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Overview of mitral regurgitation in Europe: results from the European Registry of mitral regurgitation (EuMiClip)

Juan Manuel Monteagudo Ruiz[1]*, Maurizio Galderisi[2], Agostino Buonauro[2], Luigi Badano[3], Patrizia Aruta[3], Martin J. Swaans[4], Laura Sanchis[4], Antti Saraste[5], Mark Monaghan[6], Konstantinos C. Theodoropoulos[6], Michael Papitsas[6], Noah Liel-Cohen[7], Sergio Kobal[7], Mojca Bervar[8], Boštjan Berlot[8], Gerasimos Filippatos[9], Ignatios Ikonomidis[9], Spyridon Katsanos[9], Felix C. Tanner[10], Daniela Cassani[10], Francesco F. Faletra[11], Laura A. Leo[11], Amparo Martinez[12], Javier Matabuena[13], Antonio Grande-Trillo[13], David Alonso-Rodriguez[14], Dolores Mesa[15], Teresa Gonzalez-Alujas[16], Marta Sitges[17], Fernando Carrasco-Chinchilla[18], Chi Hion Li[19], Covadonga Fernandez-Golfin[1], and José Luis Zamorano[1,20]

[1]Department of Cardiology, CIBERCV, University of Alcala, Hospital Ramon y Cajal, Carretera de Colmenar Km 9, 100, 28034 Madrid, Spain; [2]Laboratory of Standard and Advanced Echocardiography, Department of Advanced Biomedical Sciences, Federico II University Hospital, Via S. Pansini 5, 80131 Naples, Italy; [3]Department of Cardiac, Vascular, and Thoracic Sciences, Padova University Hospital, Via Giustiniani 2, 35128 Padova, Italy; [4]Department of Cardiology, St Antonius Hospital, Koekoekslaan 1, 3435 Nieuwegein, Netherlands; [5]Department of Medicine, Turku University Hospital, Kiinamyllynkatu 4-8, 20521 Turku, Finland; [6]Cardiology Department, King's College Hospital, Denmark Hill, Brixton, London SE5 9RS, UK; [7]Division of Cardiology, Soroka Medical Center and Ben Gurion University of the Negev, Yitzhack I. Rager Blvd 151, 84101 Beersheba, Israel; [8]Department of Cardiology, University Medical Centre Ljubljana, Zaloška cesta 7, 1000 Ljubljana, Slovenia; [9]Department of Cardiology, Attikon Hospital, Rimini 1, 124 62 Chaidari, Greece; [10]Department of Cardiology, University Hospital Zurich, Rämistrasse 100, 8091 Zürich, Switzerland; [11]Department of Cardiology, Cardiocentro Ticino, Via Tesserete 48, 6900 Lugano, Switzerland; [12]Department of Cardiology, University Hospital of Santiago de Compostela, Rúa Choupana, Santiago de Compostela, 15706 A Coruña, Spain; [13]Department of Cardiology, University Hospital of Virgen del Rocio, Av. Manuel Siurot, 41013 Seville, Spain; [14]Department of Cardiology, Hospital of Leon, Altos de Navas, 24071 León, Spain; [15]Department of Cardiology, University Hospital Reina Sofia, Avenida Menéndez Pidal, 14004 Córdoba, Spain; [16]Department of Cardiology, University Hospital Vall d'Hebron, Passeig de la Vall d'Hebron, 119-129, 08035 Barcelona, Spain; [17]Cardiology Department, Thorax Institute, Hospital Clinic Barcelona, Carrer de Villarroel, 170, 08036 Barcelona, Spain; [18]Department of Cardiology, University Hospital Virgen Victoria, Campus de Teatinos, 29010 Málaga, Spain; [19]Cardiology Division, Department of Medicine, Hospital de la Santa Creu i Sant Pau, Carrer de Sant Quintí, 89, 08041 Barcelona, Spain; and [20]Department of Cardiology, University Francisco de Vitoria, Hospital La Zarzuela, Calle de Pleyades, 25, 28023 Madrid, Spain

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Aims To determine the prevalence of mitral regurgitation (MR) in a large cohort of consecutive patients undergoing clinically indicated echocardiography and to examine the distribution of primary and secondary MR.

