Advanced echocardiography in characterization and management of patients with secondary mitral regurgitation

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The research described in this thesis was performed at the Heart Lung Center of the Leiden University Medical Center, Leiden, the Netherlands.

ISBN 978-94-6332-817-3
Layout Loes Kema
Print GVO Drukkers & Vormgevers

Financial support for this thesis by Namazi Trading b.v.; ABN AMRO Bank N.V.; ChipSoft b.v. is gratefully acknowledged

Advanced echocardiography in characterization and management of patients with secondary mitral regurgitation

Proefschrift

ter verkrijging van
de graad van doctor aan de Universiteit Leiden,
op gezag van rector magnificus prof.dr.ir. H. Bijl,
volgens besluit van het college voor promoties
te verdedigen op 10 mei 2022
klokke 16.15 uur

door

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geboren te Teheran
in 1989

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Financial support by the Dutch Heart Foundation for the publication of this thesis is gratefully acknowledged

Voor mijn ouders,
Farnoush en Farshad

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Chapter one

General introduction and outline of thesis

"Imaging of the mitral valve: role of echocardiography, cardiac magnetic resonance, and cardiac computed tomography".

Namazi F*, Vo NM*, Delgado V.

Curr Opin Cardiol. 2020 Sep;35(5):435-444.

Introduction

Severe mitral regurgitation is one of the most common valvular diseases worldwide [1□□]. The advent of transcatheter therapies has influenced the decision making of patients with symptomatic severe mitral regurgitation, particularly those with high-operative risk or contraindications for surgery. These therapies include devices that target the leaflets (MitraClip, Abbott Vascular, Santa Clara, CA; Neochord, Inc., St Louis Park, MN; Pascal, Edwards Lifesciences, Irvine, CA), the mitral valve annulus (Cardioband, Edwards Lifesciences; Carillon Mitral Contour System, Cardiac Dimensions, Kirkland, WA) or replace the mitral valve (apical tethered system – Tendyne [Abbott Vascular]; radial force system – Intrepid [Medtronic, Inc., Redwood City, CA]; and native leaflet engagement – Tiara valve [Neovasc Tiara]) (Fig. 1). Selection of patients for these therapies requires accurate quantification of mitral regurgitation, assessment of the mitral valve anatomy and evaluation of the left ventricular dimensions and systolic function as well as left atrial dimensions. In contrast to surgery, the mitral valve cannot be inspected during the procedure and the interventionalists need to have accurate visualization of the mitral valve apparatus. Three-dimensional-imaging techniques have become indispensable tools to plan and guide these transcatheter interventions: three-dimensional transesophageal echocardiography and computed tomography provide unparalleled views of the mitral valve and the key measurements to select the type and size of the device. In addition, three-dimensional transesophageal echocardiography provides the soft-tissue resolution that can be overlaid on to fluoroscopy to accurately guide the procedure. Cardiovascular magnetic resonance (CMR) is less frequently used but is an excellent imaging modality to quantify left ventricular dimensions and function and the severity of mitral regurgitation. In addition, late gadolinium contrast-enhanced techniques permit tissue characterization of the myocardium and may have important implications in the timing of intervention. This review will discuss the role of different imaging techniques to evaluate patients with mitral regurgitation for transcatheter interventions.

Echocardiography

Two-dimensional transthoracic echocardiography is the imaging modality of first choice in diagnosing mitral regurgitation and assessing its severity. The mechanism of mitral regurgitation can be assessed with two-dimensiontal transthoracic echocardiography; however, the advent of three-dimensional echocardiography has permitted a systematic approach to define the lesion that causes the mitral regurgitation (Fig. 2). In general, mitral regurgitation is divided into primary (when the lesion is primarily of the mitral leaflets) and secondary (when the coaptation failure is because of left ventricular dilation

and dysfunction or left atrial dilation but the mitral leaflets are structurally normal). The classification by Dr. Carpentier [2], considering the motion of the mitral valve leaflets, divides the mechanisms of mitral regurgitation into three different types: type I, when the mitral leaflets are structurally normal, the left ventricular systolic function is preserved and mitral annulus dilatation is the only mechanism responsible for mitral regurgitation; type II, when there is excessive motion of the mitral valve leaflets (causing prolapse); and type III, when there is restrictive motion of the mitral valve leaflets (IIIa, with systolic and diastolic restriction due to primary thickening of the mitral valve apparatus; IIIb, with systolic restriction due to tethering of the leaflets by dilation and severe dysfunction of the left ventricle). When there is primary damage of structurally normal leaflets, such as perforation because of endocarditis, the mechanism is also considered type I. Grading mitral regurgitation needs the integration of qualitative, semiquantitative, and quantitative echocardiographic parameters (Fig. 2). However, in very eccentric regurgitant jets or in patients with secondary mitral regurgitation, the criteria may be discordant and grading the severity of mitral regurgitation becomes challenging. In those situations, three-dimensional echocardiography or CMR may help to discern between severe and nonsevere mitral regurgitation.

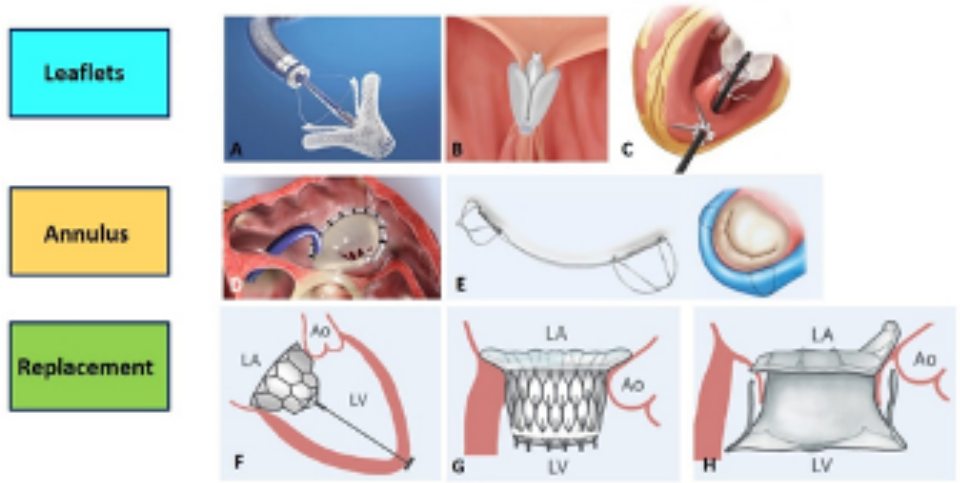

Figure 1: Transcatheter mitral valve therapies. Mitral valve devices targeting the mitral valve leaflet (Panel a = MitraClip device, Abbott Vascular, Santa Clara, California (courtesy of Abbott Vascular); panel b = Pascal, Edwards Lifesciences, Irvine, California (courtesy of Edwards Lifesciences); panel c = NeoChord, Inc., St Louis Park, Minnesota (courtesy of Neochord), mitral valve annulus (panel d = Cardioband, Edwards Lifesciences) (Courtesy of Edwards Lifesciences); panel e = Carillon Mitral Contour System, Cardiac Dimensions, Kirkland, Washington (reproduced with permission from Witte et al. [29]) and total mitral valve replacement (panel f = apical

tether system; panel g = annular winglets system; panel h = native leaflet engagement system (reproduced with permission from Regueiro et al. [30]).

		Primary MR			Secondary MR	
MR mechanism according to Carpentier classification		Type I *Normal leaflet motion (i.e. leaflet perforation)*	Type II *Excessive leaflet motion (i.e. mitral valve prolapse or flail)*	Type IIIa *Restricted opening during systole and diastole (i.e. rheumatic heart disease)*	Type I *Normal leaflet motion (i.e. annular dilation)*	Type IIIb *Restricted closure during systole (i.e. due to tethering of the leaflets secondary to LV dysfunction and dilation)*
Severe MR	**Qualitative**	Flail leaflet, ruptured papillary muscle, large perforation			Large coaptation defect	
		Very large central jet or eccentric jet adhering, swirling and reaching the posterior wall of the left atrium			Very large central jet or eccentric jet adhering, swirling and reaching the posterior wall of the left atrium	
	Semiquantitative measurements	Vena contracta width ≥7mm (>8 mm for biplane)			Vena contracta width ≥7mm (>8 mm for biplane)	
		Systolic pulmonary vein flow reversal			Systolic pulmonary vein flow reversal	
		E-wave dominant ≥1.5 m/s (according to AHA/ACC guidelines >1.2m/s)			E-wave dominant ≥1.5 m/s (according to AHA/ACC guidelines >1.2m/s)	
	Quantitative measurements	EROA ≥40 mm²			EROA ≥20 mm² (according to AHA/ACC guidelines EROA ≥40 mm²)	
		Regurgitant volume ≥60 mL/beat			Regurgitant volume ≥30 mL/beat (according to AHA/ACC guidelines RVol ≥60 mL/beat)	
		Regurgitant fraction ≥50%			Regurgitant fraction ≥50%	

Figure 2: Mechanisms of and criteria for the definition of severe mitral regurgitation [2,5,7,23]. EROA, Effective regurgitant orifice area; MR = mitral regurgitation RVol, regurgitant volume.

Three-dimensional transesophageal echocardiography has been shown to provide better information on valve morphology and function [3,4–7]. Morphological assessment of the mitral valve is key in the evaluation of patients with severe mitral regurgitation who may be candidates for transcatheter therapies (Fig. 3). For transcatheter edge-to-edge repair therapies, the leaflet coaptation depth and length (in secondary mitral regurgitation) and the width and height of the flail (in primary mitral regurgitation) need to be measured. The Neochord device is an appropriate therapy for primary mitral regurgitation preferably because of prolapse of the central scallop of the posterior mitral leaflet and with enough length of the leaflets relative to the mitral annulus dimensions to ensure proper coaptation. When evaluating patients for transcatheter mitral annuloplasty, the dimensions of the mitral annulus should be assessed. Three-dimensional transesophageal echocardiography is superior to two-dimensional transthoracic echocardiography to assess the mitral annulus perimeter and area.

Furthermore, three-dimensional transesophageal echocardiography has shown good agreement with CMR to quantify the effective regurgitant orifice area and the regurgitant volume [8–11]. Postprocessing of the three-dimensional color Doppler data using multiplanar reformation planes permits the measurement of the three-dimensional vena contracta and the anatomic regurgitant orifice area (Fig. 4). Choi et al.[12] compared mitral regurgitation quantification with the two-dimensional and three-dimensional echocardiographic proximal isovelocity surface area (PISA) methods and demonstrated that the two-dimensional PISA method significantly underestimated the mitral regurgitant volume compared with the three-dimensional PISA method (52.4 ± 19.6 ml versus 59.5 ± 25.6 ml; P = 0.005). In addition, in the subgroup of individuals with CMR data, the mitral regurgitant volume obtained by three-dimensional PISA method showed a better agreement with phase-contrast CMR than two-dimensional PISA (r = 0.97 versus 0.84, respectively).

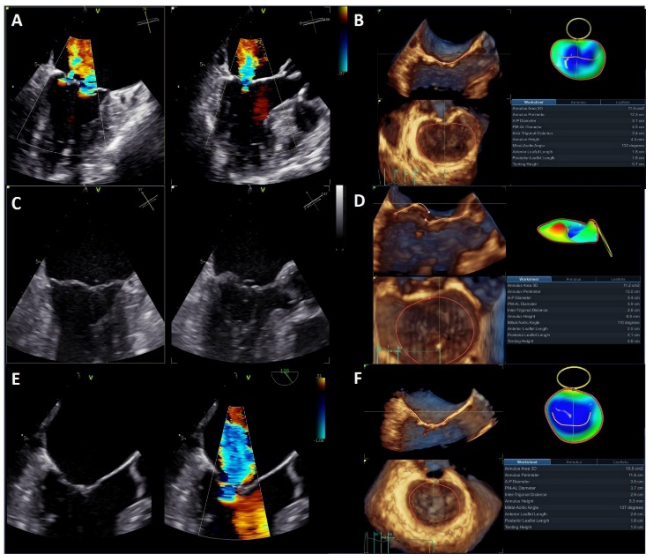

Figure 3: Examples of three-dimensional transesophageal echocardiography images of patients with suitable anatomy for various transcatheter interventions. Panels a and b demonstrate a patient suitable for cardioband, with mitral regurgitation caused by annulus dilation (annulus area of 11.4 cm2). Panels c and d demonstrate a patient suitable for Neochord, with primary mitral regurgitation because of prolapse of the central scallop of the posterior mitral leaflet and enough leaflet length (anterior leaflet length of 2.0 cm and posterior leaflet length of 2.1 cm). Panels e and f demonstrate a patient with secondary mitral regurgitation with suitable anatomy for edge-to-edge therapy device (tenting height of 1.0 cm and anterior and posterior leaflet length of 2.6 and 1.6 cm, respectively).

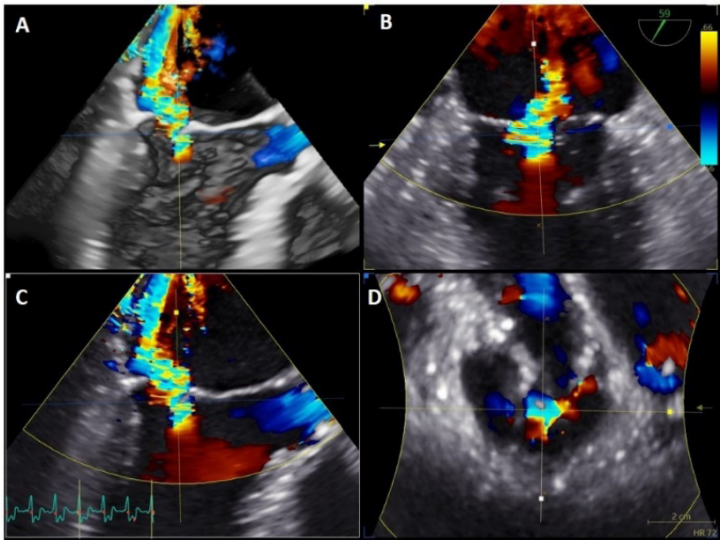

Figure 4: Three-dimensional transesophageal echocardiography color Doppler data for mitral regurgitation quantification. The multiplanar reformation planes are aligned to obtain the three-dimensional vena contracta (1.0 cm) and EROA (0.90 cm2). Panel a displays the three-dimensional rendering of the mitral valve. Panel b displays the reconstructed bicommissural mitral view, whereas panel c shows the reconstructed long-axis view. Panel d displays the transversal plane of the mitral valve at the level of the coaptation line where the anatomical vena contracta can be planimetered. EROA, effective regurgitant orifice area; mitral regurgitation, mitral regurgitation.

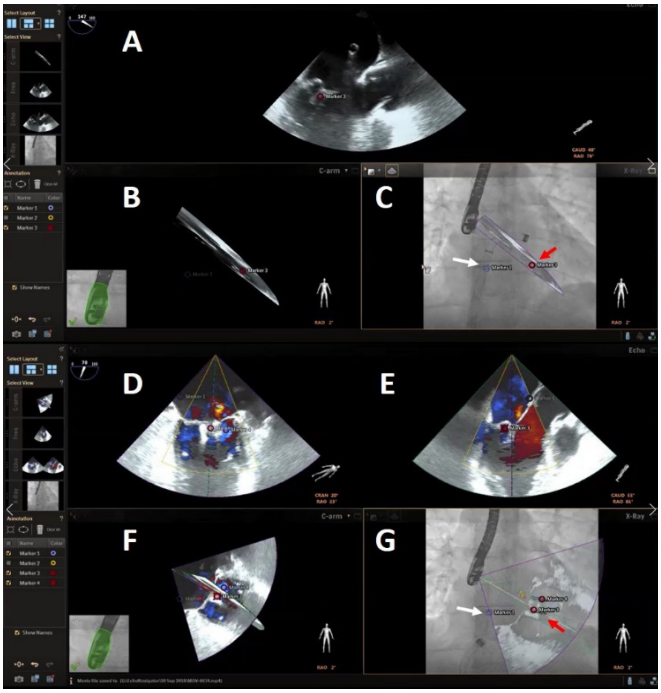

Figure 5: Fusion image of echocardiography and fluoroscopy, facilitating the procedural guidance during the MitraClip procedure. Panel a demonstrates real-time transesophageal image during the procedure whereas panel b shows the spatial orientation of that two-dimensional view based on the fluoroscopic projection. The probe is detected indicating that the position of the probe relative to the C-arm has been detected leading to the overlaid of the transesophageal echocardiographic view

on to the fluoroscopy image with markers placed at the level of the transseptal puncture to introduce the guiding catheter (Panel c, arrow) and where the MitraClip device should be positioned (Panel c, arrow). Panels d and e display the simultaneous biplane color Doppler views of the mitral valve during the MitraClip device implantation which are oriented relative to the C-arm in Panel f. Panel g demonstrates the fusion image with fluoroscopy showing the markers of the transseptal puncture and guiding catheter (arrow) and where the MitraClip device is placed (arrow).

Finally, two-dimensional and three-dimensional TEE are very important in the procedural guidance. Fluoroscopy does not have good soft-tissue resolution and needs the combination of echocardiography to guide the procedure. Current advances permit live fusion of echocardiography and fluoroscopy, facilitating the procedural guidance in key steps such as transseptal puncture and orientation of the device during the deployment of the device (Fig. 5).

Computed tomography

Multidetector row computed tomography (MDCT) is crucial to anticipate the feasibility of specific transcatheter mitral valve repair techniques. MDCT provides information on the mitral valve anatomy and geometry and its spatial relationship with surrounding structures [13,14]. When MDCT data are acquired along the entire cardiac cycle, the movement of the mitral valve leaflets can be characterized and the anatomical lesion causing the dysfunction can be identified. In addition, the narrowest three-dimensional anatomical vena contracta can be assessed by aligning the multiplanar reformation planes at the level of the tips of the mitral leaflets during systole [15].

MDCT is the imaging technique of choice to select patients and plan transcatheter therapies that target the mitral valve annulus or replace the valve. The key information that needs to be assessed with MDCT prior to transcatheter mitral annuloplasty includes the dimensions of the mitral valve annulus, the location of the coronary sinus and circumflex coronary artery relative to the mitral annulus and the presence of extensive mitral annulus calcifications, particularly at the anterolateral level (P1) where the first three anchors of the Cardioband device are implanted (Fig. 6). The size of the mitral valve annulus will determine the size of the annuloplasty device. The location of the coronary sinus relative to the mitral annulus is important when considering devices that indirectly cinch the mitral annulus (Carillon Mitral Contour System). In addition, the course of the circumflex coronary artery is important to predict the risk of impingement of this artery by the device (Fig. 6).

In the selection of patients for transcatheter mitral valve replacement, the dimensions and calcification of the mitral valve annulus should be assessed as well as the dimensions of the left ventricle and left ventricular outflow tract (LVOT). The mitral valve annulus has a characteristic saddle shape which may be difficult to conform for a tubular transcatheter expandable valve. Blanke et al.[16] proposed an MDCT-based simplified annulus description consisting of a D-shaped mitral annulus which is defined as being limited anteriorly by the intertrigonal distance, excluding the aortomitral continuity (Fig. 7). When measuring the mitral valve annulus according to the saddle shape, the area was significantly larger than when considering the D-shaped annulus (13.0 ± 3.0 cm2 versus 11.2 ± 2.7 cm2). In addition, the three-dimensional perimeter of the saddle-shaped annulus was significantly larger than the two-dimensional projected perimeter of the D-shaped annulus (136.0 ± 15.5 mm versus 128.2 ± 14.8 mm).

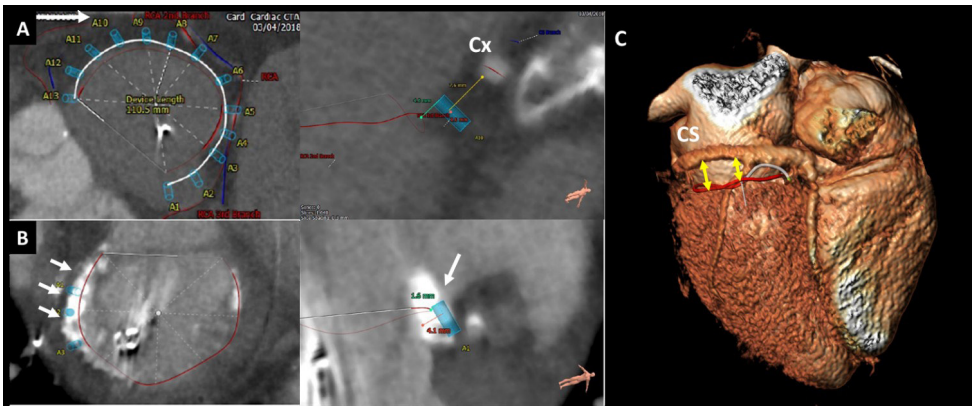

Figure 6: Multidetector row computed tomography to assess the anatomical suitability for transcatheter mitral valve annuloplasty. Panel a demonstrates a patient suitable for Cardioband. The left part shows the anchoring planning (arrow) in the mitral valve annulus. At the right is the distance measured between the anchoring and annulus (4.0 mm) and distance between anchoring and circumflex coronary artery (Cx, 7.6 mm). Panel b shows an example of a patient with unsuitable anatomy for Cardioband with massive mitral annulus calcification (arrows). In the left the anchoring would be in the calcified mitral valve annulus at the level of P1 (arrow). For indirect transcatheter mitral annuloplasty technique, the distance between the coronary sinus and the mitral annulus is relevant to efficiently reduce the size of the annulus. From three-dimensional volume rendering, the coronary sinus can be visualized coursing in this patient too high above the mitral annulus (line) as pointed out by the double arrowheads (panel C).

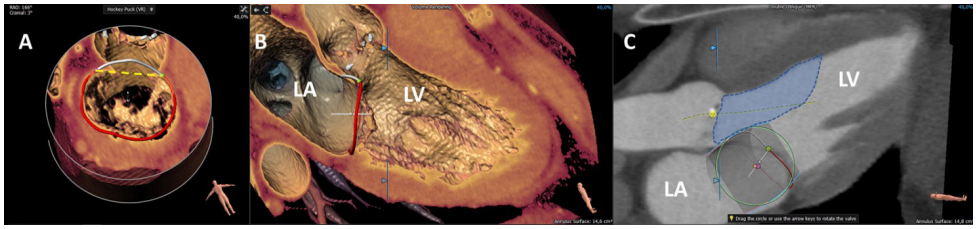

Figure 7: Mitral annulus assessment with MDCT in preprocedural planning of transcatheter mitral valve replacement. The D-shape mitral annulus reconstruction is shown in panel a with the dotted line indicating the intertrigonal distance. Panel b shows the long-axis view of the left ventricular outflow tract (LVOT) and the mitral annulus with the highest point anteriorly in relation with the aortic root. The corresponding computed tomography sagittal view shows the simulation of a tubular transcatheter mitral valve fitted in the mitral annulus and showing the LVOT clearance (or neo-LVOT, shaded area).

More important is the prediction of LVOT obstruction when considering transcatheter mitral valve replacement and that can be performed by calculating the neo-LVOT area [16–18]. Blanke et al.[16] noticed that when considering the saddle-shaped mitral valve annulus, the clearance of the LVOT was smaller than when considering the D-shaped annulus. In addition, it is also important to establish how to measure the neo-LVOT. Meduri et al.[19□□] hypothesized that the current standard MDCT-assessment performed on end-systolic images might underestimate the neo-LVOT area. Of 33 patients considered for transcatheter mitral valve replacement who were screened for the Intrepid Global Pilot Study and had high risk of LVOT obstruction based on end-systolic measurements, 11 would have been eligible if the neo-LVOT area was measured throughout the entire cardiac cycle (multiphase average) or if the neo-LVOT area was measured at early systole. Therefore, the potential enrollment would have increased by 33% if multiphase average or early systolic measurements would have been performed. In addition, in nine patients who were considered having high risk of LVOT obstruction based on end-systolic assessment, the Intrepid valve was eventually successfully implanted after the multiphase average measurements showed that the area of the neo-LVOT was acceptable [19□□]. Prediction of LVOT obstruction is also important when transcatheter mitral valve replacement is considered for patients with failed mitral bioprosthetic valves (valve-in-valve), annuloplasty rings (valve-in-ring), and mitral annular calcification (valve-in-MAC). Yoon et al.[18] showed that patients undergoing valve-in-MAC had worse prognosis as compared with patients undergoing mitral valve-in-valve or valve-in-ring. On MDCT, these patients showed the smallest predicted neo-LVOT area, which was associated with LVOT obstruction

after transcatheter mitral valve replacement needing conversion to surgery and higher mortality. The neo-LVOT was computed at two device locations: where the device is largest in diameter and at the most ventricular portion of the device. The minimum value of the two measured locations was reported as the end-systolic minimum neo-LVOT area [19??]. A substantial proportion of patients would have been not eligible for TMVR after this screening.

In addition, MDCT is useful to plan the transseptal and transapical implantation routes [14]. The transseptal puncture for mitral valve interventions is usually located 3.5–4 cm above the plane of mitral leaflet coaptation. From MDCT data, the multiplanar reformation planes can be aligned across the interatrial septum, the fossa ovalis can be detected and the transseptal puncture location can be drawn in a coaxial plane 3.5–4 cm above the mitral annulus [14]. The optimal fluoroscopic projection will be defined by the superimposition of the coaxial plane and the mitral annulus plane. For the planning of transapical procedures, the fusion of MDCT data and fluoroscopy helps to locate the puncture site with adequate distance from the left anterior descending coronary artery [20]. For transcatheter mitral valve replacement, the coplanar fluoroscopic projection angles that ensure a coaxial device deployment are derived from a compromise between the projection where the intertrigonal distance and the projection where the septal to lateral distance of the mitral annulus can be assessed. The mitral annular plane is oriented anterior and superiorly with pronounced tilting to the right leading to an S-shaped optimal projection curve that crosses the X axis (i.e., 0° cranio-caudal) at an average 38.8 ± 11.5° right anterior oblique [21].

Cardiac magnetic resonance

In the evaluation of mitral regurgitation, current guidelines recommend CMR when echocardiography is inconclusive in grading the severity of mitral regurgitation [22,23]. In the preprocedural planning of transcatheter mitral valve interventions, CMR is currently used in the assessment of mitral regurgitation severity and left ventricular volumes and function. Furthermore, CMR provides information on tissue characterization (myocardial scar/fibrosis) by using late gadolinium contrast-enhanced (LGE) techniques. However, the impact of myocardial scar/fibrosis assessment with LGE-CMR on the decision making remains unclear.

Quantification of the mitral regurgitant volume and fraction are the key parameters to assess the severity of mitral regurgitation. Several methods can be used to quantify the mitral regurgitant volume [24??]:

(1) By calculating the difference between the left ventricular stroke volume measured

on cine steady-state, free-precession images using planimetry of the left ventricular cavity and the aortic forward volume measured on phase-contrast images. This is the most frequently used method and is not affected by the presence of concomitant regurgitant valve lesions.

(2) By calculating the difference between the left ventricular stroke volume and the right ventricular stroke volume measured using planimetry of the left and right ventricular cavities on cine steady-state, free-precession images. This method cannot be used when concomitant regurgitant valve lesions or significant shunts are present.

(3) By calculating the difference between the mitral inflow stroke volume and the aortic forward volume measured on phase-contrast images.

(4) Using four-dimensional flow CMR data with retrospective mitral valve tracking.

