Review Article

Pharmacological Treatment in Patients with Advanced Heart Failure: Recommendations and Challenges

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Abstract

Heart failure is a highly prevalent condition, and a series of new therapies have emerged over the past years, improving patients' survival and quality of life, simultaneously making its management more complex. When treating patients with advanced heart failure, that is, with persistent limiting symptoms and recurrent hospitalizations, it is usually even more challenging to manage cases, given that, in addition to frequently having characteristics that would exclude them from most clinical studies, they pose a series of difficulties to optimizing therapies, mainly due to symptomatic hypotension and renal dysfunction, but also due to difficulty in adhering to the growing list of medications, high costs, and poor understanding of their own disease. The concept that is currently in vogue is that therapeutic optimization, including the 4 fundamental drugs for the treatment of heart failure with reduced ejection fraction (angiotensin-converting enzyme inhibitors/angiotensin receptor blockers/angiotensin receptor-neprilysin inhibitors, beta-blockers, aldosterone receptor antagonists, and sodium-glucose cotransporter-2 inhibitors), should be carried out quickly, within 4 weeks after diagnosis or hospitalization for decompensation, in the event that the patient is not already using the 4 classes. This may be a somewhat "daring" goal when treating patients in more advanced stages. In these cases, some strategies can help to achieve the best tolerated treatment possible, with good control of symptoms and improved survival. Furthermore, intolerance to clinical treatment is also a marker of advanced disease in itself and should be considered a reason for referral to centers specializing in advanced heart failure whenever possible.

Introduction

Heart failure (HF) is a highly prevalent condition, for which a series of pharmacological treatments and devices have been developed, with significant improvement in patient survival and quality of life. In spite of this, a portion of patients follow the natural course of the disease, reaching more advanced stages, defined as stage D.[1] Even patients who initially benefit from available therapies may eventually progress to the advanced form.

Definitions of HF differ according to the source analyzed, but they all agree on the point of persistent severe symptoms (New York Heart Association functional class [NYHA FC] III to IV) and repeated hospitalizations, in spite of optimized maximum tolerated therapy.[2-5] It is necessary to keep in mind that the concept of advanced HF goes beyond the presence of left ventricular dysfunction, given that patients with preserved ejection fraction (EF) can also be characterized as such, as well as those with congenital heart disease, severe valve disease without the possibility of intervention, and isolated right ventricular dysfunction.[3] That notwithstanding, the therapeutic options discussed in the following text are applied to patients with reduced EF. Another point of convergence in the majority of documents that deal with advanced HF is the issue of intolerance to maximal therapeutic optimization, generally due to symptomatic hypotension and renal dysfunction, with or without hyperkalemia. Moreover, as suggested by the guidelines,[3,6-8] other issues that are frequently present in this group of patients also render clinical optimization difficult, such as advanced age, associated comorbidities, and polypharmacy, with consequent difficulty in adherence, in addition to increasing costs.

The objective of this review is to bring together data from evidence on pharmacological treatment in this specific group of patients, as well as challenges in daily clinical practice.

Classical pharmacological treatment

In general, patients with more advanced disease characteristics end up being underrepresented in most clinical studies. In the PARADIGM-HF study, which randomized more than 8000 patients with EF < 40% (subsequently changed to ≤ 35%) to receive either sacubitril/valsartan (S/V) or enalapril, showing an important reduction in all-cause mortality, deaths due to cardiovascular causes, and hospitalization for HF, in addition to a reduction in sudden death, < 1% of patients were categorized as NYHA FC IV.[9] Approximately 20% of patients screened during the run-in period (4 to 6 weeks, to test drug tolerance) could not be included due to intolerance to the target drug dose, hypotension, or worsening renal function. In the PIONEER study, which evaluated the use of S/V in patients with decompensated HF, only 9% were in NYHA FC IV.[10]

