Advances in the pharmaco-therapy for Heart Failure

Dr. Sharad Agrawal
MBBS, MD (Medicine),
DM (Cardiology),
FICC, FESC;
FRCP (London),
FACC (USA)
Consultant Cardiologist
and Visiting Professor,
Sunderland Royal Hospital,

1.1 Introduction:

Heart Failure (HF) is not a single disease entity but it is a complex clinical syndrome characterised by myocardial dysfunction and progressive maladaptive neurohormonal activation leading to circulatory insufficiency and systemic congestion. It can happen due to a structural and/or functional abnormality of the heart that results in elevated intracardiac pressures and/or inadequate cardiac output at rest or during exercise.

HF is associated with high rates of morbidity and mortality. In the Framingham Heart Study, patients with HF had 4-8 times higher mortality as compared to age-matched controls. A patient with an advanced heart failure can have 1-year survival between 30-50% i.e., a mortality rate comparable or even worse than advanced malignancies.

Over the last few years, several landmark trials have shown improved outcomes in patients with HF by addition of new classes of medications on top of standard therapy. International and national guidelines are therefore needing to do a quick catching up in order to keep pace with the rate of emerging evidence. As it takes some time to develop a consensus view, there is a degree of uncertainty among healthcare professionals using the available evidence at the individual patient level.

The UK clinical practice is largely driven by the Guidelines issued by the National Institute for Health and Care Excellence (NICE). Latest NICE guideline on Heart Failure (NG106) was published in September 2018 [1]. Further advancements in the management of HF since then, have now been incorporated in European Society of Cardiology (ESC) Guidelines published in September 2021. [2]

Purpose of this article is to highlight the

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latest advances in the pharmacotherapy for HF i.e., initiation of new classes of medications as well as the order of their introduction during the HF care pathway.

2.1 Universal Definition and Classification of Heart Failure:

The diagnosis of heart failure includes a range of pathological diagnoses with marked variation in the clinical presentation. Traditionally, HF is divided into distinct phenotypes based on the echocardiographic measurement of left ventricular ejection fraction (LVEF).

The 2016 ESC guidelines on HF, proposed a new terminology describing patients with HF with reduced Ejection Fraction i.e., LVEF < 40% as HFrEF. Similarly, those with LVEF in the mid-range i.e., 41-49% as HFmrEF and those with normal or preserved EF (i.e., LVEF > 50%) as HFpEF [3].

The above classification has recently been updated by a Consensus Statement on Universal Definition and Classification of Heart Failure in February 2021 (table 1) [4]. While in 2016, HFmrEF was termed as HF with 'mid-range' EF, but it is now called as 'mildly reduced'. A new 4th category of HFimpEF has been added in the Universal definition (Table-1).

2.1 Epidemiology, natural history and prognosis of heart failure:

Currently, the incidence of HF in Europe is about 5/1000 person-years in adults and the prevalence of HF is 1-2% of adults [2]. The prevalence increases with age: from around 1% for those aged <55 years to around 10% in those aged >70 years.

Category	Acronym	Ejection Fraction	Remarks
HF with reduced EF	HFrEF	HF with LVEF ≤40%	
HF with mildly reduced EF	HFmrEF	HF with LVEF 41-49%	
HF with preserved EF	HFpEF	HF with LVEF ≥50%	
HF with improved EF	HFimpEF	HF with a baseline LVEF of ≤40% and a ≥10-point increase from baseline LVEF	2nd measurement of LVEF of >40%

Table-1: Universal Definition and Classification of Heart Failure (4)

Among the hospitalised patients with HF, about 50% have HFrEF and remaining 50% have HFpEF or HFmrEF [2]. However, in the outpatient setting, the ESC Long-Term Registry has shown 60% patients have HFrEF, 24% have HFmrEF, and 16% have HFpEF [5].

Despite significant advances in the pharmaco-therapy, the prognosis for the patients with advanced HF still remains poor along with markedly reduced quality of life (QOL). Mortality rates are higher in observational studies than in clinical trials. In the Olmsted County cohort, 1-year and 5-year mortality rates after diagnosis, for all types of HF patients, were 20% and 53%, respectively [6].

Degree of LV impairment seems to govern the prognosis. HFpEF is generally considered to confer a better survival than HFrEF. A large MAGGIC meta-analysis concluded that the adjusted mortality risk for patients with HFpEF was considerably lower than in patients with HFrEF [7]. The extent of improvement in prognosis has been largely confined to those with HF with reduced LVEF. Overall prognosis is better in HFmrEF compared to HFrEF [5]. Transition in ejection fraction over time with treatment of HF is common, and patients who progress from HFmrEF to HFrEF have a worse prognosis than those who remain stable or show improvement in ejection fraction category [7].

