Revisiting the Role of Guideline-Directed Medical Therapy for Patients with Heart Failure and Severe Functional Mitral Regurgitation

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KEYWORDS

• Heart failure • Medical therapy • Mitral regurgitation • MitraClip

KEY POINTS

- Patients with heart failure often have mitral regurgitation, which can create a vicious cycle.
- Medical therapy remains the mainstay of treatment in this setting.
- This review revisits the role of medical therapy and its optimization for severe functional mitral regurgitation.

INTRODUCTION

Heart failure (HF) is a growing epidemic that affects more than 6 million adults in the United States.[1] Functional mitral regurgitation (FMR) is common in patients with HF, and reported to be prevalent in more than 16,000 cases per 1 million population.[2] FMR frequently generates a vicious cycle of worsening HF and MR, in which a dilated left ventricle from volume overload results in a dilated mitral annulus with tethered mitral leaflets (worsening of FMR), which in turn can lead to progression in HF. A recent meta-analysis of 53 studies and 45,900 patients revealed that FMR was associated with increased risks of cardiac mortality, HF hospitalization, transplantation, and death.[3]

Worsening HF and MR can be modified in several ways in the contemporary era. The valid medical interventions include medical therapy, surgical intervention, or transcatheter intervention. Medical therapy remains the mainstay of

Conflicts of Interest: S. Kohsaka received lecture fees and research grants from Bristol Myers Squibb, Bayer Yakuhin and Daiichi Sankyo. All other authors have no relevant conflict of interest to disclose.
Funding: This work was supported by the Grants-in-Aid for Scientific Research from the Japan Society for the Promotion of Science (KAKENHI; No. 25460630, 25460777, 16H05215, https://kaken.nii.ac.jp/ja/index/).
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Cardiol Clin 39 (2021) 255–265
https://doi.org/10.1016/j.ccl.2021.01.008

treatment for patients with HF and a reduced ejection fraction (HFrEF), including patients with FMR. The American Heart Association/American College of Cardiology guidelines indicate that guideline-directed medical therapy (GDMT) is the first-line therapy for HFrEF and FMR, and the only Class I indication for treating FMR.[4] More recent large-scale randomized controlled trials have also indicated that sodium-glucose co-transporter-2 (SGLT2) inhibitors may help to decrease the risk of HF hospitalization and mortality.[5,6]

This review aims to cover the role of drug therapy and its optimization in the contemporary era for treating severe FMR.

GUIDELINE-DIRECTED MEDICAL THERAPY IN CLASSIC HEART FAILURE STUDIES

Neurohormonal antagonists can be prescribed to reduce morbidity and mortality among patients with HFrEF (**Table 1**). These drugs lead to a reduction in the left ventricular end-diastolic volume (LVEDV), which can be expected to reduce FMR if the degree of FMR is proportionate to the LVEDV. However, it is unclear whether the response of FMR to GDMT is an independent predictor of a favorable prognosis. Clinical trials of neurohormonal antagonists (usually in combination with loop diuretics) for HFrEF have typically not evaluated FMR severity before and after treatment, and the evidence to support pharmacologic interventions for FMR is derived from small-scale studies.

Treatment using angiotensin-converting enzyme inhibitors (ACEIs)/ angiotensin receptor blockers (ARBs) decreases the degree of FMR, typically in patients with mild-to-moderate MR. A high dose is usually required to achieve this benefit, and high doses are often specifically prescribed to patients who have a higher pretreatment LVEDV. A randomized trial evaluated 28 ambulatory patients with systolic ischemic HF (New York Heart Association functional class II–III; mean LVEF of 29%) who had grade 2 or higher FMR (>5 cm^2 regurgitation area on color flow Doppler ultrasound examination). The mitral regurgitation area decreased from the baseline value after the patient received a dose of 50 mg/d (3.1 cm^2), with a further decrease at a dose of 100 mg/d (5.3 cm^2), and these findings were associated with an increased forward stroke volume.[7]

Beta-blockers are also efficient for ameliorating FMR in patients with ischemic and nonischemic HF. For example, 1 study of 257 patients with chronic HF and LV systolic dysfunction revealed that carvedilol decreased the LVEDV and FMR severity (28% of patients had lower grade FMR after 24 months of treatment), with the extent of reverse ventricular remodeling being inversely related to the baseline degree of LV dilatation and independent of FMR or its severity.[8] Another study of severe MR evaluated 45 consecutive patients with chronic ischemic and nonischemic HF, who received carvedilol and were matched to a control group. After 6 months of carvedilol treatment, the LVEF had increased from 24% to 29%, which was associated with a significant reduction in the mitral regurgitant volume (50 mL/min vs 16 mL/min) that was not observed in the control group (57 mL/min vs 47 mL/min).[9]

