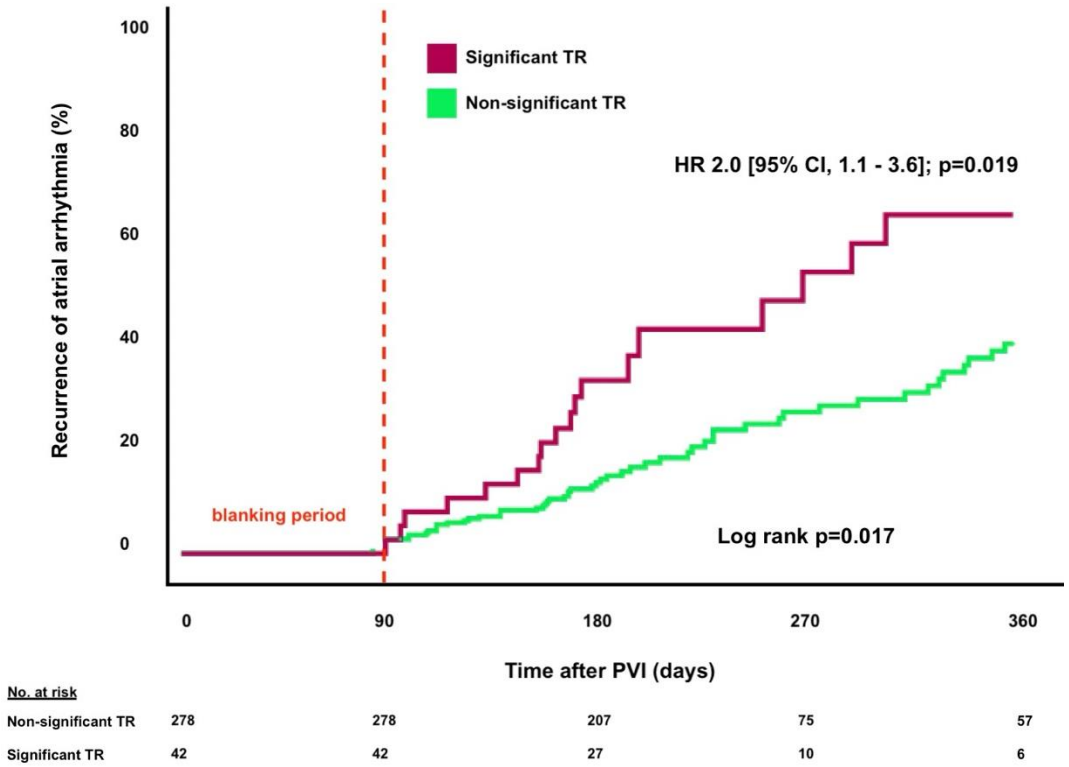
	Patients without recurrence of atrial arrhythmia (n=216)	Patients with recurrence of atrial arrhythmia (n=104)	p
Significant TR	20 (9.3%) -> 8 (3.7%)	22 (21.2%) -> 15 (14.4%)	0.070
Significant MR	26 (12.0%) ->15 (6.9%)	9 (8.7%) -> 6 (5.8%)	0.648
LAD (mm)	-1.16	-0.40	0.325
LAVi (ml/m²)	-4.37	-2.46	0.162
EF (%)	+2.39	+0.22	**0.008**
Mitral E/E ratio'	+0.33	-0.52	0.223
TAPSE (mm)	+0.43	-0.22	0.336
RA Area (cm²)	-1.64	-1.49	0.874
RVSP (mmHg)	-1.70	-1.47	0.865

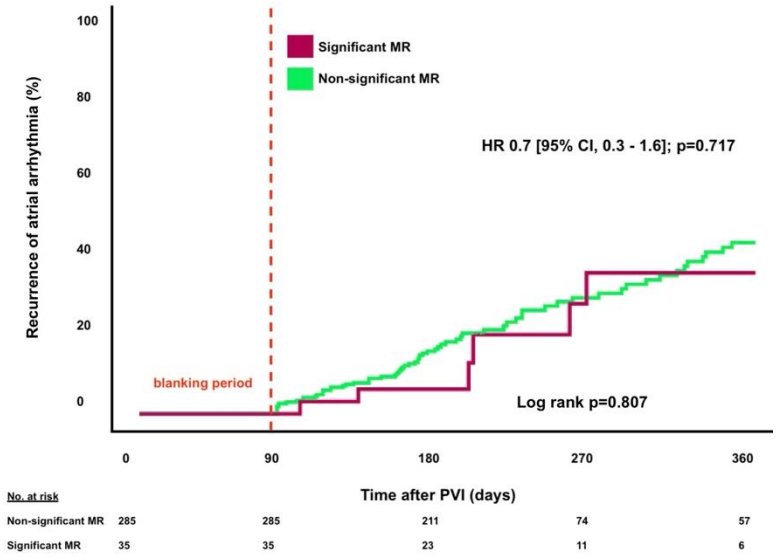
Table 10: Changes to the echocardiographic parameters throughout the 6 months following the PVI procedure, related to the recurrence of atrial arrhythmia

When examining the effect of various parameters on atrial arrhythmia recurrence (survival analysis), the presence of significant TR at baseline served as a risk predictor regarding arrhythmic recurrence after PVI (HR 2.00 [95% CI, 1.10 – 3.60]; p=0.017) (**Figure 5a**). In fact, no other echocardiographic parameter at baseline could predict the recurrence of atrial arrhythmia after the catheter ablation, including the presence of a dilated LA (HR 1.21 [95% CI, 0.81 - 1.80]; p=0.352), diastolic dysfunction (HR 1.49 [95% CI, 0.89 - 2.50]; p=0.123), as well as of significant MR (HR 0.70 [95% CI, 0.36 - 1.62]; p=0.807) (**Figure 5b)** or the concomitant presence of significant MR and TR (HR 1.38 [95% CI, 0.55 - 3.77]; p=0.529). Only the presence of persistent AF at the time of the PVI procedure tended to predict an unfavorable outcome (HR 1.42 [95% CI, 0.96 - 2.09]; p=0.077), although this relationship did not reach statistical significance (**Table 11**).

	p	HR, 95% CI
Age	0.713	0.92 (0.62 - 1.38)
Persistent AF	0.077	1.42 (0.96-2.09)
Chronic kidney disease	0.131	1.54 (0.88 - 2.69)
Diabetes Mellitus	0.891	1.04 (0.59-1.83)
Arterial hypertension	0.944	0.98 (0.60 - 1.59)
LA enlargement	0.352	1.21 (0.81 - 1.80)
Diastolic dysfunction	0.123	1.49 (0.89 - 2.50)
RA enlargement	0.609	1.22 (0.56 - 2.70)
Signs of pulmonary hypertension	0.520	1.24 (0.64 - 2.40)
Significant MR	0.807	0.70 (0.36 - 1.62)
Significant TR	0.017	2.00 (1.10 – 3.60)
Significant MR and TR	0.529	1.38 (0.55 - 3.77)

Table 11: Ability of baseline factors to predict atrial arrhythmia recurrence after PVI (univariate analysis)





Figures 5a and 5b: Kaplan-Meier curves of recurrence of atrial arrhythmia after PVI, depending on the presence of significant TR (up) and MR (down) at baseline.

