CLINICAL RESEARCH STUDY

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Mitral Regurgitation and Increased Risk of All-Cause and Cardiovascular Mortality in Patients with Type 2 Diabetes

Andrea Rossi, MD,[a] Giacomo Zoppini, MD,[b] Giovanni Benfari, MD,[a] Giulia Geremia, MD,[a] Stefano Bonapace, MD,[a] Enzo Bonora, MD,[b] Corrado Vassanelli, MD,[a] Maurice Enriquez-Sarano, MD,[c] Giovanni Targher, MD[b]

[a]Section of Cardiology, Department of Medicine and [b]Section of Endocrinology, Diabetes and Metabolism, Department of Medicine, University and Azienda Ospedaliera Universitaria Integrata of Verona, Italy; [c]Division of Cardiovascular Diseases and Internal Medicine, Mayo Clinic, Rochester, Minn.

ABSTRACT

BACKGROUND: Mitral regurgitation is the most common heart valve disease in the general population, but little is known about the prevalence and prognostic implications of mitral regurgitation in patients with type 2 diabetes.

METHODS: We retrospectively analyzed the data from 814 outpatients with type 2 diabetes who had undergone a conventional echocardiography for clinical reasons during the years 1992-2007. Mitral regurgitation was evaluated by using an integrated multiparametric echocardiographic approach. The study outcomes were all-cause and cardiovascular mortality.

RESULTS: At baseline, 261 (32%) patients had mitral regurgitation (25% mild, 5% moderate, and 2% severe). Over a mean follow-up of 9 years, 120 (14%) patients died, 50 of them from cardiovascular causes. Compared with those without valve disease, patients with mild mitral regurgitation had a 3.3-fold increased risk of all-cause mortality, whereas those with moderate-to-severe mitral regurgitation had a 5.1-fold increased risk of all-cause mortality. Results remained statistically significant after adjustment for multiple potential confounders. Similar results were found for cardiovascular mortality.

CONCLUSIONS: Mitral regurgitation is a common pathologic condition in patients with type 2 diabetes and is independently associated with an increased risk of both all-cause and cardiovascular mortality, even if the severity of mitral regurgitation is mild.

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KEYWORDS: Cardiovascular disease; Mitral regurgitation; Mortality; Type 2 diabetes

Mitral regurgitation is the most common heart valve abnormality encountered in clinical practice.[1,2] Epidemiologic studies show that moderate or severe mitral regurgitation is significantly associated with cardiac remodeling/dysfunction and excess mortality.[1,2]

To date, little attention has been paid to analyzing the characteristics of mitral regurgitation in patients with type 2 diabetes, who are at high cardiovascular risk and commonly have mitral valve calcification.[3,4] In addition, no large observational studies have explored the prognostic impact of the severity of mitral regurgitation on mortality outcomes in this patient population.

Therefore, the main aim of this observational study was to estimate the prevalence of mitral regurgitation, and to examine the long-term prognostic role of this valve abnormality on the risk of all-cause and cardiovascular mortality in a large cohort of type 2 diabetic individuals.

METHODS

Patients

The study was performed within the frame of the Verona Diabetes Study, an observational longitudinal study on

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Requests for reprints should be addressed to Andrea Rossi, MD, Division of Cardiology, University and Azienda Ospedaliera Universitaria Integrata of Verona, Piazzale Stefani 1, Verona 37126, Italy.

E-mail address: andrea.rossi@ospedaleuniverona.it

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chronic complications in outpatients with type 2 diabetes.[3] We retrospectively analyzed the electronic records of all White type 2 diabetic outpatients, who regularly attended the diabetes clinic at the University Hospital of Verona during the years 1992-2007. Of these, we selected all patients with type 2 diabetes who had undergone a first conventional echocardiography for any clinical reasons (eg, dyspnea, palpitations, chest pain, history of myocardial infarction, electrocardiographic abnormalities, assessment of left ventricular wall thickness, presence of multiple cardiovascular risk factors) at our institution during the same period of time. Thus, 814 type 2 diabetic outpatients were identified and included in final analysis.

