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LETTER TO THE EDITOR

Do Limitations in the Design of PARADIGM-HF Justify the Slow Real World Uptake of Sacubitril/Valsartan (Entresto)?

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On July 07, 2015, the US Food and Drug Administration approved sacubitril/valsartan (Entresto, Novartis) for the treatment of congestive heart failure (NYHA class II–IV). The drug was approved on the basis of a single trial, PARADIGM-HF, where 10,521 patients entered, and 8442 patients were randomized to either the combination sacubitril/valsartan or enalapril. The trial showed an impressive improvement in cardiovascular death (hazard ratio in the neprilysin group, 0.80; 95% confidence interval [CI], 0.73 to 0.87; $P < 0.001$) and an improvement in overall mortality (hazard ratio for death from any cause, 0.84; 95% CI, 0.76 to 0.93; $P < 0.001$) [1]. Despite these benefits, uptake of this drug has been poor among practicing physicians [2].

Experts have criticized physicians' reluctance to embrace a drug with a proven survival benefit, and indeed, PARADIGM-HF is a large and important study in heart failure [3, 4]. Here, however, we consider limitations in the trial underpinning sacubitril/valsartan's approval. Specific design features may have inadvertently biased the trial in favor of the novel agent. An open discussion of these limitations is important, particularly as real world use may reflect persistent uncertainty among physicians.

Was the Dose of Drugs Fair?

PARADIGM-HF enrolled 10,521 patients, of whom 8442 (80.2%) underwent randomization. Of those, 4187 subjects were randomly assigned to sacubitril/valsartan (at a dose of valsartan 320 mg twice a day, the maximum FDA-approved dose), and 4212 were assigned to receive enalapril (10 mg twice a day). Notably, although valsartan was given as maximal dosing, the dose of enalapril is half the maximum dose recommended by the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and Heart Failure Society of America.

When it comes to heart failure with reduced ejection fraction, dose matters. A randomized trial by Packer and colleagues found that administration of a high-dose ACE inhibitor lowered the risk of death or hospitalization for any reason over a low-dose ACE inhibitor [5]. A 2017 meta-analysis supports this claim, finding that high doses of angiotensin converting enzyme inhibitors (ACE-I) or angiotensin receptor blockers (ARB) modestly lowers the risk of death and the composite of death and heart failure hospitalization compared to lower doses of these agents [6]. In PARADIGM-HF, mean systolic blood pressure was lower (3.2 ± 0.4 mmHg lower) among patients taking sacubitril/valsartan, suggesting room to increase the enalapril dose in the control arm.

For these reasons, it is uncertain whether the difference seen in PARADIGM-HF reflects a benefit of sacubitril, the unequal dose of ACE-I and ARB, or the specific ACE-I and ARB chosen, or some combination of all three.

Is the Comparison of Drug A + B Vs. Drug C Fair or Common?

From 2005 to 2016, the US Food and Drug administration approved 46 drugs for cardiologic indications (https://www.centerwatch.com/drug-information/fda-approved-drugs/therapeutic-area/1/cardiology-vascular-diseases). We

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identified 141 trials underpinning the approval of these 46 drugs. We found among these 141 studies, only two studies—V-HeFT II and PARADIGM-HF—used a trial design comparing a combination of drugs A + B to drug C.

V-HeFT II compared isosorbide dinitrate/hydralazine hydrochloride, drugs which had been on the market for years, to enalapril. Yet, the US FDA did not approve this combination until a third trial, A-HEFT, showed superiority of the combination over placebo, and the drug label was restricted to the population of that study, self-described African Americans. With PARADIGM-HF, the drug of interest, sacubitril, was a novel agent paired with an established drug, valsartan, and compared to a different established drug, enalapril. This trial design was unique among all studies used to support the approval of cardiology drugs. In the Table 1, we summarize the trial design used for all regulatory approvals in cardiology. The most common study design was drug vs. placebo (n = 61) and head to head comparisons (drug A vs. drug B, n = 24).

Is the Use of Unequal Drug Run-in Periods Fair? And How Often Does it Occur?