In accordance to these results, patients with exclusively TR were more likely to suffer from atrial arrhythmia recurrences after the PVI in comparison to patients exclusively with MR (64% vs. 23%, HR 2.56 [95% CI, 0.94 - 6.97]; p=0.056). Furthermore, patients with exclusively TR were more likely to have a recurrence of atrial arrhythmia in comparison to patients without significant AVVR (HR 1.35 [95% CI, 1.04 - 1.76]; p=0.021). **(Figure 6)**.

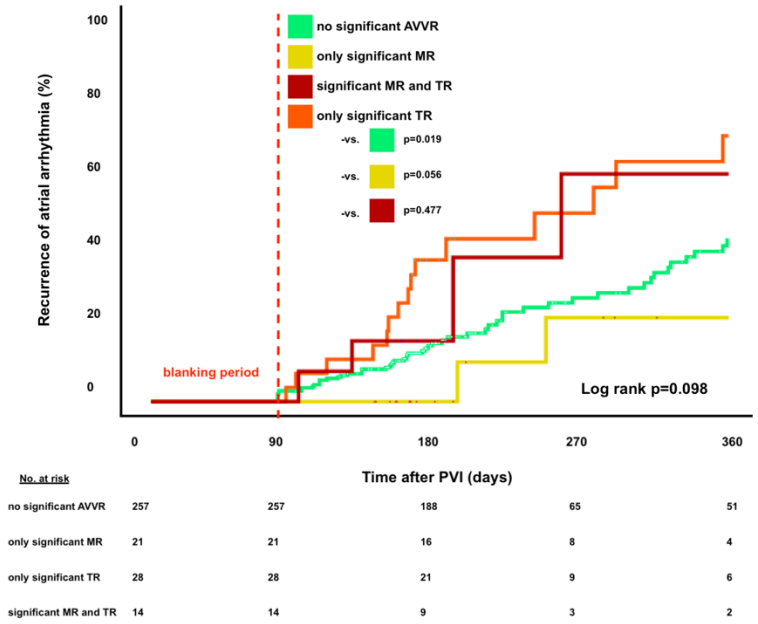
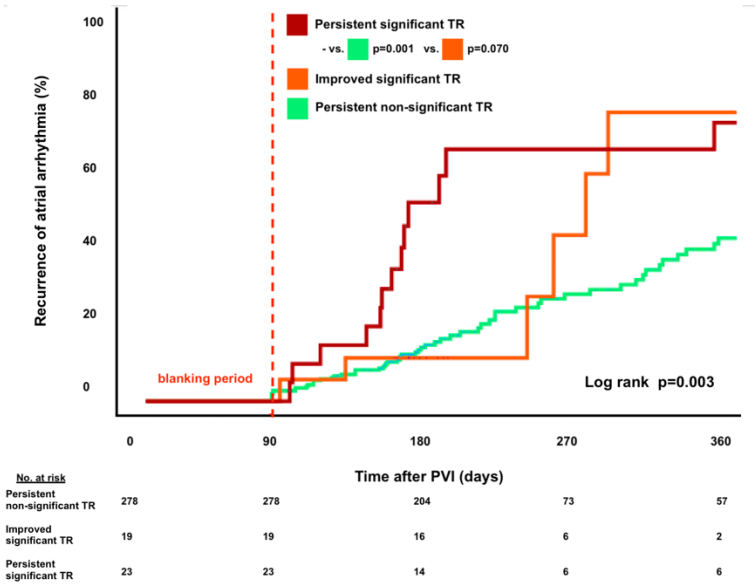
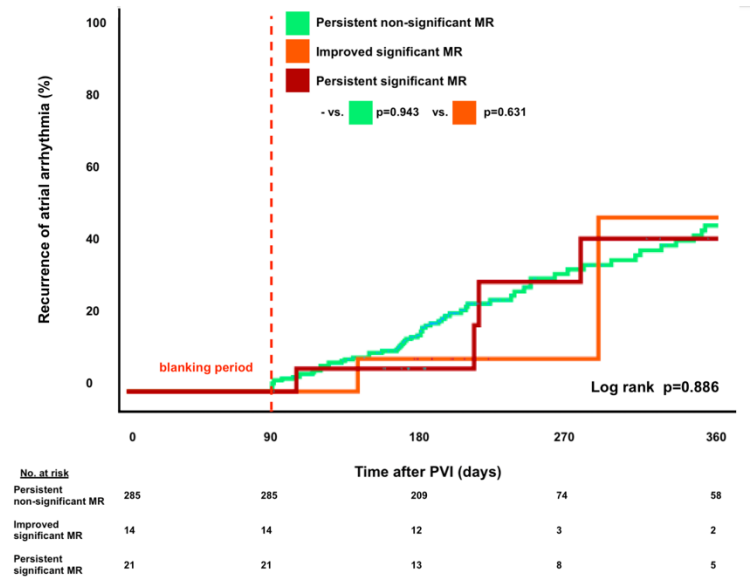


Figure 6: Kaplan-Meier curve of recurrence of atrial arrhythmia after PVI, depending on the presence of AVVR at baseline

A point raised by similar studies was whether the improvement of AVVR grade after catheter ablation could be linked with a better arrhythmic outcome. In our analysis, patients with an improvement throughout the follow-up of a baseline significant TR seemed to benefit regarding the freedom from atrial arrhythmias in comparison to those with a persistent clinically relevant TR, though this observation did not reach a statistical significance (HR 2.40 [95% CI, 0.90 - 5.90]; p=0.070). Nonetheless, patients without a significant TR both at baseline and throughout the follow-up were the ones with the least documented recurrences of atrial arrhythmia among the groups (p=0.003) **(Figure 7a)**. However, no significant relations were observed when examining the progression of the MR-grade (p=0.886) throughout the follow-up period. **(Figure 7b)**.



