**Impact of mitral regurgitation in patients with worsening heart failure: Insights from BIOSTAT-CHF**

Matteo Pagnesi, 1\* Marianna Adamo,1\* Iziah E. Sama,2 Stefan D. Anker,3 John G. Cleland,4 Kenneth Dickstein,5 Gerasimos S. Filippatos,6 Chim C. Lang,7 Leong L. Ng,8 Piotr Ponikowski,9 Alice Ravera,1 Nilesh J. Samani,8 Faiez Zannad,10 Dirk J. van Veldhuisen,2 Adriaan A. Voors,2 Marco Metra1

1 Institute of Cardiology, ASST Spedali Civili, Department of Medical and Surgical specialties, Radiological sciences and Public Health, University of Brescia, Brescia, Italy

2 University of Groningen, Department of Cardiology, University Medical Center Groningen, Groningen, The Netherlands

3 Division of Cardiology and Metabolism, Department of Cardiology (CVK) and Berlin-Brandenburg Center for Regenerative Therapies (BCRT), German Centre for Cardiovascular Research (DZHK) Partner Site Berlin, Charité Universitätsmedizin Berlin, Berlin, Germany

4 National Heart and Lung Institute, Royal Brompton and Harefield Hospitals, Imperial College, London, UK; and Robertson Centre for Biostatistics and Clinical Trials, University of Glasgow, Glasgow, UK

5 University of Bergen, Bergen, Norway; and Stavanger University Hospital, Stavanger, Norway

6 Department of Cardiology, Attikon University Hospital, National and Kapodistrian University of Athens, Athens, Greece

7 School of Medicine Centre for Cardiovascular and Lung Biology, Division of Molecular and Clinical Medicine, University of Dundee, Ninewells Hospital & Medical School, Dundee, UK

8 Department of Cardiovascular Sciences, University of Leicester, Glenfield Hospital, Leicester, UK; and NIHR Leicester Biomedical Research Centre, Glenfield Hospital, Leicester, UK

9 Department of Heart Diseases, Wroclaw Medical University, Wrocław, Poland

10 Universite de Lorraine, Inserm, Centre d'Investigations Cliniques 1433 and F-CRIN INI-CRCT, Nancy, France

\*The two authors contributed equally to this article.

**Total word count:** 3218 words (excluding references and figure legends).

**Disclosures**: Dr. Filippatos reports speaker honoraria and/or committee membership in trials and/or registries sponsored by Amgen, Bayer, Novartis, Boehringer Ingrelheim, Medtronic, Vifor, and Servier; and research grants from the European Union. Dr. Voors received consultancy fees and/or research grants from Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Cytokinetics, Merck, Myokardia, Novartis, Novonordisk, and Roche Diagnostics. Dr. Metra received personal consulting honoraria from Abbott, Actelion, Amgen, Bayer, Edwards Therapeutics, Servier, Vifor Pharma, and Windtree Therapeutics for participation to advisory board meetings and executive committees of clinical trials. All the other authors have no conflicts of interest to disclose.

**Funding:** The BIOSTAT-CHF project was funded by a grant from the European Commission (FP7-242209-BIOSTAT-CHF; EudraCT 2010–020808–29).

**Corresponding author:**

Prof. Marco Metra, MD

Institute of Cardiology, Department of Medical and Surgical Specialties, Radiological Sciences,

and Public Health, University of Brescia, Brescia, Italy

Email: metramarco@libero.it

Phone: +393356460581

**ABSTRACT (244 words)**

**Background:** Few data regarding the prevalence and prognostic impact of mitral regurgitation (MR) in patients with worsening chronic or new-onset acute heart failure (HF) are available. We investigated the role of MR in the BIOlogy Study to TAilored Treatment in Chronic Heart Failure (BIOSTAT-CHF).

**Methods and Results:** We performed a retrospective *post-hoc* analysis including patients from both the index and validation BIOSTAT-CHF cohorts with data regarding MR status. The primary endpoint was a composite of all-cause death or HF hospitalization.

Among 4,023 patients included, 1,653 patients (41.1%) had moderate-severe MR. Compared to others, patients with moderate-severe MR were more likely to have atrial fibrillation and chronic kidney disease and had larger left ventricular (LV) dimensions, lower left ventricular ejection fraction (LVEF), worse QoL, and higher plasma concentrations of NT-proBNP. A primary outcome event occurred in 697 patients with, compared to 836 patients without, moderate-severe MR (Kaplan-Meier 2-year estimate: 42.2% vs. 35.3%; hazard ratio [HR], 1.28; 95% confidence interval [CI], 1.16-1.41; log-rank p<0.0001). The association between MR and the primary endpoint remained significant after adjusting for baseline variables and the previously validated BIOSTAT-CHF risk score (adjusted HR, 1.11; 95% CI, 1.00-1.23; p=0.041). Subgroup analyses showed a numerically larger impact of MR on primary endpoint in patients with lower LVEF, larger LV end-diastolic diameter, and higher plasma NT-proBNP.

**Conclusions:** Moderate-severe MR is common in patients with worsening chronic or new-onset acute HF and is strongly associated with outcome, independently of other features related to HF severity.

**Key words**: mitral regurgitation; heart failure; valvular heart disease; mortality; hospitalization.

**INTRODUCTION**

Heart failure (HF) remains a major cause of morbidity and mortality worldwide.1,2 In particular, the prognosis of patients with worsening HF leading to hospitalizations or emergency visits is poor, with high rates of rehospitalization and mortality.3–6

Mitral regurgitation (MR) is the most common valvular heart disease in HF patients, affecting almost one-third of patients with chronic HF and about half of those with acute HF.7–9 Accordingly, it has emerged as a therapeutic target in HF patients.10,11 However, randomized trials with percutaneous treatment of functional MR yielded different results and the subsets of patients who may benefit more from this treatment remains uncertain.12–16 Previous studies demonstrated the prognostic impact of MR in patients with HF.17–28 However, only few studies included patients with worsening chronic or new-onset acute HF and/or with preserved left ventricular ejection fraction (LVEF).19,20,28–30 Thus, further assessment of the impact of MR on outcomes of HF patients seems warranted.

