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JACC REVIEW TOPIC OF THE WEEK

Optimal Background Pharmacological Therapy for Heart Failure Patients in Clinical Trials

JACC Review Topic of the Week

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ABSTRACT

With the current landscape of approved therapies for heart failure (HF), there is a need to determine the role of a standard background therapy against which novel therapies are studied. The Heart Failure Collaboratory convened a multistakeholder group of clinical investigators, clinicians, patients, government representatives including U.S. Food and Drug Administration and National Institutes of Health participants, payers, and industry in March 2021 to discuss whether standardization of background drug therapy is necessary in clinical trials in patients with HF. The current paper summarizes the discussion and provides potential conceptual approaches, with a focus on therapies indicated for HF with reduced ejection fraction. (J Am Coll Cardiol 2022;79:504–510) © 2022 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

The U.S. Food and Drug Administration (FDA) has recently approved several new drugs for chronic heart failure (HF), giving rise to a new debate regarding appropriate background therapy against which to study novel therapeutics. The Heart Failure Collaboratory, a consortium of clinical investigators, clinicians, patients, government representatives including FDA and National Institutes of Health participants, payers, and industry (Supplemental Appendix) convened a multistake-

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Christie M. Ballantyne, MD, served as Guest Editor-in-Chief for this paper.

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HIGHLIGHTS

- Guideline-directed pharmacological therapy can improve functional status and reduce morbidity and mortality in patients with HFrEF, but in clinical practice are often suboptimally employed.
- This creates a conundrum when new therapies for patients with HFrEF are evaluated in clinical trials, because uniform use of optimal background therapies may limit generalizability to patients managed in general practice.
- Potential approaches include specific drug class recommendations, scoring systems, and other strategies that meet the needs of trialists, sponsors, regulators, payers, patients, and prescribers.

holder group in March 2021 to discuss whether standardization of background drug therapy is necessary in clinical trials in patients with HF, focusing on therapies approved for heart failure patients with reduced ejection fraction (HFrEF). The current paper summarizes the discussion and provides potential conceptual approaches.

REGULATORY CONSIDERATIONS

Therapies approved in the United States to treat HF have generally shown significant benefit on morbidity and mortality, resulting in strong recommendations in treatment guidelines.[1,2] However, in practice, patients remain undertreated with guideline-directed medical therapy (GDMT) for multiple reasons, including absolute or relative contraindications and real or perceived intolerance.[3] The dilemma of trialists, sponsors, regulators, and payers is whether new therapies should be tested against a background of maximal GDMT or potentially suboptimal "usual care?" For example, what is the value of a new therapy that is shown to be beneficial in the latter circumstance? Might it have had less benefit if background therapy had been optimized? If a treatment is expected to work through distinct and independent mechanisms, the intensity of background therapy is irrelevant to assess treatment efficacy via relative risk reduction, although background therapy may augment absolute risk reduction by influencing the prevailing population event rate. What is certain is that new therapies for heart failure are needed, whether providing incremental benefit as an "add-on" treatment or as an effective alternative to a proven but contraindicated or poorly tolerated standard therapy. Assuming a drug has been shown to be safe and effective, a primary issue for U.S. regulators is to determine whether trial results are relevant to patients with heart failure in the United States.

DRUG THERAPY. Because the risk of death in heart failure is high, even in the short term, comparing a new therapy to placebo in untreated patients is not considered appropriate. Instead, it is prudent that patients with HF be treated with GDMT as comprehensively as possible. It follows that new treatments may be tested in addition to "optimized" GDMT. However, it is difficult to define "optimized" therapy, in terms of number of drugs, dose of drugs, duration of therapy, and use of devices. Moreover, GDMT

