Secondary valve regurgitation in patients with heart failure with preserved ejection fraction, heart failure with mid-range ejection fraction, and heart failure with reduced ejection fraction

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Secondary mitral regurgitation and secondary tricuspid regurgitation due to heart failure (HF) remain challenging in almost every aspect: increasing prevalence, poor prognosis, notoriously elusive in diagnosis, and complexity of therapeutic management. Recently, defined HF subgroups according to three ejection fraction (EF) ranges (reduced, mid-range, and preserved) have stimulated a structured understanding of the HF syndrome but the role of secondary valve regurgitation (SVR) across the spectrum of EF remains undefined. This review expands this structured understanding by consolidating the underlying phenotype of myocardial impairment with each type of SVR. Specifically, the current understanding, epidemiological considerations, impact, public health burden, mechanisms, and treatment options of SVR are discussed separately for each lesion across the HF spectrum. Furthermore, this review identifies important gaps in knowledge, future directions for research, and provides potential solutions for diagnosis and treatment. Mastering the challenge of SVR requires a multidisciplinary collaborative effort, both, in clinical practice and scientific approach to optimize patient outcomes.

Keywords

Secondary mitral regurgitation • Secondary tricuspid regurgitation • HFrEF • HFmrEF • HFpEF • Heart failure

Introduction

Secondary regurgitation of the atrioventricular valves (SVR) is associated with decreased quality of life, increased heart failure (HF) hospitalizations, and poor prognosis.^{1–7} The point-prevalence of significant SVR among HF patients is substantial⁸ and expected to rise exponentially with the expected increase in HF with ageing population.⁹ Secondary valve regurgitation may occur isolated or concomitantly (bivalvular secondary regurgitation), independent of the respective HF subgroup—be it with preserved (HFpEF),^{8,10} mid-range (HFmrEF),⁸ or reduced (HFrEF)^{1,4,7,8} ejection fraction (EF). In contrast to organic (primary) valve regurgitation, the valve apparatus is structurally normal in the early stage of the SVR evolution. This clinic-

al review aims to summarize the epidemiology, pathophysiologic mechanisms, as well as the diagnostic and therapeutic approach to SVR across the spectrum of HF and to provide critical information specific to the regurgitant lesion in relation to the HF subtype. Furthermore, it aims to identify important gaps of knowledge and to provide potential future perspectives for diagnostic and therapeutic advances.

Epidemiology

Evolving SVR definitions and HF subclassifications provide the foundation for a structured understanding of the disease-complex, health-

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care expenditures, and potential treatment strategies and are closely tied to the global public health burden. Most community-based studies in this field, however, were performed before the clinical introduction of HFmrEF or HFpEF, and the understanding of SVR and specifically its epidemiological projections thus remain limited. Moreover, quantitative thresholds for grading SVR severity vary^{11–13} and the terms to describe the significance of SVR are ill defined with regard to patient outcome, risk of progression, and benefit of surgery and intervention. Population-based studies, such as health record data from the CPRD,⁹ have demonstrated an increasing burden of HF in the community with increasing standardized incidence in the elderly. These trends are relevant to SVR as there is an additive increase in secondary mitral regurgitation (SMR) and secondary tricuspid regurgitation (STR) with increasing age. Data from the prospective ESC HF registry⁸ provide a rough estimate regarding the point prevalence of moderate-to-severe SMR affecting 36% of patients with HFrEF, 28% with HFmrEF, and 20% with HFpEF. In contrast, the prevalence for moderate-to-severe STR appears similar between HF subtypes ranging around 19%.⁸ Future research should address the incidence, prevalence, and impact of SVR among HF subtypes in order to provide accurate projections and estimation of the impact in the community and healthcare expenditures.

Epidemiology of secondary mitral regurgitation

In HF cohorts, moderate or severe SMR affects up to 30%^{1,7,8,14} of patients and appears to be more common in HFrEF followed by HFmrEF and HFpEF. Given an overall 1–2% prevalence of HF in the general population,⁹ rough estimations for the prevalence of HFrEF, HFmrEF, and HFpEF with moderate or severe SMR are ~0.3%, 0.1%, and 0.05% of the population, respectively. The Rochester epidemiology project reported a >2.5 times higher mortality in patients with SMR compared to the community.² In part, the adverse outcome of SMR is driven by the underlying myocardial impairment; however, mortality of HFrEF patients with vs. without SMR is increased [adjusted hazard ratio (adj. HR) 1.61, 95% confidence interval (CI) 1.22–2.12; $P=0.001$].¹ In this study, the effect was most pronounced in the upper EF range of 30–40% (adj. HR 2.37, 95% CI 1.36–4.12; $P=0.002$).¹ The association of SMR with mortality was also observed in patients with HFmrEF (adj. HR 1.72, 95% CI 1.24–2.39; $P=0.0012$),⁸ and HFpEF (adj. HR 1.40, 95% CI 1.09–1.81; $P=0.009$).¹⁰ Of note, the independent prognostic significance of SMR in very advanced HFrEF is reduced as the severity of the left ventricular (LV) dysfunction predominates.^{1,15,16} Selected studies with quantified SMR,^{3,11,14,15,17–20} the respective EF range and the clinical impact calculated from time-to-event data²¹ are listed in Table 1.

