Positive recommendation for angiotensin receptor/neprilysin inhibitor: First medication approval for heart failure without "reduced ejection fraction"

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Positive recommendation for angiotensin receptor/neprilysin inhibitor: First medication approval for heart failure without "reduced ejection fraction"

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Heart failure (HF) is a problem of epidemic proportions in Western societies and a major public health burden/source of morbidity and mortality. Traditionally, HF has been categorized according to left ventricular systolic function. Patients with heart failure and left ventricular ejection fraction (LVEF) < 40% have been referred to as having failure with reduced ejection fraction (HFrEF), and those with higher LVEF classified as having heart failure with preserved ejection fraction (HFpEF). Although these two HF types are quite similar in terms of clinical presentation, rate of hospitalization, quality of life, and symptom/caregiver burden, fundamental differences remain (1). Unlike HFrEF, where 6 approved medication classes exist for treatment to reduce CV mortality, there are no approved therapies for the nearly 300,000 patients with HFpEF. In addition, HFpEF is increasingly common and is responsible for approximately 50% of prevalent HF, along with its 75 000 annual hospitalizations in Canada. This has resulted in a large unmet clinical need for patients affected by HFpEF.

Recent developments may be the harbinger of a potential new option for these patients. On December 15, 2020, the U.S. Food and Drug Administration (FDA) Cardiovascular and Renal Drugs Advisory Committee voted 12-1 to recommend the angiotensin-receptor/neprilysin inhibitor (ARNi), sacubitril/valsartan, for the indication for treatment of HFpEF. While the FDA is not obligated, and indeed sometimes declines, to follow Advisory Committee recommendations, this decision was nevertheless an important milestone that came about due to an unmet clinical demand, new data regarding interaction of LVEF with HF therapies and a change in regulatory environment.

Previously, HFpEF was thought a homogeneous syndrome to HFrEF, only with a higher LVEF. However, profound benefits for patients observed in those with HFrEF were noted for several therapies which were not replicated for patients with HFpEF. We have also learned that HFpEF is a very heterogenous syndrome characterized by increased markers of inflammation, fibrosis, and increased comorbidity while HFrEF is more strongly associated with ischemic cardiac damage, neurohormonal activation, loss of myocyte function and chamber dilation (1). In addition, some degree of systolic dysfunction is present when LVEF lies between 40% and the lower limit of normal (LVEF < 52% for males and < 54% for females). The interaction between the benefits of certain cardiovascular therapies and LVEF appears to extend above 40%.

Consequently, a third category of HF has been proposed by the Canadian Cardiovascular Society and others. This 'mid range', or 'mildly reduced' heart failure (HFmrEF) is applied to those with LVEF between 40%- 50%, leaving HFpEF redefined to include LVEF ≥50%. This group comprises as many as 150,000 Canadians with HF or 25% of the total (1).

The primary focus of the FDA advisory meeting was the data from the Prospective Comparison of ARNI with ARB Global Outcomes in HF with Preserved Ejection Trial, (PARAGON-HF), which randomized 4822 patients with HF, LVEF≥45% and elevated natriuretic peptides to either sacubitril/valsartan (S/V) titrated to a maximum dose of 97/103 mg. bid or valsartan 160 mg bid (2). The primary endpoint was a composite of total HF hospitalization and cardiovascular death in this event driven trial. Both groups were evenly matched at baseline. Following a median 35 month follow up, there were 894 primary endpoints in the S/V group and 1009 event in the valsartan arm (HF 0.87, 95% CI 0.75- 1.01, p 0.059). There was no difference in CV or total mortality, a small improvement in quality-of-life scores and NYHA class. In terms of safety, with S/V there was a 6% increase in symptomatic hypotension, no change in serious adverse events or drug discontinuation and a reduction in renal events (HR 0.50, 05% CI 0.33- 0.77, p= 0.001). An expanded primary endpoint adding urgent HF visits (not requiring hospitalization) which showed a nominally significant 15% reduction (p= 0.04), and a similar finding when an FDA-suggested re-adjudication based on 'probable' HF events was performed. These findings occurred in the context of an active (valsartan) rather than placebo control, leading to speculation that the true benefit of S/V was underestimated.

However, another story emerged. This began with a pre-specified sub-analysis according to baseline LVEF, which showed a statistically significant 22% reduction in the likelihood of experiencing the primary endpoint in the group at or below the median 57% LVEF (95% CI 0.64-0.95, p< 0.05), while no benefit was seen in those with baseline LVEF above the median. Women also appeared to derive greater benefit than men, interesting given the known sex-dependent differences in HF prognosis with HFpEF.

To further explore the effects of S/V in HF according to a large range of baseline LVEF, data from both large S/V trials, Angiotensin-Converting– Enzyme Inhibitor to Determine Impact on Global Mortality and Morbidity in Heart Failure Trial (PARADIGM HF trial, including patients with LVEF < 40%) and PARAGON HF were combined (3). Not surprisingly, reduction of HF hospitalization with S/V extended across baseline LVEF measures below 50-55%, while the cardiovascular mortality benefit was confined to those with LVEF < 40%. Data from other trials showed similar associations. In the Candesartan in Heart failure - Assessment of moRtality and Morbidity (CHARM) study, 7000 patients with HF were randomized to candesartan or placebo in three sub-trials encompassing all LVEF values (4). Reanalysis of the primary endpoint by baseline LVEF indicated substantial reduction of HF hospitalization + CV death in those with LVEF under 50-55%, while CV mortality alone was reduced significantly only in those with baseline LVEF< 40%. This finding was also replicated in the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial, which evaluated a mineralocorticoid receptor antagonist, spironolactone (5). Benefits in all these analyses were observed to a slightly higher LVEF (55% vs. 50%) in females versus males (55% vs. 50%), values which are reminiscent of the sex-specific lower limits of normal EF. The FDA advisory panel voted for consideration of S/V as a treatment for this 'middle' group of patients such as outlined in Figure 1, which outlines a potential new algorithm for use of ARNi in HF.

While many cardiovascular therapies are approved based on one or more large, positive clinical trials, Health Canada has previously approved CV therapies based on subgroup analysis of registration trials and both the FDA and Health Canada have indicated openness to approval of therapies which benefit symptoms or hospitalization alone. In recent times of pandemic, Health Canada has also demonstrated a remarkable flexibility and responsiveness to the needs of patients and health care providers alike. A conservative estimate suggests a 20% proportion of HF prevalence (`120,000) suffer from HF with mildly reduced EF. They would be expected to experience approximately 15,000 annual HF hospitalizations (1). If we roughly assume a maximum of 70% of these patients with potential exposure to S/V in place of current therapy, one could estimate that up to 8400 HF hospitalizations might be prevented annually. This

favorable efficacy and safety data coupled with the lack of available options in this patient group combine for a strong case for approval.

Along with all of us, Health Canada will be keeping a close eye on upcoming developments at the FDA. We can hope that with adoption sacubitril/valsartan as a first approved therapy for patients with HFmrEF, help will be on the way.

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