The mitral regurgitant fraction is calculated as the coefficient between the mitral regurgitant volume and the left ventricular stroke volume × 100. Quantification of mitral regurgitation with CMR provides important prognostic data. In 109 asymptomatic patients with moderate or severe mitral regurgitation, Myerson et al.[25] showed that a mitral regurgitant volume more than 55 ml and a regurgitant fraction more than 40% identified the patients who developed indications for surgical intervention during the following five years with a sensitivity of 72 and 76%, respectively, and a specificity of 87 and 74%, respectively. More recently, Penicka et al.[26□□] showed that the majority of the discrepancies between CMR and two-dimensional echocardiography in mitral regurgitant volume quantification occurred among patients with late systolic or multiple regurgitant jets and that patients with moderate mitral regurgitation based on two-dimensional echocardiography but with severe mitral regurgitation based on CMR analysis had higher rates of all-cause mortality or developed earlier indication for surgery as compared with patients with moderate mitral regurgitation assessed both with CMR and two-dimensional echocardiography.

The consequences of chronic severe mitral regurgitation on the left ventricular dimensions and function can be also assessed with CMR. Particularly, the presence of replacement fibrosis as assessed with LGE-CMR has been described in patients with primary mitral regurgitation. In the study by Kitkungvan et al.[27] patients with mitral valve prolapse had increased regional left ventricular replacement fibrosis, particularly in the segments adjacent to the posteromedial papillary muscle. The presence of replacement fibrosis may be further related to increased symptomatic ventricular arrhythmic events in patients with mitral valve prolapse [27]. In patients with secondary mitral regurgitation where the remodeling and dysfunction of the

left ventricle is frequently the underlying pathophysiological mechanism of mitral malcoaptation, assessment of extent of myocardial fibrosis/scar has important prognostic implications (Fig. 8). Cavalcante et al.[28] showed in a cohort of 578 patients with ischemic cardiomyopathy and a mean mitral regurgitant fraction of 18% that patients with significant mitral regurgitation (defined by a regurgitant fraction ≥35%), that the presence of a myocardial scar size at least 30% of the left ventricular was associated with a hazard ratio of 5.41 for the combined endpoint of all-cause mortality or heart transplant.

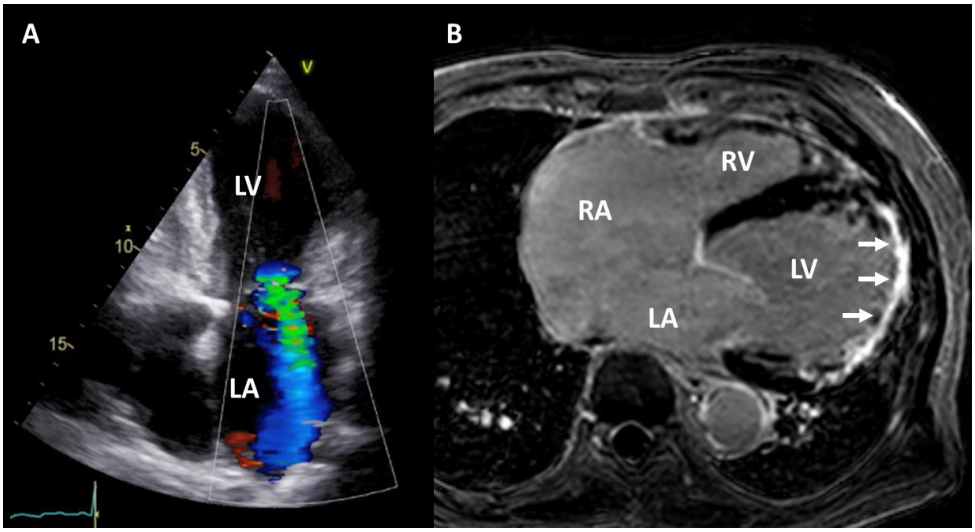

Figure 8: Late gadolinium contrast-enhanced cardiovascular magnetic resonance in patient with ischemic mitral regurgitation. Panel a shows the apical four-chamber view with severe mitral regurgitation based on color flow Doppler data. On late gadolinium contrast-enhanced cardiovascular magnetic resonance, the presence of myocardial scar extent can be assessed (arrows).

Conclusion

The growing prevalence of patients with severe mitral regurgitation and a high surgical risk or contraindications for surgery has opened the field for transcatheter therapies, which are evolving rapidly. Preprocedural imaging with three-dimensional imaging techniques, such as transesophageal echocardiography, computed tomography, and cardiac magnetic resonance, provide the anatomic and functional information needed to determine the underlying mechanism and severity of mitral regurgitation

and define the most appropriate transcatheter therapy. In addition, advances in fusion imaging, where noninvasive three-dimensional imaging modalities can be overlaid on to fluoroscopy, facilitate the communication between imagers and interventionalists and procedural guidance.

Outline of this thesis

The objective of this thesis was to evaluate the role of advanced echocardiography for the risk stratification and treatment guidance of patients with secondary mitral regurgitation.

Part I describes epidemiological characteristics of patients with mitral regurgitation and how these effect treatment and outcome. **Chapter 2** evaluates the sex differences in secondary mitral regurgitation and how it impacts outcome.

Part II focuses on the role of echocardiography and advanced echocardiography (speckle tracking) in defining predictors of outcome in patients with secondary mitral regurgitation. **Chapter 3** evaluates the incremental prognostic value of LV GLS over LVEF in secondary mitral regurgitation. **Chapter 4** has analyzed the ratio between mitral regurgitant volume and LV end-diastolic volume as a predictor of outcome in secondary mitral regurgitation. **Chapter 5** evaluates geometrical mitral valve differences in patients with secondary mitral regurgitation treated with transcatheter mitral valve repair. **Chapter 6** evaluates an echocardiographic marker for right ventricular-arterial coupling in patients with significant secondary mitral regurgitation and it association with outcome.

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Part I

Epidemiology in secondary mitral regurgitation

Chapter two

Sex differences in prognosis of significant secondary mitral regurgitation

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ESC Heart Fail. 2021 Aug 6. doi: 10.1002/ehf2.13503.

Abstract

Aims

Secondary mitral regurgitation (MR) is more frequent in men than in women. However, little is known about differences in prognosis between men and women with secondary MR. The objective of this study is to investigate the sex distribution of secondary MR and the prognostic differences between sexes.

Methods

Patients with significant secondary MR, of both ischemic and non-ischemic etiology, were identified through the departmental electronic patient files and retrospectively analyzed. The primary endpoint was all-cause mortality.

Results

A total of 698 patients (mean age 66±11 years) with significant secondary MR were included: 471 (67%) men and 227 (33%) women. Ischemic heart failure was significantly more common in men (61%), whereas non-ischemic heart failure was more prevalent in women (63%). Women had significantly smaller left ventricular (LV) volumes when compared to men and more preserved LV systolic function when assessed with LV global longitudinal strain (GLS; 8.5±4.1% vs. 7.5±3.6%; P= 0.004). Women more often underwent surgical mitral valve repair (34%) when compared to men (26%), whilst no differences were observed for transcatheter mitral valve repair. During a median follow-up of 57 [interquartile range 29-110] months, 373 (53%) patients died. Women showed significantly lower mortality rates at 1-, 2- and 5-year follow-up (9%, 16% and 33% vs. 10%, 20% and 42%) when compared to men (P= 0.001).

Conclusions

Significant secondary MR is more frequently observed in men as compared to women and is associated with worse prognosis.

Introduction

Mitral regurgitation (MR) is one of the most common valvular diseases with a growing incidence and significant MR is associated with poor prognosis [1, 2]. The frequency of significant MR in men and women is comparable [3]. However, when evaluating the etiology of MR, significant differences are observed: secondary MR is more prevalent in men, whereas primary MR is more frequently present in women [3-5]. Previous studies have shown differences between men and women undergoing surgical mitral valve repair for primary or secondary MR, with women having a higher mortality risks [4, 6, 7]. In patients undergoing transcatheter edge-to-edge mitral valve repair with the MitraClip device, no sex differences were observed [8]. However, these studies were mostly performed in patients with primary MR. A recent publication evaluating the sex differences in patients with secondary MR undergoing surgical mitral valve repair showed higher mortality risk in women as compared to men [9]. The factors underlying these differences remain elusive, particularly among patients with secondary MR [10]. Accordingly, the objective of this study is to investigate the sex distribution and long-term prognosis of patients with significant secondary MR.

Methods

Patient population

Patients with significant (moderate and severe) secondary MR were identified from 1999-2018 through the departmental echocardiographic database of the Leiden University Medical Center (Leiden, The Netherlands). Patients with previous mitral valve intervention were excluded. Baseline demographic, clinical and echocardiographic characteristics were prospectively collected through the departmental clinical database (EPD-Vision 11.8.4.0; Leiden University Medical Center, Leiden, The Netherlands) and were analyzed retrospectively. The institutional review board approved this retrospective study of clinically acquired data and waived the need for written patient informed consent.

Clinical variables included heart failure etiology (i.e. ischemic vs. non-ischemic), New York Heart Association (NYHA) functional class, comorbidities and medication use. Body surface area was calculated according to the Du Bois formula [11]. Ischemic heart failure was defined based on coronary artery disease confirmed by coronary angiography, prior coronary revascularization with percutaneous coronary intervention and/or coronary artery bypass grafting (CABG). Mitral valve intervention included surgical mitral valve repair or replacement and transcatheter edge-to-edge mitral valve repair with the MitraClip device.

Echocardiography

Transthoracic echocardiography was performed with commercially available systems (General Electric Vingmed Ultrasound, Milwaukee, USA), and images were digitally stored for offline analysis (EchoPAC 201.0.0, General Electric Vingmed Ultrasound, Milwaukee, USA). Image acquisition was performed with patients in hemodynamic stable conditions at rest in the left lateral decubitus position. Using 3.5 MHz or M5S transducers two-dimensional images, M-mode and Doppler data were acquired from parasternal, apical and subcostal views. From the apical 2- and 4-chamber views, left ventricular (LV) volumes (end-diastolic and end-systolic) were measured and the LV ejection fraction (EF) was quantified using the Simpson's biplane method [12]. LV volumes were indexed for body surface area. MR severity was assessed using a multiparametric approach according to current guidelines and graded as moderate (grade 2), moderate-to-severe (grade 3) and severe (grade 4) [13-15]. From standard 2-dimensional transthoracic echocardiography, LV global longitudinal strain (GLS) was measured using apical 4-chamber, 2-chamber and long-axis views of the LV and processed offline using commercially available software (EchoPAC 201.0.0, General Electric Vingmed Ultrasound, Milwaukee, USA) [16]. LV GLS is a measure of global shortening of the myocardium and is conventionally expressed as negative values. However, in this study we have treated this variable as absolute value and therefore, a higher LV GLS value represents better LV systolic function.

Follow-up

Patients were followed=up for the occurrence of the primary endpoint of all-cause mortality. The follow-up started from the date of the first echocardiogram showing significant secondary MR. Data on survival were collected from the departmental cardiology information system (EPD-Vision 11.8.4.0; Leiden University Medical Center, Leiden, The Netherlands) which is linked to the governmental death registry database. Follow-up was complete for all patients.

Statistical analysis

Continuous data are presented as mean ± standard deviation (when normally distributed) or as median with interquartile range (when not normally distributed). An independent sample Student t-test or Mann-Whitney U test (when appropriate) was used for the comparison of continuous data. Categorical data are presented as absolute numbers and percentages and a □2-test was used for the comparison between groups. To estimate the cumulative survival rates, a Kaplan-Meier analysis was performed and the log-rank test was used to compare the cumulative survival rates between men and women. Based on the Kaplan-Meier analysis, a post hoc landmark analysis was

performed at 36 months of follow-up to evaluate early vs. late outcomes between men and women. Independent associates for all-cause mortality were evaluated using Cox proportional hazards regression analysis. The hazard ratio (HR) and 95% confidence intervals (CI) were calculated and reported. Variables with a p-value <0.05 were considered statistically significant and were included in the multivariable model. All statistical analyses were performed using SPSS for Windows, version 23.0 (IBM, Armonk, NY, USA), with a two-tailed p-value <0.05 being considered statistically significant.

Results

Patient population

A total of 698 patients (mean age 66±11 years) with significant secondary MR were included. Ischemic heart failure was present in 53% of the total population. The majority of the patients presented with heart failure symptoms NYHA functional class III (60%). The mean LVEF was 29±11% and the mean LV GLS was 7.8±3.8%. The majority of the patients (82%) had moderate-to-severe or severe MR. Tables 1 and 2 summarize the baseline clinical and echocardiographic characteristics for the total population and the differences between sexes.

There were 471 (67%) men (mean age 67±10 years) and 227 (33%) women (mean age 65±13). No differences were observed in the prevalence of atrial fibrillation or other cardiovascular risk factors (i.e. hypertension and/or diabetes mellitus). In terms of heart failure etiology, men more frequently had ischemic heart failure (61%) whereas women more frequently had non-ischemic heart failure (63%). Although women had more severe heart failure symptoms as compared to men, the difference did not reach statistical significance. In terms of echocardiographic characteristics, women had significantly smaller LV volumes when compared to men, but no significant difference was observed in LVEF. However, LV systolic function was slightly better in women than in men when assessed with LV GLS (LV GLS 7.5±3.6% in men vs. 8.5±4.1% in women; P= 0.004). No differences were observed in MR grade between men and women.

Table 1. Clinical characteristics.

	Total population (n= 698)	Men (n= 471)	Women (n= 227)	P-value
Age (years)	66±11	67±10	65±13	0.051
BSA (m^2)	1.92±0.21	1.99±0.19	1.78±0.19	**<0.001**
Atrial fibrillation, n (%)	289 (41)	206 (44)	83 (37)	0.071
Hypertension, n (%)	275 (39)	175 (37)	100 (44)	0.081
Diabetes mellitus, n (%)	167 (24)	120 (26)	47 (21)	0.166
eGFR (mL/min/1.73m^2)	62±26	63±25	61±27	0.417
Heart failure etiology, n (%)				
Ischemic	370 (53)	287 (61)	83 (37)	**<0.001**
Non-ischemic	328 (47)	184 (39)	144 (63)	**<0.001**
NYHA class, n (%)				
I	34 (5)	26 (6)	8 (4)	0.251
II	170 (24)	116 (25)	54 (24)	0.809
III	415 (60)	282 (60)	133 (59)	0.747
IV	79 (11)	47 (10)	32 (14)	0.108
Medication, n (%)				
Beta-blockers	492 (71)	326 (69)	166 (73)	0.288
Diuretics	580 (83)	387 (82)	193 (85)	0.346
ACEi/ARB	565 (81)	390 (83)	175 (77)	0.072
MRA	304 (44)	193 (41)	111 (49)	0.048

Continuous data are presented as mean ± SD or median [interquartile range]. Categorical data are presented as numbers and percentages.

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BSA, body surface area; eGFR, estimated glomerular filtration rate; MRA, mineralocorticoid receptor antagonists; NYHA, New York Heart Association.

Table 2. Echocardiographic characteristics.

	Total population (n= 698)	Men (n= 471)	Women (n= 227)	P-value
LVEDVi (mL/m^2)	101 [76-129]	104 [81-132]	92 [68-122]	**<0.001**
LVESVi (mL/m^2)	73 [51-97]	77 [53-98]	66 [44-92]	**<0.001**
LVEF (%)	29±11	29±11	30±12	0.180
LV GLS (%) *	7.8±3.8	7.5±3.6	8.5±4.1	**0.004**
MR grade, n (%)				
Moderate	125 (18)	87 (19)	38 (17)	0.576
Moderate-to-severe	305 (44)	210 (45)	95 (42)	0.495
Severe	268 (38)	174 (37)	94 (41)	0.256

Continuous data are presented as mean ± SD or median [interquartile range]. Categorical data are presented as numbers and percentages. *LV GLS feasible in N= 660 patients.

LVEF, left ventricular ejection fraction; LVEDVi, indexed left ventricular end-diastolic volume; LVESVi, indexed left ventricular end-systolic volume; LV GLS, left ventricular global longitudinal strain; MR, mitral regurgitation.

Follow-up

During follow-up, two-thirds of the patients (64%) received cardiac resynchronization therapy, and 308 patients (44%) received mitral valve intervention: 28% underwent surgical mitral valve repair and 16% received transcatheter edge-to-edge mitral valve repair. Men more frequently received cardiac resynchronization therapy when compared to women. In terms of invasive mitral valve treatment, women more often underwent surgical mitral valve repair (34%), whilst no differences were observed in transcatheter edge-to-edge mitral valve repair. A summary of device implantation and mitral valve intervention at follow-up and differences between men and women is shown in Table 3.

Table 3. Intervention during follow-up.

	Total population (n= 698)	Men (n= 471)	Women (n= 227)	p-value
Device therapy, n (%)				
Cardiac resynchronization therapy	414 (64)	294 (68)	120 (55)	**0.001**
MV intervention, n (%)				
Medical therapy only	387 (55)	279 (59)	108 (48)	**0.004**
Mitral valve repair	198 (28)	122 (26)	76 (34)	**0.037**
Mitral valve replacement	3 (0.4)	1 (0.2)	2 (0.9)	0.206
MitraClip	110 (16)	69 (15)	41 (18)	0.246
Concomitant procedure, n (%) *				
CABG	60 (9)	46 (10)	14 (6)	0.112
Tricuspid valve annuloplasty	131 (19)	83 (18)	46 (21)	0.264
LV reconstruction	17 (2)	12 (3)	5 (2)	0.782
Cardiac support device (CoreCap)	63 (9)	39 (8)	24 (11)	0.322
MAZE	30 (4)	21 (5)	9 (4)	0.763

Continuous data are presented as mean ± SD or median [interquartile range]. Categorical data are presented as numbers and percentages. * Concomitant procedures with mitral valve treatment.
CABG, coronary artery bypass graft

Survival analysis

During a median follow-up of 57 [interquartile range 29-110] months, 373 (53%) patients died. Women showed significantly lower mortality rates at 1-, 2- and 5-years follow-up as compared to men (women 9%, 16% and 33% vs. men 10%, 20% and 42%, respectively; P= 0.001, Figure 1, panel A). Based on the Kaplan-Meier curves, an additional landmark analysis was performed at 36 months of follow-up demonstrating

that the differences in survival were significant between men and women after this time point (P< 0.001, Figure 1, panel B). In patients with ischemic heart failure, there was no significant difference in outcome between men and women (P=0.179, Figure 2, Panel A). On the contrary, in patients with non-ischemic heart failure, a significant difference in outcome between men and women was seen with women having a better outcome then men (P=0.017, Figure 2, Panel B).

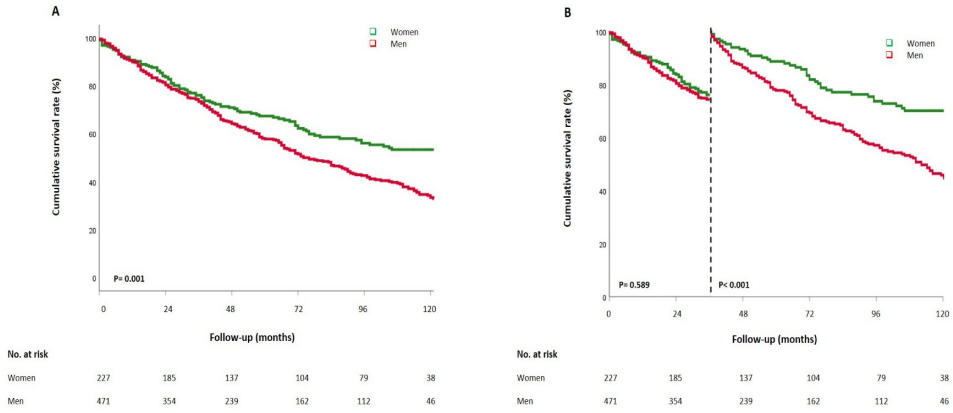

Figure 1. Kaplan-Meier curves for all-cause mortality. Panel A demonstrates time to all-cause mortality according to sex: women (green) and men (red). Panel B demonstrates the landmark analysis at 36 months of follow-up with time-to-event curves for all-cause mortality according to sex.

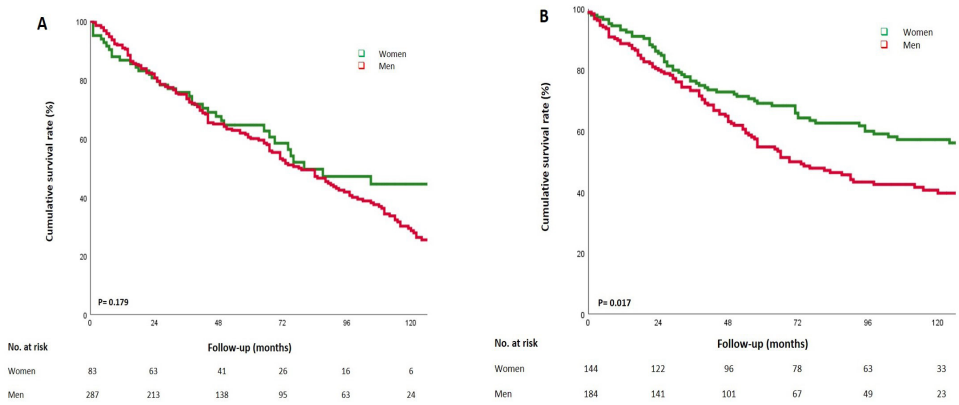

Figure 2. Kaplan-Meier curves for all-cause mortality in patients with ischemic and non-ischemic heart failure. Panel A demonstrates time to all-cause mortality according to sex in patients with ischemic heart failure: women (green) and men (red). Panel B demonstrates time to all-cause mortality according to sex in patients with non-ischemic heart failure

Considering patients receiving medical therapy only, women had lower mortality rates than men (5-year estimated rates 77% in women vs. 62% in men; P=0.001). On univariable analysis, age, male sex, chronic kidney disease, diabetes mellitus, ischemic heart failure, LVEF and LV GLS were significantly associated with all-cause mortality (Table 4). On multivariable analysis, after correcting for various clinical and echocardiographic parameters, male sex remained independently associated with all-cause mortality (HR 1.423; 95% CI, 1.109-1.826; P=0.006).

Table 4. Uni- and multivariable Cox regression analyses to identify associates of all-cause mortality.

		Univariate analysis			Multivariate analysis	
Variable	**HR**	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**
Age	1.030	1.019-1.040	<0.001	1.020	1.009-1.032	0.001
Male sex	1.474	1.175-1.850	0.001	1.423	1.109-1.826	0.006
BSA (m^2)	1.050	0.652-1.689	0.842			
eGFR (mL/min/1.73m^2)	0.977	0.972-0.981	<0.001	0.980	0.975-0.985	<0.001
Hypertension	0.940	0.762-1.160	0.566			
Diabetes mellitus	1.429	1.132-1.805	0.003	1.309	1.021-1.678	0.034
Atrial fibrillation	1.145	0.932-1.406	0.197			
Ischemic aetiology	1.291	1.052-1.585	0.015	1.071	0.855-1.342	0.550
NYHA classification ≥II	1.026	0.621-1.694	0.920			
Beta-blockers	0.845	0.681-1.048	0.125			
CRT	1.092	0.859-1.390	0.471			
MV intervention *	1.051	0.852-1.298	0.642			
LVEF (%)	0.988	0.977-0.998	0.025	0.999	0.985-1.013	0.864
LV GLS (%)	1.082	1.047-1.118	<0.001	1.066	1.024-1.109	0.002

BSA, body surface area; CI, confidence interval; CRT, cardiac resynchronization therapy; EDV, end-diastolic volume; eGFR, estimated glomerular filtration rate; HR, hazard ratio; LVEF, left ventricular ejection fraction; LV GLS, left ventricular global longitudinal strain; MV, mitral valve; NYHA, New York Heart Association.

* Combined surgical mitral valve repair, mitral valve replacement and percutaneous edge-to-edge mitral valve repair

Discussion

The present study shows that significant secondary MR is more frequent in men as compared to women. Ischemic etiology is the most frequent underlying mechanism in men whereas non-ischemic cardiomyopathy is more frequently observed in women. Men had a worse prognosis, compared to women.

Sex differences in secondary mitral regurgitation

Important differences in prevalence, pathophysiology and prognosis of various cardiovascular diseases have been described between men and women [17]. In mitral valve pathology two different mechanisms of MR can be distinguished; primary MR (i.e. the result of pathology of the MV apparatus itself) and secondary MR (i.e. the result of changes in the LV geometry due to ischemic or non-ischemic heart failure) [18]. A large echocardiography-based registry by Monteagudo Ruiz *et al*. [3] described the sex differences among 3309 patients with moderate and severe MR and showed that secondary MR was more prevalent among men vs. women (39.2% vs. 21.8%, respectively). However, the study did not elaborate further on the differences between men and women with significant secondary MR. The randomized clinical trial from the Cardiothoracic Surgical Trials Network (CTSN) comparing mitral valve repair vs. replacement in 251 patients with ischemic secondary MR showed that 38% were women while the remaining 62% were men [9]. In the present study ischemic etiology of secondary MR was observed in 61% of men vs. 37% of women. When analyzing the clinical and echocardiographic characteristics of the patients enrolled in the CTNS trial [9], men were comparable to women in terms of age, body mass index, frequency of atrial fibrillation, history of myocardial infarction and renal dysfunction; however, men more frequently had a history of ventricular arrhythmias while women presented more frequently with diabetes mellitus and hypertension. Furthermore, men had larger LV dimensions and effective regurgitant orifice areas when compared to women. However, when the effective orifice regurgitant orifice area was corrected for the LV end-diastolic volume, women had a larger ratio than men suggesting more severe MR in women than in men. These results are similar to the data reported in this study. However, it should be noted that the present study population is larger and includes both etiologies of secondary MR (ischemic and non-ischemic). Although other studies have compared sex-differences in MR[19, 20], this is the first and largest study focusing specifically on secondary MR.

Sex differences in outcomes in patients with secondary MR

Although men with significant secondary MR seem to receive interventional treatment more often than women,[1, 21-23] men seem to have a worse prognosis. A study by Estevez-Loureiro *et al*. [8] investigated the effect of gender on results after transcatheter edge-to-edge MV repair with the Mitraclip in 173 patients (64 women vs. 109 men) and showed no differences between the sexes in MR reduction, heart failure hospitalization and all-cause mortality. Similarly, data from the German TRAnscatheter Mitral Valve Interventions (TRAMI) registry, including 501 men and 327 women showed no differences in prognosis after successful transcatheter MV repair with the MitraClip [20].

Although, those studies consisted mainly of patients with secondary MR, a significant proportion of patients had other etiologies of MR and sub-analyses concerning only patients with secondary MR were not performed. In contrast, in the randomized CTNS trial, Giustino *et al*. [9] showed that among patients with secondary MR undergoing MV repair or replacement, women had a significantly higher risk for mortality when compared to men (27.1% vs. 17.4%, respectively; P= 0.03). The reasons for the worse outcome in women after MV surgery remain unclear. However, it is important to note that both men and women showed similar LV reverse remodeling at 2 years follow-up while women had smaller baseline LV volumes and larger effective regurgitant orifice areas when corrected for LV end-diastolic volume as compared to men, suggesting that women had more severe MR than men at baseline and, after correcting the volume overload with MV repair or replacement, their LVs benefited less. Data on more sensitive measures of LV systolic function such as LV GLS or tissue characterization with cardiac magnetic resonance were not available, but it can be speculated that women have stiffer, more fibrotic LVs than men.

In the present study, including ischemic and non-ischemic secondary MR, male gender was independently associated with worse outcome. However, the differences between men and women became evident 3 years after diagnosis of significant secondary MR (Figure 1) which could indicate progression of the underlying mechanism of secondary MR (progression of LV remodelling). Although no statistically significant difference was seen between men and women with ischemic heart failure (possibly due to the low number of women with ischemic heart failure in the present study), a trend of worse survival is seen in men with ischemic heart failure (Figure 2, Panel A). In men, the etiology of secondary MR was ischemic heart failure which is known to respond less well to heart failure therapies and may further progress over time, leading to worse outcome [24-26].