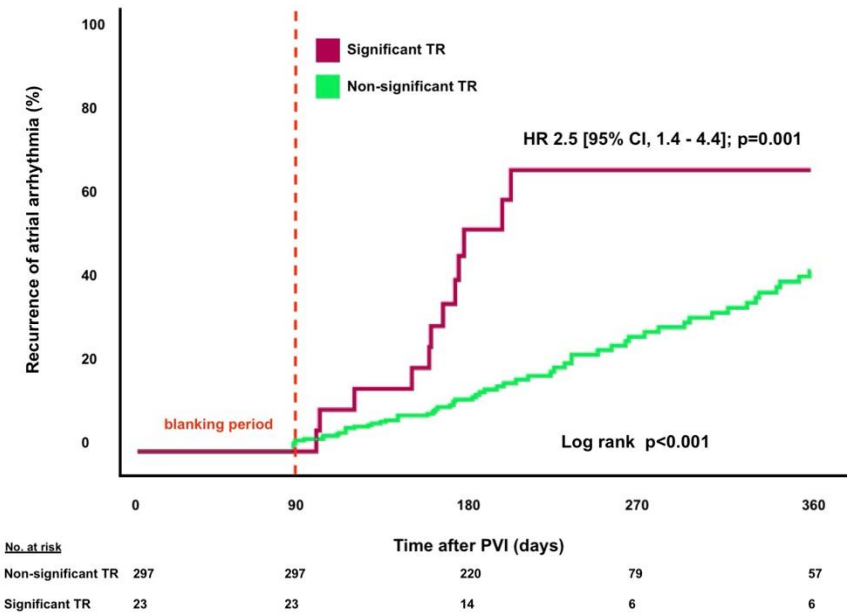


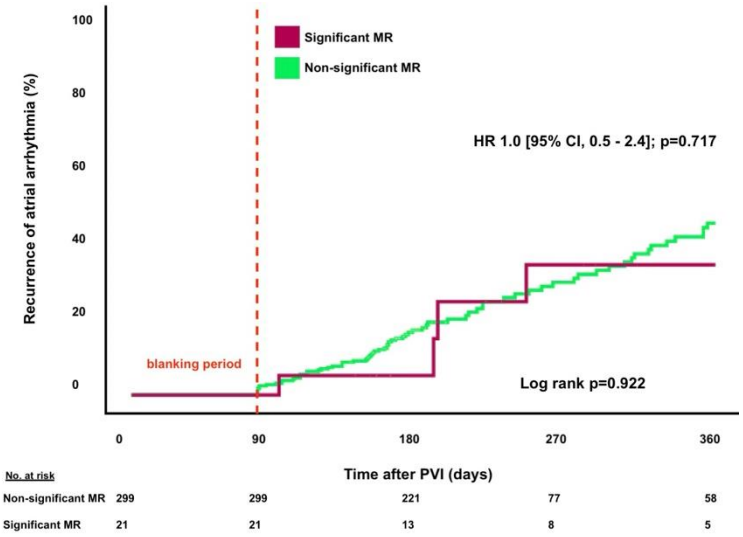
Figures 7a and 7b: Kaplan-Meier curves of recurrence of atrial arrhythmia after PVI, depending on the progression of TR (up) and MR (down) throughout the follow-up.

When re-examining the patients 6 months after the PVI procedure, the presence of significant TR at this time point was even more strongly associated with a higher risk of recurrent atrial arrhythmic episodes (HR 2.50 [95% CI, 1.44 - 4.36]; p=0.001) (**Figure 8a**). In fact, approximately one third of these patients already experienced a recurrence of atrial arrhythmia just within 6 months after the procedure. Likewise, the presence of significant TR at the follow-up appointment belonged among the few echocardiographic parameters which could predict the recurrence of atrial arrhythmia after PVI (**Table 12**), which did not include the presence of significant MR (HR 1.04 [95% CI, 0.45 - 2.39]; p=0.922) (**Figure 8b**).

	p	95% CI
Significant MR at follow-up	0.922	1.04 (0.45 - 2.39)
Significant TR at follow-up	<0.001	2.50 (1.44 - 4.36)
Significant MR and TR at follow-up	0.788	1.21 (0.29 - 4.94)
Diastolic dysfunction at follow-up	0.382	1.25 (0.75 - 2.10)
LA enlargement follow-up	0.409	1.18 (0.79 - 1.77)
RA enlargement at follow-up	0.336	1.64 (0.59 - 4.52)
Signs of pulmonary hypertension at follow-up	0.032	2.23 (1.07 - 4.63)

Table 12: Ability of echocardiographic parameters at follow-up to predict atrial arrhythmia recurrence after PVI (univariate analysis)





Figures 8a and 8b: Kaplan-Meier curves of recurrence of atrial arrhythmia after PVI, depending on the presence of significant TR (up) and MR (down) at follow-up.

A question raised by the above-mentioned results is whether significant TR could independently pose a risk predictor for the recurrence of atrial arrhythmia after PVI. In our analysis, the presence of significant TR at baseline was independently associated with a higher risk of recurrent atrial arrhythmia episodes in a multivariate Cox-regression (HR 2.00 [95% CI, 1.11 - 3.59]; p=0.019), which included established risk factors for the persistence of AF after ablation like the presence of persistent AF, CKD and diabetes mellitus, as well as the size of the LA, the presence of significant MR and diastolic dysfunction. **(Table 13)**. Likewise, this relationship was also present when examining the presence of significant TR 6 months after the PVI-procedure (HR 2.01 [95% CI, 1.05 - 3.84]; p=0.034).

	HR (95% CI)
Diabetes Mellitus	1.05 [0.56 - 1.95]
Chronic kidney disease	2.32 [1.20 - 4.48]
Persistent AF	1.19 [0.75 - 1.90]
Diastolic dysfunction at baseline	1.09 [0.61 - 1.94]
LA enlargement at baseline	1.30 [0.80 - 2.11]
Significant MR at baseline	0.71 [0.32 - 1.56]
Significant TR at baseline	2.00 [1.11 - 3.59]

Table 13: Multivariate Cox-regression for the prediction atrial arrhythmia recurrence after pulmonary vein isolation

To account for potential confounders, we additionally performed a propensity-score analysis. We matched the 42 patients with significant TR at baseline with 39 patients of similar characteristics but without relevant TR. As expected, there were no major differences between two groups, including the rates of persistent AF and concomitant significant MR, except for the rates of diabetes mellitus and characteristics of the right heart, tied to the presence of TR (**Table 14**). In this smaller group of patients, the presence of significant TR remained a predictor for the recurrence of atrial arrhythmias after the PVI (HR 2.22 [95% CI, 1.02 - 4.87]; p=0.045) (**Figure 9**).