Epidemiology of secondary tricuspid regurgitation

Three epidemiologic studies published to date have focused on tricuspid regurgitation (TR) in general without addressing specific distributions and patterns of STR within HF subtypes.^{22–24} Data from the Framingham heart study demonstrated a prevalence of TR of any cause to be 0.8%, whereas the OxVALVE study reported a TR prevalence of 2.7%. This discordance is likely due to different inclusion

criteria because the OxVALVE study exclusively included subjects >65 years of age. Topilsky et al.^{24,25} recently published an analysis from the Rochester epidemiology project and confirmed the increasing prevalence of TR with age and female sex. STR related to LV systolic dysfunction (HFrEF-STR and HFmrEF-STR) was among the leading aetiologies of STR. The ESC HF long-term registry⁸ reported STR to be equally common among HF subtypes potentially due to mechanistic similarities. The presence of STR has been associated with more symptoms, decreased quality of life, increased HF admissions, and reduced survival. Studies in specific HF subtypes show an adj. HR 1.30, 95% CI 1.06–1.60; $P=0.014$ in HFrEF⁶ and an adj. HR 2.87, 95% CI 1.61–5.09; $P<0.001$ in HFpEF for mortality.²⁶ The hazard of STR in HFmrEF has not to date been reported but mixed HFrEF and HFmrEF cohorts have demonstrated an independent risk of STR for mortality^{4,5} with an adj. HR 1.57, 95% CI 1.39–1.78; $P<0.0001$.⁴ Selected studies with quantified STR^{5,6} and the respective EF ranges are listed in Table 1. The impact of STR in the lower EF range of HFrEF remains controversial^{26–28}; quantitative assessment might add precision to the prognostic impact of STR according to underlying left ventricular ejection fraction (LVEF).^{4–6} The anticipated increase in the prevalence of HFrEF, HFmrEF, and HFpEF indicate an unmet clinical need for effective STR treatment options to potentially improve prognosis.

Pathophysiology of secondary valve regurgitation

Secondary valve regurgitation develops due to structural alterations of the myocardial geometry. Secondary valve regurgitations are typically dynamic lesions, a phenomenon that can be observed during the cardiac cycle at rest,^{29–31} with exercise,^{32,33} and with changes in loading conditions.^{32–34} Despite guideline-directed medical therapy (GDMT), a significant proportion of patients develop progressively increasing SVR^{35,36} reflecting the increasing volume overload from SVR that augments further ventricular and atrial adverse remodelling. Whereas mechanisms are similar across all HF subgroups for STR [increased wedge pressures due to LV dysfunction and tricuspid annular dilatation due to right atrial remodelling, increase in pulmonary pressure, and right ventricular (RV) dilatation], the predominant mechanism of SMR may vary between HF subgroups³⁷ (Take home figure and Figure 1).

In HFrEF, leaflet tethering due to posterior and lateral displacement of the papillary muscles is the most common underlying mechanism of SMR.^{38,39} Papillary muscle displacement also leads to a geometric distortion of the papillary muscle configuration which normally is perpendicular to the mitral valve coaptation line and parallel to the LV long axis, further inducing loss of leaflet coaptation.⁴⁰ Mechanical dyssynchrony further impairs leaflet coaptation.^{41–43} If the LV is regionally dysfunctional (e.g. after a posterobasal myocardial infarction), the mitral regurgitation (MR) jet will often be eccentric, whereas if LV is globally dysfunctional (e.g. from idiopathic dilated cardiomyopathy), the jet will often be central. Dilatation and flattening of the non-planar saddle-shaped mitral annulus,^{44,45} typically occurs late in the sequence of events and may involve restricted leaflet motion of the posterior leaflet P3 segment, enhancing jet eccentricity.⁴⁶ Based on Carpentier's classification, the morphologic substrate of HFrEF-SMR most commonly corresponds to restricted leaflet

Table 1 Selected studies with quantitative secondary valve regurgitation assessment, and the respective predictive value

Author	Year	Ref.	N	Ischemic HF	EROA	HR (95%CI)	RegVol	RF	LV size	LVEF	Predictive value of quantified SVR
Secondary mitral regurgitation											
Bartko et al.	2019	3	432	39%	30mm ²	2.53 (1.59-4.02)	45ml	50%	60mm (54-66)	<40%	EROA ≥30mm ² / RegVol≥45ml cut-off for high-risk, Integrated quantification (unifying concept) between 20mm ² and 29mm ² .
Stone et al.	2019	20	614	51%	30mm ²	0.62 (0.46-0.82)	45ml	40%	101ml/m ²	<50%	RCT, EROA≥30mm ² / RegVol≥45ml cut-off, integrated quantification for EROA<30mm ² . Significant improvement of primary and secondary endpoints with TMVR compared to GDMT alone.
Obadia et al.	2018	19	307	59%	20mm ²	1.02 (0.70-1.50)	30ml	NR	135ml/m ²	<40%	RCT, EROA≥20mm ² / RegVol≥30ml cut-off, neutral results of TMVR compared to GDMT alone.
Bartko et al.	2018	11	169	39%	20mm ²	1.30 (0.91-1.86)	30ml	NR	62mm (57-67)	<40%	Comparison between ACC/AHA and ESC/EACTS guideline cut-offs, (EROA 20 vs. 40mm ² , RegVol 40 vs. 60ml).
Rossi et al.	2011	14	1256	62%	40mm ² 20mm ²	1.66 (1.13-2.43) 2.60 (2.07-3.26)	60ml 30ml	NR	61-66mm	HFrEF	EROA≥20mm ² independent predictive of mortality.
Grigioni et al.	2005	17	173	100%	20mm ²	NA	30ml	NR	33±5mm/m ²	HFrEF	EROA≥20mm ² independent predictive of event-free survival (death and heart failure rehospitalization).
Lancellotti et al.	2005	32	161	100%	20mm ²	NR/NA	NR	NR	144±30ml	≤45%	EROA≥20mm ² independent predictive of mortality.
Patel et al.	2004	15	209	54%	20mm ²	1.14 (0.78-1.67)	NR	NR	64-72mm	≤35%	No outcome difference according to EROA cut-off 20mm ² .
Grigioni et al.	2001	18	303	100%	20mm ²	2.89 (1.73-4.82)	30ml	NR	33±5mm/m ²	HFrEF	EROA≥20mm ² independent predictive of mortality.
Secondary tricuspid regurgitation											
Bartko et al.	2019	6	382	41%	20mm ²	1.74 (1.22-2.49)	20ml	NR	N/A	<40%	EROA 20mm ² / RegVol 20ml independent predictive of mortality.
Topilsky et al.	2018	5	291	67%	40mm ²	1.71 (1.18-2.48)	NR	NR	N/A	<50%	EROA 40mm ² independent predictive of mortality.

