

# Impact of mitral regurgitation on cardiovascular hospitalization and death in newly diagnosed heart failure patients

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## Abstract

**Aims** Heart failure (HF) carries a poor prognosis, and the impact of concomitant mitral regurgitation (MR) is not well understood. This analysis aimed to estimate the incremental effect of MR in patients newly diagnosed with HF.

**Methods and results** Data from the IBM® MarketScan® Research Databases were analysed. Included patients had at least one inpatient or two outpatient HF claims. A 6 month post-period after HF index was used to capture MR diagnosis and severity. HF patients were separated into three cohorts: without MR (no MR), not clinically significant MR (nsMR), and significant MR (sMR). Time-to-event analyses were modelled to estimate the clinical burden of disease. The primary outcome was a composite endpoint of death or cardiovascular (CV)-related admission. Secondary outcomes were death and CV hospitalization alone. All models controlled for baseline demographics and co-morbidities. Patients with sMR were at significantly higher risk of either death or CV admission compared with patients with no MR [hazard ratio (HR) 1.26; 95% confidence interval (CI) 1.15–1.39]. When evaluating death alone, patients with sMR had significantly higher risk of death (HR 1.24; 95% CI 1.08–1.43) compared with patients with no MR. When evaluating CV admission alone, patients with MR were at higher risk of hospital admission vs. patients with no MR, and the magnitude was dependent upon the MR severity: sMR (HR 1.55; 95% CI 1.38–1.74) and nsMR (HR 1.23; 95% CI 1.08–1.40).

**Conclusions** Evidence of MR in retrospective claims significantly increases the clinical burden of incident HF patients. Time to death and CV hospitalizations are increased when MR is clinically significant.

**Keywords** Hospitalization; Mortality; Heart failure; Mitral regurgitation

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## Introduction

Between 2011 and 2014, the prevalence of heart failure (HF) among adults in the USA was estimated to be 6.5 million.<sup>1</sup> The current estimate of newly diagnosed, or incident, HF is nearly 1 million new cases per annum, contributing to a growing prevalence of HF among the aging US population.<sup>1,2</sup> HF carries a poor prognosis, and recent research has focused on the effect of concomitant mitral regurgitation (MR) as an unfavourable factor for patients with HF.<sup>3–9</sup> However, the impact of MR severity on key clinical

outcomes associated with HF has not been fully elucidated.<sup>10,11</sup>

A study of patients with advanced HF and MR ( $n = 558$ ) and severity ranging from non-significant [trace-to-mild MR ( $n = 276$ , 49%)] to significant [moderate-to-severe MR (moderate:  $n = 258$ , 46%; severe:  $n = 24$ , 4.3%)] found an association between clinically significant MR and higher mortality ( $P = 0.03$ ). However, when patient demographics and co-morbidities were considered, MR severity was not a significant, independent factor in predicting mortality.<sup>10</sup> Another study of similar size reported MR was strongly associated with death or heart

transplantation even after adjustments for demographic and co-morbid factors ( $P = 0.0003$ ).<sup>11</sup> However, sub-analyses indicated the association only remained true in patients that were New York Heart Association class I–II. These findings suggest that MR was predictive in lower-risk patients with HF, but not predictive of outcomes in higher-risk HF patients.

Inconsistent methods used to identify and quantify MR have been identified as a potential source of variability among studies that evaluated the impact of MR severity on clinical outcomes associated with HF. A recent meta-analysis (53 studies, 45 900 patients) found that the methods of qualifying MR (qualitative vs. quantitative) produced different magnitudes of association with all-cause mortality.<sup>7</sup> A review of sub-analyses of MR severity assessed by qualitative diagnostic methods with categories of mild, moderate-to-severe, and severe MR showed that the degree of MR had significant effects, with mortality increasing commensurately in a graded fashion with MR severity. Among studies with longer follow-up, the association of MR and all-cause mortality was attenuated, suggesting that progressive HF would lead to mortality regardless of MR status. The current study used a large population of patients with HF and focused on patients at the time of their initial HF diagnosis to build on previous results (AJC article under review). These data in aggregate suggest that worsening MR is a component of worsening chronic HF. Yet there are signals that MR itself may contribute to the downward spiral of HF, leading to death.