	All patients after propensity score matching (n=81)	Patients with non-significant TR (n=39)	Patients with significant TR (n=42)	p
Age (years)	70.7 ± 8.5	69.4 ± 9.2	71.9 ± 7.6	0.200
male sex	40 (49.4%)	22 (56.4%)	18 (42.9%)	0.228
Persistent AF	41 (50.6%)	17 (43.6%)	24 (57.1%)	0.228
Cryoablation	53 (65.4%)	29 (74.4%)	24 (57.1%)	0.379
Ablation of the cavotricuspid isthmus	18 (22.2%)	7 (17.9%)	11 (26.2%)	0.106
Arterial hypertension	67 (82.7%)	34 (87.2%)	33 (78.6%)	0.312
Diabetes Mellitus	10 (12.3%)	1 (2.6%)	9 (21.4%)	**0.010**
Chronic kidney disease	8 (9.9%)	2 (5.1%)	6 (21.4%)	0.172
Coronary artery disease	24 (29.6%)	13 (33.3%)	11 (26.2%)	0.488
Obstructive pulmonary disease	8 (9.9%)	2 (5.1%)	6 (14.3%)	0.172
Hypo-/Hyperthyroidism	18 (27.2%)	10 (25.6%)	8 (28.6%)	0.770
ACEi/ARB	56 (69.1%)	28 (71.8%)	28 (66.6%)	0.623
MRA	23 (28.4%)	11 (28.2%)	12 (28.6%)	0.971
BB	69 (85.2%)	34 (87.2%)	35 (83.3%)	0.631
AAD	36 (44.4%)	17 (43.6%)	19 (45.2%)	0.883
LAD (mm)	45.2 ± 6.2	45.4 ± 5.8	44.9 ± 6.6	0.787
LAVi (ml/m²)	46.9 ±13.4	47.5 ± 14.3	46.4 ± 12.7	0.705
EF (%)	53.9 ± 8.9	53.2 ± 9.6	54.5 ± 8.2	0.511
Mitral E/E ratio'	11.3 ± 4.7	10.6 ± 3.8	12.0 ± 5.5	0.214
TAPSE (mm)	22.7 ± 5.1	23.2 ± 5.3	22.3 ± 4.9	0.436
RA Area (cm²)	22.1 ± 6.7	20.3 ± 5.5	23.5 ± 7.3	0.071
RVSP (mmHg)	30.5 ± 10.4	26.2 ± 8.4	34.2 ± 10.6	**<0.001**
significant MR	22 (27.2%)	8 (20.5%)	14 (33.3%)	0.200
Sinus rhythm at follow-up (6 months)	71 (87.7%)	38 (97.4%)	33 (78.6%)	**0.010**

Table 14: Comparison of patients with and without significant TR at baseline, using propensity score matching**.**

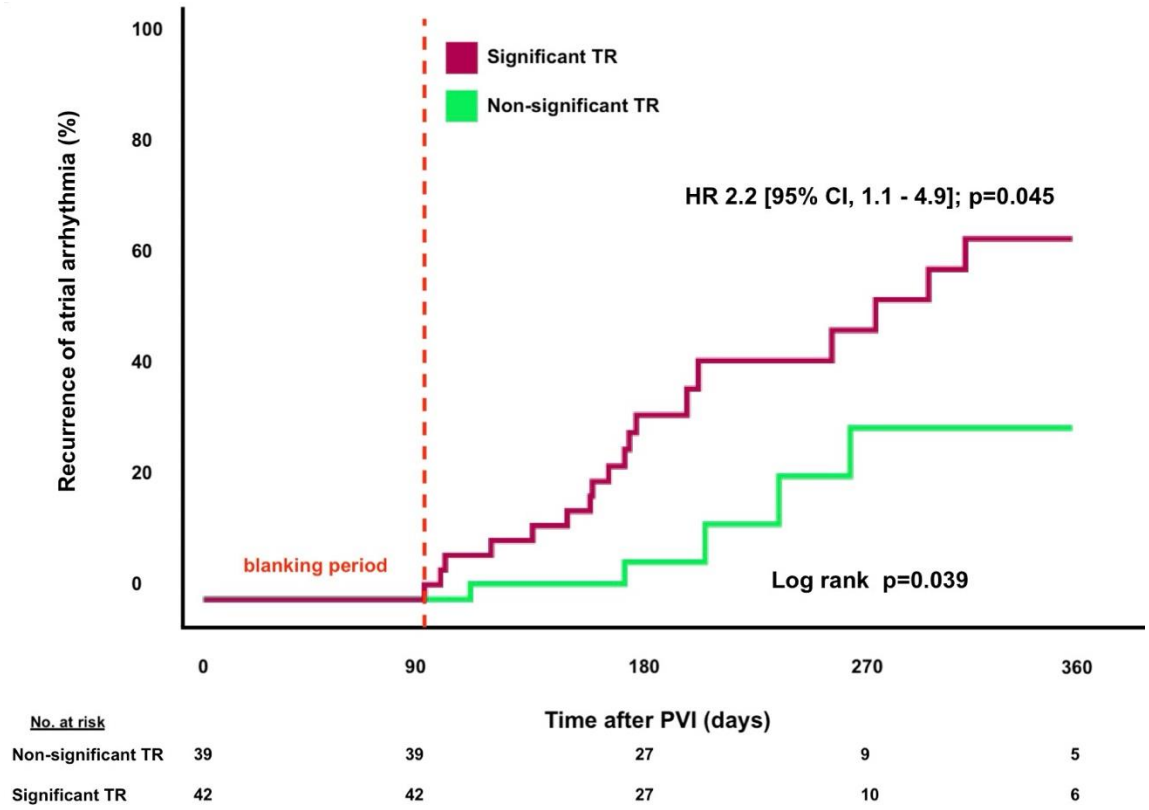


Figure 9: Kaplan-Meier curve of recurrence of atrial arrhythmia after PVI, depending on the presence of significant TR at baseline, using a subpopulation of patients after propensity score matching

6.4. Effect of the ablation of the cavotricuspid isthmus on recurrence of atrial arrhythmias in patients with significant TR

When examining the smaller group of patients with significant TR at baseline (n=42), the presence of right atrial flutter was associated with an increase in atrial arrhythmia recurrences (HR 2.69 [95% CI, 1.04 - 6.91]; p=0.039), despite the additional ablation of the cavotricuspid isthmus. Of note, the type of PVI ablation (cryoablation vs. RF), did not influence the post-ablation outcome in this group of patients (HR 1.15 [95% CI, 0.49 - 2.72]; p=0.737).

Conversely, when examining patients with documented right atrial flutter who received an additional ablation of the cavotricuspid isthmus at the time of the PVI (n=45), the proportion of moderate to severe TR at baseline was significantly higher (p=0.015). The presence of significant TR at the time of the procedure in this population continued to be associated with a significantly worse outcome (atrial arrhythmia recurrence 46% vs. 13%; p<0.001).

As a consequence, patients with history of right atrial flutter and with presence of significant TR at baseline had the worst arrhythmic outcome among the population (p=0.001) **(Figure 10)**. The baseline characteristics did not significantly differ among the groups at risk.