Of the 141 studies supporting the approval of cardiology drugs in 2005–2016, 48 (34.0%) had run-in periods, 51 (36.2%) had no run-in periods, and in 42 (29.8%), we could not identify whether run-in was used (due to lack of specification in available data). Among the 48 studies with run-in periods, PARADIGM-HF was the only study that had both a control and active run-in phase with differing periods of time. Patients first received enalapril for 2 weeks (10 mg twice daily). During this time, 10.5% (1102/10521) of patients discontinued the study. Next, patients were treated with sacubitril/valsartan for 4–6 weeks (starting at 100 mg twice daily, up-titrated to 200 mg twice daily). During this phase, 10.4% (977/9419) of patients discontinued the study. Patients who tolerated both phases of the run-in period were then randomized to either enalapril or sacubitril/valsartan.

Table 1 Trial design used for all regulatory approvals in cardiology

	Number
FDA-approved cardiology drug indications 2005–2016	46
Total number of trials supporting FDA approval*	141
Trial design	
Drug‡ vs. placebo	61 (43.3%)
A‡ vs. B	24 (17.0%)
Unknown**	18 (12.8%)
AB (‡11) vs. A (‡4) vs B	15 (10.6%)
Single arm	10 (7.1%)
AB‡ vs. A	7 (5.0%)
(A + B)‡ vs. C	2 (1.4%)
(A + B)‡ vs. placebo	2 (1.4%)
ABC‡ vs. AB vs. AC vs. BC	2 (1.4%)
Run-in periods	
Trials with run-in periods	48 (34.0%)
Trials without run-in periods	51 (36.2%)
Unknown if trial had run-in period	42 (29.8%)

‡Agent receiving FDA approval.

The longer an active run-in period is, the greater the opportunity for patients' intolerant to that particular medication(s) to discontinue, enriching the population with those who tolerate it well. Notably, the run-in phase with enalapril was one half the time of the run-in period with the active treatment of sacubitril/valsartan, a design feature that favors the combination. Although a similar proportion of patients discontinued the trial in each run-in, the sacubitril/valsartan run-in occurred after enalapril, beginning with an already-selected cohort.

Run-in periods in and of themselves are not uncommon as can be used to screen for patient compliance, identify placebo responders, and screen for tolerance/side effects of the active treatment which can limit loss of patients to follow-up [7]. However, there is a trade-off between increased power and clinical generalizability. Run-ins ensure results are limited to a subgroup of patients, whom clinicians cannot easily identify. Thus, trials with run-in periods may overestimate the effect size and underestimate the risks of the drug by screening for patients most likely to do well.

PARADIGM-HF was stopped due to early positive results and has been heralded as a major breakthrough. Indeed, a trial of this size and scope is a tremendous undertaking and deserving of praise. Yet, design features suggest that a final verdict of sacubitril, the novel agent, will require a validation study. In PARADIGM-HF, sacubitril was combined with valsartan at maximal dose and compared to enalapril, at half maximal dose, making it difficult to isolate the effects of the novel drug. Unequal duration of run-in may have further inflated the therapeutic value of sacubitril. Because the cost of sacubitril/valsartan is several times greater than that of generic alternatives, we believe confirmatory evidence is necessary to convince reluctant physicians to change their practice.

References

1. Packer M, McMurray JJ, Desai AS, et al. PARADIGM-HF Investigators and Committees. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med 2014; 371:993–1004.
2. Uptake of new heart failure drug slow, say makers. http://www.cardiomyopathy.org/news%2D%2Dmedia/latest-news/post/126-uptake-of-new-heart-failure-drug-slow-say-makers. Updated November 6, 2015. Accessed 18 Oct, 2017.
3. Packer M. Kicking the tyres of a heart failure trial: physician response to the approval of sacubitril/valsartan in the USA. Eur J Heart Fail. 2016;18:1211–9.

4. Packer M, Armstrong WM, Rothstein JM, Emmett M. Sacubitril-valsartan in heart failure: why are more physicians not prescribing it? Ann Intern Med. 2016;165:735–6.
5. Packer M, Poole-Wilson PA, Armstrong PW, Cleland JGF, Horowitz JD, Massie BM, et al. Comparative effects of low and high doses of the angiotensin-converting enzyme inhibitor, lisinopril, on morbidity and mortality in chronic heart failure. Circulation. 1999;100:2312–8.
6. Khan MS, Fonarow GC, Ahmed A, Greene SJ, Vaduganathan M, Khan H, et al. Dose of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers and outcomes in heart failure: a meta-analysis. Circulation: Heart Failure. 2017;10:e003956.
7. Pablos-Mendez A, Barr RG, Shea S. Run-in periods in randomized trials: implications for the application of results in clinical practice. JAMA. 1998;279(3):222–5.