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Association Between Sacubitril/Valsartan Initiation and Mitral Regurgitation Severity in Heart Failure With Reduced Ejection Fraction: The PROVE-HF Study

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RESEARCH LETTER

Association Between Sacubitril/Valsartan Initiation and Mitral Regurgitation Severity in Heart Failure With Reduced Ejection Fraction: The PROVE-HF Study

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Mitral regurgitation (MR) severity is an important determinant of symptom status and prognosis in heart failure with reduced ejection fraction (HFrEF). Functional MR is frequently progressive, associated with adverse myocardial remodeling, neurohormonal activation, worsened symptoms, and poor outcome.[1] Percutaneous MR repair may improve outcomes in HFrEF;[2] however, optimizing guideline-directed medical therapy (GDMT) before valve repair may reduce MR severity sufficiently to avoid need for such a procedure. Limited data suggest treatment of HFrEF with sacubitril/valsartan (sac/val) may result in improvement of MR regardless of background GDMT.[3]

We examined the association between treatment with sac/val on change in MR among participants in the PROVE-HF study (Prospective Study of Biomarkers, Symptom Improvement, and Ventricular Remodeling During Sacubitril/Valsartan Therapy for Heart Failure; URL: https://www.clinicaltrials.gov; Unique identifier: NCT02887183).[4] All study procedures were approved by local institutional review boards, and study participants provided informed consent. All supporting data are available within the article. In this study of 794 participants with HF and left ventricular (LV) ejection fraction (LVEF) <40%, sac/val was initiated and titrated to the maximally tolerated dose. An echocardiogram was performed at baseline, 6 months, and 12 months, and interpreted in a temporally and clinically blinded fashion. MR severity was graded using a combination of visual assessment of the color Doppler jet and MR/left atrial area and vena contracta width[5] and categorized on a scale of 0 (none), 1+ (trace), 2+ (mild), 3+ (moderate), and 4+ (severe). Those with previous mitral procedures (N=40) were excluded from the analysis, as were 30 study participants missing baseline MR severity.

Study participants had a mean ±SD age of 65.0±12.4 years. Most (76.4%) were receiving an ACE inhibitor or angiotensin II receptor blocker at baseline. The median LVEF was 28.3%, with LV end diastolic volume index (LVEDVi) of 87.2 mL/kg^2, LV end systolic volume index of 61.8 mL/kg^2, left atrial volume index of 37.6 mL/kg^2, E/e' (the ratio of the early diastolic transmitral Doppler velocity [E] and the early diastolic septal velocity [e']) of 11.3, and LV mass index of 125.2 g/m^2. At baseline, 42 (5.8%) and 66 (9.1%) had 3+ and 4+ MR, respectively.

From baseline through 12 months, improvement in MR was observed (Figure); by 6 months, prevalence of 3 to 4+ MR decreased to 8.2% (relative 45.0% reduction), and by 12 months, it was 8.4% (relative 44.7% reduction). Those with 3 to 4+ MR at baseline with reduction to ≤2+ by 12 months ("responders"; N=52) had similar baseline clinical characteristics (including vital signs, baseline GDMT, or previous cardiac resynchronization therapy) to those with persistent MR grade 3 to 4+ at 12 months ("nonresponders"; N=33); baseline LVEF and

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For Sources of Funding and Disclosures, see page 1640.

Nonstandard Abbreviations and Acronyms

GDMT	guideline-directed medical therapy
HFrEF	heart failure with reduced ejection fraction
LV	left ventricular
LVEDVi	left ventricular end diastolic volume index
LVEF	left ventricular ejection fraction
MR	mitral regurgitation
NT-proBNP	N-terminal pro-B-type natriuretic peptide
sac/val	sacubitril/valsartan

LV volumes were similar between groups, but responders had lower baseline left atrial volume index (43.9 versus 49.3 mL/kg^2; *P*=0.01) and LV mass index (145.0 versus 166.0 g/m^2; *P*=0.02). Neither ratio of vena contracta/LVEDVi or left atrial area/LVEDVi was significantly different between responders and nonresponders at baseline (*P*=0.11 and 0.68, respectively). Between responders and nonresponders, the average sac/val dose during the study was 276 versus 277 mg/d (*P*=0.57). By 12 months, LVEF improvement was greater in responders versus nonresponders (+11.0% versus +7.6%; *P*=0.05), and responders had lower final LVEDVi (85.2 versus 96.9 mL/kg^2; *P*=0.02), LV end systolic volume index (56.5 versus 66.0 mL/kg^2; *P*=0.04), left atrial volume index (33.4 versus 42.3 mL/kg^2; *P*<0.001), E/e' (12.6 versus 15.8; *P*=0.04), and LV mass index (125.7 versus 152.2 g/m^2). Last, by 12 months, responders had lower median NT-proBNP (N-terminal pro-B-type natriuretic peptide; 912 versus 1512 pg/mL; *P*=0.01) and higher median Kansas City Cardiomyopathy Questionnaire Overall Summary Scores (82.3 versus 72.9; *P*=0.04) despite similar results for both measures at baseline.