The objective of this analysis was to estimate the incremental effect of MR in patients newly diagnosed with HF. This analysis focused on incident HF diagnoses in a very large insurance database. The patients were categorized by MR status, which was used as a surrogate for HF severity at the time of diagnosis. Time-to-event analysis was conducted to understand the impact of MR on the key HF outcomes of hospitalization and death.

## Methods

Data from the IBM® MarketScan® Research Databases ranging from 1 October 2011 through 30 September 2016 were used in this analysis. The databases include records from more than 170 million unique patients since 1995, providing access to a fully integrated, deidentified, individual-level health care claims data. This includes complete payment records (insurance and patient payments), specialty pharmacy, and mail-order records for individuals covered by a variety of health plans located throughout the USA. Data from individual patients are integrated from all providers of care, maintaining all health care utilization and cost-record connections at the patient level. Data are nationally representative and include information from 300 employers and 25 health plans, representing 350 unique carriers.<sup>12</sup>

## Inclusion criteria

Patients were required to have 12 months of enrolment (medical and pharmacy) in the database before their index HF diagnosis (Supporting Information, *Appendix A1*). In addition to the 12 month pre-index diagnosis period, 6 months of enrolment was required post-diagnosis (landmark period) to categorize patients with MR to assign aetiology and severity. Patients were excluded if any of the following conditions were met: aged less than 18 years at index HF diagnosis, history of end-stage renal disease (Supporting Information, *Appendix A2*) at any time in the database, or record of hospice or palliative care in the 12 months pre-diagnosis or post-diagnosis. Because the focus of this analysis was on newly diagnosed patients with functional HF, patients with a diagnosis of MR before their diagnosis of HF were excluded. Other exclusions included patients with a record of degenerative MR disease (Supporting Information, *Appendix A2*), chordal rupture, rheumatic mitral insufficiency, mitral stenosis, rheumatic tricuspid insufficiency, history of left ventricular assist device, cardiac transplantation, or any diagnosis of MR after the landmark period. This investigation conforms with the principles outlined in the *Declaration of Helsinki*<sup>13</sup>; and, because all data for this analysis were deidentified and accessed in compliance with the Health Insurance Portability and Accountability Act, our study was exempt from institutional review board review under 45 CFR 46.101(b).<sup>4</sup>

## Cohort definitions

Patients with HF meeting all the inclusion and exclusion criteria defined earlier were assigned to one of the following three cohorts based on MR status: (i) no MR, (ii) not clinically significant MR (nsMR), and (iii) clinically significant MR (sMR). Patients with a diagnosis of HF and no indication of MR at any time in the database were part of the no MR cohort. Patients with a diagnosis of MR (Supporting Information, *Appendix A3*), either at the time of HF diagnosis or in the 6 month landmark period following their HF diagnosis, were flagged as having MR and further subdivided by whether their MR was considered clinically significant. Clinically significant MR (sMR) was defined by the following events: (i) diagnosis of atrial fibrillation or diagnosis of pulmonary hypertension during the baseline or landmark period or (ii) a record of MR surgery during the landmark period. See Supporting Information, *Appendix A4* for coding detail.

