JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
VOL. 84, NO. 2, 2024

PUBLISHED BY ELSEVIER

JACC STATE-OF-THE-ART REVIEW

Tricuspid Regurgitation in Patients With Heart Failure and Preserved Ejection Fraction

JACC State-of-the-Art Review

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ABSTRACT

Heart failure with preserved ejection fraction (HFpEF) is associated with high morbidity and mortality. Important risk factors for the development of HFpEF are similar to risk factors for the progression of tricuspid regurgitation (TR), and both conditions frequently coexist and thus is a distinct phenotype or a marker for advanced HF. Many patients with severe, symptomatic atrial secondary TR have been enrolled in current transcatheter device trials, and may represent patients at an advanced stage of HFpEF. Management of HFpEF thus may affect the pathophysiology of TR, and the physiologic changes that occur following transcatheter treatment of TR, may also impact symptoms and outcomes in patients with HFpEF. This review discusses these issues and suggests possible management strategies for these patients. (J Am Coll Cardiol 2024;84:195–212) © 2024 by the American College of Cardiology Foundation.

Heart failure with preserved ejection fraction (HFpEF) is a highly prevalent disease, accounting for up to 50% of all patients with heart failure (HF), associated with high morbidity and mortality.[1,2] HFpEF has become the dominant HF subtype, and is a common cause of dyspnea, exercise intolerance, hospitalizations, and mortality.[2] With increased understanding of HFpEF, there has been a growing interest in tricuspid regurgitation (TR), which is often associated with HFpEF (up to 40% of patients) and may ultimately prove treatable with pharmacologic and/or percutaneous interventions.[3,4] A report of 714,368 patient records showed the prevalence of valvular heart disease in the United States is highest in women, with TR being the most common (7.1%), followed by mitral regurgitation

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Review and acceptance occurred under Dr Valentin Fuster's term as Editor-in-Chief.
The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received February 7, 2024; revised manuscript received March 28, 2024, accepted April 2, 2024.

Listen to this manuscript's audio summary by Editor Emeritus Dr Valentin Fuster on www.jacc.org/journal/jacc.

ISSN 0735-1097/$36.00
https://doi.org/10.1016/j.jacc.2024.04.047

ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

A-STR = atrial secondary tricuspid regurgitation

HFpEF = heart failure with preserved ejection fraction

LA = left atrial

LV = left ventricular

PASP = pulmonary artery systolic pressure

PCWP = pulmonary capillary wedge pressure

RV = right ventricular

T-TEER = transcatheter tricuspid valve edge-to-edge repair

TR = tricuspid regurgitation

(MR) (6.5%), aortic stenosis (4.1%), aortic regurgitation (2.3%), and mitral stenosis (0.5%).[5] A recent analysis of the ESC-HFA (European Society of Cardiology Heart Failure Association) Long-Term Registry showed a prevalence of moderate/severe isolated mitral regurgitation, isolated TR, and combined MR and TR of 17%, 5.5%, and 11%, respectively, among patients with HF.[6] Patients with HFpEF had only one-half the risk of isolated MR (OR: 0.42) but double the risk of isolated TR (OR: 1.93). Isolated TR was independently associated with a poorer outcome.

Current registries as well as device trials for symptomatic severe TR have enrolled patients whose age is >70 years, left ventricular ejection fraction (LVEF) ≥50%, and with frequent atrial fibrillation (AF) (**Table 1**).[7-9] The EuroTR registry,[10] an international registry including patients who underwent percutaneous treatment of severe TR, reported that 72% of patients had a LVEF ≥50%. In a subgroup of patients with right heart catheterization data, 68% had a pulmonary capillary wedge pressure (PCWP) ≥15 mm Hg, suggesting many of these patients have HFpEF. This review will offer some insight into the relationship between HFpEF and TR, and suggest possible management strategies.

DEFINITIONS AND RISK FACTORS FOR HFpEF AND TR

Guidelines and consensus statements have supported a clinical definition of HFpEF as LVEF ≥50%, with evidence of increased resting or exercise-induced LV filling pressures.[11-14] Risk factors for HFpEF include age, hypertension, ischemic heart disease, obesity, metabolic dysfunction, and physical inactivity.[2] Some of these predictive parameters for HFpEF are components of the H_2FPEF score (**Figure 1A**)[15] including obesity, AF, age >60 years, treatment with ≥2 antihypertensive medications, echocardiographic early mitral inflow velocity to tissue Doppler annular early relaxation velocity (E/e′) ratio >9, and echocardiographic pulmonary artery systolic pressure (PASP) >35 mm Hg.[13,15] Evidence for increased left ventricular (LV) filling pressures could also include elevated natriuretic peptide levels and noninvasive and invasive hemodynamic measurements.[13] Supportive evidence of structural heart disease includes an increase in left atrial (LA) size and volume and/or an increase in LV mass. Additional metrics have been used in the HFA-PEFF (HF Association Pre-test assessment, Echocardiography & natriuretic peptide, Functional testing, Final etiology) scores from the European Society of Cardiology (**Figure 1B**)[16] and are commonly used as inclusion criteria together with natriuretic peptides in HFpEF clinical trials.[17]

The 4 population attributable risk factors that predict progression of TR mirror those of HFpEF, including PASP of ≥36 mm Hg, LA enlargement, age ≥60 years, and history of AF.[18] A new TR etiology classification has been developed which separates patients into 4 categories: primary TR, which abnormal leaflet anatomy, cardiac implantable electronic device (CIED)-related TR, atrial secondary tricuspid regurgitation (A-STR), and ventricular secondary tricuspid regurgitation (V-STR).[19,20] Within the new classifications of TR etiology, the phenotype of patients with HFpEF and TR is most likely A-STR. Multiple definitions of A-STR have been proposed. The 2021 American College of Cardiology/American Heart Association guidelines characterize "isolated" or A-STR as patients with AF, LVEF >60%, PASP <50 mm Hg, and absence of left-sided valve disease, with normal-appearing tricuspid valve (TV) leaflets.[21] More recently, a clustering approach has been used to define A-STR as TV tenting height ≤10 mm, mid chamber right ventricular (RV) diameter ≤38 mm, and LVEF ≥50%.[22] Although the Tricuspid Valve Academic Research Consortium has attempted to strictly define criteria for A-STR and V-STR (**Table 2**), chronic volume overload may result in maladaptive remodeling of the RV such that differentiating atrial from ventricular secondary disease becomes more difficult, and many patients present with overlapping phenotypes.[20,23]

The similarities of predictive parameters as well as common clinical presentation have led investigators to presume that HFpEF and TR may indeed be related (**Central Illustration**). The prevalence of moderate/severe TR in the general population is ~3% to 6%; however, in patients with HF (with reduced or preserved ejection fraction [EF]), the prevalence is 10% to 29%,[6,24,25] and up to 39% in patients with HFpEF and AF.[25] Both HFpEF[2,26] and TR[27] are more prevalent in women in the older age group. Population studies of valvular heart disease have found a 4:1 female-to-male prevalence of TR by the eighth decade of life, and early feasibility trials for a variety of transcatheter TV devices have enrolled >70% females.[28-30] Interestingly, females with HFpEF tend to have a poorer quality of life but better survival, which may play a role in outcomes for TR device therapies.[26] New onset AF, another key risk factor for TR, is associated with a higher risk for prevalent and incident diastolic dysfunction, greater burden of TR, and high probability of underlying HFpEF.[31] Only one

TABLE 1 Comparison of Baseline Clinical Characteristics in TRILUMINATE Pivotal, TRISCEND EFS, and TRISCEND II

	TRILUMINATE T-TEER Group (N = 175)	TRILUMINATE Control Group (N = 175)	TRISCEND EFS (N = 176)	TRISCEND II TTVR Group (N = 96)[a]	TRISCEND II Control Group (N = 54)[a]
Age, y	78.0 ± 7.4	77.8 ± 7.2	78.7 ± 7.3	79.4 ± 7.7	78.2 ± 8.3
Female	56.0	53.7	71.0	82.3	75.9
NYHA functional class III/IV	59.4	55.4	75.4	79.2	75.9
KCCQ score	56.0 ± 23.4	54.1 ± 24.2	46.0 ± 21.8	49.1 ± 21.5	49.7 ± 22.3
HFH within 1 y	25.1	25.1	40.8	31.3	31.5
Hypertension	81.1	80.6	84.1	91.7	87.0
Diabetes mellitus	16.0	15.4	20.5	NR	NR
Atrial fibrillation	87.4	92.6	92.0	97.9	96.3
Prior stroke	6.3	10.9	13.6	19.8	5.6
Renal dysfunction	35.4	35.4	58.5	50.0	57.4
COPD	10.9	13.7	NR	19.8	16.7
PVD	9.1	10.3	6.3	NR	NR
Prior CABG	17.7	20.6	16.5	10.4	24.1
LVEF, %	59.3 ± 9.3	58.7 ± 10.5	55.3 ± 10.5	55.1 ± 8.6	52.4 ± 11.6
RV TAPSE, mm	1.6 ± 0.4	1.6 ± 0.4	15.3 ± 5.2	NR	NR
RV FAC, %	36.6 ± 5.5	37.2 ± 6.3	37.6 ± 9.3	NR	NR
Baseline PASP, mm Hg[b]	39.7 ± 9.2	40.1 ± 10.1	40.1 ± 10.5	NR	NR
Baseline PCWP, mm Hg[b]	14.8 ± 4.6	15.1 ± 4.3	NR	NR	NR
Baseline PVR, WU[b]	2.5 ± 1.1	2.4 ± 1.1	NR	NR	NR
Prior aortic intervention	15.4	15.4	18.8	NR	NR
Prior mitral intervention	19	22.8	26.1	NR	NR
Functional TR	94.8	92.9	82.4[a]	77.4[a]	70.4[a]
Baseline TR severity					
Moderate	2.3	1.2	11.9	0	0
≥Severe	97.3	98.3	98.1	100	100
Permanent PPM/ICD	16.0	13.7	32.4	36.5	42.6

Values are mean ± SD or %. [a]Report of the first 150 patients, complete data set pending. [b]Measured at or derived from invasive right heart catheterization.