The LIFE study was developed in an attempt to fill this gap in relation to the use of S/V in patients with advanced HF (defined as EF ≤ 35%, NYHA FC IV, BNP ≥ 250 pg/mL or NT-proBNP ≥ 800 pg/mL, and ≥ 1 objective finding of advanced disease).[11] Patients were randomized to receive S/V or valsartan alone after a 7-day run-in period to evaluate

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tolerance to the initial S/V dose of 24/26 mg twice daily. The primary endpoint included proportional change in NT-proBNP at 24 weeks, evaluated by the area under the curve. Secondary outcomes included cardiovascular mortality, hospitalization for HF, hypotension, and other markers of drug tolerance. It was necessary to interrupt the study early due to the COVID-19 pandemic, and the analysis of the results was performed with the 335 patients included up to the moment the study was interrupted; the initial objective had been 400 patients. There were no differences between the groups in any of the outcomes evaluated, and the achieved medication dose was < 50% of the target dose for both groups. In spite of the study limitations, it is starting to become clear that patients in this group do in fact have their own peculiarities in terms of management, and they should not be treated in the same way as patients in earlier stages. Intolerance to clinical treatment should be considered a reason for referral to centers specializing in advanced HF to evaluate indication of other (non-pharmacological) therapies.

Among the studies evaluating the effects of sodium-glucose cotransporter-2 (SGLT2) inhibitors in patients with HF and reduced EF, with or without type 2 diabetes, < 1% of patients in the DAPA-HF study[12] were in NYHA FC IV. Compared to this, patients included in the EMPEROR-REDUCED study[13] had lower EF, higher levels of NT-proBNP, and lower glomerular filtration rate (GFR), reflecting a population with greater severity. A meta-analysis that included both studies showed a 13% reduction in all-cause mortality, a 14% reduction in cardiovascular mortality, and an important reduction in hospitalizations for HF, which had already been demonstrated by both studies individually. However, in subgroup analysis, the effect was shown to be attenuated, although still significant, in patients in NYHA FC III to IV.[14] Because these medications have modest effects on blood pressure, in addition to an excellent safety profile, they tend to be well tolerated, even by the most borderline patients, and their initiation in conjunction with beta-blockers has been proposed as a first step in treatment-naive patients or patients whose treatment has been suspended due to more severe decompensation, because, thanks to their natriuretic effect, they can help to counterbalance the symptoms of clinical worsening that may arise at the beginning of beta-blocker therapy.[15]

In relation to older treatments for HF, there are some studies available that have included outpatients in more advanced stages,[16-20] demonstrating consistently beneficial results. The COPERNICUS study[17] was the largest study that evaluated patients with NYHA FC III to IV and EF < 25%, with a significant reduction in deaths and hospitalizations due to HF, in addition to good patient tolerance to the drug. Meta-analysis of randomized trials evaluating the effect of beta-blockers in patients in NYHA FC IV reiterated this concept.[21]

In spite of this, concerns still exist in relation to beta-blocker use, especially at the recommended doses, in patients with more advanced disease. A non-randomized study that evaluated the use of carvedilol in patients in NYHA FC IV showed that, although patients were more likely to experience worsening HF soon after starting the medication, the majority were able to continue with the therapy after an initial period of adjustments, and they showed a greater magnitude of symptomatic improvement after 3 months of treatment.[22,23] Hypotension and hyponatremia, which are conditions that reflect more severe and possibly more congested patients, are predictors of worsening HF after starting carvedilol.[22,23] Patients in more advanced stages require closer follow-up when starting beta-blockers, often requiring a temporary increase in diuretic dose, but these patients tolerate the therapy well and they benefit even more from it. Prior to initiation or progression of the beta-blocker dose, patients must be minimally compensated in order to tolerate the elevated filling pressures and reduced cardiac output, which are mild, yet relevant in these cases.