Although valve repair in those with 3 to 4+ MR may improve symptoms and reduce adverse outcomes in HFrEF, optimizing GDMT is important before such an intervention. In this analysis, despite the majority of study participants previously receiving an ACE inhibitor or angiotensin II receptor blocker, we observed a substantial shift to lesser degrees of MR after 12 months of treatment with sac/val, including a nearly 50% reduction in 3 to 4+ MR. Reduction in MR from 3 to 4+ was associated with considerable reverse cardiac remodeling, reduced NT-proBNP, and improved health status.

The baseline clinical and echocardiographic characteristics of those with 3 to 4+ MR who had a reduction to ≤2+ MR by 12 months were similar to those who had persistent 3 to 4+ MR by 12 months, and both groups had comparable baseline LVEF, LV volumes, and ratio of MR severity to LVEDVi despite comparable degrees of MR at baseline. Thus, predicting presence of MR caused by LV dilation versus intrinsic valve dysfunction without a course of sac/val treatment may be difficult.

Limitations of this study include the single-arm, observational design; thus, improvement in MR might have been due to factors other than sac/val. Nonetheless, the results of this study provide important insights into potential change in MR after initiation of sac/val in usual care.

With growth in use of percutaneous approaches for mitral valve repair for those with HFrEF and 3 to 4+ MR,

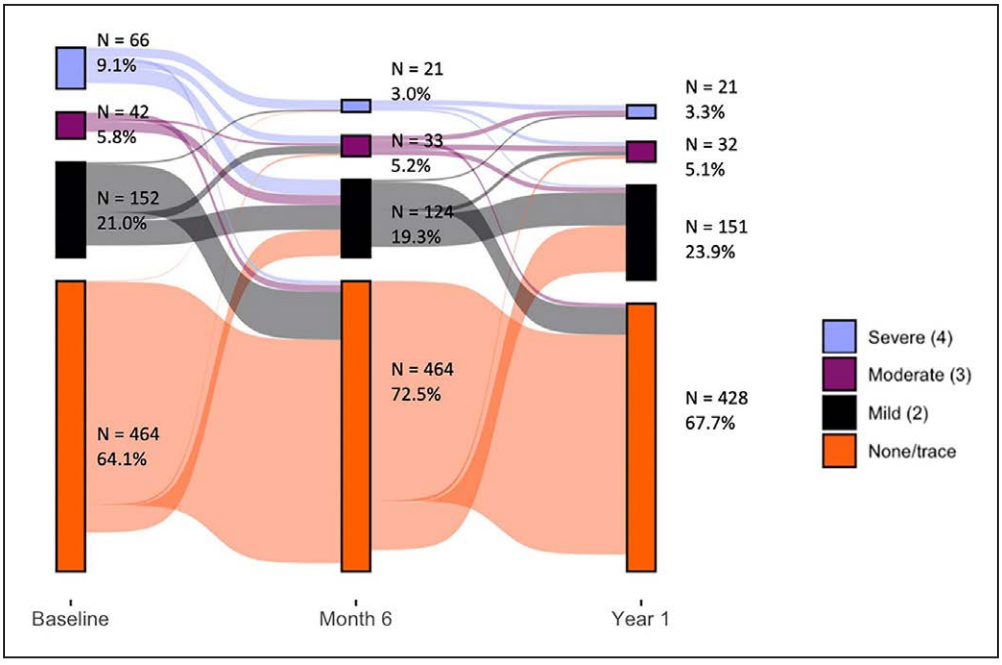

Figure. Sankey diagram detailing severity of mitral regurgitation at baseline, 6 months, and 12 months among study participants with heart failure and reduced ejection fraction treated with sacubitril/valsartan.

the results of this study reinforce importance of ensuring optimal GDMT before such decisions.

ARTICLE INFORMATION

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