ABBREVIATIONS AND ACRONYMS

FDA = U.S. Food and Drug Administration

EF = ejection fraction

GDMT = guideline-directed medical therapy

HF = heart failure

HFpEF = heart failure with preserved ejection fraction

HFrEF = heart failure with reduced ejection fraction

TABLE 1 Case Example of SGLT2is

The Pros (Purist Perspective)	The Cons (Pragmatic Perspective)
• Highly effective, well-tolerated, and easy to use treatment • Will have Class 1, Level of Evidence: A guideline recommendation • Will become "standard of care" • Will want to know whether new therapies are beneficial (and safe) in addition to SGLT2i • Mechanisms are still being understood, and this ensures that incremental efficacy and safety is tested (even if mechanisms are ultimately found to be partially overlapping) • Requiring use of therapy forces a change in practice that benefits patients	• New drug approval globally may take years and national guideline recommendations may take time to be updated • New, patented treatments such as SGLT2is are not available to many patients worldwide, and clinical practice changes slowly • Comorbidities may limit maximization • Need to establish whether SGLT2is work through distinct but complementary pathways and their benefits are independent (and additive)—a *different stance than if new drug works through the same pathway as an existing drug* • Takes time to educate providers and patients about emerging therapies, and/or reluctance to alter therapies when patients appear "well" • Increased complexity of the overall HF medication regimen and/or polypharmacy-induced nonadherence
The compromise: Early after benefit of a treatment is demonstrated, try to ensure that at least, a reasonable large subgroup of patients in new trials is on that treatment	

SGLT2i = sodium-glucose transporter-2 inhibitor.

TABLE 2 Arguments for and Against a Standard Background Therapy Requirement in Heart Failure Clinical Trials

For Standard Background Therapy ⊕	*Against* Standard Background Therapy ⊖
• Requiring standard therapy encourages positive change in practice • Better understanding of incremental benefit achieved with trial drug on top of other therapies • Necessary if overlapping mechanisms of action between background therapy and trial drug • Limits differential uptake of other HF therapies during follow-up that may occur more often in the comparator group	• Does not reflect real-world practice • No evidence of better therapeutic development • Global variation in regulatory approval and guideline recommendations • Cost barriers • Coverage barriers • May potentiate disparities of therapy limited in certain populations if drugs are not available in certain regions or because of cost

optimization remains poor in routine clinical practice, and although it is better in clinical trials, is often less than ideal. For example, in the GUIDE-IT (Guiding Evidence-Based Therapy Using Biomarker Intensified Treatment in Heart Failure) trial, triple optimal therapy (any combination of ≥50% target dose of beta blocker, angiotensin-converting enzyme inhibitor [ACEI]/angiotensin receptor blocker [ARB], any dose of mineralocorticoid receptor antagonist [MRA]) was achieved in only 15% of patients, despite a protocol-driven approach to maximize treatments.[3,4] In recent trials, differences in HFrEF therapy optimization were among possible reasons to explain conflicting results of the COAPT (Transcatheter Mitral-Valve Repair in Patients with Heart Failure) and the MITRA-FR (Percutaneous Repair or Medical Treatment for Secondary Mitral Regurgitation) trials.[5]

With differing tolerability of drugs in different populations, variable availability and affordability of both drugs and devices, and other considerations described in the following text, it is impossible to define "optimal" guideline-directed therapy for all patients, let alone mandate it. Requiring maximal use and dosing of drug therapies may not be possible and not desirable in many cases. For example, in protocol-driven titration studies of various neurohormonal antagonists, only 40%-70% tolerated a maximal dose of most agents, although some studies have achieved higher doses.[6] In a quality improvement study, although 89%-95% patients were on beta-blockers, only 18%-27% achieved maximal (target) drug dose, with mean daily carvedilol dose equivalents of 25-28 mg vs a target dose of at least 50 mg.[7]

Several relevant considerations are summarized in Table 1, using SGLT2 inhibitors as an example, including economic factors, speed of global regulatory approval and guideline incorporation, tolerability of drugs by class and dose, comorbidities that may limit maximization, and local or regional practice differences.

DEVICE THERAPY. Standardization of background device therapy across HF clinical trials is even more challenging. Although both primary prevention implantable cardiac devices and cardiac resynchronization therapy have relatively uniform Class I indications across international guidelines, their use varies widely reflecting similar issues to those described for drugs, and attempting to mandate specific targets for device use in multicenter global trials is unrealistic.[8,9] Additional device therapies, including cardiac contractility modulation and baroreflex activation therapy, improved symptoms and quality of life[10,11] in patients with HFrEF, but are not likely to be included as a current standard background therapy.