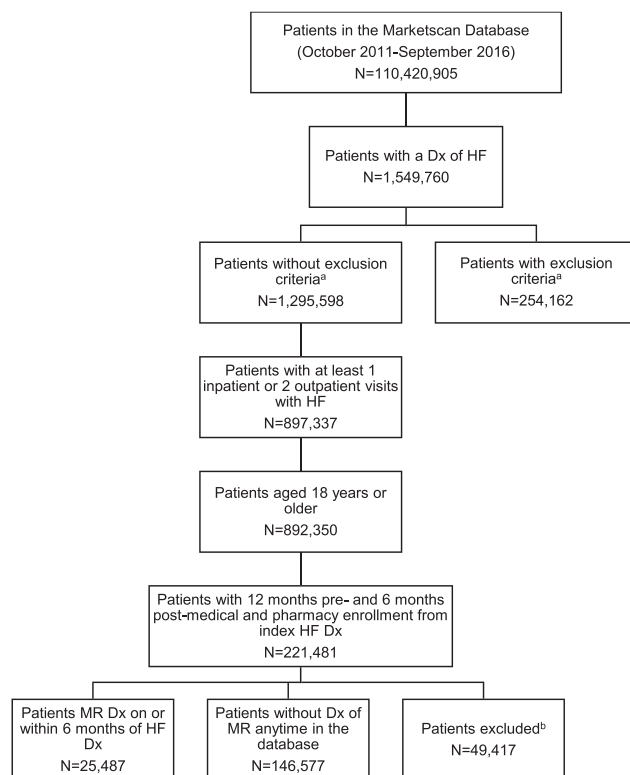
## Statistical analysis

The primary outcome for this analysis was a composite end-point of death or cardiovascular (CV)-related inpatient hospitalization. Each variable that comprised the composite

endpoint was analysed separately. CV-related inpatient hospitalization was characterized by a hospitalization where the primary diagnosis on admissions claim fell under the category of 'total cardiovascular disease' per ICD10 codes I00-99. This definition is recommended by the American Heart Association<sup>1</sup> and includes the following ICD10 coding categories [Acute rheumatic fever (I00-02); Chronic rheumatic heart disease (I05-09); Hypertensive diseases (I10-16), Ischaemic heart diseases (I20-25), Pulmonary heart disease and disease of pulmonary circulation (I26-28), Other forms of heart disease (I30-52), Cerebrovascular diseases (I60-69), Diseases of arteries, arterioles and capillaries (I70-79), Diseases of veins, lymphatic vessels and lymph nodes, not otherwise classified (I80-89), and Other and unspecified disorders of the circulatory system (I95-99)].

Patient demographics (age, sex, region, and insurance type) and co-morbidities, as measured by the Elixhauser Comorbidity Index (ECI),<sup>14</sup> were summarized by cohort. The ECI is a validated set of 31 categories of co-morbidities that are associated with mortality and identified using ICD9/10 diagnosis codes (Supporting Information, *Appendix A5*) that

**Figure 1** Attrition diagram. <sup>a</sup>Exclusion criteria are as follows: patients with a left ventricular assist device, heart transplant, or Dx of chordal rupture, mitral stenosis, rheumatic mitral insufficiency, rheumatic tricuspid insufficiency, hospice restriction, or end-stage renal disease. <sup>b</sup>Patients were excluded because their Dx of MR was either before their HF Dx or outside the 6 month landmark period. Dx, diagnosis; HF, heart failure; MR, mitral regurgitation.



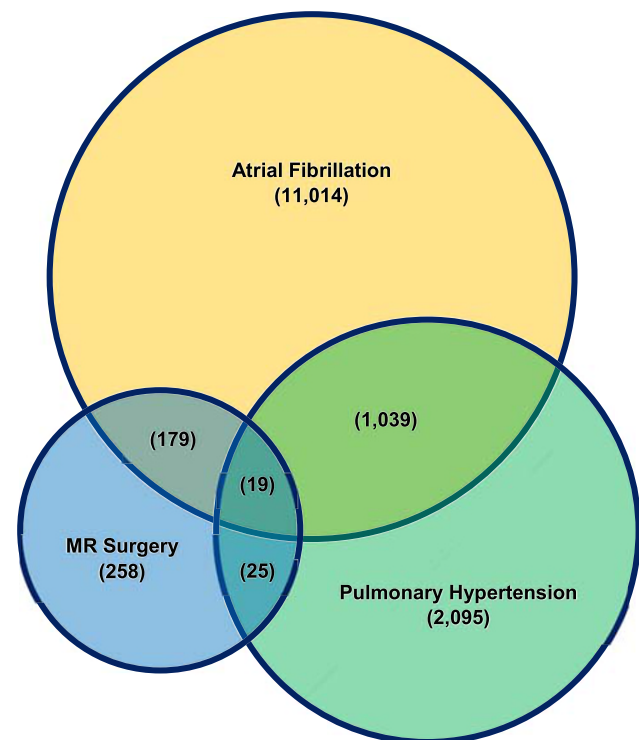
appeared in the 12 month baseline period before their index diagnosis of HF. The co-morbidity frequencies are reported along with a number summary of the composite ECI score (representing the number of the 31 co-morbid conditions). Ischaemic heart disease status (yes or no) was another co-morbidity that was examined in this analysis (Supporting Information, *Appendix A6*).