The aim of this study was to assess the prognostic impact of MR in a selected population with worsening chronic or new-onset acute HF enrolled in the large, prospective, multicentre BIOlogy Study to TAilored Treatment in Chronic Heart Failure (BIOSTAT-CHF), focussed on guideline-directed medical therapy optimization.31

**METHODS**

**Study design and study population**

We retrospectively analysed data from BIOSTAT-CHF, a multicentre European study enrolling patients with new-onset or worsening chronic HF between 2010 and 2014.31–33 It included an index cohort of 2516 patients enrolled from 69 centres in 11 European countries and a validation cohort of 1738 patients from 6 centres in Scotland. Patients from the index cohort had symptoms of new-onset or worsening chronic HF, confirmed either by LVEF ≤40% or B-type natriuretic peptide (BNP) >400 pg/mL and/or N-terminal pro-BNP (NT-proBNP) > 2000 pg/mL and were treated with oral or intravenous furosemide ≥40 mg/day or equivalent at inclusion. Patients from the validation cohort had an HF diagnosis based on left ventricular (LV) dysfunction or a previous admission with HF requiring diuretic treatment and had to be treated with furosemide ≥20 mg/day or equivalent. The study was approved by the ethics committees of all participating centres and all patients provided written informed consent.

For the purposes of the present study, the index and validation cohorts were merged (n=4254 patients). Patients without echocardiography performed at inclusion (n=180) and patients with available echocardiography but without information on MR (n=51) were excluded. Therefore, a total of 4023 patients were included in the final analysis.

**Definitions and study endpoints**

Patients underwent 2-dimensional transthoracic echocardiography at inclusion using a commercially available echocardiography (3.5 MHz probe). MR was identified and evaluated using 2-dimensional and color Doppler echocardiography.34 According to the study protocol, only the presence of moderate or severe MR at baseline echocardiography (as compared to no or mild MR) was recorded. Both patients with primary and secondary MR were enrolled, but detailed data on MR mechanism or aetiology were not collected. Quantification of left ventricular (LV) diameters, LVEF according to the modified Simpson rule, and left atrium diameter were also performed. LV remodelling was evaluated according to the relative wall thickness and LV mass index as previously reported.35 Baseline clinical characteristics, quality-of-life (QoL) measures and laboratory data at inclusion, and clinical outcomes at follow-up were also analysed.

The primary endpoint was the composite of all-cause mortality or HF hospitalization. Secondary outcomes of interest were all-cause mortality and cardiovascular (CV) mortality as individual endpoints.

**Statistical analyses**

Continuous variables are presented as mean ± standard deviation or median (interquartile range, IQR), as appropriate, and were compared with the unpaired Student’s *t*-test or the Mann-Whitney U test, respectively. Categorical variables are presented as number and percentages and were compared with the χ2 test. Baseline characteristics, echocardiography data, QoL measures, laboratory data, primary and secondary endpoints were compared between patients with vs. without moderate-severe MR. The first occurrence of primary and secondary endpoint was evaluated in patients with or without moderate-severe MR using the Kaplan-Meier method (log-rank test). For all evaluated endpoints, follow-up was censored at 2 years. Cox proportional hazards regression analysis was also performed to assess the prognostic impact of moderate-severe MR on primary and secondary endpoints. Such impact was evaluated by means of univariable analysis and multiple multivariable models adjusting the presence of MR for the following covariates of interest: age and sex (demographic model); primary ischemic HF aetiology, peripheral oedema, New York Heart Association (NYHA) class, and previous HF hospitalization in last year (clinical model); and the already validated BIOSTAT-CHF risk prediction models.32 Results of the Cox regression analyses are reported as unadjusted or adjusted HR and 95% confidence interval. Subgroup analysis was also performed to evaluate the impact of moderate-severe MR on primary endpoint in subgroups of interest by means of multivariable Cox regression adjusted for age and sex.

All reported p-values are 2-sided, and a p<0.05 was considered statistically significant.

Statistical analyses were performed using STATA version 13.0 (STATA Corp., College Station,

Texas) and R version 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria).

**RESULTS**

**Baseline patient characteristics**

Among the 4,023 patients included in the present study, 1,653 patients (41.1%) had moderate-severe MR and 2,370 patients (58.9%) had no moderate-severe MR at baseline. Baseline characteristics of the study population are reported in **Table 1**. Compared to patients with no or mild MR, patients with moderate-severe MR were less likely to be men and to have a history of ischemic heart disease, myocardial infarction, percutaneous coronary intervention, prior valve surgery, peripheral artery disease, diabetes mellitus, and chronic obstructive pulmonary disease. They were more likely to have history of atrial fibrillation, HF hospitalization in the last year, and chronic kidney disease, had higher heart rate and more advanced symptoms as shown by their higher NYHA functional class. β-blockers were more frequently used at baseline in patients with, compared to those without, moderate-severe MR, whereas use of angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARBs) was similar between the two groups.

Detailed baseline characteristics in the index cohort and validation cohort are reported in **Supplementary Table 1** and **Supplementary Table 2**, respectively.

**Echocardiographic data, laboratory findings, and QoL measures**

Echocardiographic, laboratory, and QoL characteristics are reported in **Table 2**. Mean LVEF was lower in patients with moderate-severe MR compared to those with no or mild MR. Accordingly, patients with moderate-to-severe MR were more likely to have HF with reduced ejection fraction (HFrEF; LVEF <40%) rather than with mid-range (HFmrEF; LVEF 40-49%) or preserved LVEF (HFpEF; LVEF ≥50%). Moreover, mean LV end-diastolic diameter (LVEDD), LV end-systolic diameter (LVESD), and left atrium diameter were greater in patients with, compared to those without, moderate-severe MR.

Regarding laboratory data, patients with moderate-severe MR had higher values of serum creatinine, urea, and plasma NT-proBNP, and lower estimated glomerular filtration rate compared to those with no or mild MR. Regarding QoL measures, the Kansas City Cardiomyopathy Questionnaire (KCCQ) clinical summary score, KCCQ overall summary score, and EuroQol - 5 Dimension (EQ-5D) Visual Analogue Scale score were lower among patients with moderate-severe MR compared to those with no or mild MR (**Table 2**).

