# WHAT IS NEW AND WHAT HAS CHANGED IN THE 2026 GLOBAL HEART FAILURE IMPLEMENTATION GUIDELINES AND WHY

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Note: After finalization of this document, all recommendations and figures, will then be incorporated into the updated 2026 Global HF Guideline → the title of that document will then be:
"2026 iCARDIO Alliance Global Implementation Guidelines on Heart Failure."

## *Preamble*

*The International CARDIO Alliance to Improve Disease Outcomes (iCARDIO Alliance: https://icardioalliance.org) aims to bring together leading cardiovascular societies around the globe as partner organizations to improve the quality of cardiovascular care, from prevention and diagnosis to treatment and follow-up. The goal of these global implementation guidelines is to achieve global representation on writing panels and to produce concise and practical guidelines applicable to all cardiovascular care world-wide. In contrast to clinical practice guidelines developed by other medical associations, the recommendations by iCARDIO Alliance take into account availability of resources, with specific recommendations for resources severely limited.*

*The final full iCARDIO Alliance guideline documents represent a consensus document reviewing different guidelines about the topic and are written by a team including world-renowned experts with a maximum of 50% of the writing task force representing Europe and North America and 50% or more from the rest of the world. The peer review team of each guideline is made up of global experts further enriching these documents. In the final phase of the iCARDIO Alliance guideline development process, a public review process is implemented, so that the viewpoints of persons with lived experience can be embedded within this global implementation guideline process.*

*The document here, describes what changes are suggested to be made why in the 2026 focused update of the original "iCARDIO Alliance Global Implementation Guidelines on Heart Failure 2025". We now enter the public review phase for this update document which will last until 18th July, 2026. All comments must be submitted via the dedicated comment form, which can be downloaded from the Global Cardiology website (www.globalcardiology.info) as well as from the iCARDIO Alliance website (www.icardioalliance.org). Please use page, line, and/or table and recommendation numbers for reference in your commentaries as appropriate. Comments received will be taken into consideration, but will not be published. Anonymous comments will be disregarded*

***The deadline for receiving comments is 18th of July, 2026.***
*To submit your comments please use the comment form and send it to: guidelines@icardio.org*

## ABSTRACT

Inequities in healthcare access, infrastructure, resource availability, differing society recommendations, and local clinical practices continue to limit the global applicability and implementation of existing heart failure (HF) guidelines. Accordingly, there remains a need for concise and practical recommendations that address the diverse challenges faced by patients and healthcare providers in different areas of the world. The iCARDIO Alliance Global Implementation Guidelines aim to integrate contemporary evidence on heart failure diagnosis and treatment with implementation considerations applicable across diverse economic and healthcare settings. This 2026 focused update of the original iCARDIO Alliance Global Implementation Guidelines on Heart Failure published in 2025 incorporates emerging evidence relevant to acute and chronic HF, including heart failure with reduced ejection fraction (HFrEF), heart failure with preserved ejection fraction (HFpEF), and cardiomyopathies. When patients with HFrEF experience substantial improvement in LVEF and diagnostically move from the HFrEF to the HFpEF category they are commonly diagnosed as having HF with improved EF (HFimpEF). Hence, we now define HFimpEF to be present, when in a patient who previously was diagnosed with HFrEF an improvement in the LVEF of at least 10 percentage points to an LVEF ≥50% is observed.

The main updates in the therapeutic recommendations of the Global Implementation Guidelines on Heart Failure pertain to evolving data on the soluble guanylate cyclase stimulator vericiguat, cardiac glycosides, GLP-1 receptor agonists, cardiac myosin inhibitors, and preventive vaccination strategies. Revised recommendations were informed by recently published randomized trials, and selected additional post-hoc analyses and meta-analyses demonstrating improvements in symptoms, quality of life, HF hospitalization or mortality among patients receiving contemporary guideline-directed medical therapy (GDMT) regarding the approaches mentioned above. Consistent with the overarching iCARDIO Alliance framework, these recommendations additionally consider the feasibility, monitoring requirements, multidisciplinary expertise, and globally varying levels of healthcare resources. In selected cases, specific implementation guidance is provided for settings in which resources are somewhat limited or severely limited. Accordingly, this document provides a concise, evidence-informed, and globally applicable focused update to HF management strategies, aiming to support clinicians in optimizing HF care and improving patient outcomes across a broad range of healthcare systems worldwide.


## INTRODUCTION

Heart failure (HF) remains a major global public health challenge associated with substantial morbidity, mortality, recurrent hospitalization, and healthcare expenditure [1,2]. Since publication of the 2025 iCARDIO Alliance Global Implementation Guidelines on Heart Failure [3], several important randomized trials, post-hoc analyses, and meta-analyses have emerged that may influence contemporary clinical practice and implementation strategies across diverse healthcare settings. Accordingly, this focused document aims to provide clinically relevant updates to selected recommendations from the original guideline document, particularly where evolving new evidence may impact therapeutic decision-making. In the absence of new data, this update does not re-evaluate evidence that was already known before 2025. Given several recently published randomized trials and contemporary meta-analyses [4-8], this focused update addresses selected developments in soluble guanylate cyclase stimulation with vericiguat, the evolving role of digoxin and digitoxin, cardiac

myosin inhibitors, and preventive vaccination strategies in patients with HF. In addition, the present update re-evaluates the recommendation strength for GLP-1 receptor agonists in HFpEF and obesity in light of additional analyses and evolving interpretation of quality-of-life outcomes and the need for further long-term safety data in HF populations. Similar to the original guideline document, the updates in the recommendations aim to balance evidence-based findings on HF management with their applicability across healthcare systems with varying levels of resources [9].

For the last decade and in most international guidelines, the classification of HF based on three distinct categories: “reduced" (HFrEF), “preserved" (HFpEF), and "mildly reduced” [initially in some guidelines also referred to as “mid-range"] (HFmrEF). These guidelines – when first published in 2025 – designated HF for diagnostic and therapeutic purposes as either HFrEF (LVEF <50%) or HFpEF (LVEF ≥50%). Patients that in other guidelines are deemed to have “midrange” or “mildly reduced” LVEF (termed “HFmrEF” and typically defined by a LVEF of 41–49%) already in the 2025 guideline are considered as patients with HFrEF. We continue to recognize that diagnostic certainty in patients with LVEF 41–49% is somewhat reduced (due to the variability of LVEF assessment), although available evidence suggests that many GDMT remain effective across the spectrum of LVEF below 50% [10]. This has and will have implications for both guideline recommendations and, in turn, clinical practice. It is clear that the tripartite classification was not a reflection of distinct underlying pathophysiology, but rather a result of clinical trial designs that required a homogenous high-risk population to demonstrate the efficacy of neurohormonal antagonists. By enrolling only patients with a LVEF below 35–40%, investigators successfully demonstrated that this cohort had a clear benefit with neurohormonal antagonists. Conversely, investigators designated patients with a LVEF ≥50% as having HFpEF. Therefore, patients with LVEF of 41%–49% were excluded from the population deemed to have reduced LVEF not because of a distinct biology, but because they had been excluded from trials of HFrEF. As a result, these patients were included in clinical trials for HFpEF. However, since HFmrEF patients share pathophysiological and clinical characteristics with HFrEF individuals, but were studied as a sub-group of HFpEF trials, guidelines have retroactively justified separate recommendations for this third phenotype without clinical trials specific for this group. When the available data are examined, patients with LVEF between 40% and 50% do not appear to represent a distinct pathophysiological phenotype, but rather occupy a continuum between traditional HFrEF and HFpEF categories. Indeed, HFmrEF patients benefit in similar ways from the therapies that are considered GDMT for HFrEF patients, including from sodium glucose co-transporter-2 inhibitor (SGLT2i), mineralocorticoid receptor antagonists (MRAs), and angiotensin receptor neprilysin inhibitors (ARNIs) [11,12]. Therefore, the consensus for this Authors’ group remains that maintaining the HFmrEF label would introduce unnecessary complexity for clinicians when implementing these guidelines.