CABG = coronary artery bypass grafting; COPD = chronic obstructive pulmonary disease; EFS = early feasibility study; FAC = fractional area change; HFH = heart failure hospitalization; ICD = implantable cardioverter-defibrillator; KCCQ = Kansas City Cardiomyopathy Questionnaire; LVEF = left ventricular ejection fraction; MV = mitral valve; NR = not reported; PASP = pulmonary artery systolic pressure; PCWP = pulmonary capillary wedge pressure; PPM = permanent pacemaker; PVD = peripheral vascular disease; PVR = pulmonary vascular resistance; RV = right ventricular; T-TEER = transcatheter tricuspid valve edge-to-edge repair; TAPSE = tricuspid annular plane systolic excursion; TR = tricuspid regurgitation; TRILUMINATE = The Trial to Evaluate Cardiovascular Outcomes in Patients Treated with the Tricuspid Valve Repair System; TRISCEND = Tricuspid Valve Replacement: Investigation of Safety and Clinical Efficacy after Replacement of Tricuspid Valve with Transcatheter Device.

study has evaluated longitudinal changes in TR in patients with HFpEF. Obokata et al[25] showed that the prevalence of RV dysfunction increased over time, and the strongest risk factors were prevalent and incident AF. The prevalence of moderate or severe TR increased from 15% to 39% in patients developing new onset AF during the study period.

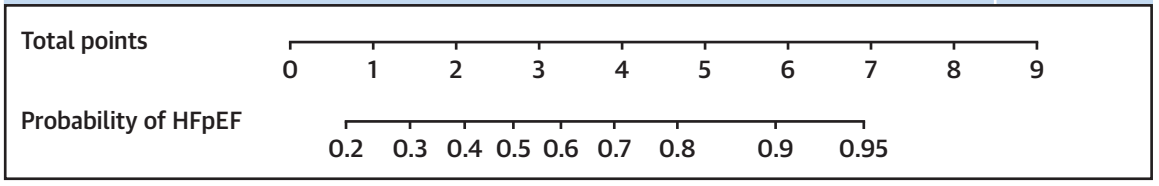
PATHOPHYSIOLOGY OF TR IN THE SETTING OF HFpEF

The pathophysiology of TR secondary to HFpEF can be explained in part by the increase in LV filling pressures (**Central Illustration**).[1,13] Postcapillary pulmonary hypertension associated with HFpEF may result in TR by several mechanisms: 1) biatrial myopathy; 2) atrial fibrillation; and 3) progressive dilatation of the RV causing an impairment of LV diastolic function through ventricular interdependence.[24] Symptoms of right HF and low cardiac output (CO) in the setting of TR may result due to: 1) reduced forward stroke volume due to regurgitation; 2) reduced RV contractility; and 3) abnormal RV-LV interaction. Because of the fixed pericardial space, progressive RV dilatation results in a leftward septal shift, contributing to reduced LV filling and abnormal diastolic LV function.[32] Reduced RV function and right HF symptoms also contribute to the poor outcomes associated with severe TR. Dietz et al[33] defined 4 stages of TR based on the presence of RV dysfunction and/or right HF symptoms: stage 3 included RV dysfunction and signs of right HF and stage 4 was defined as RV dysfunction and refractory signs of right HF at rest. Stages 3 and 4 were associated with more comorbidities and worse renal and LV systolic function and were independently associated with increased mortality compared with stage 1 (HR: 2.110; 95% CI:

FIGURE 1 Proposed Risk Scores for Prediction of HFpEF

A

	Clinical Variable	Values	Points
H_2	Heavy	Body mass index >30 kg/m^2	2
	Hypertensive	2 or more antihypertensive medicines	1
F	Atrial Fibrillation	Paroxysmal or persistent	3
P	Pulmonary Hypertension	Doppler echocardiographic estimated Pulmonary artery systolic pressure >35 mm Hg	1
E	Elder	Age >60 years	1
F	Filling Pressure	Doppler echocardiographic E/e' >9	1
H_2FPEF score			Sum (0-9)



B

	Functional	Morphological	Biomarker (SR)	Biomarker (AF)
Major	Septal e' <7 cm/s or Lateral e' <10 cm/s or Average E/e' ≥15 or TR velocity >2.8 m/s (PASP >35 mm Hg)	LAVI >34 mL/m^2 or LVMI ≥149/122 g/m^2 (m/w) and RWT >0.42	NT-proBNP >220 pg/mL or BNP >80 pg/mL	NT-proBNP >660 pg/mL or BNP >240 pg/mL
Minor	Average E/e' 9-14 or GLS <16%	LAVI 29-34 mL/m^2 or LVMI >115/95 g/m^2 (m/w) or RWT> 0.42 or LV wall thickness ≥12 mm	NT-proBNP 125-220 pg/mL or BNP 35-80 pg/mL	NT-proBNP 365-660 pg/mL or BNP 105-240 pg/mL

Major Criteria: 2 points	≥5 points: HFpEF
Minor Criteria: 1 point	2-4 points: Diastolic Stress Test or Invasive Hemodynamic Measurements

(A) The H_2FPEF score, which relies on simple clinical characteristics and echocardiography, enabling discrimination of heart failure with preserved ejection fraction (HFpEF) from noncardiac causes of dyspnea. (B) The HFA-PEFF (HF Association Pre-test assessment, Echocardiography & natriuretic peptide, Functional testing, Final aetiology) score uses functional, morphologic, and biomarker parameters to assess the likelihood of HFpEF. A total score ≥5 points is considered diagnostic of HFpEF, while a score of ≤1 point makes HFpEF unlikely. (A) Reproduced with permission from Reddy et al[15] and (B) Pieske B, Tschöpe C, de Boer RA, et al. How to diagnose heart failure with preserved ejection fraction: the HFA-PEFF diagnostic algorithm: a consensus recommendation from the Heart Failure Association (HFA) of the European Society of Cardiology (ESC). *Eur J Heart Fail*. 2020;22(3):391-412. AF = atrial fibrillation; BNP = B-type natriuretic peptide; e' = tissue Doppler mitral annular early relaxation velocity; E/e' = ratio of the Doppler early mitral inflow velocity to e'; GLS = global longitudinal strain; LAVI = left atrial volume index; LV = left ventricular; LVMI = left ventricular mass index; m/w = men/women; NT-proBNP = N-terminal pro-B-type natriuretic peptide; PASP = pulmonary artery systolic pressure; RWT = relative wall thickness; SR = sinus rhythm; TR = tricuspid regurgitation.

1.163-3.828; and HR: 3.318; 95% CI: 1.795-6.133, respectively).[33]

CLINICAL PRESENTATION

Right HF associated with TR can be characterized by: 1) systemic fluid retention, leading to elevated jugular venous pressure, peripheral edema, ascites, hepatic distention, reduced intestinal absorption, and anasarca; 2) decreased systolic reserve and low CO, resulting in exercise intolerance, dyspnea, and fatigue; and 3) atrial or ventricular arrhythmias. Significant chronic TR is associated with signs and symptoms of profound reduction in CO including malnutrition, anemia, and reduced cognitive function.[34] The downstream consequences of chronic severe TR and right HF include chronic kidney disease (cardiorenal syndrome) and liver disease (cardiohepatic syndrome).

A small study of patients with TR showed that PCWP and RA pressure were low at rest, but with exercise both measures increased with a larger increase in RA pressure, resulting in a decrease in transmural pressure (measured as PCWP minus RA pressure) and inadequate LV diastolic filling (**Figure 2**).[35] Thus impaired exercise capacity (and symptoms of dyspnea on exertion) in patients with TR is related not only to reduced CO reserve, but also elevated systemic and pulmonary venous pressure in the setting of diastolic dysfunction, features that one could also describe for patients with HFpEF.

Patients with HFpEF may also develop impaired RV dysfunction. Obokata et al[25] showed that over a median follow-up time of 4 years, there was a 10% decline in RV fractional area change and 21% increase in RV diastolic area, with no change in LV size or function. The prevalence of TR increased by 45% likely related to RV remodeling (**Figure 3**). Impaired RV function and dilatation were also associated with both prevalent and incident AF. Thus, the RV failure and TR phenotype may represent not a separate phenotype, but rather a more advanced stage, in the progression from exercise-induced elevation in filling pressure, to pulmonary hypertension, to RV dilatation and failure and both atrial and ventricular STR.[2] These patients with HFpEF and more severe RV dysfunction may accordingly be prone to development of both A-STR and V-STR.