Detailed echocardiographic, laboratory and QoL data in the index cohort and validation cohort are reported in **Supplementary Table 3** and **Supplementary Table 4**, respectively.

**Clinical outcome**

A primary outcome event at 2 years occurred in 697 patients (42.2%) with moderate-severe MR and in 836 patients (35.3%) without moderate-severe MR. Accordingly, the incidence of 2-year primary endpoint was higher in patients with moderate-severe MR compared to those with no moderate-severe MR at Kaplan-Meier analysis (log-rank p<0.0001; **Figure 1**). Both 2-year individual secondary endpoints were higher in patients with moderate-severe MR compared to the others (**Figure 1**): all-cause death (26.3% vs. 22.6%; log-rank p=0.002) and CV death (18.3% vs. 13.7%; log-rank p<0.0001).

Univariable Cox regression analysis confirmed the significant association between moderate-severe MR and the primary endpoint, all-cause death, and CV death. As shown in **Table 3**, the significant impact of moderate-severe MR on the primary endpoint was confirmed also after multivariable adjustment for different models including, respectively, age and sex (model 1); primary ischemic HF aetiology, peripheral oedema, NYHA class, and previous HF hospitalization in last year (model 2); and the BIOSTAT-CHF risk prediction score (model 3). The risk of both individual secondary endpoints remained higher in patients with moderate-severe MR also after multivariable adjustment for model 1 and model 2 (**Table 3**). After adjustment for model 3, moderate-severe MR remained significantly associated with CV death, but not with all-cause death.

At subgroup analyses, the impact of moderate-severe MR on primary endpoint was significant for both patients with and without HF hospitalization in previous year, with and without ischemic HF aetiology, with or without history of atrial fibrillation, and with estimated glomerular filtration rate ≤60 and >60 mL/min/1.73 m2. On the other hand, the impact of moderate-severe MR on primary endpoint was significant only in patients with NYHA class I-II and III, in the two lowest LVEF tertiles (≤30% and 31-39%), in the two largest LVEDD tertiles (56-63 mm and ≥64 mm), and in the highest NT-proBNP tertile (≥3621 pg/mL) (**Figure 2**). Kaplan-Meier curves for the primary endpoint according to LVEF subgroups are reported in **Supplementary Figure 1**, confirming the significant impact of moderate-severe MR in the two lowest LVEF tertiles (≤30% and 31-39%) but not in the highest one (LVEF ≥40%). Furthermore, the significant impact of moderate-severe MR on primary endpoint in the highest NT-proBNP tertile was observed only in patients with history of atrial fibrillation (**Supplementary Table 5**).

**DISCUSSION**

Our study shows that moderate-severe MR is associated with an increased risk of death or HF hospitalizations in patients with worsening chronic HF or new-onset acute HF enrolled in BIOSTAT-CHF. The prognostic impact of moderate-severe MR is additive to a validated risk model including relevant clinical and laboratory features and seems to be more pronounced in patients with HFrEF, larger LV dimensions, higher plasma NT-proBNP, and NYHA class I to III. To the best of our knowledge, this is the largest study available exploring the prognostic impact of MR on clinical outcomes in patients with HF. Our cohort included more than 4,000 well-phenotyped patients with worsening chronic or new-onset acute HF enrolled in a prospective study.

Prevalence of moderate-severe MR was 41%, in line with previous studies reporting rates ranging from 29% to 53% in patients with HF.7–9,22,23 These studies also showed an association between MR and poor prognosis, with a correlation between MR severity and poorer outcomes.4,17,18,21–24,26,28 However, available evidence was mainly derived from relatively small and/or single-centre studies on unselected HF populations including mostly patients with reduced LVEF and stable clinical conditions.17,18,22,23 In contrast, our analysis includes mostly patients with worsening HF and with a wide range of LVEF. Our data may be compared with those of a recent analysis of the Atherosclerosis Risk in Communities (ARIC) study showing a significant impact of moderate or severe MR on 1-year mortality in a community-derived cohort of 3878 patients hospitalized for HF and with echocardiographic data available.20 The prevalence of moderate or severe MR was 44.5% and it was independently associated with increased 1-year mortality (odds ratio, 1.30; 95% CI, 1.16 to 1.45).20 Our study confirms and extends these results to the European population enrolled in BIOSTAT-CHF. The analysis of the ARIC cohort had only 1-year all-cause mortality as endpoint, whereas we were able to confirm the independent value of MR also on the combined endpoint of all-cause death or HF hospitalization and with a 2-year follow-up. In addition, the value of MR was additive compared with a risk prediction model already validated and strongly associated with outcome.32

In subgroup analyses, we noted an association between moderate-severe MR and the primary endpoint only in patients with HFrEF. Accordingly, moderate-severe MR emerged as a predictor of prognosis in patients with dilated left ventricles (LVEDD >56 mm). Similar results were also found in the ARIC analysis where moderate or severe MR was an independent predictor of 1-year mortality only in patients with LVEF <50%.20 These findings may be related to the different mechanisms and pathogenesis of MR in patients with normal or reduced LVEF so that the contribution of MR, as well as that of left ventricular remodelling, is larger in patients with a reduced LVEF.11,29,36,37

Our analysis of a large study group allowed the assessment of the role of MR according to the severity of HF. In our study, the prognostic impact of moderate-severe MR on clinical outcome seemed more evident in patients with NT-proBNP ≥3619 pg/mL and, consistently, in those with reduced LVEF and larger LV volumes. In the study by Goliasch et al., the prognostic impact of severe MR was predominantly observed in a specific phenotype characterized by NYHA class II and III, moderately increased NT-proBNP and LVEF between 30% and 40%.23 This result may reflect different patients’ population. The study by Goliasch et al. included only patients with HFrEF and they were younger than in our study, on optimal medical therapy and with a lower burden of comorbidities. Furthermore, in their subgroup analysis the authors evaluated the impact of severe MR, rather than moderate or severe MR, on a different endpoint (all-cause mortality). Finally, the number of patients included in the subgroups and consequently the number of events were much lower compared to our population, hence potentially impacting statistical power.