A more recent study of 163 consecutive patients with HFrEF (LVEF of <40%) and grade 3 to 4+ FMR receiving maximally tolerated neurohormonal antagonists demonstrated that 38% of the 50 patients with severe FMR at baseline improved to nonsevere FMR, and 18% of the patients with nonsevere FMR at baseline progressed to severe FMR (median follow-up period of 50 months). Patients with sustained severe FMR or worsening of FMR had a 13% increase in their LVEDV index, and patients who experienced an improvement in their severe FMR had a 2% decrease in their LVEDV index.[10] Moreover, severe FMR was the most important independent predictor of major adverse cardiac events (a composite of all-cause death

Table 1
The drug agents listed in the clinical practice guidelines (guideline-directed medical therapy) for HF and their proven effects

Drug Agent	Proven Effect
Beta-blockers	Decrease the risks of HF hospitalization and mortality
ACEIs or ARBs	Decrease the risks of HF hospitalization and mortality
Angiotensin receptor neprilysin inhibitors to replace ACEIs or ARBs	Decrease the risks of HF hospitalization and mortality
Mineralocorticoid receptor antagonists	Decrease the risk of mortality
Ivabradine	Decrease the risk of HF hospitalization

Abbreviations: ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers.

and heart transplantation or hospitalization for HF and/or malignant arrhythmias), regardless of sustained or worsening FMR status, with an adjusted odds ratio of 2.5 (95% confidence interval, 1.5–4.3).[10]

Among the studies described, FMR improvement was observed in less than one-half of the treated population.[7–10] Thus, it is important to consider whether it is possible to achieve earlier identification of patients who will not respond to medical therapy or who will develop more severe FMR. The increasing complexity of FMR treatment among patients with HF also highlights the need to achieve earlier and more frequent referrals to centers with expertise in treating these patients. Thus, early involvement of HF teams is essential for rapid treatment optimization in patients with FMR and HF, because other interventions might be possible if medical therapy fails, depending on the patient's condition.

Interestingly, patients who do not experience an improvement in MR severity after medical therapy have a high incidence of left bundle branch block.[10] Thus, in addition to pharmacologic management, cardiac resynchronization therapy (CRT) can also facilitate LV reverse remodeling and decrease FMR, especially in patients with ventricular dyssynchrony.[11] A study of 24 patients with HF with left bundle branch block revealed that CRT was associated with a 50% decrease in the effective regurgitant orifice area (EROA; from 25 mm^2 to 13 mm^2) during the acute phase of HF treatment.[12] Longer term beneficial effects have also been identified in large-scale randomized trials, such as the Multicenter InSync Randomized Clinical Evaluation (MIRACLE) trial, in which CRT produced significant reductions in the LV end-systolic and end-diastolic dimensions and the mitral regurgitant jet area (-2.7 cm^2 [CRT] vs -0.5 cm^2 [control] at 6 months).[13] The detailed effects of CRT on moderate-to-severe FMR were evaluated in a study of 98 consecutive patients who underwent CRT according to the current guidelines,[11] in which a significant improvement (reduction by at least 1 severity grade) was observed in 49% of patients. The survival rate was higher among patients with MR improvement, relative to among patients without MR improvement, and MR improvement was an independent prognostic factor (hazard ratio, 0.35; 95% confidence interval, 0.13–0.94).[11]

These findings highlight the importance of care when selecting CRT treatment for patients with FMR. A lack of response to CRT may be related to an inability to pace scarred regions, especially in patients with ischemic MR. The reported independent predictors of FMR reduction after CRT include anteroseptal to posterior wall radial strain dyssynchrony (>200 ms), an end-systolic dimension index of less than 29 mm/m^2, and lack of scarring at the papillary muscle insertion.[14]

GUIDELINE-DIRECTED MEDICAL THERAPY IN SURGICAL STUDIES

The surgical treatment of isolated FMR is associated with improvements in symptoms, quality of life, and reverse LV remodeling. However, its effects on FMR with LV dysfunction remains controversial, because the prognosis of FMR is mainly associated with LV dysfunction and its etiology.[15] Surgical intervention for FMR has been evaluated in randomized controlled trials conducted by the Cardiothoracic Surgical Trials Network, which revealed that mitral valve repair was associated with a significantly higher rate of recurrent moderate or severe MR at 2 years (58%), relative to mitral valve replacement (3.8%). Although the 30-day mortality rate tended to be higher in the replacement group (4.0% vs 1.6%), there were no significant differences in the rates of all-cause mortality and major adverse cardiac or cerebrovascular events at 2 years.[16] The second Cardiothoracic Surgical Trials Network trial compared coronary artery bypass grafting (CABG) alone to CABG plus mitral valve repair in 301 patients with coronary artery disease and moderate FMR. Moderate or severe MR was significantly more common in the CABG group (32.3%) than in the CABG plus mitral repair group (11.2%), although the 2 groups had similar rates of all-cause mortality, major adverse cardiac or cerebrovascular events, readmission, and cardiovascular readmission.[17]