Hazard ratios were estimated for 5-year time-to event/number at risk data, except for RCTs where the reported 2-year results are shown.

CI, confidence interval; EF, ejection fraction; EROA, effective regurgitant orifice area; HR, hazard ratio; LV, left ventricular; NA, not applicable; NR, not reported; RCT, randomized clinical trial; RegVol, regurgitant volume; RF, regurgitant fraction.

motion during systole with leaflet tenting and lack of coaptation (Type IIb).

Conversely, in HFpEF, dilatation of the atrioannular unit is the structural deficit which most commonly leads to SMR, typically with a central jet direction, also referred to as 'atrial SMR'^{37,47} corresponding to Carpentier's classification Type I with no or only mild leaflet tenting. Atrial fibrillation might play an important contributing role in the development of atrial SMR, especially in HFpEF, as it leads to progressive left atrial remodelling with fibrotic mitral annular and leaflet changes.^{37,48,49} However, causality remains uncertain as LV systolic or diastolic dysfunction itself might trigger atrial fibrillation due to

elevated filling pressures resulting in left atrial stretch and fibrosis.³⁷ Most likely, a uniform risk factor profile for HFpEF and atrial fibrillation^{50,51} leads to concomitant development of diastolic dysfunction and atrial structural and electrical remodelling inducing the evolution of atrial SMR.

Notably, atrial and ventricular SMR (Carpentier Type I and IIb mechanisms) can coexist, with the overlap greatest in HFmrEF-SMR. Conceptually, atrial SMR in HFmrEF could play an important role in the transition between HF stages by promoting LV volume overload and dilatation, with progression to HFrEF. Conversely, STR in HFmrEF might promote transition to HFpEF by restricted LV filling

(diastolic ventricular interdependence)⁵² and LV constraint secondary to STR-induced RV enlargement, thereby resulting in a pseudo-normalization of LV EF. The exact mechanisms and pathophysiological role of SVR in HFmrEF, however, remain unclear and should be examined in future studies.

Hallmarks of STR evolution (Figure 2) are RV and tricuspid annular dilatation in the early phase, followed by progressive RV and

rightatrial as well as tricuspid annular dilatation. Long-standing STR, specifically in the setting of increased pulmonary pressures might promote irreversible structural RV and atrial remodelling including tricuspid annular dilatation and loss of leaflet coaptation. The exact mechanisms and pathophysiological role of SVR in HFmrEF, however, remain unclear and need to be addressed by future studies.

Figure 1 Pathophysiologic mechanisms of secondary mitral regurgitation. Distortion of the atrial annular unit feature the development of secondary mitral regurgitation in heart failure with preserved ejection fraction characterized by increased filling pressures, left atrial dilatation and subsequent mitral valve annular dilatation, and decreased annular contraction. In contrast, distortion of the ventricular annular unit promote the development of secondary mitral regurgitation in heart failure with reduced ejection fraction characterized by increased filling pressures, leaflet restriction, dyssynchrony, and left ventricular dilatation with subsequent mitral valve annular dilatation. Notably, distortion of the atrial annular unit and ventricular annular unit coexist with presumably the largest overlap in heart failure with mid-range ejection fraction secondary mitral regurgitation.

Diagnostic challenges in secondary valve regurgitation

Comprehensive assessment of SVR remains challenging. Transthoracic echocardiography (TTE) serves as a gatekeeper to identify HF patients in need of more advanced imaging to improve diagnostic accuracy and, therefore, subsequent therapeutic management.^{12,13,54} Complementary imaging includes transoesophageal and three-dimensional echocardiography as well as cardiac magnetic resonance imaging (MRI), computed tomography (CT), and nuclear imaging.⁵⁵ Exercise testing can expose the dynamic nature of SVR,

^{33,54} although symptoms and comorbidities may limit the ability to exercise in patients with HF, potentially reducing standardization and diagnostic accuracy of such tests. Nonetheless, stress testing using various approaches to observe dynamic changes of lesion severity with altered loading and contractility is feasible in the majority of patients and is increasingly recognized as an important diagnostic tool, especially in symptomatic patients with non-severe lesions at rest.⁵⁶ Further societal or expert consensus efforts to standardize and validate the utility of such tests are warranted. Analogously, current guidelines^{12,51} highlight a potential value of biomarkers for SVR—specifically natriuretic peptides—for risk stratification and