AF is a strong predictor of developing significant TR[18,36] and may also be a marker for HFpEF because many or most patients with AF and dyspnea, in fact, have HFpEF.[15,37] In the ESC-HFA registry, AF was associated most strongly with isolated TR (OR for isolated TR: 3.63; for isolated MR: 1.24; for combined MR/TR: 2.50).[6] Among 21 risk markers studied, AF was the strongest risk marker for isolated TR, even stronger than female sex and HFpEF. This strong association between AF and isolated TR persisted after multivariable adjustment (OR: 2.78). Echocardiographic measures of LA strain or LA volume can predict the probability of developing AF.[37] Using artificial intelligence-enabled electrocardiography (ECG) deep learning algorithms to detect the probability of AF in patients with HFpEF, investigators found a higher probability of AF was associated with progressively lower LA reservoir strain and a progressively higher prevalence of TR (**Figure 4A**).[38] AF is associated with atrial and annular enlargement, resulting in both atrial secondary MR[39] and A-STR.[40] In patients with AF and LV dysfunction, the tricuspid and mitral annular dilatation are equally

TABLE 2 Suggested Anatomic and Functional Parameters to Define A-STR and V-STR

	A-STR Phenotype[a]	V-STR Phenotype[a]
Leaflet morphology[b]		
Tenting height (4Ch), mm	≤9	>9
Tenting area (4Ch), cm^2	<2.1	≥2.1
Tenting volume, mL	<2.5[c]	≥2.5
Right heart chamber size[b]		
RV midventricular diameter, mm	≤38[c]	>38
RV midventricular diameter index, mm/m^2	<21	≥21
RV end-diastolic volume index, mL/m^2	<80	≥80
RV end-systolic volume index, mL/m^2	<21	≥21
2D sphericity index[d]	<55	≥55
End-systolic RA:RV area ratio[d]	>1.5	<1.5
RV systolic function[b]		
TAPSE, mm	>17	<17
FAC, %	≥35	<35
RVFWS, %	≥20	<20
RV TDI S′, cm/s	≥9	<9
3D RVEF, %	≥50	<50
LVEF, %	≥50[c]	(variable)[e]
Invasive pulmonary vascular hemodynamics[b]		
PCWP, mm Hg	≤15	(variable)[e]
mPAP, mm Hg	<20	usually >20[e]
PVR, WU	<2.0	(variable)[e]

Reproduced with permission from Hahn et al.[20] [a]Assumes no primary TR or cardiac implantable electronic device-causative TR. [b]In the setting of discordant measures within the anatomic or functional categories, an integrative approach should be used to define A-STR (absence of significant leaflet tethering in the setting of a dilated right atrium, and normal RV size and function) and V-STR (significant leaflet tethering with dilated RV). Within each category, the volumetric assessment and the indexed values may be preferred for research studies when available. [c]From Schlotter et al.[22] [d]From Florescu DR, Muraru D, Florescu D, et al. Right heart chambers geometry and function in patients with the atrial and the ventricular phenotypes of functional tricuspid regurgitation. *Eur Heart J Cardiovasc Imaging*. 2022;23(7):930-940. [e]Critieria cannot be strictly defined given the heterogeneous etiologies of V-STR (ie, precapillary, postcapillary, or combined pre/postcapillary pulmonary hypertension, and primary RV cardiomyopathies).

2D = 2-dimensional; 3D = 3-dimensional; 4Ch = 4-chamber view; A-STR = atrial secondary tricuspid regurgitation; LV = left ventricular; mPAP = mean pulmonary artery pressure; RA = right atrial; RVEF = right ventricular ejection fraction; RVFWS = right ventricular free wall strain; TDI = tissue Doppler imaging; V-STR = ventricular secondary tricuspid regurgitation; other abbreviations as in **Table 1**.

CENTRAL ILLUSTRATION **Clinical Characteristics, Pathophysiology, and Management Strategy of HFpEF and TR**

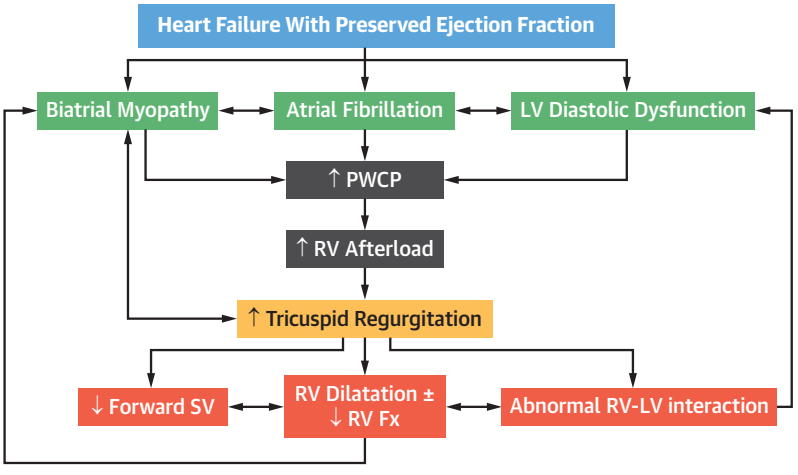
A Risk Factors for HFpEF and A-STR

Risk Factors and Findings of Symptomatic HFpEF	Criteria Identifying High Risk for A-STR
• Advanced age (age ≥70 y in ♂ or ≥75 y in ♀)	• Elderly patient (>70 y)
• Female	• Female
• Overweight/obesity	• Nonparoxysmal AF (or atrial flutter)
• Metabolic syndrome/diabetes mellitus	• Rate control strategy
• Arterial hypertension	• HFpEF
• Concentric LV hypertrophy with reduced LV compliance with reduced LA function	• Tricuspid annular dilation
• Atrial fibrillation	• Mild A-STR with RA dilation and increased end-systolic RA:RV area ratio (>2.1)
• Elevated natriuretic peptide levels (if available, BNP ≥35 pg/mL or NT-proBNP ≥125 pg/mL)	• A-SMR
	• Intermediate likelihood for PH (peak TRV 2.9-3.4 m/s)

After Pieske B, et al. How to diagnose heart failure with preserved ejection fraction: the HFA-PEFF diagnostic algorithm: a consensus recommendation from the Heart Failure Association (HFA) of the European Society of Cardiology (ESC). Eur J Heart Fail. 2020;22(3):391-412.

After Muraru D, et al. Atrial secondary tricuspid regurgitation: pathophysiology, definition, diagnosis, and treatment. Eur Heart J. 2024;45(11):865-911.

B Pathophysiology of HFpEF and TR



Hahn RT, et al. J Am Coll Cardiol. 2024;84(2):195-212.

(A) The risk factors associated with heart failure with preserved ejection fraction (HFpEF) and parameters that identify a high risk for progression to significant, symptomatic tricuspid regurgitation (TR). Importantly, HFpEF is a risk factor for development of atrial secondary tricuspid regurgitation (A-STR). (B) A schematic of the interrelationship of pathophysiologic factors associated with HFpEF and how these can result in TR. (C) A diagnostic and management algorithm for patients with HFpEF and TR. 4Ch = 4-chamber view; A-SMR = atrial secondary mitral regurgitation; AF = atrial fibrillation; BNP = B-type natriuretic peptide; CIED = cardiac implantable electronic device; HF = heart failure; LA = left atrial; LV = left ventricular; NT-proBNP = N-terminal pro-B-type natriuretic peptide; PCWP = pulmonary capillary wedge pressure; PH = pulmonary hypertension; RA = right atrial; RV = right ventricular; SV = stroke volume.

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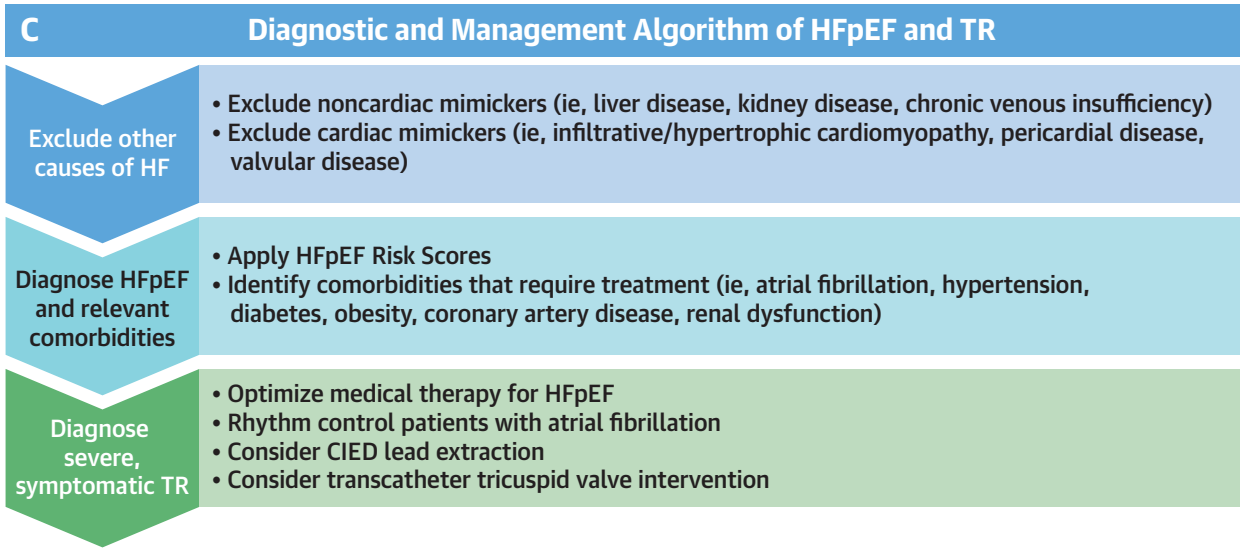
CENTRAL ILLUSTRATION Continued



Hahn RT, et al. J Am Coll Cardiol. 2024;84(2):195–212.

dilated. However in patients with normal LV function, likely representing a HFpEF population, AF was associated with greater tricuspid than mitral annular dilation.[41] Because tricuspid annular dimensions and RA volumes are closely associated with TR severity,[42] HFpEF and AF both likely contribute to an A-STR phenotype.