Consistent with previous data,22,23 in our study the prognostic impact of MR seemed to be less pronounced in patients with NYHA class IV. These data may be explained by the relatively small number of patients with NYHA class IV in our study. However, Bursi et al. showed that the impact of MR on outcomes was not evident in a subgroup of patients with advanced HF.22 Thus, severe HF symptoms might be a marker of an advanced stage of HF and treating MR in NYHA class IV patients could be futile from a prognostic point of view. Patients in NYHA class IV have been reported to have a poor outcome after percutaneous mitral valve repair.38,39 In a recent analysis from the Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation (COAPT) trial, no differences were observed in the impact of percutaneous MR treatment on outcomes in patients with NYHA class IV compared to the other classes.40 However, patients with non-ambulatory NYHA class IV were excluded from COAPT but included in BIOSTAT-CHF.6,41

**Limitations**

The present study is a *post-hoc* retrospective analysis of a database collected in a large, prospective, multicentre, observational study of patients with worsening chronic or new-onset acute HF. Its main limitations are the lack of a central core-laboratory analysis of echocardiographic images and hence the lack of detailed data regarding MR severity and aetiology. Thus, we could not investigate the influence of these important variables on patients’ outcome. However, a strong, independent, impact of moderate-severe MR on the outcome of patients with worsening chronic or new-onset acute HF was shown by our study, despite its intrinsic limitations, and these data may have a major impact for patients’ assessment and possibly treatment indications. Furthermore, the sample size was relatively small in some subgroups of interest (i.e., HFpEF), thus preventing us from performing detailed sub-analyses in such subgroups.

**CONCLUSIONS**

In patients with worsening chronic or new-onset HF, moderate-severe MR is highly prevalent and has a strong impact on clinical outcome, independently from other relevant variables related with patients’ outcomes and HF severity.

**REFERENCES**

1. Metra M, Teerlink JR. Heart failure. *Lancet* 2017;**390**:1981–1995.

2. Tomasoni D, Adamo M, Lombardi CM, Metra M. Highlights in heart failure. *ESC Hear Fail* 2019;**6**:1105–1127.

3. Crespo-Leiro MG, Anker SD, Maggioni AP, Coats AJ, Filippatos G, Ruschitzka F, Ferrari R, Piepoli MF, Delgado Jimenez JF, Metra M, Fonseca C, Hradec J, Amir O, Logeart D, Dahlström U, Merkely B, Drozdz J, Goncalvesova E, Hassanein M, Chioncel O, Lainscak M, Seferovic PM, Tousoulis D, Kavoliuniene A, Fruhwald F, Fazlibegovic E, Temizhan A, Gatzov P, Erglis A, Laroche C, et al. European Society of Cardiology Heart Failure Long-Term Registry (ESC-HF-LT): 1-year follow-up outcomes and differences across regions. *Eur J Heart Fail* 2016;**18**:613–625.

4. Tavazzi L, Senni M, Metra M, Gorini M, Cacciatore G, Chinaglia A, Lenarda A Di, Mortara A, Oliva F, Maggioni AP. Multicenter Prospective Observational Study on Acute and Chronic Heart Failure. *Circ Hear Fail* 2013;**6**:473–481.

5. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, González-Juanatey JR, Harjola V-P, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GMC, Ruilope LM, Ruschitzka F, Rutten FH, Meer P van der. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J* 2016;**37**:2129–2200.

6. Ferreira JP, Metra M, Mordi I, Gregson J, Maaten JM Ter, Tromp J, Anker SD, Dickstein K, Hillege HL, Ng LL, Veldhuisen DJ van, Lang CC, Voors AA, Zannad F. Heart failure in the outpatient versus inpatient setting: findings from the BIOSTAT-CHF study. *Eur J Heart Fail* 2019;**21**:112–120.

7. Chioncel O, Lainscak M, Seferovic PM, Anker SD, Crespo-Leiro MG, Harjola V-P, Parissis J, Laroche C, Piepoli MF, Fonseca C, Mebazaa A, Lund L, Ambrosio GA, Coats AJ, Ferrari R, Ruschitzka F, Maggioni AP, Filippatos G. Epidemiology and one-year outcomes in patients with chronic heart failure and preserved, mid-range and reduced ejection fraction: an analysis of the ESC Heart Failure Long-Term Registry. *Eur J Heart Fail* 2017;**19**:1574–1585.

8. Chioncel O, Mebazaa A, Harjola V-P, Coats AJ, Piepoli MF, Crespo-Leiro MG, Laroche C, Seferovic PM, Anker SD, Ferrari R, Ruschitzka F, Lopez-Fernandez S, Miani D, Filippatos G, Maggioni AP, ESC Heart Failure Long-Term Registry Investigators. Clinical phenotypes and outcome of patients hospitalized for acute heart failure: the ESC Heart Failure Long-Term Registry. *Eur J Heart Fail* 2017;**19**:1242–1254.

9. Cleland JGF, Swedberg K, Follath F, Komajda M, Cohen-Solal A, Aguilar JC, Dietz R, Gavazzi A, Hobbs R, Korewicki J, Madeira HC, Moiseyev VS, Preda I, Gilst WH van, Widimsky J, Freemantle N, Eastaugh J, Mason J, Study Group on Diagnosis of the Working Group on Heart Failure of the European Society of Cardiology. The EuroHeart Failure survey programme-- a survey on the quality of care among patients with heart failure in Europe. Part 1: patient characteristics and diagnosis. *Eur Heart J* 2003;**24**:442–463.

10. Asgar AW, Mack MJ, Stone GW. Secondary Mitral Regurgitation in Heart Failure. *J Am Coll Cardiol* 2015;**65**:1231–1248.

11. Coats AJS, Anker SD, Baumbach A, Alfieri O, Bardeleben RS von, Bauersachs J, Bax JJ, Boveda S, Čelutkienė J, Cleland JG, Dagres N, Deneke T, Farmakis D, Filippatos G, Hausleiter J, Hindricks G, Jankowska EA, Lainscak M, Leclercq C, Lund LH, McDonagh T, Mehra MR, Metra M, Mewton N, Mueller C, Mullens W, Muneretto C, Obadia J-F, Ponikowski P, Praz F, et al. The management of secondary mitral regurgitation in patients with heart failure: a joint position statement from the Heart Failure Association (HFA), European Association of Cardiovascular Imaging (EACVI), European Heart Rhythm Association (EHRA), and European Association of Percutaneous Cardiovascular Interventions (EAPCI) of the ESC. *Eur Heart J* 2021;**42**:1254–1269.