To date, no studies have shown that mitral valve surgery improves survival in FMR cases, relative to GDMT alone.[18–22] However, no surgical studies have required medical therapy to be optimized by HF specialists. One study evaluated whether mitral valve annuloplasty or HF medications influenced mortality among patients with FMR and LV dysfunction using propensity score matching analysis. That study revealed no demonstrable change in mortality after annuloplasty, although reduced risks of mortality were associated with treatment using ACEIs (hazard ratio, 0.65; 95% confidence interval, 0.44–0.95) or beta-blockers (hazard ratio, 0.59; 95% confidence interval, 0.42–0.83), and a significantly increased risk of mortality was associated with digoxin treatment (hazard ratio, 1.66; 95% confidence interval, 1.15–2.39).[23] The Effectiveness of Surgical Mitral Valve Repair versus Medical Treatment for People with Significant Mitral Regurgitation and Non-

ischemic Congestive Heart Failure trial (SMMART-HF, NCT0068140) was designed to compare the safety and effectiveness of GDMT with or without surgical mitral annuloplasty for nonischemic patients with HF with FMR, although the trial was terminated early owing to inadequate enrollment. A similar patient population was tested in the Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional MR trial (COAPT). Therefore, the current guideline recommendations for mitral valve surgery as FMR treatment are more conservative than for other therapeutic options. According to the 2020 Focused Update of the American College of Cardiology Expert Consensus Decision Pathway, mitral valve surgery (either replacement or repair) is considered reasonable at the time of other cardiac surgery and can be considered as an isolated procedure for select patients with advanced New York Heart Association functional class, despite guideline-directed management including CRT when indicated.[24] In addition, patients who do not respond to CRT may be considered for transcatheter mitral valve repair using the MitraClip device if the anatomic findings are appropriate and the procedure is selected by a multidisciplinary heart team.

The main determinants of surgical failure to treat FMR might be related to the heterogeneity of the patients who were included in the clinical trials, and it is unclear whether more advanced surgical techniques and/or better patient selection might improve outcomes. For example, atrial FMR (FMR solely owing to annular dilation) is a distinct clinical form of FMR only recently recognized. Its prevalence and efficacy of surgical and medical therapy is still scarcely investigated, although small-scale studies have shown a possible benefit of ARB to leaflet remodeling in patients with atrial FMR, the entity is still under-recognized and under-reported.[25]

The trials listed in the present section typically included a broad range of patients with MR based on annular dilation, multiple jets, advanced ventricular remodeling, excessive tethering, end-systolic interpapillary muscle distance, and systolic sphericity index. A recent meta-analysis revealed that mitral valve repair is associated with lower operative mortality than valve replacement in patients with ischemic MR.[26] This finding also agrees with evidence from the first Cardiothoracic Surgical Trials Network trial that suggested that repair tended to produce better perioperative survival, although the 30-day mortality rate was almost 3-fold higher, which is likely because that study was not powered to evaluate 30-day mortality.[16]

GUIDELINE-DIRECTED MEDICAL THERAPY IN MitraClip STUDIES

The MITRA-FR trial was a multicenter, randomized, open-label clinical trial of transcatheter mitral valve repair using the MitraClip, which was compared with medical therapy among symptomatic French patients with FMR. The key inclusion criteria were severe MR (EROA of >20 mm^2 or a regurgitant volume of >30 mL/beat), an EF of 15% to 40%, at least one HF-related hospitalization during the previous year, and ineligibility for surgery. Medical therapy was optimized by local investigators and most patients were receiving loop diuretics, beta-blockers, and ACEIs, ARBs, or angiotensin receptor neprilysin inhibitors (ARNIs). The rates of CRT were 30% in the MitraClip arm and 23% in the control arm.[27]

The COAPT trial was an American multicenter randomized controlled trial that compared the MitraClip and GDMT with GDMT alone for patients with symptomatic moderately severe or severe MR. The key inclusion criteria were moderately severe (3+) or severe (4+) MR confirmed by a core echocardiography laboratory, an EF of 20% to 50%, an LVEDV of 70 mL or less, at least 1 HF-related hospitalization during the last year, and/or an elevated B-type natriuretic peptide concentration (>300 pg/mL adjusted for body mass index), and not a candidate for mitral valve surgery at the enrolling center. A central eligibility committee confirmed that all patients fulfilled the enrollment criteria (including the use of maximal GDMT doses).[28]

Both trials included high and very similar proportions of patients who were receiving GDMT at baseline. The baseline use of renin–angiotensin system inhibitors was higher in the MITRA-FR trial (mean, 73.7%; device arm, 73.0%; control arm, 74.3%) than in the COAPT trial (mean, 67.1%; device arm, 71.5%; control arm, 62.8%). Furthermore, more patients in the MITRA-FR trial received a combination of renin–angiotensin system inhibitors and ARNIs (11.1% vs 3.6%). However, similar rates of beta-blocker use were observed in the MITRA-FR trial (mean, 89.5%; device arm, 88.2%; control arm, 90.8%) and in the COAPT trial (mean, 90.4%; device arm, 91.1%; control arm, 89.7%).