Study limitations

This is a single center retrospective study, which limits the generalizability of the results. In addition, this is a tertiary referral center where the patients are referred for specific treatments which may have introduced some selection bias. Measures for heart failure, such as NT-proBNP unfortunately were not systematically available and therefore could not be provided for the present study. Cardiac mortality was not systematically documented in our centre and due to the retrospective design of the study these data could not be acquired. However, to the best of our knowledge, this is the first and largest registry evaluating gender differences and long-term outcome in heart failure patients with secondary MR. The present study did not evaluate changes

over time in LV systolic function and dimensions which could shed more light into the association between heart failure progression and outcomes.

Conclusion

Significant secondary MR is more frequently observed in men as compared to women and is associated with worse prognosis.

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Part II

Echocardiography and prognosis in secondary mitral regurgitation

Chapter three

Prognostic Value of Left Ventricular Global Longitudinal Strain in Patients With Secondary Mitral Regurgitation

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J Am Coll Cardiol. 2020 Feb 25;75(7):750-758.

Abstract

Background
Left ventricular (LV) systolic function may be overestimated in patients with secondary mitral regurgitation (MR) when using LV ejection fraction (EF). LV global longitudinal strain (GLS) is a less load-dependent measure of LV function. However, the prognostic value of LV GLS in secondary MR has not been evaluated.

Objectives
This study sought to demonstrate the prognostic value of LV GLS over LVEF in patients with secondary MR.

Methods
A total of 650 patients (mean 66 ± 11 years of age, 68% men) with significant secondary MR were included. The study population was subdivided based on the LV GLS value at which the hazard ratio (HR) for all-cause mortality was >1 using a spline curve analysis (LV GLS <7.0%, impaired LV systolic function vs. LV GLS ≥7.0%, preserved LV systolic function). The primary endpoint was all-cause mortality.

Results
During a median follow-up of 56 (interquartile range: 28 to 106 months) months, 334 (51%) patients died. Patients with a more impaired LV GLS showed significantly higher mortality rates at 1-, 2-, and 5-year follow-up (13%, 23%, and 44%, respectively) when compared with patients with more preserved LV systolic function (5%, 14%, and 31%, respectively). On multivariable analysis, LV GLS <7.0% was associated with increased mortality (HR: 1.337; 95% confidence interval: 1.038 to 1.722; p = 0.024), whereas LVEF ≤30% was not (HR: 1.055; 95% confidence interval: 0.794 to 1.403; p = 0.711).

Conclusions
In patients with secondary MR, impaired LV GLS was independently associated with an increased risk for all-cause mortality, whereas LVEF was not. LV GLS may therefore be useful in the risk stratification of patients with secondary MR.

Introduction

The results of current landmark randomized trials evaluating the prognostic impact of transcatheter mitral valve repair therapy (using the MitraClip device [Abbott Vascular, Menlo Park, California]) in patients with secondary mitral regurgitation (MR) have underscored the relevance of patient selection for this treatment (1,2). MitraClip therapy did not confer a survival benefit compared with optimal medical therapy in the MITRA-FR (Multicentre Study of Percutaneous Mitral Valve Repair MitraClip Device in Patients With Severe Secondary Mitral Regurgitation) trial (1), whereas in the COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation) trial, patients randomized to the MitraClip arm had significant reduction in the composite endpoint of heart failure hospitalization and all-cause mortality (2). One of the factors underlying these discrepant results is the difference in left ventricular (LV) volumes between the study populations. Besides differences in grading MR between the 2 trials, patients enrolled in the MITRA-FR trial had larger LV volumes as compared with patients included in the COAPT trial. In contrast, LV ejection fraction (LVEF) was comparable in the 2 study populations. These facts suggest that patients included in the MITRA-FR trial had more advanced LV remodeling status as compared with patients included in the COAPT trial and that LVEF may not be an appropriate parameter to identify the patients who will benefit from mitral valve intervention. However, current guidelines base the recommendation to perform mitral valve surgery in heart failure patients with secondary MR on LVEF (3). In light of the available evidence, the method to assess LV systolic function in severe secondary MR that will identify the patients who will improve their prognosis with mitral valve intervention remains an unmet clinical need (4). Two-dimensional (2D) LV global longitudinal strain (GLS) measured with speckle tracking echocardiography has demonstrated more advanced LV damage (myocardial fibrosis) than LVEF in patients with nonischemic cardiomyopathy and severe secondary MR (5). However, the prognostic implications of LV GLS in patients with secondary MR have not been investigated. Accordingly, the aim of the present study was to evaluate the prognostic value of LV GLS over LVEF in a large cohort of patients with significant secondary MR.

Methods

Patient population

Patients with moderate and severe secondary MR, of both ischemic and nonischemic etiology, were identified retrospectively from the departmental clinical database (EPD-Vision 11.8.4.0, Leiden University Medical Center, Leiden, the Netherlands) and

echocardiographic database. The first echocardiogram performed with the patient in hemodynamic stable conditions and showing moderate and severe secondary MR defined the time point of entry in the analysis. Patients with previous invasive mitral valve intervention and patients with echocardiographic data not analyzable with 2D speckle-tracking echocardiography were excluded (Online Figure 1). The Institutional Review Board approved this retrospective analysis of clinically acquired data and waived the need of written patient informed consent.

Clinical variables included the New York Heart Association (NYHA) functional class, etiology of heart failure, heart rhythm, comorbidities, and medications. Ischemic etiology was defined by the presence of coronary artery disease diagnosed on invasive coronary angiography or a history of coronary revascularization with percutaneous coronary intervention or coronary artery bypass grafting (CABG). Mitral valve intervention included surgical therapy (i.e., surgical mitral valve repair, mitral valve replacement) and percutaneous edge-to-edge mitral valve repair.

Echocardiography

Transthoracic echocardiography was performed with patients at rest in the left lateral decubitus position, using a commercially available system (GE Vingmed Ultrasound, General Electric, Milwaukee, Wisconsin). Parasternal, apical, and subcostal views were acquired using 3.5 MHz or M5S transducers. Two-dimensional, M-mode, and Doppler data were stored for offline analysis (EchoPAC 201.0.0, GE Vingmed Ultrasound). LV volumes (end-systolic and end-diastolic) were measured in the apical 2- and 4-chamber views and LVEF was calculated according to Simpson's biplane method and indexed for body surface area (6). MR severity was graded according to current recommendations using an integrative approach that includes qualitative, semiquantitative, and quantitative data: mild (grade 1), moderate (grade 2), moderate to severe (grade 3), and severe (grade 4) (7, 8, 9). Significant MR was defined by a grade of ≥2+. Parameters for LV diastolic function included peak early diastolic wave and late diastolic wave measured on pulsed wave Doppler of mitral inflow, and the peak early diastolic wave-to-late diastolic wave ratio was calculated. Using tissue Doppler imaging, the septal and lateral peak early diastolic mitral annular velocities were measured in the apical 4-chamber view (10). As a measure of LV filling pressures, the ratio between peak early diastolic transmitral flow velocity and peak early diastolic mitral annular tissue velocity ratio was calculated. The tricuspid regurgitation was assessed on continuous-wave Doppler and tricuspid regurgitation velocity was calculated. To evaluate right ventricular function, tricuspid annular plane systolic excursion was measured on the apical 4-chamber view using the M-mode (11). LV GLS was measured from standard

2D transthoracic echocardiography using the apical 4-chamber, 2-chamber, and long-axis views of the LV (12). LV GLS was determined offline using commercially available software (EchoPAC 201.0.0). LV GLS measures the shortening of the myocardial fibers and is presented as negative values conventionally: more negative values indicate better systolic function (shortening), whereas less negative values, closer to 0, indicate more impaired systolic function. However, in this study, absolute values of LV GLS are presented (Figure 1). The intraclass correlation coefficients for the interobserver and intraobserver reproducibility of LV GLS measurements in this population was 0.89 (95% confidence interval [CI]: 0.63 to 0.96; $p < 0.001$) and 0.93 (95% CI: 0.84 to 0.97; $p < 0.001$), respectively.

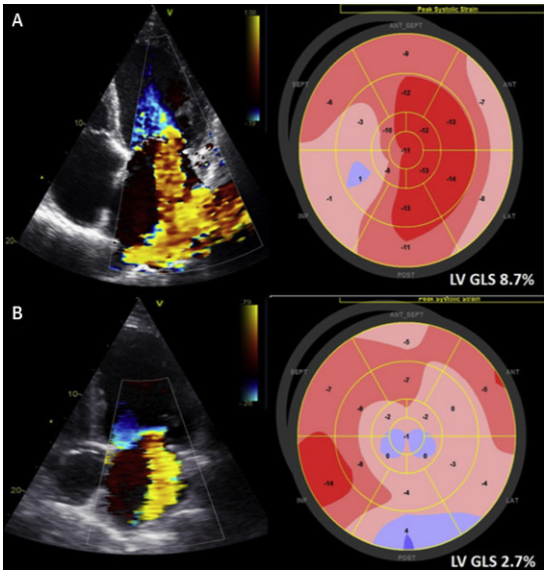


Figure 1. Measurement of LV GLS in Patients With Secondary MR
(A) A 59-year old patient with ischemic cardiomyopathy, in New York Heart Association functional class IV with severe mitral regurgitation (MR) and a left ventricular ejection fraction (LVEF) of 21%. (B) A patient with severe MR and an LVEF of 20%. Despite having the same degree of MR and a comparable LVEF, the LV global longitudinal strain (GLS) was highly different, which demonstrates that patient in A had a better LV systolic function when compared with the patient in B.

Follow-up

Patients were followed-up for the primary endpoint of all-cause mortality. Data on mortality were obtained from the departmental cardiology information system (EPD-Vision 11.8.4.0), which is linked to the governmental death registry database. Follow-up data were complete for all patients.

Statistical analysis

Categorical data are presented as absolute numbers and percentages. Continuous data are presented as mean ± SD when normally distributed or as median with interquartile range, when not normally distributed. To compare baseline characteristics between 2

groups, chi-square tests were used for categorical data and the unpaired Student's t-test or Mann-Whitney U test, as appropriate, for continuous data. Changes in hazard ratio (HR) for all-cause mortality across the LV GLS values (as a continuous variable) were investigated by fitting a spline curve (Figure 2). A threshold of LV GLS to dichotomize the population was derived from the spline curve (i.e., in which the predicted HR is ≥1). Cumulative survival rates were estimated by the Kaplan-Meier method for all-cause mortality, and a log-rank test was used to compare groups. Cox proportional hazards regression analysis was performed to investigate the association between clinical and echocardiographic parameters with all-cause mortality. The HR and 95% CI were calculated and reported. In the univariable analysis, p values <0.05 were considered statistically significant and were included in the multivariable model. To investigate the incremental value of LV GLS over clinical and conventional echocardiographic parameters to predict outcome, the likelihood ratio test was performed. The change in global chi-square values was calculated and reported. A 2-tailed p value <0.05 was considered statistically significant. Statistical analysis was performed using SPSS for Windows, version 23.0 (IBM Corporation, Armonk, New York) and R version 3.4.4 (R Foundation for Statistical Computing, Vienna, Austria).

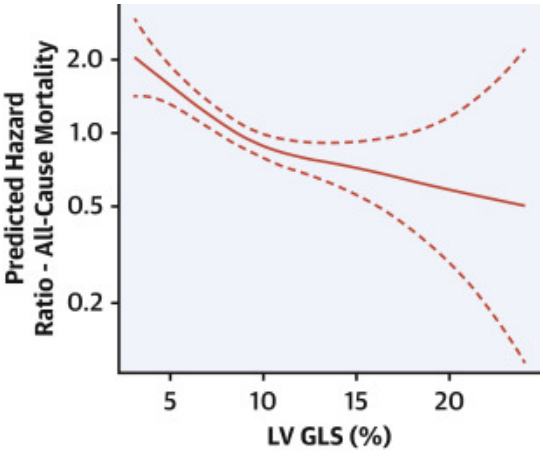


Figure 2. Spline Curve for All-Cause Mortality According to LV GLS
Prediction of all-cause mortality across a range of LV GLS, plotted as a fitted spline model on a log-hazard scale with overlaid confidence intervals. Red dashed lines represent 95% confidence intervals. Abbreviations as in Figure 1.

Results

Patient population

A total of 650 patients (mean 66 ± 11 years of age, 68% men) were included. The majority of patients were in NYHA functional class II and III, and 52% of patients had ischemic heart failure (Table 1). Table 2 summarizes the echocardiographic data for the overall population. The median LV GLS was 7.2% (interquartile range: 5.2% to 9.9%) in

the overall population, while the mean LVEF was 29 ± 10%. The majority of patients (83%) had grade 3 to 4 MR.

Table 1. Clinical Characteristics at Baseline

	Total Population (N = 650)	GLS ≥7.0% (n = 349)	GLS <7.0% (n = 301)	p Value
Age, yrs	66 ± 11	67 ± 11	65 ± 11	0.009
Male	439 (68)	225 (65)	214 (71)	0.072
BSA, m²	1.9 ± 0.2	1.9 ± 0.2	1.9 ± 0.2	0.512
Atrial fibrillation	269 (41)	152 (44)	117 (39)	0.227
Hypertension	255 (39)	153 (44)	102 (34)	0.010
Diabetes mellitus	147 (23)	85 (24)	62 (21)	0.254
Creatinine level, mmol/l	102 (83–133)	97 (82–126)	106 (87–142)	0.002
NYHA functional class				
I	32 (5)	16 (5)	16 (5)	0.667
II	156 (24)	93 (27)	63 (21)	0.089
III	386 (59)	208 (60)	178 (59)	0.905
IV	76 (12)	32 (9)	44 (15)	0.031
Heart failure etiology				
Ischemic	340 (52)	190 (54)	150 (50)	0.241
Nonischemic	310 (48)	159 (46)	151 (50)	0.241
Medication				
Beta-blockers	455 (70)	257 (74)	198 (66)	0.029
Diuretics	543 (84)	274 (79)	269 (89)	<0.001
ACE inhibitor/ARB	529 (81)	286 (82)	243 (81)	0.691

Values are mean ± SD, n (%), or median (interquartile range). Patients were divided according to less impaired LV GLS (≥7.0%) vs. more impaired LV GLS (<7.0%).

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BSA = body surface area; GLS = global longitudinal strain; LV = left ventricular; NYHA = New York Heart Association.

Follow-up

After a median follow-up of 56 (interquartile range: 28 to 106) months, 334 (51.4%) patients died. Cardiac resynchronization therapy (CRT) was received by 453 (70%) patients (before mitral valve intervention). In 270 (42%) patients, mitral valve intervention was performed after a median follow-up of 35 (interquartile range: 17 to 65) months. Invasive treatment performed after baseline echocardiography is summarized in Table 3.

To investigate the association between LV GLS and all-cause mortality, spline curve analysis was performed. The assumption of linearity for all-cause mortality, predicted from the baseline LV GLS, was not violated (chi-square = 3.0489; p = 0.23) (i.e.,

demonstrating a nonlinear relation of LV GLS vs. all-cause mortality). After an initial plateau and slow rise of HR, there was an increase in the HR for more impaired values of LV GLS (<7.0%) (Figure 2). Based on the spline curve, a value of LV GLS 7.0% was used to dichotomize the population. Patients with more impaired LV systolic function (LV GLS <7.0%) were younger, had more impaired renal function, were more symptomatic (NYHA functional class IV), used less frequently beta-blockers and more often received CRT before invasive mitral valve intervention as compared with patients with more preserved LV systolic function (LV GLS ≥7.0%) (Tables 1, 2, and 3). Patients with more preserved LV GLS (≥7.0%) had a significantly higher prevalence of hypertension. In terms of echocardiographic data, patients with more impaired LV GLS (<7.0%) had significantly larger LV volumes and lower LVEF, compared with the group of patients with more preserved LV GLS (≥7.0%) (Table 2). During follow-up, patients with more preserved LV GLS (≥7.0%) underwent more frequently surgical mitral valve repair with concomitant CABG, whereas those with more impaired LV GLS (<7.0%) were less likely to undergo any invasive mitral valve intervention (Table 3).

Table 2. Echocardiographic Characteristics at Baseline

	Total Population (N = 650)	GLS ≥7.0% (n = 349)	GLS <7.0% (n = 301)	p Value
LVEDVi, ml	107 ± 41	92 ± 31	124 ± 45	<0.001
LVESVi, ml	79 ± 37	63 ± 27	96 ± 40	<0.001
LVEF, %	29 ± 10	33 ± 11	23 ± 7	<0.001
LV GLS, %	7.2 (5.2–9.9)	9.6 (8.0–11.7)	5.1 (3.4–6.0)	<0.001
MR grade				
2	113 (17)	57 (16)	56 (19)	0.446
3	290 (45)	165 (47)	125 (42)	0.141
4	247 (38)	127 (36)	120 (40)	0.362
LAVI, ml/m²	34 (26–45)	33 (24–45)	35 (27–46)	0.047
E′	4.5 ± 2.0	5.0 ± 2.1	4.0 ± 1.7	<0.001
E/E′ ratio	25 ± 22	23 ± 27	26 ± 16	0.084
TR velocity, m/s	2.7 ± 0.6	2.6 ± 0.6	2.7 ± 0.6	0.021
SPAP, mm Hg	40 ± 13	39 ± 13	42 ± 14	0.020
TAPSE, mm	16 ± 5	16 ± 5	15 ± 4	<0.001

Values are mean ± SD, median (interquartile range), or n (%). Patients were divided according to less impaired LV GLS (≥7.0%) vs. more impaired LV GLS (<7.0%).

E = peak early diastolic transmitral flow velocity; E′ = peak early diastolic mitral annular tissue velocity; LAVI = left atrial volume index; LVEDVi = left ventricular end-diastolic volume index; LVEF = left ventricular ejection fraction; LVESVi = left ventricular end-systolic volume index; MR = mitral regurgitation; SPAP = systolic pulmonary artery pressure; TAPSE = tricuspid annular plane systolic excursion; TR = tricuspid regurgitation; other abbreviations as in Table 1.

Table 3. Data on Device and Invasive Mitral Valve Treatment Received During Follow-Up

	Total Population (N = 650)	GLS ≥7.0% (n = 349)	GLS <7.0% (n = 301)	p Value
Device therapy				
CRT	453 (70)	221 (63)	232 (77)	<0.001
Valvular intervention				
None	380 (59)	186 (53)	194 (65)	0.004
MVr	177 (27)	110 (32)	67 (22)	0.008
MVR	3 (1)	2 (1)	1 (<1)	0.651
Percutaneous edge-to-edge mitral valve repair	90 (14)	51 (15)	39 (13)	0.542
Concomitant procedure				
CABG	47 (7)	34 (10)	13 (4)	0.008
TVP	117 (18)	71 (20)	46 (15)	0.094
LV reconstruction, Dor procedure	16 (3)	6 (2)	10 (3)	0.188
CorCap	60 (9)	24 (7)	36 (12)	0.026
Surgical MAZE	23 (4)	12 (3)	11 (4)	0.882

Values are n (%). Patients were divided according to less impaired LV GLS (≥7.0%) vs. more impaired LV GLS (<7.0%).

AVR = aortic valve replacement; CABG = coronary artery bypass grafting; CRT = cardiac resynchronization therapy; GLS = global longitudinal strain; MVr = surgical mitral valve repair; MVR = mitral valve replacement; TVP = tricuspid valvuloplasty.

∗ Device implanted before invasive mitral valve treatment. † With mitral valve treatment.

Survival analysis

Patients with more impaired LV GLS (<7.0%) experienced significantly higher mortality rates as compared with patients with more preserved LV GLS (≥7.0%) (13%, 23%, and 44% vs. 5%, 14%, and 31% at 1-, 2-, and 5-year follow-up, respectively; $p < 0.001$) (Figure 3). To investigate the association between LV GLS and all-cause mortality, a Cox proportional hazards model was constructed (Table 4). LVEF was introduced as categorical variable, taking the threshold of LVEF of 30% proposed by current guidelines (3). In addition, LV GLS was also introduced as a categorical variable, taking the threshold derived from the spline curve analysis. On multivariable analysis, age, impaired renal function, diabetes mellitus, the use of diuretics, and LV end-diastolic volume index were independently associated with all-cause mortality. Furthermore, more impaired LV GLS (<7.0%) remained independently associated with all-cause mortality (HR: 1.337; 95% CI: 1.038 to 1.722; $p = 0.024$), whereas LVEF ≤30% was not associated with the outcome (HR: 1.055; 95% CI: 0.794 to 1.403; $p = 0.711$).

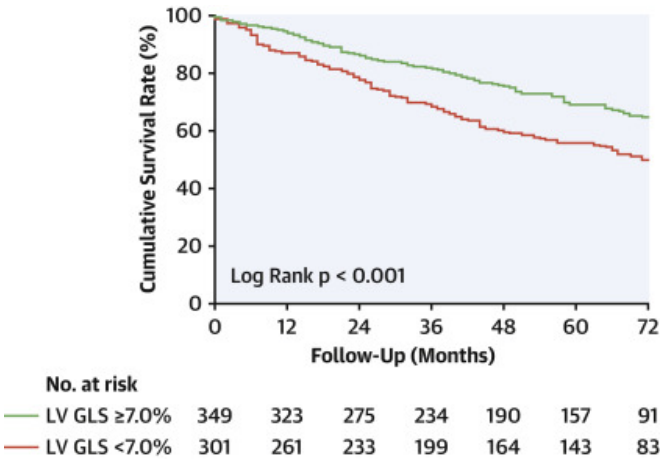


Figure 3. Kaplan-Meier Curves for All-Cause Mortality

Time to all-cause mortality, according to baseline LV GLS: ≥7.0% (less impaired, green) and LV GLS <7.0% (more impaired, red). Abbreviations as in Figure 1.

Table 4. Univariable and Multivariable Cox Regression Analyses to Identify Associates of All-Cause Mortality

	Univariate Analysis			Multivariate Analysis		
	HR	95% CI	p Value	HR	95% CI	p Value
Age	1.030	1.018–1.041	<0.001	1.031	1.018–1.044	<0.001
Male	1.530	1.201–1.948	0.001	1.256	0.954–1.654	0.104
Creatinine	1.004	1.003–1.004	<0.001	1.003	1.002–1.004	<0.001
Hypertension	0.899	0.719–1.123	0.348			
Atrial fibrillation	1.187	0.956–1.475	0.121			
Diabetes mellitus	1.329	1.031–1.712	0.028	1.397	1.070–1.826	0.014
Ischemic etiology	1.344	1.082–1.669	0.008	1.105	0.864–1.414	0.425
NYHA functional class ≥II	1.122	0.644–1.955	0.685			
Beta-blockers	0.803	0.641–1.007	0.057			
Diuretics	1.994	1.411–2.818	<0.001	1.614	1.128–2.309	0.009
CRT	1.171	0.904–1.517	0.231			
Invasive mitral treatment	1.071	0.854–1.342	0.554			
LAVI	1.010	1.004–1.016	0.001	1.006	1.000–1.013	0.065
TAPSE	0.966	0.943–0.991	0.007	1.002	0.975–1.029	0.905
LVEDVi	1.005	1.003–1.008	<0.001	1.004	1.000–1.007	0.030
E′	0.941	0.886–0.999	0.046	0.956	0.895–1.022	0.188
LVEF ≤30%	1.392	1.096–1.769	0.007	1.055	0.794–1.403	0.711
LV GLS <7.0%	1.548	1.246–1.922	<0.001	1.337	1.038–1.722	0.024

CI = confidence interval; HR = hazard ratio; other abbreviations as in Tables 1, 2, and 3.

∗ Device implanted before invasive mitral valve treatment. † Combined surgical MVr, MVR, and percutaneous edge-to-edge MVr.

Incremental prognostic value of LV GLS for all-cause mortality

To determine the incremental value of impaired LV GLS (<7.0%) in addition to clinical and conventional echocardiographic parameters, a likelihood ratio test was performed. A baseline model comprised parameters associated with all-cause mortality in univariable Cox regression analysis. After the addition of LVEF ≤30% to the baseline model, no significant increase in the chi-square value was observed (chi-square difference = 0.1; p = 0.443). However, sequential addition of LV GLS <7.0% to the model including baseline parameters and LVEF ≤30% did show a significant increase in the chi-square value (chi-square difference = 3.6; p = 0.024), demonstrating the incremental prognostic value of LV GLS in patients with secondary MR (Figure 4).

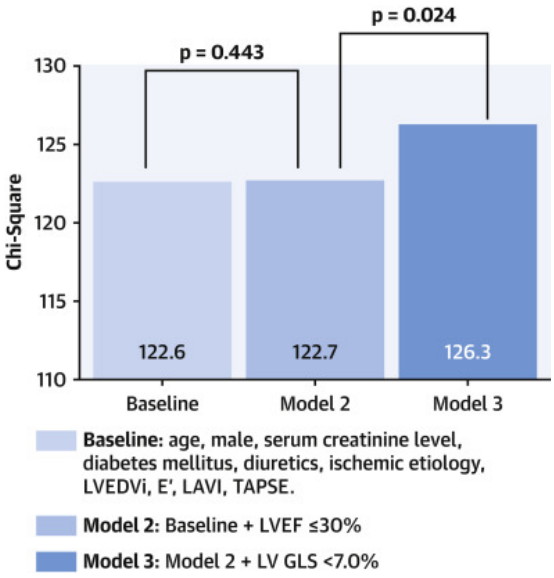


Figure 4. Incremental Value of LV GLS
The incremental value of LV GLS over clinical and traditional echocardiographic parameters for the prediction of all-cause mortality. E′ = peak early diastolic mitral annular tissue velocity; LAVI = left atrial volume index; LVEDVi = left ventricular end-diastolic volume index; TAPSE = tricuspid annular plane systolic excursion; other abbreviations as in Figure 1.

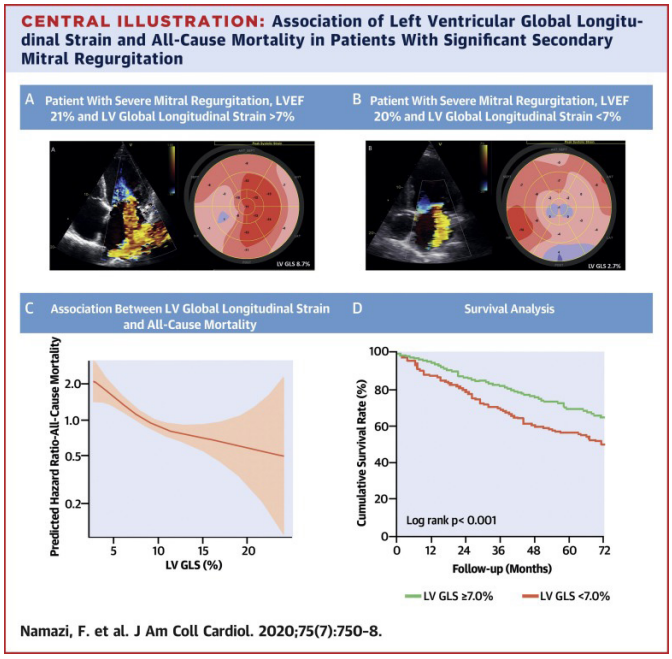
Discussion

The present study demonstrated that in patients with secondary MR, impaired LV GLS was independently associated with an increased risk for all-cause mortality, whereas LVEF was not (Central Illustration).