Some have suggested to use the term “HFnEF” instead of “HFpEF”, where “n” stands for “normal” [13]. We prefer the term “preserved” because a) it indicates that LVEF is not below 50%, and b) it implies that such value represents a quasi normal for the context (but not necessarily entirely healthy) LVEF for a particular patient when other variables that influence LVEF (including age, sex, LV wall thickness and loading conditions) are considered. In summary, we decided to continue to classify HF as either HFrEF (LVEF <50%) or HFpEF (LVEF ≥50%) as already done in the 2025 edition of the Global Guidelines on HF. We believe that this simplified two-category classification better reflects the continuum of HF biology, facilitates implementation of guideline-directed therapy, and provides a more pragmatic framework for routine clinical practice. The Task Force recognizes that this may complicate comparisons with prior clinical trials and existing other guideline recommendations. The Task Force also recognizes that some patients with HFrEF experience substantial improvement in LVEF following initiation of GDMT and – when technically moving from the HFrEF to the HFpEF category – are commonly described as having HF with improved EF (HFimpEF). Consequentely, we now define HFimpEF to be

present, when in a patient who previously diagnosed with HFrEF an improvement in LVEF of at least 10 percentage points to an LVEF ≥50% is observed. Although these patients often have a more favorable prognosis than those with persistently reduced ejection fraction, improvement in LVEF should not prompt withdrawal of GDMT, which we consider as strongly recommended (see **Table 2**).

The present focused update should therefore be interpreted within the conceptual framework adopted in the original iCARDIO Alliance guideline document, which emphasizes a pragmatic and therapeutically oriented classification of HF phenotypes while recognizing the continuous biological spectrum of ventricular dysfunction. Several guideline recommendations were changed and **Table 1** summarizes these changes by showing the recommendations of the 2026 focussed update compared with the respective recommendations of the 2025 iCardio Alliance Global Implementation Guidelines. For all these changed recommendations, we kept the related recommendation number identical. The new recommendations introduced are discussed in the respective chapters below. In order to fit in the the overall order of numbered recommendations, we gave numbers that stay in sequence of the respective recommendation table, we we added letters ("A" or "B" or "C", respectively) in order to stay in the correct numbering system. In some cases, one previous recommendation became two new recommendations.

**Table 1**. **Summary of changed recommendations in the 2026 guideline update (vs the 2025 edition of the guideline)**

| Section | Recommendation No. | 2025 Guideline Statement (LOE) | 2026 Focused Update Statement (LOE) |
|---|---|---|---|
| Vericiguat | **4-17** | Use of oral soluble guanylate cyclase stimulator (vericiguat) to reduce HF hospitalization and CV death in high-risk patients with HFrEF and recent worsening of HF despite GDMT who have NT-proBNP < 5000 pg/Ml.(R) | Use oral soluble guanylate cyclase stimulator (vericiguat) to reduce HF hospitalization and CV death with HFrEF and recent worsening of HF despite GDMT who have a NT-proBNP <6000 pg/mL.(R) |
| Cardiac glycosides | **4-19** | Use digoxin in patients with HFrEF who remain symptomatic despite GDMT as tolerated and without severe renal insufficiency (eGFR < 30 mL/min/1.73m2) to decrease HF hospitalization (Su) | Use low-dose digoxin or digitoxin (target serum concentration 0.5-0.9 ng/mL) in patients with HFrEF who remain symptomatic despite GDMT as tolerated to decrease worsening HF events and HF hospitalization (R)<br>Do not initiate digoxin therapy in patients with severe renal insufficiency (eGFR <30mL/min/1.73m2) in settings where both reliable clinical follow-up and therapeutic drug monitoring cannot be ensured.<br>Note: At least one of the following should be available: reliable clinical follow-up or therapeutic drug monitoring.At least one of these features should be available to initiate cardiac glycoside therapy (DND) |
| HFimpEF | **4-20** | Continue GDMT even if patients are asymptomatic after improvement in LVEF (HFimEF), to prevent relapse of HF and LV dysfunction. (SR) | Patients with HF with improved ejection fraction (HFimpEF), defined as an improvement in LVEF of at least 10 percentage points to ≥50%, should generally<br>continue GDMT for HFrEF despite recovery of LVEF (SR) |

| | | | |
|---|---|---|---|
| GLP-1 therapies | **4-24** | Use GLP-1RA-based therapies (tirzepatide or semaglutide) in patients with obesity and HFpEF to achieve weight loss and to improve symptoms and QoL (SR) | Use GLP-1RA-based therapies (tirzepatide or semaglutide) in patients with obesity (BMI > 30 kg/m$^2$) and HFpEF to achieve weight loss and to improve symptoms and QoL. (R) |
| Transthyretin cardiac amyloidosis | **7-04** | Use TTR tetramer stabilizer therapy (tafamidis [partial stabilizer], and acromadis [near complete stabilizer]) to improve symptoms, and reduce cardiovascular death and HF hospitalizations in patients with wild or variant type TTR cardiac amyloidosis and NYHA class I to III symptoms. (SR) | Use a TTR tetramer stabilizer therapy (tafamidis, acoramidis) or TTR tetramer silencer (vutisiran) to improve symptoms and reduce cardiovascular death and HF hospitalizations in patients with wild-type or hereditary type TTR cardiac amyloidosis and NYHA class I to III symptoms. (SR) |
| Cardiac myosin inhibitors | **7-08** | Use cardiac myosin inhibitors (mavacamten/aficamten) in patients with symptomatic obstructive HCM despite beta-blockers or non-dihydropyridine calcium channel blockers to improve QoL and decrease the need for septal reduction therapies. (R) | Use cardiac myosin inhibitors (mavacamten/aficamten) in patients with symptomatic obstructive HCM despite beta-blockers or non-dihydropyridine calcium channel blockers to improve QoL and decrease the need for septal reduction therapies. (SR) |
| Vaccinations | **8-08** | Administer pneumococcal and influenza vaccines in patients with HF to reduce the risk of hospitalization for HF. (SR) | Influenza vaccination once yearly (preferably at high dosages) in patients with HF in accordance with local vaccination policies and regional public health recommendations. (SR)<br>Pneumococcal vaccination in eligible patients with HF, preferably as a single-dose higher-valent conjugate vaccine (e.g., PCV20 or PCV21) where appropriate, in accordance with regional and national vaccination schedules. (SR) |

**R**, Recommend; **SR**, Strongly recommend; **Su**, Suggest; **HF**, heart failure; **HFrEF**, heart failure with reduced ejection fraction; **HFpEF**, heart failure with preserved ejection fraction; **NT-proBNP**, N-terminal pro-B-type natriuretic peptide; **GDMT**, guideline-directed medical therapy; **HCM**, hypertrophic cardiomyopathy; **TTR**, transthyretin; **GLP-1**, glucagon-like peptide-1; **RSV**, respiratory syncytial virus; **COVID-19**, coronavirus disease 2019.