The discrepancy in the results of these 2 trials might be related to only the COAPT trial requiring patients to use maximally tolerated GDMT before enrollment. In addition, it is not clear what proportion of patients in the COAPT trial were receiving target doses of the recommended drugs or had blood pressure levels that would have prohibited further dose titration. Nevertheless, the device

arm of the COAPT trial had a significantly higher beta-blocker dose, relative to the control arm. Furthermore, blood pressure levels increased after the MitraClip procedure and allowed for further treatment optimization in the device arm (increase dose by >100% or new drug class started: 8.6% in the device arm and 3.8% in the control arm; $P = .01$). Thus, patients who undergo transcatheter mitral valve repair using the MitraClip might be able to tolerate higher GDMT doses that were not previously tolerated.[29]

MEDICAL THERAPY IN PROPORTIONATE AND DISPROPORTIONATE MITRAL REGURGITATION

The patients in the COAPT trial had MR severity that was disproportionate to their LV remodeling, whereas patients in the MITRA-FR trial had larger LV volumes and less severe MR.[30] The difference in the prevalences of proportionate and disproportionate MR is widely thought to be related to different definitions of MR severity that are used in the American and European clinical practice guidelines. For example, the 2017 American guidelines characterize MR severity according to the magnitude of regurgitant flow, with severe MR identified based on a regurgitant fraction of 50% or greater, a regurgitant volume of 60 mL or greater, or an EROA of 40 mm^2 or greater.[4] In contrast, the European guidelines determined the severity of MR based on prognosis; patients with an EROA higher than 20 mm^2 are known to have a mortality risk compared with those with normal EROA values, severe MR was considered present for all patients with an EROA of 20 mm^2 or greater.[31] It is noteworthy that many of these patients with MR might have had their prognosis determined by the severity of LV dysfunction, rather than MR.

The COAPT trial protocol required all patients to be receiving maximally tolerated GDMT, which might have promoted the inclusion of patients with disproportionate MR. For example, patients with proportionate MR might have responded favorably to GDMT (based on the regurgitant flow magnitude) and thus been excluded from the COAPT trial. In contrast, the MITRA-FR trial participants seemed to have a higher likelihood of proportionate MR based on the echocardiographic inclusion criteria (eg, low EROA criteria without a designated upper limit for LV volumetry). In this context, it might be difficult to achieve and maintain coaptation of the valve leaflets using mechanical clips for a markedly dilated LV that remains dilated during long-term follow-up (as in the MITRA-FR trial).[29] Thus, based on the distinction between proportionate and disproportionate MR, recent reviews and commentaries have suggested that medical therapy should be directed primarily at improving LV function in patients with proportionate MR. If LV dilatation explains the degree of MR, treatments that lead to reversal of LV remodeling can decrease the degree of MR and thus decrease morbidity and mortality. In contrast, patients with disproportionate MR should undergo interventions that are directed toward the mitral valve apparatus (including the annulus, chordae, and papillary muscles). In these patients, drugs that decrease the LV volume would not be expected to ameliorate the MR, which might respond only to treatments that restore the integrity of the leaflets or supporting structures. **Table 2** includes a summary of the findings from related studies.

The MITRA-FR and COAPT trials revealed that amelioration of functional MR might be achieved using ACEIs, ARBs, beta-blockers, and ARNIs.[27,28] Patients whose MR responds favorably to these drugs have the largest pretreatment LVEDV,[32] whereas patients with disproportionate MR do not respond favorably to medical therapy.[28] The presence of a left bundle branch block is a principal factor that is associated with MR nonresponse to neurohormonal antagonists.[10,28] Later subsets of patients (defined based on the degree of regurgitation, degree of LV remodeling/dysfunction, or the combination of these parameters) from the MITRA-FR trial were evaluated to identify patients that might benefit from percutaneous repair or medical therapy alone.[27,33] However, in both the intention-to-treat and per-protocol analyses, there were no significant interactions between the trial group and any of those subsets in terms of a composite outcome involving all-cause death or unplanned hospitalization for HF at 24 months. Nevertheless, it should be noted that the most disproportionate subset was defined as an EROA 30 mm^2 or greater and an LVEDV of less than 242 mL. Bartko and colleagues[34] recently characterized the prognostic importance of proportionate and disproportionate MR among 291 patients with functional MR and LV systolic dysfunction. In that study, patients with disproportionate functional MR had a nearly 2-fold increase in mortality, although it is interesting that similar survivals were observed for patients with severe proportionate MR and patients with nonsevere MR. Therefore, it is possible that patients with proportionate MR might respond favorably to GDMT, whereas patients with disproportionate MR might not, although further studies are needed to validate this attractive concept in the clinical setting.