12. Stone GW, Lindenfeld J, Abraham WT, Kar S, Lim DS, Mishell JM, Whisenant B, Grayburn PA, Rinaldi M, Kapadia SR, Rajagopal V, Sarembock IJ, Brieke A, Marx SO, Cohen DJ, Weissman NJ, Mack MJ, COAPT Investigators. Transcatheter Mitral-Valve Repair in Patients with Heart Failure. *N Engl J Med* 2018;**379**:2307–2318.

13. Obadia J-F, Messika-Zeitoun D, Leurent G, Iung B, Bonnet G, Piriou N, Lefèvre T, Piot C, Rouleau F, Carrié D, Nejjari M, Ohlmann P, Leclercq F, Etienne C Saint, Teiger E, Leroux L, Karam N, Michel N, Gilard M, Donal E, Trochu J-N, Cormier B, Armoiry X, Boutitie F, Maucort-Boulch D, Barnel C, Samson G, Guerin P, Vahanian A, Mewton N, et al. Percutaneous Repair or Medical Treatment for Secondary Mitral Regurgitation. *N Engl J Med* 2018;**379**:2297–2306.

14. Iung B, Armoiry X, Vahanian A, Boutitie F, Mewton N, Trochu J-N, Lefèvre T, Messika-Zeitoun D, Guerin P, Cormier B, Brochet E, Thibault H, Himbert D, Thivolet S, Leurent G, Bonnet G, Donal E, Piriou N, Piot C, Habib G, Rouleau F, Carrié D, Nejjari M, Ohlmann P, Etienne C Saint, Leroux L, Gilard M, Samson G, Rioufol G, Maucort-Boulch D, et al. Percutaneous repair or medical treatment for secondary mitral regurgitation: outcomes at 2 years. *Eur J Heart Fail* 2019;**21**:1619–1627.

15. Senni M, Adamo M, Metra M, Alfieri O, Vahanian A. Treatment of functional mitral regurgitation in chronic heart failure: can we get a ‘proof of concept’ from the MITRA-FR and COAPT trials? *Eur J Heart Fail* 2019;**21**:852–861.

16. Mack MJ, Lindenfeld J, Abraham WT, Kar S, Lim DS, Mishell JM, Whisenant BK, Grayburn PA, Rinaldi MJ, Kapadia SR, Rajagopal V, Sarembock IJ, Brieke A, Rogers JH, Marx SO, Cohen DJ, Weissman NJ, Stone GW, COAPT Investigators. 3-Year Outcomes of Transcatheter Mitral Valve Repair in Patients With Heart Failure. *J Am Coll Cardiol* 2021;**77**:1029–1040.

17. Grigioni F, Enriquez-Sarano M, Zehr KJ, Bailey KR, Tajik AJ. Ischemic mitral regurgitation: long-term outcome and prognostic implications with quantitative Doppler assessment. *Circulation* 2001;**103**:1759–1764.

18. Amigoni M, Meris A, Thune JJ, Mangalat D, Skali H, Bourgoun M, Warnica JW, Barvik S, Arnold JMO, Velazquez EJ, Werf F Van de, Ghali J, McMurray JJ V, Køber L, Pfeffer MA, Solomon SD. Mitral regurgitation in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both: prognostic significance and relation to ventricular size and function. *Eur Heart J* 2007;**28**:326–333.

19. Kubo S, Kawase Y, Hata R, Maruo T, Tada T, Kadota K. Dynamic severe mitral regurgitation on hospital arrival as prognostic predictor in patients hospitalized for acute decompensated heart failure. *Int J Cardiol* 2018;**273**:177–182.

20. Arora S, Sivaraj K, Hendrickson M, Chang PP, Weickert T, Qamar A, Vaduganathan M, Caughey MC, Pandey A, Cavender MA, Rosamond W, Vavalle JP. Prevalence and Prognostic Significance of Mitral Regurgitation in Acute Decompensated Heart Failure: The ARIC Study. *JACC Heart Fail* 2021;**9**:179–189.

21. Rossi A, Dini FL, Faggiano P, Agricola E, Cicoira M, Frattini S, Simioniuc A, Gullace M, Ghio S, Enriquez-Sarano M, Temporelli PL. Independent prognostic value of functional mitral regurgitation in patients with heart failure. A quantitative analysis of 1256 patients with ischaemic and non-ischaemic dilated cardiomyopathy. *Heart* 2011;**97**:1675–1680.

22. Bursi F, Barbieri A, Grigioni F, Reggianini L, Zanasi V, Leuzzi C, Ricci C, Piovaccari G, Branzi A, Modena MG. Prognostic implications of functional mitral regurgitation according to the severity of the underlying chronic heart failure: a long-term outcome study. *Eur J Heart Fail* 2010;**12**:382–388.

23. Goliasch G, Bartko PE, Pavo N, Neuhold S, Wurm R, Mascherbauer J, Lang IM, Strunk G, Hülsmann M. Refining the prognostic impact of functional mitral regurgitation in chronic heart failure. *Eur Heart J* 2018;**39**:39–46.

24. Pecini R, Thune JJ, Torp-Pedersen C, Hassager C, Køber L. The relationship between mitral regurgitation and ejection fraction as predictors for the prognosis of patients with heart failure. *Eur J Heart Fail* 2011;**13**:1121–1125.

25. Trichon BH, Felker GM, Shaw LK, Cabell CH, O’Connor CM. Relation of frequency and severity of mitral regurgitation to survival among patients with left ventricular systolic dysfunction and heart failure. *Am J Cardiol* 2003;**91**:538–543.