Secondary Tricuspid Regurgitation

HFpEF / HFmrEF / HFrEF

Figure 2 Stages of functional tricuspid regurgitation. Regardless of the underlying heart failure phenotype, increased left ventricular filling pressures will lead to increase pressures in the pulmonary circulation with effects on the right ventricle and tricuspid annulus as well as the right atrium that induce secondary tricuspid regurgitation (Phase I). Progressive right ventricular and atrial dilatation as well as annular remodelling will further increase secondary tricuspid regurgitation (Phase II). Progressive volume overload might lead to irreversible alteration of right ventricular and atrial as well as annular structure representing the late, often irreversible, phase of secondary tricuspid regurgitation (Phase III). Adapted from Ref.⁵³

timing of intervention. In SMR, the gold -standard biomarker N-terminal pro-b-type natriuretic peptide might allow to differentiate between HFpEF patients with valvular driven HF progression, which might benefit from transcatheter mitral valve replacement (TMVR), and patients in advanced HF stages, where TMVR might be futile.¹ Additionally, biomarkers, such as MR-proANP and MR-proADM, might allow to identify patients at high risk for SMR progression.⁵⁷ In contrast, little is known regarding the potential clinical applicability of biomarkers for risk stratification specific to STR.

Diagnostic approach to secondary mitral regurgitation in patients with heart failure

Secondary mitral regurgitation is most commonly evaluated by TTE. This modality is broadly available, has high temporal resolution, and

can accurately classify the underlying HF phenotype⁵¹ as well as the mechanism and severity of SMR in the majority of patients.⁵⁴ Transoesophageal echocardiography often provides more detailed assessment of the mitral valve complex and the aetiology of MR. To rule out organic valve disease might be specifically important in patients with HFpEF, where valve tenting is not necessarily evident and the mechanism of SVR often concealed. In the setting of general anaesthesia, the severity of MR might be underestimated as patients are heavily sedated, often dehydrated and have received vasodilatory anaesthesia.^{34,58} Different levels of blood pressures are central for variations in SMR severity, therefore, need to be reported along with the quantification of SMR. Furthermore, RV systolic pressures and LV filling pressures are intrinsically tied to SMR severity.^{59,60} It is important to recognize that the severity of SMR as assessed by TTE will often vary over time. These changes reflect the dynamic nature of SMR,

Table 2 Proposed definition and implications of the severity of secondary mitral regurgitation

	Mild (1+)	Moderate (2+)	Moderate-severe (3+)	Severe (4+)
Potential thresholds				
EROA (mm ²)	<20	20–29	30–39	≥40
Regurgitant volume (mL)	<30	30–44	45–59	≥60
Regurgitant fraction (%)	<30	30–39	40–49	≥50
Pulmonary vein systolic flow reversal	None	None	Bidirectional	Dominant
Risk implications				
Heart failure rehospitalization	Low	Intermediate	High	High
Progressive LV and LA remodelling	Low	Intermediate	High	High
SMR progression	Low	High	High	N/A
Dynamic increase	None	Mild	Significant	N/A
Potential impact of TMV repair or replacement				
Heart failure rehospitalization	—	Unknown	↓	↓↓
Progressive LV and LA remodelling	—	Unknown	↓	↓↓
SMR progression	—	Unknown	↓	↓↓
Symptoms and quality of life	—	Unknown	↓	↓↓
Mortality	—	Unknown	↓	↓↓

LA, left atrial; LV left ventricular; EROA, effective regurgitant orifice area; SMR, secondary mitral regurgitation.

intra- and interobserver variability associated with the modality,⁵⁴ and the natural history as the underlying LV disease either progresses or improves.^{35,36,61–63} These longitudinal changes across HF subtypes, as well as SMR severity *per se*, carries prognostic information potentially impacting on subsequent therapeutic management.^{35,36,61,62}

Common to both atrial and ventricular SMR mechanisms are deficient leaflet size in relation to annular, ventricular, or atrial size.^{49,64,65} Active adaptation of the mitral valve apparatus occurs in response to atrial and ventricular remodelling^{64,66}; however, excessive matrix turnover and fibrotic remodelling may occur in response to exuberant molecular signalling, limiting leaflet adaptation and inducing counterproductive leaflet thickening with inferior mechanical tissue properties that may further augment SMR.^{64,67} Morphological features, such as leaflet tenting, annular size, and leaflet-ventricular or leaflet-atrial mismatch, may provide prognostic information beyond quantitative assessment of SMR, a topic that should be addressed by future studies.

Assessment of secondary mitral regurgitation severity

It is important to determine the presence of atrial and/or ventricular SMR mechanisms (Figure 1). Typically, one of these mechanisms can be determined to predominate. However, assessment of SMR severity and mechanism may be challenging for several reasons: (i) structural remodelling of the LV and the left atrium may be present even in the absence of significant MR. (ii) Distinct features of SMR such as a non-circular regurgitant orifice, non-holosystolic regurgitant flow, and often multiple jets challenge technical assumptions often made with traditional SMR quantification.^{3,11,29,31} (iii) Echocardiographic methods to measure different parameters used to assess SMR severity, such as effective regurgitant orifice area (EROA), total stroke volume and regurgitant volume and fraction, and LV volumes vary and are not interchangeable. (iv) Although there are specific criteria for echocardiographic

appearance of SMR grading, the terms mild, moderate and severe SMR are poorly defined with respect to risk implications (HF rehospitalizations, mortality, SMR progression, and adverse remodelling).

