Reviewer’s report

Title: Global longitudinal strain is a hallmark of cardiac damage in mitral regurgitation. The Italian arm of the European registry of mitral regurgitation (EuMiClip)

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Reviewer: Oriana Belli

Reviewer's report:

In this Paper the authors analyse differences between GLS and LVEF in detecting myocardial damage in patients with different etiology and mechanism of MR.

There are some points that the authors should deeper discuss and address:

- The pooled population is too heterogeneous; 'primary' and 'secondary' MR are distinctly different diseases. They are almost entirely different in their etiologies, in their pathophysiology and in their therapies. It's very important to highlight key distinctions between the two diseases and it's not easy to make common considerations.

- As we can see from literature, baseline resting left ventricular global longitudinal strain could provide incremental prognostic utility in asymptomatic patients with ≥3+ primary MR and preserved left ventricular ejection fraction. It could also aid in helping determine the timing of surgery. In this study the authors describe in the mild MR subgroup, which mainly consists of primary etiology, a substantially greater number of individuals with reduced GLS, in comparison with LVEF. These findings could support the ability of GLS to detect subclinical cardiac involvement, however we'd need to understand why GLS is low in this subpopulation, if cardiac damage and mitral regurgitation are two different diseases or should other risk factors have a role in this. Furthermore, this consideration could call into question the use of GLS as a parameter for the choice of cardiac surgery in patients with significant mitral regurgitation and preserved LVEF. Please discuss this point.

- Currently, the definition of "normal" LV-GLS values in subjects free of cardiovascular disease remains to be fully elucidated. In literature, there are studies that describe the higher-than-normal LV-GLS values in chronic severe MR, as the pathophysiological state (reduced afterload and increased preload) results in a state of hypernormal LV function. This finding also suggests that LV-GLS is likely load-dependent and might have to be corrected for LV volumes. Please highlight this point.

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