26. la Espriella R De, Santas E, Miñana G, Bodí V, Valero E, Payá R, Núñez E, Payá A, Chorro FJ, Bayés-Genis A, Sanchis J, Núñez J. Functional Mitral Regurgitation Predicts Short-Term Adverse Events in Patients With Acute Heart Failure and Reduced Left Ventricular Ejection Fraction. *Am J Cardiol* 2017;**120**:1344–1348.

27. Wada Y, Ohara T, Funada A, Hasegawa T, Sugano Y, Kanzaki H, Yokoyama H, Yasuda S, Ogawa H, Anzai T. Prognostic Impact of Functional Mitral Regurgitation in Patients Admitted With Acute Decompensated Heart Failure. *Circ J* 2016;**80**:139–147.

28. Kajimoto K, Minami Y, Otsubo S, Sato N, investigators of the Acute Decompensated Heart Failure Syndromes (ATTEND) registry. Ischemic or Nonischemic Functional Mitral Regurgitation and Outcomes in Patients With Acute Decompensated Heart Failure With Preserved or Reduced Ejection Fraction. *Am J Cardiol* 2017;**120**:809–816.

29. Tamargo M, Obokata M, Reddy YN V, Pislaru S V, Lin G, Egbe AC, Nishimura RA, Borlaug BA. Functional mitral regurgitation and left atrial myopathy in heart failure with preserved ejection fraction. *Eur J Heart Fail* 2020;**22**:489–498.

30. Dziadzko V, Clavel M-A, Dziadzko M, Medina-Inojosa JR, Michelena H, Maalouf J, Nkomo V, Thapa P, Enriquez-Sarano M. Outcome and undertreatment of mitral regurgitation: a community cohort study. *Lancet* 2018;**391**:960–969.

31. Voors AA, Anker SD, Cleland JG, Dickstein K, Filippatos G, Harst P van der, Hillege HL, Lang CC, Maaten JM ter, Ng L, Ponikowski P, Samani NJ, Veldhuisen DJ van, Zannad F, Zwinderman AH, Metra M. A systems BIOlogy Study to TAilored Treatment in Chronic Heart Failure: rationale, design, and baseline characteristics of BIOSTAT-CHF. *Eur J Heart Fail* 2016;**18**:716–726.

32. Voors AA, Ouwerkerk W, Zannad F, Veldhuisen DJ van, Samani NJ, Ponikowski P, Ng LL, Metra M, Maaten JM ter, Lang CC, Hillege HL, Harst P van der, Filippatos G, Dickstein K, Cleland JG, Anker SD, Zwinderman AH. Development and validation of multivariable models to predict mortality and hospitalization in patients with heart failure. *Eur J Heart Fail* 2017;**19**:627–634.

33. Ouwerkerk W, Voors AA, Anker SD, Cleland JG, Dickstein K, Filippatos G, Harst P van der, Hillege HL, Lang CC, Maaten JM ter, Ng LL, Ponikowski P, Samani N., Veldhuisen DJ van, Zannad F, Metra M, Zwinderman AH. Determinants and clinical outcome of uptitration of ACE-inhibitors and beta-blockers in patients with heart failure: a prospective European study. *Eur Heart J* 2017;**38**:1883–1890.

34. Lancellotti P, Tribouilloy C, Hagendorff A, Popescu BA, Edvardsen T, Pierard LA, Badano L, Zamorano JL, Scientific Document Committee of the European Association of Cardiovascular Imaging. Recommendations for the echocardiographic assessment of native valvular regurgitation: an executive summary from the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 2013;**14**:611–644.

35. Nauta JF, Hummel YM, Tromp J, Ouwerkerk W, Meer P van der, Jin X, Lam CSP, Bax JJ, Metra M, Samani NJ, Ponikowski P, Dickstein K, Anker SD, Lang CC, Ng LL, Zannad F, Filippatos GS, Veldhuisen DJ van, Melle JP van, Voors AA. Concentric vs. eccentric remodelling in heart failure with reduced ejection fraction: clinical characteristics, pathophysiology and response to treatment. *Eur J Heart Fail* 2020;**22**:1147–1155.

36. Meta-analysis Global Group in Chronic Heart Failure (MAGGIC). The survival of patients with heart failure with preserved or reduced left ventricular ejection fraction: an individual patient data meta-analysis. *Eur Heart J* 2012;**33**:1750–1757.

37. Guazzi M, Ghio S, Adir Y. Pulmonary Hypertension in HFpEF and HFrEF. *J Am Coll Cardiol* 2020;**76**:1102–1111.

38. Capodanno D, Adamo M, Barbanti M, Giannini C, Laudisa ML, Cannata S, Curello S, Immè S, Maffeo D, Bedogni F, Petronio AS, Ettori F, Tamburino C, Grasso C, GRASP-IT Investigators. Predictors of clinical outcomes after edge-to-edge percutaneous mitral valve repair. *Am Heart J* 2015;**170**:187–195.

39. Puls M, Lubos E, Boekstegers P, Bardeleben RS von, Ouarrak T, Butter C, Zuern CS, Bekeredjian R, Sievert H, Nickenig G, Eggebrecht H, Senges J, Schillinger W. One-year outcomes and predictors of mortality after MitraClip therapy in contemporary clinical practice: results from the German transcatheter mitral valve interventions registry. *Eur Heart J* 2016;**37**:703–712.

40. Giustino G, Lindenfeld J, Abraham WT, Kar S, Lim DS, Grayburn PA, Kapadia SR, Cohen DJ, Kotinkaduwa LN, Weissman NJ, Mack MJ, Stone GW. NYHA Functional Classification and Outcomes After Transcatheter Mitral Valve Repair in Heart Failure: The COAPT Trial. *JACC Cardiovasc Interv* 2020;**13**:2317–2328.

41. Davison BA, Senger S, Sama IE, Koch GG, Mebazaa A, Dickstein K, Samani NJ, Metra M, Anker SD, Cleland JG, Ng LL, Mordi IR, Zannad F, Filippatos GS, Hillege HL, Ponikowski P, Veldhuisen DJ van, Lang CC, Meer P van der, Núñez J, Bayés-Genís A, Edwards C, Voors AA, Cotter G. Is acute heart failure a distinctive disorder? An analysis from BIOSTAT-CHF. *Eur J Heart Fail* 2021;**23**:43–57.