Survival analyses were conducted using Cox hazards models to estimate the risk of a CV-related admission, death, and combined outcome of CV-related admission or death for patients with incident HF and MR in the 12 months following the landmark period. The time-to-event models included patient demographics, ECI score, and ischaemic heart disease as confounding variables. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated as measures of strength of association and precision, respectively. All statistical analyses in this study were performed using SAS software, version 9.4 (SAS Institute Inc., Cary, NC, USA).

## Results

Overall, patients with MR were at a higher risk of CV hospital admission or death, compared with patients with no MR, and

**Figure 2** Venn diagram defining significant mitral regurgitation (MR). Adjusted survival curves for the composite and each of its components (cardiovascular-related admission or death) are shown for patients with heart failure and varying levels of MR severity.



the magnitude of the effect was dependent upon the severity of MR. Three cohorts of patients with incident HF were established following the inclusion and exclusion criteria described earlier (Figure 1). Filtering for presence of HF, age greater than 18, and an absence of degenerative MR, end-stage renal disease, heart transplantation, or hospice care reduced the sample to 892 350 patients. The final data set of 221 481 (25%) patients came from further examining the aforementioned data set for a 12 month enrolment before and 6 months following an index HF diagnosis. Three cohorts were created from this set based on MR severity. Patients with HF and no MR formed the largest cohort with 66% of the eligible set (HF, no MR:  $n = 146\ 577$ ). Patients with evidence of MR within 6 months of HF index ( $n = 25\ 487$ ) were separated into two cohorts based on the clinical significance of MR: (i) sMR,  $n = 12\ 143$ , and (ii) nsMR,  $n = 13\ 344$ . Almost all patients (12 070, 99%) with sMR were classified as having clinically significant disease due to a diagnosis of pulmonary hypertension or atrial fibrillation. Figure 2 displays a Venn diagram demonstrating the intersections of the following three criteria used to define sMR: (i) atrial fibrillation, (ii) pulmonary hypertension, and (iii) MR surgery.

The sMR cohort had the highest mean age [73.83, standard deviation (SD) 12.91 years] compared with the no MR (69.8, SD 14.9 years) and nsMR cohorts (67.31, SD 15.15 years). The distribution of insurance type revealed a higher

percentage of Medicare Supplemental insurance in the sMR cohort compared with the other two cohorts, possibly a result of an older mean age (Table 1). The cohorts had similar regional and sex distributions. The mean ECI scores also varied by cohort, with the sMR cohort having the highest mean ECI score ( $5.5 \pm 2.19$ ), followed by no MR ( $4.9 \pm 2.21$ ) and nsMR ( $4.8 \pm 2.14$ ). Within the ECI score, multiple components were higher within the sMR cohort, including arrhythmias and pulmonary disorders (Supporting Information, Appendix A7). Rates of ischaemic heart disease were higher in the sMR cohort (46.4%), followed by the nsMR cohort (44.5%) and the no MR cohort (42.0%).

Figure 3A–3C displays the adjusted survival curves for the composite and each of its components (CV-related admission or death). For all outcomes, estimated event rates were very low, and there were a high percentage of patients at 12 months who did not have the outcomes of interest. Given that these are patients with newly diagnosed, or incident, HF, these data are consistent with expectation.