Multiparametric echocardiographic assessment is required to quantify SMR.^{3,13,68–70} A unifying classification and the implications of varying severity of SMR is offered in Table 2. Central to this concept is that the risk of SMR is tied to the amount of the regurgitant load, its likelihood of progression and the potential benefit of transcatheter mitral valve repair (TMVr) strategies. The reference baseline risk is that of HF patients on GDMT with absent or only trace SMR. Whatever the subgroup, the final evaluation of the severity of SMR should be done in patients who are in stable condition and receive optimal medical management including cardiac resynchronization therapy (CRT) if indicated.

Mild secondary mitral regurgitation (1)

Commonly present in patients with HF and generally benign regarding its risk specific to the regurgitant driving force. Thresholds tied to the term mild should indicate a low add-on risk (compared to those without SMR) of HF events, progressive remodelling due to volume overload and therefore low probability of SMR progression as well as a low likelihood of significant dynamic increase in SMR with increased loading conditions.

Moderate secondary mitral regurgitation (2)

Quantitative thresholds for the term moderate SMR indicate an increased risk of HF events (in relation to patients without SMR) likely with progressive volume overload and, therefore, structural remodelling justifying a close follow-up in specialized HF centres. Whether mitral valve repair or replacement is beneficial for moderate MR, however, is uncertain.

Figure 3 Theoretical plot of secondary valve regurgitation severity across the entire heart failure spectrum (at any ejection fraction). Regurgitant volume is plotted against left ventricular total stroke volume, the black line roughly separates haemodynamic significant secondary valve regurgitation (red area, top) from haemodynamic non-severe secondary valve regurgitation (green area, bottom) by assuming a regurgitant fraction cut-off of 50%. There is an area of uncertainty attributable to methodological measurement variability and the different heart failure background risk across the ejection fraction spectrum depicted in yellow. Using a regurgitant volume vs. total left ventricular stroke volume plot has the advantage that it can be uniformly used across the entire heart failure spectrum where ejection fractions and left ventricular volumes are different.

Severe secondary mitral regurgitation (3 or 4)

The term severe SMR is linked to treatment response and thus potential referral for TMVr or TMVR, or advanced HF therapies (e.g. heart transplant, LV assist devices) in those patients that also display an exhausted compensatory reserve specific to the amount of myocardial impairment. Therefore, quantitative thresholds should not only indicate a high risk of HF events due to volume overload by SMR but more importantly a high probability for the patient to draw survival benefits with TMVR.

A recently proposed^{71,72} conceptual framework has introduced new terms (proportionate and disproportionate SMR) for the significance of SMR in patients with HF.⁷¹ The framework describes that the severity of SMR as assessed by the EROA depends on the LV end-diastolic volume (LVEDV). Thus, as LV volumes are typically largest in HFrEF, intermediate in HFmrEF and smallest in HFpEF,⁸ the threshold of EROA signifying severe SMR would be typically smallest in HFpEF followed by HFmrEF and highest in HFrEF. In essence, the framework interprets a lesion to be disproportionate (representing very severe SMR) if the regurgitant fraction (RF) ($RF\% = \frac{FMR_{regurgitant\ volume}}{total\ LV\ stroke\ volume}$) exceeds 50% including a margin of methodological imprecision inherent to the proximal isovelocity surface area method. As the denominator of the RF equation is total LV stroke volume, the RF relationship depends on LVESV and LVEDV. Therefore, the essential component of the equation is the total stroke volume and the thresholds for the EROA and the regurgitant volume remain relatively stable throughout the spectrum of HF subtypes (Figure 3). In other words, if the RF is $\geq 50\%$, the SMR should be considered to be clinically relevant, specifically in the grey-zone of an

EROA of 20–30 mm²/a RegVol of 30–45 mL.^{3,73} The RF, however, is prone to compound error due to multiple measurements. In case of remaining uncertainty, additional tests to confirm the RF, such as cardiac MRI, should be performed. Of note, quantitative thresholds of SMR severity have been validated in HFrEF,^{3,11} and clinical benefits were observed in selected patients with HFmrEF and 3+ or 4+ SMR in the subgroup analysis of the COAPT trial^{20,68} but remain essentially uncertain in patients with HFpEF. In fact, variations of quantitative thresholds for SMR severity might exist across the HF due to different HF background risk. These considerations need to be validated by future studies.

