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Evolution of Functional Mitral Regurgitation and Prognosis in Medically Managed Heart Failure Patients With Reduced Ejection Fraction

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ABSTRACT

OBJECTIVES The purpose of this study was to assess whether medical management may alter the severity of functional mitral regurgitation (FMR) and its prognosis in patients who have heart failure with reduced ejection fraction (HFrEF).

BACKGROUND FMR in patients who have HFrEF is associated with a worse prognosis. It is uncertain to what extent medical management may alter the severity of FMR and its prognosis.

METHODS The extent of FMR was assessed at baseline and after a median follow-up period of 50 months in 163 consecutive HFrEF patients (left ventricular ejection fraction <40%). Severe FMR was defined as mitral regurgitation (MR) grade 3-4. All of the patients received the maximal tolerable doses of their heart failure (HF) medications. Major adverse cardiac events were defined as a composite of all-cause death and the need for heart transplantation or hospitalization for HF and/or malignant arrhythmias.

RESULTS A total of 50 (31%) patients had severe MR at baseline. During the follow-up period, 38% of the severe FMR patients showed an improvement to nonsevere FMR (MR grade <3), whereas 18% of the nonsevere FMR patients developed severe FMR despite optimal HF treatment. Cox regression analysis revealed that the presence of sustained severe FMR or worsening of FMR was the most important independent prognostic determinant with an adjusted odds ratio of 2.5 (95% confidence interval: 1.5 to 4.3, major adverse cardiac events 83% vs. 43%). In addition, those patients showed a 13% increase in left ventricular end-diastolic volume index (LVEDVI), whereas the patients with improvement in their severe MR showed a 2% decrease in LVEDVI ($p = 0.01$).

CONCLUSIONS Severe FMR was successfully treated with medication in almost 40% and was associated with prevention of left ventricular adverse remodeling and with an improved long-term prognosis.
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Functional mitral regurgitation (FMR) is a common finding in patients with underlying myocardial dysfunction and results from decreased left ventricular (LV) closing forces and from distortion of the LV geometry tethering the structurally normal mitral leaflets (1). Severe FMR has been shown to be associated with increased morbidity and mortality independent of both LV ejection fraction (LVEF) and clinical markers of heart failure (HF) (2-6). In the study by Bursi et al. (2), moderate or severe mitral regurgitation (MR) was observed in 12% of early post-myocardial infarction (post-MI) patients and was associated with a 3-fold increase in the risk of HF and a 1.6-fold increased risk of death during 5 years of follow-up. In a more recent study by Rossi et al. (3), severe FMR was

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present in 24% of patients with systolic HF (both ischemic and nonischemic) and was related to a 2-fold increase in death and rehospitalization due to HF during an average of 3 years of follow-up. The negative impact of FMR on prognosis has been linked to progressive adverse LV remodeling due to ongoing volume overload, although this association is still controversial. Current therapies targeting pathological ventricular remodeling, such as the use of inhibitors of the renin-angiotensin-aldosterone axis and beta-blocking agents, have manifested significant effectiveness in reducing morbidity and mortality in patients with systolic HF (7–9), and there is some evidence from small-sized studies that those agents can reduce the severity of FMR in the short term (10). It is uncertain, however, to what extent optimal medical HF management may steadily improve the severity of FMR and its long-term prognosis in a general population of patients with systolic HF. This information is of paramount importance to optimize patient selection for surgical or percutaneous repair of severe FMR.

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Therefore, the present study evaluated the evolution of FMR in HF patients with reduced ejection fraction (HFrEF) within a structured and standardized HF clinic and relates alterations in the severity of FMR to their long-term morbidity and mortality as well as to changes in LV volumes.

METHODS

PATIENT POPULATION. All of the HF patients with a LVEF ≤40% (HFrEF) who were followed-up in the HF clinic at the Antwerp University Hospital between January 2007 and December 2013 were enrolled in this observational study. From the 220 recruited patients, a total of 56 patients were excluded because of the following: a history of surgical mitral valve treatment or presence of severe degenerative mitral valve disease (n = 11), incomplete echocardiogram data (n = 8), and a follow-up period of <1 year (n = 38). The final study population consisted of 163 patients with a median follow-up period of 56 months (range 13 years to 94 years).

The clinical management of the study patients, as well as the indications for resynchronization therapy and implantation of an internal defibrillator, were standardized according to the HF guidelines and within the Belgium reimbursement criteria (reimbursement for resynchronization therapy only for patients with New York Heart Association [NYHA] functional class ≥2 and left bundle branch block [LBBB] with QRS duration ≥150 ms) (7,11). Doses of standard treatment medications were titrated to the maximally tolerated dose, and each patient's filling status was assessed during each consultation by clinical and/or echocardiographic evaluation. The diuretic doses were adapted according to the patients' filling status. For each patient, the percent of the optimal dosage of angiotensin-converting enzyme inhibitor (ACEI)/angiotensin receptor blocker (ARB), beta blockers, and aldosterone antagonists were calculated at baseline and at follow-up based on the target recommended dose in the 2016 European Society of Cardiology (ESC) HF guidelines.

Information about the patients' medical history, baseline risk profile, electrocardiographic parameters, laboratory results, functional status, cardiac function, cardiac valve function, treatment modalities, and clinical follow-up were retrieved from the HF database and the patients' hospital files.

The study was approved by the ethics committee of the Antwerp University Hospital.

ECHOCARDIOGRAPHY. All of the echocardiographic examinations were performed by trained sonographers using high-quality cardiovascular ultrasound systems (Vivid 7 GE Healthcare or iE33 [Chicago, Illinois] and Philips Healthcare [Amsterdam, the Netherlands]) and were reviewed at the time of the examination by expert supervisors.

MR severity was graded according to the American Society of Echocardiography guidelines, based on a validated multi-integrative method (12). Both qualitative (color flow mapping) as well as quantitative measurements (proximal isovelocity surface area whenever feasible) were used to grade the MR severity from grade 0 to grade 4. In the present study, severe MR was defined as MR grade 3 or 4 and was graded by an effective regurgitant orifice area >20 mm^2 and/or a vena contracta width >4 mm and/or a jet area of at least 4 cm^2 (13).

For this study, all of the echocardiogram images were reviewed a second time off-line by 1 expert, and in cases of discordance with the initial evaluation, a third expert was invited to review the images and make the final decision. All of the expert reviewers were blinded to the clinical status of the patient.

LV function (LVEF) was quantified by measurements of LV dimensions or by visual estimation in the cases when ventricular volume measurements were

ABBREVIATIONS AND ACRONYMS

ACEI = angiotensin-converting enzyme inhibitor

AHT = arterial hypertension

ARB = angiotensin receptor blocker

CRT = cardiac resynchronization therapy

FMR = functional mitral regurgitation

HF = heart failure

HFrEF = heart failure with reduced ejection fraction

ICD = implantable cardioverter defibrillator

LAVI = left atrium volume index

LBBB = left bundle branch block

LVEF = left ventricular ejection fraction

LVEDVI = left ventricular end-diastolic volume index

LVESVI = left ventricular end-systolic volume index

MACE = major adverse cardiac event(s)

MR = mitral regurgitation

NYHA = New York Heart Association

OR = odds ratio