

Sequencing of Pharmacotherapy for Heart Failure with Reduced Ejection Fraction: A Clinical Profile-Based Approach

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A Brief History of Heart Failure (HF) Treatment

Until 1987, HF treatment consisted in:

- Recommendation of a low-sodium diet;
- Diuretics for manifestations of congestion;
- Digoxin;
- Rest.

None of these recommendations was based on clinical or epidemiological evidence, instead relying on the pathophysiological knowledge of the disease at the time, the pharmacological effect of medications, and good sense.

In 1987, a new era of HF treatment began with the publication of the first large randomized clinical trial that tested a drug that could inhibit a hormonal axis involved in causing, maintaining, and increasing risk for this disease. This axis was the renin-angiotensin-aldosterone system (RAAS), and this drug was enalapril.¹ At that moment, the addition of a drug to the clinical treatment of patients with HF could reduce relative risk of death by 50%.

Subsequently, the history of HF treatment would change consistently. If inhibiting the RAAS generated such a significant and relevant response, the inhibition of the adrenergic system (knowingly activated in patients with HF) would be the next hypothesis to be tested. At that time, medical textbooks contraindicated the use of adrenergic blockers in patients with HF, since the rationale was that these would worsen ventricular performance and patients' clinical picture. Scandinavian researchers pursued the hypothesis that an adrenergic blockade would be beneficial, and we all know the outcome of this chapter of HF treatment history. Multicenter randomized clinical trials ensued, testing β -blockers in patients with HF and discovering the second drug class capable of changing the natural history of this disease.²⁻⁴

In the last decades, there was significant progress in the pathophysiological understanding of HF and in the awareness

of the utility of the inhibition of counterregulatory hormones with damaging effects in the disease. Additional inhibition of the RAAS was the new hypothesis after the confirmation of β -blockers.⁵ Low-dose spironolactone, more through its hormonal effect than its diuretic effect, was the next drug to be proven beneficial to the prognosis of HF.⁶

After the publication of RALES⁶ and the quick implementation of this knowledge on clinical practice, we went through a period of almost 20 years of apparent stagnation in the pharmacological treatment of HF. The most relevant innovations in this period either did not present an isolated effect on mortality⁷ or provided benefits to specific subgroups only.⁸

For 2 decades, the basic treatment of patients with HF consisted in an angiotensin-converting enzyme inhibitor (ACEI) or an angiotensin receptor blocker (ARB), a β -blocker, and spironolactone.

A new era in HF treatment

A new, modern era in HF treatment begins with the arrival of new drugs with prognostic effects in the prognostic of patients with HF.

– Angiotensin receptor-neprilysin inhibitors (ARNI).

Unequivocal evidence has been established by at least 2 large-scale studies with enalapril, which showed that interfering with the renin-angiotensin system reduces mortality in patients with HF and reduced ejection fraction.^{1,9} This approach was reinforced by studies with ACEI and ARB in patients with HF and/or left ventricular systolic dysfunction after acute myocardial infarction.^{10,11}

Subsequently, the new hypothesis considered for HF treatment was inhibiting the degradation of natriuretic peptides (BNP) and other vasoactive peptides with potentially “compensatory” effects through neprilysin inhibition and observing the clinical effect. By inhibiting BNP degradation, the increase in circulating BNP results in more vasodilation and natriuresis mediated by endogenous BNP. The PARADIGM-HF study tested a neprilysin inhibitor called sacubitril in association with valsartan, a known ARB, in direct comparison with enalapril in the treatment of patients with HF. This large multicenter, randomized clinical trial with over 7000 patients established the superiority of sacubitril/valsartan over enalapril, thus cementing the importance of the simultaneous inhibition of neprilysin and the RAAS.¹² When compared to enalapril, the relative risk reduction with sacubitril/valsartan was 20% for cardiovascular mortality and 20% for hospitalizations

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due to HF; both effects were demonstrated at statistically significant evidence levels ($p < 0.00001$). When performing a putative comparison with placebo, the estimated benefits of sacubitril/valsartan were a 30–35% reduction in cardiovascular death and a 45–50% reduction in hospitalizations for HF.¹³

– Sodium–glucose co-transporter 2 inhibitors (SGLT2i).

This innovative drug class, initially tested as antidiabetic drugs,¹⁴ became a recent innovation in the pharmacological treatment of HF.