## GRADING / RECOMMENDATIONS

Based on the available evidence and consensus among the committee members regarding the risks and benefits of interventions, the recommendations were classified as strongly recommend (SR), recommend (R), suggest (Su), and do not do (DND). To make the document more readable and concise, we decided to not reference each recommendation. Also, we acknowledge that there have been discussions on whether to use the term “people with HF” versus “patients with HF”. In this document, we will use “patients with HF” as this is more commonly used globally.

This focused update incorporates newly available evidence from recent trials and analyses that informed revised recommendations, including VICTORIA and VICTOR evaluating vericiguat therapy, DIGIT-HF and DECISION evaluating cardiac glycosides, MAPLE-HCM and ACACIA-HCM evaluating cardiac myosin inhibitors, and emerging evidence supporting updated preventive vaccination strategies in patients with HF [4-8].

## VERICIGUAT

Recommendation Table 4 has been updated to incorporate emerging evidence regarding soluble guanylate cyclase stimulation (vericiguat) and cardiac glycoside therapy in patients with HFrEF. Based on findings from the VICTORIA trial, which enrolled patients with symptomatic chronic HFrEF (LVEF <45%) and recent worsening HF, Vericiguat was previously recommended for patients with these characteristics and NT-proBNP concentrations below 5,000 pg/mL. In VICTORIA, vericiguat produced a clinically modest reduction in the composite risk of cardiovascular death or HF hospitalization compared with placebo, corresponding to an approximately 10% relative risk reduction (Hazard Ratio (HR) with 95% CI: 0.90; 0.82–0.98) [14]). The original NT-proBNP threshold of <5,000 pg/mL was informed by findings from VICTORIA, where the boundary separating the lower three NT-proBNP quartiles from the highest quartile was 5,314 pg/mL and was subsequently rounded to 5,000 pg/mL for clinical application. Patients in the lower three NT-proBNP quartiles appeared to derive greater benefit from vericiguat, with HRs for the combined endpoint of cardiovascular death or first HF hospitalization across the lower three NT-proBNP quartiles (HR 0.78 [0.62–0.99], HR 0.73 [0.60–0.90], and HR 0.82 [0.69–0.99] for quartiles 1–3, respectively), whereas treatment effects were attenuated in the highest quartile (i.e. >5,314 pg/mL: HR 1.16 [0.99–1.35]) (p<0.001 for interaction). The upper boundary of the third NT-proBNP quartile was approximately 5,314 pg/mL in VICTORIA, which formed the basis for the original pragmatic threshold of <5,000 pg/mL used in the 2025 guideline. Patients with the highest NT-proBNP concentrations represented a particularly high-risk subgroup in whom the clinical benefit of vericiguat may be attenuated. These observations were derived from post hoc subgroup analyses rather than a prospectively specified hypothesis and should therefore be interpreted with appropriate caution, although they provided an important rationale for subsequent evaluation in later studies.

VICTOR evaluated a more stable ambulatory population of HFrEF patients (LVEF≤40%) with NT-proBNP concentrations up to 6,000 pg/mL and was specifically designed and powered to evaluate cardiovascular mortality. While the trial missed its primary composite endpoint of CV death or first HF hospitalization (HR 0.93; 0.83–1.04; p=0.22), it demonstrated a 17% reduction in CV death (HR 0.83; 0.71–0.97) [15]. A subsequent pooled participant-level analysis of more than 11,000 patients from the VICTORIA and VICTOR trials reinforced this clinically modest effect, demonstrating an approximately 9% relative risk reduction in the composite endpoint of cardiovascular death or HF hospitalization (HR 0.91; 0.85–0.98; p=0.01), cardiovascular death alone (HR: 0.89; 0.80–0.98; p=0.02) as well as all-cause mortality (HR 0.90; 0.82–0.99; p=0.025); however, these findings were outside the prespecified alpha control and should be interpreted cautiously. Importantly, clinical benefit appeared to extend to patients with higher NT-proBNP concentrations than initially proposed, supporting revision of the NT-proBNP threshold in Recommendation 4-17 from <5,000 pg/mL to <6,000 pg/mL. This modification reflects recognition that patients with persistently elevated natriuretic peptides continue to experience substantial residual risk despite contemporary GDMT. Given the modest treatment effect observed in VICTORIA (with better results in the lowest 3 quartiles of patients by NT-proBNP levels) and the neutral primary outcome of VICTOR, vericiguat should be considered selectively in appropriately chosen patients with persistent residual risk despite standard GDMT. The available evidence supports benefit in patients with NT-proBNP concentrations up to 6,000 pg/mL [8] (see **Figure 2**, **Table 4**).

## CARDIAC GLYCOSIDES

Updated recommendations address the evolving role of cardiac glycosides in the contemporary GDMT era. Although utilization of digoxin has declined over recent decades because of concerns regarding toxicity and narrow therapeutic index, and older trials that did not demonstrate a survival benefit, recent randomized data have renewed interest in the use of cardiac glycosides in selected symptomatic patients with HFrEF despite optimized therapy [16,17,18]. In the DIGIT-HF trial, 1,212 patients with symptomatic chronic HFrEF (LVEF ≤40%) receiving contemporary GDMT were randomized to low-dose digitoxin or placebo (starting dose 0.07mg once daily). Eligible patients had LVEF ≤40% with NYHA III–IV symptoms or LVEF ≤30% with NYHA II symptoms. Digitoxin therapy reduced the composite risk of all-cause death or first HF hospitalization for worsening HF compared with placebo (39.5% vs 44.1%; HR 0.82, 0.69–0.98) (Recommendation 4-19A) [7]. Importantly, only a single plasma digitoxin assessment was routinely required approximately 6 weeks after randomization for dose adjustment, which provides a practical advantage in settings where infrequent follow-up or therapeutic monitoring may be difficult.