LVEF: Role in prognosis and intervention of secondary MR

According to current guidelines, patients with secondary MR are considered for mitral valve surgery when there is indication for coronary revascularization (3,13). When revascularization is not indicated, LVEF is one of the main variables to weigh

the indication of surgical mitral valve repair or replacement (3). Heart failure patients who remain symptomatic despite optimal medical therapy (including CRT) and who have a LVEF >30% may be considered for mitral valve surgery if the surgical risk is low (Class IIb) or percutaneous edge-to-edge repair if the surgical risk is high or there are contraindications (Class IIb) (3). The prognostic benefit of reducing secondary MR remains controversial due to a lack of convincing evidence showing improved survival with any intervention (14, 15, 16). Although it is well known that patients with secondary MR have a poor prognosis (17,18), it is less well known if secondary MR affects prognosis independently of LV systolic dysfunction (19). Recently, a long-term observational study demonstrated that secondary MR has an adverse prognostic impact in patients with heart failure and reduced LVEF, but it was only independently associated with all-cause mortality in those with a LVEF of 30% to 40% (20). This intriguing finding suggests that the benefit of mitral valve intervention may be limited to a certain range of LVEF.



Central Illustration. Association of Left Ventricular Global Longitudinal Strain and All-Cause Mortality in Patients With Significant Secondary Mitral Regurgitation

(A) Example of a patient with severe secondary mitral regurgitation (MR) and a left ventricular ejection fraction (LVEF) of 21%. (B) Example of another patient with severe secondary MR and an LVEF of 20%. Despite having the same degree of MR and a comparable LVEF, it is shown that the LV global longitudinal strain (GLS) is highly different, indicating that patient in panel A had a better LV systolic function when compared with the patient in panel B. (C) Prediction of all-cause mortality across a range of LV GLS, plotted as a fitted spline model on a log-hazard scale with overlaid confidence intervals. Dashed lines represent 95% confidence intervals. (D) Kaplan-Meier curves for all-cause mortality according to baseline LV GLS: ≥7.0% (less impaired, green) and LV GLS <7.0% (more impaired, red). It is shown that patients with an impaired LV GLS have higher mortality rates.

Deja et al. (21) showed a trend toward improved survival in patients with a LVEF ≤35% and moderate-to-severe MR when adding mitral valve surgery to CABG versus CABG or medical treatment alone. Two randomized trials, evaluating the prognostic effect of transcatheter mitral valve treatment in patients with secondary MR, were recently published (1,2). Patients in the MITRA-FR trial did not benefit from transcatheter mitral valve treatment in terms of the combined endpoint of heart failure hospitalization and all-cause mortality, whereas in the COAPT trial, patients experienced a significantly lower rate of heart failure hospitalization and all-cause mortality as compared with patients receiving guideline-directed medical therapy. In the MITRA-FR trial, patients had larger LV volumes at baseline (LV end-diastolic volume index 136.2 ± 37.4 ml/m2 in the intervention group vs. 134.5 ± 33.1 ml/m2 in the control group) than did those included in the COAPT trial (LV end-diastolic volume 194.4 ± 69.2 ml in the intervention group vs. 191.0 ± 72.9 ml in the control group). This might reflect more advanced baseline LV disease in the MITRA-FR trial, which was not evident when comparing only the baseline LVEF (similar in both study populations). This finding emphasizes the fact that LVEF may overestimate LV systolic function in patients with secondary MR, owing to its load-dependent nature (22). LVEF may therefore not be the optimal parameter to select patients with secondary MR for intervention. Even in the presence of advanced LV systolic dysfunction, LVEF may be preserved, leading to the unmasking of LV disease after intervention, with subsequent poor outcome (16,22). Novel, more sensitive parameters for assessing LV systolic function in the presence of secondary MR, are therefore required.

LV GLS and outcome in secondary MR

Kamperidis et al. (5) demonstrated that LV GLS is a more sensitive marker of LV systolic dysfunction than is LVEF in patients with nonischemic dilated cardiomyopathy and significant secondary MR. Despite having comparable LVEF, patients with severe MR had more impaired LV GLS values than did those with mild MR. This highlights the fact that LV systolic dysfunction is better reflected by LV GLS than by LVEF in secondary MR. LV GLS has shown incremental prognostic value in addition to LVEF in patients with heart failure (23,24) and can be used in the risk stratification and timing of surgery in patients with aortic regurgitation and primary MR (25,26). However, the prognostic value of LV GLS in patients with secondary MR remained unknown.

This is the first study evaluating the incremental prognostic value of LV GLS (in addition to LVEF) in secondary MR. Patients with a more impaired LV GLS (<7.0%) experienced higher mortality rates than did those with a more preserved LV GLS (≥7.0%). Because no clear consensus exists whether intervention for secondary MR translates into

prognostic benefit, it remains debatable whether mitral valve intervention at an earlier stage of LV systolic dysfunction could impact outcome (3,13). The results of the current study suggest that LV GLS, likely reflecting LV myocardial damage and fibrosis, is a better prognostic marker than LVEF. LV GLS could therefore aid further risk stratification of patients with secondary MR and help to identify those who will benefit from earlier mitral valve intervention.

Study limitations

The single-center, retrospective nature of this study may limit the generalizability of results; however, it represents a large, unselected cohort. The severity of secondary MR depends on prevailing hemodynamic conditions, but only stable patients were included. It should be acknowledged that LV GLS measurement is vendor-specific, although the difference with other platforms has been demonstrated to be moderate (27). In this study, vendor-specific software was used, and this must be taken into consideration when assessing LV GLS with different software. Quantitative measurements such as effective regurgitant orifice area were only feasible in 67% of the patients; therefore, this parameter was not included in the present analysis.

Conclusions

In patients with significant secondary MR, impaired LV GLS was independently associated with an increased risk of all-cause mortality. LV GLS may therefore be useful in the risk stratification of patients with secondary MR, as well as in the candidate selection and timing of mitral valve intervention.

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Chapter four

Regurgitant Volume/Left Ventricular End-Diastolic Volume Ratio: Prognostic Value in Patients With Secondary Mitral Regurgitation

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JACC Cardiovasc Imaging. 2020 Aug 16:S1936-878X(20)30608-2

Abstract

Objectives
The purpose of this study was to investigate the prognostic implications of the ratio of mitral regurgitant volume (RVol) to left ventricular (LV) end-diastolic volume (EDV) in patients with significant secondary mitral regurgitation (MR).

Background
Quantification of secondary MR remains challenging, and its severity can be over- or underestimated when using the proximal isovelocity surface area method, which does not take LV volume into account. This limitation can be addressed by normalizing mitral RVol to LVEDV.

Methods
A total of 379 patients (mean age 67 ± 11 years; 63% male) with significant (moderate and severe) secondary MR were divided into 2 groups according to the RVol/EDV ratio: RVol/EDV ≥20% (greater MR/smaller EDV) and <20% (smaller MR/larger EDV). The primary endpoint was all-cause mortality.

Results
During median (interquartile range) follow-up of 50 (26 to 94) months, 199 (52.5%) patients died. When considering patients receiving medical therapy only, patients with RVol/EDV ratio ≥20% tended to have higher mortality rates than those with RVol/EDV ratio <20% (5-year estimated rates 24.1% vs. 18.4%, respectively; p = 0.077). Conversely, when considering the entire follow-up period including mitral valve interventions, patients with a higher RVol/EDV ratio (≥20%) had lower rates of all-cause mortality compared with patients with RVol/EDV ratio <20% (5-year estimated rates 39.0% vs. 44.8%, respectively; p = 0.018). On multivariable analysis, higher RVol/EDV ratio (per 5% increment as a continuous variable) was independently associated with lower all-cause mortality (0.93; p = 0.023).

Conclusions
In patients with significant secondary MR treated medically, survival tended to be lower in those with a higher RVol/EDV ratio. Conversely, a higher RVol/EDV ratio was independently associated with reduced all-cause mortality. when mitral valve interventions were taken into consideration.

Introduction

Secondary mitral regurgitation (MR) in patients with heart failure (HF) arises from impaired left ventricular (LV) geometry and function (1,2). Although patients with secondary MR have a poor prognosis, whether the dysfunctional LV or mitral valve (MV) (i.e., MR) predominantly dictates patient outcomes may be difficult to distinguish (1,3,4). In addition, LV reverse remodeling after MR reduction has been associated with improved prognosis (5,6). However, when selecting patients with severe secondary MR for medical, surgical, or transcatheter treatments, identifying those patients who will show LV reverse remodeling and improvement in LV systolic function, HF symptoms, and prognosis may be difficult. MR quantification is challenging due to its dynamic nature and its dependence on loading conditions as well as LV size and function (2,7). The effective regurgitant orifice area (EROA) and regurgitant volume (RVol) derived using the proximal isovelocity surface area (PISA) method can over- or under-estimate the severity of MR (7), and LV volumes are not directly taken into consideration, which are important for understanding volume overload (1,7). Therefore, a multiparametric approach is recommended when assessing the severity of secondary MR. Current recommendations take the dimensions of the LV into consideration as a binary variable (i.e., dilated vs. nondilated) instead of a continuous variable (8, 9, 10). The relationship between RVol and LV dimensions can be reflected by the ratio between RVol and LV end-diastolic volume (EDV) (7,11,12). For a given RVol, a larger LVEDV will result in a smaller RVol/EDV ratio, suggesting that the degree of LV dilation is disproportionate to the severity of MR. Eliminating MR in such cases offers less potential for reduction in LVEDV than in patients with smaller LVs (11). The prognostic implications of this ratio have not been investigated. Accordingly, we sought to investigate the prognostic implications of the RVol/LVEDV ratio in a large population of patients with significant (moderate and severe) secondary MR.

Methods

Patient population

Patients with HF and at least moderate secondary MR were identified through the departmental echocardiographic database (Imagevault EchoPAC, General Electric Vingmed Ultrasound, Horten, Norway) of Leiden University Medical Center, Leiden, the Netherlands. Patients with previous MV intervention were excluded. Demographic, clinical, and echocardiographic characteristics were collected in the departmental clinical (EPD-Vision 11.8.4.0, Leiden University Medical Center, Leiden, the Netherlands) and echocardiographic databases, and were analyzed retrospectively. For this retrospective study with clinically acquired data, the institutional review board

waived the need for written patient informed consent.

Clinical characteristics included New York Heart Association (NYHA) functional class, HF etiology, and medication use. Ischemic HF was defined based on previous coronary revascularization with percutaneous coronary intervention or coronary artery bypass grafting and/or coronary artery disease diagnosed on invasive coronary angiography.

Echocardiography

Transthoracic echocardiography was performed with patients in hemodynamically stable condition at rest in the left lateral decubitus position, using a commercially available system (General Electric Vingmed Ultrasound, Milwaukee, Wisconsin). Parasternal, apical, and subcostal views were acquired using 3.5-MHz or M5S transducers. Two-dimensional images and M-mode and Doppler data were digitally stored for off-line analysis (EchoPAC 201.0.0, General Electric Vingmed Ultrasound). MR severity was assessed using a multiparametric approach (7,9). EROA was measured using the PISA method, and RVol was derived by multiplying EROA times the MR velocity time integral. Severe MR was defined as EROA ≥20 mm2 and/or RVol ≥30 ml/beat (7, 8, 9). LV end-systolic volume (ESV) and LVEDV were measured in the apical 2- and 4-chamber views and calculated using the Simpson biplane method (13). Subsequently, LV ejection fraction (EF) was derived as stroke volume (SV) (calculated as EDV – ESV) divided by EDV. The regurgitant fraction (RF) was calculated by measuring the difference between SV measured at the MV annulus and SV at the LV outflow tract and dividing the difference by SV measured at the MV (10). Although the difference between SV measured at the MV annulus and SV measured at the LV outflow tract represents RVol, in the present study, RVol derived using the PISA method was used. The RVol/LVEDV index was calculated and based on previous report (11). The population was dichotomized as RVol/EDV ratio ≥20% (larger RVol and/or smaller LVEDV) and RVol/EDV ratio <20% (smaller RVol and/or larger LVEDV) (Figure 1).

Follow-up

Patients underwent follow-up for the primary endpoint of all-cause mortality after the first echocardiogram showing moderate-to-severe and severe MR. Survival data were obtained from the departmental cardiology information system (EPD-Vision 11.8.4.0, Leiden University Medical Center), which is linked to the governmental death registry database. All patients underwent complete follow-up.

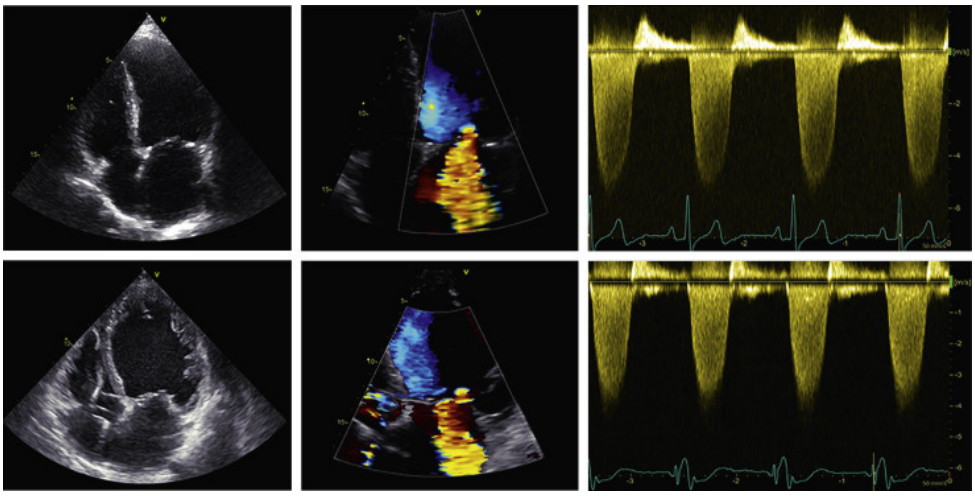


Figure 1. (Top row) Patient with severe secondary MR, LVEDV 153 ml, LVEF 38%, EROA 49.93 mm2, and RVol 88 ml/beat. This patient had RVol/EDV ratio ≥20%. (Bottom row) Patient with severe secondary MR, LVEDV 505 ml, LVEF 21%, EROA 19.46 mm2, and RVol 23 ml/beat. This patient had RVol/EDV ratio <20%. EDV = end-diastolic volume; EROA = effective regurgitant orifice area; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; MR = mitral regurgitation; PISA = proximal isovelocity area; RVol = regurgitant volume.

Statistical analysis

All statistical analyses were performed using SPSS for Windows, version 23.0 (IBM Corp., Armonk, New York). A 2-tailed $p < 0.05$ was considered statistically significant. Continuous data are presented as mean ± SD or median (interquartile range [IQR]) when not normally distributed. Categorical data are presented as absolute number (percentage). For comparison of continuous data, independent-samples Student's t-tests or Mann-Whitney U tests, as appropriate, were used. For comparison of categorical data, the chi-square test was used. To investigate the relationship between RVol/EDV ratio and all-cause mortality as a continuous variable, spline curve analyses were performed, demonstrating the changes in hazard ratio (HR) for all-cause mortality across the range of RVol/EDV ratio. Kaplan-Meier analysis was performed to estimate cumulative survival rates for all-cause mortality of patients with RVol/EDV ≥20% and patients with an RVol/EDV <20% and were compared with a log-rank test. The first set of analyses was performed with patients censored at the time of MV interventions, including surgical MV repair, surgical MV replacement, and percutaneous edge-to-edge MV repair with the MitraClip device (Abbott, Chicago, Illinois). Additional survival analyses were performed, including outcomes after MV interventions. To identify the

independent predictors of all-cause mortality, a Cox proportional hazards regression analysis was performed. The proportional hazards assumption was confirmed using statistics and graphs on the basis of the Schoenfeld residuals. HR and 95% confidence interval (CI) were calculated and reported. The $p < 0.05$ in univariable analysis was considered statistically significant and included in the multivariable model.

Results

Patient population

A total of 379 patients (mean age 67 ± 11 years; 63% male) were included. Baseline clinical and echocardiographic characteristics are summarized in Tables 1 and 2. Nonischemic HF was present in 51% of the total population, and the majority of the patients were in NYHA functional class II to III. Mean LVEF was 30% ± 11%. Median LVEDV was 189 ml (IQR: 138 to 245 ml). Mean EROA and mean RVol were 24 ± 11 mm2 and 34 ± 15 ml/beat, respectively. During median follow-up of 5 months (IQR: 1 to 114 months), 234 patients received MV intervention.

Table 1. Clinical Characteristics at Baseline According to RVol/EDV Ratio

	Total Population (N = 379)	RVol/EDV Ratio <20% (n = 244)	RVol/EDV Ratio ≥20% (n = 135)	p Value
Age (yrs)	67 ± 11	66 ± 11	68 ± 11	0.070
Male	240 (63)	173 (71)	67 (50)	<0.001
BSA (m²)	1.92 ± 0.2	1.94 ± 0.21	1.89 ± 0.22	0.023
Atrial fibrillation	164 (43)	86 (52)	78 (58)	<0.001
Hypertension	163 (43)	95 (39)	68 (50)	0.031
Diabetes mellitus	95 (25)	64 (26)	31 (23)	0.482
eGFR (ml/min/1.73 m²)	61 ± 25	60 ± 25	63 ± 26	0.345
Heart failure etiology				
Ischemic	187 (49)	124 (51)	63 (47)	0.439
Nonischemic	192 (51)	230 (49)	72 (53)	0.439
NYHA functional class				0.041
I	28 (7)	20 (8)	8 (6)	
II	85 (22)	44 (18)	41 (30)	
III	214 (57)	147 (60)	67 (50)	
IV	52 (14)	33 (14)	19 (14)	
Medication				
Beta-blockers	265 (70)	163 (67)	102 (76)	0.075
Diuretics	321 (85)	217 (89)	104 (77)	0.002

table continues

	Total Population (N = 379)	RVol/EDV Ratio <20% (n = 244)	RVol/EDV Ratio ≥20% (n = 135)	p Value
ACE inhibitor/ ARB	297 (78)	193 (79)	104 (77)	0.641
MRA	184 (49)	124 (51)	60 (44)	0.234
ICD therapy	57 (15)	42 (17)	15 (11)	0.112

Continuous data are mean ± SD. Categorical data are n (%).

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BSA = body surface area; EDV = end-diastolic volume; eGFR = estimated glomerular filtration rate; ICD = implantable cardioverter-defibrillator; MRA = mineralocorticoid receptor antagonist; NYHA = New York Heart Association; RVol = regurgitant volume.

Table 2. Echocardiographic Characteristics at Baseline According to RVol/EDV Ratio

	Total Population (N = 379)	RVol/EDV Ratio <20% (n = 244)	RVol/EDV Ratio ≥20% (n = 135)	p Value
LVEDV (ml)	189 (138–245)	222 (181–276)	123 (95–170)	<0.001‡
LVESV (ml)	136 (92–184)	165 (131–210)	77 (53–107)	<0.001
LVEF (%)	30 ± 11	26 ± 8	38 ± 12	<0.001
VC width (mm)	6.0 ± 0.18	6.0 ± 0.18	6.1 ± 0.18	0.557
PISA				
EROA (mm²)	24 ± 11	22 ± 11	27 ± 12	<0.001
RVol (ml)*	34 ± 15	29 ± 10	44 ± 18	<0.001‡
LAVI (ml/m²)	33 (25–44)	33 (25–41)	34 (25–48)	0.324
RVol/EDV ratio	21 ± 14	13 ± 4	35 ± 14	<0.001
RF (%)	77 (71–83)	76 (71–83)	78 (72–84)	0.226
RVol (ml)†	174 ± 79	171 ± 74	181 ± 90	0.259

Continuous data are mean ± SD or median (interquartile range). Categorical data are n (%).

EROA = effective regurgitant orifice area; LAVI = left atrial volume index; LVEF = left ventricular ejection fraction; LVEDV = left ventricular end-diastolic volume; LVESV = left ventricular end-systolic volume; PISA = proximal isovelocity surface area; RF = regurgitant fraction; VC = vena contracta; other abbreviations as in Table 1.

* RVol measured according to the PISA method; † RVol derived from RF; ‡ The p value for LVEDV and RVol demonstrating significance is indicated for illustrative purpose, due to confounding.

A total of 244 (64.4%) patients had RVol/EDV ratio <20%; the remaining 135 (35.6%) patients had RVol/EDV ratio ≥20%. Patients with a high RVol/EDV ratio (≥20%) were more frequently male and had a higher prevalence of atrial fibrillation and hypertension compared with those with a low RVol/EDV ratio (<20%). Those with a high RVol/EDV ratio (≥20%) had less severe HF symptoms and were less frequently using diuretic agents than their counterparts. In terms of echocardiographic characteristics, patients with a high RVol/EDV ratio (≥20%) had smaller LV volumes with higher LVEFs compared with those with a low RVol/EDV ratio (<20%). In addition, patients with a high RVol/EDV ratio (≥20%) had larger EROA and RVol compared with those with a low RVol/EDV

ratio (<20%). Patients with a low RVol/EDV ratio (<20%) were more frequently treated with cardiac resynchronization therapy, whereas those with a high ratio (≥20%) more frequently underwent surgical MV repair (Table 3).

Table 3. Device and Mitral Valve Interventions During Follow-Up According to RVol/EDV Ratio

	Total Population (N = 379)	RVol/EDV Ratio <20% (n = 244)	RVol/EDV Ratio ≥20% (n = 135)	p Value
Device therapy				
CRT-PM	8 (2)	5 (2)	3 (2)	0.911
CRT-ICD	191 (50)	157 (64)	34 (25)	<0.001
MV interventions				
Surgical MVr	156 (41)	80 (33)	76 (56)	<0.001
Surgical MVR	2 (0.5)	1 (0.4)	1 (0.7)	0.670
MitraClip	76 (20)	43 (18)	33 (24)	0.112

Values are n (%).

CRT = cardiac resynchronization therapy; ICD = implantable cardioverter-defibrillator; MV = mitral valve; MVr = mitral valve repair; MVR = mitral valve replacement; PM = pacemaker; other abbreviations as in Table 1.

Survival analysis

During median follow-up of 50 months (IQR: 26 to 94 months) 199 (52.5%) patients of the total study population died, including 169 (44.6%) who died during medical treatment. When considering patients receiving medical therapy only, patients with a high RVol/EDV ratio (≥20%) had higher mortality rates than those with a low RVol/EDV ratio (<20%), although the difference did not reach statistical significance (5-year estimated rates 24.1% vs. 18.4% respectively; p = 0.077) (Figure 2A). Changes in HR across the range of RVol/EDV ratio (as a continuous variable) for all-cause mortality before any MV interventions are demonstrated with a fitted spline curve in Figure 3A. The assumption of linearity was not violated ($\chi 2$ = 0.849; p = 0.36). When considering patients on medical therapy only, RVol/EDV ratio was significantly associated with all-cause mortality after correcting for age and renal function (HR per 5% increment: 1.08; 95% CI: 1.01 to 1.14; p = 0.017).

Conversely, when considering the entire follow-up period including the period after MV interventions, patients with a high RVol/EDV ratio (≥20%) had lower cumulative mortality event rates compared with those with a low RVol/EDV ratio (<20%): 5-year estimated rates 39.0% vs. 44.8% respectively; p = 0.018) (Figure 2B). The changes in HR across the range of RVol/EDV ratio (as a continuous variable) for all-cause mortality including MV interventions during follow-up are demonstrated as a fitted spline curve

in Figure 3B. The HR for all-cause mortality gradually decreased as the RVol/EDV ratios increased. The assumption of linearity was not violated ($\chi 2 = 0.695$; $p = 0.884$). In this model, a high RVol/EDV ratio was independently associated with reduced all-cause mortality (HR per 5% increment: 0.93; 95% CI: 0.87 to 0.99; $p = 0.023$) (Table 4).

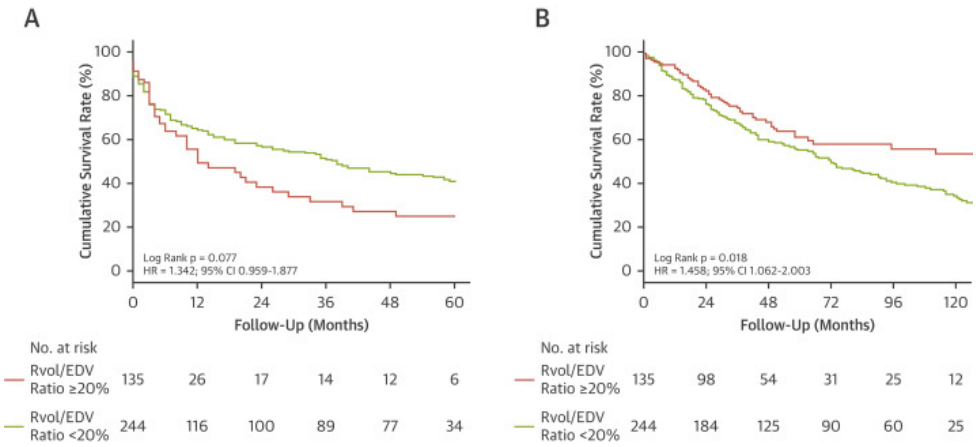


Figure 2. Kaplan-Meier Curves for All-Cause Mortality

(A) Patients were censored at the time of mitral valve interventions. (B) All follow-up data, including after mitral valve interventions. Time to all-cause mortality according to RVol/EDV ratio: ≥20% (green) and <20% (red). CI = confidence interval; EDV = end-diastolic volume; HR = hazard ratio; RVol = regurgitant volume.

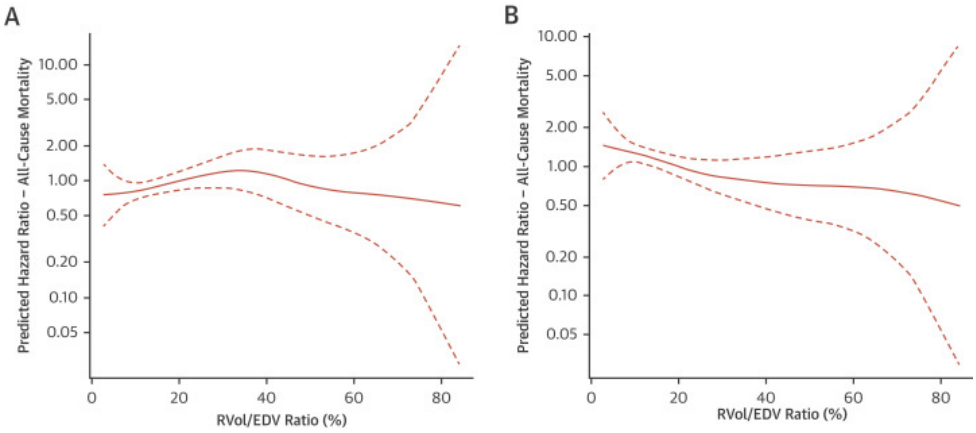


Figure 3. Spline Curve for All-Cause Mortality According to RVol/EDV Ratio

All-cause mortality across the range of RVol/EDV ratios, plotted as a cubic spline on a log-hazard scale with overlaid confidence intervals. (A) Patients were censored at the time of mitral valve

interventions. (B) All follow-up data, including after mitral valve interventions. Dashed lines represent 95% confidence intervals. EDV = end-diastolic volume; RVol = regurgitant volume.

Table 4. Univariable and Multivariable Predictors of All-Cause Mortality in All Patients (Including Those Undergoing Mitral Valve Interventions)

	Unadjusted			Adjusted		
	HR	95% CI	p Value	HR	95% CI	p Value
Age (yrs)	1.02	1.01–1.04	0.001	1.01	1.00–1.03	0.077
Male	1.32	0.98–1.77	0.069	—	—	—
BSA (m^2)	1.01	0.54–1.90	0.975			
eGFR (ml/min/1.73 m^2)	0.98	0.97–0.99	<0.001	0.98	0.97–0.99	<0.001
Hypertension	1.09	0.82–1.44	0.556			
Diabetes mellitus	1.33	0.97–1.82	0.080	—	—	—
Atrial fibrillation	0.96	0.72–1.27	0.755			
Ischemic etiology	1.16	0.88–1.54	0.287	—	—	—
NYHA functional classification ≥II	1.12	0.64–1.97	0.691			
Beta-blockers	0.83	0.62–1.11	0.200	—	—	—
MV interventions*	0.87	0.65–1.15	0.310			
MV interventions†	0.99	0.99–1.00	0.084			
LAVI (ml/m^2)	1.01	0.99–1.01	0.119			
RVol/EDV ratio (per 5% increment)	0.93	0.87–0.99	0.015	0.93	0.87–0.99	0.023

BSA = body surface area; CI = confidence interval; EDV = end-diastolic volume; eGFR = estimated glomerular filtration rate; HR = hazard ratio; LAVI = left atrial volume index; MV = mitral valve; NYHA = New York Heart Association; RVol = regurgitant volume.