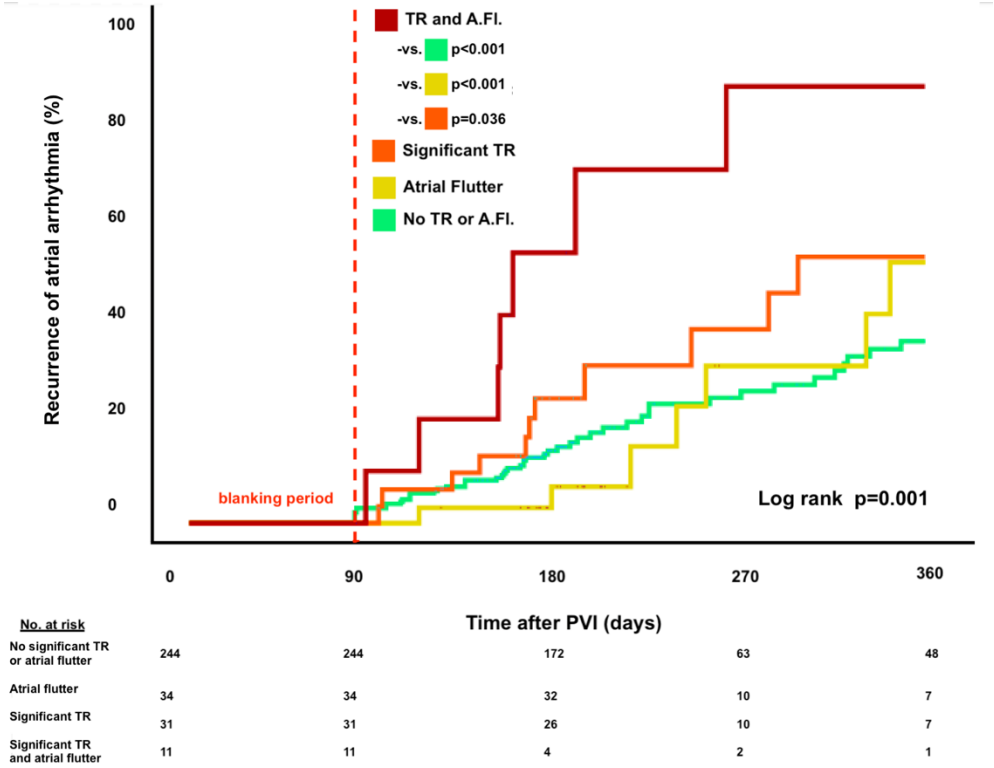


Figure 10: Kaplan-Meier curve of recurrence of atrial arrhythmia after PVI, depending on the presence of significant TR and right atrial flutter at baseline.

7. Discussion

In the present study, catheter ablation for AF resulted in a freedom from atrial arrhythmia in 67.5% of patients. Relevant improvement of the TR and MR severity, within 6 months after the procedure, was observed in 45.2% and 40% of the patients respectively. Moreover, the presence of significant TR (moderate to severe TR according to the ESC guidelines) was associated with an increased risk for atrial arrhythmia recurrences, especially in patients without improvement of TR severity after the PVI. Of note, the presence of significant MR was neither at baseline nor at follow-up associated with the recurrence of atrial arrhythmias.

7.1. Study population and characteristics

For the purpose of our study, we included 320 patients in our analysis. The mean age of the patients was 66.3 ± 10 years, which coincides with the fact that AF is an arrhythmia that mainly affects people of older age (19, 50, 112). The majority of the patients who presented themselves for PVI received beta-blockers (BB), while almost half of them also were on medical rhythm control, rates which are comparable to some of the established trials of the last few years (5, 6, 44, 46, 106). However, it is important to notice that 40% of the cases were classified as persistent AF at the time of the procedure, a rate above the overall incidence of persistent AF at the whole population (33) as well as in comparison to some of the aforementioned trials. Although the duration of AF at the time of the catheter ablation was not documented, the high rate of persistent AF could also hint at a longer duration of AF in our population.

In line with the mean age and the high rate of persistent AF of our population, the documented burden of comorbidities was high, with arterial hypertension being the most commonly reported concomitant disease. The incidence of stroke was relatively low, however a considerable number of patients were treated for congestive heart failure, a finding in accordance with the recorded incidence of heart failure in AF patients (10, 13, 57). AF more commonly leads to heart failure with preserved ejection fraction (55), which was also the case in our population, as most patients had a normal ejection fraction.

7.2. Atrial fibrillation and atrioventricular valve regurgitation

As previously described, AF is associated through atrial remodeling with significant enlargement of the of the LA (43, 63, 73) and particularly of the RA (16, 31, 48, 54, 60, 63, 73, 101, 103, 108), which has also been confirmed in 3D-echocardiographic studies (70). In particular, the RA is more prone to dilatation due to AF because of its thinner walls, its underdeveloped fibrotic tissue and its more complex anatomy (36, 60, 111). Indeed, most of our patients at baseline had a dilated RA (mean RAA 19.8 ± 5.6 cm^2) and LA (mean LAVi 43.6 ± 13.2 ml/m^2).

It has also been demonstrated that a relevant TR may develop in the absence of structural abnormalities of the tricuspid valve or its apparatus, constituting FTR. Functional TR is much more common than primary TR and accounts for approximately 90% of all cases of TR (15, 77). The leading pathophysiologic mechanism is attributed to tricuspid valve annular dilatation or tricuspid leaflet tethering (8, 58, 67, 102). AF belongs to the conditions most often associated with the development and progression of FTR (12, 47, 48, 58, 62, 74). Independent of the presence of left heart disease, AF is associated with right atrial and tricuspid annular remodeling (70). Thus, AF promotes right atrial enlargement and dilation of the TA (9, 16, 54, 59, 60, 63, 73, 101, 108, 111) and through loss of coaptation due to increased tenting volumes (31, 108) leads to TR.

In our analysis, the incidence of a clinically significant TR and MR at baseline was 13.2% and 10.9% respectively, while in 4.4% both of the valves presented a relevant regurgitation. This incidence rate of TR is comparable with the reported prevalence of TR in patients AF (1, 64, 72, 75, 78, 91, 101), which is usually described around 15-20%. Furthermore, in our study significant TR developed alongside (54), though being slightly more common than MR, which has also been displayed in other investigations (64) and could be attributed to the special anatomy of the RA. Additionally, most of the patients who developed TR tended to have mild to moderate TR (96%), which is supported by the existing literature (54). However, this finding could be possibly affected by exclusion of patients with severe AVVR. Moreover, as the process of atrial enlargement in the setting of AF naturally corresponds to its duration, it has been hypothesized that persistent AF has a greater effect on TR severity than paroxysmal AF (73). This hypothesis could be supported by our data, as patients with persistent AF had a higher prevalence of significant TR (19% vs. 9%; $p=0.015$) in comparison to those with paroxysmal AF.

In accordance with similar investigations, patients in our analysis with significant TR at baseline were more likely to have a dilated RA (RAA 23.5 ± 7.3 vs. 19.2 ± 4.9 cm^2, $p<0.001$)

in comparison to patients with no TR. Utsunomiya et al. already reported a higher RA/LA ratio in patients with AF-TR (101), while Najib et al. demonstrated an impressive doubling of the RA size in patients with AF and severe TR (63). However, the same degree of RA enlargement can lead to extremely variable degrees of TR severity, perhaps due to a different extent of leaflet areas adaptation in response to the dilatation (22, 96). This finding could also be supported by our data, as only a little over half (57.1%) of the cases with noticeably dilated RA (≥ 30 cm²) at baseline were classified, according to ESC guidelines, with moderate to severe TR. Thus, more echocardiographic investigations are required in order to better describe the pathophysiological relationship between RA enlargement, TA dilatation and TR severity.