Biatrial myopathy is now recognized to be increasingly common in patients with HFpEF. In a study of HFpEF patients functional assessment by strain imaging, patients could be grouped into those with no atrial myopathy (26%), patients with isolated RA myopathy (4%), patients with isolated LA myopathy (31%), and patients with biatrial myopathy (39%).[43] With each successive group, there was a direct association with age, inverse association with body mass index and obesity, worse renal function, and higher N-terminal pro-B-type natriuretic peptide (NT-proBNP). Each successive group had progressively lower LA strain with a markedly increased prevalence of significant TR in the patients with biatrial myopathy (**Figure 4B**). Patients with biatrial myopathy had the lowest CO, less ability to increased CO despite an increase in central venous pressure, and worse event-free survival. Importantly, studies have now shown that restoration of sinus rhythm can induce anatomical and/or functional cardiac chamber reverse remodeling and reduce severity of functional regurgitation.[44]

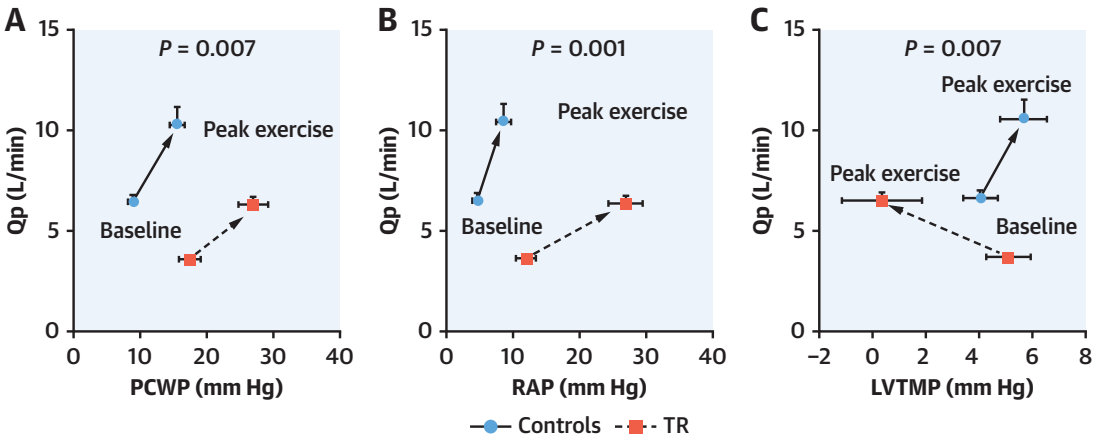
Functional MR and TR are common in HFpEF,[37,43,45] usually of mild or moderate severity. These valve lesions relate in large part to underlying atrial myopathy of the left and/or right atrium, and are associated with more adverse hemodynamic responses to exercise, poorer CO reserve, and more severe impairments in exercise capacity. It is important to identify HFpEF in these settings so that appropriate treatment can be administered.

In later stages of HFpEF disease progression, patients may develop pulmonary vascular remodeling and elevation in pulmonary vascular resistance from functional vasoconstriction and in some cases pulmonary arterial and venous remodeling.[46] This leads to combined pre- and postcapillary pulmonary hypertension. These patients have more pulmonary edema, poorer exercise capacity, and higher risk of death or HF hospitalization, and likely, greater severity of TR.[47] The development of significant TR may contribute to combined pre- and postcapillary pulmonary hypertension with the change in diastolic function previously discussed.

GUIDELINE-DIRECTED MANAGEMENT OF HFpEF AND OF TR

The guideline-directed management of HFpEF focuses on: 1) risk stratification and management of comorbidities; 2) nonpharmacological management, including the role of exercise and weight loss and the use of wireless, implantable pulmonary artery pressure monitors; and 3) symptom management and disease-modifying therapy with loop diuretic agents,

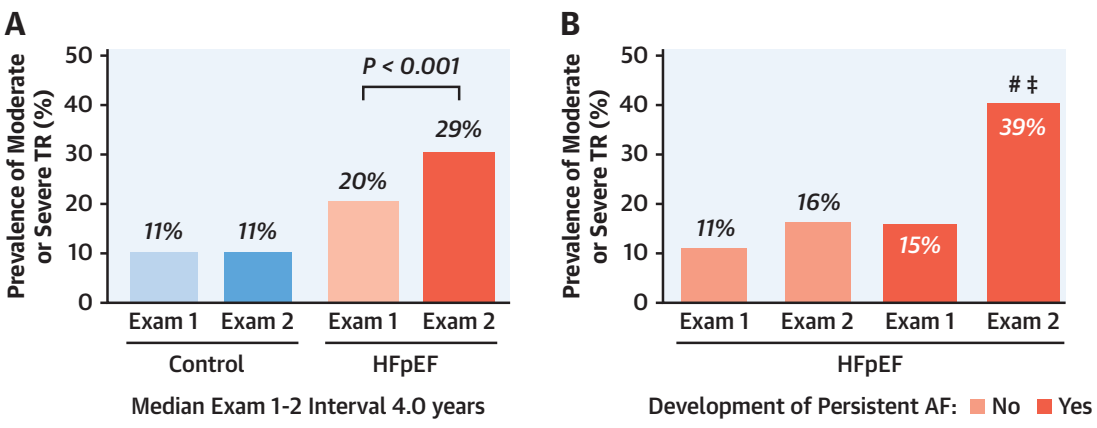
FIGURE 2 Hemodynamic Response to Exercise in Patients With TR



In a patient with tricuspid regurgitation (TR), (A) pulmonary capillary wedge pressure (PCWP) and (B) right atrial (RA) pressure are low at rest, but with exercise, both measures increase with a larger increase in RA pressure, resulting in a decrease in (C) left ventricular transmural pressure (LVTMP) and inadequate left ventricular diastolic filling. Reproduced with permission from Andersen et al.[35]

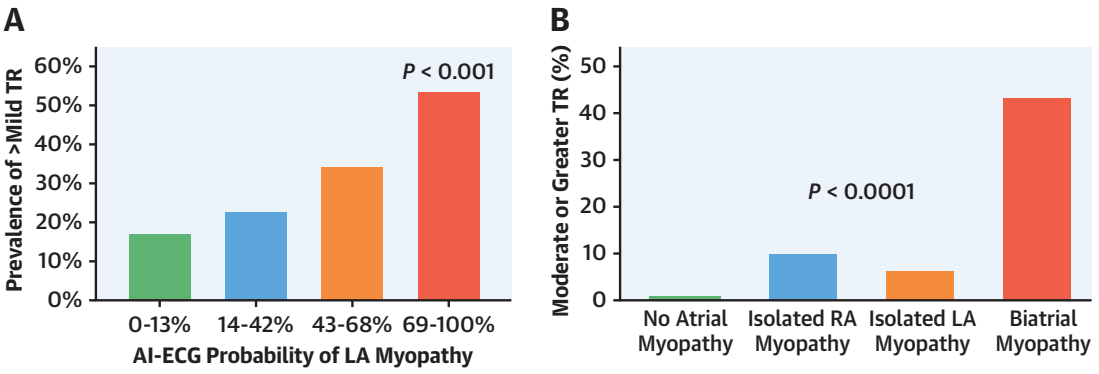
sodium-glucose cotransporter 2 inhibitors (SGLT2i), and potentially mineralocorticoid antagonists, angiotensin receptor-neprilysin inhibitors, and angiotensin receptor blockers. The recent 2023 European Society of Cardiology guideline update mandates diuretics for congestion relief, use of SGLT2i dapagliflozin or empagliflozin and treatment of comorbidities for patients with HFpEF.[14] A proposed management algorithm is shown in Figure 5. If a high prevalence of HFpEF does exist in the patient population with severe, symptomatic TR, then the medication use for the TRILUMINATE (The Trial to Evaluate Cardiovascular Outcomes in Patients Treated with the Tricuspid Valve Repair System) Pivotal trial (Table 3)[48] highlights a possible area of improvement in the implementation of optimal medical therapy since the trial was completed prior to the addition of SGLT2 recommendations.[48]

FIGURE 3 Progression of Tricuspid Regurgitation Over Time in HFpEF



(A) Over a median follow-up interval of 4 years, the prevalence of moderate or greater TR increased by 45%. (B) The strongest risk factor for TR progression was development of new onset persistent atrial fibrilaltion (AF), which was associated with a 2.6-fold increase in the prevalence of moderate or greater TR. Reproduced with permission from Obokata et al.[25] Abbreviations as in Figure 1.

FIGURE 4 Atrial Myopathy and Prevalence of TR



(A) Artificial intelligence using electrocardiography (AI-ECG) can accurately detect left atrial (LA) myopathy, and the greater the likelihood there is of a myopathy, the higher the prevalence is of >mild tricuspid regurgitation (TR). Reproduced with permission from Verbrugge FH, et al.[38] (B) A significantly higher prevalence of moderate or greater TR in the setting of biatrial myopathy. Reproduced with permission from Omote et al.[43] RA = right atrial.

