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VIEWS AND REVIEWS

NO HOLDS BARRED

Margaret McCartney: Only data can say if new is better

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Managing heart failure is often hard work for patients and professionals. Steering between fluid overload and postural hypotension, while keeping the kidneys perfused and quality of life maintained in a life limiting condition, is a difficult and draining business.

A new drug, then, would be welcomed, and LCZ696 was described to me as "the next big thing" by a cardiology specialist even before the first trial appeared. With the brand name Entresto, it's a combination of valsartan (an old drug, an angiotensin receptor blocker) and sacubitril (a newer neprilysin inhibitor).[1] It was going to be a bit of a revolution, we were promised. The double blind trial of valsartan-neprilysin versus enalapril in heart failure was published in the *New England Journal of Medicine* in 2014.[2] The National Institute for Health and Care Excellence (NICE) approved it for use in 2016.[3]

The trial was stopped prematurely because it found an "overwhelming benefit" from the new combination drug. The primary outcome was a composite of admission to hospital for heart failure and death from cardiovascular causes. After 27 months, 21.8% of patients in the test group and 26.5% of patients in the enalapril group had reached that endpoint. The difference in mortality alone was smaller: 17% in the test group and 19.8% in the enalapril group. Is this reason enough for NICE approval?

Sacubitril costs almost £100 a month, and the obvious question is why it was approved without knowing whether the valsartan (costing around half the price) or the sacubitril was responsible for any benefits. Modelling studies by Novartis have been cited by NICE, but they can't be considered good replacements for randomised controlled trials. Furthermore, the average age of patients in the trial was just under 64; the average age of patients with heart failure in the UK is 76. The primary endpoints were not statistically significant in the pre-specified subgroup of people over 75. Only 22% of the trial population were women. And the dose of enalapril in the control group was a flat rate of 20 mg daily, which was not up-titrated according to symptoms.

So, are the benefits useful for our population—and how big are they, compared with usual, optimal care? A previous trial with a similar new drug showed no benefit.[4] The logical thing would surely be an amber light and use only in research: if we're going to use the drug, surely we'd do better to gather high quality data on whether it's better than standard care? Heart failure is a disease with a high death rate—but death is not the only outcome that matters. Patients given the test drug had a higher risk of symptomatic hypotension: I suspect that, in the older UK population, the rate of this side effect will be higher.

Quality of life is of fundamental importance. If the trials of palliative care in heart failure show that it gives similar or better value,[5] I hope that it's funded and delivered just as quickly.

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