CLINICAL SIGNIFICANCE

- Mitral regurgitation is frequent in patients with type 2 diabetes mellitus.
- Main causes are valve alteration and impairments of regional or global left ventricular function.
- Mitral regurgitation is a predictor of all-cause mortality and cardiovascular mortality.

The local ethics committee approved the study protocol. The informed consent requirement for this study was exempted by the ethics committee because researchers only accessed retrospectively a de-identified database for analysis purposes.

Clinical and Laboratory Data

A detailed clinical history was recorded in each patient. Body mass index was measured as kilograms divided by the square of height in meters. A physician measured blood pressure in duplicate with a mercury sphygmomanometer. Subjects were considered to have hypertension if their blood pressure was $\geq$140/90 mm Hg or if they were taking any antihypertensive drugs. Dyslipidemia was defined as total cholesterol concentrations $>$ 200 mg/dL or use of any lipid-lowering drugs. Presence of a previous history of cardiac diseases (ie, myocardial infarction, angina, or revascularization procedures) was also recorded from clinical charts. Serum lipids, creatinine, glucose, and other biochemical blood measurements were determined in the same laboratory using standard laboratory procedures. Hemoglobin A1c was measured by an automated high-performance liquid chromatography analyzer. Estimated glomerular filtration rate (eGFR) was calculated from the 4-variable Modification of Diet in Renal Disease study equation. Urinary albumin excretion rate was measured from a 24-hour urine sample using an immunonephelometric method. The diagnosis of diabetic retinopathy was based on fundoscopy by a single ophthalmologist.

Transthoracic Echocardiography

All echocardiographic examinations were performed at our institution by experienced cardiologists. Left ventricular chamber dimensions and wall thickness were measure from M-mode recordings and left ventricular mass was calculated. Ejection fraction was either measured from left ventricular diameters or 2-dimensional area changes in systole and diastole, or estimated visually, a method comparable with other modalities for ejection fraction assessment.[5] Regional left ventricular function was evaluated by means of wall motion score index (WMSI) on the basis of its motion and systolic thickening. Left ventricular segments were scored as follows: 1 = normal; 2 = hypokinetic; 3 = akinetic; and 4 = dyskinetic or aneurysmatic. WMSI was derived as the sum of all scores divided by the number of ventricular segments visualized. Aortic-valve sclerosis was defined as focal or diffuse calcification and thickening of aortic valve leaflets with or without restriction of leaflet motion on echocardiography.[3] Mitral valve abnormalities were considered as follows: nonspecific mitral valve leaflet thickening, mitral annulus calcification, mitral valve prolapse, or rheumatic valve disease. The severity of mitral regurgitation was assessed by an integration of color Doppler jet area, vena contracta, or proximal isovelocity surface area and graded from 0 to 3 (ie, none, mild, moderate and severe).

Mortality Follow-Up Data

Vital status on September 30, 2007 was ascertained for all patients through examination of the electronic databases of the Social Health Unit of the Veneto Region, which include all records of death as well as the specific causes of death. Death certificates were coded by trained nosologists using the International Classification of Diseases, Ninth Revision; death was attributed to cardiovascular causes when these codes were 390-459. A selected sample of death certificates was reviewed manually to validate the process.

Statistical Analysis

Data are presented as means $\pm$ SD or percentages. Skewed variables were logarithmically transformed to improve normality prior to analysis. Comparisons between groups were made using the one-way analysis of variance and the chi-squared test. Given the low number of patients with severe mitral regurgitation (n = 18), we merged patients with either moderate or severe mitral regurgitation into a single subgroup. Univariate survival analysis was performed by the Kaplan-Meier analysis; the overall significance was calculated by the log-rank test. Cox regression analysis was used to determine the association between the severity of mitral regurgitation and risk of all-cause and cardiovascular mortality after adjustment for multiple potential confounders.

Three forced-entry Cox regression models were performed: an unadjusted model; a model adjusted for age

(model 1); and, finally, a model adjusted for age, sex, diabetes duration, dyslipidemia, hypertension, eGFR, WMSI score, ejection fraction ≤50%, presence of aortic-valve sclerosis, or mitral valve abnormalities (model 2). The covariates included in these regression models were chosen as potential confounding factors on the basis of their biological plausibility or their significance in univariable analyses (see Appendix, Supplementary Table, available online). Results of Cox proportional hazard models were presented as hazard ratios and 95% confidence intervals. Analyses were performed using statistical package SPSS 19.0 (IBM, Armonk, NY) and statistical significance was assessed at the 2-tailed $P < .05$ threshold.