The DECISION trial randomized 1,001 patients with symptomatic chronic HF and LVEF ≤50% to low-dose digoxin or placebo, targeting serum digoxin concentrations of 0.5–0.9 ng/mL. All patients had a LVEF below or equal to 50% and the majority were treated with contemporary background GDMT. Although the primary composite endpoint of worsening HF events or cardiovascular mortality was not significantly reduced (rate ratio 0.81, 0.61–1.07; p=0.133), low-dose digoxin reduced worsening HF events and was generally well tolerated at low serum digoxin concentrations. Serum digoxin concentrations were assessed at 4 weeks and every 6 months thereafter. Concentrations were also measured in cases of ≥30% decrease in eGFR and 2-4 weeks after HF hospitalization. Serum digoxin concentrations remained remarkably stable over time outside of hospitalization, and fewer than 1% of all measurements exceeded 1.2 ng/mL, supporting the favorable safety profile of the low-dose treatment strategy [6]. Unlike the original DIG trial, that enrolled only patients in sinus rhythm, both DIGIT-HF and DECISION included patients with and without atrial fibrillation, thereby broadening the applicability of these findings to contemporary HF populations. In addition, these trials demonstrated a favorable safety profile across patient subgroups, including women, helping to address concerns raised from earlier analyses of the DIG trial. A prespecified blinded withdrawal analysis of the DECISION trial further suggested that discontinuation of long-term digoxin therapy was associated with an increased risk of worsening heart failure events compared with placebo withdrawal (Risk ratio (RR) 7.37 [1.56–34.88], p=0.012), supporting caution when considering withdrawal of digoxin in selected patients. [19].

Digitoxin and digoxin are both cardiac glycosides that exert similar therapeutic effects through inhibition of the Na+/K+-ATPase pump, resulting in positive inotropy and enhanced parasympathetic tone [20]. However, pharmacokinetically, digoxin is predominantly eliminated via kidneys and may accumulate in patients with impaired kidney function, whereas digitoxin undergoes hepatic metabolism and exhibits more stable pharmacokinetics with minimal dependence on kidney clearance [21]. Conversely, digoxin has a shorter half-life, which may facilitate more rapid elimination should toxicity occur. These pharmacokinetic properties make digitoxin theoretically attractive for patients with severe kidney dysfunction, although this potential advantage has not been demonstrated in dedicated clinical studies. These findings are further supported by a recent meta-analysis by Damman et al. [22], which pooled data from the DIG, DIGIT-HF, and DECISION trials (in total 9,013 patients). Digitalis glycosides were associated with a 15% relative reduction in the composite of cardiovascular death or first worsening HF event (HR 0.85, 0.80–0.90), driven primarily by a reduction in worsening heart failure events (HR 0.75, 0.69–0.81), with no significant reduction in cardiovascular or all-cause mortality. Importantly, the treatment effect was consistent regardless of the type of cardiac glycoside used or the extent of background

guideline-directed medical therapy, reinforcing the role of low-dose cardiac glycosides as adjunctive therapy in selected symptomatic patients despite optimized GDMT.

Compared with the previous guideline version, the present focused update also provides more explicit recommendations regarding therapeutic drug monitoring and clinical follow-up during cardiac glycoside therapy. Although contemporary trials of low-dose cardiac glycosides demonstrated a favorable safety profile with simplified dosing algorithms and a low incidence of toxicity, the Task Force recommends periodic plasma digoxin/digitoxin monitoring and most importantly regular clinical reassessment, particularly in patients at increased risk of toxicity, to support safe long-term therapy (Recommendation 4-19B). Consequently, the updated recommendations additionally advise against initiation of digoxin therapy in settings where both reliable clinical follow-up and therapeutic drug monitoring cannot be ensured or in patients at increased risk of toxicity (i.e. low weight, elderly, impaired kidney function) (Recommendation 4-19C) (see **Figure 2**, **Table 4**).

Given their low cost and widespread availability, cardiac glycosides may also offer important health-economic advantages by reducing HF hospitalizations, particularly in resource-limited healthcare settings. Overall, cardiac glycosides should be considered as adjunctive therapy in carefully selected patients who remain symptomatic despite optimized GDMT or who are unable to tolerate further intensification of standard GDMT, recognizing the absence of a consistent mortality benefit, their narrow therapeutic window, and the importance of appropriate therapeutic monitoring.

## HEART FAILURE WITH IMPROVED EJECTION FRACTION

Recent evidence continues to support long-term continuation of GDMT also in patients with HFimpEF. Accordingly, patients with HFimpEF, defined as an improvement in LVEF of at least 10 percentage points to ≥50% (in patients previously diagnosed as HFrEF patients), should generally continue GDMT for HFrEF despite recovery of LVEF (Recommendation 4-20).

## GLP-1 RECEPTOR AGONISTS

Recommendations in **Table 4** and **Figure 5** have been updated to re-evaluate the strength of recommendation for GLP-1 receptor agonists in patients with HFpEF and obesity (BMI $\geq$30 kg/m$^2$). In STEP-HFpEF, semaglutide improved KCCQ-CSS by 7.8 points versus placebo and reduced body weight by 10.7%, while the SUMMIT trial demonstrated a 6.9-point improvement in KCCQ-CSS together with a reduction in the composite of cardiovascular death or worsening HF (HR 0.62, 0.41–0.95) [23,24]. Although these improvements in KCCQ are among the largest reported for pharmacological trials in HFpEF, recent discussions regarding the interpretation of patient-reported outcomes and the magnitude of change required to represent a clinically meaningful benefit within the trial (based on anchoring approaches) have prompted a more conservative assessment of the available evidence [25,26]. It is recognized that the SUMMIT and STEP-HFpEF trials demonstrated favorable clinical event reductions (driven by fewer HF events), but both trial programs accrued relatively few events (<100 in each case), limiting the power of these studies. Hence, the Task Force considered the current evidence insufficient to extend the recommendation to clinical outcomes, pending confirmation from additional large event-driven trials.

The Task Forces believes there is a need for additional long-term safety data for GLP-1 receptor agonists, particularly as there are also some safety concerns (including somewhat higher AF event rates [23] and unfavourable results reported for HFrEF patients [27]). Larger event-driven trials to strengthen the evidence base for GLP1 receptor agonists in HFpEF are ongoing, including MARITIME-HF with maridebart cafraglutide (NCT07037459), HF-POLARIS with zenagamtide (Trial ID: 2025-523717-29-00), and ELEVATE-HF with elecoglipron (NCT06678841), that are expected to provide more robust evidence regarding clinical outcomes in this population.

In summary, we changed recommendation 4-24 from "Strongly Recommended" to "Recommended" (see **Figure 5**, **Table 4**). We understand that implementation of these recommendations may be limited in some healthcare settings by availability and regulatory approvals that are lacking for HF patients per se, and general resource constraints. Treatment decisions should therefore consider local access and affordability.