ROLE OF NOVEL HEART FAILURE AGENTS

Recent clinical evidence has identified benefits in cases of HFrEF after treatment using some novel

Table 2
GDMT for proportionate and disproportionate functional moderate-to-severe mitral regurgitation

Cohort	Proportionate or Disproportionate	GDMT	LVEF	LVEDV	EROA	Effect on MR	Effect on clinical Events	Ref.
COAPT (control arm)	Disproportionate	Anti-HF therapy using loop diuretics (89%), beta-blockers (90%), ACEIs (27%), ARBs (23%), and ARNIs (3%), according to the 2017 AHA guidelines.[31] The therapy was maximized at the time of enrollment and optimized by a heart team, which included HF specialists, during follow-up (control arm only).	30	191 ± 73	40 ± 15	Decreased, but less effective than the Mitra-Clip arm (reduction of MR ≤2: 40% vs 87% at 12 mo)	Less effective than the Mitra-Clip arm (composite outcome: 66% vs 45% at 24 mo)	Stone et al,[28] 2018
MITRA-FR (control arm)	Proportionate	Pre-enrollment anti-HF therapy using loop diuretics (98%), beta-blockers (91%), ACEI/ARB (74%), and ARNI (12%), according to the 2016 ESC guidelines.[32] Therapy was optimized by local investigators (control arm only).	33	250 ± 75	31 ± 11	Unchanged and less effective than the Mitra-Clip arm (ΔRV: −4 mL vs −24 mL at 12 mo)	Comparable with the Mitra-Clip arm (composite outcome: 51% vs 57% at 12 mo)	Obadia et al,[27] 2018

MITRA-FR (subgroup in control arm)	Equivocal or disproportionate	Pre-enrollment anti-HF therapy using loop diuretics (98%), beta-blockers (91%), ACEI/ARB (74%), and ARNI (12%), according to the 2016 ESC guidelines.[32] Therapy was optimized by local investigators (control arm only).	33 (control arm only)	<242	≥30	N/A	Comparable with the Mitra-Clip arm (composite outcome: 63% vs 48% at 24 mo)	Bartko et al,[34] 2019
Severe MR	Disproportionate (if LBBB)	Anti-HF therapy using loop diuretics (86%), beta-blockers (94%), and ACEI/ARBs (76%).	27	~200	N/A	Decrease from severe to nonsevere MR	Mortality rate of ~20% at 56 mo	Nasser et al,[10] 2017
Severe MR	Disproportionate	Anti-HF therapy using ACEI/ARBs (93%), beta-blockers (86%), and MRAs (63%).	25 (total)	~200	~30	N/A	Less effective than the proportionate group (mortality rate: 50% vs 25% at 80 mo)	McMurray et al,[35] 2014

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; AHA, American Heart Association; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; EROA, effective regurgitant orifice area; ESC, European Society of Cardiology; LBBB, left bundle branch block; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; MRA, mineralocorticoid receptor antagonist; N/A, not applicable.

agents in addition to GDMT (ACEIs, ARBs, beta-blockers, and mineralocorticoid receptor antagonists). However, there are few data regarding the effects of these agents on cardiac structure, cardiac function, and FMR.

Sacubitril/valsartan is an ARNI that is associated with a decrease (vs enalapril) in clinical adverse events, such as cardiovascular death or hospitalization for acute HF, among patients with HFrEF.[35] Some studies have identified reverse LV remodeling after ARNI administration,[36–38] and one of those studies revealed that a decrease in MR was associated with an improved LVEF and a decreased LV volume.[37] Kang and colleagues[39] performed a multicenter prospective study of patients with HFrEF who were randomized to receive sacubitril/valsartan or valsartan, and evaluated the longitudinal change in FMR as a primary end point. At 12 months after randomization, the sacubitril/valsartan group had significant decreases in the EROA and regurgitant volume, although the lack of a significant difference in blood pressure between the 2 groups suggests that the effects of sacubitril/valsartan on FMR were not related to reduced afterload.

Improved clinical outcomes can also be observed after treatment using SGLT2 inhibitors, such as empagliflozin[6] and dapagliflozin,[5] especially in terms of the acute HF hospitalization rate, regardless of whether the patient has diabetes.[5,6] These agents also consistently provide a decrease in LV mass and an improvement in LV diastolic function (represented by E/e' and left atrial volume) in patients with diabetes.[40–42] Nevertheless, other studies revealed only a modest improvement in LVEF after SGLT2 inhibitor treatment for patients with HF,[40,43] and these drugs' effects on LV systolic function or geometry remain controversial.[42,44–46] One study used MRI to compare cardiac geometry between patients who received SGLT2 inhibitors or a placebo, and revealed that SGLT2 inhibitors did not produce any noticeable change in cardiac geometry.[46] However, those studies only evaluated small samples of patients ($n < 100$) and did not directly evaluate whether SGLT2 inhibitors influenced FMR. Thus, further large-scale studies are needed to determine whether SGLT2 inhibitors can influence FMR in patients with HF.

Vericiguat is a soluble guanylate cyclase stimulator that was shown to decrease the incidences of cardiovascular death or HF hospitalization among patients with HFrEF.[47] A phase II trial also revealed that vericiguat provided a marginal increase in LVEF, but did not influence LV volume.[48] No reports have described its effects on other echocardiographic parameters, including FMR.