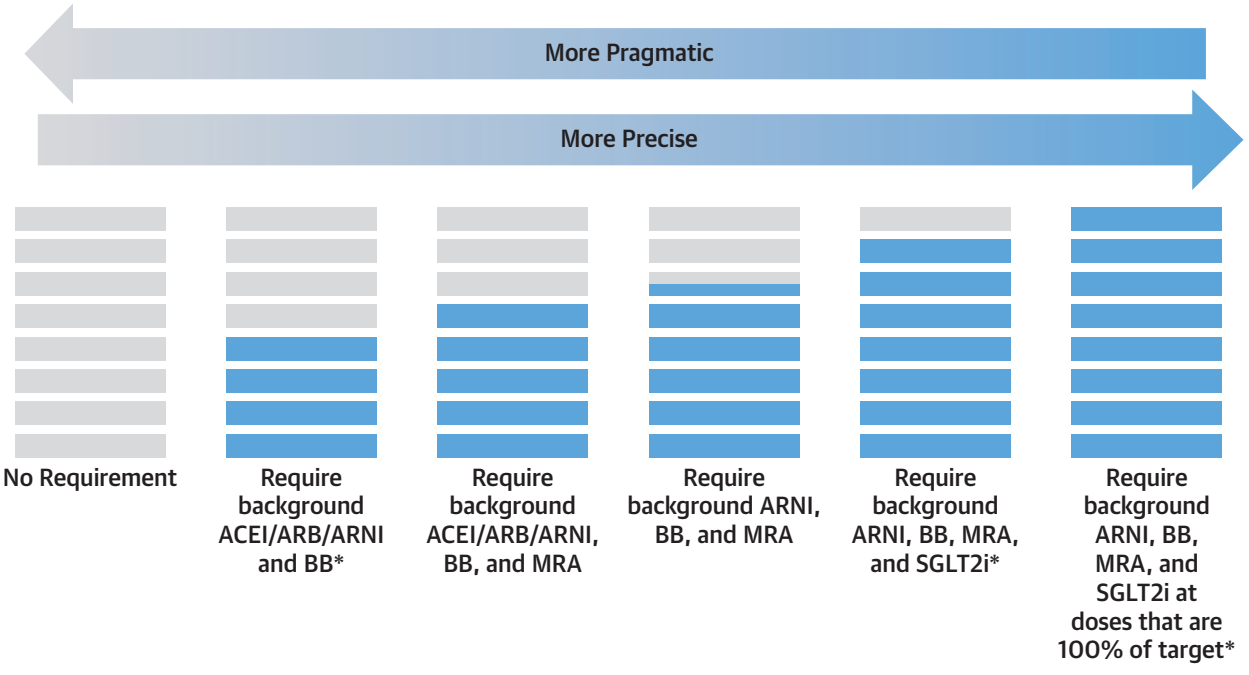
THE CLINICAL TRIAL DEBATE: DO WE NEED A STANDARD FOR BACKGROUND DRUG THERAPY?

THE CASE FOR STANDARD BACKGROUND THERAPY. There is agreement among the collaboratory expert panel that encouraging the best tolerated background GDMT in clinical trials fosters best practice and may facilitate maximization of therapy. Additionally, a minimum standard of background therapy across all participating countries increases the likelihood that trial results are globally applicable. Furthermore, when background therapy is not optimized at enrollment, there is the potential for differential "drop-in" of known effective HF therapies in the placebo group that might attenuate between-group differences of the experimental therapy. For new devices, it is particularly important to have adequate background medical therapy, particularly where sample sizes may be modest and device implantation is often permanent.

THE CASE AGAINST STANDARD BACKGROUND THERAPY. Although the concept of a standardized background regimen may be ideal, there are several reasons as to why it may be difficult or impossible to achieve, as described earlier. There is substantial global variation in the availability and affordability of therapeutics. Device therapies vary widely, particularly between the United States, Europe, South America, and Asia, and differences in guidelines pose a challenge. Because most new therapies may have a mechanism of action distinct from approved therapies, incremental benefit can be assumed to be independent of background treatment.[12]

Table 2 summarizes the advantages and disadvantages of requiring or not requiring a standard.

FIGURE 1 Specific Versus Pragmatic Approaches to Background Heart Failure Drug Therapy



A more pragmatic approach would include minimal requirements of background medical therapy, whereas a more precise approach involves treatment with all classes of goal directed therapy and target doses. *In absence of contraindications or documented intolerance. ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; ARNI, = angiotensin receptor neprilysin inhibitor; BB = beta-blocker; MRA = mineralocorticoid receptor antagonist; SGLT2i = sodium-glucose transporter-2 inhibitor.

