PARADIGM-HF: Does Dose Matter?

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Glossary

ATLAS: Assessment of Treatment with Lisinopril and Survival

PARADIGM-HF: prospective comparison of angiotensin receptor neprilysin inhibitor (ARNI) with angiotensin converting-enzyme (ACE) inhibitors to determine impact on global mortality and morbidity in heart failure trial

PARAGON-HF: Efficacy and Safety of Sacubitril-Valsartan Compared to Valsartan, on Morbidity and Mortality in Heart Failure Patients With Preserved Ejection Fraction

The PARADIGM-HF trial showed unequivocal superiority of sacubitril-valsartan 200mg twice daily over enalapril 10mg twice daily in clinically stable patients with HFrEF and mostly mild symptoms who were initially able to tolerate the protocol-specified target doses of each agent(1). The trial was designed to satisfy regulators' requirements and was not meant to be a practical blueprint for a clinical care-plan. Like most clinical trials, it should be regarded as an aid to clinical judgement rather than a precise set of instructions. Clinicians must extrapolate evidence from clinical trials to individual patients and judge what is in their patients' best interests rather than merely decide whether the patient fulfils the trial entry criteria. A very conservative stance on dose, as in recent European Society of Cardiology guidelines on sacubitril/valsartan(2), may apply to rather few patients; a more liberal stance, as suggested by the European Medicines Agency or National Institute for Health Clinical Excellence may apply to many(3). Who's right? Does dose matter?

PARADIGM-HF required all patients to tolerate pre-specified doses of both medications. It did not set out to prove that the target dose of either agent was optimal. Indeed, the concept of a single universal target-dose appropriate for all patients is implausible. Plasma concentrations of medicines will depend on absorption, body size and composition, the rate of clearance by the kidney, liver and other mechanisms and not just the dose ingested. For many patients, higher doses will be tolerated and might be more effective; for others they will not be tolerated and might be deleterious. Lower doses will usually be better tolerated in the short-term but might offer less long-term protection from disease progression(4). Identifying the optimal dose for an individual patient is difficult. Clearly a zero-dose must be ineffective, although not necessarily suboptimal for some individuals, and there will be a dose above which the medicine is not tolerated or lethal. Randomized clinical trials comparing higher

compared to lower doses of ACE inhibitors(5) or angiotensin receptor blockers (ARB)(6) failed to show substantial differences, although perhaps because higher doses were poorly tolerated amongst the sickest patients (Figure). This confounds analysis by intention-to-treat because there may be little difference in the dose actually ingested amongst the sickest patients who are most likely to have events. Also, dose-comparison trials recruit patients younger and with fewer co-morbidities than in clinical practice and often exclude those who are unable to tolerate substantial doses of medication. With beta-blockers or ivabradine heart rate achieved(7) and for mineralocorticoid antagonists serum potassium(8) may be better targets than guideline-recommended doses; other biomarkers, including the ratio of biologically active to pro-peptide fragments of natriuretic peptides for sacubitril-valsartan, might also provide useful guidance. It is sobering to think that after 200 years of digoxin and 50 years of cardiovascular aspirin we are still uncertain of the optimal dose of either, which could still prove to be zero. Optimal dosing is difficult to study and to achieve.

In a post-hoc analysis, Vardeny and colleagues (9) now show that many patients who had initially tolerated target doses of each agent in PARADIGM-HF subsequently had doses reduced either temporarily or permanently; some had to discontinue medication altogether. Information on adherence, which is difficult to measure robustly, is not reported but a proportion of patients will have taken substantially less medication than prescribed, even amongst those who down-titrated their dose(10). Although reductions in dose were associated with a worse outcome regardless of assigned therapy, the superiority of sacubitril-valsartan over enalapril persisted in such patients. This analysis was not pre-specified, dose reductions will not have occurred at random and the reasons for dose reduction probably differed between agents. Why were differences still observed in the sub-population taking lower doses? The obvious explanation is that even at lower doses, sacubitril-valsartan is superior to

enalapril. Alternatively, there may have been a persisting 'legacy effect' from a period of treatment at higher doses(11). Intolerance to enalapril might also identify a sicker population than does intolerance to sacubitril-valsartan. Accordingly this analysis should be extrapolated with caution to other clinical populations or settings.

Patients with heart failure who are unable to tolerate target doses of disease modifying therapies usually have a worse prognosis(12), as confirmed in PARADIGM-HF. This may be because low blood pressure and worse renal function lead to a lethal therapeutic triad (**Figure**). High doses of medication will be less likely to be prescribed for, or tolerated by, patients with low blood pressure or glomerular filtration rate (GFR), who have a worse prognosis; reduction or cessation of therapy may lead to loss of therapeutic benefit; excessive lowering of blood pressure or glomerular filtration rate may neutralize or reverse the benefits of the therapy, if taken.