REGIONAL DIFFERENCES IN HEART FAILURE CARE

Among patients with chronic HF, numerous studies have identified substantial regional variations in the patterns of GDMT prescriptions for patients with HFrEF.[49–51] A report from the National Cardiovascular Registry Practice Innovation and Clinical Excellence (PINNACLE) evaluated 40 American cardiology institutions and revealed substantial variability in the use of ACEIs/ARBs (44%–100%) and beta-blockers (49%–100%).[49] A study of an international registry that included 547 centers in 36 countries from Africa, Asia, Australia, Europe, the Middle East, and the Americas revealed globally satisfactory adherence to GDMT for HFrEF, albeit with low adherence in some regions, particularly in Central and Eastern Europe.[50] The latest report from the multinational ASIAN-HF registry, which included 46 centers in 11 Asian countries, revealed that physicians in high-income countries (eg, Singapore, Hong Kong, Korea, and Japan) were more likely to prescribe the guideline-recommended combination of ACEIs/ARBs and beta-blocker therapies, relative to physicians in the low-income countries.[51] Furthermore, that study revealed regional variations in using the guideline-recommended doses and the mean doses that were achieved during GDMT therapy. Interestingly, Japan had the second highest use of beta-blockers (91%) but the lowest achieved dose, with 41% of patients receiving less than 25% of the guideline-recommended dose. These variations in prescription patterns are likely related to several factors: (1) differences in patient age, frailty, and comorbidities, (2) physician tendency to focus on symptom relief, rather than mortality reduction, as well as under-recognition of the importance of GDMT, and (3) treatment costs or access to medical care. There is also significant variability in the etiologic factors, precipitants, and points of hospital entry in cases of acute HF.[52] Finally, the difference may reflect variations in treatment algorithms, a lack of guideline implementation, local medication availability, variability in regional practice patterns, or difficulty in generalizing clinical trial data to different regions of the world.

Maggioni and colleagues[53] have demonstrated that patients with MR are likely to receive inappropriate GDMT. However, to date, no studies have identified regional variations in GDMT among patients with HF and severe FMR. Given that patients with HFrEF with severe FMR are generally older,

frail, and have comorbidities,[28,54] physicians may be less likely to optimize GDMT and may instead emphasize symptom relief over a decrease in the risk of mortality.[55] Thus, it is plausible that similar regional variations exist in the optimization of GDMT among patients with severe FMR. Research is needed to identify barriers to implementing the recommended GDMT and learning from practice patterns in other regions, which may help to improve the quality of medical management and outcomes for patients with HFrEF with FMR.

SUMMARY

Baseline GDMT remains the cornerstone of treatment for FMR when considering surgical or transcatheter treatments. Early involvement of clinical teams including physicians who are familiar with GDMT is essential for the rapid treatment optimization in patients with FMR and HF. Surgical and percutaneous interventions would become valid options if medical therapy fails after thorough investigation of patient's overall condition. However, systematic evaluation on the effect of GDMT in broader spectrum of FMR outside of substudies from recent clinical trials (eg, MITRA-FR or COAPT) is lacking. Future clinical studies, with well-structured clinical and echocardiographic variables with their serial assessment, along with implementation of GDMT (including novel HF agents) are needed.

CLINICS CARE POINTS

- Guideline-directed medical therapy remains the mainstay of treatment for patients with functional mitral regurgitation.
- This review revisits the role of medical therapy and its optimization for severe functional mitral regurgitation.

REFERENCES

1. Benjamin EJ, Muntner P, Alonso A, et al. Heart disease and stroke statistics – 2019 update: a report from the American Heart Association. Circulation 2019;139:e56–528.
2. de Marchena E, Badiye A, Robalino G, et al. Prevalence of the different Carpentier classes of mitral regurgitation: a stepping stone for future therapeutic research and development. J Card Surg 2011;26:385–92.
3. Sannino A, Smith RL, Schiattarella GG, et al. Survival and cardiovascular outcomes of patients with secondary mitral regurgitation: a systematic review and meta-analysis. JAMA Cardiol 2017;2:1130–9.
4. Nishimura RA, Otto CM, Bonow RO, et al. 2017 AHA/ACC focused update of the 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines. Circulation 2017;135:e1159–95.
5. McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. N Engl J Med 2019;381:1995–2008.
6. Packer M, Anker SD, Butler J, et al. Cardiovascular and renal outcomes with empagliflozin in HF. N Engl J Med 2020. https://doi.org/10.1056/NEJMoa2022190.
7. Seneviratne B, Moore GA, West PD. Effect of captopril on functional mitral regurgitation in dilated heart failure: a randomised double blind placebo controlled trial. Br Heart J 1994;72:63–8.
8. Kotlyar E, Hayward CS, Keogh AM, et al. The impact of baseline left ventricular size and mitral regurgitation on reverse left ventricular remodeling in response to carvedilol: size does not matter. Heart 2004;90:800–1.
9. Capomolla S, Febo O, Gnemmi M, et al. Beta-blockade therapy in chronic heart failure: diastolic function and mitral regurgitation improvement by carvedilol. Am Heart J 2000;139:596–608.
10. Nasser R, Van Assche L, Vorlat A, et al. Evolution of functional mitral regurgitation and prognosis in medically managed heart failure patients with reduced ejection fraction. JACC Heart Fail 2017;5:652–9.
11. van Bommel RJ, Marsan NA, Delgado V, et al. Cardiac resynchronization therapy is a therapeutic option in patients with moderate-to-severe functional mitral regurgitation and high operative risk. Circulation 2011;124:912–9.
12. Breithardt OA, Sinha AM, Schwammenthal E, et al. Acute effects of cardiac resynchronization therapy on functional mitral regurgitation in patients with advanced systolic heart failure. J Am Coll Cardiol 2003;41:765–70.
13. Abraham WT, Fisher WG, Smith AL, et al. Cardiac resynchronization in chronic heart failure. N Engl J Med 2002;346:1845–53.
14. Onishi T, Onishi T, Marek JJ, et al. Mechanistic features associated with improvement in mitral regurgitation after cardiac resynchronization therapy and their relation to long-term patient outcomes. Circ Heart Fail 2013;6:685–93.
15. De Bonis M, Lapenna E, Verzini A, et al. The recurrence of mitral regurgitation parallels the absence of left ventricular reverse remodeling after mitral