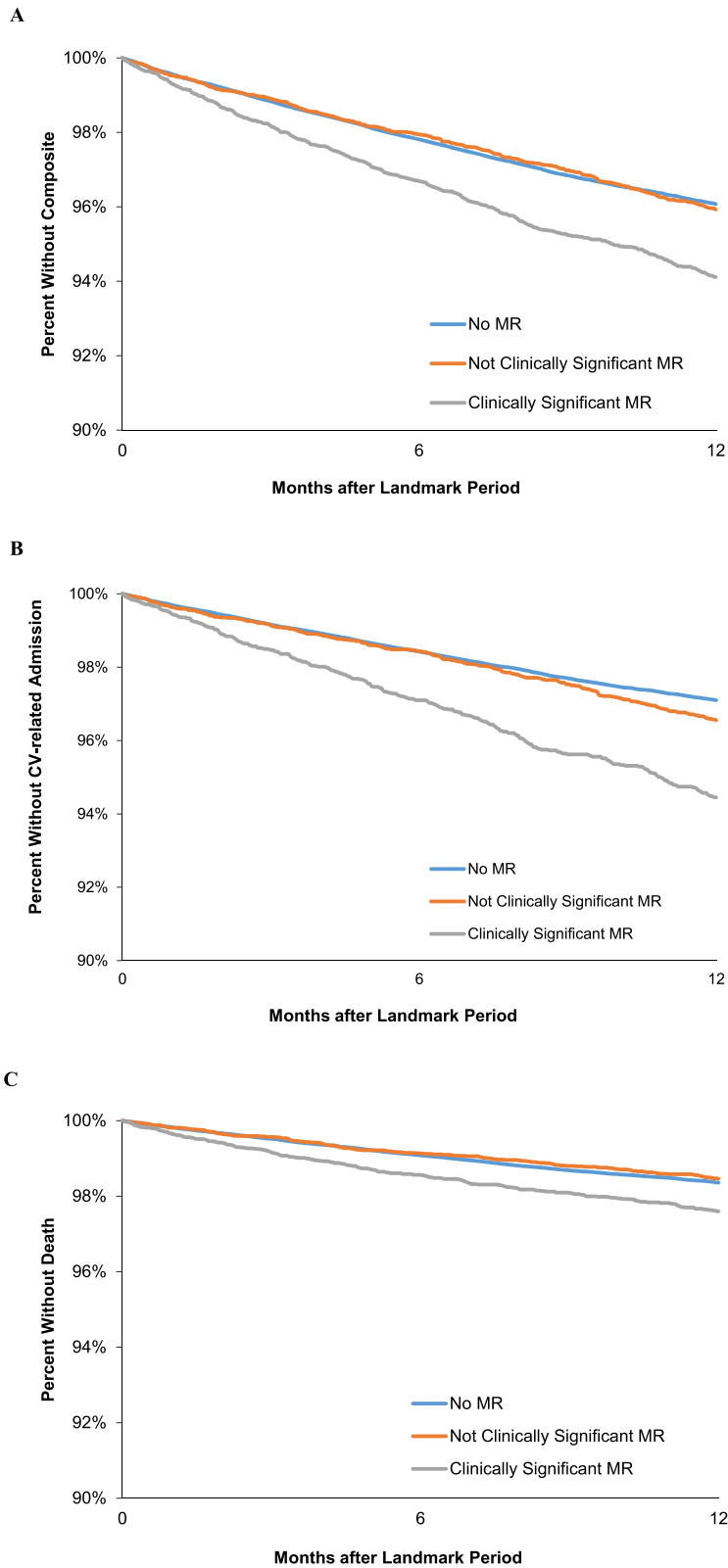
Hazard ratios, CIs, and corresponding *P*-values were estimated for each outcome of interest and are shown in Table 2. In each of the time-to-event models displayed in Table 2, covariates of age, sex, region, insurance type, and ischaemic heart disease status were controlled for in the comparisons of sMR and nsMR to the reference group of no MR. Survival analysis found that patients with MR were at a higher risk of a