* Surgical mitral valve repair, mitral valve replacement, and percutaneous edge-to-edge mitral valve repair compared with optimal medical therapy alone.

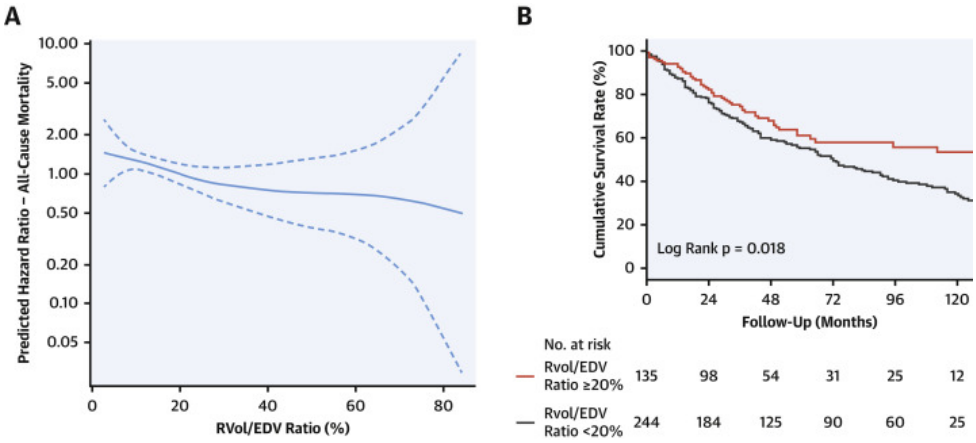
† Mitral valve interventions introduced as a time-dependent covariate.

Discussion

In the present study, a high RVol/EDV ratio was associated with a trend toward increased all-cause mortality during medical therapy in patients with moderate and severe secondary MR. Conversely, allowing for the effects of MV interventions, a high RVol/EDV ratio was independently associated with lower all-cause mortality during follow-up.

In contrast to other Doppler echocardiographic measures of secondary MR, the RVol/EDV ratio takes into consideration the degree of LV remodeling as well as MR severity. Thus, this ratio may help identify patients who are likely to benefit from transcatheter and surgical therapies that aim to reduce MR. For the same value of RVol, a patient

with low RVol/EDV ratio may not benefit as much as a patient with a high RVol/EDV ratio because the patient with a low RVol/EDV ratio has a much larger degree of LV remodeling that may not respond to MR reduction therapies. Similarly, for the same LVEDV, a patient with a high RVol/EDV ratio may benefit more from transcatheter or surgical therapies than a patient with a low RVol/EDV ratio because the volume overload caused by the MR is relatively greater in the former patient. This perspective is consistent with the concept of proportionate and disproportionate secondary MR as proposed by Packer and Grayburn (14).



Central Illustration. Association of RVol/EDV Ratio and Long-Term All-Cause Mortality in Patients With Secondary Mitral Regurgitation During Medical Treatment and After Surgical and Transcatheter Mitral Reduction Therapies

(A) All-cause mortality across a range of RVol/EDV ratios, plotted as a fitted spline model. The spline curve demonstrates a linearly increasing risk for mortality for lower RVol/EDV ratios. (B) Kaplan-Meier curves demonstrating the cumulative survival rate for all-cause mortality stratified according to a RVol/EDV ratio cutoff of 20%. EDV = end-diastolic volume; RVol = regurgitant volume.

In the present study, patients with a high RVol/EDV ratio (≥20%) tended to have worse survival during medical management than those with a low RVol/EDV ratio (<20%), suggesting that more severe MR with less LV dilation is associated with a worse prognosis. As expected, patients with a high RVol/EDV ratio (≥20%) more frequently underwent surgical correction of the MR, whereas patients with a low RVol/EDV ratio (<20%) more frequently received cardiac resynchronization therapy. After MV interventions, the relative prognosis changed such that a baseline high RVol/EDV

ratio was independently associated with improved survival. For both therapies, the degree of LV remodeling has been associated with response to treatment and survival (5,6). Therefore, when evaluating patients with HF and secondary MR, assessment of the degree of LV remodeling is likely to be fundamental in estimating the potential benefit of interventional therapies. However, patients in the present analysis were not randomized to MV interventions according to RVol/EDV ratio. Thus, further investigations are warranted to assess the utility of this ratio in predicting the benefits from surgical or transcatheter interventions. Such an analysis should be possible from the recently completed COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation) and MITRA-FR (Percutaneous Repair with the MitraClip Device for Severe Functional/ Secondary Mitral Regurgitation) randomized trials (15,16).

Grading secondary MR in HF patients

Grading secondary MR remains challenging for various reasons. RVol usually is smaller than that observed in primary MR because the total LV SV is reduced. In contrast to RVol calculated according to the PISA method, RF takes into consideration the degree of LV remodeling measured either with quantitative pulsed Doppler (because the mitral annulus dimensions are included) or volumetrically (via LVEDV and LVESV). Accordingly, it has been suggested that RF provides a metric of proportionality of the secondary MR to LV dimensions and function (17). However, measurement of RF with echocardiography is prone to error. When using the quantitative pulsed Doppler method, calculation of RF can be inaccurate because of failure in tracing the modal velocity on spectral Doppler, locating the sample volume, and assuming that the mitral or aortic valve annuli are circular (leading to a squared error in the formula) (10). When the quantitative volumetric method is used, foreshortened images of the LV may lead to underestimation of SV (10). Various studies have suggested that cardiac magnetic resonance (CMR) may be a more accurate method to quantify secondary MR, although the majority of studies did not have a reference standard to resolve discrepancies between techniques (18, 19, 20). Lopez-Mattei et al. (18) showed a modest agreement between transthoracic echocardiography and CMR in quantifying RVol and RF. The discrepancy between techniques was more prominent among patients with secondary MR.

The RVol/EDV ratio proposed in the present study shares some of the limitations mentioned but provides a metric of proportionality of secondary MR and can be used in patients with concomitant aortic regurgitation (in whom RF cannot be used).

RVol/EDV ratio and outcome in secondary MR

The cutoff values of EROA ≥20 mm2 and RVol ≥30 ml/beat to define severe secondary MR included in European guidelines (8,21) are based on outcomes studies showing that patients with secondary MR and EROA or RVol values above those cutoffs have a worse prognosis (4,22, 23, 24). However, the U.S. guidelines suggest higher thresholds to define severe secondary MR (25,26). In this regard, even mild secondary MR has been associated with poor outcomes (24,27). However, MV repair in patients with moderate ischemic (secondary) MR (mean EROA ~0.20 mm2) undergoing coronary revascularization did not show improved outcomes in a randomized trial (28). Whether the association between EROA and poor outcomes relies on the severity of MR itself, the underlying LV dysfunction/remodeling, or both remains unclear (10). By adjusting RVol for LV volume in the RVol/LVEDV ratio, the extent of LV remodeling is taken into consideration, and we demonstrated that when considering surgical and transcatheter options for correction of MR, patients with a higher RVol/EDV ratio (≥20%) had improved long-term outcomes, suggesting that the long-term prognosis is determined by the lesser severity of LV dysfunction after MR reduction. Bartko et al. (29) showed in 423 HF patients with various grades of secondary MR that the measurement of RF had incremental discriminative power over RVol and EROA in identifying patients with poor prognosis. RF partially takes into consideration the severity of LV remodeling and has been proposed as a parameter that reflects the proportionality of MR. Similarly, RVol/EDV may reflect the proportionality of secondary MR and impact of available therapies. We hypothesize that for patients with a low RVol/EDV, resolving the volume overload caused by the MR, either by surgery or transcatheter techniques, may not have a major impact on outcome because the severity of MR may be less prognostically relevant than the extent of LV remodeling. In contrast, in patients with a high RVol/EDV, the volume overload caused by MR may have a major influence on LV hemodynamics and symptoms, and thus appropriate repair or replacement may improve outcomes. This hypothesis requires validation in prospective studies.

Study limitations

The present study has several limitations related to the retrospective nature of data analysis. However, to the best of our knowledge, this is the largest series evaluating the prognostic value of RVol/EDV ratio in patients with secondary MR. External validation of the present results is warranted. Symptomatic status could only be assessed based on NYHA functional class, and other quantitative measures such as 6-min walked distance or quality-of-life scores were not systematically available. In addition, patients with mild MR were excluded, and the value of RVol/EDV ratio was not assessed in this population. Assessment of EROA and RVol in secondary MR using echocardiography

is limited by various previously described assumptions (30), and CMR data were not systematically available. Furthermore, a significant proportion of patients were referred for intervention, which limits the power to demonstrate the association between RVol/EDV and all-cause mortality while receiving medical therapy. Finally, the sample size limited our ability to examine which MV interventions were beneficial or hazardous according to RVol/EDV ratio.

Conclusions

In patients with significant secondary MR who were treated medically, survival tended to be lower in those with a higher RVol/EDV ratio. Conversely, a high RVol/EDV ratio was independently associated with reduced all-cause mortality if this group received therapies to correct the MR. By accounting for the relative severity of both MR and LV volume, the RVol/EDV ratio may further improve risk stratification of patients with secondary MR and identify those who may benefit from transcatheter and surgical therapies to reduce severe secondary MR.

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Chapter four
Part I

Letter to the editor: Regurgitant Volume/ Left Ventricular End-Diastolic Volume Ratio: The Influence of Aortic Stiffness

Caterina Maffeis, Stefano Bonapace, Andrea Rossi

JACC Cardiovasc Imaging. 2021 Apr;14(4):880

Letter to the editor

We read with great interest the paper by Namazi et al. (1). The aim of the study was to analyze the clinical impact of mitral regurgitant volume (RV) in relation with the degree of left ventricular enlargement (RV/end-diastolic volume [EDV] ratio) in secondary mitral regurgitation. As underscored by the investigators, the focus is in line with the proposed concept of disproportionate or proportionate secondary mitral regurgitation. Analogously, the editorial comment underscores that the mitral regurgitant fraction (RF), a ratio between mitral RV and left ventricular total stroke volume, might unravel the disproportionate and/or proportionate nature of secondary mitral regurgitation (2). Although this pathophysiological approach might be intriguing, we have some concerns to reconcile. The total ventricular stroke volume includes forward stroke volume besides mitral RV; consequently, for the same value of RV, a different forward stroke volume, gives a different RF. Because of the fact that the amount of forward stroke volume is the result of both physiological requests and global ventricular and vascular functions, we have previously shown that an increased aortic stiffness for the same degree of ventricular dysfunction provides a reduced forward stroke volume (through a reduction of ventricular ejection time) (3) and increased RV, and therefore, an increased RF (4). This suggests that different factors other than degree of RV, including aortic stiffness, might affect the proportionality of mitral regurgitation. In the paper by Namazi et al. (1), those patients characterized by a higher RV/EDV ratio had a low total left ventricular stroke volume (46 ml/beat, as extrapolated from the mean value of ventricular volumes reported in Table 2), and considering the mean reported mitral RV (44 ml/beat), the forward stroke volume appeared uncommonly low. Therefore, it may be considered that the main pathophysiological feature of patients with a lower RV/EDV ratio is the remarkably low forward aortic stroke volume, possibly due to aortic stiffening, which might be the cause of the high mortality rate observed in patients treated medically (5). Considering the impact of arterial stiffness on all the main hemodynamic determinants of functional mitral regurgitation in the failing heart, its evaluation should be considered as an additional tool in the assessment of secondary mitral regurgitation, not only to better understand its pathophysiology but also to better interpret the different response to procedural and medical therapy in disproportionate or proportionate secondary mitral regurgitation.

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Chapter four
Part II

Reply to the editor: Regurgitant Volume/Left Ventricular End-Diastolic Volume Ratio: The Influence of Aortic Stiffness

Farnaz Namazi, Victoria Delgado, Jeroen J Bax

JACC Cardiovasc Imaging. 2021 Apr;14(4):880-881

Reply to the editor

We thank Dr. Maffeis and colleagues for their interest in our study that evaluated the association of the ratio of mitral regurgitant volume (RV) to left ventricular (LV) end-diastolic volume (EDV) in patients with significant secondary mitral regurgitation (MR) and all-cause mortality (1). A multiparametric approach is recommended for quantification of MR. However, current recommendations do not take LV dimensions as a continuous variable into consideration. As previously described by Gaasch et al. (2), RV is influenced by LVEDV, and therefore, the use of an absolute value of RV is limited in defining severe MR. A new concept of indexing RV for LVEDV was proposed that in essence takes into account the interplay between RV and LV remodeling (LVEDV) and reflects the impact of the RV on the LV. In our study, patients with a RV/EDV ratio ≥20% more frequently underwent mitral valve (MV) intervention and when the MR was resolved, these patients had a better outcome compared with their counterparts (RV/EDV ratio <20%). This might suggest, in these patients, that the degree of MR contributed more to their underlying disease than the LVEDV. The concept that aortic stiffness may affect forward stroke volume and RV in patients with heart failure and significant secondary MR is of interest (3), and as previously shown, it may affect clinical outcomes (4). A previous study showed that in patients with heart failure, increased aortic stiffness was independently associated with the composite endpoint of all-cause death and heart failure hospitalization after correcting for LV ejection fraction, transmitral early wave peak velocity, LV stroke volume, systolic blood pressure, and heart rate (4). An increased aortic stiffness may affect the forward stroke volume; however, the calculation of the forward stroke volume, based on 2-dimensional measurement of the LVEDV and RV calculation, which is based on proximal isovelocity surface area (PISA) needs to be considered with caution because the method has important limitations (5). In secondary MR, the regurgitant orifice is usually elliptical or crescent shaped, and therefore, the quantification of the effective regurgitant orifice area based on the PISA method may lead to significant underestimation. In addition, patients with heart failure present with low-flow status, which may lead to reduced RV. Other methods to quantify RV have been proposed, but they also have limitations (5). Selection of patients with heart failure and severe secondary MR who may benefit from intervention remains challenging, and assessment of the severity of MR is only one part of the evaluation. The clinical condition of the patients, associated comorbidities, and optimization of heart failure therapy (including cardiac resynchronization therapy and coronary revascularization) need to be considered. Aortic stiffness is not assessed routinely, but as previously shown (4), it is an important factor to be addressed in the treatment of patients with heart failure.

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Chapter five

Prognostic Implications of Mitral Valve Geometry in Patients with Secondary Mitral Regurgitation: The COAPT Trial

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European Heart Journal - Cardiovascular Imaging, 2021

Abstract

Aims

The impact of mitral valve geometry on outcomes after MitraClip treatment in secondary MR has not been examined. We therefore sought to evaluate the association between mitral valve geometry and outcomes of patients with heart failure (HF) and secondary mitral regurgitation (MR) treated with guideline-directed medical therapy (GDMT) and MitraClip.

Methods and Results

Mitral valve geometry was assessed from the baseline echocardiograms in 614 patients from the COAPT trial. The primary endpoint for the present study was the composite of all-cause mortality or HF hospitalization (HFH) within 2 years. Effect of treatment arm (MitraClip plus maximally-tolerated GDMT versus GDMT alone) on outcomes according to baseline variables was assessed.

Among 29 baseline mitral valve echocardiographic parameters, increasing antero-posterior mitral annular diameter was the only independent predictor of the composite endpoint of all-cause mortality or HFH (adjusted hazard ratio (aHR) per cm 1.49; p=0.04). The effective regurgitant orifice area (EROA) was independently associated with all-cause mortality alone (aHR per cm^2 2.97; p=0.04) but not with HFH, whereas increasing anteroposterior mitral annular diameter was independently associated with HFH alone (aHR per cm 1.85; p=0.005) but not all-cause mortality. Other mitral valve morphologic parameters were unrelated to outcomes. MitraClip reduced HFH and mortality independent of anteroposterior mitral annular diameter and EROA ($P_{interaction}$= 0.77 and 0.27 respectively).

Conclusion

In patients with HF and severe secondary MR, a large anteroposterior mitral annular diameter and greater EROA were the strongest echocardiographic predictors of HFH and death in patients treated with GDMT alone and with the MitraClip.

Introduction

In prior studies of patients with heart failure (HF) and secondary mitral regurgitation (MR), quantification of MR severity, indices of left ventricular (LV) function and remodeling, and clinical symptoms have been the principal parameters used to assess prognosis and select the most appropriate therapy (1,2). Guideline-directed medical therapy (GDMT) for HF is foundational for all patients and may reduce MR by decreasing LV dimensions (3,4). Cardiac resynchronization therapy has been shown to further reduce MR in some patients with HF (5,6). When surgical coronary revascularization is needed, concomitant mitral annuloplasty is often performed (1,2). However, recurrent MR after annuloplasty is not uncommon and has been associated with increased mortality and morbidity (7,8). In patients with non-ischemic cardiomyopathy and severe secondary MR, surgical mitral valve repair has also been associated with high operative risk and its variable durability (7,8). Specific mitral valve geometric abnormalities and the extent of LV remodeling have been associated with recurrence of MR after surgical mitral valve repair and reduced survival (7-10).

More recently, transcatheter mitral valve repair (TMVr) has been introduced for the treatment of HF patients with severe secondary MR, the most widely studied of which is transcatheter mitral leaflet edge-to-edge approximation with the MitraClip. A decade ago, numerous mitral valve anatomic criteria were established that predicted success (or failure) of the MitraClip (11,12). However, these studies were performed before widespread usage of this device. Procedural success rates have greatly improved within the last decade, and in the present era less is known about the mitral valve anatomic parameters that predict procedural success and long-term outcomes with the MitraClip (and may vary in primary and secondary MR). In this regard, disparate outcomes of HF patients enrolled in the Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation (COAPT) (13) and the Multicentre Study of Percutaneous Mitral Valve Repair MitraClip Device in Patients With Severe Secondary Mitral Regurgitation (MITRA-FR) (14) trials were reported, which has most often been attributed to inter-study differences in LV dilation, LV function and MR severity. However, a detailed analysis of mitral valve geometry and its interplay with LV remodeling and MR severity in determining the clinical outcomes of patients randomized to MItraClip plus GDMT versus GDMT alone has not been performed in either study. Accordingly, in the present sub-study from the COAPT trial, we assessed the association between various geometric mitral valve parameters and clinical outcomes. We hypothesized that more advanced mitral valve apparatus deformation would be associated with worse outcomes independent of

treatment arm, and that MitraClip treatment would mitigate the impact from these prognostic risk factors.

Methods

Study design and patient population

Details concerning the COAPT study design and patient population have been published previously (13,15). In brief, HF patients with ischemic or non-ischemic cardiomyopathy and with moderate-to-severe (grade 3+) or severe (grade 4+) secondary MR who remained symptomatic despite the use of maximally-tolerated GDMT were enrolled. Patients were randomized to TMVr using the MitraClip device (Abbott Vascular, Santa Clara, CA) plus GDMT or GDMT alone. Procedural data have been published previously (13). The primary endpoint of the present analysis was the composite of all-cause death or heart failure hospitalization (HFH) at 24-month follow-up. Secondary endpoints included all-cause mortality and HFH alone. The protocol was registered on ClinicalTrials.gov (#NCT01626079) and was approved by the investigational board of each participating center. All patients provided written informed consent. The sponsor participated in site selection and management and in data analysis. The principal investigators had unrestricted access to the data, wrote the manuscript, and vouch for the accuracy and completeness of the data and analyses and for the fidelity of the trial to the protocol.

Echocardiography

Baseline conventional echocardiographic measurements were performed by an independent echocardiographic core laboratory (MedStar Health Research Institute, Washington DC) and have been published previously (13,16). Left and right ventricular dimensions and function were measured according to current recommendations (17,18). MR was quantified using a multiparametric algorithm based on recommendations from the American Society of Echocardiography (13,19). Tricuspid regurgitation (TR) was also graded based on a multiparametric approach consisting of qualitative and semiquantitative parameters (19).

For the present post hoc analysis, mitral valve geometric analysis was performed using commercially available software for offline analysis (TomTec-Arena, version 20.18, 2017). Table 1 and Figures 1 and 2 summarize the mitral valve geometrical variables measured (9,10,20-22). All measurements were done on transthoracic echocardiograph. The measurements were performed per multiple beats if atrial fibrillation was present. The

diameters of the mitral valve annulus were measured in the anteroposterior direction from the parasternal long-axis view and in the intercommissural direction from the apical 2-chamber view. Mitral valve tethering was assessed measuring the distance between the coaptation point to septum, tenting height (the distance between the coaptation point of the mitral valve leaflets and the mitral valve annular plane) and tenting area (the area enclosed by the mitral valve leaflets and the mitral annular plane). The length of the anterior and posterior mitral valve leaflets were measured in mid-diastole on the parasternal long-axis view. The maximal tethering location was determined according to the scallops of the posterior mitral leaflet. The distance from the posterior papillary muscle to the mitral annulus was measured in the apical 4- and 2-chamber views while the distance from the anterior papillary muscle to the mitral annulus was measured in the apical 2-chamber view. The mitral posterior leaflet angle and the basal and distal anterior leaflet angles were measured on the apical long-axis view.

Statistical analysis

Categorical data are presented as frequencies and were compared by Chi-square test or Fisher's exact test, as appropriate. Continuous variables are presented as means and standard deviation or median [Q1, Q3] and were compared by Student's t-test or Wilcoxon Rank Sum test. The independent association between the various clinical and echocardiographic parameters with the occurrence of the endpoint was assessed with univariate and multivariable Cox proportional hazards regression analysis. The relative effect of treatment vs. control arms on the risk of the endpoints associated with clinical and echocardiographic variables was assessed by formal interaction testing. Statistical analyses were performed with SAS version 9.4 (SAS Institute, Cary, NC).

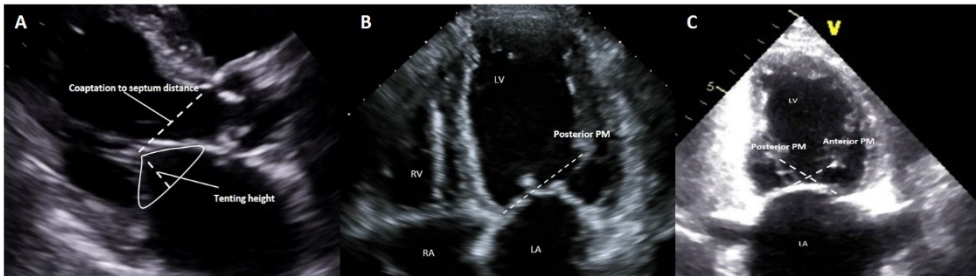


Figure 1. Examples of mitral valve geometry measurements on two-dimensional transthoracic echocardiography.

Panel A shows the parasternal long-axis view, demonstrating the measurements of coaptation to septum distance, tenting height and tenting area (the area enclosed by white lines). Panel B shows the apical 4-chamber view, demonstrating the measurement of posterior papillary muscle

tethering length (the white dashed line from the posterior papillary muscle to the contralateral mitral valve annulus). Panel C shows the apical 2-chamber view, demonstrating the posterior papillary muscle to the mitral valve annulus distance (the white dashed line from the posterior papillary muscle to the contralateral mitral valve annulus) and the anterior papillary muscle to the mitral valve annulus distance (the white dashed line from the anterior PM to the contralateral mitral valve annulus).

Table 1. Summary of mitral valve geometry measurements using two-dimensional transthoracic echocardiography.

Parameter	Definition	TTE view	Timing on TTE
Anterior-posterior mitral annulus diameter	The distance between the anterior point and posterior point of the mitral annulus	Parasternal long-axis	End-diastole
Intercommissural mitral annulus diameter	The distance from commissure to commissure of the mitral annulus	Apical 2-chamber view	End-diastole
Anterior and posterior mitral valve leaflet length	The length of the mitral valve leaflet measured from the hinge point of the leaflet to the leaflet tip	Parasternal long-axis	Diastole, maximum extension of leaflets
Coaptation to septum distance	The distance between the coaptation point of the mitral valve leaflets and the septum at the hinge point of the aortic valve cusps	Parasternal long-axis	Mid-systole
Tenting height	The distance between the coaptation point of the mitral valve leaflets and the mitral annular plane	Parasternal long-axis	Mid-systole
Tenting area	The area enclosed by the mitral valve leaflets and the mitral annular plane	Parasternal long-axis	Mid-systole
Anterior- and posterior papillary muscle to mitral valve annulus distance	The distance between the PM tips to the contralateral mitral annulus, providing an estimation of PM displacement	Apical 2-chamber view (if not visible, measured on apical 4-chamber view)	Mid-systole
Basal mitral anterior leaflet angle	The angle between the basal anterior leaflet and mitral annulus (traced from mitral annular plane to the bending point of the anterior mitral valve leaflet)	Apical 4-chamber view	Mid-systole
Distal mitral anterior leaflet angle	The angle between the anterior leaflet and mitral valve annulus (traced from mitral annular plane to the bending point of the anterior mitral valve leaflet)	Apical 4-chamber view	Mid-systole
Posterior mitral leaflet angle	The angle between the posterior leaflet and mitral valve annulus (traced from mitral annular plane to the tip of the posterior mitral valve leaflet)	Apical 4-chamber view	Mid-systole

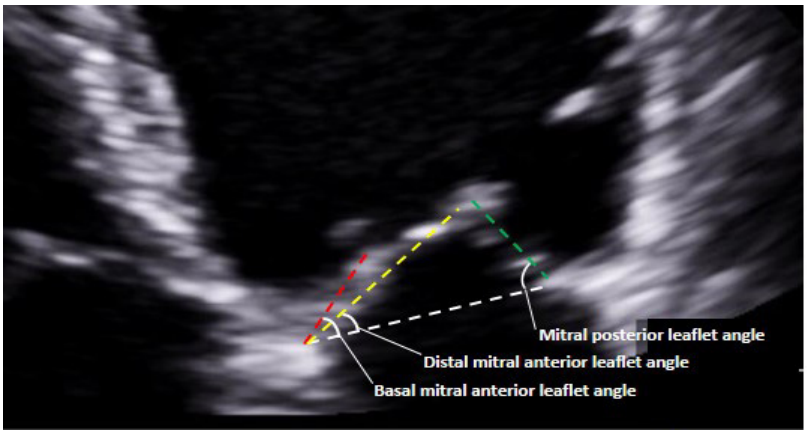


Figure 2. Example of mitral valve angle quantification on echocardiography.
The white dashed line represents the mitral valve annular plane. The red dashed line represents the line from the mitral valve annulus to the bending point of the anterior mitral leaflet, defining the basal mitral anterior leaflet angle (ALA_{base}). The yellow dashed line represents the line from the mitral valve annulus to the tip of the anterior mitral leaflet, defining the distal mitral anterior leaflet angle (ALA_{dist}). The green dashed line represents the line from the mitral valve annulus to the tip of the posterior mitral leaflet, defining the posterior mitral leaflet angle (PLA).