RESULTS

Among the 814 patients included in the study, 261 (32%) patients had any degree of mitral regurgitation: 203 (25%) patients had mild mitral regurgitation, and 58 (7%) had moderate or severe mitral regurgitation. Overall, 596 (73%) patients had morphologically normal mitral valve, 144 (18%) patients had isolated calcification of the mitral valve, and 74 (9%) patients had other mitral valve abnormalities/diseases (eg, nonspecific mitral leaflet thickening, mitral prolapse, or rheumatic mitral valve disease). In addition, among patients without cardiac/ischemic diseases (n = 485), the overall prevalence of mitral regurgitation was 28%, whereas the prevalence of this valve abnormality was 39% among patients with established cardiac/ischemic diseases.

As shown in **Table 1**, patients with increasing severity of mitral regurgitation were older and more likely to be male. They also had higher values of WMSI score, cardiac mass, and hemoglobin A1c levels, and lower values of eGFR and ejection fraction. The prevalences of prior cardiac/ischemic diseases and mitral valve abnormalities also increased progressively with the severity of mitral regurgitation. However, mitral valve abnormalities were also found in 19% of patients without mitral regurgitation. No significant differences were found in terms of conventional cardiovascular risk

Table 1 Baseline Clinical, Biochemical, and Echocardiographic Characteristics of Patients with Type 2 Diabetes Stratified by the Echocardiographic Severity of Mitral Regurgitation (MR)

	Overall Population	Without Mitral Regurgitation	Mild Mitral Regurgitation	Moderate-Severe Mitral Regurgitation	*P* Value
n	814	553	203	58	
Age (y)	68 ± 9	67 ± 8	69 ± 8	71 ± 8	<.001
Female sex (%)	37	54	43	9	<.001
Body mass index (kg/m^2)	28 ± 5	29 ±4	28 ± 5	29 ± 5	.14
Systolic blood pressure (mm Hg)	139 ± 18	137 ± 18	140 ± 18	142 ± 20	.09
Diastolic blood pressure (mm Hg)	80 ± 9	80 ± 10	80 ± 9	79 ± 10	.46
Hypertension (%)	90	88	90	91	.73
Smoking history (%)	25	25	33	33	.90
Dyslipidemia (%)	27	28	24	34	.32
HDL cholesterol (mmol/L)	1.34 ± 0.39	1.33 ± 0.39	1.37 ± 0.42	1.31 ± 0.33	.42
LDL cholesterol (mmol/L)	3.31 ± 0.88	3.28 ± 0.90	3.35 ± 0.84	3.39 ± 0.83	.50
Triglycerides (mmol/L)	1.75 ± 1.22	1.82 ± 1.36	1.63 ± 0.89	1.52 ± 0.61	.056
eGFR (mL/min/1.73 m^2)	65 ± 18	67 ± 18	64 ± 20	59 ± 19	<.05
Fasting glucose (mmol/L)	9.04 ± 2.90	9.15 ± 2.91	8.71 ± 2.84	9.17 ± 2.92	.22
HbA1c (%)	7.72 ± 1.59	7.74 ± 1.53	7.54 ± 1.59	8.11 ± 2.06	.05
Diabetes duration (y)	15 ± 9	15 ± 9	15 ± 9	17 ± 8	.25
Albuminuria (mg/L)	60 ± 130	67 ± 143	43 ± 93	60 ± 108	.20
Diabetic retinopathy (%)	32	29	29	47	.07
Ejection fraction (%)	57 ± 13	59 ± 11	53 ± 13	47 ± 16	<.001
Ejection fraction ≤50% (%)	20	14	29	55	<.001
Left ventricular diastolic diameter (mm)	52 ± 7	51 ± 6	53 ± 7	55 ± 10	<.005
Left ventricular systolic diameter (mm)	33 ± 8	32 ± 7	35 ± 9	36 ± 14	<.01
Left ventricular mass (g)	244 ± 82	241 ± 78	247 ± 88	273 ± 105	.21
WMSI score	1.1 ± 0.4	1.13 ± 0.28	1.26 ± 0.40	1.49 ± 0.54	<.001
WMSI >1 (%)	33	26	42	55	<.001
Aortic-valve sclerosis (%)	41	32	58	62	<.001
Known cardiac diseases (%)	40	35	48	60	<.001
Prior myocardial infarction (%)	24	20	32	27	<.01
Mitral valve abnormalities (%)	27	19	33	67	<.001