Two studies (DAPA-HF and EMPEROR-Reduced) demonstrated a 30% reduction in the risk of hospitalization for HF when patients were treated with dapagliflozin or empagliflozin when compared to placebo.^{15,16} The benefit of these drugs was observed both in patients with diabetes and HF and those without diabetes but with a similar degree of HF.

Moreover, SGLT2i were demonstrated to reduce the risk of cardiovascular death or total mortality in clinical trials with patients with chronic HF, type 2 diabetes, and chronic kidney disease.^{15–17}

After the publication of these pivotal studies, the benefits of SGLT2i to survival were supported by a meta-analysis of studies with patients with HF and reduced ejection fraction, as well as a meta-analysis of studies with patients with diabetes.^{18,19}

With this evidence, SGLT2i became the fourth pillar of the clinical treatment of HF, together with ACEI/ARNI, β -blockers, and spironolactone.

Sequencing of HF Treatment

With the emergence of 5 drug classes, distributed on 4 main pillars, with consistent effects on the increase in patient survival, the concept of sequencing was created. Based on expert opinions and comparative analyses of clinical trials, here we discuss “how to make” an increasingly more complex prescription.

Option 1: historical sequencing

Historical sequencing aims to reproduce, in the patient’s prescription, the historical order in which medications were studied. It thus begins with an ACEI, followed by β -blockers and spironolactone. Subsequently, the ACEI would be swapped by an ARNI, and an SGLT2i would be added to the prescription.

In this option,

- ✓ each drug dose is increased to its maximum before moving on to the next drug class;
- ✓ many visits are required;
- ✓ reaching optimal treatment may take 6 or more months;
- ✓ the benefit is delayed.

An argument against this sequencing method is that foundational drugs already reduce mortality in small initial doses, in an independent manner, and a significant beneficial effect is observed in less than 30 days. Therefore, delaying the start of a new therapeutic class would not be justified.²⁰ Figure 1.

Option 2: Packer and McMurray sequencing

The sequencing strategy recently proposed by Milton Packer and John McMurray²⁰ proposes that HF treatment be initiated with a β -blocker and an SGLT2i. Subsequently, an ARNI or spironolactone would be added to the prescription. In case of hypotension, the ARNI would be postponed; in case of hyperkalemia, spironolactone should be postponed. Figure 2.

The reasons given by the authors are based in part on pathophysiological reasoning, where the adrenergic system is the first to be activated in the neurohormonal cascade of HF and thus should be the first to be inhibited; and in part on clinical and epidemiological reasoning based on clear evidence of prevention of sudden death by β -blockers. The authors recognize the need to achieve clinical euolemia for the safe start of β -blockers and argue that the concomitant start of SGLT2i, a drug class that affects the SGLT2 in the proximal tubule of the nephron (thus having a diuretic effect), would compensate for the risk of worsening congestion attributable to β -blockers.

The arguments of caution regarding the Packer e McMurray sequencing method are basically the following:

- ✓ many patients, especially treatment-naïve ones, are initially congested, thus not being candidates for the use of β -blockers as initial drugs;
- ✓ Most of them will require diuretics to reach the desired euolemia, since the diuretic effect of SGLT2i is, at best, discrete;
- ✓ In this time window while we cannot start a β -blocker, why not initiate treatment with a vasodilator (ARNI or ACEI) to offer this immediate benefit to patients? The Packer and McMurray sequencing method does not contemplate this frequent clinical scenario;
- ✓ From a clinical and epidemiological standpoint, the hypothesis of using a β -blocker as the initial approach in the pharmacological treatment of HF was specifically tested by CIBIS III. This clinical trial compared an approach that started therapy with enalapril (ACEI) to one that started therapy with bisoprolol (β -blocker). In this trial, although the result was neutral, therapy starting with a β -blocker presented an increase (RR = 1.25) in hospitalizations for HF (not statistically significant).

Therefore, starting with a β -blocker was not a superior strategy and showed a trend of increase in hospitalizations.

Considering these favorable and unfavorable aspects of a fixed suggestion of drug sequencing when initiating clinical treatment of HF, it is important to note that the authors themselves postulated that “safety and tolerance improve with appropriate class sequencing”.²⁰ With this aim, we seek to describe what would be an appropriate sequencing of drug classes, which would certainly adapt its priorities to the patient’s clinical profile.