**FIGURE LEGENDS**

**Figure 1: Kaplan-Meier curves for clinical outcomes in patients with versus without moderate-severe MR.**

The figure shows Kaplan-Meier curves for 2-year all-cause mortality (upper left panel), CV mortality (lower left panel), and the combined endpoint of all-cause mortality or HF hospitalization (upper right panel) in patients with vs. without moderate-severe MR.

CV = cardiovascular; HF = heart failure; MR = mitral regurgitation.

**Figure 2: Impact of moderate-severe MR on 2-year primary endpoint in subgroups of interest.**

The figure shows the impact of moderate-severe MR on 2-year all-cause mortality or HF hospitalization at 2 years according to relevant subgroups. Such impact was evaluated by means of multivariable Cox regression adjusted for age and sex, and results are presented as adjusted HR and 95% CI.

CI = confidence interval; eGFR = estimated glomerular filtration rate; HF = heart failure; HR = hazard ratio; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; MR = mitral regurgitation; NYHA = New York Heart Association; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

**Table 1 – Baseline clinical characteristics.**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Overall**  **(n=4023)** | **Moderate or Severe MR**  **(n=1653)** | **No or Mild MR**  **(n=2370)** | ***p*-value** |
| Age (years) | 70.8 ± 11.7 | 70.6 ± 11.8 | 71.0 ± 11.6 | 0.279 |
| Men | 2843 (70.7) | 1139 (68.9) | 1704 (71.9) | **0.040** |
| BMI (kg/m2) | 28.3 ± 5.9 | 27.4 ± 5.5 | 28.9 ± 6.1 | **<0.001** |
| HF hospitalization in last year | 1184 (29.6) | 528 (32.1) | 656 (27.9) | **0.004** |
| Primary ischemic HF aetiology | 2125 (61.2) | 822 (56.1) | 1303 (64.8) | **<0.001** |
| Smoking |  |  |  | 0.849 |
| Past | 1705 (42.5) | 698 (42.4) | 1007 (42.6) |  |
| Current | 561 (14.0) | 225 (13.7) | 336 (14.2) |  |
| Medical history |  |  |  |  |
| Hypertension | 2438 (60.7) | 974 (59.1) | 1464 (61.8) | 0.081 |
| Diabetes mellitus | 1301 (32.4) | 501 (30.3) | 800 (33.4) | **0.019** |
| Atrial fibrillation | 1810 (45.1) | 799 (48.5) | 1011 (42.8) | **<0.001** |
| Myocardial infarction | 1711 (42.6) | 651 (39.4) | 1060 (44.8) | **0.001** |
| PCI | 809 (20.2) | 298 (18.1) | 511 (21.7) | **0.005** |
| CABG | 704 (17.5) | 278 (16.8) | 426 (18.0) | 0.339 |
| Prior valvular surgery | 272 (6.8) | 92 (5.6) | 180 (7.6) | **0.012** |
| Peripheral artery disease | 609 (15.3) | 218 (13.3) | 391 (16.7) | **0.003** |
| COPD | 716 (17.9) | 270 (16.4) | 446 (18.9) | **0.044** |
| Stroke | 520 (13.0) | 195 (11.8) | 325 (13.8) | 0.073 |
| Current malignancy | 163 (4.1) | 60 (3.6) | 103 (4.4) | 0.257 |
| CKD | 1390 (34.8) | 610 (37.0) | 780 (33.2) | **0.012** |
| Device therapy |  |  |  | **0.001** |
| Pacemaker | 280 (7.0) | 112 (6.8) | 168 (7.1) |  |
| ICD | 248 (6.2) | 121 (7.3) | 127 (5.4) |  |
| CRT-P | 66 (1.6) | 33 (2.0) | 33 (1.4) |  |
| CRT-D | 202 (5.0) | 104 (6.3) | 98 (4.1) |  |
| NYHA functional class |  |  |  | **0.014** |
| I | 70 (1.8) | 25 (1.5) | 45 (1.9) |  |
| II | 1511 (38.2) | 578 (35.5) | 933 (40.1) |  |
| III | 1880 (47.5) | 805 (49.4) | 1075 (46.2) |  |
| IV | 498 (12.6) | 222 (13.6) | 276 (11.9) |  |
| Clinical profile |  |  |  |  |
| Peripheral oedema | 1022 (29.6) | 438 (30.7) | 584 (28.8) | 0.209 |
| Hepatomegaly | 397 (10.2) | 210 (13.1) | 187 (8.2) | **<0.001** |
| SBP (mmHg) | 125 ± 22 | 123 ± 21 | 127 ± 22 | **<0.001** |
| DBP (mmHg) | 73 ± 14 | 73 ± 13 | 72 ± 14 | 0.120 |
| HR (bpm) | 78 ± 19 | 79 ± 19 | 77 ± 18 | **<0.001** |
| Type of visit |  |  |  | 0.124 |
| Inpatient hospitalization | 2462 (61.2) | 1035 (62.6) | 1427 (60.2) |  |
| Outpatient clinic | 1561 (38.8) | 618 (37.4) | 943 (39.8) |  |
| HF therapy |  |  |  |  |
| ACEi/ARB use | 2884 (71.8) | 1171 (71.0) | 1713 (72.4) | 0.347 |
| β-blocker use | 3172 (79.0) | 1329 (80.6) | 1843 (77.9) | **0.037** |
| MRA use | 1803 (44.9) | 838 (50.8) | 965 (40.8) | **<0.001** |
| Loop diuretic use | 3988 (99.3) | 1642 (99.6) | 2346 (99.1) | 0.083 |
| Digoxin use | 764 (19.0) | 375 (22.7) | 389 (16.4) | **<0.001** |
|  |  |  |  |  |

Data are presented as n (%) and mean ± standard deviation.

ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BMI = body mass index; CABG = coronary artery bypass graft; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; CRT-D = cardiac resynchronization therapy with defibrillator; CRT-P = cardiac resynchronization therapy with pacemaker; DBP = diastolic blood pressure; HF = heart failure; HR = heart rate; ICD = implantable cardioverter-defibrillator; JVP = jugular venous pressure; MR = mitral regurgitation; MRA = mineralocorticoid receptor antagonist; NYHA = New York Heart Association; PCI = percutaneous coronary intervention; SBP = systolic blood pressure.