Data are expressed as means ± SD and relative frequencies.

Note: Information on smoking history was available for only 516 patients.

eGFR = estimated glomerular filtration rate; HbA1c = hemoglobin A1c; HDL = high-density lipoprotein; LDL = low-density lipoprotein; WMSI = wall motion score index.

factors, duration of diabetes, and diabetic retinopathy between the groups. At multivariate logistic regression analysis, male sex, higher body mass index, lower ejection fraction, and presence of mitral valve abnormalities were independently associated with a greater severity of mitral regurgitation (data not shown).

Interestingly, 376 (46%) patients had morphologically normal mitral valve and normal ventricular global and regional systolic function of whom 61 had mild mitral regurgitation and only 2 had moderate-to-severe valve disease.

Survival Analysis

During a mean follow-up period of 9 years, 120 (14%) patients died, 50 of them from cardiovascular causes.

As shown in the **Figure**, the severity of mitral regurgitation was significantly associated with an increased risk of all-cause mortality. For example, at 10 years of follow-up, patients without mitral regurgitation had a survival rate of ~90%, those with mild mitral regurgitation of 69%, and those with moderate-to-severe mitral regurgitation of 47% ($P < .001$ for differences by the log-rank test). Notably, after excluding patients with moderate-to-severe mitral regurgitation, the survival rates for patients with mild mitral regurgitation and those without valve disease remained significantly different ($P < .001$ by the long rank test). The univariable Cox regression analysis (**Table 2**, first column) revealed that compared with patients without mitral regurgitation, those with mild mitral regurgitation had a 3.31-fold increased risk of all-cause mortality, whereas patients with moderate-to-severe mitral regurgitation had a 5.1-fold increased risk of all-cause mortality. Similar results were found for cardiovascular mortality. The Supplementary Table (Appendix, available online) shows other univariable significant predictors of all-cause mortality considered as covariates in multivariable regression models.

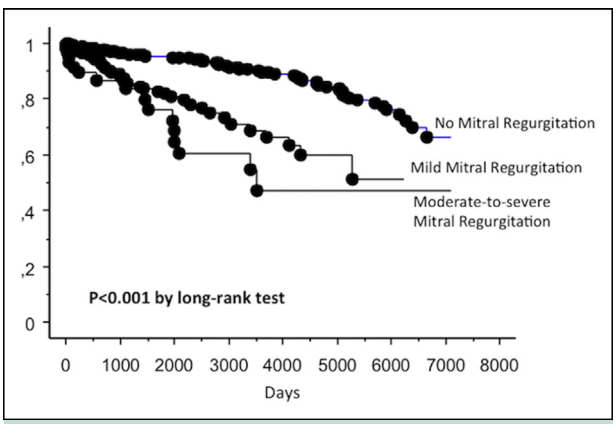

Figure Kaplan-Meier survival analysis for all-cause mortality in 814 outpatients with type 2 diabetes stratified by mitral regurgitation severity at baseline.

As also shown in **Table 2** (second and third columns), the significant and positive relationships between the severity of mitral regurgitation and the risk of both all-cause and cardiovascular mortality were little affected by adjustment for age, sex, diabetes duration, dyslipidemia, hypertension, eGFR, WMSI score, ejection fraction ≤50%, and presence of aortic-valve sclerosis and mitral valve abnormalities (adjusted model 1 and 2). Further adjustment for smoking history did not change these results, although the strength of associations between moderate-to-severe mitral regurgitation and mortality risk was attenuated, possibly due to the smaller number of patients included in the final multivariate regression model (ie, information on smoking status was available in only 516 patients). Other variables that were independently associated with higher all-cause and cardiovascular mortality in the fully adjusted regression model were older age, longer duration of diabetes, presence of aortic-valve sclerosis, and lower eGFR values; mitral valve abnormalities and hypertension were also independently associated with higher all-cause mortality but not with cardiovascular mortality (data not shown).