Additionally in patients with relevant TR at baseline signs of mild pulmonary hypertension (RVSP 34.2 ± 10.6 vs. 26.4 ± 7.9 mmHg, p<0.001) were observed. As our analysis was composed of a varying population of patients with symptomatic AF who presented themselves for PVI, we did not categorize TR exclusively as 'AF-TR' or 'iTR', as some of them presented pulmonary disease or left-heart disease, including MR. Furthermore, as often experienced in clinical practice, it is common that a variety of mechanisms can lead to the development of FTR in selected patients. The effect of an increased sPAP on patients with AF and TR has also been varied in the literature (16, 23, 54, 63, 101, 103), probably due to differing patient-selection. A possible explanation of this finding could be that AF through LA enlargement could cause a subsequent increase in pulmonary pressures (75). However, it can't be ruled out that other entities could parallelly increase PAP and thus contribute to the development or persistence of FTR. When comparing patients with exclusively MR and exclusively TR at baseline, the latter demonstrated higher systolic pressure of the right ventricle (RVSP 25.7 ± 6.2 vs. 32.4 ± 9.8 mmHg, p=0.028), which could hint at a multifactorial generation of the FTR in our population. In any case, the presence of a multifactorial but mainly AF-related FTR could still lead through the described pathomechanism to the development or persistence of an arrhythmogenic substrate.

7.3. Characteristics of patients with significant tricuspid and/or mitral regurgitation and atrial fibrillation

In our analysis, significant TR at baseline was more frequent in female and older patients, a finding which is quite prevalent in most similar investigations (63, 68, 73, 74, 75, 103). In general, patients with AF and TR are reported to suffer more frequently from a higher burden of comorbidities, expressed by the CHA2DS2-VASc score (78, 103). Indeed, in our

investigation, patients with relevant TR were more likely to have diabetes mellitus (21.4% vs. 9.7%; p=0.025) as well as obstructive pulmonary disease (14.3% vs 6.5%; p=0.074). However, the most cited factor in the literature for the development of TR is without a doubt the presence of persistent AF (31, 38, 45, 64, 73, 74, 75, 103, 108). Nevertheless, an association of significant TR with paroxysmal AF has also been described (16). In our analysis, a greater prevalence of persistent AF in patients with moderate to severe TR at baseline was observed (57.1% vs. 37.4%; p=0.015). Moreover, we describe a strong statistical connection between TR and concomitant MR (33.3% vs 7.6%; p<0.001), which is in line with the previously described pathophysiology of AVVR and AF (54, 64).

In a similar manner, patients with significant MR at baseline were more likely to have a concomitant significant TR (40.0% vs 9.8%; p<0.001) as well as a dilated LA (LAVi 51.2 ± 14.8 vs. 42.7 ± 12.8 mL/m²; p<0.001). These findings support many studies which have described an association between atrial remodeling in AF and larger left atrial and mitral valve orifice areas (28, 64, 83). However, the size of the LA was not significantly larger in patients with exclusively MR compared to those with exclusively TR at baseline (LAVi 52.6 ± 15.5 vs. 44.8 ± 6.9 mL/m²; p=0.187). Overall, no major differences between patients with exclusively MR or TR were observed, with the exception of RVSP. This finding could be affected by the small sample size in the selected groups.

7.4. Improvement of atrioventricular valve regurgitation after catheter ablation for atrial fibrillation

Improvement of severe FTR with conservative means in AF patients is not uncommon (22.5%) (109). A growing body of literature suggests that restoration of AF in the sinus rhythm with medical or electrical cardioversion can lead to a decrease of atrial size, annular dimensions and thus severity of the regurgitation of the atrioventricular valves (26, 82). Analogously, a number of studies in the last few years have suggested a beneficial effect on right atrial remodeling and subsequently TR severity through sufficient rhythm control early in the natural history of the disease, especially after catheter ablation of AF (31, 103). Most of these are retrospective, observational investigations, however they demonstrated that catheter ablation can lead to an improvement of echocardiographic parameters like the TR jet area, the RAA and the TA diameter (38, 68, 69, 105) as well as of the TR grade (38, 51, 68, 100, 105). More specifically, Itakura et al. demonstrated that restoring sinus rhythm through catheter ablation in patients with persistent AF decreased right atrial size, correlating with a change in tricuspid regurgitant jet area (38). In a similar manner, Nishiwaki et al. documented a significant

improvement of TR severity, TR jet area as well as RA and LA area after catheter ablation for AF (68). Markmann et al. observed that rhythm control and thus preservation of SR may have a durable effect on the atrial hemodynamics, promoting an improvement of TR (51), which correlates with the findings of Topilsky et al. (96) and Gertz et al. (26). However, there are some important limitations that need to be acknowledged. For instance, Soulat-Dufour et al. (89) assessed TR severity only by the Vena contracta method, and did not report severity according to the ESC guidelines. Moreover, Nishiwaki et al. (68) as well as Markmann et al. (51) studied only small patient cohorts, and focused mainly on patients with advanced TR. Nonetheless, this body of literature hints at a possible beneficial effect of catheter ablation on right atrial hemodynamics as well as TR severity, which could have therapeutic implications for patients with TR of 'atrial' origin. Following this line of thought, in our study, a significant improvement of the size of the LA (LAVi 43.6 ± 13.2 vs. 39.9 ± 12.1 mL/m²; p<0.001) and the RA (mean RAA 19.8 ± 5.6 vs. 18.7 ± 5.6 cm²; p<0.001) after the ablation could be documented. Moreover, the severity of TR improved throughout the follow-up in a significant proportion of the patients (13.2% vs. 7.2%; p<0.001). A similar pattern was observed when examining the progression of MR (10.9% vs. 6.6%; p<0.001). Thus, our findings support the beneficial effect of rhythm control through ablation on the atrial hemodynamics as well as on the AVVR severity.