**Table 1** Patient characteristics by mitral regurgitation severity cohorts

	No MR		nsMR		sMR	
	<i>N</i>	%	<i>N</i>	%	<i>N</i>	%
Total <i>N</i>	146 577	100.0	13 344	100.0	12 143	100.0
Age (years) of first HF date						
Mean	69.78		67.31		73.83	
Standard deviation	14.86		15.15		12.91	
Sex						
Male	76 365	52.1	6445	48.3	6525	53.7
Female	70 212	47.9	6899	51.7	5618	46.3
Region						
Northeast Region	29 132	19.9	2685	20.1	2728	22.5
North Central Region	46 702	31.9	4099	30.7	4078	33.6
South Region	50 160	34.2	5082	38.1	3929	32.4
West Region	19 770	13.5	1378	10.3	1345	11.1
Unknown region	813	0.6	100	0.8	63	0.5
Insurance						
Commercial	55 211	37.7	5850	43.8	3120	25.7
Medicare Supplemental	91 366	62.3	7494	56.2	9023	74.3
Cardiac history						
Ischaemic cardiomyopathy	61 591	42.0	5944	44.5	5634	46.4
CAD	55 488	37.9	5016	37.6	4906	40.4
AMI	22 259	15.2	2806	21.0	2165	17.8
PCI	7656	5.2	1130	8.5	605	5.0
CABG	3562	2.4	498	3.7	462	3.8
ICD/PPM	14 493	9.9	863	6.5	1697	14.0
Elixhauser Comorbidity Index						
Mean	4.91		4.83		5.52	
Standard deviation	2.21		2.14		2.19	

AMI, acute myocardial infarction; CABG, coronary artery bypass graft; CAD, coronary artery disease; HF, heart failure; ICD/PPM, implantable cardioverter-defibrillator/permanent pacemaker; MR, mitral regurgitation; nsMR, not significant MR; PCI, percutaneous coronary intervention; sMR, significant MR.

**Figure 3** (A) Adjusted survival curve for composite variable (CV-related admission and death). (B) Adjusted survival curve for CV-related admission. (C) Adjusted survival curve for death. Adjusted survival curves for the composite and each of its components (CV-related admission or death) are shown for heart failure patients with varying levels of MR severity. CV, cardiovascular; MR, mitral regurgitation.



**Table 2** Multivariable model results—time to event for composite (cardiovascular-related admission or death)

Time-to-event outcome	nsMR vs. no MR		sMR vs. no MR	
	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value
Composite	1.093 (0.987–1.211)	0.0889	1.261 (1.149–1.384)	<0.0001
Death	1.019 (0.867–1.198)	0.8172	1.243 (1.081–1.431)	0.0023
CV-related admission	1.229 (1.084–1.393)	0.0013	1.549 (1.379–1.739)	<0.0001

CI, confidence interval; CV, cardiovascular; MR, mitral regurgitation; nsMR, not significant MR; sMR, significant MR.

Time-to-event models controlled for the following covariates: age, sex, region, insurance type, Elixhauser Comorbidity Index score, and ischaemia status.

hospital admission compared with patients with no MR. The magnitude was dependent upon the severity of MR: sMR (HR 1.55; 95% CI 1.38–1.74) or nsMR (HR 1.23; 95% CI 1.08–1.40). In the time-to-death analysis, only patients with sMR were at a higher risk of death compared with patients with no MR (HR 1.24; 95% CI 1.08–1.43). When both events were combined into a composite endpoint, time-to-first CV-related admission or death, only patients with sMR were at a statistically significantly higher risk of an event compared with patients with no MR (HR 1.26; 95% CI 1.15–1.39).

## Discussion

In this retrospective, real-world analysis of the incremental effect of secondary MR on patients newly diagnosed with HF, this study found that patients with an additional diagnosis of MR were at a higher risk for time-to-first CV-related admission or death compared with patients with no MR. The magnitude of this was dependent on MR severity, with a 26% excess risk for patients with clinically significant MR.

Our findings help solidify the contention that administrative claims data can be used to not only identify patients with MR but also stratify them based on clinical significance and, by doing so, pinpoint patients at higher risk for shortened survival to CV hospitalization or death. Because there are many clinical priorities (medications, laboratory testing, implantable cardiac devices, etc.) in HF management, there is great interest towards harnessing the power of automated data to enhance HF care management. Our approach appears to be sufficiently simple and epidemiologically tractable such that it can be generalized to other populations not only in the USA but also across the globe. Our reliance on incident HF also gives an opportunity for clinical effectiveness and an approach for development to screen, detect, and manage the impact of MR in patients before the occurrence of CV hospitalization or death.