Option 3: sequencing based on clinical profiles

The start and sequencing of foundational drugs for the appropriate treatment of patients with HF should follow some basic premises that are highly grounded in epidemiological and clinical evidence. These are:

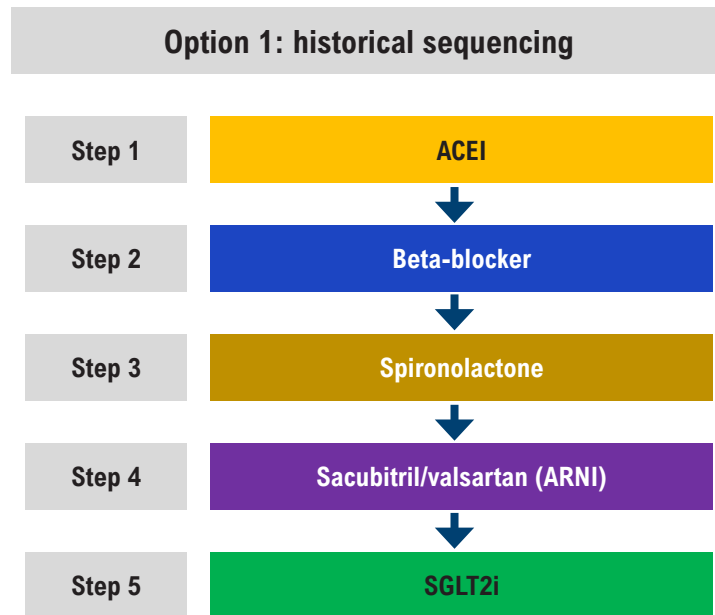


Figure 1 – Historical sequencing of HF treatment. ACEI: angiotensin-converting enzyme inhibitor; SGLT2i: sodium-glucose co-transporter 2 inhibitor.

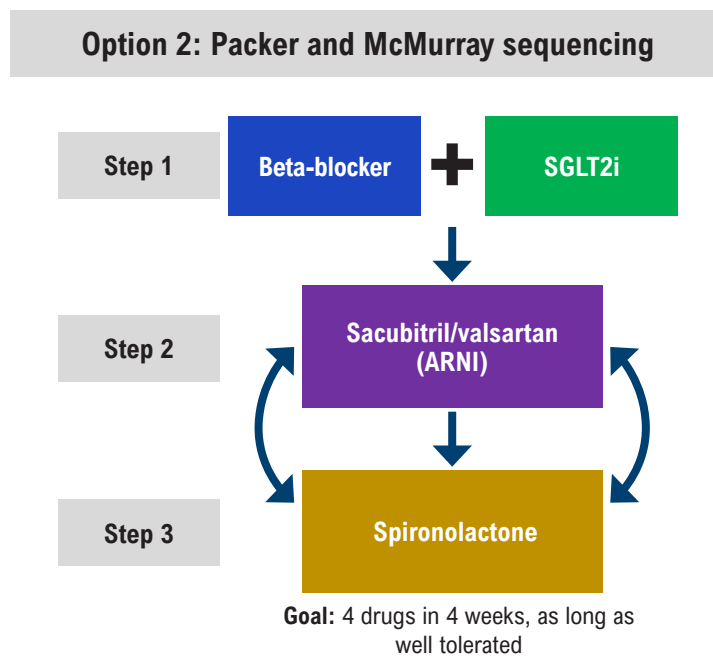


Figure 2 – Sequencing of HF treatment according to Packer and McMurray. *Adapted from M. Packer and J.J.V. McMurray. *European Journal of Heart Failure* (2021).²⁰ ARNI: Angiotensin receptor-neprilysin inhibitors.

1. Five drug classes must occupy the 4 foundational pillars of HF treatment: a. ACEI or ARNI; b. β -blocker; c. spironolactone; d. SGLT2i;

2. The magnitude of the benefit provided by each drug class does not depend on treatment with other classes. A modern example of this evidence is the fact that, among patients in the DAPA-HF¹⁵ and EMPEROR Reduced studies,¹⁶ the subgroups who used ARNI or not had similar benefits (for a composite outcome of cardiovascular death or hospitalization for HF: RR = 0.68 [95%CI 0.53–0.89] with ARNI and RR = 0.75 [95%CI 0.68–0.84] without ARNI);

3. The foundational drugs reduce morbidity and mortality already in their low initial doses.²¹ Benefits are relevant and noticeable within the first 30 days. An example is the great separation of survival curves in the COPERNICUS study, noticeable at 4 weeks, with a mean dose of 6.5 mg twice a day;²²

4. The addition of a new drug class provides greater benefit than an increase in dose of an already employed drug.²⁰

Considering these fundamental premises, we believe that the same result cannot be obtained by using the same drug sequence in all patients. Therefore, Figure 3 expresses the choices made by this author for prioritizing drugs based on patients' clinical profiles.