Methods and results All patients undergoing an echocardiographic study in 19 European centres within a 3-month period were prospectively included. MR assessment was performed as recommended by the European Association of Cardiovascular Imaging (EACVI). MR was classified according to mechanism as primary or secondary and aetiologies were reported. A total of 63 463 consecutive echocardiographic studies were reviewed. Any degree of MR was described in 15 501 patients. Concomitant valve disease of at least moderate grade was present in 28.5% of patients, being tricuspid regurgitation the most prevalent. In the subgroup of moderate and severe MR ($n = 3309$), 55% of patients had primary MR and 30% secondary MR. Both mechanisms were described in 14% of the studies. According to Carpentier's classification, 26.7% of MR were classified as I, 19.9% of MR as II, 22.4% of MR as IIIa, and 31.1% of MR as IIIb.

Conclusion To date, this is the largest echocardiography-based study to analyse the prevalence and aetiology distribution of MR in Europe. The burden of secondary MR was higher than previously described, representing 30% of patients

* Corresponding author. Tel: +34 (66) 5841134; Fax: +34 91 336 85 15. E-mail: J5469M@gmail.com

with significant MR. In our environment, degenerative disease is the most common aetiology of primary MR (60%), whereas ischaemic is the most common aetiology of secondary MR (51%). Up to 70% of patients with severe primary MR may have a Class I indication for surgery. However, the optimal therapeutic approach for secondary MR remains uncertain.

Keywords echocardiography • mitral regurgitation

Introduction

Mitral regurgitation (MR) is one of the most common valve disease in our environment. Its frequency and severity increase with age, and its presence is associated with a worse prognosis.[1] The most commonly used classification divides MR, according to its mechanism, in primary and secondary forms.[2]

Few studies have addressed the aetiologies and mechanisms behind MR and most of them are based on surgical specimen examination to determine the aetiology. Prevalence of mitral valve prolapse, as defined by echocardiographic criteria, has been assessed in a population-based series. Freed *et al.*[3] found a prevalence of mitral valve prolapse of 2.4%, though in most cases the regurgitation was classified as trace or mild. In the Euro Heart Survey on Valvular Heart Disease, aetiologies of MR were classified following surgical and echocardiographic findings along with clinical context. MR degenerative aetiology was the most common followed by rheumatic disease and ischaemic.[4] However, primary and secondary MR were not considered separately, despite the fact that they are managed differently.

In secondary MR, valve components are structurally normal and MR results from left ventricle (LV) dysfunction, due to dilated cardiomyopathy or coronary artery disease. Increasing severity of secondary MR is associated with higher mortality.[5,6] However, in contrast with primary MR, outcomes of mitral valve surgery in secondary MR are poor and there are no clinical trials evaluating the benefits of surgical treatment against medical therapy in terms of survival. This lack of evidence is reflected in the guidelines. In patients with severe MR, left ventricular ejection fraction (LVEF) >30%, who remain symptomatic despite optimal management and have low comorbidity, isolated surgical correction of secondary MR is considered a Class IIb recommendation.[2] Furthermore, patients with secondary MR usually have a high surgical risk, due to left ventricular dysfunction and other comorbidities.

The purpose of this study is: (i) To determine the prevalence of MR in a large cohort of consecutive patients undergoing clinically indicated echocardiography. (ii) To determine the distribution of primary and secondary MR.

Methods

Study population

Nineteen European centres participated in this study. All patients undergoing an echocardiographic study in the participant hospitals were prospectively included. All studies with at least mild MR were selected for analysis and were included in the case report form. The Local Ethics Committee approved the study.

Echocardiography

The evaluation was conducted according to the usual practice of the laboratory. MR assessment was performed as recommended by the European Association of Cardiovascular Imaging.[7] 2D transthoracic echocardiography (TTE) was used as first-line imaging modality. 2D and 3D transoesophageal echocardiography were indicated when TTE resulted insufficient or in patients with complex valve lesions. The decision to indicate TTE was left to the performing echocardiographist.

After the assessment of valve morphology, MR was classified according to aetiology as primary, when structural abnormalities were described or secondary otherwise. In patients with both LV remodelling and resulting tethering of the mitral valve and structural lesions of the valve, MR was classified as mixed. Causes of primary and secondary MR were reported.

A careful assessment of the regurgitant jet in multiple views by colour Doppler was performed to diagnose mild regurgitation, with no further quantification. In cases with significant regurgitation, vena contracta and proximal isovelocity surface area were, when feasible, performed to evaluate the severity. Concomitant valvular heart disease was also reported. Pulmonary systolic arterial pressure (PSAP) was determined as tricuspid regurgitation gradient plus right atrial pressure.