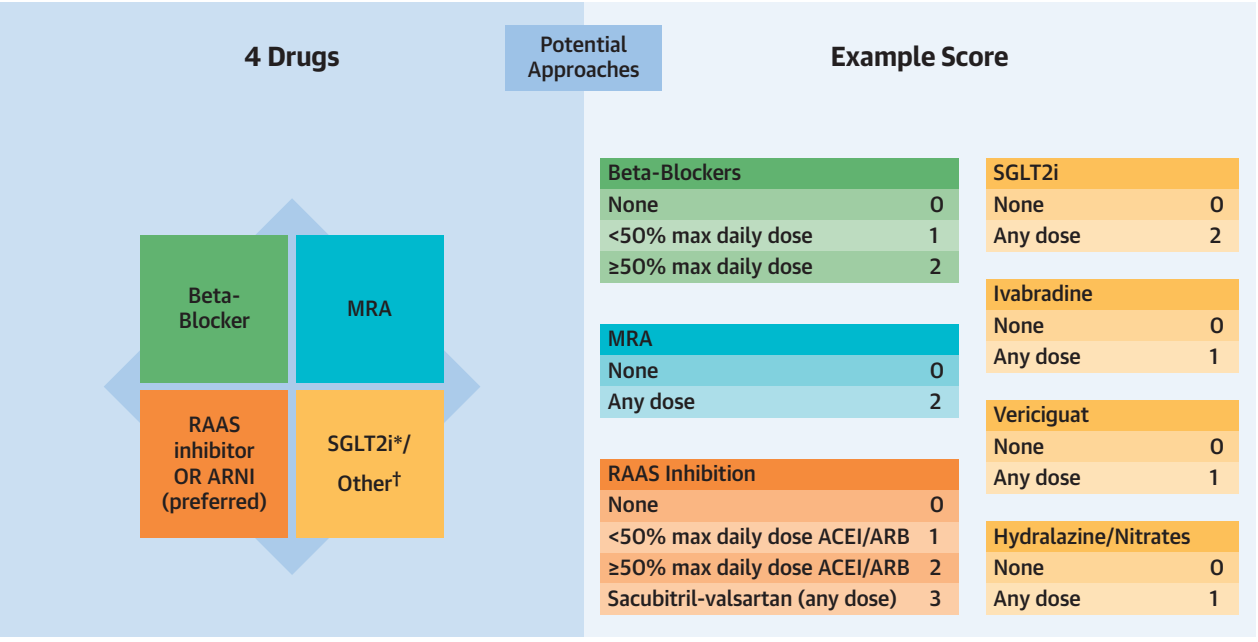
THE CASE FOR SPECIFIC DRUG THERAPIES

CURRENT GDMT. To encourage adherence to guidelines, and best treatment of patients, a balance may be sought that is reasonable and achievable. Figure 1 outlines a range of options tailored to the type of clinical trial. Because of their simplicity, pragmatic clinical trials utilize a real-world approach.[13] Alternatively, requiring some degree of specification of HF medical therapy while allowing a gradient of clinical decision-making improves flexibility and ensures some standardization.

SACUBITRIL-VALSARTAN. The angiotensin receptor-neprilysin inhibitor sacubitril-valsartan reduced morbidity and mortality in patients with HFrEF.[14] It is currently integrated into guideline recommendations as standard therapy for patients with symptomatic HFrEF as a replacement for ACEI/ARB.[15,16] More recently, recommended use has expanded to include patients with HF with a wider range of left ventricular ejection fraction.[17] Use of sacubitril-valsartan has increased over time and, hopefully, in new trials, a sufficient number of patients on this therapy will allow a reasonably robust estimate of the effect.

SGLT2 INHIBITORS. SGLT2 inhibitors consistently demonstrated substantial relative and absolute and risk reductions across multiple endpoints.[18,19] Treatment was highly effective, well-tolerated and easy to use, and they have a Class I, Level of Evidence: A guideline recommendation in the European and Canadian HF guidelines.[1,16] An argument could be made that future trials should test new interventions in addition to SGLT2 inhibitors, recognizing that global uptake may be slow. As with sacubitril-valsartan, one option for new trials is to ensure that at least a reasonably large subgroup of patients receive this therapy at baseline, to allow an estimate of the effect of the new therapy when added to an SGLT2 inhibitor.

CENTRAL ILLUSTRATION **Potential Approaches to Background Drug Therapy for Heart Failure Patients**



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(Left) 4 drug class approach; **(right)** GDMT score example. *Majority of patients on SGLT2i. †Drugs shown to improve outcomes in specific patient cohort. ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor neprilysin inhibitor; MRA = mineralocorticoid receptor antagonist; RAAS = renin angiotensin aldosterone system; SGLT2i = sodium-glucose transporter-2 inhibitor.