We conducted sensitivity analyses to evaluate the robustness of our findings. As shown in **Table 3**, the severity of mitral regurgitation was significantly associated with higher all-cause mortality in all subgroups evaluated, except for a borderline significance in patients with both mild mitral regurgitation and mitral valve abnormalities.

Finally, among the 376 patients who had morphologically normal mitral valve and normal systolic function, the presence of mild mitral regurgitation was significantly associated with higher all-cause mortality (hazard ratio 3.21; 95% confidence interval, 1.6-6.7; $P = .001$). Similar results were also found for cardiovascular mortality (data not shown).

DISCUSSION

To our knowledge, this is the first observational study to specifically address the prognostic role of mitral regurgitation in predicting all-cause and cardiovascular mortality in a large cohort of type 2 diabetic outpatients referred for clinically indicated echocardiograms.

The main findings of our study were that: 1) the overall prevalence of mitral regurgitation was very high (32%) in this patient population, even in patients without established cardiac/ischemic heart diseases (28%); 2) mitral valve abnormalities and the WMSI score were the strongest determinants of mitral regurgitation; and 3) the severity of mitral regurgitation, even if mild, was strongly and progressively associated with an increased risk of both all-cause and cardiovascular mortality, independently of multiple potential confounders.

Although the overall prevalence of mitral regurgitation in this study was high, it is important to remark that most of our patients had mild mitral regurgitation. This is important because mild mitral regurgitation is clinically silent and often remains undetected,[6] highlighting the

Table 2 Univariable and Multivariable Cox Regression Models Showing the Significant Associations Between the Severity of Mitral Regurgitation and the Risk of Both All-Cause and CVD Mortality in Patients with Type 2 Diabetes

	Cox Regression Models					
	Unadjusted Model	*P* Value	Adjusted Model 1	*P* Value	Adjusted Model 2	*P* Value
All-cause mortality						
Mitral regurgitation						
Absent	Ref.		Ref.		Ref.	
Mild	3.32 (2.20-5.05)	<.001	2.69 (1.77-4.10)	<.001	2.33 (1.40-3.88)	<.001
Moderate-severe	5.10 (2.93-8.84)	<.001	4.74 (2.72-8.27)	<.001	2.79 (1.25-6.24)	<.01
Cardiovascular mortality						
Mitral regurgitation						
Absent	Ref.		Ref.		Ref.	
Mild	4.78 (3.65-12.6)	<.001	5.28 (2.82-9.90)	<.001	4.37 (2.08-9.21)	<.001
Moderate-severe	7.42 (3.11-17.7)	<.001	6.75 (2.81-16.2)	<.001	5.58 (1.76-17.6)	<.005

Results are expressed as odds ratios ± 95% confidence intervals (in parenthesis) as assessed by univariable (unadjusted) or multivariable Cox regression analyses. Rates of all-cause mortality or cardiovascular mortality were the dependent variable.

Covariates included in multivariate regression models were as follows: model 1: age; and model 2: age, sex, duration of diabetes, dyslipidemia, hypertension, estimated glomerular filtration rate, wall motion score index, ejection fraction ≤50%, and echocardiographic presence of aortic-valve sclerosis and mitral valve abnormalities.

CVD = cardiovascular disease; Ref. = reference category.

importance of echocardiography for a better risk assessment and stratification of mortality in patients with type 2 diabetes.