**Table 4. Recommendations for pharmacological therapies in patients with heart failure**

| No. | Guideline Statement | Level of Recommendation |
|---|---|---|
| **4-17** | Use oral soluble guanylate cyclase stimulator (vericiguat) to reduce HF hospitalization and CV death with HFrEF and recent worsening of HF despite GDMT who have a NT-proBNP <6,000 pg/mL. | **R** |
| **4-19A** | Use **low dose** digoxin or digitoxin (target serum concentration 0.5-0.9 ng/mL)_ in patients with HFrEF who remain symptomatic despite GDMT as tolerated to decrease worsening HF events and HF hospitalization. | **R** |
| **4-19B** | If feasible, perform a plasma digitoxin / digoxin level assessment approximately 4–6 weeks after initiation or dose adjustment, while recognizing that earlier assessment may be appropriate when clinically indicated, to guide therapy and reduce the risk of toxicity. Particularly this should be considered for patients with low BMI and CKD. | **R** |
| Resources somewhat limited | Consider digitoxin rather than digoxin when therapeutic drug monitoring and clinical follow-up are available, but difficult to perform frequently, as plasma level assessment and dose adjustment may be required less often. | |
| **4-19C** | Do not initiate digoxin therapy in patients with severe renal insufficiency (eGFR <30mL/min/1.73m$^2$) in settings where both reliable clinical follow-up and therapeutic drug monitoring cannot be ensured.<br>Note: At least one of the following should be available: reliable clinical follow-up or therapeutic drug monitoring. | **DND** |
| **4-20** | Patients with HF with improved ejection fraction (HFimpEF), defined as an improvement in LVEF of at least 10 percentage points to ≥50%, should generally continue GDMT for HFrEF despite recovery of LVEF. | **SR** |
| **4-24** | Use GLP-1RA-based therapies (tirzepatide or semaglutide) in patients with obesity (BMI ≥ 30 kg/m$^2$) and HFpEF to achieve weight loss and to improve symptoms and QoL. | **R** |

SR, strongly recommend; R, recommend; DND, do not do; CV, cardiovascular; eGFR, estimated glomerular filtration rate; GDMT, guideline-directed medical therapy; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; NT-proBNP, N-terminal prohormone of B-type natriuretic peptide; Only recommendations updated in this 2026 focused guideline are reproduced. Recommendation numbers not shown correspond to unchanged recommendations from the 2025 iCARDIO Alliance Global Implementation Guidelines on Heart Failure.

## TRANSTHYRETIN AMYLOIDOSIS

Recommendation 7-04 has been revised to simplify the description of TTR stabilizer therapy by removing the terms "partial stabilizer" and "near-complete stabilizer," while maintaining the underlying recommendation and level of evidence unchanged. *(see **Table 7**)*.

## CARDIAC MYOSIN INHIBITORS

Recommendation Table 7 has been updated to strengthen recommendations regarding cardiac myosin inhibitor (CMI) therapy in patients with symptomatic obstructive hypertrophic cardiomyopathy (HCM). Previous recommendations supported use of mavacamten or aficamten in selected patients with persistent symptoms despite beta-blockers or non-dihydropyridine calcium channel blockers. However, more recent randomized evidence has further established the efficacy of CMI as monotherapy in improving symptoms, exercise capacity, hemodynamics, and patient-reported outcomes in obstructive HCM.

In MAPLE-HCM, 175 adults with symptomatic obstructive HCM, LVEF ≥60%, NYHA class II–III symptoms, KCCQ-CSS ≤90, and resting left ventricular outflow tract (LVOT) gradient ≥30 mmHg or post-Valsalva gradient ≥50 mmHg were randomized to aficamten or metoprolol monotherapy. At 24 weeks, aficamten was superior to metoprolol in improving peak oxygen uptake, with a between-group difference of 2.3 mL/kg/min (1.5–3.1; p<0.001), NYHA class, KCCQ-CSS, LVOT gradients, and NT-proBNP levels. [4]. In ACACIA-HCM, aficamten was evaluated in symptomatic non-obstructive HCM with LVEF ≥60%, NYHA class II–III symptoms, KCCQ-CSS ≤85, peak $VO_2$ ≤90% predicted, and elevated NT-proBNP. While pending formal presentation and publication, topline resulting in a company press release reported that aficamten met both dual primary endpoints at 36 weeks, improving KCCQ-CSS versus placebo by 3.0 points (0.5–5.5; p=0.021) and peak $VO_2$ by 0.67 mL/kg/min (0.22–1.1; p=0.003) [5]. Accordingly, Recommendation 7-08 has been upgraded from "recommend" to "strongly recommend" for use of CMI in patients with symptomatic obstructive HCM despite beta-blockers or non-dihydropyridine calcium channel blockers to improve quality of life and reduce the need for septal reduction therapies. In contrast, Mavacamten did not achieve its primary endpoints in a non-obstructive HCM cohort in the ODYSSEY-HCM trial [28].

Recommendation 7-08A suggests use of aficamten based on the favorable results observed in ACACIA-HCM more comprehensive discussion of CMI therapy, patient selection, monitoring, and HCM management will be provided in the forthcoming dedicated iCARDIO Alliance HCM Guidelines planned for the near future. (*see **Figure 5**, **Table 7***).

**Table 7. Recommendations for the special conditions in patients with heart failure**

| No. | Guideline Statement | Level of Recommendation |
|---|---|---|
| **7-04** | Use a TTR tetramer stabilizer (tafamidis, acoramidis) or TTR tetramer silencer (vutisiran) to improve symptoms, and reduce cardiovascular death and HF hospitalizations in patients with wild type or hereditary TTR cardiac amyloidosis and NYHA class I to III symptoms. | **SR** |

| | | |
|---|---|---|
| | **Hypertrophic Cardiomyopathy** | |
| **7-08** | Use cardiac myosin inhibitors (mavacamten/aficamten) in patients with symptomatic obstructive HCM despite beta−blockers or non−dihydropyridine calcium channel blockers to improve QoL and decrease the need for septal reduction therapies. | **SR** |
| **7-08A** | Use aficamten in selected patients with symptomatic non-obstructive HCM to improve symptoms, exercise capacity, and quality of life. | **Su** |

SR, Strongly recommend; HCM, hypertrophic cardiomyopathy; QoL, quality of life; TTR: Transthyretin; Su: Suggest; R: Recommend

## VACCINATIONS

Table 8 has been updated to revise recommendations regarding influenza and pneumococcal vaccination in patients with HF. Previous recommendations strongly supported routine pneumococcal and influenza vaccination to reduce HF hospitalization risk. However, the present focused update aligns vaccination strategies more closely with contemporary regional and national immunization guidance, while acknowledging variability in vaccine availability, healthcare infrastructure, and local epidemiology across healthcare systems.

Seasonal influenza infection remains associated with increased risk of respiratory complications, HF decompensation, hospitalization, and adverse cardiovascular outcomes in patients with HF [29]. Accordingly, the updated recommendations strongly recommend yearly influenza vaccination, preferably with high-dose vaccines where available and appropriate, in accordance with local vaccination policies and regional public health recommendations. This recommendation is supported by the FLUNITY-HD pooled analysis of 466,320 randomized older adults [30] (Recommendation 8-08A).

The updated document also clarifies pneumococcal vaccination strategies in patients with HF. Patients with HF remain at increased risk of invasive pneumococcal disease, respiratory infections, and HF worsening following pneumococcal pneumonia [31]. Accordingly, pneumococcal vaccination is strongly recommended in eligible patients with HF, preferably as a single-dose higher-valent conjugate vaccine (e.g., PCV20 or PCV21) where appropriate, in accordance with regional and national vaccination schedules (Recommendation 8-08B).