Regarding left atrial (LA) and LV measurements, they were performed complying with 2015 EACVI/ASE Recommendations Cardiac Chamber Quantification by Echocardiography in Adults.[8]

Statistical analysis

Baseline characteristics are expressed as mean and standard deviation (SD) for continuous variables, and frequencies and percentages for categorical ones. Equality of variances between groups was tested using Levene's robust test statistic. Student *t*-test was used for comparison between two groups for quantitative variables. The χ^2 tests were used to identify significant variation in proportions across subgroups. Bonferroni–Holm adjustment was used for multiple comparisons. *P*-value < 0.05 was considered significant. Statistical analysis was performed with Stata statistical analysis software, version 14.1 (Stata Corporation, College Station, TX, USA).

Results

Study population

A total of 63 463 consecutive echocardiographic studies were performed in the participant hospitals during the recruitment period. Any degree of MR was described in 15 501 patients. Mild MR was detected in 12 192 (78.7%) studies. In 2397 (15.5%) studies MR severity was moderate and in 912 (5.9%) was severe. At the time of the study 19.8% of patients had symptoms. Mean age was 70.6 (SD = 13.8) and 49.8% were women. Moreover 28.5% of patients had concomitant valve disease of at least moderate grade, being tricuspid regurgitation the most prevalent (19.0%), followed by

aortic stenosis (8.2%), aortic regurgitation (4.8%), and mitral stenosis (1.7%).

Primary and secondary MR

In the subgroup of moderate and severe MR ($n = 3309$), there were 1806 (55.1%) patients with primary MR and 1010 (30.1%) patients with secondary MR. The concomitant presence of both mechanisms of MR was described in 14.1% of the studies. In most of these, the predominant component was the functional one. TEE was performed in 150 cases (4.5%). Symptoms were present in 31.6% of patients with primary MR and 46.8% of patients with secondary MR *Figure 1*.

According to Carpentier classification, 26.7% had normal leaflet motion, 19.9% had leaflet prolapse, 22.4% had restricted leaflet motion during diastole and systole, and 31.1% only during systole.

Degenerative disease was the most common aetiology of primary MR (59.8%), followed by Barlow disease (14.4%), rheumatic disease (10.1%), endocarditis (1.6%), and congenital disease (1.5%).

Additionally, ischaemic was the most common aetiology of secondary MR, present in 51.4% of cases while about 31.9% of patients had dilated cardiomyopathy.

Gender differences

In the group of patients with significant MR both sexes were similarly represented, 53% being men and 47% women. However, mechanisms seem to differ between genders. Women were, on average, 3.1 years older than men (72.8 vs. 69.7, $P < 0.001$).Severe LV dysfunction (ejection fraction <30%) was significantly more common in men (17.3 vs. 8.7%, $P < 0.001$) whereas severe calcification of the mitral valve was more common in women (13.5 vs. 6.1%, $P < 0.001$). This translates into a different distribution of MR regurgitation forms and aetiologies in men and women as shown in *Figure 2* and *Table 1*.

Applicability of current guidelines

Over 70% of patients with severe primary MR had a Class I indication for surgery. According to current European guidelines,[2] Class I indications for surgery in severe primary MR are:

- Symptomatic patients with LVEF >30% and left ventricular end-systolic diameter (LVESD) <55 mm.
- Asymptomatic patients with LV dysfunction (LVESD ≥45 mm and/or LVEF ≤60%).

Several IIa and IIb indications for surgery are considered in the guidelines. However only a minor proportion of our sample (7%) met any of them.

As previously mentioned there is no Class I indication for isolated valve surgery in chronic secondary MR. In patients with severe MR, LVEF >30%, who remain symptomatic despite optimal management and have low comorbidity, isolated surgical correction of secondary MR is considered a Class IIb recommendation. In this study, population only 13.1% of patients with significant secondary MR met this indication. Severe left ventricular dysfunction (LVEF <30%) was found in 38.8% of patients with significant secondary MR. Furthermore, the proportion of patients aged over 80 in this group stood at 25.7%.

Discussion

The participant hospitals comprise a diverse group of secondary and tertiary, urban and rural, and public and private centres. They serve a population of several millions Europeans. Thus, we believe this large cohort is a reliable sample of the European population referred for an echocardiography. Considering that, nowadays, the diagnose of MR without an echocardiography study is inconceivable, we can conclude that the vast majority of clinically significant MR are included in the cohort. Moreover, though a consensual protocol for MR