Diagnostic approach to secondary tricuspid regurgitation in patients with heart failure

Secondary tricuspid regurgitation is no less challenging to evaluate than SMR, and a multimodality approach is increasingly recommended by expert consensus and guideline documents.^{13,54} The mechanism of STR in HF patients is complex and often multifactorial. Imaging is key to decipher the principal and contributing structural and functional components of STR⁷⁴ which likely will impact the choice of the evolving treatment armamentarium pertinent to a personalized treatment approach.⁵³ As with SMR, the initial imaging approach to STR is cross-sectional echocardiography which provides important information to contributing conditions, such as the severity of pulmonary systolic pressure, the presence of eccentric right heart remodelling with associated leaflet tethering, and the extent of right atrial and tricuspid annular dilatation. Cardiac CT provides

Figure 4 Current and proposed treatment concepts for secondary mitral regurgitation according to heart failure subtype and haemodynamic significance. Guideline-directed medical therapy is the first-line treatment in heart failure with reduced ejection fraction and heart failure with mid-range ejection fraction. Medical therapy for heart failure with preserved ejection fraction relates to controlling risk factors as well as rhythm and rate with atrial fibrillation. Treatment of heart failure with reduced ejection fraction on top of guideline-directed medical therapy and cardiac resynchronization depends on the competing heart failure background risk and secondary valve regurgitation severity. Patients with very severe secondary valve regurgitation but relatively mild myocardial impairment are expected to derive benefits from transcatheter repair, whereas patients with severe myocardial impairment and relatively non-severe secondary mitral regurgitation are not expected to derive immediate benefits and should be evaluated for circulatory support and transplantation without delay. In heart failure with mid-range ejection fraction, transcatheter therapy is expected to improve outcome but rather a perspective than an established therapy which needs to be addressed by controlled trials. Regular follow-up in specialized heart failure and valve clinics is key as secondary valve regurgitation can progress (multicolour arrow, bottom) necessitating regular readjustments of therapeutic strategies.

complementary information and will likely become crucial for potential planning structural interventions. Assessment of the tricuspid annular shape, perimeter, and diameters and localization of the right coronary artery and its course within the AV groove, as well as its distance from the tricuspid annulus, are specific strengths of CT.

Assessment of secondary tricuspid regurgitation severity

Grading of STR relies on specific qualitative and semiquantitative criteria.^{13,54} If STR severity remains uncertain, quantitative Doppler and vena contracta measurements are indicated and can help in adjudication to one out of three grades. Similarly to SMR, the terms used for reporting STR severity are not clearly defined. A potential definition of these terms for STR is more challenging because current knowledge of STR risk is limited, data from randomized clinical trials of TTVR are not available and the evolution of STR has not been studied in pure HF cohorts to date. Recent trends will likely redefine the terminology and adjacent

thresholds for grading STR in both directions: the tail end of the STR spectrum grouped under the umbrella term 'severe' seems to be far more heterogeneous than for SMR with EROAs >80 mm². Severe TR may thus be further classified as massive or torrential, although studies on the natural history of such profound degrees of STR are limited to one study using the vena contracta width to define these terms.⁷⁵ Further validation and prospective studies are required to establish the utility of these terms.

The independent impact of STR has been demonstrated by observational studies in cohorts with HFrEF and HFmrEF^{4,5} as well as a pure HFrEF cohort.⁶ In addition to EROA and regurgitant volume, the RF can be calculated for STR and may add incremental information for procedural timing in HF patients. However, due to the complex RV and tricuspid annular shape, RF and potential thresholds for assessing STR severity remain unvalidated. Three-dimensional echocardiography and CMR may provide further risk stratification. For example, three-dimensional imaging of the vena contracta area avoids geometrical assumptions and might more precisely quantify STR.⁷⁶

Moreover, the interplay between MR and TR has been inadequately studied. Presumably, STR may develop secondary to SMR. Therefore, the dynamics of STR related to changes in pulmonary pressure and SMR have to be evaluated holistically as treatment options for STR are more widely studied. Long-term, STR HFmrEF, and STR-HFrEF is associated with worse survival, independently of pulmonary hypertension and RV function.^{4–6}

Predictors of STR progression have not been sufficiently characterized according to specific HF subtypes, representing an important gap of knowledge. For example, evolving treatments might depend on timely identification of valvular-driven HF before the development of irreversible structural damage.

Therapeutic approaches to secondary valvular regurgitation

A close collaboration between valve specialists, imaging experts, interventionalists, and mitral surgeons (the 'mitral heart team')¹¹ is essential in the therapeutic approach to patients with SVR. Maximally tolerated doses of GDMT for patients with HFrEF must be ensured⁵¹ and CRT offered if specific indications are met.^{41,51} Although there are no specific medical therapies for HFmrEF or HFpEF, underlying risk factors must be treated. Secondary prevention through cardiac rehabilitation might be a supportive treatment option after assessment of peak exercise capacity by maximal symptom-limited cardiopulmonary exercise testing to maintain or improve functional capacity after valve repair in stable HF patients.^{77,78} Depending on the patient's prognosis and course, the heart team may be expanded to include experts from disciplines, such as electrophysiology and advanced HF therapists offering mechanical circulatory support and transplant options. Figure 4 depicts the current treatment paradigm utilizing available options tailored to the HF subtype and the severity of the regurgitant lesion.

