Drug Revolution in Heart Failure: A Big Step Toward Improving Outcome

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Heart failure (HF) is a deadly disease; more people die from it than from acute myocardial infarction (MI). Unlike acute MI, where there is a quick fix in the form of primary angioplasty, no such quick fix exists for the treatment of HF. The human myocyte is not endowed with an endogenous capacity for repair; once dead, it is dead forever. Therefore, HF has a high morbidity and mortality rate; the 5-year mortality rate is to the tune of 50%, a figure higher than most malignant lesions. But with current pharmacotherapy, the mortality rate is likely to decline in the future. HF is akin to malignancy. Once it sets in, it runs a malignant progression and has a high mortality rate, polypharmacy is the rule, and remission and relapses are common. Remission in HF or significant improvement in symptoms should not be taken as freedom from disease because stable HF is a myth. These patients can succumb to sudden cardiac death (SCD) or get admitted with HF without any warning signs because there is always ongoing apoptosis, as evidenced by mild, persistent elevations of serum markers like troponin in the blood. In the context of diabetes, HF is frequent, forgotten, and fatal, and HFrEF is the dominant scenario.

But the last couple of years have witnessed a sea change in the management of HF and currently, we have a panoply of drugs to target multiple pathways of HF (Fig. 1).

The four foundational drugs for HF, that is, β-blockers, sodium-glucose cotransporter-2 (SGLT2), sacubitril/valsartan (angiotensin receptor neprilysin inhibitor), and mineralocorticoid receptor antagonists (MRAs), have kicked off a drug revolution in HF that never existed before. All four of these drugs have a class I recommendation, are guideline-directed therapies that produce incremental benefits on top of each other and are poised to improve the outcome of HF with reduced ejection fraction (HFrEF). It is estimated that the projected mean overall survival would increase by 6.3 years if all four foundational drugs were started in patients with HFrEF at the age of 55. Suboptimal guideline-directed medical therapy (GDMT) in India for HF patients is a very important cause of increased all-cause mortality. All four drugs should be initiated early because the 30-day mortality rate for acute decompensated HF is 10% and one out of every four patients hospitalized for HF dies or is rehospitalized within 30 days of discharge. Hospitalization for HF is a serious event in the natural history of the disease because every hospitalization and rehospitalization brings the patient closer to death. Of the four foundational drugs for HFrEF, SGLT2 has the most impressive effect on hospitalization for HF, both in patients with Atherosclerotic cardiovascular disease and in patients with multiple risk factors. In patients with worsening HF, vericiguat is used to decrease hospitalization for HF.

Just as in acute MI to initiate early therapy, we had the dicta of door-to-balloon time, a new variant of the 90-minutes door-to-balloon time. Similarly, we had the dicta of door-to-GDMT, a 3-week door-to-GDMT time. Hence, the new message is to optimize the use of sacubitril/valsartan before discharge and to achieve the target dose of 125 mg BID before discharge and door-to-maximum dose GDMT time. So the current trend is to initiate in-hospital quadruple medical therapy on days 1–4 and try to achieve the target dose preferably before discharge but not later than 1–4 weeks.

So powerful is the reverse remodeling effect of the four foundational drugs that the committee members of the third universal definition of HF were forced to create a new subset of improved HFpEF that had never existed before. Prior to 2021, HF with preserved EF (HFrEF) was considered an orphan disease, and all trials failed to show a positive outcome. But now we have two positive trials with SGLT2i in HFrEF, that is, the empagliflozin outcome trial in patients with chronic HFrEF/Empagliflozin Outcome Trial in Chronic Heart Failure With Preserved Ejection Fraction 2021 and the dapagliflozin evaluation to improve the lives of patients with preserved EFHF (DELIVER) trial 2022, which have shown positive cardiovascular (CV) outcomes in patients with HFrEF. So HFrEF no longer exists as an orphan disease. After the above two trials, SGLT2i can be used in all patients with HF, irrespective of EF, and this is a big feather in the cap of SGLT2 (Fig. 2).

Moreover, sacubitril/valsartan has shown excellent reverse remodeling in the prospective study of biomarkers, symptom improvement, and ventricular remodeling during sacubitril/valsartan therapy for HF (PROVE-HF) trial. It also showed that patients eligible for implantable cardioverter-defibrillator (ICD) with an EF < 35% can be transformed into ICD-ineligible patients by increasing their EF > 35%. In an analysis of 613 patients who had left ventricular (LV) EF < 35% and were eligible for ICD, after 6 months, in 32% of patients, the EF increased >35%, and after 1 year, in 61% of patients, the EF was >35%. Therefore, the new message is to optimize the use of sacubitril/valsartan before discharge.