Aldosterone receptor antagonists are one of the most underused classes in patients with HF and reduced EF,[24-27] although they have shown 15% to 30% reduction in mortality and up to 40% reduction in rehospitalization in the main studies.[19,28,29] The main precautions are related to worsening renal function, hyperkalemia, and eventually hypotension. Regarding this last issue, an interesting study retrospectively analyzed patients included in the RALES and EPHESUS studies (4396 patients in total), subdivided according to baseline systolic blood pressure (≤ 105, > 105 and ≤ 115, > 115 and ≤ 125, > 125 and ≤ 135, and > 135 mmHg) showing no significant reduction in blood pressure between the drug and placebo, in contrast to what occurs in the treatment of hypertensive patients.[30] Furthermore, the benefit of relative reduction in mortality was consistent across all subgroups analyzed. Taking into account that patients with systolic blood pressure ≤ 105 mmHg were more severe patients due to several characteristics analyzed, these patients benefit even more from the proposed treatment. The concern regarding a possible worsening of renal function and hyperkalemia is justified; however, we currently have some strategies to minimize these effects, which will be described subsequently.

In patients with refractory symptoms, the use of digoxin can also be considered, especially as an adjunct to heart rate control in cases of atrial fibrillation, paying attention to the risk of toxicity, especially in women, patients with low weight, and patients with renal dysfunction.[31,32] The therapy should ideally be adjusted according to drug serum level. Data from more contemporary cohorts of patients with HF are conflicting in relation to the benefits and safety of using digoxin, especially when in sinus rhythm.[31,33] Discontinuation of digoxin in patients hospitalized for HF seems to be associated with higher rates of rehospitalization, even when they are receiving optimized treatment with other therapies.[34]

The study that evaluated the effects of ivabradine in patients with HF and reduced EF did not include patients on NYHA FC IV.[35] However, the drug seems interesting for the profile of more advanced patients in certain contexts, as it reduces heart rate, without a negative inotropic effect.[36] A subanalysis of the SHIFT study using echocardiography assessment showed an increase in systolic volume, by improving ventricular-arterial coupling with a reduction in heart rate.[37] It has been postulated that ivabradine may be useful in patients with sinus tachycardia induced by the use of inotropes, especially dobutamine.[38] Sinus tachycardia is usually a compensatory mechanism, which attempts to maintain minimally adequate cardiac output. However, the direct physiological relationship

between increased heart rate and increased myocardial contractility observed in normal hearts is lost when there is myocardial dysfunction, a condition in which there is a paradoxical reduction in contractile force with higher frequencies.[39] Accordingly, ivabradine could contribute to mitigating excessive tachycardia in patients using an inotrope, controlling heart rate without causing negative inotropism and potentially improving hemodynamics. This hypothesis has only been tested in animal studies and small studies in patients with HF, evaluating short-term hemodynamic effects, and the data cannot be extrapolated to clinical practice.[40,41] Formally, the indication for the use of ivabradine in patients with advanced HF is the same as that applied to other profiles of patients with HF and reduced EF.

Given the various therapeutic options with proven positive impact on HF with reduced EF, taking into account that the benefit of each drug is independent of the presence of the others and that the mechanisms of action are complementary, individualization appears to be the best strategy.[42] Patients present with different phenotypes, which reflect different needs, and it seems to be a suitable method define the pharmacological strategy in a more personalized manner, maintaining the objective of including all of the fundamental classes (angiotensin-converting enzyme inhibitors/angiotensin receptor blockers/angiotensin receptor-neprilysin inhibitors [ACEI/ARB/ARNI], beta-blockers, aldosterone antagonists, and SGLT2 inhibitors).

New pharmacological treatments

Omecamtiv mecarbil is a more recent medication that has been tested in HF. It acts as a specific ligand of cardiac myosin, optimizing the actin-myosin interaction in the heart muscle, promoting improved contractility (known as the "myotropic" effect). Unlike other medications that increase myocardial contractility, omecantiv does not increase the influx of calcium into the myocyte, considerably reducing the risk of arrhythmias and myocardial ischemia. Initial pharmacokinetic studies showed an increase in ventricular ejection time and systolic volume, in addition to a reduction in left ventricular end-systolic and diastolic volumes.[43]