The present update also incorporates recommendations regarding COVID-19, herpes zoster, and respiratory syncytial virus (RSV) vaccination [32,33]. Patients with HF remain particularly vulnerable to adverse outcomes following respiratory viral infections, including hospitalization, HF decompensation, and cardiovascular complications. Accordingly, COVID-19 vaccination is strongly recommended in accordance with contemporary public health guidance (Recommendation 8-09). The strong recommendation reflects the consistent evidence supporting vaccination in patients with HF, while recognizing that the specific vaccine formulation, timing, and implementation should follow regional and national public health guidance. In addition, herpes zoster and RSV vaccination may be considered in eligible patients based on age, comorbidity burden, vaccine availability, affordability and regional vaccination policies (Recommendations 8-10 and 8-11). (*see* ***Table 8***).

**Table 8. Recommendations for special considerations**

| No. | Definition | Level of Recommendation |
|---|---|---|
| **8-08A** | Influenza vaccination once yearly (preferably at high dosages) in patients with HF in accordance with local vaccination policies and regional public health recommendations. | **SR** |
| **8-08B** | Pneumococcal vaccination in eligible patients with HF, preferably as a single-dose higher-valent conjugate vaccine (e.g., PCV20 or PCV21) where appropriate, in accordance with regional and national vaccination schedules.. | **SR** |
| **8-09** | Administer COVID-19 vaccination in patients with HF in accordance with current regional and national public health recommendations to reduce the risk of severe infection, hospitalization, and cardiovascular complications. | **SR** |
| **8-10** | Consider herpes zoster (shingles) vaccination in eligible patients with HF according to age-based and regional vaccination recommendations. | **Su** |
| **8-11** | Consider respiratory syncytial virus (RSV) vaccination in eligible patients with HF according to age-based and regional vaccination recommendations. | **Su** |

SR: Strongly recommend; Su: Suggest HF, heart failure; PCV20, 20-valent pneumococcal conjugate vaccine. PCV21, 21-valent pneumococcal conjugate vaccine; PCV20, 20-valent pneumococcal conjugate vaccine.

## NEW CLASSIFICATION OF HEART FAILURE

The Task Force believes that future HF research should increasingly align trial design with underlying pathophysiology rather than historical EF-based trial inclusion criteria. In particular, future studies should either adopt a simplified classification of HFrEF (LVEF <50%) and HFpEF (LVEF ≥50%) or evaluate therapies across the entire LVEF spectrum irrespective of predefined EF categories. Future trials should increasingly consider enrolling patients also based on underlying pathophysiological mechanisms or disease phenotypes, rather than relying solely on LVEF thresholds, to better match therapies with specific biological processes. This would also be consistent with the evolving concepts outlined in the First and Second Universal Definitions of Heart Failure [35,36]. Such approaches may generate more clinically relevant evidence for patients currently classified as having HFmrEF and facilitate translation of trial findings into routine clinical practice [34]. (see **Table 9**) At the same time, it is recognized that many previous clinical trials enrolled patients using the HFmrEF classification, and careful interpretation of the existing data will be required when applying the binary LVEF-based HF classification in future research and clinical practice.

**Table 9. Recommendations for future HF trial design**

| No. | Definition | Level of Recommendation |
|---|---|---|
| **9-01** | Future clinical trials in HF should preferentially classify patients as HFrEF (LVEF <50%) or HFpEF (LVEF ≥50%). | **R** |
| **9-02** | Patients with LVEF 41–49% should generally be included within HFrEF trial populations, unless there is a specific scientific rationale otherwise. | **R** |
| **9-03** | Future therapeutic trials may alternatively enroll patients across the entire LVEF spectrum or according to underlying disease phenotypes and evaluate treatment effects continuously rather than using arbitrary EF categories. | **Su** |

R: Recommend; Su: Suggest; HFrEF: Heart Failure with reduced ejection fraction; LVEF: left ventricular ejection fraction; HFpEF: heart failure with preserved ejection fraction.

## IMPLEMENTATION FOR THE FUTURE

While some guidelines may still respect the three-group structure, we recommend a shift in both clinical practice and future research to consider only two populations with either LVEF below 50% (HFrEF) or ≥ 50% (HFpEF). Given the dynamic nature of left ventricular function over time, serial assessment of LVEF could be performed where feasible to evaluate changes and guide optimization of HF therapy [37]. This will provide clearer guidance on the approach to the large population of patients currently caught in the "mildly reduced" group, which lacks specifically dedicated trials. By including the mildly reduced LVEF into HFrEF, the classification will better align with pathophysiological evidence rather than with an arbitrary distinction historically created by drug development. While there may be concerns that this could dilute the modifiable event rate by including patients with LVEF between 41% and 49%, this could be addressed by incorporating additional selection criteria for this subgroup such as elevated natriuretic peptides or recent HF hospitalisation. Future evidence emerging from the binary classification of HFrEF and HFpEF seems to be more justifiable from the pathophysiological standpoint, simplifies guideline recommendations, and, in turn, facilitates translation into clinical practice.

## CONCLUSION

This 2026 update to the previously published 2025 iCARDIO Alliance Global Implementation Guidelines on Heart Failure incorporates emerging evidence with important implications for contemporary HF management. Updated recommendations address evolving data regarding vericiguat, cardiac glycosides, cardiac myosin inhibitors, and preventive vaccination strategies in patients with HF. Several revised recommendations were informed by recently published randomized trials and meta-analyses demonstrating a favorable effect of these approaches on symptoms, quality of life, HF hospitalization, and selected clinical outcomes. Accordingly, this focused update aims to provide concise, evidence-informed, and clinically applicable guidance based on this new evidence to support HF management across diverse healthcare settings.