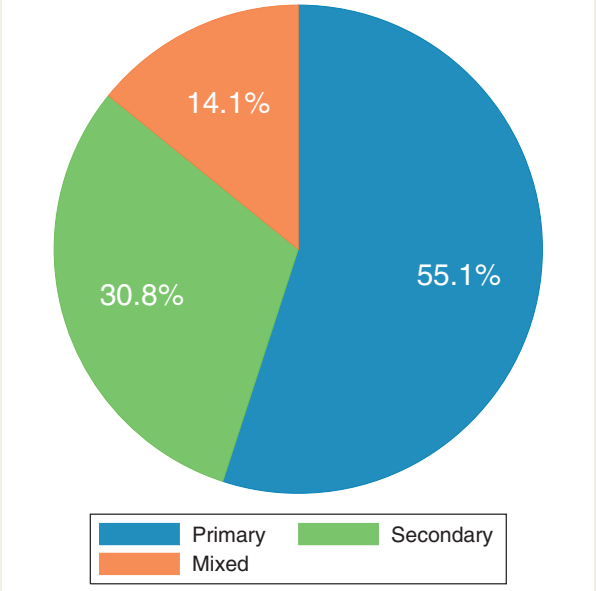

Figure 1 Mitral regurgitation forms.

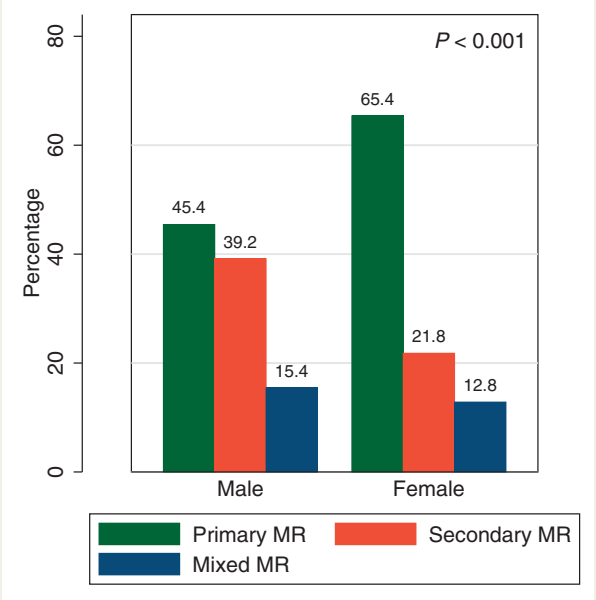

Figure 2 Mitral regurgitation forms by gender.

Table I Clinical and echocardiographic characteristics by gender

	Female ($n = 1547$)	Male ($n = 1740$)
Age (years), mean (SD)	72.5 (14.2)	69.6 (13.1)
BMI (kg/m^2), mean (SD)	26.6 (6.7)	26.5 (4.3)
BSA (m^2), mean (SD)	1.68 (0.18)	1.90 (0.18)
Atrial fibrillation (%)	32.8	30.3
Symptoms (%)	37.1	39.1
Mechanism (%)		
Primary	65.4	45.4
Secondary	21.8	39.2
Mixed	12.8	15.4
MR aetiology (%)		
Degenerative	38.9	32.4
Rheumatic	11.0	3.7
Barlow	7.8	13.0
Annular calcification	11.0	5.7
Secondary	19.6	34.5
Other	11.7	10.8
Indexed LAV (mL/m^2), mean (SD)	53.5 (25.3)	55.6 (26.1)
Indexed LVEDV (mL/m^2), mean (SD)	63.7 (30.0)	81.0 (32.2)
Indexed LVESV (mL/m^2), mean (SD)	34.0 (26.1)	47.4 (30.2)
Ejection fraction (%)	53.0	46.9
PSAP (mmHg), mean (SD)	43.6 (15.4)	43.1 (15.3)
Severe calcification (%)	13.5	6.1
Indexed valve area (cm^2/m^2), mean (SD)	2.2 (1.0)	2.3 (1.0)

BMI, body mass index; BSA, body surface area; LAV, left atrial volume; LVEDV, left ventricle end-diastolic volume; LVESV, left ventricle end-systolic volume; PSAP, pulmonary systolic arterial pressure.

evaluation and general measurements was established, in other respects, the studies were performed according to the usual practice of the participant laboratories and therefore, they represent real life conditions.

According to our results, significant MR may be present in up to 5% of the echocardiography studies. Giving its prognostic implications, we are confronted with a major health problem. An appropriate assessment is paramount and determining the aetiology and underlying mechanism is an essential part of this evaluation, as these features dictate the appropriate management.