These data provide considerable validation of findings from much smaller observational studies. Trichon *et al.*<sup>4</sup> found that the presence of MR was an independent predictor of worsened survival in patients with left ventricular systolic dysfunction (HR 1.23; 95% CI 1.13–1.34,  $P = 0.0001$ ). Some recent randomized controlled trials have evaluated medically managed patients with HF in relation to secondary MR from a clinical perspective. In general, moderate or greater MR has

been associated with increased risk of CV (HF) hospitalization and death.<sup>15</sup> The COAPT trial<sup>16</sup> examined the effect of transcatheter mitral valve leaflet repair among patients with HF and moderate-to-severe or severe secondary MR who remained symptomatic despite guideline-directed medical therapy (GDMT). The randomized trial demonstrated that transcatheter mitral valve repair plus GDMT resulted in lower rates of HF hospitalizations and all-cause mortality through 24 months follow-up compared with GDMT alone. Our data are important in this context as we demonstrated the high clinical burden of HF patients with clinically significant MR compared with HF patients with no MR. The availability of a beneficial therapy for HF patients with severe MR is promising as our data indicate that MR is a contributor towards HF mortality and morbidity. Of note, the COAPT trial included chronic, severe MR patients, which differ from our study of newly diagnosed HF and varying severities of MR.

In patients with HF, MR is independently associated with CV hospitalization and death. Specifically, patients with clinically significant MR determined by proxy variables have a 26% increased risk of CV hospitalization or death over the ensuing years after the diagnosis of HF is established.

## Limitations

Our study has all the limitations of retrospective studies using automatic claims data to examine clinical events in community populations. We did not have any method to standardize or validate the finding of MR or its worsening over time. Additionally, we relied on clinical surrogates to classify MR as significant or non-significant. This study used statistical modelling to control for potentially confounding between-group differences for known confounders but had no means to determine or handle confounders not in the database (e.g. echocardiographic results). We used time-to-first CV hospitalization as an outcome of interest, but the burden of disease is likely derived from recurrent CV hospitalizations.

Additionally, the continuous enrolment requirement (12 months pre-index and 6 months post-index diagnosis) led to a loss in sample size and potentially a loss in generalizability. However, these requirements were necessary to capture important confounding variables (patient co-morbidities) and categorize patients with MR to assign aetiology and severity. The study's strength, however, is that the data reflect real-



world treatment patterns in a large population with outcomes across the country from different hospitals and physicians as compared with evidence from controlled clinical trials.

## Conflict of interest

D.P.C., P.A.M., H.S.M., and C.M.B. have consulting relationships with Edwards Lifesciences. D.P.C. has a consulting relationship with Abbott Laboratories and participates in a speaker's bureau for Boston Scientific. H.S.M. has a consulting relationship with Abbott Laboratories and Boston Scientific and participates in a speaker's bureau for Actelion Pharmaceuticals, Bayer Healthcare Pharmaceuticals, and Bristol-Myers Squibb Company. C.M.B. is an advisory board member for Medtronic and Boston Scientific. M.P.R. and E.R.B. are employees of CTI Clinical Trial & Consulting Services, and C.G. is a consultant to CTI Clinical Trial & Consulting Services, which is a consultant to Edwards Lifesciences. J.V.H., S.M., and P.V. are employees of Edwards Lifesciences, the study sponsor.

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## Permissions

All figures are original and were not published previously; therefore, no permissions were required.

## Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Appendix A1.** Heart failure diagnosis codes.

**Appendix A2.** Exclusion criteria - ICD-9, ICD-10 and CPT codes.

**Appendix A3.** Mitral regurgitation ICD-9 and ICD-10 diagnosis codes.

**Appendix A4.** Atrial fibrillation, pulmonary hypertension, echocardiograms ICD-9, ICD-10 and CPT codes.

**Appendix A5.** Elixhauser comorbidity index.

**Appendix A6.** Ischemia ICD-9, ICD-10 and CPT codes.

**Appendix A7.** Elixhauser comorbidity index by mitral regurgitation (MR) severity cohorts.

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