The risk of HF hospitalisation is 1.5 times higher in patients with diabetes compared to controls. In addition, atrial fibrillation, a higher body mass index (BMI), and a low estimated glomerular filtration rate (eGFR) are strong predictors of HF hospitalizations [8]. Due to population growth, ageing, and the increasing prevalence of comorbidities, the absolute number of hospital admissions for HF is expected to increase considerably in the future [2,8].

3.1 Pharmaco-therapy for patients with HF

(A) NICE guideline on Chronic Heart Failure in adults (NG-106) [1] recommended a step-by-step approach to start different classes of medications in patients with HFrEF as follows:

1. Offer as first line an Angiotensin Converting Enzyme (ACE) Inhibitor at a low dose and up-titrate every 2 weeks to maximally tolerated dose. An Angiotensin Receptor blocker (ARB) can be used as an alternative if intolerable side effects with ACE inhibitor.
2. Introduce a beta-blocker (like Bisoprolol, Metoprolol or Carvedilol) also as a first line therapy unless contra-indicated in a 'start low, go slow' manner
3. Offer mineralocorticoid receptor antagonist (MRA), like spironolactone or eplerenone, in addition to an ACE inhibitor (or ARB) and beta-blocker, and up-titrate the dose
4. Ivabradine is recommended in patients with HF in sinus rhythm with a heart rate of 75 beats per minute (bpm) or more, in combination with standard therapy including beta-blocker therapy. Ivabradine should only be initiated after a stabilisation period of 4 weeks on optimised standard therapy with ACE inhibitors, beta-blockers and aldosterone antagonists.
5. Sacubitril – Valsartan combination or Angiotensin receptor neprilysin inhibitor (ARNI) is recommended as an option for treating symptomatic patients with LVEF < 35%, who are already taking a stable dose of angiotensin-converting enzyme (ACE) inhibitors or ARBs.
6. Diuretics should be routinely used for the relief of fluid retention in people with heart failure, and titrated (up and down) according to need following the initiation of heart failure therapies.

(B) ESC2021 guidelines on Heart Failure[2] now also recommended:

7. Dapagliflozin or empagliflozin for patients with HFrEF to reduce the risk of HF hospitalization and death. They are

a new class of HF medication called sodium-glucose co-transporter 2 (SGLT-2) inhibitors.

3.2 Four pillars of contemporary pharmaco-therapy for HFrEF [9]:

All the major international HF guidelines like ACC/AHA 2017 [10]; NICE 2018 [1] and ESC 2021 [2] have a consensus view on first line therapy for patients with HF, with an objective to inhibit two fundamental neuro-hormonal pathways i.e., the renin-angiotensin system (by ACEi / ARB / ARNI) and the sympathetic nervous systems (by Beta-blockers).

Additional therapies (like MRA and SGLT-2 inhibitors) are also recommended for patients who 'remain symptomatic' with persistently impaired left ventricular (LV) function despite maximally tolerated doses of ACEi and beta-blockers.

The above four classes of drugs i.e., 1. ACEi / ARB / ARNI; 2 Beta-blocker / Ivabradine; 3 MRA and 4 SGLT2 inhibitors; are complementary to each other and they are now established as 4 pillars of heart failure medications. Guidelines may differ subtly regarding the timing of initiations of 3rd and 4th pillars.

The recommendation of using the above 4 pillars in a step-by-step fashion by the major guidelines is based on trial evidence and it possibly also helps to avoid 'unnecessary' treatments in patients who respond to first line therapy. However, this approach inevitably results in delays in initiating additional life-saving therapies (such as MRA and SGLT2 inhibitors) as well as contributes to further follow-up and imaging costs [9, 11]. In clinical practice it typically takes many months before these patients reach optimal doses of these medications, and many never do, even where integrated hospital and community care is available [11].

A new concept of initiating all 4 drug classes (i.e., the 4 pillars of HF medications) as a comprehensive disease modification strategy soon after confirmation of the diagnosis of HF is now emerging [9]. A typical patient aged 65 years can expect to live an additional 5 years if receiving a comprehensive strategy with the Four Pillars, compared with conventional therapy [12].

Conclusion:

Pharmaco-therapy for HF has significantly expanded over last few years helping to improve patient-outcomes. Most international guidelines (such as NICE, ACC/AHA and ESC) have recommended a step-by-step approach in terms of starting medications which are proven to be effective. A new concept is emerging where all 4 classes of HF medications are started in parallel (like the Four Pillars of Heart Failure) very early in the patient journey with subsequent optimisation of dosages where required. More evidence about the safety and cost-effectiveness will be required before adopting this approach.

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