JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 75, NO. 7, 2020
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PUBLISHED BY ELSEVIER

EDITORIAL COMMENT

Put a Strain on Secondary Mitral Regurgitation

Functional or Dysfunctional?*

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Secondary mitral regurgitation (MR) has poor prognosis regardless of management strategy, and guidelines remain conservative for intervention (1). With rapid advances in percutaneous mitral interventions, there is renewed interest in secondary MR, with 2 randomized trials, the MITRA-FR (Multicentre Study of Percutaneous Mitral Valve Repair MitraClip Device in Patients With Severe Secondary Mitral Regurgitation) and COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation) trials, evaluating the MitraClip device (Abbott Vascular, Menlo Park, California) (2,3). Stark contrast in their findings have triggered many investigations for identifying which patients most benefit from percutaneous repair.

Left ventricular ejection fraction (LVEF) and dimensions (end-diastolic or end-systolic) contribute to guideline indications for valvular interventions (1). Left ventricular global longitudinal strain (LV GLS) adds incremental prognostic value in valvular diseases (4). A meta-analysis of 10 studies and 1,067 asymptomatic aortic stenosis patients with preserved LVEF found reduced LV GLS predicted mortality with an optimal cutoff of -14.7% and hazard ratio of 2.62 (5). Another large observational study of 865 aortic regurgitation patients found LV GLS had a cutoff of -19%, patients had higher mortality, with a hazard ratio of 1.62, and both worsening LV GLS or persistent reduced LV GLS after surgery had worse survival (6). In primary MR, a meta-analysis of 11 studies and 2,415 patients found reduced LV GLS to predict mortality, need for surgery, and post-operative LV dysfunction (7).

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In this issue of the *Journal*, Namazi et al. (8) evaluate the prognostic utility of LV GLS in 650 secondary MR patients. This was a high-risk group with 51% mortality during a median follow-up of 56 months. The mean LVEF and LV GLS were 29% and 7.2% (absolute value for LV GLS), respectively. LV GLS $<7.0\%$ remained an independent predictor of mortality (adjusted hazard ratio: 1.3). LV GLS had incremental prognostic value to clinical and echocardiographic parameters (chi-square difference $= 3.6$; $p = 0.024$). Patients in the LV GLS $<7.0\%$ group were more likely to receive a cardiac resynchronization therapy device (77% vs. 63%) but were less likely to undergo cardiac surgery (22% vs. 33%), and had similarly low rates of MitraClip implantation (overall 14%). **Figure 1** illustrates this increasingly encountered case of secondary MR from dilated cardiomyopathy with LV GLS $<7.0\%$ undergoing MitraClip implantation.

This was a timely study riding the wave of interest in secondary MR. In part, this is because most patients have reduced LVEF, whereas LV GLS is predominantly applied to those with preserved LVEF, demonstrating improved sensitivity for subclinical and early LV systolic dysfunction (4–7). However, there are some limitations to this study. The spline curve analysis did not show a significant nonlinear

*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of *JACC* or the American College of Cardiology.