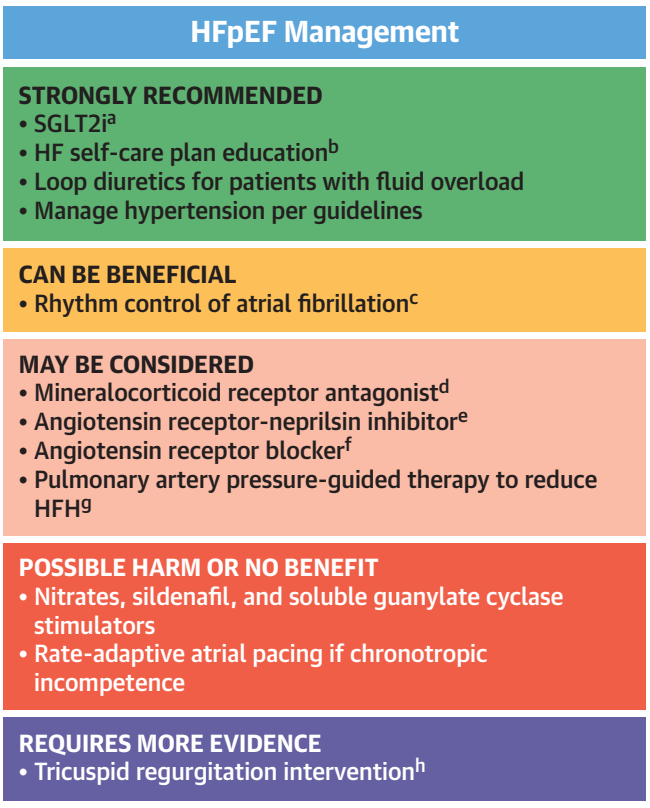
Guidelines have no Class I recommendation for medical management of TR.[21,49] As TR is the strongest multivariable predictor of persistent congestion in patients admitted with acute HF in Europe,[50] management of congestion should be a primary goal for patients with TR.[3] However, given the paucity of data regarding the treatment of these patients, diuretics have a guideline Class IIa level of recommendation for TR and right-sided HF. Diuretic therapy should be titrated to ensure that proper decongestion is achieved, which often requires tolerating mild-to-moderate increases in serum creatinine with increasing diuretic doses.[3] In a recent meta-analysis of randomized controlled trials of implantable hemodynamic monitoring-guided care, monitoring reduced total HF hospitalizations (HR: 0.74; 95% CI: 0.66-0.82) and total worsening HF events (HR: 0.74; 95% CI: 0.66-0.84) across the range of EF,[51] but the effect of monitoring-guided care on total worsening HF events in patients with HFpEF was uncertain.[4] Studies are needed to evaluate the benefit of implantable monitors for patients with symptomatic, severe TR.

Guidelines also give a Class IIa level of recommendation to treat patients with signs and symptoms of right-sided HF attributable to severe TR (stages C and D), with therapies to treat the primary cause of HF (eg, pulmonary vasodilators to reduced elevated pulmonary artery pressures in precapillary pulmonary hypertension, guideline-directed medical therapy for HFrEF and HFpEF, and rhythm control of AF). Given the association of HFpEF with TR, pharmacologic management as noted above should also be considered when this diagnosis is suspected, particularly given the strong evidence base for SGLT2i for HFpEF in whom congestion by direct hemodynamic assessment, may contribute to the presence of TR. Patients whose TR responds to medical therapy may not have the HFpEF-TR phenotype but are earlier in their HFpEF disease process (**Figure 6**).

AF is commonly seen with both HFpEF and TR, and rhythm control may be an important additional therapeutic intervention. A population-based study of 691 patients with new onset AF found one-third developed moderate or greater TR.[36] A higher risk of developing significant TR was seen in women (HR: 1.83) and those with persistent or permanent AF (HR: 2.96). Similarly, in patients with HFpEF, development of new onset AF is associated with 2.6-fold increased prevalence of moderate or severe TR.[25]

A strategy of rhythm control with catheter ablation may reduce TR.[36,52-54] Patlolla et al[36] showed patients who pursued a rhythm control strategy had a reduced risk of developing significant TR (HR: 0.71). Compared with those with persistent AF, patients in sinus rhythm 1 year postablation had reductions in RA area, tricuspid annular diameter, and TR jet area.[52] Freedom from AF was associated with a greater likelihood of improvement in TR by at least 1 grade (100% vs 41%). In recently hospitalized patients with AF, active restoration of sinus rhythm by cardioversion or ablation led to sustained reductions in RA and RV volumes along with improvement in atrial and ventricular function.[44] Importantly, cardioversion and/or

FIGURE 5 Treatment Algorithm for Guideline-Directed Medical Therapy in HFpEF



Proposed medical management algorithm for HFpEF. [a]Unless type 1 diabetes, history of diabetic ketoacidosis, or eGFR 30 mL/min/1.73 m^2; [b]includes adherence to medications and sodium, calorie and fluid restrictions, along with monitoring of weight, vital signs and HF symptoms; [c]Class 2a for both HFpEF guidelines and VHD guidelines; [d]if EF <60%, BNP elevated, recent HFH, eGFR >30 mL/min/1.73 m^2 or Cr <2.5 mg/mL, serum potassium <5.0 mmol/L, and adherent to laboratory monitoring; [e]if EF <45% , <60% , with risk factors for HFH; [f]benefit seen only on post hoc analysis when EF <55%; [g]if NYHA functional class II-III and BNP or NT-proBNP or recent HFH; [h]if NYHA functional class ≥II with HF symptoms despite guideline-directed medical therapy. Adapted with permission from Redfield MM, Borlaug BA. Heart failure with preserved ejection fraction: a review. *JAMA*. 2023;329(10):827-838. Cr = creatinine; EF = ejection fraction; eGFR = estimated glomerular filtration rate; HFH = heart failure hospitalization; SGLT2i = sodium-glucose cotransporter 2 inhibitor; VHD = valvular heart disease; other abbreviations as in Figure 1.

ablation within the first year was the only variable associated with RA reverse remodeling. The recent consensus document by Muraru et al[23] suggests that for patients with AF who meet high risk for A-STR progression criteria (Central Illustration), regular clinical and echocardiographic follow-up (every year, or sooner in case of clinical worsening or HFpEF) and rhythm control management should be implemented.

Finally, the management of patient with CIED-related TR is a complex shared decision making process which balances the risk of lead extraction (ie, worsening of TR) and the availability of alternative pacing strategies, with the risks of either surgical or transcatheter "jailing" (ie, inability to extract in the setting of endocarditis) or lead dysfunction.[55,56] For both rhythm control and CIED management, the inclusion of an electrophysiologist on the heart team is essential.

INDICATIONS FOR AND TIMING OF INTERVENTION

While addressing TR may affect several pathophysiologic changes that improve patient outcomes, the indications and timing of intervention are poorly defined. Although intervening at the time of left heart valve intervention is the only Class I indication for surgical intervention on the TV, multiple Class IIa and IIb recommendations allow for isolated tricuspid valve surgery (ITVS) in the absence of severe RV dysfunction or pulmonary hypertension.[21] However, the late presentation of patients with severe symptomatic TR is in large part responsible for the 10% to 12% in-hospital mortality rate associated with ITVS.[57,58] In fact, one study showed no mortality benefit of ITVS compared with medical therapy.[59] Conventional wisdom has held that a dilated and failing RV does not tolerate correction of TR. However, low CO requiring inotropic support following transcatheter device therapy was seen in only 14 (2.8%) of 500 patients in the TriValve registry, only 2 of whom were felt to have RV failure as the etiology.[60] This may not be the case for ITVS in which cardiogenic shock is significantly more common following surgical compared with transcatheter intervention.[61]

Transcatheter devices are currently under investigation,[3] with only 1 device having completed a pivotal randomized controlled trial,[8] and another device approved for commercial use in the United States.[62] Although inclusion and exclusion criteria differ slightly between both early feasibility and randomized control trials, most have excluded comorbidities that may determine outcomes independent of TR reduction (Table 4).[23] The definition of severe RV dysfunction has only recently been proposed in the TVARC document and validation of this grading schemed requires further study.[20] Given these exclusions and the baseline characteristics published for device trials (Table 1), a high prevalence of HFpEF is likely.

The TRILUMINATE Pivotal trial (Table 1) randomized severe, symptomatic TR patients to optimal medical therapy or transcatheter tricuspid edge-to-edge repair (T-TEER) with medical therapy.[8] With T-TEER, 87.1% had ≤ moderate TR (49.7% had mild or

less TR) at 30 days. Device therapy was associated with an improvement in quality of life but failed to show an improvement in all-cause mortality or TV surgery, or HF hospitalizations. Interpretation of the favorable effect on quality of life of T-TEER is confounded by the absence of blinding and sham control, particularly as it is known that there is a strong placebo effect for patient-reported outcomes, especially among those with very poor health status at baseline.[63] The U.S. Food and Drug Administration (FDA) approved the The TriClip™ G4 System (Abbott Vascular) on April 2, 2024. The approved indication is for improving quality of life and functional status in patients with symptomatic severe TR despite optimal medical therapy, who are at intermediate or greater risk for surgery and in whom T-TEER is clinically appropriate and is expected to reduce TR severity to moderate or less, as determined by a multidisciplinary heart team.

The FDA approved the commercial use of the EVOQUE transcatheter TV replacement device (Edwards Lifesciences), on February 1, 2024. The indication for use of the EVOQUE system is for the improvement of health status in patients with symptomatic severe TR despite optimal medical therapy, for whom tricuspid valve replacement is deemed appropriate by a heart team. This approval was based on the early data analysis (n = 150) showing a large improvement in Kansas City Cardiomyopathy Questionnaire Overall Summary score, and a strong trend for improvement in mortality and HF hospitalization.[62] Compared with the TRILUMINATE trial, TRISCEND (Tricuspid Valve Replacement: Investigation of Safety and Clinical Efficacy after Replacement of Tricuspid Valve with Transcatheter Device) early feasibility study,[64] and TRISCEND II Pivotal Study[9] enrolled patients who were more often female, with a higher prevalence of hypertension, AF, and renal dysfunction; with greater prevalence of NYHA functional class III/IV, and lower Kansas City Cardiomyopathy Questionnaire scores (Table 1). This likely indicates a patient population that is later in the disease process. The TRISCEND II study randomized patients who remained symptomatic on optimal medical therapy to the EVOQUE transcatheter replacement device, against continued medical therapy, and showed 93.9% of patients could achieve mild or less TR at 30 days with device therapy. Although the full cohort of patients has not yet been reported, the FDA's Breakthrough Device Pathway allowed an evaluation of those patients completing the 1-year endpoint and found that device therapy had significantly improved the primary hierarchical composite endpoint compared with medical therapy alone, with strong favorable trends for the device related to components of the endpoint including all-cause mortality, assist device or heart transplant, RV surgery or intervention, annualized HF hospitalization, Kansas City Cardiomyopathy Questionnaire, NYHA functional class, and 6-minute walk distance. Further analysis of the patients with HFpEF and TR in this study may change the management algorithm for these late-stage patients.