Guideline-directed medical therapy

In patients with HFrEF, GDMT is the first-line therapeutic approach.^{12,51} Treatment with beta-blockers,^{79,80} renin-angiotensin-aldosterone system antagonists,^{81,82} and most recently angiotensin receptor neprilysin inhibitor⁸³ therapy may result in LV unloading, reverse remodelling and pleiotropic drug effects, secondarily reducing SMR. In the randomized PRIME trial, neprilysin inhibition (sacubitril) with valsartan (ARNI) reduced quantitative metrics of SMR (regurgitant volume difference of 7.3 mL, 95% CI 1.9–12.6; $P=0.009$). Although numerical reductions in SMR were small, absolute reductions in quantitative metrics may be clinically meaningful during long-term follow-up. Of note, ARNI led to a significant reduction in LVEDV which might reduce leaflet tethering and SMR. ARNI also reduced LVESV; the combined effect of higher stroke volume and reduced regurgitant volume translated to a meaningful reduction in RF and SMR. PRIME included patients with LVEF 25–50%, indicating that ARNI might be beneficial in HFmrEF and HFrEF. The use of diuretics is recommended for patients with HFrEF and HFpEF for decongestion and symptom relieve until euvolaemia is achieved.⁵¹ Effective medical therapy of HFpEF remains elusive and is mainly symptom oriented regardless of SVR. Considering the potential mechanistic role of atrial fibrillation in patients with HFpEF and SVR, rhythm and rate

control are additional important therapeutic targets and may prevent disease progression.⁸⁴

In patients with STR, medical therapy targets the underlying left-sided myocardial impairment. Initiation and titration of medical therapy for HFrEF and HFmrEF may diminish STR by improving LV systolic and diastolic function. Loop diuretics are used to reduce volume load and thereby reduce pulmonary pressures (i.e. RV afterload) and the use of mineralocorticoid antagonists in natriuretic doses might improve decongestion in the setting of hyperaldosteronism due to hepatic congestion.⁵¹ As atrial fibrillation is a risk factor for tricuspid annular dilatation⁸⁵ and progressive STR,³⁶ rhythm and rate control may play an important role across the entire EF spectrum.

Cardiac resynchronization therapy

Intraventricular mechanical dyssynchrony augments SMR in patients with HFrEF.^{41,86} Cardiac resynchronization therapy can reduce SMR and its associated morbidity and mortality in 30–50% of patients.^{41,87} Treatment is indicated according to current guidelines after initiation and titration of medical therapy in symptomatic patients with an LVEF $\leq 35\%$ and a QRS duration of ≥ 150 ms with left bundle branch block configuration.⁵¹ The response to CRT is biphasic and may be attributed to an acute increase in systolic mitral valve closing forces by direct improvement of synchronicity⁸⁸ and late effects due to LV reverse remodelling.^{42,43} Close follow-up before referral for transcatheter mitral valve interventions is therefore reasonable. Whether patients with SMR and evidence of mechanical dyssynchrony might derive benefit from CRT beyond current Class I indications^{41,51} remains unclear and should be addressed by future research.

Surgical approach to secondary valve regurgitation in heart failure

The surgical approach to SVR in patients with HF is controversial. Indications are particularly restrictive when concomitant revascularization is not an option¹² due to generally high-risk of surgery and frequent recurrence of SMR after standard surgical annular ring reduction. In patients with ischaemic or viable myocardium and SMR, coronary artery bypass grafting can reverse LV remodelling and blunt SMR,^{89,90} however, up to one half of the patients will encounter persistent or worsening SMR.^{12,91} Therefore, mitral valve surgery on top of surgical revascularization is recommended by current guidelines. The state-of-the-art surgical approach entails restrictive annuloplasty utilizing complete (semi) rigid rings and chordal sparing valve replacement. The latter has the advantage of more durable SMR correction and less HF events.^{92,93} Left ventricular to annuloplasty ring mismatch is associated with increased risk of SMR recurrence and might guide the procedure on whether to repair or replace.⁹⁴ Furthermore, the importance of maximizing anterior leaflet opening during surgery needs to be considered^{95,96} and targeting the subvalvular apparatus during repair might improve outcomes.^{97,98} In patients with moderate SMR that are scheduled for surgical revascularization addition of repair is associated with less SMR persistence but an increased risk of early neurological events and supraventricular arrhythmias.^{99,100}

Transcatheter repair for secondary valve regurgitation

Patients with HF and severe SVR who remain symptomatic despite maximally tolerated doses of GDMT and CRT if indicated have a poor prognosis.^{2,6,7,24,101} Transcatheter repair and replacement for SVR might allow the detrimental effects of the regurgitant load to be safely reduced and disrupt the vicious circle of valvular-driven HF progression.^{20,102,103} In the future, the evolving toolset of devices for SVR may lead to a mechanism-tailored approach that addresses specific anatomical features of SVR. Current systems can roughly be classified as leaflet-based devices (e.g. MitraClip and Pascal), annuloplasty devices [direct annuloplasty (e.g. CardioBand, Mitralign, Millipede), indirect annuloplasty (e.g. Carillon), and ventriculoplasty devices (e.g. Accucinch)], bioprosthetic valve implantation and a variety of other approaches including muscle slings, spacers, and more. The phenotype with relatively preserved LVEF and dilatation of the annulus as the leading mechanism, for instance, might benefit from annular reduction. As with any procedure/device, there is a clear link between operator experience and procedural results as most recently shown for MitraClip by data from the STS/ACC TVT Registry.¹⁰⁴

The MitraClip system remains the only system evaluated in large randomized clinical trials. The MITRA-FR^{19,105} study randomized 302 symptomatic HFrEF patients with SMR as defined by an EROA >20 mm² or a regurgitant volume >30 mL to either GDMT alone or TMVR plus GDMT. There were no significant differences in the primary endpoint of all-cause death or hospitalization for HF at 12 or 24 months. COAPT randomized 614 HFrEF and HFmrEF patients with moderate-to-severe or severe SMR defined using a multiparametric approach (most having an EROA >30 mm² or pulmonary systolic vein flow reversal) to MitraClip plus maximally tolerated doses of GDMT vs. GDMT alone. A marked decrease in the primary endpoint of all HF hospitalizations within 2 years was noted, along with reduced all-cause mortality and improved quality of life and exercise capacity.¹⁰⁶ No subgroups were identified that did not benefit.