Results

Baseline clinical characteristics have been previously reported (13) and are summarized in Supplemental Appendix Table 1. The echocardiographic characteristics including the mitral valve geometry analysis are outlined in Table 2. The mean intercommissural (3.56 ± 0.43 cm) and anteroposterior (3.26 ± 0.39 cm) mitral annulus diameters were comparable demonstrating a circular rather than an elliptical shape of the mitral annulus. Significant tethering of the mitral valve leaflets was observed as indicated by the large distance between the point of coaptation and the interventricular septum, the increased tenting height/area and the increased posterior leaflet angle. Leaflet tethering was most frequently observed at the central level of the posterior mitral leaflet (P2). Intraobserver reproducibility of all the mitral valve echocardiographic measurements was tested in a randomly selected sample of 20 cases. Agreement was very good or excellent for all mitral valve measurements (intraclass coefficient [ICC] >0.7), except for the length of the anterior and posterior mitral valve leaflets (ICC 0.5; 95% CI 0.24 to 0.78 and ICC 0.57; 95% CI 0.15 to 0.74, respectively), and the anterior papillary muscle to mitral valve annulus distance (ICC 0.26; 95% CI -0.14 to 0.58). As previously described, patients had severe MR with a mean effective regurgitant orifice

area (EROA) of 0.41 cm^2, regurgitant volume of 26.8 ml/beat and regurgitant fraction of 36.4%. Moderately severe LV remodeling was observed with a mean LV end-systolic diameter of 5.3 cm and end-diastolic diameter of 6.2 cm. Mean LV end-systolic volume was 134.7 ml and end-diastolic volume 192.8 ml resulting in a mean LV ejection fraction of 31.3%. Mean right ventricular fractional area change was impaired with a mean value of 32.0%. The mean right ventricular systolic pressure (RVSP) was increased (44.3 ± 13.7 mmHg) and the majority of patients had mild tricuspid regurgitation.

Impact of mitral valve geometry and cardiac structure and function on MR reduction

Among 274 patients who were randomized to and treated with the MitraClip, at 30 days grade 0 or 1+ MR was present in 199 patients (72.6%), grade 2+ MR was present in 54 patients (19.7%) and grade 3+ or 4+ MR was present in 21 patients (7.7%). As shown in Table 3, patients with 3+ or 4+ MR at 30 days post-MitraClip had a significantly larger mitral posterior leaflet angle at baseline than those with £2+ MR. The tethering location was also significantly different between the groups; specifically, while mitral leaflet tethering at P3 was uncommon (7 patients), 3 of these patients (42.9%) had ^{3}3+ MR at 30 days after MitraClip. No other significant differences were observed in mitral valve geometry at baseline according to MR grade 30 days after MitraClip. In terms of conventional echocardiographic characteristics, patients with grade 3+ or 4+ MR 30-days after MitraClip had more severe MR at baseline, larger total stroke volume, larger LV end-diastolic volume index and higher RVSPs.

Table 2. Echocardiographic characteristics at baseline for the total population.

Mitral valve geometrical measurements	
Intercommissural mitral valve annulus diameter (cm)	3.56 ± 0.43 (577)
Anteroposterior mitral valve annulus diameter (cm)	3.26 ± 0.39 (575)
Coaptation to septum distance (cm)	4.04 ± 0.46 (559)
Tenting height (mm)	9.9 ± 2.4 (569)
Tenting area (cm^2)	2.16 ± 0.68 (568)
Anterior mitral valve leaflet length (cm)	2.25 ± 0.37 (551)
Posterior mitral valve leaflet length (cm)	1.35 ± 0.24 (472)
Tethering location, n/N (%)	
None	21/465 (4.5)
P1	60/465 (12.9)
P1-P2	109/465 (23.4)
P2	183/465 (39.4)
P2-P3	68/465 (14.6)
P3	22/465 (4.7)
All	2/465 (0.4)

Mitral valve geometrical measurements	
Posterior papillary muscle to annulus distance (cm; 4CH view)	4.19 ± 0.59 (275)
Posterior papillary muscle to annulus distance (cm; 2CH view)	4.02 ± 0.58 (256)
Anterior papillary muscle to annulus distance (cm)	3.81 ± 0.57 (226)
Basal mitral anterior leaflet angle (°)	32 ± 7 (244)
Distal mitral anterior leaflet angle (°)	19 ± 6 (516)
Mitral posterior leaflet angle (°)	38 ± 9 (501)
Mitral valve regurgitation quantification	
Mitral regurgitation, n/N (%)	
(3+) Moderate to severe	320/613 (52.2)
(4+) Severe	293/613 (47.8)
Effective regurgitant orifice area (cm^2)	0.41 ± 0.15 (591)
Regurgitant volume (mL/beat)	26.8 ± 16.2 (260)
Regurgitant fraction (%)	36.4 ± 14.5 (259)
Left ventricular measures	
LV end-systolic diameter (cm)	5.3 ± 0.9 (607)
LV end-diastolic diameter (cm)	6.2 ± 0.7 (608)
LV end-systolic volume (mL)	134.7 ± 58.2 (574)
LV end-diastolic volume (mL)	192.8 ± 71.1 (574)
Total stroke volume (mL)	58.0 ± 22.6 (574)
LV end-systolic volume index (mL/m^2)	71.1 ± 29.1 (567)
LV end-diastolic volume index (mL/m^2)	101.4 ± 34.4 (567)
LV ejection fraction (%)	31.3 ± 9.3 (575)
LV sphericity index*	0.65 ± 0.1 (524)
Right ventricular measures	
RV fractional area change (%)	32.04 ± 8.98 (417)
RV systolic pressure (mmHg)	44.3 ± 13.7 (528)
Tricuspid regurgitation, n/N (%)	
(0) None	12/599 (2.0)
(1+) Mild	489/599 (81.6)
(2+) Moderate	92/599 (15.4)
(3+) Moderate to Severe	5/599 (0.8)
(4+) Severe	1/599 (0.2)
Left atrial measures	
Left atrial volume (mL)	91.4 ± 40.8 (595)

Data presented as mean ± SD (n) or n/N (%). CH = chamber; LV = left ventricular; RV = right ventricular; MV = mitral valve; PM = papillary muscle. *LV sphericity index was defined as LV short axis / LV long axis. Both axis measurements were taken in 4-chamber view.

Table 3. Impact of Baseline Echocardiographic Parameters on Post-MitraClip Severity of Mitral Regurgitation at 30 Days.

	MR grade at 30 days			
	Grade 0 or 1+	**Grade 2+**	**Grade 3+ or 4+**	**P-value**
Mitral valve geometrical measurements				
Intercommissural mitral valve annulus diameter (cm)	3.56 ± 0.42 (188)	3.53 ± 0.34 (49)	3.66 ± 0.41 (18)	0.50
Anteroposterior mitral valve annulus diameter (cm)	3.26 ± 0.40 (188)	3.24 ± 0.30 (48)	3.36 ± 0.34 (20)	0.44
Coaptation to septum distance (cm)	4.07 ± 0.44 (182)	4.01 ± 0.44 (47)	4.08 ± 0.38 (20)	0.68
Tenting height (mm)	9.8 ± 2.5 (186)	10.2 ± 2.5 (48)	9.5 ± 1.5 (20)	0.48
Tenting area (cm^2)	2.13 ± 0.71 (186)	2.16 ± 0.69 (48)	2.26 ± 0.59 (20)	0.71
Anterior mitral valve leaflet length (cm)	2.26 ± 0.34 (174)	2.25 ± 0.43 (47)	2.37 ± 0.37 (19)	0.47
Posterior mitral valve leaflet length (cm)	1.34 ± 0.25 (141)	1.34 ± 0.23 (39)	1.29 ± 0.17 (19)	0.70
Tethering location, n/N (%)				**0.05**
None	5/149 (3.4)	1/38 (2.6)	0/17 (0.0)	
P1	18/149 (12.1)	2/38 (5.3)	2/17 (11.8)	
P1-P2	43/149 (28.9)	10/38 (26.3)	3/17 (17.6)	
P2	61/149 (40.9)	16/38 (42.1)	8/17 (47.1)	
P2-P3	18/149 (12.1)	8/38 (21.1)	1/17 (5.9)	
P3	4/149 (2.7)	0/38 (0.0)	3/17 (17.6)	
All	0/149 (0.0)	1/38 (2.6)	0/17 (0.0)	
Posterior papillary muscle to annulus distance (cm; 4CH view)	4.17 ± 0.61 (95)	4.25 ± 0.58 (27)	4.61 ± 0.50 (10)	0.08
Posterior papillary muscle to annulus distance (cm; 2CH view)	4.07 ± 0.55 (83)	3.88 ± 0.49 (24)	3.91 ± 0.66 (12)	0.24
Anterior papillary muscle to annulus distance (cm)	3.84 ± 0.69 (77)	3.62 ± 0.50 (17)	4.02 ± 0.72 (7)	0.34
Basal mitral anterior leaflet angle (°)	31 ± 6 (81)	33 ± 6 (22)	28 ± 8 (9)	0.13
Distal mitral anterior leaflet angle (°)	18 ± 6 (164)	20 ± 6 (47)	20 ± 7 (17)	0.11
Mitral posterior leaflet angle (°)	37 ± 9 (161)	41 ± 8 (45)	41 ± 11 (14)	**0.04**
Mitral valve regurgitation quantification				
Mitral regurgitation, n/N (%)				**0.0001**
(3+) Moderate to severe	116/199 (58.3)	19/54 (35.2)	4/21 (19.0)	
(4+) Severe	83/199 (41.7)	35/54 (64.8)	17/21 (81.0)	

	MR grade at 30 days			
	Grade 0 or 1+	**Grade 2+**	**Grade 3+ or 4+**	**P-value**
Effective regurgitant orifice area (cm^2)	0.40 ± 0.16 (189)	0.43 ± 0.13 (53)	0.45 ± 0.15 (21)	0.35
Regurgitant volume (mL/beat)	28.2 ± 14.7 (78)	28.2 ± 23.2 (26)	33.6 ± 19.3 (14)	0.56
Regurgitant fraction (%)	37.2 ± 12.9 (77)	38.5 ± 15.1 (26)	40.9 ± 16.9 (14)	0.65
Left ventricular measures				
LV end-systolic diameter (cm)	5.3 ± 0.9 (199)	5.3 ± 0.8 (53)	5.2 ± 0.7 (21)	0.89
LV end-diastolic diameter (cm)	6.2 ± 0.7 (199)	6.2 ± 0.8 (53)	6.3 ± 0.6 (21)	0.84
LV end-systolic volume (mL)	133.2 ± 57.5 (188)	139.5 ± 57.1 (50)	148.8 ± 53.7 (19)	0.46
LV end-diastolic volume (mL)	191.0 ± 69.4 (188)	199.1 ± 70.6 (50)	224.4 ± 67.7 (19)	0.12
Total stroke volume (mL)	57.7 ± 20.5 (188)	59.5 ± 24.2 (50)	75.6 ± 27.0 (19)	**0.003**
LV end-systolic volume index (mL/m^2)	69.1 ± 27.6 (188)	76.0 ± 32.0 (48)	78.1 ± 28.3 (19)	0.18
LV end-diastolic volume index (mL/m^2)	99.1 ± 32.5 (188)	107.8 ± 38.7 (48)	117.0 ± 32.1 (19)	**0.04**
LV ejection fraction (%)	31.4 ± 8.9 (188)	31.1 ± 9.6 (50)	34.4 ± 9.2 (19)	0.35
Right ventricular measures				
RV fractional area change (%)	32.43 ± 8.24 (131)	30.63 ± 8.87 (40)	34.09 ± 8.06 (14)	0.33
RV systolic pressure (mmHg)	42.2 ± 13.4 (162)	47.0 ± 13.2 (49)	47.9 ± 15.5 (18)	**0.04**
Tricuspid regurgitation, n/N (%)				0.79
(0) None	4/197 (2.0)	3/54 (5.6)	1/20 (5.0)	
(1+) Mild	168/197 (85.3)	45/54 (83.3)	16/20 (80.0)	
(2+) Moderate	23/197 (11.7)	6/54 (11.1)	3/20 (15.0)	
(3+) Moderate to Severe	2/197 (1.0)	0/54 (0.0)	0/20 (0.0)	
(4+) Severe	0/197 (0)	0/54 (0.0)	0/20 (0.0)	

Data presented as mean ± SD (n) or n/N (%). CH = chamber; LV = left ventricular; RV = right ventricular; MV = mitral valve; PM = papillary muscl

Impact of mitral valve geometry on all-cause death or HFH at 24 months

In the entire patient population, larger baseline anteroposterior and intercommissural mitral annular diameters were the only mitral valve anatomic parameters that were significantly associated with the composite risk of death or HFH at 24 months (Table 4). Severe MR, moderate or greater TR and increasing mitral EROA and RVSP were

also significantly associated with the primary endpoint. By multivariable analysis, the baseline anteroposterior mitral annulus diameter was the only echocardiographic variable independently associated with the primary endpoint. Of note, baseline mitral EROA was not an independent predictor of the 2-year composite clinical outcome. A history of atrial fibrillation or flutter, New York Heart Association (NYHA) class and baseline BNP plasma levels were also independently associated with occurrence of the primary composite endpoint within 2 years.

Table 4. Univariable and multivariable predictors of the composite outcome of all-cause mortality or heart failure hospitalization at 2-year follow-up.

	Univariable analysis		Multivariable analysis	
Variable	**HR (95% CI)**	**p-Value**	**HR (95% CI)**	**p-Value**
Echocardiographic parameters at baseline				
Anterior-posterior mitral annulus diameter (per cm)	**1.55 (1.16 - 2.08)**	**0.003**	**1.49 (1.02 - 2.19)**	**0.04**
Intercommisural mitral annulus diameter (per cm)	**1.38 (1.07 - 1.80)**	**0.01**		
Anterior mitral valve leaflet length (per cm)	1.30 (0.95 - 1.78)	0.10		
Posterior mitral valve leaflet length (per cm)	1.09 (0.65 - 1.83)	0.75		
Coaptation to septum distance (per cm)	1.00 (0.77 - 1.28)	0.97		
Tenting height (per cm)	1.25 (0.79 - 1.98)	0.35		
Tenting area (per cm^2)	1.17 (1.00 - 1.38)	0.054	1.06 (0.85 - 1.33)	0.59
Anterior papillary muscle to MV annulus distance (per cm)	1.17 (0.87 - 1.58)	0.30		
Posterior papillary muscle to MV annulus distance (per cm)	1.22 (0.91 - 1.64)	0.18		
Basal mitral anterior leaflet angle (per degree)	1.01 (0.99 - 1.03)	0.42		
Distal mitral anterior leaflet angle (per degree)	1.01 (0.99 - 1.03)	0.34		
Posterior mitral leaflet angle (per degree)	1.00 (0.99 - 1.01)	0.76		
Tethering location	1.01 (0.91 - 1.12)	0.87		
Inferior basal/inferolateral LV aneurysm	1.10 (0.83 - 1.45)	0.50		
Posterior PM to annulus distance, 4CH (per cm)	0.98 (0.75 - 1.27)	0.86		
Left ventricular ejection fraction (per 10% increment)	0.90 (0.80 - 1.02)	0.09	0.91 (0.79 - 1.05)	0.21
Mitral regurgitation grade 4+ (vs. 3+)	**1.32 (1.07 - 1.64)**	**0.01**	0.93 (0.69 - 1.27)	0.13
Left ventricular end-diastolic dimension (per cm)	1.10 (0.95 - 1.27)	0.22		

	Univariable analysis		Multivariable analysis	
Variable	**HR (95% CI)**	**p-Value**	**HR (95% CI)**	**p-Value**
Right ventricular systolic pressure (per 10 mmHg)	1.20 (1.11 - 1.30)	<0.0001		
Tricuspid regurgitation severity ≥2+ (vs <2+)	**1.49 (1.13 - 1.95)**	**0.005**	1.29 (0.92 - 1.82)	0.15
Left ventricular end-diastolic volume (per 100 mL)	1.08 (0.92 - 1.26)	0.36		
Effective regurgitant orifice area, by PISA (per 1 cm^2)	**2.48 (1.29 - 4.79)**	**0.007**	1.72 (0.68 - 4.37)	0.25
Clinical variables at baseline				
Age (per 10 years)	**1.11 (1.01 - 1.23)**	**0.036**	0.99 (0.85 - 1.16)	0.94
MitraClip plus GDMT versus GDMT alone	**0.55 (0.44 - 0.69)**	**<0.0001**	**0.52 (0.40 - 0.67)**	**<0.0001**
Sex, male	1.21 (0.97 - 1.53)	0.10	1.17 (0.87 - 1.58)	0.29
Diabetes	1.24 (1.00 - 1.54)	0.053	1.26 (0.97 - 1.64)	0.08
Hypertension	1.17 (0.89 - 1.54)	0.26		
Hypercholesterolemia	1.09 (0.88 - 1.35)	0.44		
Previous myocardial infarction	1.13 (0.91 - 1.40)	0.27		
Previous percutaneous coronary intervention	1.11 (0.90 - 1.38)	0.33		
Previous stroke or transient ischemic attack	0.82 (0.61 - 1.11)	0.20		
Peripheral vascular disease	**1.33 (1.02 - 1.73)**	**0.04**	1.02 (0.73 - 1.42)	0.90
Chronic obstructive lung disease	1.22 (0.96 - 1.57)	0.11	1.08 (0.79 - 1.47)	0.65
History of atrial fibrillation or flutter	**1.33 (1.07 - 1.66)**	**0.01**	**1.44 (1.10 - 1.90)**	**0.009**
Body mass index (per 10 kg/m^2)	1.01 (0.83 - 1.22)	0.94		
Creatinine clearance (per 10 mL/min)	**0.93 (0.88 - 0.97)**	**0.001**	0.95 (0.89 - 1.01)	0.11
Anemia	1.26 (0.99 - 1.61)	0.06	1.22 (0.92 - 1.63)	0.17
Ischemic cardiomyopathy (vs. non-ischemic)	1.12 (0.89 - 1.39)	0.33		
New York Heart Association class IV (vs. II or III)	**2.25 (1.61 - 3.14)**	**<0.0001**	**1.90 (1.23 - 2.92)**	**0.004**
Heart failure hospitalization within the prior year	0.95 (0.76 - 1.18)	0.64		
Kansas City Cardiomyopathy Questionnaire score (per point)	**0.92 (0.88 - 0.97)**	**0.001**	0.97 (0.91 - 1.03)	0.35
Six-minute walk distance (per 50 meters)	**0.90 (0.86 - 0.94)**	**<0.0001**	0.95 (0.89 - 1.02)	0.13
B-type natriuretic peptide level (per 100 pg/mL)	**1.03 (1.02 - 1.03)**	**<0.0001**	**1.02 (1.01-1.03)**	**0.0005**

Death or HFH at 24 months occurred in 44.8% of patients randomized to MitraClip plus GDMT and in 66.1% of the patients randomized to GDMT alone (P<0.0001). MitraClip treatment was an independent predictor of a 48% reduction in the primary composite endpoint (P<0.0001; Table 4). By formal interaction testing, increasing anteroposterior mitral annular diameter was associated with a similar risk of the composite primary endpoint for both treatment arms (Central Illustration, Panel A). Similarly, no significant interactions between atrial fibrillation, NYHA class or BNP plasma levels and treatment arm were present for the primary composite outcome.

Impact of mitral valve geometry on all-cause death and heart failure hospitalization as separate outcomes

A larger mitral EROA was the only echocardiographic variable independently associated with an increased risk of all-cause mortality within 2 years (Supplemental Appendix Table 2). Other independent correlates of increasing mortality were creatinine clearance, 6-minute walk distance, BNP levels and EROA. MitraClip treatment was an independent predictor of a 38% reduction in 2-year mortality (P=0.003).There were no significant interactions noted between these variables and treatment arm on 24-month all-cause mortality (Central Illustration, Panel B).

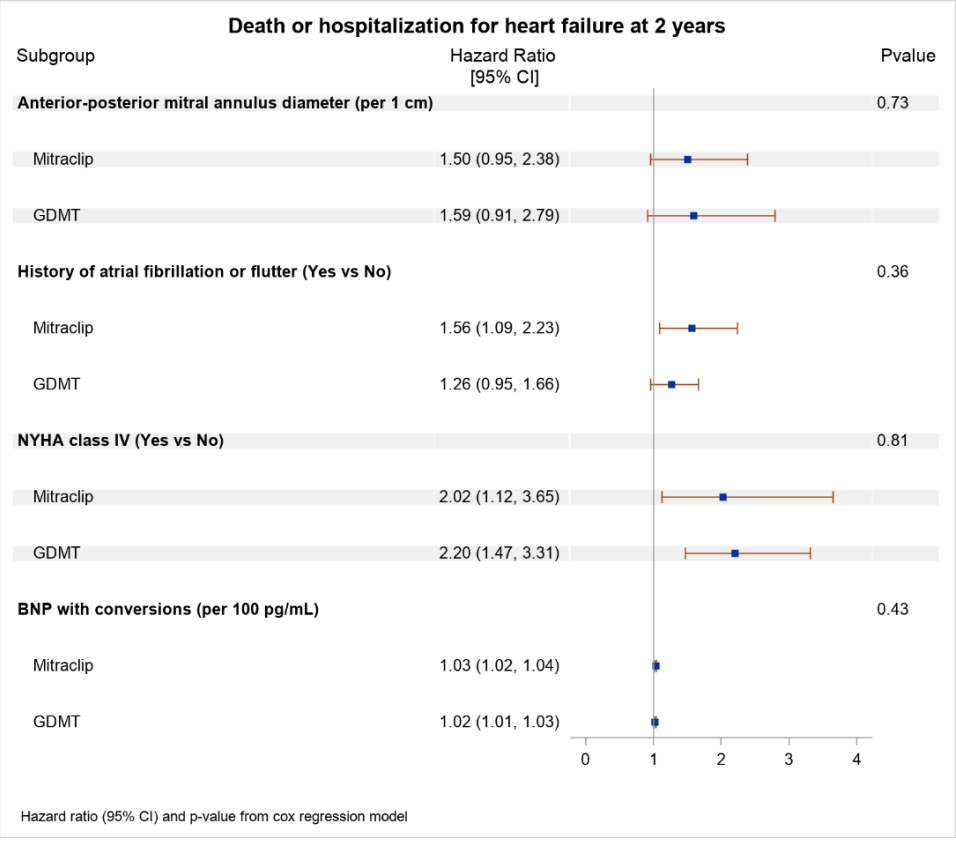
Among the echocardiographic and mitral valve geometric variables, only the anteroposterior mitral annular diameter was independently associated with 2-year HFH (Supplemental Appendix Table 3). Other independent correlates of increasing mortality were history of atrial fibrillation or flutter, NYHA class, and BNP levels. MitraClip treatment was an independent predictor of a 57% reduction in 2-year HFH (P<0.001). There were no significant interactions noted between these variables and treatment arm on 24-month HFH (Central Illustration, Panel C).

Discussion

In the present sub-study from the COAPT trial, among HF patients with severe secondary MR, an increasing anteroposterior mitral annular diameter was associated with the 2-year composite endpoint of all-cause mortality or heart failure hospitalization, an association that was driven by an increasing risk of HFH more so than mortality. In contrast, baseline EROA was independently associated with the 2-year rate of all-cause mortality but not HFH. Treatment with MitraClip compared with GDMT alone reduced the relative 2-year risks of all-cause death, HFH and the composite of death or HFH consistently in all subgroups, including larger vs. smaller anteroposterior mitral annular

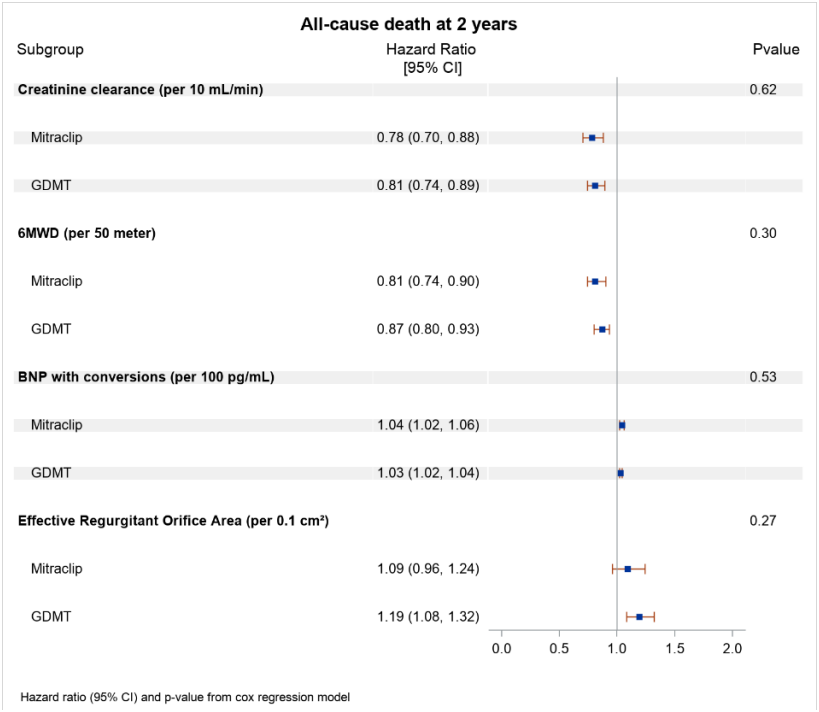
diameter and EROA. These findings demonstrate the complementary deleterious effects of a greater EROA (reflecting the severity of secondary MR) and an enlarged anteroposterior mitral annular diameter (reflecting long-standing volume overload). By reducing MR and having long-term favorable effects on LV remodeling (13,16), treatment of severe secondary MR with the MitraClip plus GDMT thus improves freedom from both death and HFH during long-term follow-up in selected patients with HF.

Central Illustration. Interactions between treatment arm and baseline mitral valve geometry and regurgitation severity for the 2-year composite endpoint of all-cause death or heart failure hospitalization (A), all-cause death alone (B) and heart failure hospitalization alone (C).

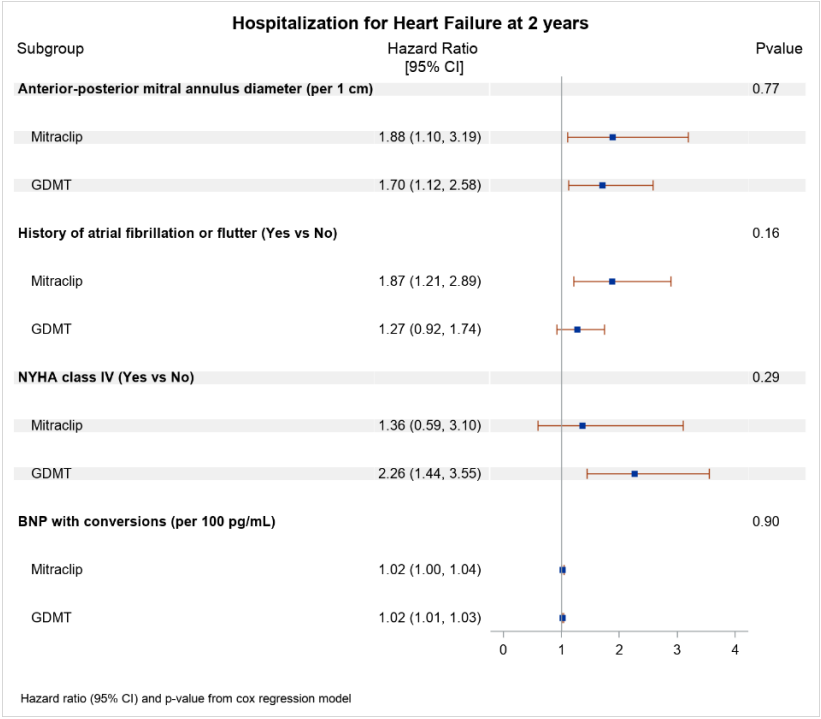


Panel A

Panel B



Panel C



Mitral valve geometry, MR severity and clinical outcomes

LV remodeling in patients with ischemic and non-ischemic cardiomyopathy causes tethering of the mitral valve leaflets and reduced mitral valve closing forces (23). Specifically, global and regional LV remodeling results in increased LV sphericity, papillary muscle displacement, mitral annular dilation and planar flattening. Mitral valve closing forces are reduced due to impaired LV contractility, LV dyssynchrony and reduced mitral annular contraction. The deleterious effects of mitral leaflet tethering and impaired mitral valve closing force leads to lack of leaflet coaptation. The deformation of the mitral valve apparatus may vary greatly depending on the extent of LV remodeling and dysfunction (24). How the various alterations of the mitral valve geometry influence the outcomes of HF patients treated with MitraClip compared with GDMT alone has not been extensively investigated. Mantegazza et al showed that a severely enlarged anteroposterior mitral annular diameter (≥4.44 cm) was associated with significant residual MR after MitraClip implantation, but the authors did not report its effect on outcomes (25). The present substudy from the COAPT trial provides novel evidence by demonstrating an independent association between increasing anteroposterior mitral annular dilation and the composite 2-year outcome of all-cause mortality and HFH, and with the endpoint of HFH alone. Moreover, these associations were similar in both treatment arms suggesting that MitraClip plus GDMT will improve the relative prognosis across the range of anteroposterior mitral annular diameters enrolled within the COAPT trial, with the absolute benefits being greater with larger anteroposterior diameters.