As previously mentioned, distinguishing between primary and secondary MR is a first step toward ascertaining these mechanisms. In the Euro Heart Survey,[4] over 85% of MR were primary forms, a higher proportion than that found in our study. This is probably due to surgical cases, and so, primary MR, being over-represented in the Euro Heart Survey. Mitral valve surgery in primary MR is associated with low risk and an improved long-term event rate[9] and it is considered the treatment of choice. Our results show that up to 70% of patients with severe primary MR may have a Class I indication for surgery according to current European guidelines.[2]

Additionally, secondary MR has emerged as a leading cause of MR. In this large cohort, the predominant mechanism of MR was functional in over half of the patients (Carpentier Type I or IIIb). Carpentier's classification delves into the mechanism of valvular dysfunction. It is based on the opening and closing motions of the mitral leaflets. Four types are described. Patients with Type I dysfunction have normal leaflet motion and MR is usually caused by annular dilatation or leaflet perforation. In Type II dysfunction there is an increased leaflet motion, and MR is usually due to chordae or papillary muscle elongation or rupture. Patients with Type IIIa dysfunction have restricted leaflet motion during both systole and diastole and MR is most commonly caused by rheumatic changes in the valve apparatus (thickening, calcification, retraction. . .). In Type IIIb dysfunction there is restricted leaflet motion during systole and is due to LV dilation.

Optimal therapeutic approach for secondary MR remains one of the most important unmet clinical need in the field of structural heart disease. Secondary MR is often symptomatic (46.8% of patients) and therefore results in worse quality of life. It is also associated with excess mortality. Despite these facts, the majority of these patients are denied any mitral valve intervention due to advanced age or comorbidities. In the Euro Heart Survey, up to half of patients with severe symptomatic MR did not undergo surgery. Non-ischaemic aetiology, decreased LVEF, advanced age and comorbidity were common characteristics of patients who did not undergo surgery.[10]

In our study population only 13.1% of patients had indication for isolated surgical correction of secondary MR. Patients aged over 80 accounted for 25.7% of the group of patients with significant secondary MR and severe left ventricular dysfunction (LVEF <30%) was found in 39% of these patients. Furthermore, there is no solid evidence to support that surgery improves survival or clinical outcomes.[11]

Thus, there is a significant need for improved therapies in secondary MR. In the last decade, several percutaneous devices to treat MR have been developed. The most widely applied percutaneous approach is the MitraClip procedure. Although initial MitraClip trials included patients with low to medium surgical risk, in real life experience, the majority of patients who underwent MitraClip implant were high-risk, elderly patients, mainly affected by secondary MR.[12] Careful patient selection, with special attention to MR mechanisms is critical for the success of the procedure. It has been often stated that the applicability of MitraClip is limited because precise anatomical criteria have to be fulfilled. However, according to our result, up to 70% of patients with significant secondary MR may have a suitable mitral valve morphology for MitraClip if the recommendations of the German Society of Cardiology are employed.[13]

The complexity of the mitral valve has hindered the design of an optimal device. That said, even an optimal device would not necessarily be a generalizable solution for secondary MR. Secondary MR is a consequence of a left ventricular myocardial affection and though the loss of mitral valve function is involved in the pathological process, its restitution is not curative per se. Therefore, the development of more effective criteria beyond LV size and ejection fraction to assess potential improvement in LV function and prognosis is imperative. This could translate into an improve patient selection for transcatheter intervention, but also for medical treatment, mitral surgery, ventricular assistance device, transplantation, or palliative care.[14]

Limitations

This work is not a population-based epidemiological study and it doesn't reflect the prevalence of MR in the general population.

However, we believe that this cohort is a good sample of the clinical population and that it encompasses clinically significant MR. All echocardiographic studies were conducted according to the usual practice of the participant laboratories and a common protocol for the evaluation of MR. Though they were not audited in a core laboratory, they represent real-life conditions.

Conclusions

To date, this is the largest echocardiography-based study to analyse the prevalence and aetiology distribution of MR in Europe. Significant MR may be present in up to 5% of the echocardiographic studies. Primary MR was described in 55% of the studies. The burden of secondary MR has increased compared to previous studies, representing 30% of patients with significant MR and 1.6% of all echocardiograms. In the remaining 15%, both mechanisms were reported, though the functional component was predominant in most of these cases. In our environment, degenerative disease is the most common aetiology of primary MR (60%), whereas ischaemic is the most common aetiology of secondary MR (51%). According to Carpentier's classification, 26.7% of MR were classified as I, 19.9% of MR as II, 22.4% of MR as IIIa, and 31.1% of MR as IIIb.

Up to 70% of patients with severe primary MR may have a Class I indication for surgery according to current guidelines. However, the optimal therapeutic approach for secondary MR remains one of the most important most important unmet clinical need in cardiology, even though secondary MR has emerged as a leading cause of MR and is associated with excess mortality.

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Conflict of interest: None declared.

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