The similarities, differences, and complementary features of these studies have been reviewed extensively.^{71,107–109} The principles that likely explain the disparate results of these trials are as follows: (i) severity of SMR: baseline EROA measures demonstrate that SMR was less severe in MITRA-FR (EROA <30 mm² 52%) than in COAPT (EROA <20 mm² in only 14%), reflective of different quantitative thresholds for the definition of severe SMR.¹¹ In addition, unlike MITRA-FR, the COAPT trial placed a limit on LV dimensions (LVESD ≤70 mm). Thus, the outcome in MITRA-FR might have been more related to the severity of myocardial impairment rather than the severity of SMR. As a result, COAPT enrolled a larger proportion of disproportionately severe SMR patients than did MITRA-FR. (ii) Heart failure spectrum: while MITRA-FR was a pure HFrEF study by inclusion criteria (LVEF 15–40%), the COAPT trial also included patients with HFmrEF (LVEF 20–50%). Nonetheless, the two studies ended up with similar baseline mean EF (33.1% in MITRA-FR vs. 31.3% in COAPT)—potentially a result of a more restrictive selection process with additional evaluation by a central eligibility committee in COAPT. In COAPT, the reduction in death or HF hospitalization rates were similar in the ~20% of patients with HFmrEF as those with HFrEF. Nonetheless, given the relatively small sample size of HFmrEF patients, confirmatory studies are warranted

in this subgroup. As previous findings have suggested a loss of prognostic significance of SMR in more severe HF¹ stages, it is possible that MITRA-FR enrolled patients with more advanced HF¹¹⁰ (consistent with the larger LVEDV in MITRA-FR). (iii) In contrast to COAPT, patients enrolled in MITRA-FR were not required to be on maximally tolerated GDMT, and background medical therapies were allowed to vary during follow-up in MITRA-FR (but not in COAPT). In fact, the protocol in MITRA-FR clearly stated that medical therapy should be maximal but its assessment was done by the local heart team and not a central eligibility committee which most probably makes a difference. As a result, the control group symptomatically improved to a greater degree during follow-up in MITRA-FR compared with COAPT.

Both MITRA-FR and COAPT will follow patients through 5 years which might address important questions regarding late prognosis after TMVR. In addition, the COAPT and MITRA-FR investigators plan to pool their datasets to facilitate identifying which patients with HF and SMR are likely to benefit (and not benefit) from MitraClip treatment. Until pending results of these analyses, TMVR should be considered in selected patients, however, clear recommendations cannot be given yet. Finally, despite the marked clinical benefits noted with TMVR in COAPT, the long-term rates of death and HF hospitalization were still high, reflecting the underlying degree of LV dysfunction. Further studies are warranted to determine whether earlier treatment of SMR in HFrEF and HFmrEF patients may halt progressive LV dysfunction and improve prognosis.

As for transcatheter tricuspid interventions, no randomized trials have been performed. Recently, however, the TriValve¹⁰² registry provided a propensity-matched analysis with two large retrospective cohort studies in an attempt to gain insights into effectiveness of transcatheter tricuspid interventions. This analysis suggested a greater survival and freedom from HF hospitalizations with STR interventions after adjustment for confounders. The baseline LVEF of study participants reflects more the HFmrEF and HFpEF spectrum in which STR has been consistently associated with worse outcomes. However, improved outcomes with transcatheter tricuspid interventions were also observed in the subgroup of patients with an LVEF ≤35%. This observation is of potential importance as the significance of STR in this cohort of patients has been debated.^{4,7,27} These data now provide the basis to perform randomized studies that address this unmet clinical need across all HF stages. In addition, studies looking at the impact of initial RV function on the results following valve repair are needed.

Summary and perspectives

Secondary valve regurgitation is highly prevalent across the HF spectrum with significant impact on symptomatic status, quality of life, adverse cardiac remodelling, HF hospitalizations, and mortality. Accurate assessment of SVR is challenging and requires additional training of imaging experts well versed in the nuances of SMR and STR analysis. Definition of SMR significance is needed specifically validated in HFrEF HFmrEF and HFpEF cohorts where different HF background risk are expected to result in slightly different thresholds. Guideline-directed medical therapy is the first-line treatment in HFrEF and should be administered in maximally tolerated doses to

optimize effect. Therapeutic escalation includes CRT if indications are met, TMVR for selected HF subgroups and, as a last resort for very advanced HF, mechanical circulatory support or cardiac transplantation. New drugs and devices need to be tested in order to advance therapeutic management of SMR. Additional randomized trials are needed to provide therapeutic guidance for SVR in other stages of the HF life cycle to expand the indications for valve repair, and to establish the potential role for emerging non-leaflet-based devices. Moreover, optimal timing of intervention for STR needs further research specifically in view of deteriorating RV function and in the presence of pulmonary hypertension. Evidence from randomized clinical trials on new HF drugs targeting RV function and pulmonary hypertension and devices for STR repair and replacement are an unmet clinical need that needs to be addressed in the near future. Heart valve and HF clinics remain central in the diagnostic and therapeutic approach to SVR, and collaborative heart teams are imperative to provide the best possible care.

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