Quantitative measures of MR severity (such as the EROA) have been associated with impaired outcomes. In secondary MR, an EROA >0.2 cm^2 has been associated with poor survival (19). However, randomized controlled trials have shown that surgical or TMVr techniques in patients with secondary MR have a prognostic benefit when the EROA (as a measure of MR severity) is at least 0.3 cm^2 (13,14,26).

In the COAPT trial, in which the vast majority of patients had a baseline EROA ^{3}0.3 cm^2,(15) an increasing EROA was independently associated with increased risk of all-cause mortality alone but not with HFH. MitraClip reduced mortality to a similar relative degree regardless of baseline EROA; as such, the absolute reduction of mortality was greater in patients with greater severity baseline MR treated with the MitraClip.

Grayburn, Packer and colleagues have ventured that the MitraClip is especially likely to improve event-free survival in patients with secondary MR with an EROA that is disproportionate to the extent of LV remodeling (8). Many patients with proportionate

MR are also likely to benefit from MR reduction. In contrast, patients with very advanced LV remodeling and marked dilatation may not respond to MR reduction with the MitraClip, even if the baseline EROA is abnormal. In COAPT, enrollment was strictly controlled to require 3+ or 4+ secondary MR (confirmed by a echocardiographic core laboratory prior to randomization), and LV dimensions were restricted by requiring a LV end-systolic diameter of <7 cm. This requirement likely limited the degree of mitral annular dilatation present in the patients enrolled. Whether the MitraClip would be effective if used in patients with greater LV remodeling and anteroposterior mitral annular diameters than studied with COAPT cannot be addressed by this study. Moreover, whether therapies such as mitral valve annuloplasty may be of greater benefit than the MitraClip or further improve outcomes if used in combination with the MitraClip when the mitral annulus is dilated deserves further study. Similarly, identifying when LV dilatation and mitral annular diameters are too abnormal to benefit from the MitraClip (or other therapies aimed at reducing secondary MR) is essential for optimal patient triage to transcatheter mitral valve repair or replacement versus an LV assist device or heart transplantation.

Predictors of mitral regurgitation reduction after MitraClip

Procedural success rates with the MitraClip have steadily improved with increasing operator experience and advanced imaging guidance. In the present trial 92.3% of MitraClip-treated patients achieved a reduction in baseline MR grade of 3+ or 4+ to <2+ at 30 days. Residual secondary MR ^{3}3+ has not surprisingly been shown in COAPT and other studies to be strongly associated with subsequent adverse events (27-30). In a study of 300 patients with secondary MR undergoing MitraClip treatment, the EROA, mitral valve orifice area (MVOA), and transmitral pressure gradient were associated with inadequate MR reduction (28). The early EVEREST II trial also excluded patients with LV end-systolic dimension >55 mm, MVOA <4.0 cm^{2}, and those with secondary MR and advanced tethering with either coaptation depth >11 mm or vertical coaptation length <2 mm (31). In contrast, COAPT excluded patients with degenerative mitral valve disease, LV end-systolic dimension >70 mm, MVOA <4.0 cm^{2} and those who in the opinion of the site operator had leaflet anatomy that may preclude MitraClip implantation, proper positioning or sufficient reduction in MR; specific anatomic exclusion criteria were not otherwise provided (11). Among patients meeting the enrollment criteria, we identified MR severity 4+ rather than 3+ (but not EROA), tethering location (especially P3), greater mitral posterior leaflet angle, stroke volume, LV end-diastolic volume index and RVSP as predictors of greater residual MR after MitraClip implantation. Further analyses are underway to characterize the mechanisms and implications of these observations.

Limitations

As a post hoc analysis the present results should be considered exploratory and hypothesis generating. The potential impact of unmeasured confounders cannot be excluded; thus, demonstrating associations in multivariable analysis does not prove causality. The operators participating in COAPT in general were very experienced; similar results may not be achieved by operators who have not yet traversed the learning curve (32). Not all echocardiographic parameters of interest were assessed in the present study, and additional insights might have been gained by 3D echocardiographic assessment (33). Finally, by protocol patients with marked LV dysfunction were excluded, some pathologies (e.g. P3 tethering) were infrequently present, and of course the results apply solely to treatment of functional MR. Further studies are thus warranted to examine the prognostic implications of mitral valve anatomies not included in the present study.

Conclusions

In the present echocardiographic core laboratory study from the multicenter COAPT trial, among HF patients with 3+ or 4+ secondary MR, a large anteroposterior mitral annular diameter was associated with increased risk of the composite outcome of all-cause death or HFH and HFH alone. Greater EROA was an independent predictor of mortality. Treatment with the MitraClip plus GDMT compared with GDMT lone reduced death and HFH consistently in patients with and without these extremes.

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Chapter six

Right ventricular - pulmonary artery coupling: prognostic value in patients with secondary mitral regurgitation

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Submitted

Abstract

Background

Right ventricular (RV) dysfunction and pulmonary artery systolic pressure (PASP) are predictors of outcome in patients with secondary mitral regurgitation (MR). The right heart and the pulmonary circulation are however, interdependent and the relationship between RV contractility and afterload known as RV-PA coupling, can be estimated non-invasively. Accordingly, the purpose of this study is to investigate the incremental prognostic value of the ratio of tricuspid annular plane systolic excursion (TAPSE) and PASP (TAPSE/PASP) in patients with significant secondary MR.

Methods

A total of 591 patients (mean age 66±11 years, 67% male) with symptomatic secondary MR were included. The ratio TAPSE/PASP was measured and its association with the primary endpoint (all-cause mortality) was assessed.

Results

Based on spline curve analysis, a TAPSE/PASP ratio <0.35 was associated with an excess mortality. The patient population was divided into two groups: 229 (39%) patients with TAPSE/PASP<0.35 (impaired RV-PA coupling) and 362 (61%) with TAPSE/PASP≥0.35 (preserved RV-PA coupling). During a median follow-up of 54 [28, 105] months, 295 (50%) patients died. Patients with a TAPSE/PASP≥0.35 showed significantly better survival rates at 5-year follow-up than those with a TAPSE/PASP<0.35 (68% vs 53%, respectively, P= 0.001). On multivariable analysis, a TAPSE/PASP<0.35 remained independently associated with all-cause mortality (HR 1.283, 95% CI 1.008-1.633, P= 0.043).

Conclusions

In heart failure patients with secondary MR, TAPSE/PASP is independently associated with all-cause mortality and has an incremental prognostic value over TAPSE. By taking into account TAPSE/PASP ratio (as a measure for RV-PA coupling), it may improve further risk stratification of patients with secondary MR.

Introduction

Patients with heart failure (HF) and reduced left ventricular (LV) ejection fraction (EF) may develop secondary mitral regurgitation (MR) which leads to chronic volume overload, further LV and left atrial (LA) remodelling, LV dysfunction, distortion of the mitral valve apparatus and eventually increasing MR volume which constitutes a self-perpetuating cycle (1, 2). The chronic volume overload, LV dysfunction and increasing LV filling pressures lead to pulmonary hypertension (PH) and right ventricular (RV) dysfunction with an increased risk of morbidity and mortality (1). The emergence of transcatheter therapies has influenced the management of patients with severe secondary MR. However, two major trials evaluating transcatheter edge-to-edge mitral valve repair in HF patients with secondary MR demonstrated different results in survival and symptomatic improvement (3, 4). These conflicting results demonstrate that patient selection of those who might benefit from transcatheter treatment of MR remains challenging. RV dysfunction, assessed by tricuspid annular plane systolic excursion (TAPSE), has been demonstrated to provide strong prognostic value in patients with HF (5) and to be a major predictor of outcome in patients with moderate to severe secondary MR (6). PH also appears to be associated with increased risk of mortality in patients with secondary MR undergoing transcatheter edge-to-edge repair (7). RV dysfunction and pulmonary pressures are commonly evaluated as separate components. However, RV function is highly dependent on its afterload (8) and evaluation of RV systolic function should be corrected for pulmonary pressures. The ratio between TAPSE and pulmonary arterial systolic pressure (PASP) has been proposed to predict patient prognosis in several diseases (9, 10). This ratio, a measure of RV to pulmonary artery (RV-PA) coupling, assesses RV systolic function adjusted for the degree of afterload (11, 12) and has prognostic value in patients with HF (9) and those undergoing transcatheter aortic valve replacement (10). However, the potential utility of TAPSE/PASP has not yet been evaluated in HF patients with secondary MR. Accordingly, our objective herein was to investigate the prognostic value of RV-PA coupling as assessed by the TAPSE/PASP ratio in patients with secondary MR.

Methods

Patient population

Through the departmental echocardiographic database (Imagevault EchoPAC, General Electric Vingmed Ultrasound, Norway) of Leiden University Medical Center, Leiden, The Netherlands, patients with HF and significant (moderate or severe) secondary MR

were identified from April 1999 to July 2017 and included in this retrospective analysis. Patients with previous mitral valve intervention and missing echocardiographic data were excluded. Clinical and demographic characteristics at baseline were collected through the departmental clinical database (EPD-Vision 11.8.4.0; Leiden University Medical Center, Leiden, The Netherlands) and included cardiovascular comorbidities, New York Heart Association (NYHA) functional class, HF etiology and medication use. The institutional review board waved the need for written patient informed consent for this retrospective study with clinically acquired data.

Echocardiography

Using commercially available systems (General Electric Vingmed Ultrasound, Milwaukee, USA) equipped with 3.5 MHz or M5S transducers, transthoracic echocardiography data were acquired in hemodynamically stable patients in the left lateral decubitus position. Parasternal, apical, and subcostal views were acquired and two-dimensional images, M-mode and Doppler data were digitally stored for offline analysis (EchoPAC 201.0.0, General Electric Vingmed Ultrasound, Norway). LV volumes (end-systolic and end-diastolic) were measured in the apical 2- and 4-chamber views and LVEF was calculated according to Simpson's biplane method (13). LA volume was calculated at end-systole from the apical 4- and 2-chamber views (13). LV and LA volumes were indexed for body surface area. LV global longitudinal strain (GLS) was measured from standard 2-dimensional transthoracic echocardiography using the apical 4-chamber, 2-chamber, and long-axis views of the LV (14). LV GLS was determined offline using commercially available software (EchoPAC 201.0.0, General Electric Vingmed Ultrasound, Norway). According to current recommendations, an integrative approach (including qualitative, semiquantitative, and quantitative data) was used to grade MR severity given the following definitions: moderate (grade 2), moderate to severe (grade 3), and severe (grade 4) (15, 16). The vena contracta width was measured on the parasternal long-axis view at the narrowest part of the MR jet (17). The effective regurgitant orifice area (EROA) and regurgitant volume (RVol) were measured according to the proximal isovelocity surface area (PISA) method. An EROA of ≥20mm^2 and/or a RVol of ≥30 mL/beat defined prognostically severe MR (15, 18, 19). As a measure of LV filling pressures, the ratio between peak early diastolic transmitral flow velocity and peak early diastolic mitral annular tissue velocity ratio (E/e') was calculated (20). TAPSE was measured on the apical 4-chamber view using the M-mode to evaluate RV systolic function (21). The PASP was estimated using the peak velocity of the tricuspid regurgitant jet and the Bernoulli equation and, depending on the diameter and collapsibility of the inferior vena cava, 3, 8 or 15 mmHg were added (21). In patients with atrial fibrillation the average of 3 cardiac beats were calculated. As previously suggested (12), the TAPSE/PASP ratio

was calculated as a measure of RV-PA coupling.

Follow-up

The primary endpoint was all-cause mortality. Survival data were obtained from the departmental cardiology information system (EPD-Vision 11.8.4.0; Leiden University Medical Center, Leiden, The Netherlands) which is linked to the governmental death registry database. Data at follow-up was complete for all patients.

Statistical analysis

Continuous data are presented as mean ± standard deviation when normally distributed or as median [Q1, Q3] when not normally distributed. Categorical data are presented as absolute numbers and percentages. Independent samples t-tests or Mann-Whitney U tests were used to compare continuous data, as appropriate. Categorical data were compared with the chi-square test. The changes in hazard ratio (HR) for all-cause mortality over a range of TAPSE/PASP (as a continuous variable) were investigated by a fitted spline curve. Kaplan-Meier analysis was performed to estimate cumulative survival rates for all-cause mortality and comparisons between groups were performed with the log-rank test. First the Kaplan-Meier analysis was performed with patients censored at the time of mitral valve interventions (i.e. Surgical mitral valve repair, surgical mitral valve replacement or transcatheter edge-to-edge mitral valve repair). Second the analyses was performed including the outcome after mitral valve interventions. Cox proportional hazards regression analysis was performed to identify the independent predictors of all-cause mortality. P-values <0.05 in univariable analysis were included in the multivariable model. HRs and 95% confidence intervals were calculated and reported. A likelihood ratio test was performed to investigate the incremental value of TAPSE/PASP over clinical and echocardiographic characteristics for the prediction of all-cause mortality. Changes in global chi-square values were calculated. All statistical analyses were performed using SPSS for Windows, version 23.0 (IBM, Armonk, NY, USA) and R version 3.4.4 (R Foundation for Statistical Computing, Vienna, Austria). A two-tailed p-value <0.05 was considered statistically significant for all analyses.

Results

Patient population

A total of 591 patients (mean age 66±11 years, 67% male) were included. Ischemic heart failure was present in 51% of the patient population. The majority of patients had NYHA II and III heart failure symptoms. The mean LVEF was 29±11% whereas the median

LV GLS was -7.3% [-9.9, -5.2]. The mean TAPSE was 16±5 mm and the mean PASP was 30±13 mmHg for the total population. During a median follow-up of 35 [17, 63] months, mitral valve intervention was performed in 258 (43.7%) patients, including 168 (28.4%) surgical mitral valve repairs, 2 (0.3%) surgical mitral valve replacements, and 88 (14.9%) transcatheter mitral valve repairs. Baseline clinical and echocardiographic characteristics are summarized in Tables 1 and 2.

Table 1. Baseline clinical characteristics according to TAPSE/PASP ratio.

	Total population (n= 591)	**TAPSE/PASP ratio < 0.35 (n= 229)**	**TAPSE/PASP ratio ≥ 0.35 (n= 362)**	**p-value**
Age (years)	66 ± 11	68 ± 10	65 ± 11	0.008
Male, n (%)	395 (67)	165 (72)	230 (64)	0.032
BSA (m^2)	1.92 ± 0.21	1.92 ± 0.21	1.93 ± 0.21	0.773
Prior CABG	101 (17)	53 (23)	48 (13)	0.002
Atrial fibrillation, n (%)	248 (42)	120 (52)	128 (35)	<0.001
Hypertension, n (%)	240 (41)	98 (43)	142 (39)	0.390
Diabetes mellitus, n (%)	138 (23)	57 (25)	81 (22)	0.481
COPD, n (%)	68 (12)	29 (13)	39 (11)	0.483
eGFR (mL/min/1.73m^2)	62 ± 24	58 ± 23	65 ± 24	0.001
Ischemic heart failure, n (%)	304 (51)	131 (57)	173 (78)	0.026
NYHA class, n (%)				0.121†
I	31 (5)	12 (5)	19 (5)	
II	145 (25)	51 (22)	94 (26)	
III	343 (58)	192 (56)	214 (59)	
IV	72 (12)	37 (16)	35 (10)	
Medication, n (%)				
Beta-blockers	419 (71)	163 (71)	256 (71)	0.904
Diuretics	496 (84)	210 (92)	286 (79)	<0.001
ACEi/ARB	480 (81)	177 (77)	303 (84)	0.052
Device therapy, n (%)				
ICD	94 (16)	53 (15)	41 (18)	0.291
CRT*	401 (68)	148 (65)	253 (70)	0.182

Continuous data are presented as mean ± SD or median [Q1, Q3]. Categorical data are presented as numbers and percentages. *CRT at baseline and follow-up. † overall P-value. ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BSA = body surface area; COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration rate; NYHA = New York Heart Association.

Table 2. Baseline echocardiographic characteristics according to TAPSE/PASP ratio.

	Total population (n= 591)	TAPSE/PASP ratio < 0.35 (n= 229)	TAPSE/PASP ratio ≥ 0.35 (n= 362)	p-value
LVEDVi (mL/m²)	105 ± 40	103 ± 37	107 ± 42	0.260
LVESVi (mL/m²)	77 ± 36	76 ± 34	78 ± 38	0.606
LVEF (%)	29 ± 11	28 ± 12	29 ± 10	0.160
LV GLS (%)	-7.3 [-9.9, -5.2]	-6.5 [-9.2, -4.7]	-7.6 [-10.2, -5.8]	<0.001
LAVI (mL/m²)	37 ± 18	42 ± 21	35 ± 16	<0.001
VC width (mm)*	6 ± 2	6 ± 2	6 ± 3	0.927
EROA (mm²)†	22 ± 11	22 ± 11	21 ± 11	0.599
RVol (mL)‡	31 ± 15	30 ± 14	31 ± 16	0.305
TAPSE (mm)	16 ± 5	13 ± 3	18 ± 4	<0.001
PASP (mmHg)	30 ± 13	49 ± 13	34 ± 10	<0.001
E/e'	25 ± 23	26 ± 19	24 ± 25	0.382

Continuous data are presented as mean ± SD or median [Q1, Q3]. Categorical data are presented as numbers and percentages. *VC width available in 511 patients; †EROA available in 415 patients; ‡RVol available in 414 patients.

E = peak early diastolic transmitral flow velocity; e' = peak early diastolic mitral annular tissue velocity; EROA = effective regurgitant orifice area; LAVI = left atrial volume index; LVEF = left ventricular ejection fraction; LVEDVi = left ventricular end-diastolic volume index; LVESVi = left ventricular end-systolic volume index; LV GLS = left ventricular global longitudinal strain; PASP = pulmonary artery systolic pressure; RVol = regurgitant volume; TAPSE = tricuspid annular plane systolic excursion; VC = vena contracta.

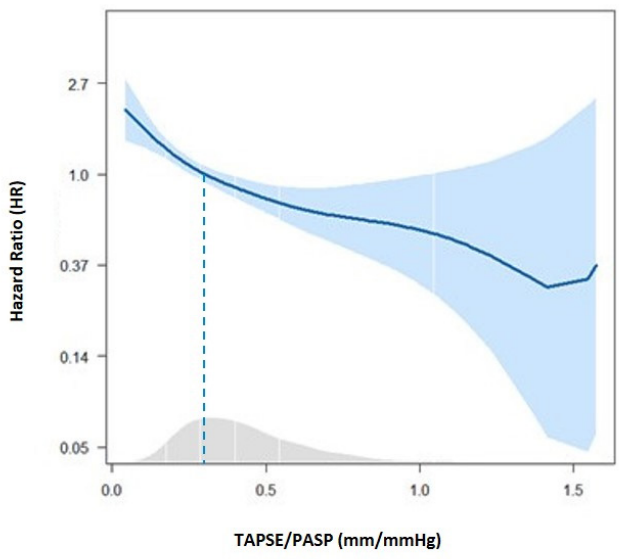

Figure 1. Spline curve for all-cause mortality according to TAPSE/PASP ratio.

All-cause mortality across the range of TAPSE/PASP ratio, plotted as a cubic spline on a log-hazard scale with overlaid 95% confidence intervals. The histogram representing the distribution of TAPSE/PASP ratio in the population is plotted on the X-axis. The shaded light blue region

represents the 95% confidence interval range for each hazard ratio. The vertical dotted line representing the cut-off value TAPSE/PASP 0.35. PASP = pulmonary artery systolic pressure; TAPSE = tricuspid annular plane systolic excursion.

Survival analysis

During a median follow-up of 54 [28, 105] months, 295 patients (49.9%) died. Based on spline curve analysis, a threshold of TAPSE/PASP ratio <0.35 was associated with an excess risk of all-cause death (Figure 1). The assumption of linearity was not violated (χ^2: 4.236, P= 0.13). This cut-off value was used to identify the patients with more RV-PA uncoupling.

Tables 1 and 2 show the baseline clinical and echocardiographic characteristics for patients with more impaired RV-PA uncoupling (n=229 [38.7%] TAPSE/PASP ratio <0.35) vs. those with more preserved RV-PA coupling (n=362 [61.3%] TAPSE/PASP ≥0.35). Patients with a TAPSE/PASP <0.35 were slightly older, were more frequently male, had a higher prevalence of atrial fibrillation and more impaired renal function compared to patients with a TAPSE/PASP ≥0.35. Patients with a TAPSE/PASP <0.35 were more symptomatic and were more frequently using diuretics compared to those with a TAPSE/PASP ≥0.35.

In terms of echocardiographic characteristics, patients with a TAPSE/PASP ≥0.35 had less impaired LV systolic function assessed by LV GLS. However, there were no significant differences in LV volumes and LVEF, E/e' ratio or MR severity. Patients with a TAPSE/PASP <0.35 had a larger left atrial volume index compared to those with a TAPSE/PASP ≥0.35.

Survival analysis censored for occurrence of mitral valve intervention showed that patients with a TAPSE/PASP ≥0.35 had better survival rates as compared to patients with a TAPSE/PASP <0.35 (5-year estimated survival rates 81.1% vs. 66.7% respectively, P=0.002; Figure 2, panel A). Patients with a TAPSE/PASP ≥0.35 also had better survival rates than those with a TAPSE/PASP<0.35 when all patient follow-up data was analyzed, including after the performance of mitral valve intervention (5-year estimated survival rates 68.3% vs. 52.6% respectively, P=0.001; Figure 2, panel B). After correcting for age, male sex, impaired renal function, diabetes mellitus, ischemic aetiology, the use of diuretics, LV GLS and the performance of mitral valve intervention, by Cox proportional hazards modelling a TAPSE/PASP <0.35 was independently associated with all-cause mortality (HR 1.28, 95% CI 1.01-1.63, P=0.04) (Table 3).

Table 3. Univariate and multivariable cox regression analysis to identify associates of all-cause mortality.

	Univariate analysis			Multivariable analysis		
Variable	**HR**	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**
Age	1.030	1.019-1.043	<0.001	1.021	1.008-1.034	0.002
Male	1.582	1.224-2.046	<0.001	1.470	1.117-1.936	0.006
BSA (m^2)	1.172	0.689-1.995	0.558			
eGFR <60 (mL/min/1.73m^2)	2.845	2.242-3.611	<0.001	2.372	1.840-3.058	<0.001
Hypertension	0.936	0.741-1.183	0.581			
Diabetes mellitus	1.362	1.045-1.774	0.022	1.294	0.988-1.697	0.062
Atrial fibrillation	1.209	0.961-1.522	0.106			
Ischaemic aetiology	1.340	1.064-1.688	0.013	1.111	0.870-1.418	0.398
NYHA classification ≥ II	1.098	0.629-1.915	0.743			
Diuretics	2.204	1.493-3.253	<0.001	1.799	1.206-2.682	0.004
MV intervention*	1.148	0.906-1.455	0.253			
LV GLS (%)	1.090	1.051-1.131	<0.001	1.067	1.027-1.109	0.001
E/e'	1.002	0.997-1.007	0.406			
TAPSE/PASP ratio <0.35	1.637	1.300-2.061	<0.001	1.283	1.008-1.633	0.043

BSA = body surface area; CI = confidence interval; E = peak early diastolic transmitral flow velocity; e' = peak early diastolic mitral annular tissue velocity; eGFR = estimated glomerular filtration rate; LV GLS = left ventricular global longitudinal strain; NYHA = New York Heart Association; PASP = pulmonary artery systolic pressure; TAPSE = tricuspid annular plane systolic excursion.

*Surgical mitral valve repair, surgical mitral valve replacement or transcatheter edge-to-edge mitral valve repair, compared to optimal medical therapy alone

Incremental prognostic value of TAPSE/PASP

A likelihood ratio test was performed to determine the incremental prognostic value of TAPSE alone and TAPSE/PASP over clinical and echocardiographic parameters, both as a continuous variable and as a dichotomous variable. No significant increase in the chi-square value was observed after the addition of TAPSE alone (as a continuous variable) to the baseline model ($\chi 2$ difference = 0.29, P= 0.790, Figure 3, Panel A). However, addition of TAPSE/PASP (as a continuous variable) to the baseline model did show a significant increase in the chi-square value ($\chi 2$ difference = 8.48, P= 0.002, Figure 3, Panel A). Similarly, introducing TAPSE alone as a dichotomous variable (<17 mm, according to contemporary guidelines)(13)

did not significantly increase the chi-square value (χ2 difference = 0.02, P= 0.95, Figure 3, Panel B). However, adding TAPSE/PASP <0.35 resulted in a significant increase in the chi-square value (χ2 difference = 5.65, P=0.04, Figure 3, Panel B), demonstrating the incremental prognostic value of TAPSE/PASP.

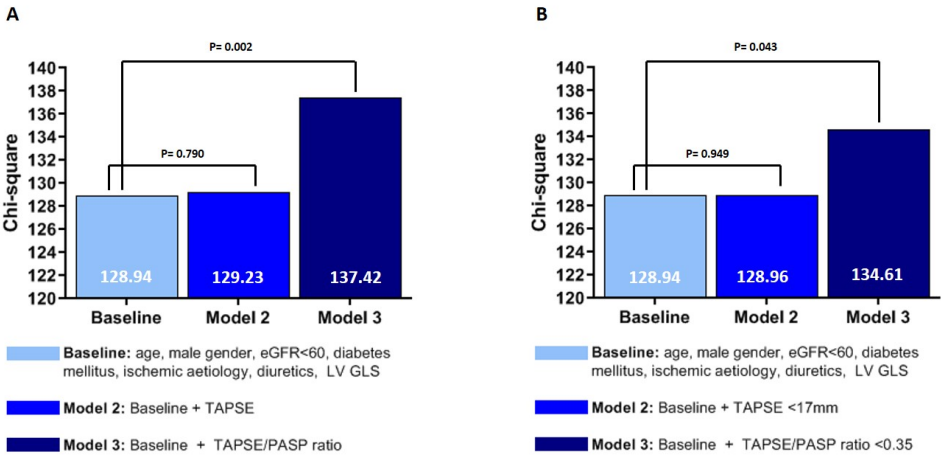

Figure 3. Incremental prognostic value of TAPSE/PASP ratio.

The incremental value of TAPSE/PASP ratio, as a continuous value *(A)* and dichotomized *(B)*, over clinical and echocardiographic parameters for the prediction of all-cause mortality.

eGFR = estimated glomerular filtration rate; LV GLS = left ventricular global longitudinal strain; PASP = pulmonary artery systolic pressure; TAPSE = tricuspid annular plane systolic excursion.