In our study, patients with a relevant improvement of the TR grade (n=19) were more likely to have a smaller RA at baseline (RAA 20.2 ± 4.4 vs. 26.6 ± 8.3 cm²; p=0.002) in comparison to those with persistent significant TR throughout the follow-up, without significant differences regarding the rates of persistent AF or concomitant MR. These findings further highlight the underlying pathomechanism in patients with TR. When re-examining patients with and without TR at the echocardiographic follow-up appointment 6 months after PVI, some changes were observed compared to the baseline features: along with the differences already displayed at baseline, like older age, a more frequent concomitant MR, a dilated RA, signs of pulmonary hypertension and higher rates of persistent AF, patients with significant TR at follow-up also had higher rates of CKD (21.7% vs. 8.1%; p=0.028) as well as a dilated LA (LAVi 48.8 ± 12.9 vs. 43.3 ± 13.2 mL/m²; p=0.066) at baseline, compared to those without one. The even higher prevalence of persistent AF in these patients (69.6%) could hint at a more advanced right atrial remodeling: tricuspid regurgitation cases which could not be aided by rhythm control through PVI are more likely to have had persistent and possibly longer lasting AF, which could cause more severe and potentially non-reversible changes in the RA.

Of note, patients without recurrence of atrial arrhythmia during the follow-up were more likely to have had an improvement in the TR grade after PVI (60% vs. 32%; p=0.070). However, this

change narrowly did not reach statistical significance, possibly due to small sample size. Similar results have already been described in other investigations, where it was demonstrated that the absence of atrial arrhythmia recurrence after catheter ablation was associated with an improvement in TR-severity (51, 100). Interestingly, the grade of MR did not improve significantly more in patients without a recurrence of atrial arrhythmia (42% vs. 33%; p=0.648). These findings could hint at a closer interplay between AF and the tricuspid valve; just as the TA dilates more easily at the presence of AF, it could be hypothesized that a restoration of the sinus rhythm, especially early at the natural history of the disease, could halt or even reverse the structural remodeling.

All in all, our study supports the existing data regarding the possible beneficial role of catheter ablation in atrial hemodynamics and specifically in AVVR severity. As previously mentioned, only a very small fraction of the patients, not only in our study population but also in the existing literature, seems to develop a severe or even torrential TR related to AF. However, it must be mentioned, that patients with severe AVVR are seldom referred to PVI in clinical practice. So, whether catheter ablation at the early stage of the disease could play a role on halting its progression or even on reverting an already advanced disease demands further investigation.

7.5. Role of atrioventricular valve regurgitation in atrial arrhythmia recurrence after pulmonary vein isolation

It has already been demonstrated that AVVR may represent an important risk factor for the onset and persistence of AF. It remains to be made clear whether a preexisting AVVR and especially TR triggers the appearance of AF or whether a long-lasting AF leads to functional AVVR by right atrial dilatation. In this cycle, the identification of the leading pathomechanism can pose a clinical challenge and greatly impact the therapeutic approach (60). Gertz et al. displayed that MR was associated with worse arrhythmic outcome after PVI, an impact mainly affected by LA size (27). Zhao et al. demonstrated that the MR grade was independently associated with atrial arrhythmia recurrence in patients with long-standing AF (110). In line with LA size (82), right atrial structural remodeling has also been shown to pose a risk for AF-recurrences after PVI (90), especially with concurrent LA enlargement (107). However, some of these studies had a serious limitation in that the effects of TR were not properly clarified. For example, in the analysis by Gertz et al. the presence of TR was not documented. Similarly, Zhao et al. singled out significant MR as the valve regurgitation most frequently leading to AF recurrence, but patients with exclusively MR and TR were not directly compared.

Considering that TR is more common in patients with AF, the role of TR in atrial arrhythmia recurrence should be further investigated. In this direction, interesting findings of observational studies have hinted at the role of TR as a predictor of AF-recurrences after catheter ablation (51, 64, 100). These were in accordance with our investigation, as the presence of significant TR at baseline was associated with a worse post-interventional outcome in terms of atrial arrhythmia recurrence (HR 2.00 [95% CI, 1.10 – 3.60]; p=0.017), which remained significant in multivariate Cox regression as well as in a subgroup of patients after propensity score matching. Additionally, patients with exclusively TR had more frequently a recurrence of atrial arrhythmia after the ablation in comparison to those with exclusively MR (64% vs. 23%, HR 2.56 [95% CI, 0.94 - 6.97]; p=0.056).

However, another trial composed of patients with moderate to severe TR, failed to show a significant interaction between one-year recurrence of AF and TR severity at pre-ablation echocardiography (68). This finding could be possibly explained by our data: our analysis was the first one to show that the presence of moderate to severe TR 6 months after the ablation was an even stronger independent predictor for atrial arrhythmia recurrences after the ablation (HR 2.50 [95% CI, 1.44 - 4.36]; p<0.001). Analogously, we found that patients with improvement of TR grade tended to less likely suffer from atrial arrhythmia recurrences than those with persistent relevant TR throughout the follow-up (HR 2.40 [95% CI, 0.90 – 5.90]; p=0.070), which was also reported by Markman et al. (51). The absence of improvement in the TR severity could hint at a more pronounced right atrial remodeling, which cannot be altered by the conventional PVI. Thus, these findings pose a challenge to properly identify the ‘high risk’ patients who won’t benefit from a conventional PVI and who are more likely to suffer from atrial arrhythmia recurrence.

On the other hand, significant MR was not associated in our analysis with an increased risk of arrhythmia recurrences, either at baseline or at follow-up. Of note, Nakamura et al. found that not MR itself, but only the combination of MR and TR served as a risk predictor regarding arrhythmia recurrences in 239 AF patients that underwent catheter ablation (64). In our analysis, the presence of significant TR and MR was surprisingly not associated with a worse outcome, possibly due to small sample size. Furthermore, patients without a recurrence of atrial arrhythmia in our analysis were not more likely to experience an improvement in MR. These findings suggest that TR and not MR severity could be more strongly connected to the development of an arrhythmia substrate, leading to recurrences after PVI.

7.6. Future considerations

All in all, our data support the growing amount of evidence that RA enlargement as well as relevant TR could play an equal, if not greater, role in the development and progression of atrial arrhythmias, compared to the better-established risk factor of LA enlargement and MR severity. In our analysis of 320 patients undergoing PVI for the first time due to symptomatic AF, we demonstrated that TR severity is an independent risk predictor for atrial arrhythmia recurrence after catheter ablation, which proved far more significant than the presence of MR. In this direction, the categorization of AF patients according to the presence of AVVR is of paramount importance, in order to better understand and treat the underlying electrophysiologic substrate. These findings imply that a deeper anatomical and electrophysiological connection between TR and AF may exist. Patients with significant TR and advanced right atrial remodeling could be stratified as 'high risk' cases and could require an individualized therapeutic approach instead of conventional PVI. Interestingly, patients with persistent relevant TR throughout the follow-up despite the ablation, had high rates of persistent AF (69.6%) as well as a dilated RA. Of note, one third of them experienced a recurrence of atrial arrhythmia just within 6 months after the ablation. Thus, this echocardiographic finding after the ablation should prompt a clinical response, either through more intense medical rhythm control or through prophylactic re-ablation, focusing on the RA.