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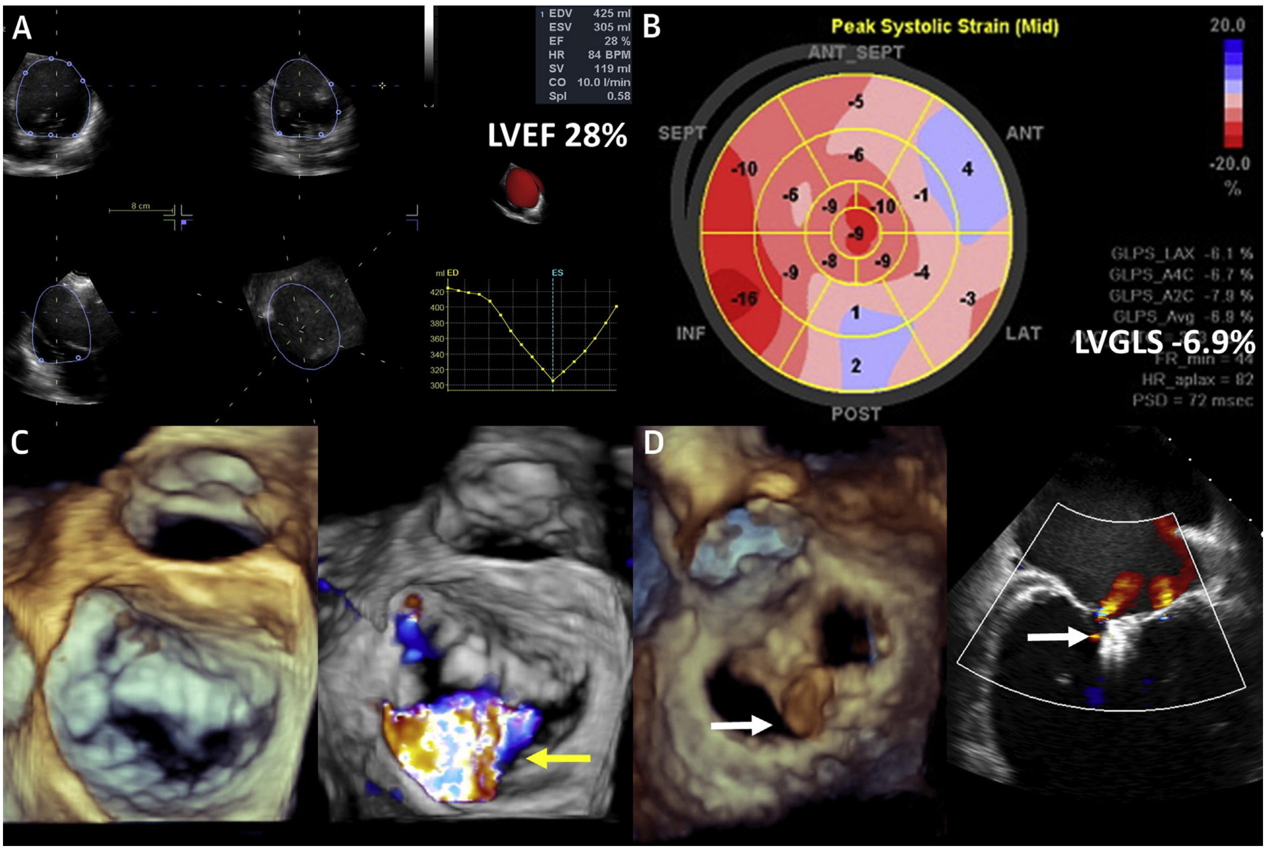
ISSN 0735-1097/$36.00 https://doi.org/10.1016/j.jacc.2019.12.025

FIGURE 1 **Echocardiography of Secondary MR Case**



(A) Left ventricle (LV) 3-dimensional (3D) measurements; **(B)** LV global longitudinal strain (GLS); **(C)** mitral valve 3D en face view from the left atrium without and with color Doppler (**yellow arrow** for mitral regurgitation [MR]); **(D)** MitraClip device (Abbott Vascular, Menlo Park, California) **(white arrows)** with trivial MR (3D from LV and bicommissural views).

relationship between the hazard ratio and LV GLS, so there was no cutpoint beyond which risk markedly increased. The adjusted hazard ratio of LV GLS $<7.0\%$ was only 1.34 for mortality, less impressive than that in the aforementioned LV GLS studies in aortic valve disease (5). Furthermore, the multivariable model's performance adding LV GLS had borderline statistical significance (the chi-square difference gave a p value of 0.058 by our calculations), possibly a result of inevitable collinearity with LVEF. Consequently, the clinical significance of LV GLS is uncertain, likely just one of many pieces in the secondary MR puzzle. Four other studies, 1 case-control and 3 prospective, have examined LV GLS in secondary MR, and are summarized in **Table 1** (9–12). The current retrospective study was the largest study to date for strain evaluation in secondary MR.