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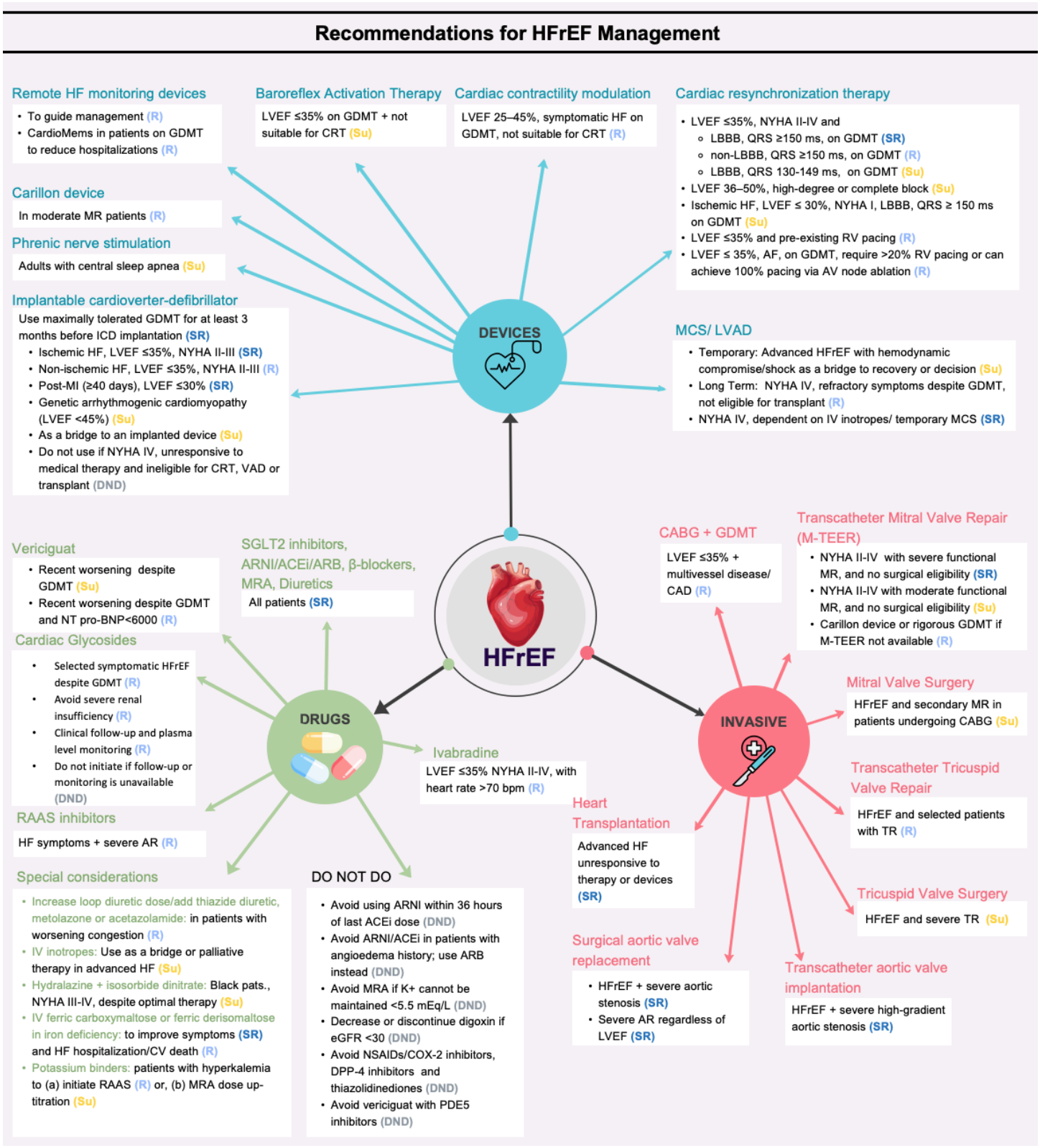
**Figure 2: Recommendations for the Management of Heart failure with Reduced Ejection Fraction**

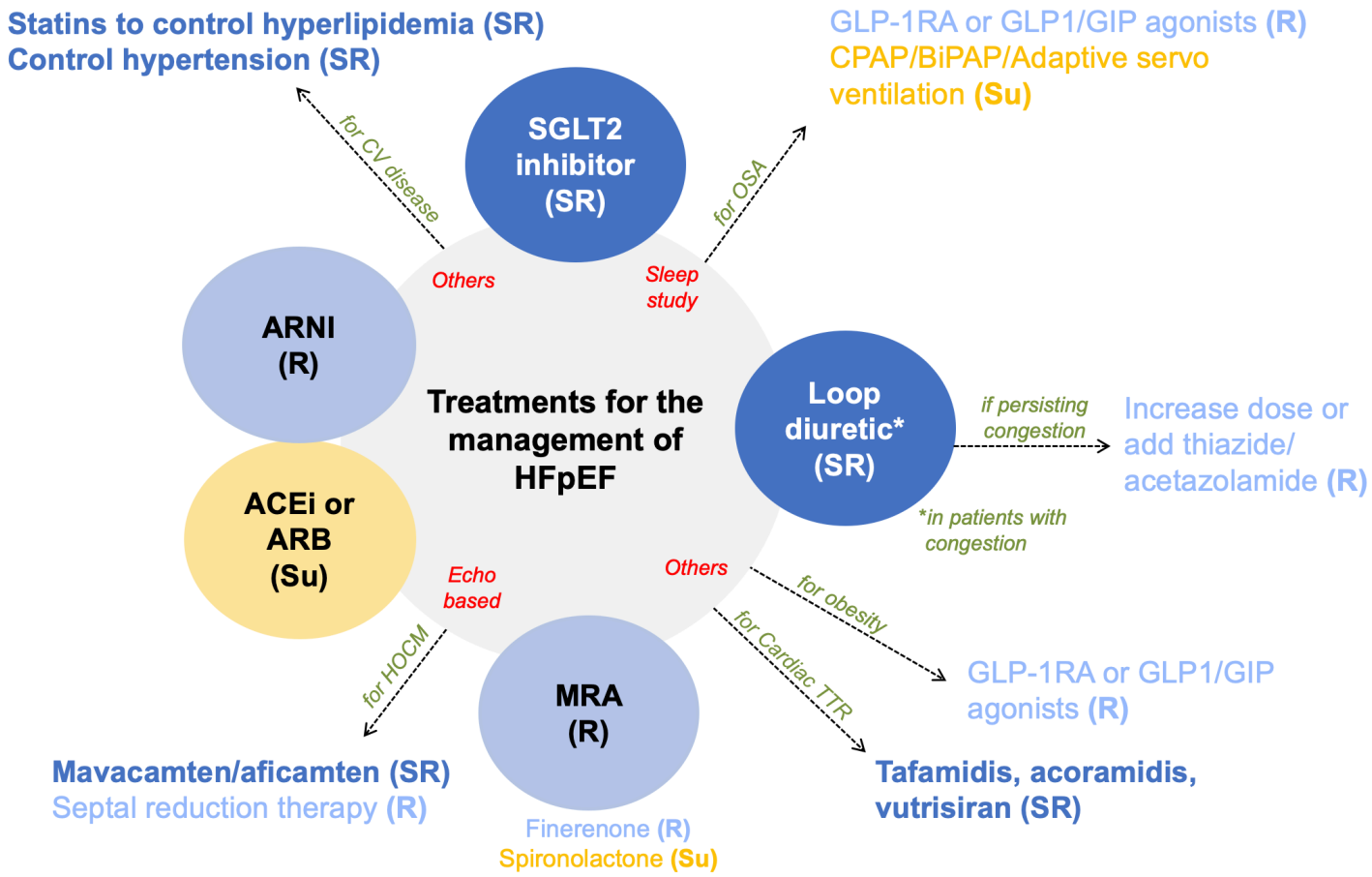



SR, Strongly recommend; R, Recommend; Su, Suggest; and DND, Do not do.
ACEi, angiotensin-converting enzyme inhibitors; AF, atrial fibrillation; ARB, angiotensin receptor blocker; AHF, acute heart failure; AR, aortic regurgitation; AS, aortic stenosis; AV, atrioventricular; ARNI, angiotensin receptor neprilysin inhibitor; CAD, coronary artery disease; CABG, coronary artery bypass grafting; COX-2, cyclo-oxygenase-2; CRT, cardiac resynchronization therapy, DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; GDMT, guideline-directed medical therapy; HCM, hypertrophic cardiomyopathy; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; ICD, implantable cardioverter-defibrillator; LBBB, left bundle branch block; LVAD, left ventricular assist device; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MR, mitral regurgitation; MRA, mineralocorticoid receptor antagonist; M-TEER, mitral transcatheter edge-to-edge repair; NSAIDs,

non-steroidal anti-inflammatory drugs; NT-proBNP, N-terminal prohormone of B-type natriuretic peptide; NYHA, New York Heart Association; PDE5, phosphodiesterase-5;RAAS, Renin-angiotensin-aldosterone system; RV, right ventricle; SGLT2, sodium-glucose co-transporter 2; TSAT, transferrin saturation; TR, tricuspid regurgitation; VAD, ventricular assist device.