As expected, a morphological alteration of mitral valve leaflets was a strong determinant of valve insufficiency. We believe that the observed significant univariable association between the severity of mitral regurgitation and mitral valve abnormalities is at least partly due to the fact that mitral valve calcification is a marker of coronary artery calcification,[7] and then mitral regurgitation is likely a direct consequence of coronary artery disease on left ventricular function. Accordingly, abnormal WMSI score and lower ejection fraction were independently associated with the presence of mitral regurgitation, and this may also explain why most of our diabetic patients had mitral regurgitation even with a morphologically normal valve (ie, the so-called "functional mitral regurgitation" that occurred in up to ~70% of our patients). The presence of functional mitral regurgitation has been reported in patients with a dysfunctional left ventricle (ie, dilated cardiomyopathy or acute myocardial infarction). In these pathologic conditions, functional mitral regurgitation is thought to be mainly due to the dilation of mitral annulus and the tethering of the papillary muscle, displaced by left ventricular remodeling, on the mitral leaflets.[8,9] Interestingly, in our study, mitral regurgitation was also found among patients with morphologically normal mitral valve and normal ejection fraction and WMSI. It has been reported that in other clinical conditions, such as aortic-valve stenosis, the degree of functional mitral regurgitation is related to an impaired longitudinal systolic function occurring in the setting of normal WMSI and ejection fraction.[10,11] Recent data also showed that type 2 diabetic patients without established cardiovascular disease and with normal conventional

Table 3 Subgroup Analyses - Hazard Ratios for Mild and Moderate-to-Severe Mitral Regurgitation in Predicting All-Cause Mortality Risk in Different Subgroups of Patients with Type 2 Diabetes

	Mild Mitral Regurgitation HR (95% CI)	*P* Value	Moderate-severe Mitral Regurgitation HR (95% CI)	*P* Value
Ejection fraction >50% (n = 654)	3.22 (1.97-5.25)	.001	3.42 (1.57-7.62)	<.005
Ejection fraction ≤50% (n = 160)	2.81 (1.31-6.22)	.01	5.72 (2.2-14.71)	.01
Men (n = 510)	3.52 (2.12-5.99)	<.001	4.31 (2.16-8.57)	<.001
Women (n = 304)	2.73 (1.39-5.30)	<.005	5.22 (2.05-13.3)	<.001
Age >65 years (n = 507)	2.92 (1.88-4.60)	<.001	5.23 (2.86-9.58)	<.001
Age ≤65 years (n = 307)	3.53 (1.26-9.55)	.01	3.84 (1.26-9.57)	.06
Diabetes duration >16 years (n = 323)	2.73 (1.39-5.57)	<.005	6.24 (2.78-13.5)	<.001
Diabetes duration ≤16 years (n = 491)	3.22 (2.01-4.97)	<.001	4.76 (2.53-8.95)	<.001
With mitral valve abnormalities (n = 217)	1.76 (0.87-3.51)	.08	2.93 (1.13-5,04)	<.05
Without mitral valve abnormalities (n = 597)	4.09 (2.42-6.98)	<.001	8.13 (3.14-21.0)	<.001

CI = confidence interval; HR = hazard ratio.

echocardiographic parameters of global systolic function have impaired left ventricular longitudinal contraction.[12] This suggests that functional mitral regurgitation is a reliable marker of (early) ventricular dysfunction in patients with type 2 diabetes, and it might partly explain the negative impact of functional mitral regurgitation on mortality outcomes in this patient population.

We believe that the most striking observation of our study was the strong, graded association between the severity of mitral regurgitation and the risk of both all-cause and cardiovascular mortality. Notably, this association remained statistically significant after adjusting for several potential confounders, including relevant echocardiographic parameters (ie, WMSI score, ejection fraction $\leq$50%, aortic-valve sclerosis, and mitral valve abnormalities). Even more interesting is our observation that the presence of mild mitral regurgitation was independently associated with an increased risk of both all-cause and cardiovascular mortality. A plausible explanation for these findings is that a small volume overload might adversely affect the pressure-volume relationship of the diabetic left ventricle that frequently exhibits left ventricular diastolic dysfunction and decreased preload reserve.[13] Thus, the presence of mitral regurgitation might displace the left ventricular pressure-volume loop upwards, forcing the ventricle to operate at higher filling pressure. However, we believe that the prognostic role of mitral regurgitation cannot be entirely explained by its adverse impact on left ventricular volume overload; in fact, aortic valve regurgitation, which causes a similar degree of volume overload, was not independently associated with poor prognosis in our study (data not shown). On the contrary, for the same reason(s) explained above, we believe that functional mitral regurgitation is a reliable marker of left ventricular dysfunction even when ejection fraction is preserved, and so its presence may help identify patients at increased mortality risk.