**Table 2 – Baseline** **echocardiographic data, laboratory characteristics, and QoL measures.**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Overall**  **(n=4023)** | **Moderate or Severe MR**  **(n=1653)** | **No or Mild MR**  **(n=2370)** | ***p*-value** |
| ***Echocardiographic data*** |  |  |  |  |
| LVEF (%) | 35 (25-42) | 30 (25-38) | 35 (30-45) | **<0.001** |
| LVEF categories |  |  |  | **<0.001** |
| HFrEF (LVEF <40%) | 2514 (66.7) | 1215 (77.5) | 1299 (59.0) |  |
| HFmrEF (LVEF 40-49%) | 679 (18.0) | 220 (14.0) | 459 (20.8) |  |
| HFpEF (LVEF ≥50%) | 577 (15.3) | 132 (8.4) | 445 (20.2) |  |
| LV remodeling |  |  |  | **<0.001** |
| Normal geometry | 440 (18.5) | 175 (15.8) | 265 (20.8) |  |
| Concentric remodeling | 143 (6.0) | 36 (3.3) | 107 (8.4) |  |
| Concentric hypertrophy | 509 (21.4) | 186 (16.8) | 323 (25.3) |  |
| Eccentric hypertrophy | 1290 (54.2) | 708 (64.1) | 582 (45.6) |  |
| LVEDD (mm) | 59 (52-65) | 62 (56-68) | 57 (50-63) | **<0.001** |
| LVESD (mm) | 49 (41-56) | 52 (44-58) | 46 (39-54) | **<0.001** |
| Left atrium diameter (mm) | 46 (42-51) | 48 (44-53) | 45 (40-50) | **<0.001** |
| ***Laboratory data*** |  |  |  |  |
| Haemoglobin (g/dL) | 13.3 (11.9-14.5) | 13.2 (11.9-14.4) | 13.3 (11.9-14.6) | 0.202 |
| Creatinine (µmol/L) | 100 (82-128) | 104 (83-133) | 98 (81-125) | **<0.001** |
| eGFR CKD-EPI (mL/min/1.73 m2) | 60 (44-78) | 57 (42-76) | 61 (45-79) | **<0.001** |
| Urea (mmol/L) | 9.6 (7.0-15.1) | 10.7 (7.5-17.1) | 9.2 (6.8-13.8) | **<0.001** |
| Sodium (mmol/L) | 139 (137-141) | 139 (137-142) | 139 (137-141) | 0.606 |
| NT-proBNP (ng/L) | 2080 (824-4868) | 2847 (1211-6100) | 1632 (590-4025) | **<0.001** |
| ***QoL measures*** |  |  |  |  |
| KCCQ clinical summary score | 48 (30-69) | 45 (27-65) | 49 (31-70) | **<0.001** |
| KCCQ overall summary score | 48 (32-67) | 46 (31-65) | 49 (33-68) | **<0.001** |
| EQ-5D index value | 0.72 (0.57-0.84) | 0.72 (0.57-0.84) | 0.74 (0.57-0.84) | 0.168 |
| EQ-5D VAS | 55 (45-70) | 52 (40-70) | 59 (45-70) | **0.003** |
|  |  |  |  |  |

Data are presented as n (%) and median (Q25-Q75).

CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; eGFR = estimated glomerular filtration rate; EQ-5D = EuroQol - 5 Dimension; HFmrEF = heart failure with mid-range ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; KCCQ = Kansas City Cardiomyopathy Questionnaire; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; LVESD = left ventricular end-systolic diameter; MR = mitral regurgitation; NT-proBNP = N-terminal pro-B-type natriuretic peptide; QoL = quality-of-life; VAS = Visual Analogue Scale.

**Table 3 – Cox regression models for the impact of moderate-severe MR on 2-year combined endpoint (all-cause death or HF hospitalization), all-cause death and CV death.**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **Combined endpoint** | | **All-cause death** | | **CV death** | |
|  | **HR (95% CI)** | ***p*-value** | **HR (95% CI)** | ***p*-value** | **HR (95% CI)** | ***p*-value** |
| Univariable analysis | 1.28 (1.16-1.41) | **<0.001** | 1.22 (1.08-1.39) | **0.002** | 1.40 (1.19-1.63) | **<0.001** |
|  |  |  |  |  |  |  |
| Multivariable model 1 (adjusted for age and sex) | 1.30 (1.18-1.44) | **<0.001** | 1.25 (1.10-1.42) | **<0.001** | 1.43 (1.22-1.67) | **<0.001** |
|  |  |  |  |  |  |  |
| Multivariable model 2 (adjusted for primary ischemic HF aetiology, peripheral oedema, NYHA class, and previous HF hospitalization in last year) | 1.23 (1.09-1.38) | **<0.001** | 1.19 (1.03-1.38) | **0.017** | 1.40 (1.17-1.67) | **<0.001** |
|  |  |  |  |  |  |  |
| Multivariable model 3 (adjusted for BIOSTAT-CHF risk prediction models)\* | 1.11 (1.00-1.23) | **0.041** | 1.08 (0.95-1.22) | 0.249 | 1.22 (1.04-1.43) | **0.014** |
|  |  |  |  |  |  |  |

Data are presented as HR and 95% CI.

\*In multivariable model 3, moderate-to-severe MR was adjusted for the BIOSTAT-CHF risk prediction models, including the following covariates: age, HF hospitalization in last year, systolic blood pressure, peripheral oedema, log-NT-proBNP, haemoglobin, sodium, high-density lipoprotein, and use of β-blockers at baseline for the combined endpoint; age, log-urea, log-NT-proBNP, haemoglobin, and use of β-blockers at baseline for all-cause death and CV death; age, HF hospitalization in last year, systolic blood pressure, peripheral oedema, and estimated glomerular filtration rate for HF hospitalization.

CI = confidence interval; CV = cardiovascular; HF = heart failure; HR = hazard ratio; MR = mitral regurgitation; NYHA = New York Heart Association; NT-proBNP = N-terminal pro-B-type natriuretic peptide.