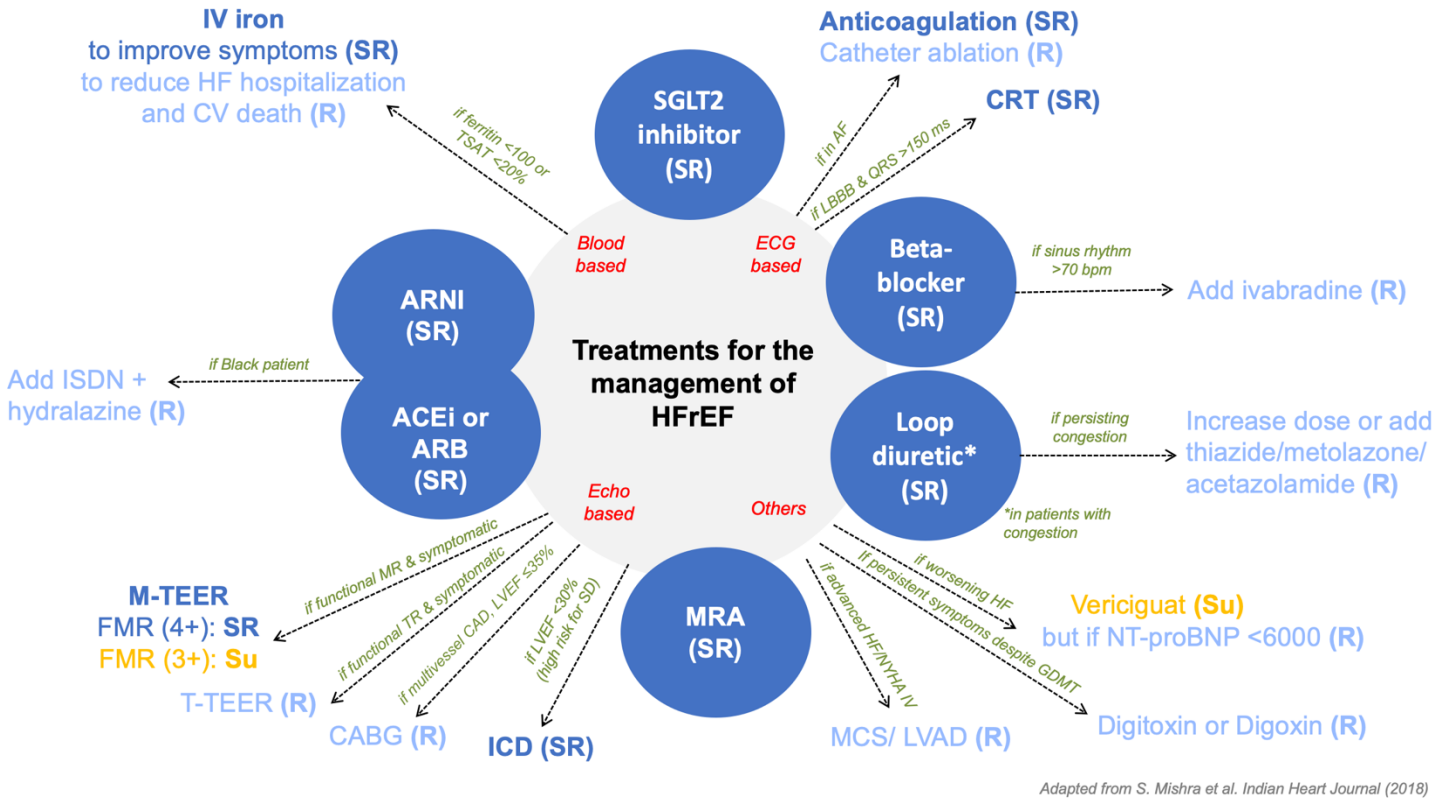
Note: In patients with LVEF 40–49%, diagnostic accuracy of test is less certain (due to the variability of LVEF assessments) and the absolute amount of therapeutic benefit of GDMT is somewhat less than in patients with LVEF <40%.

**Figure 5: Overview of HFpEF Management**




SR, Strongly recommend; R, Recommend; and Su, Suggest.
ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blocker; ARNI, Angiotensin receptor neprilysin inhibitor; bi-PAP, bilevel positive airway pressure; CV, cardiovascular; CPAP, continuous positive airway pressure; GLP-1RA, glucagon-like peptide 1 receptor agonist; HCM, hypertrophic cardiomyopathy; HFpEF, heart failure with preserved ejection fraction; MRA, mineralocorticoid receptor antagonist; OSA, obstructive sleep apnea; SGLT2, sodium-glucose co-transporter 2.

**Figure 6: Overview of HFrEF Management**




SR, Strongly recommend; R, Recommend; and Su, Suggest.
ACEi, angiotensin-converting enzyme inhibitors; AF, atrial fibrillation; ARB, angiotensin receptor blocker; ARNI, Angiotensin receptor neprilysin inhibitor; bi-PAP, bilevel positive airway pressure; CPAP, continuous positive airway pressure; CAD, coronary artery disease; CABG, coronary artery bypass grafting; CRT, cardiac resynchronization therapy, GLP-1RA, glucagon-like peptide 1 receptor agonist; HCM, hypertrophic cardiomyopathy; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; ICD, implantable cardioverter-defibrillator; ISDN, isosorbide dinitrate; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; LVAD, left ventricular assist device; MCS, mechanical circulatory support; MR, mitral regurgitation; MRA, mineralocorticoid receptor antagonist (spironolactone or eplerenone); M-TEER, mitral transcatheter edge-to-edge repair; T-TEER, tricuspid transcatheter edge-to-edge repair; NT-proBNP, N-terminal prohormone of B-type natriuretic peptide; NYHA, New York Heart Association; OSA, obstructive sleep apnea; SD, sudden death; SGLT2, sodium-glucose co-transporter 2; T2DM, type 2 diabetes mellitus; and TSAT, transferrin saturation.

Note: In patients with LVEF 40–49%, diagnostic accuracy is less certain (due to the variability of LVEF assessments) and the absolute amount of therapeutic benefit of GDMT is somewhat less than in patients with LVEF <40%.