repair in patients with advanced dilated cardiomyopathy. Ann Thorac Surg 2008;85(3):932–9.
16. Goldstein D, Moskowitz AJ, Gelijns AC, et al. Two-year outcomes of surgical treatment of severe ischemic mitral regurgitation. N Engl J Med 2016; 374:344–53.
17. Michler RE, Smith PK, Parides MK, et al. Two-year outcomes of surgical treatment of moderate ischemic mitral regurgitation. N Engl J Med 2016; 374:1932–41.
18. Bolling SF, Pagani FD, Deeb GM, et al. Intermediate-term outcome of mitral reconstruction in cardiomyopathy. J Thorac Cardiovasc Surg 1998;115:381–8.
19. Rothenburger M, Rukosujew A, Hammel D, et al. Mitral valve surgery in patients with poor left ventricular function. Thorac Cardiovasc Surg 2002;50(6):351–4.
20. Gummert JF, Rahmel A, Bucerius J, et al. Mitral valve repair in patients with end-stage cardiomyopathy: who benefits? Eur J Cardiothorac Surg 2003;23(6): 1017–22.
21. Bishay ES, McCarthy PM, Cosgrove DM, et al. Mitral valve surgery in patients with severe left ventricular dysfunction. Eur J Cardiothorac Surg 2000;17: 213–21.
22. Chen FY, Adams DH, Aranki SF, et al. Mitral valve repair in cardiomyopathy. Circulation 1998;98: II124–7.
23. Wu AH, Aaronson KD, Bolling SF, et al. Impact of mitral valve annuloplasty on mortality risk in patients with mitral regurgitation and left ventricular systolic dysfunction. J Am Coll Cardiol 2005;45(3):381–7.
24. Bonow RO, O'Gara PT, Adams DH, et al. 2020 focused update of the 2017 ACC Expert Consensus Decision Pathway on the management of mitral regurgitation: a report of the American College of cardiology Solution Set Oversight committee. J Am Coll Cardiol 2020;75(17):2236–70.
25. Deferm S, Bertrand PB, Verbrugge FH, et al. Atrial functional mitral regurgitation: JACC review topic of the week. J Am Coll Cardiol 2019;73(19):2465–76.
26. Dayan V, Soca G, Cura L, et al. Similar survival after mitral valve replacement or repair for ischemic mitral regurgitation: a meta-analysis. Ann Thorac Surg 2014;97(3):758–65.
27. Obadia JF, Messika-Zeitoun D, Leurent G, et al. Percutaneous repair or medical treatment for secondary mitral regurgitation. N Engl J Med 2018; 379:2297–306.
28. Stone GW, Lindenfeld J, Abraham WT, et al. Transcatheter mitral valve repair in patients with heart failure. N Engl J Med 2018;379:2307–18.
29. Grayburn PA, Sannino A, Packer M. Proportionate and disproportionate functional mitral regurgitation: a new conceptual framework that reconciles the results of the MITRA-FR and COAPT Trials. JACC Cardiovasc Imaging 2019;12:353–62.
30. Packer M, Grayburn PA. New evidence supporting a novel conceptual framework for distinguishing proportionate and disproportionate functional mitral regurgitation. JAMA Cardiol 2020;5:469–75.
31. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J 2016;37:2129–200.
32. Packer M, Grayburn PA. Contrasting effects of pharmacological, procedural, and surgical interventions on proportionate and disproportionate functional mitral regurgitation in chronic heart failure. Circulation 2019;140:779–89.
33. Messika-Zeitoun D, Iung B, Armoiry X, et al. Impact of mitral regurgitation severity and left ventricular remodeling on outcomes after Mitraclip implantation: results from the Mitra-FR trial. JACC Cardiovasc Imaging 2020. https://doi.org/10.1016/j.jcmg.2020.07.021. S1936-878X:30645–8.
34. Bartko PE, Heitzinger G, Arfsten H, et al. Disproportionate functional mitral regurgitation: advancing a conceptual framework to clinical practice. JACC Cardiovasc Imaging 2019;12:2088–90.
35. McMurray JJ, Packer M, Desai AS, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med 2014;371:993–1004.
36. Almufleh A, Marbach J, Chih S, et al. Ejection fraction improvement and reverse remodeling achieved with sacubitril/valsartan in patients with heart failure with reduced ejection fraction. Am J Cardiovasc Dis 2017;7:108–13.
37. Martens P, Beliën H, Dupont M, et al. The reverse remodeling response to sacubitril/valsartan therapy in heart failure with reduced ejection fraction. Cardiovasc Ther 2018;36:e12435.
38. Bayard G, Da Costa A, Pierrard R, et al. Impact of sacubitril/valsartan on echo parameters in heart failure patients with reduced ejection fraction: a prospective evaluation. Int J Cardiol Heart Vasc 2019; 25:100418.
39. Kang DH, Park SJ, Shin SH, et al. Angiotensin receptor inhibitor neprilysin inhibitor for functional mitral regurgitation. Circulation 2019;139:1354–65.
40. Soga F, Tanaka H, Tatsumi K, et al. Impact of dapagliflozin on left ventricular diastolic function in patients with type 2 diabetes mellitus with chronic heart failure. Cardiovasc Diabetol 2018;17:132.
41. Matsutani D, Sakamoto M, Kayama Y, et al. Effect of canagliflozin on left ventricular diastolic function in patients with type 2 diabetes. Cardiovasc Diabetol 2018;17:73.
42. Zhang DP, Xu L, Wang LF, et al. Effects of antidiabetic drugs on left ventricular function/dysfunction:

