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# DELIVERing Therapeutic Efficacy Across the Ejection Fraction Spectrum of Heart Failure

Carolyn S.P. Lam, MBBS, PhD; Scott D. Solomon, MD

For decades, ejection fraction (EF) has been the principal metric we use to clinically characterize cardiac function, and yet its use to phenotype heart failure (HF) has hindered our understanding of the syndrome and its possible therapies. Results from clinical trials of candesartan, spironolactone, and sacubitril/valsartan in HF have shown attenuation of treatment benefit in the highest range of EF. These observations have led to a fundamental question: is the attenuation of benefit observed with increasing EF because of specific properties of the tested therapies, or is this a more fundamental property of the syndrome itself?

This question is more significant in light of the DELIVER (Dapagliflozin Evaluation to Improve the LIVEs of Patients with Preserved Ejection Fraction Heart Failure) trial in which the SGLT2 (sodium-glucose cotransporter 2) inhibitor dapagliflozin reduced cardiovascular death or worsening HF across the full spectrum of HF, without attenuation at the upper end of EF. In DELIVER, 1891 (30%) patients had EF ≥60%; the hazard ratio for the primary outcome was 0.78 (95% CI, 0.62–0.98) versus 0.83 (95% CI, 0.73–0.95) among patients with EF <60%).[1] Before DELIVER, many, including us, concluded that patients with HF and EF in the highest range might be pathophysiologically distinct from those in lower ranges. Patients with truly normal or supranormal EF and clinical signs/symptoms of HF have always confused us. They tend to have small hearts with limited ability to dilate rapidly during diastole and hence are less capable of augmenting their stroke volume during exercise, resulting in exaggerated increases in filling pressures that produce the classic signs and symptoms of HF.[2] Moreover, there is growing evidence of contamination of this high EF population with distinct diseases such as hypertrophic or amyloid cardiomyopathy, although these carve-out diseases may only represent a small proportion of HF at the high end of EF.

Is it a surprise that patients with such small, concentrically remodeled, hypercontractile hearts do not seem to benefit from therapies that work principally through left ventricular reverse remodeling, including renin–angiotensin–aldosterone inhibitors and sacubitril/valsartan? Admittedly, these therapies have been enormously effective in treating patients with severely hypocontractile and eccentrically remodeled dilated hearts. That their benefit extends to patients with mildly reduced EF, in which hearts are somewhat eccentrically remodeled and contractile function is compromised, albeit less severe, is not a very big leap of faith. In contrast with prior trials of neurohormonal blockade, DELIVER demonstrated no hint of therapeutic heterogeneity in the higher range of EF, where dapagliflozin was as effective as it was at the lower end of the EF spectrum. These results helped to abrogate concern about reduced treatment effect in patients with left ventricular EF >65% in the EMPEROR-Preserved trial, a post hoc finding that contrasted with the lack of significant heterogeneity by prespecified EF subgroups in primary analyses of EMPEROR-Preserved, as well as a lack of significant linear relationship between continuous EF and the effect of empagliflozin on the primary end point in the pooled EMPEROR trials; furthermore, results appeared to vary with different post hoc EF cutpoints, showing benefit in the EF >72.5% subgroup despite lack of benefit in the 62.5–67.5% and 67.5–72.5% subgroups—all suggesting that previous finding may have been because of chance.[3]

So why might SGLT2 inhibitors have been successful in an EF range where other therapies have failed? The

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Correspondence to: Carolyn S.P. Lam, MBBS, PhD, National Heart Centre Singapore, 5 Hospital Drive, Singapore 169609, Email carolyn.lam@duke-nus.edu.sg; or Scott D. Solomon, MD, Cardiovascular Division, Brigham and Women's Hospital, 75 Francis Street, Boston, MA 02115, Email ssolomon@bwh.harvard.edu

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mechanism of action of SGLT2 inhibitors in HF, although incompletely understood, is clearly distinct from that of prior therapies that focused on reverse left ventricular remodeling via blocking the deleterious effects of neurohormonal activation (such as renin–angiotensin–aldosterone inhibitors), or on augmenting endogenous neurohormonal pathways (such as neprilysin inhibitors). Although these neurohormonal agents have also been shown to have favorable kidney effects, their established role in reducing left ventricular size in those with dilated ventricles (ie, reverse remodeling) is likely central to their mechanism of action, resulting in reduced ventricular wall stress and reduction in natriuretic peptides. In contrast, evidence of reverse left ventricular remodeling with SGLT2 inhibitors is sparse and inconsistent despite overwhelming evidence of their clinical outcome benefits. Natriuretic peptide lowering with SGLT2 inhibitors is similarly much less profound than with neurohormonal agents. On the other hand, there is strong evidence of the kidney protective effects of SGLT2 inhibitors.[4] SGLT2 inhibitors may work, at least in part, by fundamentally addressing kidney function and its role in hemodynamic homeostasis, counteracting the congestive state that defines HF regardless of EF or extent of left ventricular remodeling.