Of course, a proper intervention earlier in the history of the disease, at the time of the first ablation, would be more appropriate. In the last decades, a plethora of ectopic sources triggering atrial arrhythmia were identified outside of the pulmonary veins, including for instance the vena cavae, the crista terminalis, and the coronary sinus in the RA (15, 79). It has been demonstrated that ablation of these atrial foci originating outside of the pulmonary-veins could lead to reduction of AF-recurrence rates (34). Considering the specific features of patients with AF and FTR, it is tempting to hypothesize that a contrasting, underlying electrophysiological substrate revolving the RA may warrant tailored ablation strategies. In our study, the presence of significant TR was more prominent in patients receiving an additional ablation of the cavotricuspid isthmus at the time of the PVI due to history of right atrial flutter. Furthermore, the presence of significant TR in this smaller group continued to be associated with a far worse outcome (atrial arrhythmia recurrence 46% vs. 13%; $p<0.001$). On the other hand, when examining the subgroup of patients with significant TR, the presence of right atrial flutter was surprisingly associated with a worse outcome, despite the successful additional ablation of the cavotricuspid isthmus. As a result, patients with significant TR at baseline and right atrial flutter had the worst arrhythmic outcome among the population. It could be argued, that in some of the patients with significant TR, the development of a more complex right atrial

arrhythmogenic substrate has occurred, which was ‘represented’ by the concomitant presence of right atrial flutter. Thus, a detailed mapping of the RA and subsequently more sophisticated ablation strategies could be required for these patients. Hocini et al. demonstrated that an additional ablation of the RA substrate was required to achieve durable long-term results in patients without prolongation of AF cycle length, who tended to have a larger RA diameter (35). Further trials to better understand the underlying right atrial substrate as well as to examine possible ablation strategies for patients with advanced right atrial remodeling are needed.

7.7. Limitations

Our explorative analysis had some limitations. First of all, this was a retrospective analysis, performed at a single center. Secondly, although the categorization of AVVR severity was in compliance with the current ESC guidelines, the vena contracta and effective regurgitant orifice area (EROA) was not routinely measured in all patients. Particularly in those with mild AVVR, EROA measurement was often not feasible. Furthermore, we did not routinely conduct more thorough measurements of the TA and thus could not investigate the relationship among RA enlargement, TA dilatation and TR severity. Thirdly, as our study included patients undergoing PVI due to symptomatic AF, this means that we did not include exclusively patients with an ‘iTR’ or ‘AF-TR’ but rather with a multifactorial TR. However, although TR can develop exclusively in the setting of AF, the presence of TR regardless of its cause could still alter the atrial substrate and thus predict the risk of recurrences after PVI. Furthermore, in the whole population as well as the patients with TR, a sufficient cause for the development of TR other than AF could not be found; the rates of heart failure and pulmonary disease were low and comparable between the groups, while signs of pulmonary hypertension were only mild. A fourth limitation of our study was that 6 months might not be enough time to assess beneficial effects of PVI treatment on atrial remodeling, and therefore AVVR severity. Furthermore, we did not take into consideration possible medication changes or other clinical entities which could have altered the severity of AVVR. Additionally, the duration of the follow-up was rather short and recurrences as well as burden of atrial arrhythmia were not followed closely (eg. implantable cardiac monitor) and thus we could not fully assess the effect of AVVR regarding atrial arrhythmia recurrences in the long term. Finally, although rates of persistent AF were relatively high, the duration of AF at baseline was not documented.

7.8. Conclusion

In conclusion, we demonstrated that a reasonable number of patients who undergo PVI for the first time due to symptomatic AF have a significant AVVR (TR 13.1%, MR 10.9%). Functional AVVR can occur in the setting of AF, as these patients tend to have a dilated atrium. Tricuspid and mitral regurgitation severity decreased in a significant proportion of the population within 6 months after AF ablation. However, whether the effect of catheter ablation could halt the long-term progression of AVVR or if these findings could also be applied to more severe cases of AVVR related to AF remains to be seen. In addition, the presence of AVVR can lead through volume overloading to atrial remodeling and thus the development of an arrhythmogenic substrate. In our analysis, patients with moderate to severe TR, especially without improvement during the follow-up period after the ablation, had an increased risk of atrial arrhythmia recurrences. Persistent TR was particularly documented in patients with pronounced right atrial dilatation, suggesting advanced right atrial remodeling. Future trials are needed to better understand the underlying atrial substrate, and to improve the therapeutic options for these patients.

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9. Publications/ Acknowledgements

9.1. Publications

The following presentation was made during the preparation of the doctoral thesis:

- D. Bismpos, J. Wintrich, A. Teusch, V. Pavlicek, M. Böhm, F. Mahfoud, C. Ukena; Impact of tricuspid regurgitation on atrial fibrillation recurrence after pulmonary vein isolation, 89. DGK-Jahrestagung

The publication of the following supplementary analysis was underway at the time of the submission of the doctoral thesis:

- J. Wintrich, D. Bismpos, A. Teusch, V. Pavlicek, P. Fischer, F. Mahfoud, M. Böhm, C.Ukena ; Severity of tricuspid regurgitation predicts risk of atrial fibrillation recurrence after pulmonary vein isolation

Other publications

- Bismpos D., Wintrich J., Hövelmann J., Böhm M. Latest pharmaceutical approaches across the spectrum of heart failure (under publication, Heart Failure Reviews)
- Whitlock RP, Belley-Cote EP, Paparella D, et al. Left Atrial Appendage Occlusion during Cardiac Surgery to Prevent Stroke [published online ahead of print, 2021 May 15]. N Engl J Med. 2021;10.1056/NEJMoa2101897. doi:10.1056/NEJMoa2101897 (Investigator)
- Bismpos D., Ketikoglou D. Recent advances in Functional Tricuspid Regurgitation.hellenicjcardiol, [S.l.],v.61,n.6,p.418-430,feb.2021
- Bismpos D., Ketikoglou D. Recent advances in Takotsubo Syndrome, hellenicjcardiol, [S.l.], v. 62, n. 2, p. 157-172, aug. 2021
- Tigkiropoulos K, Papoutsis I, Abatzis-Papadopoulos M, et al. Thirty-Day Results of the Novel CGuard-Covered Stent in Patients Undergoing Carotid Artery Stenting. Journal of Endovascular Therapy. April 2021. doi:10.1177/15266028211007466
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- Tirta M.,Balapanidis C.,Bismpos D.,Zarifis H.,Tzamou V.,Sidiropoulou D.,Bitzika S.,Timotheadou E. Primary Prevention of Lung Cancer.Smoking Habits and Opinion of Greek Medical Students About Smoke-Free Legislation.

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10. Curriculum Vitae

The curriculum vitae was removed from the electronic version of the doctoral thesis for reasons of data protection.

Tag der Promotion: 30. September 2024

Dekan: Univ.-Prof. Dr. med. M. D. Menger

Berichterstatter: Prof. Dr. Christian Ukena

Prof. Dr. Hashim Abdul-Khaliq