a systematic review and network meta-analysis. Cardiovasc Diabetol 2020;19:10.
43. Tanaka H, Soga F, Tatsumi K, et al. Positive effect of dapagliflozin on left ventricular longitudinal function in patients with type 2 diabetes mellitus and chronic heart failure. Cardiovasc Diabetol 2020;19:6.
44. Bonora BM, Vigili de Kreutzenberg S, Avogaro A, et al. Effects of the SGLT2 inhibitor dapagliflozin on cardiac function evaluated by impedance cardiography in patients with type 2 diabetes. Secondary analysis of a randomized placebo-controlled trial. Cardiovasc Diabetol 2019;18:106.
45. Hsu JC, Wang CY, Su MM, et al. Effect of empagliflozin on cardiac function, adiposity, and diffuse fibrosis in patients with type 2 diabetes mellitus. Sci Rep 2019;9:15348.
46. Singh JSS, Mordi IR, Vickneson K, et al. Dapagliflozin versus placebo on left ventricular remodeling in patients with diabetes and heart failure: the REFORM trial. Diabetes Care 2020;43:1356–9.
47. Armstrong PW, Pieske B, Anstrom KJ, et al. Vericiguat in patients with heart failure and reduced ejection fraction. N Engl J Med 2020;382:1883–93.
48. Gheorghiade M, Greene SJ, Butler J, et al. Effect of vericiguat, a soluble guanylate cyclase stimulator, on natriuretic peptide levels in patients with worsening chronic heart failure and reduced ejection fraction: the SOCRATES-REDUCED randomized trial. JAMA 2015;314:2251–62.
49. Peterson PN, Chan PS, Spertus JA, et al. Practice-level variation in use of recommended medications among outpatients with heart failure insights from the NCDR PINNACLE Program. Circ Heart Fail 2013;6:1132–8.
50. Komajda M, Anker SD, Cowie MR, et al. Physicians' adherence to guideline-recommended medications in heart failure with reduced ejection fraction: data from the QUALIFY global survey. Eur J Heart Fail 2016;18:514–22.
51. Teng THK, Tromp J, Tay WT, et al. Prescribing patterns of evidence-based heart failure pharmacotherapy and outcomes in the ASIAN-HF registry: a cohort study. Lancet Glob Heal 2018;6:e1008–18.
52. Filippatos G, Angermann CE, Cleland JGF, et al. Global differences in characteristics, precipitants, and initial management of patients presenting with acute heart failure. JAMA Cardiol 2020;5:401–10.
53. Maggioni AP, Van Gool K, Biondi N, et al. Appropriateness of prescriptions of recommended treatments in Organisation for Economic Co-operation and development health systems: findings based on the long-term registry of the European Society of cardiology on heart failure. Value Health 2015;18:1098–104.
54. Maucort-Boulch D, Carrié D, Guerin P, et al. Percutaneous repair or medical treatment for secondary mitral regurgitation. N Engl J Med 2018;379:2297–306.
55. Akita K, Kohno T, Kohsaka S, et al. Current use of guideline-based medical therapy in elderly patients admitted with acute heart failure with reduced ejection fraction and its impact on event-free survival. Int J Cardiol 2017;235:162–8.