What are the implications for other therapies in HF? Treatment approaches that address aspects of the HF syndrome apart from left ventricular remodeling may similarly be expected to be effective across the EF spectrum. For instance, cardiac rehabilitation, by addressing peripheral mechanisms of physical function and frailty, was beneficial in HF regardless of EF.[5]

Do the findings of DELIVER call for a different approach to the treatment of HF? Although many have debated the pros and cons of EF, EF has anchored decades of trial evidence on which therapeutic advances in HF were made, and remains key for determining appropriate medications and devices, predicting the expected therapeutic response, and prognostication among patients with HF. Yet, these new data suggest that we may have become myopic in our focus on EF and may need to take a step back remembering that regardless of EF, all patients have HF, a syndrome in which multiple organ systems (heart, vasculature, kidneys, lungs, skeletal muscles) play a part. Viewed this way (Figure), therapy may begin with those that address the presenting congestive state that defines the HF syndrome, including diuretics and SGLT2 inhibitors, as well as the precipitants of decompensation. A determination of whether left ventricular remodeling and/or dyssynchrony is present—reflected as an EF below normal among other parameters—remains important for decisions regarding neurohormonal agents and device therapies. Cardiac imaging is critical, independent of EF assessment, for the recognition of differential

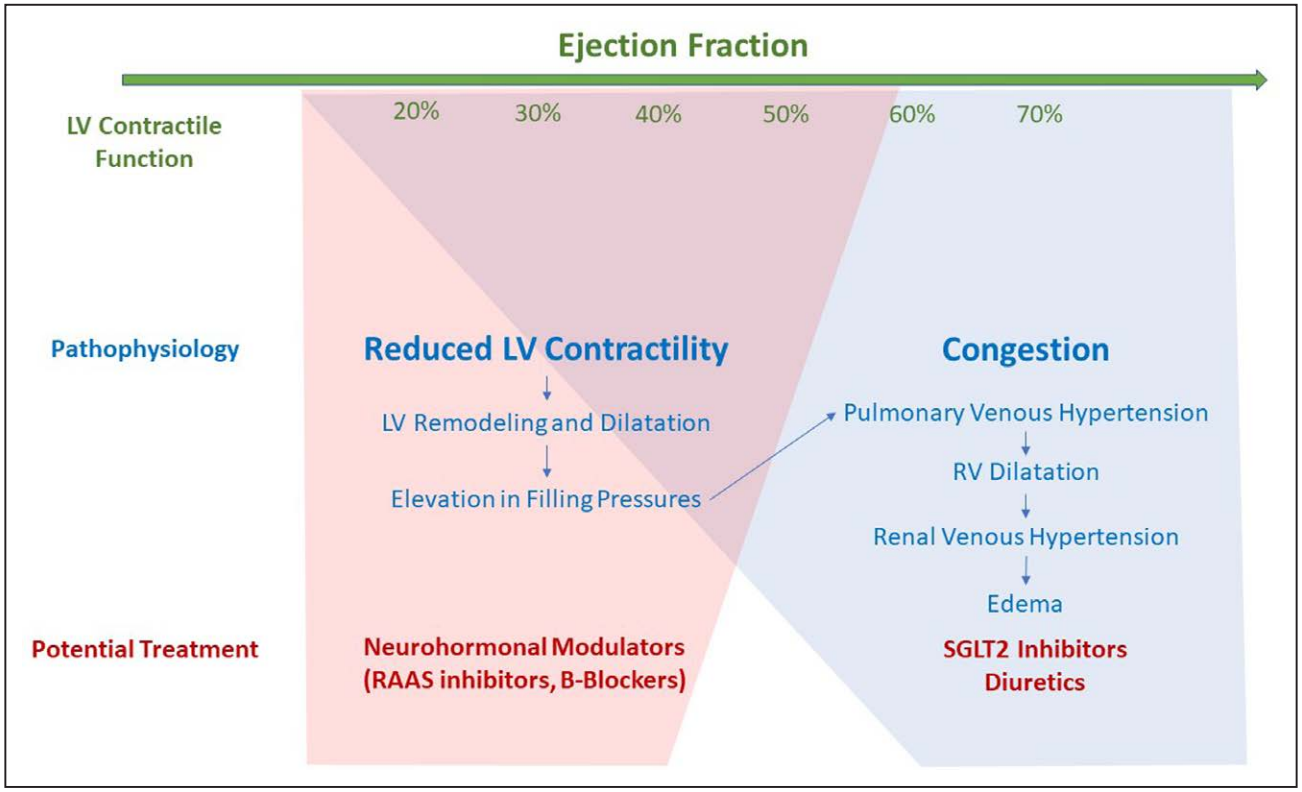


**Figure. Schematic showing a suggested approach to heart failure treatment across the ejection fraction spectrum, where some therapies are used in the presence of reduced LV contractility or eccentric LV remodeling, whereas others are used to address the congestive state regardless of ejection fraction.**

LV indicates left ventricular; RAAS, renin–angiotensin–aldosterone system; RV, right ventricular; and SGLT2, sodium-glucose cotransporter 2.

diagnoses such as valve, pericardial, and infiltrative myocardial diseases requiring specific therapies. Treatment of comorbidities, cardiac rehabilitation, multidisciplinary management/monitoring, and advanced treatments remain crucial regardless of EF.

## ARTICLE INFORMATION

### Affiliations

National Heart Center Singapore and Duke-National University of Singapore (C.S.P.L.); University Medical Center Groningen, The Netherlands (C.S.P.L.). Cardiovascular Division, Brigham and Women's Hospital, Harvard Medical School, Boston, MA (S.D.S.).

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