VERICIGUAT. The soluble guanylate cyclase stimulator, vericiguat, was effective when added to standard therapies in the VICTORIA (Vericiguat Global Study in Subjects with Heart Failure with Reduced Ejection Fraction) trial.[20] The drug was also safe and well-tolerated in the high-risk HFrEF population studied, including those with comorbidities such as renal impairment. The benefit was greater in patients with lower N-terminal pro-brain natriuretic peptide levels and less effective in patients with a recent hospital admission.[21] Vericiguat has limited regulatory approval at present (to reduce risk of CV death and HF hospitalization following HF hospitalization or need for outpatient intravenous diuretic agents in adults with symptomatic HF and EF <45%), and its place in GDMT is currently uncertain. As a result, it is unrealistic to expect wide use in contemporary trials.[21]

HF WITH PRESERVED EF. Although there are no FDA-approved therapies for the treatment of heart failure with preserved ejection fraction (HFpEF) specifically, blood pressure (BP) control is a critical component caused by the clear evidence that lowering BP reduces HF hospitalizations in these patients.[22] Other targets include symptomatic treatment with diuretic agents, treatment of comorbidities, rate control in atrial fibrillation, and treatment of ischemia. In appropriately selected patients, the use of spironolactone may be considered to lower hospitalizations for HF. Despite the absence of guideline-recommended therapy for HFpEF, in clinical trials, HFpEF patients have largely received similar background therapy to HFrEF patients (typically used to manage comorbidities). At present, there is no basis on which to recommend specific pharmacological therapies in HFpEF trials, although this is a rapidly changing field.

POTENTIAL APPROACHES IN CLINICAL TRIALS

4 STANDARD DRUG CLASSES IN HFrEF. One approach to achieve some degree of conformity while allowing flexibility in clinical decision-making could be a 4-drug class approach. The Central Illustration outlines this option, which includes background

therapy with HF-specific beta-blockade (BB), a RAS inhibitor (ACEI, ARB) or ARNI (preferred), an MRA, and 1 "other" class, eg, sodium-glucose transporter-2 inhibitors. The fourth class might be determined by the individual patient's profile. This approach ensures guideline Class I recommendations are followed, including titration of doses to target (according to guideline recommendations), and require documentation of contraindications and intolerance of GDMT. For patients not on all 4 drug classes, the reason(s) should be documented.

GDMT SCORE. Using a score may be an alternative approach to permit comparison of background therapy within and across trials, without mandating which drugs are used. The **Central Illustration** offers an example scoring system. The score was previously developed as a result of a consensus Heart Failure Academic Research Consortium meeting.[23] To develop the score, current American College of Cardiology/American Heart Association/Heart Failure Society of America and European Society of Cardiology guidelines and the GDMT definition in 9 HF clinical trials were evaluated. A score was created based on quality of evidence, literature review, and data regarding dose effects, and established thresholds for optimal, acceptable, or suboptimal therapy based on median doses derived from landmark clinical trials and clinical use for each drug. The score was tested in clinical scenarios based on likely combinations in the COAPT trial. Work is underway to refine the score, determine the score distribution in several contemporary trials and in routine clinical practice, and determine appropriate cutpoints as related to outcomes.

With this approach, a point value is assigned based on class of drug, and in some cases, dose of drug (for BB and ACEI). Target doses are based on current guidelines, and SGLT2 inhibitors were incorporated given the strength of data and inclusion in European Union and Canadian guidelines, despite not being incorporated in U.S. guidelines at the time of publication. Although this approach is imperfect and dynamic, it accounts for personalized background therapy and provides a framework for comparing background regimens across trials. The score is not intended to create entry criteria, per se, although it could be used in this manner. It is intended to be a tool for comparison within a trial and across trials. Further, it may allow background drugs to be selected based on being mechanistically distinct from the new therapy being studied in the clinical trial.

CONCLUSIONS

There is agreement among the clinical trial community, regulators, industry, patients, and other key stakeholders such as payers, that some standard of baseline drug therapy is important for studying new therapies, and it would be ethically untenable for trial participants to be enrolled without any background GDMT. However, the more the baseline drug therapy is constrained, the less opportunity there may be to understand interactions, to determine the need for additional and alternative therapies, or to evaluate new mechanisms. In addition, considerations of relative value and safety of interaction with other therapies requires some ability to understand the interplay with other treatments. A wide range of options exists for determining what the standard baseline drug therapy should be. We provide several concepts as to how this question might be approached in future clinical trials.

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APPENDIX For a list of meeting attendees, please see the online version of this paper.