The first study to evaluate clinical outcomes of omecantiv mecarbil in HF was the GALACTIC-HF, which randomized more than 8000 patients between 18 and 85 years of age, NYHA FC II to IV (although there were only 124 NYHA FC IV patients in each group), with EF < 35%, who were hospitalized or had been hospitalized during the last year, to receive placebo or omecantiv, with dose guided by serum level measurement. Patients using inotropes, patients with systolic blood pressure < 85 mmHg, and patients with GFR < 20 mL/min/1.73 m^2 were excluded. The primary endpoint included time to first HF-related event (hospitalization, urgent emergency room, or outpatient visit) or death due to cardiovascular causes. There was an 8% reduction in the primary outcome (hazard ratio 0.92, 95% confidence interval 0.86 to 0.99; p = 0.03), with no reduction in cardiovascular mortality. There was no difference in the number of adverse events between the groups. Hypotension, worsening of renal function, and hyperkalemia also did not occur.[44]

Subgroup analysis was performed according to EF (divided into quartiles: EF ≤ 22%, EF 23% to 28%, EF 29% to 32%, and EF ≥ 33%); this analysis had already been pre-specified in the initial study design. The primary endpoint event rate was significantly higher (up to 80% higher) in the quartile with the lowest EF compared to the one with the highest EF, and the benefit of therapy was significantly greater in patients with EF ≤ 28% (hazard ratio 0.84; 95% confidence interval: 0.77 to 0.92; p = 0.0003), when compared to patients with EF > 28% (hazard ratio 1.04; 95% confidence interval: 0.94 to 1.16; p = 0.45). This difference was due to the reduction in hospitalizations rather than cardiovascular mortality.[45] In spite of the observed drop in natriuretic peptide levels, there was no symptomatic improvement (evaluated by the Kansas City Cardiomyopathy Questionnaire).

With these data, it is possible to speculate regarding the potential use of this medication in patients with advanced HF, considering the pathophysiological rationale behind its functioning, the evidence of greater benefit in subgroups with greater ventricular dysfunction, and the absence of side effects that are common in this group of patients, such as hypotension and renal dysfunction, but more studies will be needed to confirm these conclusions.

Vericiguat is a molecule that acts by stimulating soluble cyclic guanosine monophosphate through a mechanism that is independent of nitric oxide, but it also increases the sensitivity of cyclic guanosine monophosphate to endogenous nitric oxide, stabilizing the binding of nitric oxide with its receptor, finally improving myocardial function and exerting a vasodilating effect. The medication was approved by the United States Food and Drug Administration in January 2021, following the favorable results of the VICTORIA study,[46] which randomized patients with EF < 45%, NYHA FC II to IV, and elevated natriuretic peptides (NT-proBNP > 1000 pg/mL or > 1600 pg/mL with atrial fibrillation), with recent worsening (hospitalization during the past 6 months or use of parenteral diuretic therapy on an outpatient basis) to receive placebo or vericiguat, at a target dose of 10 mg/day. Patients with systolic blood pressure < 100 mmHg and patients who were receiving inotropes were excluded. It is interesting to note that patient recruitment occurred more rapidly than expected, and the number of primary outcome events was also higher than initially calculated, thus representing a more severe population. There was a significant reduction in the outcome of rehospitalization for HF at a mean follow-up of 10 months. Symptomatic hypotension was more frequent in patients using the drug, but there was no significant difference with the placebo group. Anemia was a more common adverse event in patients receiving vericiguat, and the mechanism of this change is not well understood. Subgroup analysis according to NT-proBNP levels (divided into quartiles) showed no benefit in the quartile with higher dosages (> 5314 pg/mL), possibly reflecting a population with very advanced disease, with indication for other non-pharmacological therapies, or even palliative care. Vericiguat became a class IIb recommendation in the 2021 European HF Guideline, for patients with HF with reduced EF, NYHA FC II to IV, and worsening HF in spite of treatment with beta-blockers, ACEI/ARB or ARNI, and aldosterone antagonists.[7]