The major limitations of our study were its retrospective, longitudinal design, and a possible selection bias of excluding patients who had missing echocardiographic data at baseline. There was also a relatively small number of clinical events during the follow-up period (ie, the cumulative incidence rate of all-cause mortality was 14% [120 total deaths]), and therefore, the results should be interpreted with some caution. In addition, although our statistical models were extensive, unmeasured confounders could potentially explain the observed associations. Another limitation of the study is that despite the quantification of mitral regurgitation severity being multiparametric, there was no systematic measurement of quantitative echocardiographic parameters (eg, effective regurgitant orifice area and mitral valve regurgitant volume). As previously reported, the use of quantitative echocardiographic parameters might provide more relevant prognostic information.[1] Thus, although our data might have underestimated the prognostic relevance of mitral regurgitation, the results of the present study should be considered as conservative estimates of the relationship between mitral regurgitation and mortality outcomes. We also did not have any data on left ventricular longitudinal systolic function because this information was not consistently provided in the original echo reports. In addition, although we adjusted our results for both WMSI and ejection fraction $\leq$50%, we did not have complete coronary angiographic data for all patients; so the specific links of mitral regurgitation with the severity of coronary atherosclerosis or mortality outcomes cannot be definitely elucidated. Finally, because our cohort comprised white, type 2 diabetic individuals who were followed at an outpatient diabetes clinic and who were referred for echocardiography for clinical reasons, our results may not necessarily be generalizable to other diabetic populations.

Notwithstanding these limitations, the current study has a number of important strengths, including the large number of patients of both sexes, the long duration of the follow-up period, the complete nature of the dataset, and the ability to adjust for several risk factors and potential confounders.

In conclusion, these results indicate that mitral regurgitation is highly prevalent in patients with type 2 diabetes and is independently associated with an increased risk of both all-cause and cardiovascular mortality, even if the degree of this valve abnormality is mild. However, further larger studies are needed to confirm the reproducibility of these results, and to elucidate whether pharmacological interventions aimed at decreasing the development and progression of mitral regurgitation may reduce mortality rates in patients with type 2 diabetes.

SUPPLEMENTARY DATA

Supplementary table accompanying this article can be found in the online version at http://dx.doi.org/10.1016/j.amjmed.2016.07.016.

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Supplementary Table Univariable Associations Between Main Clinical, Laboratory, and Echocardiographic Variables and the Risk of All-Cause Mortality in Patients with Type 2 Diabetes

	Hazard Ratio (95% CI)	*P* Value
Age (y)	1.08 (1.05-1.10)	<.001
Female sex (%)	1.02 (0.73-1.44)	.80
Systolic blood pressure (mm Hg)	1.01 (0.99-1.01)	.09
Diastolic blood pressure (mm Hg)	0.98 (0.97-1.01)	.33
Hypertension (%)	1.48 (0.88-2.49)	.10
Dyslipidemia (%)	1.68 (1.19-2.38)	<.005
Smoking status (%)*	1.74 (1.06-3.11)	<.05
Diabetes duration (y)	1.04 (1.02-1.06)	<.001
eGFR (mL/min/1.73 m^2)	0.97 (0.96-0.98)	<.001
Fasting glucose (mmol/L)	0.96 (0.90-1.03)	.23
HbA1c (%)	1.03 (0.93-1.15)	.49
Left ventricular diastolic diameter (mm)	1.01 (0.98-1.05)	.20
Left ventricular systolic diameter (mm)	1.02 (0.99-1.04)	.12
Ejection fraction ≤50% (%)	2.04 (1.44-2.89)	<.001
WMSI score	3.12 (2.01-4.75)	<.001
Aortic-valve sclerosis (%)	3.20 (2.19-4.66)	<.001
Mitral valve abnormalities (%)	2.48 (1.71-3.59)	<.001

CI = confidence interval; eGFR = glomerular filtration rate; HbA1c = hemoglobin A1c; WMSI = wall motion score index.

*Information on smoking status was available for only 516 patients.