**Fig. 1:** Multiple pathways for the treatment of HF

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Drug Revolution in Heart Failure

selecting the patient for ICD implantation for the primary prevention of sudden cardiac death. Some people call sacubitril/valsartan a medical ICD.

What is very exciting is that the use of four foundational drugs is poised to postpone device therapy, that is, ICD, cardiac resynchronization therapy, LV assist device, and even cardiac transplantation. No cardiologist would recommend the implantation of these devices unless all four foundational drugs, in addition to the conventional therapy, have been maximally utilized.

Sudden Cardiac Death

Sudden cardiac death (SCD) is more common in mild HF compared to severe HF. In patients with HF, SCD occurs in 64, 59, and 33% of patients with New York Heart Association (NYHA) classes II, III, and IV, respectively. The adverse LV remodeling fibrosis creates a fragile and highly venerable subset. Occasionally, there may be an identifiable pathological trigger like ischemia, electrolyte imbalance, catecholamine surges, etc., but usually, there is no acute precipitating mechanism. The drugs for treating HF, like β-blockers, MRAs, and sacubitril/valsartan, have decreased the incidence of SCD.

In an analysis of over 40,000 patients from 12 pivotal HF trials, rates of SCD decreased by 44% over the 20-year period (from mid-1990–2015). This is almost certainly due to advances in HF treatment, as many key guideline-recommended therapies have been developed, including β-blockers, MRAs, and sacubitril/valsartan.

In a meta-analysis of 30 trials that randomized 24,779 patients with HF, β-blockers reduced the risk of SCD by 31%, CV death by 29%, and all-cause mortality by 33%. Sacubitril/valsartan showed a reduction in SCD by 20% in patients with chronic HF and a 50% decrease in the risk of death in patients with baseline ICD.

In a meta-analysis of 11,032 patients recruited in three placebo-controlled randomized trials, MRAs reduced the risk of SCD in 23% of patients with HF and LV systolic dysfunction. Sodium-glucose cotransporter-2 inhibitors (SGLT2i) have no good data on their effect on SCD, although a subgroup analysis from the Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure trial has shown a reduction in ventricular arrhythmias.

The guidelines for primary prevention of SCD in HF recommend an ICD to reduce the risk of sudden death and all-cause mortality in patients with symptomatic HF (NYHA class II–III) of an ischemic etiology (unless they have had a MI in the prior 40 days) and an LVEF < 35% despite >3 months of optimal medical therapy, provided their expected survival is >1 year with good functional status (class I). The recommendation of an ICD for the primary prevention of SCD in nonischemic HF is less strong (class IIa).

New Drugs for Heart Failure

Besides the four foundational drugs and the other drugs, we have two other new drugs that act on entirely new pathways in HF that have never been targeted. Vericiguat directly stimulates intracellular soluble guanylate cyclase, which stimulates the production of cyclic guanosine monophosphate, which has a protective action on the cardiac myocytes and vasculature. It was tested in the vericiguat global study in subjects with HFREF (VICTORIA) trial in patients with worsening HF and has shown positive results. The primary composite endpoint of CV death and first HF hospitalization showed a statistically significant reduction of 10%, driven by a decrease in HF hospitalization. The CV death was not affected. The absolute primary event reduction was 4.2/100 patient-years on top of guideline-based care, and the number needed to treat for 1 year is only 24. The drug is administered once daily, does not require monitoring of estimated glomerular filtration rate or potassium levels, and hardly has any side effects. The initial dose is 2.5 mg, and it can be titrated to a maximum dose of 10 mg. The drug is approved for clinical use in India and is commercially available.

Omecamtiv mecarbil, which is a myosin activator, has also shown positive results in the Global Approach to Lowering Adverse Cardiac Outcomes Through Improving Contractility in HF trial. There was a statistically significant reduction in the primary endpoints of HF events and CV deaths by 8%, driven mainly by the decrease in HF events. The CV death was not affected. The benefit was generally consistent across most prespecified subgroup analyses; however, there was heterogeneity seen for baseline EF; with a greater treatment effect with LVEF < 28%. The drug is not yet approved by the guidelines and is not available for clinical use.

Therefore, we are currently equipped with a panoply of wonderful new drugs that are poised to improve the outcome of HF in the years to come.

References