Renal dysfunction and hyperkalemia in patients with advanced HF

The presence of renal dysfunction in patients with HF is a marker of higher morbidity and mortality, as well as advanced disease, when considering that the loss of renal function is secondary to the hemodynamic changes imposed by HF. In spite of this, these patients are known to receive the therapies classically indicated for this condition,[47,48] mainly renin-angiotensin-aldosterone system antagonists, less frequently.[49] Moreover, patients with chronic kidney disease are at an increased risk of developing HF, regardless of the presence of coronary artery disease.[50] In relation to patients with more advanced chronic kidney disease (grades 3 or 4), they are also extremely underrepresented in clinical studies. Data on the benefits and safety of the use of ACEI/ARB in these cases come mostly from observational studies. In general, the use of ACEI/ARB can worsen renal function, especially in the short term, and this implies worse prognosis; however, the benefit of therapy with ACEI/ARB is maintained, and it may even be greater.[51] In patients who initially present with chronic kidney disease (GFR ≤ 30 mL/min/m^2 or creatinine > 2.5 mg/dL), the benefit of using this class of drugs, when tolerated, is maintained.[52] Thus, the presence of renal dysfunction should not exclude the patient from trying to use ACEI/ARB and, more recently, ARNI, given that these patients, who are a at higher risk of events, tend to benefit more from treatments, even if at low doses, below those defined as target doses by classical studies, provided that they are followed more closely, with more frequent clinical and laboratory reassessments.

With respect to more recent therapies, subsequent analysis of the PARADIGM study showed that the reduction in GFR was smaller in the S/V group compared to patients who received enalapril, regardless of baseline renal function, in spite of an increase in urine albumin-creatinine ratio caused by S/V.[53] This increase was shown to be mild, and it stabilized after a few weeks of treatment. It is worth noting that the study excluded patients with GFR < 30 mL/min/1.73 m^2.

SGLT2 inhibitors have also been shown to be very favorable in this scenario, with results of less progression of renal dysfunction in long-term use,[54,55] in addition to a lower risk of hyperkalemia when used in conjunction with aldosterone antagonists.[56]

In relation to aldosterone receptor antagonists, recommendations tend to be more conservative when there is renal dysfunction, and their use is contraindicated when creatinine is > 2 mg/dL in women or > 2.5 mg/dL in men, due to the greater risk of worsening of renal function and hyperkalemia, without a clear accompanying benefit.[57] Once a patient already using an aldosterone antagonist develops more important renal dysfunction (GFR ≤ 30 mL/min/1.73 m^2), the medication should not routinely be discontinued, and each case may be individualized.[58]

Hyperkalemia is another frequent challenge during management of patients with HF, especially in those with some degree of impaired renal function, and it is associated with worse outcomes, mainly due to the lower use of therapies that block the renin-angiotensin-aldosterone system.[59-61] When there is mild hyperkalemia, routine non-suspension of these therapies was proposed by Ferreira JP et al.[62] in a recent review, where an algorithm for managing these patients was proposed to minimize the underutilization of therapies that have been proven to improve prognosis. The risk of hyperkalemia associated with the concomitant use of aldosterone antagonists is lower when using S/V when compared to enalapril,[63] which is one of the strategies proposed if the patient is not already using ARNI. The risk of hyperkalemia is also lower when an SGLT2 inhibitor is associated with treatment.[56]

The use of potassium chelators is another possibility. The use of patiromer (potassium ligand) has been tested in patients with HF, showing to be effective for this purpose,[64] and it is approved for management of hyperkalemia secondary to the use of renin-angiotensin-aldosterone system blockers in the United States and Europe, but it is still unavailable in Brazil. There are no data on efficacy and safety for calcium polystyrene sulfonate in this context. Studies are underway with the objective of evaluating whether the use of chelators, with a consequent increase in the use of renin-angiotensin-aldosterone system blockers, improves outcomes in patients with HF.