TABLE 3 TRILUMINATE Pivotal Trial Medication Use

Medication	Baseline % of Patients	Decrease Use >50% or Stop Use at 1 y		Increase Use >100% or New Use at 1 y	
		Device	Control	Device	Control
Diuretic	97.1	4.2 (7/168)	5.7 (10/174)	7.7 (13/168)	6.3 (11/174)
β-receptor antagonist	72.6	4.5 (6/132)	7.4 (10/135)	5.3 (7/132)	4.4 (6/135)
ACEI	42.3	20.7 (6/29)	4.2 (1/24)	10.3 (3/29)	8.3 (2/24)
ARB or ARNI		4.1 (2/49)	9.8 (6/61)	4.1 (2/49)	6.6 (4/61)
Vasodilator	10.9	0.0 (0/18)	9.5 (2/21)	11.1 (2/18)	9.5 (2/21)

Values are % or % (n/N). From the FDA Executive Summary, prepared for the February 13, 2024, Meeting of the Circulatory System Devices Panel.

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor neprilysin inhibitor; TRILUMINATE = The Trial to Evaluate Cardiovascular Outcomes in Patients Treated with the Tricuspid Valve Repair System.

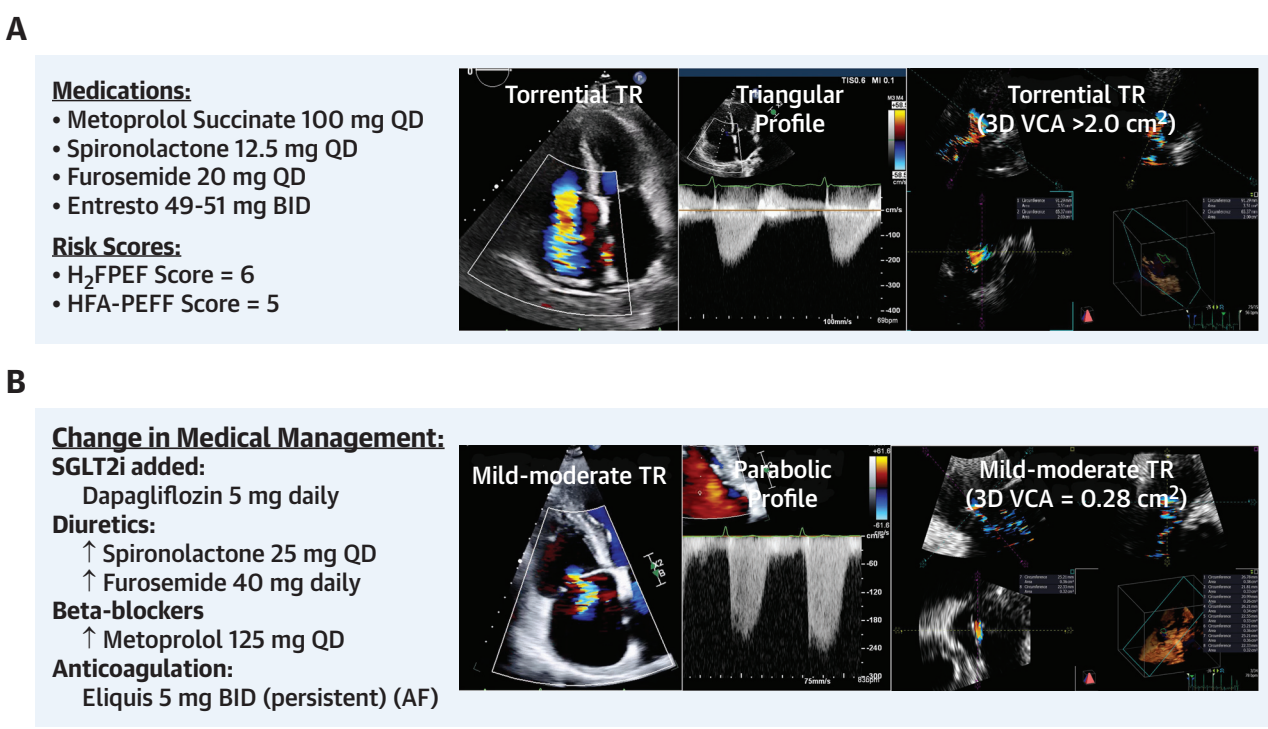
Defining the methods and cutoffs for determining both timing and outcomes of intervention remain important unresolved issues particularly because the interplay between the degree of TR reduction and resulting RV function are likely related.[3] The benefits of transcatheter device therapies may also depend on RV function and reserve capacity.[65,66] RV assessment is particularly challenging in the presence of significant TR. A significant proportion of stroke volume is ejected into the low-pressure RA; thus, changes in RV size (ie, fractional area change) and volume (ie, EF) and a dilated RV may also result in higher than expected RV longitudinal function (ie, tricuspid annular plane systolic excursion and free wall strain). The complex contraction pattern of the RV is incompletely characterized by either isolated measures of longitudinal function or circumferential shortening and global function assessed by RVEF may improve the prediction of outcomes.[65,67,68] Assessment of RV

TABLE 4 Common Exclusion Criteria in TR Trials

Severe, irreversible pulmonary arterial hypertension (typically a systolic pulmonary artery pressure of >60-70 mm Hg and/or PVR >5-6 WU)
Poor LVEF (≤20%-25%)
"Severe" RV dysfunction
Severe concomitant left valve disease
Hepatic insufficiency or cirrhosis with Child-Pugh score class C
Severe renal dysfunction (eGFR ≤25 mL/min/1.73 m^2)

eGFR = estimated glomerular filtration rate; other abbreviations as in Table 1.

FIGURE 6 Case Example of Medically Managed TR



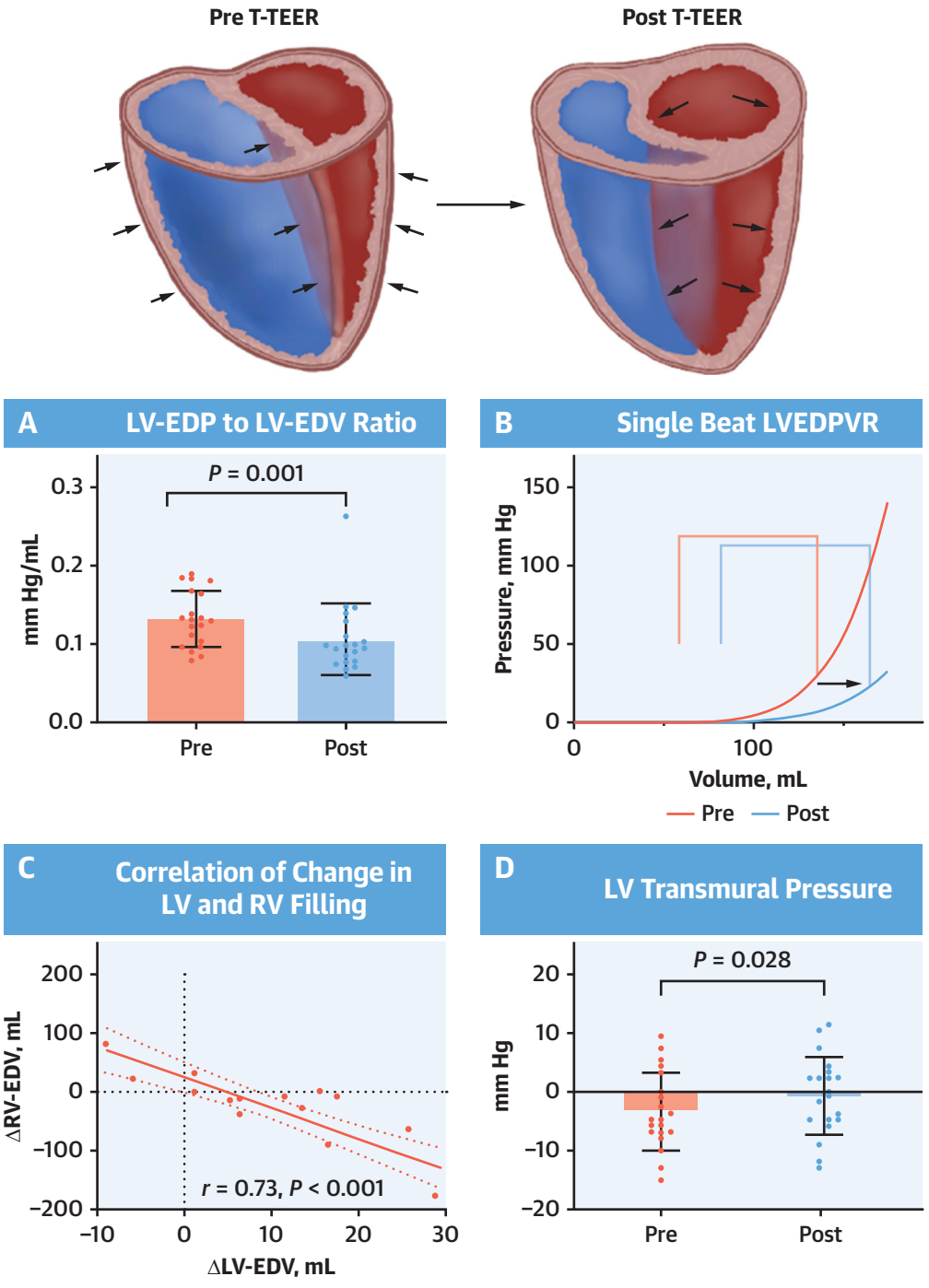
A 71-year-old female patient with history of hypertension and paroxysmal atrial fibrillation presents with increasing peripheral edema and abdominal girth, early satiety, fatigue, and dyspnea. Her H_2FPEF Score was 6 and her HFA-PEFF score was 5. (A) Baseline medications and echocardiogram with torrential TR quantified by both Doppler and 3-dimensional parameters. (B) Following medical management, the echocardiogram shows right ventricular remodeling with reduction in TR.
3D = 3-dimensional; AF = atrial fibrillation; BID = twice daily; QD = once daily; SGLT2i = sodium-glucose cotransporter 2 inhibitor; VCA = vena contracta area; other abbreviations as in Figure 1.