What are the clinical implications from these studies combined? First, lower LV GLS is associated with higher mortality and cardiac event rates during follow-up, regardless of management strategy, although the significance may be restricted in a multivariable model setting. Having lower baseline LV GLS also means having a lower chance of reverse remodeling of the LV after fixing the MR, while having LV contractile reserve with an increase in LV GLS during dobutamine stress is associated with improved symptoms and chance of reverse remodeling. Overall, LV GLS may contribute toward the decision making in the management of secondary MR.

How might these findings be explained? We know that LV GLS is a robust and sensitive measure of LV systolic function (4). Reducing LV GLS correlates with greater severity of secondary MR (9). A compensating LV would expect to initially have higher LVEF and LV GLS in the setting of increased preload and reduced afterload of MR, which would later fall as MR progresses, reflecting systolic impairment (13). These

TABLE 1 Studies Investigating LV GLS in Secondary MR

First Author (Ref #)	Year	Study Design	Sample	Inclusion	Main Finding
Kamperidis et al. (9)	2016	Case-control	75 (+75 control subjects)	Nonischemic cardiomyopathy with MR	Secondary MR associated with lower LVEF and LV GLS
Citro et al. (10)	2017	Prospective	41	Secondary MR undergoing MitraClip implantation	Reduced LV GLS (<9.25%) predicts cardiac events and lack of reverse LV remodeling after MitraClip implantation
Cimino et al. (11)	2019	Prospective	45	Secondary MR undergoing MitraClip implantation	Reverse LV remodeling after MitraClip implantation associated with improvement in LVEF and LV GLS (although LV GLS was not a predictor of reverse LV remodeling)
De Luca et al. (12)	2019	Prospective	33	Secondary MR and candidate for MitraClip implantation	Contractile reserve (LV GLS rise 2%+) associated with improved MR, symptoms, reverse LV remodeling, and less cardiac events after MitraClip implantation
Namazi et al. (8)	2019	Retrospective	650	Secondary MR	Reduced LV GLS (<7.0%) predicts mortality

GLS = global longitudinal strain; LV = left ventricular; LVEF = left ventricular ejection fraction; MR = mitral regurgitation.

could then lead to worse prognosis and difficulty in reversing LV remodeling after intervention. Slight improvements in LV systolic function measured detectable by LV GLS as contractile reserve with stress suggest greater chance of LV recovery after intervention.

Another question is whether LV GLS contributes to the recently described concept of proportionate and disproportionate secondary MR (14). Patients in the MITRA-FR trial had larger LV end-diastolic volume (LVEDV) and smaller effective regurgitant orifice area (EROA) than did COAPT trial patients. The EROA can be estimated from LVEF and LVEDV from the Gorlin hydraulic orifice equation—if this was similar to a patient's measured EROA, it is termed proportionate MR; however, if it is significantly lower, then it is disproportionate MR (14). It is hypothesized that the MitraClip device may have no benefit for proportionate MR (MITRA-FR-type patients) but improves outcomes in disproportionate MR (COAPT-type patients). Namazi et al. (8) also found the LVEDV index to be associated with mortality, similar to LV GLS but not to LVEF. Very low LV GLS may be a reason not to undertake intervention because of lower survival, lesser chance of reverse remodeling, and higher likelihood of proportional MR.

Gaps in current studies remain. The question about which patients with severe secondary MR should percutaneous Mitraclip device be indicated or contraindicated based on LV GLS cutpoints remains unknown. There is significant room for improvement of existing multivariable models in secondary MR for it to be used clinically. Approaches include analyzing other types of strain (i.e., circumferential, regional, right ventricular, or left atrial), mechanical dispersion, newer model derivation methodology such as machine learning, and other outcomes beyond mortality.

The authors are to be congratulated on reporting this largest cohort to date assessing the prognostic use of LV GLS in secondary MR. Together with other related studies, reduced LV GLS appears to be associated with worse prognosis and less chance of LV reverse remodeling after intervention. Further research is warranted to establish who exactly should be selected for mitral valve procedures based on LV GLS and other factors. However, we can postulate from current evidence that LV GLS may be one of the important determinants for the indication, or contraindication, of intervening in secondary MR.

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KEY WORDS echocardiography, left ventricle, secondary mitral regurgitation, strain