Despite previous failures with other agents, further randomized controlled trials should be considered to determine the optimal dose of sacubitril-valsartan. Lower doses might have fewer side-effects and may retain full therapeutic potency and could even be superior to higher doses if they exert less reduction in blood pressure. Of course, lower doses might be less effective and higher doses than those used in PARADIGM-HF might be even better. Ultimately, a particular dose of sacubitril-valsartan will not be optimal for all patients, which makes the design of studies comparing doses difficult to do and to interpret. PARADIGM-HF also does not exclude the possibility that higher doses of ACE inhibitors would have been as effective as sacubitril-valsartan. In the ATLAS trial, those with milder symptoms who were more likely to remain on assigned therapy (placebo or 30mg of lisinopril on an open-label

background of 2.5-5.0mg of lisinopril), higher-doses were associated with a significantly lower mortality(5). This was a post-hoc, sub-group analysis and therefore does not constitute robust evidence of greater efficacy with higher doses of ACE inhibitors. Recently, intense inhibition of the renin-angiotensin-aldosterone system (RAAS) with a combination of enalapril and aliskiren (a renin inhibitor) on a background of substantial MRA use was shown not to be superior to enalapril alone at a dose of 10mg bd(13), providing strong, contemporary evidence of the limits of intense RAAS inhibition.

However, discussions about the hypothetical outcomes of hypothetical trials are of little practical value to the patient or doctor faced with making a decision today. It will take years before the results of any dose-ranging study could be known. Who would fund such a trial? The obvious answer is health services, since if they are willing to pay for a medication then they should ensure that they are using it to best effect. In the absence of such information, this analysis of PARADIGM-HF(9) provides the best available information to guide decisions.

What are the implications for clinical practice? Strict application of the PARADIGM-HF protocol to clinical practice would require all patients to be treated with an ACE inhibitor first, titrated to doses similar to those achieved in the protocol and then demonstrate that left ventricular ejection fraction is still low (HFrEF) and natriuretic peptides still elevated before contemplating treatment with sacubitril-valsartan(3). This is time-consuming and potentially deprives the patient of the benefits of a better treatment for a considerable time. In PARADIGM-HF, the superiority of sacubitril-valsartan became apparent within a few weeks of randomization(1). Also, many patients will not tolerate the high doses of ACE inhibitors

required in the PARADIGM-HF study and would technically never be eligible for sacubitril-valsartan. Practically, there are at least four common scenarios.

Scenario 1: Stable patients with known HFrEF already treated with guideline-recommended doses of ACE inhibitors or ARB. If absolute risk is low then even a substantial reduction in relative risk will provide only a small absolute benefit that may be neither efficient nor cost-effective. Demonstration of increased plasma concentrations of natriuretic peptides (a small, one-off cost) before initiating sacubitril-valsartan (a substantial daily cost) will ensure that resources are used wisely both for patients and health services. Moreover, measurement of natriuretic peptides is a catalyst for the clinician to act and also provides an explanation for patients, who may feel well, of why they should change.

Scenario 2: Stable patients with known HFrEF but not receiving target doses of ACE inhibitors or ARBs, which might include treatment naïve patients identified by screening. For these patients, the clinician must choose between titrating ACEi/ARB to recommended doses and re-evaluating the patient before switching or, alternatively, initiating low-dose sacubitril-valsartan immediately. Again, measurement of natriuretic peptides will be helpful. If plasma concentrations are only slightly elevated, then it is reasonable to titrate ACEi/ARB first and re-evaluate. However, if plasma concentrations are grossly elevated it is improbable that titration of ACEi/ARB will reduce NT-proBNP sufficiently; initiation of sacubitril-valsartan is likely to be in the patient's best interest, saves time and effort and reduces management complexity.

Scenario 3: Most de-novo presentations of HFrEF are either associated with symptoms of decompensation that are severe enough to warrant hospital admission(14) or occur in the context of an acute myocardial infarction. On current evidence, such patients should first be stabilized on conventional treatments, with sacubitril-valsartan introduced at a later date; the precise timing is uncertain but 4-8 weeks would be consistent with PARADIGM-HF. Advice

may change as experience grows, with further analyses of PARADIGM-HF focussing on patients who experienced acute heart failure whilst receiving sacubitril-valsartan during the trial and, in due course, with evidence from further clinical trials.

Scenario 4: Patients with heart failure and a normal left ventricular ejection fraction (HFpEF) currently under investigation in the PARAGON-HF trial or with heart failure due to valve disease. It is not yet known whether sacubitril-valsartan is effective in such patients.

Does dose matter? One dose of any effective medicine certainly matters and that dose is 'zero'. Avoid it whenever possible! Educate individual patients about the doses of medication you think might be best for them. Maybe once they know what the targets are, they might help you achieve them. After all, it's in their own interests.

Figure Legend

Diagrammatic illustration showing the lethal triad linking inability to tolerate full doses of medication and poor outcome in patients with heart failure. Sicker patients have lower blood pressure (BP) and glomerular filtration rate (GFR) and therefore physicians may be less willing to prescribe or patients less willing to try full doses of medication. Medication often further reduces already low BP and GFR; there must be a critical point where reduction in BP and GFR is deleterious, leading to a reduction or loss of therapeutic benefit or even harm. A fall in BP or GFR may also lead to medication being stopped or used at lower doses, with potential loss of benefit. However, dose is really only a surrogate measure for plasma or tissue concentrations of medicines. Many medicines are excreted by the kidney and therefore their tissue concentration may be similar in patients with a low GFR on low doses of medication compared to healthier patients with a normal GFR on high doses of medication.

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