reserve may ultimately prove useful.[69] A novel approach to partition afterload into pulmonary arterial and atrial elastances has also been proposed.[70] The Tricuspid Valve Academic Research Consortium[20] has made a proposal for grading the severity of RV function, which will require validation.

IMPACT OF STRUCTURAL TR INTERVENTION

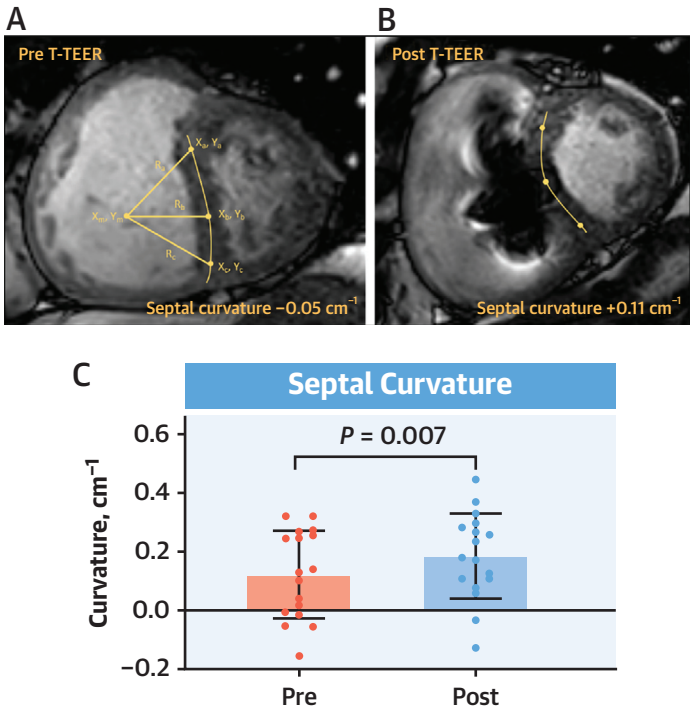
The TRILUMINATE Pivotal multimodality imaging substudy showed an increase in forward stroke volume following T-TEER.[48] An increase in forward flow into the LA and therefore the LV, with an attendant increase in LV filling pressures, could theoretically lead to worsening HF symptoms. This theoretical construct was disproven by the HERACLES-HFpEF study, which evaluated 20 patients with HFpEF and severe TR following T-TEER (Figure 7).[71] In this study, HFpEF was diagnosed if the left ventricular end-diastolic pressure (LVEDP) was >15 mm Hg and LVEF was ≥50%, and the primary outcome was a change in LVEDP/LV end-diastolic volume (LVEDV). If an increase in flow following T-TEER results in higher LV filling pressures with no improvement in diastolic filling (LVEDV), then this ratio would increase. The study, however, showed that LVEDP/LVEDV was reduced (Figure 7A), due to a rightward shift of the end-diastolic pressure-volume relationship curve and improvement in diastolic function (Figure 7B). This shift may be attributable to improvement in LV-RV interaction with RV unloading, shown by the opposite changes in ventricular volumes: improvement of LVEDV (Δ median +6 mL; P = 0.003), with a decrease in RVEDV (Δ median −16 mL; P = 0.028) (Figure 7C). An improvement in transmural pressure (measured as LVEDP-RA pressure) (Figure 7D) promotes increase LV diastolic filling, further supported by the shift from an abnormal to normal septal curvature (Figure 8).[32,71,72] Restoring the LV-RV interaction was associated with reduced LV filling pressures; in this study, the LVEDP numerically decreased from 19 to

FIGURE 7 Hemodynamic Changes Associated With T-TEER



Immediately following transcatheter tricuspid valve edge-to-edge repair (T-TEER), (A) the ratio of the left ventricular end-diastolic pressure (LVEDP) to left ventricular end-diastolic volume (LVEDV) decreases with a rightward shift of the end-diastolic pressure-volume relationship (EDPVR), (B) thus lowering end-diastolic pressures despite increases in filling. (C) One month after T-TEER, the increased left ventricular (LV) volumes were accompanied by decreased right ventricular (RV) volumes. (D) T-TEER is associated with an immediate increase in LV transmural pressure. Reproduced with permission from Kresoja KP, Rommel KP, Rosch S, et al. Hemodynamic implications of transcatheter tricuspid valve repair in HFpEF patients: HERACLES-HFpEF. *Eur Heart J*. 2024;44(Suppl_2):ehad655.1763.

FIGURE 8 Ventricular Septal Morphology Before and After Percutaneous Tricuspid Valve Repair



(A) Cardiac magnetic resonance short-axis images show flattening of the septum at the time of early left ventricular (LV) diastole before T-TEER. One-month after T-TEER, the septal curvature (B) is shifted more toward a physiological rightward bowing, (C) representing a significant change. Reproduced with permission from Kresoja et al.[71] Abbreviations as in Figure 7.

16 mm Hg ($P = 0.094$), which is all the more remarkable considering the increase in LVEDV. Reduced LV filling pressure may allow for an increase in LV preload, which will improve CO by enhancing Frank-Starling reserve. In fact, meta-analyses of transcatheter device therapies have shown that an improvement in LV CO can be seen following reduction in TR, in the setting of RV reverse remodeling.[73] Supportive evidence from the TRILUMINATE Pivotal study showed improvements in renal and liver function associated with a reduction in TR following T-TEER (Figure 9A), with reciprocal changes in LV and RV remodeling (Figure 9B).[48] One can also appreciate how the potential for pericardial restraint in severe TR may complicate the concomitant hemodynamic diagnosis of HFpEF, or possibly become a therapeutic target for this phenotype.[74]

NT-proBNP varies directly with LV chamber dimension, and in conditions of excess pericardial restraint, such as obesity, this results in lower NT-proBNP relative to PCWP.[75] This phenomenon may also apply to extrinsic restraint with TR which is often associated with severe RV failure, congestion and high NT-proBNP.[6] Interestingly, isolated TR intervention with T-TEER failed to show reductions in NT-proBNP (Figure 9A),[48] and although the increase in effective afterload of the RV and RV strain may account for this finding, it seems more likely that the change in septal shift resulting in a change in the radius of curvature of the LV with increase in LV filling, which may increase LV wall stress (through the law of LaPlace), accounting for the persistent elevation in NT-proBNP.

Given the early transcatheter device therapy development, it is premature to define the parameters that may dictate device choice. Leaflet gap distances or annular dimensions may be the most obvious anatomic restrictions; however, the safety and efficacy of each device and the effects on right and left heart pathophysiology will also be important. The complex pathophysiological interplay of the TV, RV, and LV is at this point speculative and requires further study.

Invasive hemodynamic evaluation can provide important insight into the mechanisms of TR, including the presence of HFpEF or other causes of precapillary pulmonary hypertension.[76] Ideally, this would require assessment of right and left heart filling pressures, pulmonary artery pressures, and CO both at rest and during exercise. Roughly one-third of patients with HFpEF present with normal PCWP at rest, with abnormalities only brought out by the stress of exercise,[77] though the proportion with HFpEF based on resting hemodynamics is probably higher in the setting of TR, which appears to be a marker of more advanced HFpEF. Other provocative maneuvers may be considered in centers without the ability to perform exercise hemodynamics, including passive leg raise and saline loading, though exercise is the most physiologically relevant and preferred stressor.[76]

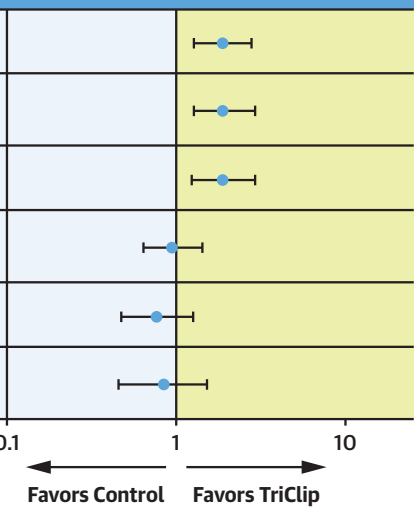
THE FUTURE OF CARDIOVASCULAR DISEASE DETECTION

Earlier diagnosis of both HFpEF and valvular heart disease holds promise for improving outcomes for our patients before progression to irreversible stages. Use of machine learning and deep learning may play an important role in earlier diagnosis.[78] In a study of 960 patients with HFpEF, patterns of fragmented QRS were associated with significantly altered cardiac structure/function, more impaired diastolic indices, and higher risk of HF hospitalization, cardiovascular