Hypotension and difficulty in dose progression

Optimizing therapy and managing symptoms in patients with more advanced disease can be quite challenging. One of the most limiting issues in this regard is symptomatic hypotension. When this occurs, it is important to assess the possibility of hypovolemia, with the eventual need to reduce diuretic use[65] and carefully review all medications in use to check if there are any that are not related to the treatment of HF that may be contributing to hypotension, such as calcium channel blockers and medications for benign prostatic hyperplasia, among others. Fractioning the administration of medications throughout the day, avoiding simultaneous intake of ACEI/ARB/ARNI and beta-blockers can also be useful. It is possible to prioritize beta-blockers without alpha-adrenergic effect (metoprolol and bisoprolol), which therefore have less potential to cause hypotension.

Intolerance to ACEI/ARB use due to circulatory limitation (symptomatic hypotension) or renal limitation (significant worsening of renal function) is an important marker of severity and high risk of death, as well as need for mechanical circulatory support or heart transplantation within 6 months.[66] In this manner, these patients should ideally be referred for specialized evaluation.

Initiation of beta-blocker therapy in more advanced patients, although safe, when the disease is minimally compensated, can be more difficult for the patient to tolerate, as patients often experience a feeling of "clinical worsening," with fatigue, tiredness and drowsiness. In these cases, it is worthwhile to warn patients about this possible feeling of worsening and inform them that, with persistent use, it tends to improve. While more stable patients may have their medication titrated every 7 days, in patients with advanced HF, a longer interval between beta-blocker dose increments may be prudent.[67]

Beta-blocker intolerance is not a class effect; therefore, it is valid to try more than one option before defining a patient as intolerant to the drug.[68]

The benefits of fundamental pharmacological therapies (ACEI/ARB/ARNI, beta-blockers, and aldosterone antagonists) are evident and significant, even at low doses, and they are seen in the short term, on average in 30 days.[69-73] Thus, the association of therapies, even at doses below those considered as target doses, is a superior strategy for reducing outcomes in patients with HF,[74] and it often ends up being used in patients with more severe disease. The concept that using a low dose is better than not using the drug should always be taken into account when dealing with a more severe patient who does not tolerate progression.[75]

Reconsidering therapeutic goals in advanced HF

Keeping in mind the scarcity of quality data related to the real benefit of classically recommended therapies for HF with reduced EF in the subgroup of patients with advanced disease, much of daily practice ends up being based on the personal experience of professionals who routinely treat these patients.

As a rule, the treatments instituted aim to reduce disease progression and increase survival, but, when treating patients in more advanced stages, improvement of symptoms and quality of life should become one of the goals to be pursued, given that the vast majority will end up not being eligible or will not have access to advanced therapies, such as heart transplantation or circulatory assist devices.

In most cases, the hemodynamic alteration that generates limiting symptoms is the increase in resting filling pressures, caused by hypervolemia. When there is systemic congestion, gastrointestinal symptoms, such as loss of appetite, abdominal discomfort, and early satiety may predominate. A good part of referred patients with refractory symptoms can improve with adequate volume adjustment, which can be difficult to assess, especially in chronic patients.[76] In some cases, in addition to dose optimization and eventual association of diuretics, the use of nitrates can be both beneficial and symptomatic.[77]

Refractory congestion, with resistance to diuretics, is a scenario commonly found in patients with advanced disease, and it requires a targeted and specific approach for this purpose, which is not within the scope of this review.

Finally, it is important to discuss expectations regarding treatment with patients who have advanced HF. In some cases, symptom control becomes a priority, to the detriment of prolonging survival, and pharmacological treatment should be guided by prioritizing this objective.

Conclusion

Patients with advanced HF present several particularities in pharmacological management and optimization, with increasing complexity. This group of patients is expected to grow progressively, with increased survival promoted by the therapies that are currently available. Therefore, it is essential for there to be more studies focused on this profile of patients, as well as greater representation in clinical trials. Given that it is a marker of worse prognosis, difficulty in pharmacological management should be considered a reason for referral to specialized centers.

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