Discussion

In the present study, we evaluated the prognostic value of TAPSE/PASP (an echocardiographic surrogate of RV-PA coupling) in HF patients with significant secondary MR (Figure 4). Our findings demonstrated an independent association of TAPSE/PASP with all-cause mortality and an incremental prognostic value of the TAPSE/PASP ratio compared with use of individual parameters of RV systolic function not corrected for afterload.

Secondary MR and prognosis: role of pulmonary hypertension and right ventricular function

Secondary MR results from an imbalance between closing and tethering forces on the mitral valve due to LV dilation and dysfunction (22, 23). The chronic volume overload caused by secondary MR leads to a self-perpetuating cycle characterized by LV dilation

and dysfunction, distortion of the mitral valve apparatus and increasing MR volume which can lead to pulmonary congestion, increased pulmonary pressures and RV dilation and dysfunction (1, 2). PH is observed in approximately 40% of patients with secondary MR (24) and is associated with adverse outcomes, even after correcting MR with surgical or transcatheter edge-to-edge mitral valve repair (7, 25). In addition, RV dysfunction has been associated with an increased risk of mortality in patients with HF (5) and is a major predictor of outcome specifically in patients with secondary MR (6, 26). However, RV systolic function is highly dependent on pulmonary pressures and different afterload conditions can significantly influence its estimation (2). Integration of PH (assessed by PASP) and RV function (assessed by TAPSE) using the TAPSE/PASP ratio enables an estimation of RV-PA coupling. Until recently, measures for RV-PA coupling were evaluated invasively. A study by Tello *et al*. (12) validated TAPSE/PASP ratio as a surrogate of RV-PA coupling in 52 patients with PH. A TAPSE/PASP <0.31 mm/mmHg defined RV-PA uncoupling and was associated with poor outcome. Guazzi *et al*. (9) investigated the TAPSE/PASP ratio in 293 HF patients with both preserved and reduced LVEF. A TAPSE/PASP ratio <0.36 mm/mmHg was the best cutoff value associated with prognosis (area under the curve 0.78; 95% CI 0.75-0.86; P<0.001). The TAPSE/PASP cutoff values most strongly associated with mortality in these prior studies were similar to that observed in the current large-scale study of patients with secondary MR. In the present population, a TAPSE/PASP <0.35 mm/mmHg was independently associated with long-term mortality. In contrast, TAPSE alone was not an independent predictor of long-term outcomes.

Clinical implications of TAPSE/PASP in secondary MR

The use of transcatheter mitral valve repair in HF patients with secondary MR is increasing. Two major trials that evaluated the prognostic impact of transcatheter edge-to-edge mitral valve repair in HF patients with secondary MR reported varying results in terms of mortality and symptomatic improvement (3, 4). Although patients were selected for these trials according to contemporary guidelines (18, 27), their conflicting results highlight the challenge of identifying patients who may benefit from intervention. In this regard baseline RV dysfunction has been shown to be an important predictor of outcomes after mitral valve intervention (28, 29). Osterech *et al*. (30) demonstrated higher all-cause mortality in patients with compared without baseline RV dysfunction (assessed by TAPSE) in 130 patients with secondary MR undergoing transcatheter mitral valve repair. However, RV dysfunction is significantly affected by afterload and the sole use of TAPSE may provide an imprecise estimation of RV contractility. As demonstrated in the present study, by taking into account loading conditions the TAPSE/PASP ratio (reflecting RV-PA coupling) may further improve

risk stratification of patients with secondary MR. Patients with a lower TAPSE/PASP (indicating RV-PA uncoupling) may be considered to have more advanced disease as the RV is not able to further increase its contractility (TAPSE) to cope with the increased afterload (PASP). In such patients RV function might recover less from the afterload reduction following correction of the MR. In this regard, in our study a TAPSE/PASP <0.35 was independently associated with worse outcomes in patients with secondary MR. However, future prospective studies are warranted to investigate whether the selection of candidates for valvular interventions would be improved by considering this measure of RV-PA uncoupling. Nonetheless, the present study confirms the importance of assessing RV function in HF patients with secondary MR and has demonstrated that correcting for RV afterload when evaluating RV performance (e.g. with the TAPSE/PASP ratio) provides greater prognostic utility than considering RV performance alone (e.g. TAPSE). The prognostic utility of TAPSE/PASP ratio is even confirmed in patients with significant secondary tricuspid regurgitation (TR) (31).

Study limitations

The single center and retrospective nature of this study limits the generalizability of the results. Data on BNP or NT-proBNP were not systematically acquired in our centre. A recent study by Karam et al. (32) also evaluated RV-PA coupling in patients with secondary MR undergoing transcatheter mitral valve repair (TMVR). Although the results are similar, our study evaluated the prognostic value of RV-PA coupling in all patients with SMR and not only the patients requiring intervention. Pressure-volume loops derived from right heart catheterization are the gold standard to measure ventricular and arterial elastances and RV-PA coupling (33), and there are inherent limitations to the use of non-invasive measures of contractility and total (pulsatile and resistive) afterload. Although the evaluation of RV function with TAPSE might be considered a limitation of the current study, TAPSE is a robust and recommended parameter to assess longitudinal RV function (21). In addition, the pulsatile component of afterload contributes only ~23% to total afterload in normal patients and those with arterial PH (34) supporting the use of PASP for this analysis. Finally correcting TAPSE for PASP as an index of RV-PA coupling had been demonstrated to be the best echocardiographic indicator of RV-PA coupling against invasive measurements (11, 12).

Conclusions

In the present large-scale study of HF patients with significant secondary MR treated medically and with mitral valve interventions, RV-PA uncoupling as assessed by the TAPSE/PASP ratio was independently associated with long-term all-cause mortality and had incremental prognostic utility compared with TAPSE alone.

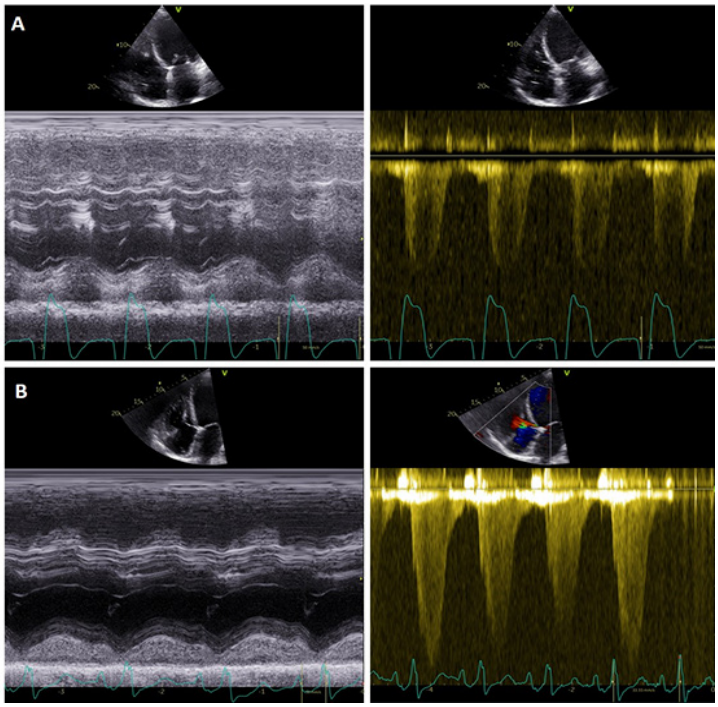

Figure 4. TAPSE/PASP ratio in patients with secondary MR

(A) A patient with severe secondary MR, TAPSE of 20 mm and PASP of 32.37 mmHg. This patient had a TAPSE/PASP ratio of 0.62 (more preserved RV-PA coupling) and did not die during follow-up. **(B)** A patient with severe secondary MR, TAPSE of 17 mm and PASP of 67.55 mmHg. This patient had a TAPSE/PASP ratio of 0.25 (more impaired RV-PA coupling) and died during follow-up. Despite both patients having preserved RV function according to TAPSE, the TAPSE/PASP ratio and outcome were significantly different. MR = mitral regurgitation; PA = pulmonary arterial; PASP = pulmonary artery systolic pressure; RV = right ventricular; TAPSE = tricuspid annular plane systolic excursion.

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Chapter seven

Summary, conclusions and future perspectives

Samenvatting, conclusie en toekomstperspectieven

Summary

In this thesis the role of advanced echocardiography was evaluated in the risk stratification and management of patients with secondary mitral regurgitation (MR).

The general introduction **(Chapter 1)** provided insights in the role of multimodality imaging in the evaluation of patients with mitral regurgitation referred for transcatheter interventions. An important part of patient selection for transcatheter MV therapies is MR quantification and an accurate assessment of the mitral valve anatomy. These parts cannot be visualized during transcatheter intervention and therefore interventionalist need visualization of the MV apparatus. Three-dimensional imaging techniques, i.e. transesophageal echocardiography, computed tomography, and cardiovascular magnetic resonance, are key in the evaluation of anatomical assessment of the MV apparatus and the suitability of the patient for transcatheter intervention. Fusion imaging is being implemented in catheterization laboratories to precisely guide the procedure and to maximize safety and optimal results.

Part I: epidemiology in secondary mitral regurgitation

In this first part epidemiological characteristics of patients with secondary MR is evaluated. Secondary MR is more prevalent in men than women, but little is known about its association with prognosis. In **Chapter 2** the sex distribution of secondary MR and the prognostic differences between sexes has been evaluated. We demonstrated that secondary MR was more frequently seen in men and associated with a worse prognosis. Also ischemic heart failure was more significantly common in men, whereas non-ischemic heart failure was more prevalent in women. The underlying ischemic etiology of secondary MR is known to respond less well to heart failure therapies and may further progress over time, leading to worse outcome.

Part II: Echocardiography and prognosis in secondary mitral regurgitation

In this second part we focused on the role of echocardiography in defining predictors of outcome in patients with secondary mitral regurgitation. Left ventricular (LV) systolic function may be overestimated in patients with secondary MR when using LV ejection fraction (LVEF). LV global longitudinal strain (LVGLS) derived from speckle tracking echocardiography has shown it is more sensitive to detect LV systolic dysfunction. **Chapter 3** evaluates the incremental prognostic value of LVGLS. Patients with more impaired LV systolic function according to a LVGLS value of less than 7% showed significantly higher mortality rates. LVGLS also demonstrated to be of incremental prognostic value over LVEF. The results of the current study suggest that LV GLS

might be a better prognostic marker than LVEF and therefore could aid further risk stratification of patients with secondary MR.

Quantification of secondary MR remains challenging and its severity can be over- or underestimated. **Chapter 4** evaluates the ratio of mitral regurgitant volume (RVol) and LV end-diastolic volume (LVEDV) and its association with prognosis. Patients with a RVol/EDV ratio <20%, defining a smaller RVol/larger EDV (i.e. more LV remodeling), had significantly higher mortality rates when compared to their counterparts. When considering patients receiving medical therapy only, patients with RVol/EDV ratio ≥20% tended to have higher mortality rates than those with RVol/EDV ratio <20%. Higher RVol/EDV ratio was independently associated with all-cause mortality. These results reflect the importance to take the relative severity of both MR and LV volume into account. RVol/EDV ratio may further improve risk stratification of patients with secondary MR and identify those who may benefit from transcatheter and surgical therapies to reduce severe secondary MR.

Chapter 5 examines the impact of MV geometry on outcomes after transcatheter edge-to-edge mitral valve repair with the MitraClip device (Abbott Vascular, Santa Clara, CA) compared to patients treated with guideline-directed medical therapy (GDMT). This present echocardiographic core laboratory study from the multicenter COAPT trial demonstrated that amongst many geometrical characteristics of the MV, a large anteroposterior mitral annular diameter and greater effective regurgitant orifice area (EROA) were the strongest echocardiographic predictors of HFH and death in patients treated with GDMT alone and with the MitraClip. A large anteroposterior mitral annular diameter was associated with increased risk of the composite outcome of all-cause death or HFH and HFH alone. Greater EROA was an independent predictor of mortality. Treatment with the MitraClip plus GDMT compared with GDMT alone reduced death and HFH consistently in patients with and without these extremes.

The chronic volume overload in patients with secondary MR eventually leads to pulmonary hypertension and right ventricular (RV) dysfunction with an increased risk of morbidity and mortality. In **Chapter 6** we evaluated the ratio between tricuspid annular plane systolic excursion (TAPSE) and pulmonary arterial systolic pressure (PASP) as a non-invasively measure of RV to pulmonary artery (RV-PA) coupling (the relationship between RV contractility and afterload). A TAPSE/PASP ratio <0.35, defined as an impaired RV-PA coupling, was associated with an excess mortality. Patients with a TAPSE/PASP≥0.35 showed significantly better survival rates. TAPSE/PASP ratio also remained independently associated with all-cause mortality and showed to have an

incremental prognostic value over TAPSE. By taking into account TAPSE/PASP ratio (as a measure for RV-PA coupling), it may improve further risk stratification of patients with secondary MR.

Conclusions and future perspectives

Secondary MR is a result of changes in the LV geometry and MV annular dilation and has an increasing incidence. Severe secondary MR is known to be associated with a worse prognosis, whilst the effect of reducing MR on prognosis has still been unclear. The question remains what influences the prognosis of these patients: is it the LV or the valve (i.e. the MR)? Characterization and risk-stratification of patients with secondary MR therefore remains challenging. Until recently the decision to intervene for secondary MR was based also on the LVEF. However, LVEF is subject to many limitations. The conflicting results of two major trials evaluating transcatheter mitral valve repair therapy using the MitraClip device (Abbott Vascular, Menlo, CA) demonstrated differences in LV volumes, but had similarities in LVEF suggesting that LVEF is not the best parameter to assess LV systolic function in patients with secondary MR. Advanced echocardiography, such as speckle tracking echocardiography, from which LVGLS could be derived has shown to be of much more diagnostic and prognostic value in various valvular heart disease and is currently being implemented more in valvular heart disease guidelines. This supports the fact that LVGLS can detect LV dysfunction in an earlier stage and therefore guide physicians to refer patients for intervention before it is too late. Also the mitral valve geometry has an important role in the technical feasibility of intervention, but also could elaborate on which specific transcatheter intervention is more appropriate according to their targets (i.e. leaflets, annulus or sub apparatus). Additionally, multimodality imaging remains key in characterization and quantification of secondary MR and may help further risk-stratification.

Samenvatting

In dit proefschrift is de rol van geavanceerde echocardiografische technieken geëvalueerd voor de risicostratificatie en behandeling van patiënten met secundaire mitralisklepinsufficiëntie.

De algemene introductie **(Hoofdstuk 1)** biedt inzicht in de rol van verschillende modaliteiten in de beeldvorming als middel in de evaluatie van patiënten met mitralisklepinsufficiëntie die verwezen worden voor percutane interventie.
Een belangrijke rol die speelt in de selectie van patiënten voor percutane mitralisklep interventie is de kwantificatie van de mitralisklepinsufficiëntie, naast een nauwkeurige beoordeling van de mitralisklep anatomie. Deze onderdelen kunnen niet gevisualiseerd worden tijdens de interventie, des te belangrijker het is voor de interventie cardioloog om de mitralisklep goed te kunnen visualiseren. Driedimensionale beeldvormingstechnieken, bijvoorbeeld transoesofageale echocardiografie, CT en MRI, zijn een belangrijk onderdeel in het beoordelen van de anatomie van de mitralisklep en de geschiktheid van de patiënt voor een percutane interventie. De techniek waarbij meerdere beeldvormende technieken worden gefuseerd, wordt momenteel geïmplementeerd in meerdere interventiecentra om de procedure hiermee te begeleiden en de veiligheid en optimale resultaten te vergroten.

Deel I: epidemiologie in secundaire mitralisklepinsufficiëntie

In dit eerste deel wordt de epidemiologische kenmerken van patiënten met secundaire mitralisklepinsufficiëntie geëvalueerd. Secundaire mitralisklepinsufficiëntie komt vaker voor bij mannen dan bij vrouwen. Echter er is maar weinig bekend over de associatie tussen mannen en vrouwen en de prognose. In **Hoofdstuk 2** worden de invloed van de verschillen op prognose beschreven. Dit onderzoek toonde aan dat secundaire mitralisklepinsufficiëntie vaker voorkwam bij mannen en geassocieerd was met een slechtere prognose. Ischemische hartziekten kwam vaker voor bij mannen, terwijl non-ischemische hartziekten vaker bij vrouwen voorkwam. Het is bekend dat de onderliggende ischemische etiologie van secundaire mitralisklepinsufficiëntie vaker minder goed reageert op hartfalen therapie en kan verergeren over tijd. Dit op zijn beurt leidt tot een slechtere uitkomst bij deze patiënten.

Deel II: echocardiografie en prognose in secundaire mitralisklepinsufficiëntie

In dit tweede deel is het focus gelegd op de rol van echocardiografie in het definiëren van parameters die geassocieerd kunnen zijn met de uitkomst van patiënten met secundaire mitralisklepinsufficiëntie. De linkerventrikelfunctie (LVF) kan overschat

worden in secundaire mitralisklepinsufficiëntie als deze bepaald wordt middels de linkerventrikel ejectie fractie (LVEF). Het is aangetoond dat de parameter linkerventrikel "global longitudinal strain" (LV GLS), afgeleid van speckle tracking echocardiografie, sensitiever is om linkerventrikel (LV) dysfunctie te detecteren. **Hoofdstuk 3** evalueert de toegevoegde prognostische waarde van deze parameter. Patiënten met een verminderde LVF volgens de LV GLS met een waarde minder dan 7%, hadden een significant hoger risico op mortaliteit. LV GLS was van prognostische waarde boven LVEF. De resultaten van deze studie suggereren dat LV GLS een betere prognostische marker kan zijn en meegenomen kan worden in de risicostratificatie van patiënten met secundaire mitralisklepinsufficiëntie.

Kwantificeren van mitralisklepinsufficiëntie blijft een uitdaging en kan de ernst over- of onderschatten. **Hoofdstuk 4** evalueert de ratio tussen het regurgiterend volume van de mitralisinsufficiëntie (RVol) en de linker ventrikel eind-diastolische volume (LVEDV) en prognose. Patiënten met een RVol/EDV ratio <20% (staat voor een kleiner RVol en/ of een groter LVEDV en daarmee meer remodelering van de LV), hadden een hoger risico op overlijden. Patiënten die alleen medicamenteus behandeld werden, leken degene die een RVol/EDV ratio ≥20% hadden een hoger risico op mortaliteit te hebben. Deze resultaten onderstrepen het belang van het meenemen van zowel de ernst van de mitralisklepinsufficiëntie als de LV volume in de evaluatie van deze patiënten. Deze ratio kan helpen de patiënten de identificeren die voordelen kunnen ervaren van invasieve therapie.

Hoofdstuk 5 heeft de impact van de mitralisklep geometrie op uitkomsten na een percutane interventie middels de MitraClip (Abbott Vascular, Santa Clara, CA) vergeleken met patiënten die medicamenteus volgens de richtlijnen (guideline-directed medical therapy (GDMT)) werden behandeld. Deze echocardiografische studie van een multicenter gerandomiseerde trial (COAPT) demonstreerde dat naast vele geometrische parameters, een groter anteroposterior mitralisklep annulus diameter en een groter "effective regurgitant orifice area" de sterkste echocardiografische voorspellers waren voor hartfalen hospitalisatie en overlijden. Een percutane behandeling middels de MitraClip naast GDMT vergeleken met GDMT alleen, toonde een reductie van het risico op hartfalen hospitalisatie en overlijden in patiënten met secundaire mitralisklepinsufficiëntie.

Patiënten met secundaire mitralisklepinsufficiëntie hebben chronische volume overbelasting, dat leidt tot hoge drukken in de longen en rechterventrikel dysfunctie. Dit leidt tot meer morbiditeit en mortaliteit. In **Hoofdstuk 6** hebben we de ratio

tussen “TAPSE” (een maat voor rechter ventrikel functie) en de systolische druk in de long arterie (PASP) geëvalueerd als een maat voor RV-PA coupling (de relatie tussen contractiliteit van de rechterventrikel en de afterload). Een TAPSE/PASP ratio <0.35 was geassocieerd met een verhoogd risico op mortaliteit. TAPSE/PASP ratio was van prognostische waarde boven TAPSE.

Conclusie en toekomstperspectieven

Secundaire mitralisklepinsufficiëntie is het gevolg van veranderingen in de LV geometrie en mitralisklep annulus dilatatie. Ernstige mitralisklepinsufficiëntie is geassocieerd met een slechte prognose. Het verminderen van de mitralisklepinsufficiëntie en verbetering van prognose is nog niet duidelijk. De vraag blijft wat de prognose beïnvloed. Behandelen van patiënten met secundaire mitralisklepinsufficiëntie blijft hiermee uitdagend. Recentelijk was de LVEF een belangrijke parameter om de mitralisklepinsufficiëntie invasief te behandelen. Twee grote trials die het effect van percutane mitralisklep therapie hebben geëvalueerd toonde discrepanties in de resultaten. Onder andere de LV volumina waren anders, terwijl de LVEF vergelijkbaar was, hetgeen suggereert dat de LVEF niet de beste parameter is om de LVF te bepalen. Geavanceerde echocardiografische technieken, zoals speckle tracking echocardiography waarvan LVGLS wordt afgeleid, kunnen van diagnostische als prognostische waarde zijn en worden langzamerhand in de huidige richtlijnen opgenomen. LVGLS kan LV dysfunctie in een eerder stadium detecteren en artsen helpen in de beslisvorming voor interventie voordat het “te laat” is. De anatomie van de mitralisklep speelt hierin ook een belangrijke rol in het technische aspect van invasieve therapieën, maar ook in welke specifieke percutane therapie geschikt is om het probleem aan te pakken (b.v. klepbladen, annulus of mitralisklep subapparatus). Als aanvulling hierop kunnen beeldvormende technieken van verschillende modaliteiten een belangrijke en centrale rol spelen in het karakteriseren en kwantificeren van secundaire mitralisklepinsufficiëntie en helpen in de risicostratificatie van patiënten.

Appendix

List of publications

Dankwoord

Curriculum vitae

List of publications

Namazi F, van der Bijl P, Hirasawa K, Kamperidis V, van Wijngaarden SE, Mertens B, Leon MB, Hahn RT, Stone GW, Narula J, Ajmone Marsan N, Delgado V, Bax JJ.
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Dankwoord

De artikelen die in dit proefschrift staan beschreven zijn tot stand gekomen op de afdeling cardiologie van het Leids Universitair Medisch Centrum. Graag wil ik iedereen bedanken met wie heb ik mogen samen werken gedurende de afgelopen jaren, waaronder ook alle medewerkers op het staf, het secretariaat, research verpleegkundigen, verpleegkundig specialisten en andere medewerkers van het Hartcentrum. Een aantal mensen wil ik in het bijzonder noemen en bedanken.

Prof. dr. J. J. Bax, beste Jeroen, heel erg bedankt voor het vertrouwen en de kans die jij mij hebt gegeven om mijn promotieonderzoek te doen en de mogelijkheid die ik heb gekregen om ook onderzoek in het buitenland te mogen ervaren.

Dear Victoria, I don't have enough words to express my gratitude for all your support I received during my PhD. I have learned so much from you, and not only about research. I will never forgot you.

Dear Nina, thank you so much for all your input and creativity during the journal clubs and helping me with my manuscripts.

Al mijn "Tuin" collega's, waar ik de afgelopen jaren veel van heb mogen ontmoeten. Bedankt voor de discussies over research tot de leuke momenten aan de koffie tafel en alle congressen die wij samen hebben mogen bijwonen.

To the international fellows from our imaging group, thank you for the time I could spend with you, discussions about research and dinners we had.

Alle collega's van het Haaglanden Medisch Centrum, dank jullie wel voor de mooie en leerzame tijd die ik heb mogen ervaren bij jullie als een dokter vers uit de schoolbanken.

Dear Federico and all colleagues from MedStar Washington Hospital Center, thank you so much for the opportunity to do research in the corelab and making me feel as part of the team.

Al mijn collega's in het Hartcentrum Isala Zwolle, bedankt voor jullie warme welkom nadat ik na jaren onderzoek weer de kliniek in mocht. Ik zal mijn tijd bij jullie nooit vergeten.

Mijn huidige collega's van de KLM Health Services; ontzettend bedankt dat ik een onderdeel mag zijn van jullie team, voor jullie begeleiding om mij al het fijne van het vak bedrijfsgeneeskunde te leren en jullie enthousiasme in deze laatste sprint van mijn promotie.

Dilek, door mijn promotieonderzoek heb ik jou mogen leren kennen, waar ik erg blij mee ben. Ik ben dankbaar dat jij naast mij wil staan als mijn paranimf.

Mijn lieve vriendinnen, Geerke, Reim, Amira, Elif, we go way back! Dank jullie wel voor alle support die ik heb mogen ontvangen tijdens mijn promotieonderzoek en dat ik altijd bij jullie terecht kon, wat er ook was.

Mijn lieve familie, daei Javad mehraboon, daei Hamid aziz va Zohre joon, dank jullie wel dat jullie naast mij hebben gestaan tijdens dit promotieonderzoek.

Mijn lieve oma,
مادرجون عزیزم امیدوارم همیشه سایتون بالای سر ما باشه

Lieve Farshad, mijn broertje! Ook al zat jij in een hele andere levensfase (wat logisch is met 15 jaar leeftijdsverschil), wist jij toch de juiste dingen tegen mij te zeggen en mij te steunen. Siawash, mijn "verworven" broertje, bedankt dat je naast mij hebt gestaan tijdens dit promotieonderzoek.

Lieve Farnoush, mijn zusje! Ik kan niet met zo weinig woorden omschrijven hoe dankbaar ik ben. Jij hebt mij altijd geholpen op alle mogelijke manieren en jouw positiviteit is onbetaalbaar. Ik ben blij dat jij naast mij staat als mijn paranimf.

Mijn lieve ouders, bedankt voor jullie onvoorwaardelijke steun, jullie liefde en vertrouwen in mij vanaf dag 1. Door jullie aan mijn zijde heb ik mij mogen en kunnen ontwikkelen tot de persoon die ik ben vandaag. Zonder jullie had ik dit promotieonderzoek nooit tot stand kunnen brengen.

Curriculum vitae

Farnaz Namazi werd geboren op 9 oktober 1989 in Teheran, Iran. In 2008 behaalde zij haar Gymnasiumdiploma aan het Baken Park Lyceum te Almere. Van 2008 tot en met 2014 studeerde zij geneeskunde aan de Universiteit van Amsterdam. Na het behalen van haar artsenexamen startte zij in 2015 als arts-assistent niet in opleiding (ANIOS) op de afdeling cardiologie van het Haaglanden Medisch Centrum te Den Haag.
In 2016 startte zij als ANIOS op de afdeling cardiologie van het Leids Universitair Medisch Centrum (LUMC). Na dit 6 maanden te hebben gedaan, begon zij met haar promotieonderzoek op de afdeling cardiologie onder leiding van prof dr. J. J. Bax en dr. V. Delgado. De resultaten van dit onderzoek staan beschreven in dit proefschrift. Zij presenteerde een deel van haar promotieonderzoek op meerdere internationale congressen. Op het European Society of Cardiology congress te München in 2018 won zij de prijs voor best poster. Tevens heeft zij in 2019 gedurende 3 maanden onderzoek gedaan op het gebied van mitraliskleplijden in het MedStar Washington Hospital Center, te Washington D.C., USA.
Farnaz heeft besloten om een pad buiten de cardiogie te bewandelen. Zij zal de uitdaging aan gaan binnen de wereld van de bedrijfsgeneeskunde en werkt momenteel bij de KLM Health Services.