FIGURE 9 Biomarker and Ventricular Changes by TRILUMINATE Trial Treatment Group

A

		Average Biomarker Change (n size)		Odds of 15% Biomarker Improvement Between 12 Months LOCF and Baseline (95% CI)
		Control	TriClip	
Liver Function	MELD-XI	0.5 ± 3.3 (250)	−0.4 ± 3.3 (263)	4
	GGT (U/L)	−1.0 ± 55.3 (179)	−10.9 ± 67.8 (191)	3
Renal Function	eGFR (mL/min/1.73 m^2)	−2.5 ± 13.9 (253)	0.8 ± 12.8 (266)	2
	BUN (mg/dL)	0.9 ± 12.7 (249)	0.1 ± 14.4 (266)	1
Cardiac Function	BNP (pg/mL)	9.8 ± 226.5 (126)	29.6 ± 487.2 (142)	6
	NT-proBNP (pg/mL)	−61.5 ± 1,752 (106)	438 ± 2,195 (116)	5



B

	Control (n)	TriClip (n)
ΔLVED volume (mL)	−4.80 ± 23.49 (114)	3.91 ± 25.02 (129)
ΔLVES volume (mL)	−2.93 ± 12.52 (114)	2.31 ± 15.28 (129)
ΔRVED diameter-mid (4Ch, cm)	−0.02 ± 0.85 (134)	−0.18 ± 0.73 (140)
ΔRVED diameter-base (4Ch, cm)	−0.12 ± 0.76 (134)	−0.21 ± 0.71 (142)

(A) The odds of improvement in parameters by treatment group in the TRILUMINATE trial (N = 572). (B) changes in left ventricular end-diastolic volume (ΔLVED Volume), left ventricular end-systolic volume (ΔLVES Volume), mid right ventricular end-diastolic dimension (ΔRVED diameter-mid) and basal right ventricular end-diastolic dimension (ΔRVED diameter-base). Data are reproduced from the Triluminate Pivotal Sponsor Executive Summary for the Circulatory Systems Device Panel held on February 13, 2024. BUN = blood urea nitrogen; eGFR = estimated glomerular filtration; GGT = gamma-glutamyltransferase; LOCF = last observation carried forward; LVED = left ventricular end-diastolic; LVES = left ventricular end-systolic; MELD-XI = Model for End-Stage Liver Disease excluding international normalized ratio; RVED = right ventricular end-diastolic; 4Ch = 4-chamber view; other abbreviations as in Figure 1.

and all-cause death.[79] Other investigators have shown that a high Cornell product (≥1,800 mm × ms), an ECG voltage-duration product, was significantly associated with HFpEF as well as with a higher composite endpoint of all-cause mortality and HF hospitalizations.[80] As noted previously, artificial intelligence (AI)–enabled ECG to detect underlying LA myopathy was also highly predictive of TR,[38] likely due to the common presence of biatrial myopathy in such patients.[43]

In addition to the promise of earlier TR detection by ECG, there is a growth of AI applications in echocardiography that have already been shown to improve image acquisition and processing, as well as the precise determination of both basic and advanced quantitative measures of heart disease severity.[81] Given the complexity of TV anatomy and the heterogeneity of disease etiologies, AI methods to automate quantitation of TR severity would be integral to the earlier detection and management of these patients.

Given the diagnostic and management challenges of HFpEF and TR, referrals to heart teams with experience in managing both diseases are highly advised by all consensus and guideline recommendations.[1,20,21,49] The tendency for these patients to be underdiagnosed, or have their underlying conditions untreated, could be reduced by

referral to these centers of excellence. The complex pathophysiological interplay of the TV, RV, and LV underscores the importance of a thorough pathophysiological assessment of patients with a special emphasis on hemodynamics. Indeed, the 3 strongly interrelated syndromes of HFpEF, AF, and TR are all increasing in prevalence. Historically, they have been conservatively managed without specific treatment options. Recent developments in all 3 syndromes, such as SGLT2i for HFpEF, ablation for AF (in HF), and transcatheter therapies for TR, underscore the importance of early recognition, referral, and treatment. This will also facilitate trials of medical therapies and catheter- and device-based interventions for these syndromes.

Thus, the management algorithm for patients with HFpEF and significant TR (**Central Illustration**) should begin with identifying patients with HFpEF and excluding etiologies like primary valvular heart disease that may mimic it. Once severe TR is diagnosed, a multidisciplinary heart team is required for shared decision making and should include not only a surgeon, an interventionalist, an imaging specialist, and an HF specialist, but also a pharmacist and electrophysiologist to optimally treat congestive symptoms and expeditiously address patients who develop AF or require a CIED lead extraction.

CONCLUSIONS

An emerging understanding of TR holds that it is particularly common and consequential in patients with HFpEF, and that it is a marker of more advanced HFpEF with greater AF, biatrial myopathy, greater RV dilatation with ventricular interaction, more impaired CO and output reserve, more lung edema (in patients with pulmonary vascular disease), and increased risk for adverse outcomes. Numerous studies adjusting for comorbidities including RV function have shown that TR is not just a risk marker, but a risk factor.[6,82] Gaps in evidence for the management of TR result in lack of referral and treatment for HFpEF and AF. Understanding the relationship between HFpEF and TR also may impact future trial designs, as well as management decisions for the multidisciplinary heart team.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Dr Böhm was supported by the Deutsche Forschungsgemeinschaft (SFB TTR 219, S-01). Dr Lund was supported by Karolinska Institutet, the Swedish Research Council (grant 523-2014-2336), the Swedish Heart Lung Foundation (grants 20150557, 20190310), and the Stockholm County Council (grants 20170112, 20190525). Dr Borlaug was supported by the National Institutes of Health (R01 HL128526, R01 HL162828, and U01 HL160226) and the U.S. Department of Defense (W81XWH2210245). Dr Hahn has received speaker fees from Abbott Structural, Baylis Medical, Edwards Lifesciences, Medtronic Philips Healthcare, and Siemens Healthineers. Dr Lindenfield has received consulting fees from Abbott Structural, Abiomed, AstraZeneca, Alleviant, Axon, Bayer, Boston Scientific, CVRx, Edwards Lifesciences, Merck, Medtronic, VWave, Vascular Dynamics, and Whiteswell. Dr Böhm has received support from AstraZeneca, Bayer, Boehringer Ingelheim, Medtronic, Novartis, ReCor, Servier, and Vifor. Dr Lund has received grants and honoraria from and served as a consultant for Alleviant, AstraZeneca, Bayer, Biopeutics, Boehringer Ingelheim, Edwards, Merck/MSD, Novartis, Novo Nordisk, Owkin, Pharmacosmos, and Vifor Pharma; and has stock ownership in AnaCardio. Dr Lurz has received institutional fees and research grants from Abbott Vascular, Edwards Lifesciences, and ReCor; has received honoraria from Edwards Lifesciences, Abbott Medical, Innoventric, ReCor, and Boehringer Ingelheim; and has stock options with Innoventric. Dr Metra has received consulting honoraria from Abbott Structural, AstraZeneca, Bayer, Boehringer Ingelheim, Edwards Lifesciences, and Roche Diagnostics in the last 3 years. Dr Tedford is the co-chair of the Pulmonary Hypertension due to left heart disease task force for 7th World Symposium on Pulmonary Hypertension; is the Deputy Editor for *The Journal of Heart and Lung Transplantation*; has served as a consultant for Abbott, Acorai, Aria CV Inc, Acceleron/Merck, Alleviant, Boston Scientific, Cytokinetics, Edwards Lifesciences, Gradient, Lexicon Pharmaceuticals, Medtronic, and United Therapeutics; has served on the steering committee for Merck, Edwards, and Abbott; has served on the research advisory board for Abiomed; and has completed hemodynamic core lab work for Merck. Dr Butler has served as a consultant for Abbott, American Regent, Amgen, Applied Therapeutic, AskBio, Astellas, AstraZeneca, Bayer, Boehringer Ingelheim, Boston Scientific, Bristol Myers Squibb, Cardiac Dimension, Cardiocell, Cardior, CSL Bearing, CVRx, Cytokinetics, Daxor, Edwards, Element Science, Faraday, Foundry, G3P, Innolife, Impulse Dynamics, Imbria, Inventiva, Ionis, Lexicon, Lilly, LivaNova, Janssen, Medtronics, Merck, Occlutech, Owkin, Novartis, Novo Nordisk, Pfizer, Pharmacosmos, Pharmain, Prolaio, Regeneron, Renibus, Roche, Salamandra, Sanofi, SC Pharma, Secretome, Sequana, SQ Innovation, Tenex, Tricog, Ultromics, Vifor, and Zoll. Dr Borlaug has received research grant funding from AstraZeneca, Axon, GlaxoSmithKline, Medtronic, Mesoblast, Novo Nordisk, and Tenax Therapeutics; has served on the advisory board, on the steering committee, or as a consultant for Actelion, Amgen, Aria, Axon, BD, Boehringer Ingelheim, Cytokinetics, Edwards Lifesciences, Eli Lilly, Janssen, Merck, Novo Nordisk, and Tenax; and is named inventor (U.S. Patent No. 10,307,179) for the tools and approach for a minimally invasive pericardial modification procedure to treat heart failure. Dr Edelmann has reported that he has no relationships relevant to the contents of this paper to disclose.

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KEY WORDS heart failure, preserved ejection fraction, tricuspid regurgitation