Take-home messages

✓ The pharmacological treatment of HF is based on 4 pillars according to the prognostic effect of drugs considered foundational.

✓ Efforts must be made to prioritize the benefit of all drugs with the concept that “a little of each drug is better than a lot of fewer drugs.”

✓ It is recommended that all 4 classes of foundational drugs be initiated in the short-term (4–6 weeks).

✓ We advise that the start and sequencing of HF treatment be done by respecting the clinical profile of each patient in order to increase tolerance, safety, and therapeutic success.

Author Contributions

Conception and design of the research, Writing of the manuscript and Critical revision of the manuscript for intellectual content: Beck-da-Silva L.

Potential Conflict of Interest

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Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

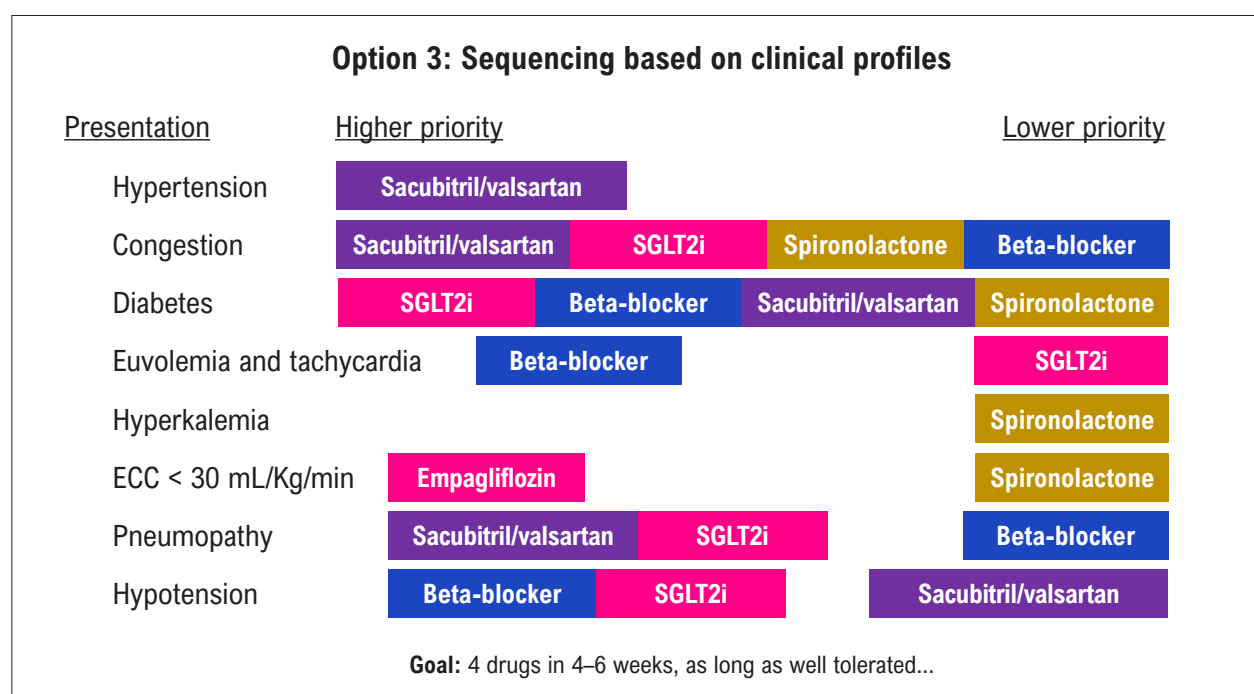


Figure 3 – Sequencing of HF treatment based on clinical profiles. SGLT2i: sodium–glucose co-transporter 2 inhibitors; ECC: endogenous creatinine clearance.

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