ESC European Society of Cardiology

European Heart Journal - Cardiovascular Imaging (2022) **23**, 765–766
https://doi.org/10.1093/ehjci/jeac066

EDITORIAL

Optimization of guideline-directed medical treatment to reduce secondary mitral regurgitation: treat the ventricle, not only the valve

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Online publish-ahead-of-print 25 April 2022

This editorial refers to 'Guideline directed *medical* therapy and reduction of secondary mitral regurgitation' by Spinka G. *et al.*, https://doi.org/10.1093/ehjci/jeac068.

Secondary mitral regurgitation (SMR) is frequently observed in patients with heart failure with reduced ejection fraction (HFrEF).[1,2] In these patients, left ventricular (LV) remodelling results in papillary muscle displacement and tethering of the mitral valve leaflets, thereby disturbing the delicate balance between tethering and closing forces. Significant SMR increases the pulsatile load on the left atrium and the pulmonary vasculature and causes an additional volume overload on the failing LV, thereby increasing diastolic wall stress and accelerating LV adverse remodelling.[3,4] It is therefore not surprising that SMR is associated with reduced quality of life as well as an increased risk of heart failure (HF) hospitalization and all-cause mortality.[1,2]

Significant efforts have been undertaken to reduce SMR severity and improve long-term prognosis in patients with significant SMR. However, recent trials have mainly focused on intervening at the level of the mitral valve leaflets instead of targeting the LV myocardium. Although the Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation (COAPT) trial demonstrated that percutaneous edge-to-edge repair may improve outcomes in selected patients with SMR,[5] a significant percentage of patients who underwent transcatheter mitral valve repair still had HF hospitalization or died within 2 years after MitraClip.[5] These data emphasize the need for further research to improve prognosis of patients with SMR. From a pathophysiological point of view, it seems evident that LV dysfunction is a major driving force of SMR and therapies should therefore aim at improving the imbalance between tethering and closing forces by treating the underlying, diseased LV myocardium. The Heart Failure Association (HFA), the European Association of Cardiovascular Imaging (EACVI), the European Heart Rhythm Association (EHRA), and the European Association of Percutaneous Cardiovascular Interventions (EAPCI) recently published a joint position statement on the management of mitral regurgitation in patients with HFrEF, underscoring the importance of optimizing the guideline-directed medical therapy (GDMT) as the first essential step in the management of symptomatic moderate or severe SMR.[6] However, echocardiographic evidence of improvement in SMR during the GDMT is limited and the question remains whether the GDMT can effectively reduce SMR severity and change the outcome.

Spinka[7] further addresses this gap in knowledge and specifically targets the issue of improvement in SMR during the GDMT, using echocardiography. The authors retrospectively included 261 patients with HFrEF (i.e. LV ejection fraction <40% with HF signs and/or symptoms), excluding patients with primary mitral valve disease or other significant primary valve diseases and previous mitral valve repair/replacement. Accordingly, the patients were divided into two groups: the first group representing patients with maximally tolerated GDMT and the second group containing patients in whom GDMT titration was still in progress. Titration of the GDMT was defined as (i) initiation of HF medication, (ii) an increase of at least 25% while reaching at least 50% of the maximum recommended dosage of the GDMT, or (iii) therapy switch from angiotensin-converting enzyme inhibitor (ACEi)/angiotensin-receptor blocker (ARB) to angiotensin-receptor-neprilysin inhibitor (ARNI). To analyse the differences in LV remodelling between patients with and without a reduction in SMR, echocardiographic measurements were performed at two time intervals and compared between the two cohorts. Reduction of SMR was defined as a decrease of at least one degree of integratively assessed SMR with transition to at least moderate SMR from baseline to follow-up. The authors demonstrate that

The opinions expressed in this article are not necessarily those of the Editors of *EHJCI*, the European Heart Rhythm Association or the European Society of Cardiology.

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SMR severity improved by at least one degree in 39% of patients undergoing GDMT titration and that this reduction in SMR severity was accompanied by reverse LV remodelling and clinical improvement. Furthermore, the effects of GDMT titration were significantly associated with SMR reduction. Angiotensin-receptor-neprilysin inhibitor, as well as the combined dosage effects of (i) ACEi/ARB and mineralocorticoid receptor antagonists (MRAs), (ii) beta-blockers and MRAs, and (iii) ACEi/ARB, beta-blockers, and MRAs were all significantly associated with SMR improvement. It is important to note that most patients in whom titration was still in progress, already received at least some dose of the GDMT (i.e. 91% beta-blocker, 88% ACEi/ARB/ARNI, and 69% MRAs) and therefore the main effects on reduction in SMR severity were likely caused by uptitration or a switch from ACEi/ARB to ARNI.

The results of the current study expand on previous studies, showing that the GDMT can reduce SMR severity by attenuating or partially reversing LV remodelling, thereby improving LV geometry and function.[8–11] Multiple underlying mechanisms may explain the reduction in SMR severity by uptitration of the GDMT. First, the GDMT reduces afterload and/or pre-load and improves LV contractility, thereby (partially) restoring the imbalance between tethering and closing forces. Second, the reduction in LV volume decreases the annular area, thereby improving leaflet coaptation. Third, mitral valve leaflet tethering causes an overexpression of tissue growth factor beta, which induces profibrotic changes of the leaflets and prevents adequate leaflet coaptation.[12] Losartan has been shown to suppress tissue growth factor beta overexpression, thereby potentially reducing or reversing these profibrotic changes.[12]

Whether the beneficial effects of the GDMT on SMR are long-lasting and whether these beneficial effects will translate into improved prognosis remain currently unknown. In addition, the role of recently introduced HF treatments, such as sodium-glucose co-transport 2 inhibitors, in the treatment of SMR requires further investigation. The data presented by Spinka,[7] however, support contemporary HF guidelines with respect to the fact that the (optimized) GDMT is the first essential step in the management of symptomatic moderate or severe SMR, before resorting to percutaneous valve repair, cardiac resynchronization, or revascularization.

Conflict of interest: The Department of Cardiology of Leiden University Medical Centre received research grants from Abbott Vascular, Bayer, Biotronik, Bioventrix, Boston Scientific, Edwards Lifesciences, GE Healthcare, and Medtronic. J.J.B. received speaker fees from Abbott Vascular. J.S. and P.v.d.B. have nothing to disclose.

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