Sacubitril/Valsartan for Heart Failure: Exciting Times but Are Doctors Informed and Ready?

Prithwish Banerjee

1. University Hospitals Coventry & Warwickshire, UK

Corresponding author:
Professor Prithwish Banerjee, Department of Cardiology, University Hospitals Coventry & Warwickshire, Clifford Bridge Road, Coventry, CV2 2DX, UK.
E-mail: Prithwish.Banerjee@uhcw.nhs.uk

Abstract

Sacubitril/Valsartan is now being prescribed by heart failure/cardiology teams across the United Kingdom following the publication of the NICE technology appraisal guidance, but is everyone ready for it? This article discusses the practical aspects of what to do and what not to do in relation to the drug, based on real world experience from our centre.

Keywords: Sacubitril/Valsartan; heart failure; symptomatic hypotension

Citation: Banerjee P. Sacubitril/Valsartan for Heart Failure: Exciting Times but Are Doctors Informed and Ready?. International Cardiovascular Forum Journal 2017;12:3-4, DOI: 10.17987/icfj.v12i0.464

Introduction

Following the publication of the PARADIGM-HF study[1] the new drug Sacubitril/valsartan (Entresto) has now been included in the guidelines for treatment of patients with heart failure and reduced ejection fraction (HFREF) by the European Society of Cardiology [2], the American Heart Association/American College of Cardiology [3] and the Scottish Intercollegiate Guidelines Network [4]. The study, performed in over 8,000 patients showed a substantial reduction of the primary composite endpoint of cardiovascular death or heart failure hospitalization (and in other endpoints of cardiovascular mortality, heart failure hospitalisation and all cause mortality) in the Sacubitril/Valsartan group when compared to the well established ACE inhibitor Enalapril. The National Institute for Care and Clinical Excellence in England and Wales (NICE) provided it’s technology appraisal guidance [5,6] in April 2016 which limits the use of the drug to symptomatic HFREF patients with NYHA Class II to IV symptoms, a left ventricular ejection fraction of ≤ 35%, and to those that are already taking ACE inhibitors or ARBs. NICE has also specified that this drug should be started only by a heart failure specialist with access to a multidisciplinary heart failure team but once initiated and uptitrated by them continuing prescription will need to come from general practitioners.

While this is an exciting development as it brings an alternative, more effective, relatively simple, non invasive option to the HFREF patient who remains symptomatic despite standard evidence based medical therapy, there are some important practical considerations for all physicians and general practitioners (GPs) in relation to usage of Sacubitril/valsartan as it continues to be rolled out to heart failure patients across the UK. As of today, although there is great interest in this drug, many centres in the UK are still in the stage of very early experience in using it. As initiation and uptitration of the drug is confined to heart failure teams (or cardiologists), other physicians and general practitioners are unlikely to gain experience with the drug quickly. Some anticipated difficulties are outlined below with suggestions to tackle them.

1) Sacubitril/valsartan is indicated as a replacement for ACE inhibitors and ARBs. This means that it should not be prescribed alongside ACE and ARBs. While switching from an ACE inhibitor a 36 hour washout period is needed as there is a risk of precipitating angioedema if it is prescribed together with an ACE inhibitor. This is not a problem with an ARB but Valsartan is already present in the drug meaning that an ARB should not be co-prescribed either. In the PARADIGM-HF study [1], 0.5% of patients treated with Sacubitril/valsartan and 0.2% of patients treated with enalapril had angioedema, the difference being statistically non-significant. Lack of awareness of this new drug, however, is still a clinical risk as there is always a chance that junior doctors on a busy on call would inadvertently make the error of co-prescription. Awareness of this is actually needed by all physicians and GPs although the heart failure teams will clearly be in charge of initiating the drug. The practice in our centre is to discontinue ACE inhibitors/ARBs for 48hrs (2 days) before starting Sacubitril/valsartan in order to keep the process simple and uncomplicated for patients and GPs.
2) As a way of preventing co-prescription with ACE inhibitors, each patient taking Sacubitril/valsartan needs to be educated by the prescribing team and given alert cards that outline the caution. Such cards are already being provided by Novartis, the pharmaceutical company manufacturing the drug.

3) There is a greater risk of symptomatic hypotension with Sacubitril/valsartan than with an ACE inhibitor. In the PARADIGM HF study 14% patients in the Sacubitril/valsartan arm had symptomatic hypotension compared to 9.2% in the Enalapril arm (p =<0.001) [7]. This needs to be borne in mind while co-prescribing with drugs that reduce blood pressure (BP). The heart failure team that initiates the drug will also need to be aware and monitor accordingly. Our own experience [7] so far suggests that hypotension is the most important adverse effect of the drug, but this can be managed by reducing or stopping non-heart failure drugs such as antihypertensives and antianginals as well as non-essential heart failure drugs such as loop diuretics (if fluid overload is not a problem anymore). Although the advice from the manufacturing company is to commence Sacubitril/valsartan with a starting dose of 49/51 mg (100 mg dose) twice a day when switching from any dose of ACE or ARB, we have had to be cautious about the dose in patients with a systolic blood pressure of close to 100 mm Hg as postural dizziness due to a significant drop in BP has been a feature. Our practice has been to bring these patients with lowish systolic BP back to our nurse-led clinics to recheck the BP after stopping the ACE/ARB for 48 hrs. In patients with a systolic blood pressure of 100 to 110 mm of Hg off ACE/ARB our heart failure team has increasingly resorted to starting at the lowest dose of 24/26 mg (50 mg dose) twice a day and then gradually up-titrating while consideration is given to reducing or stopping other drugs mentioned above.

4) As with ACE/ARB, close monitoring of renal function and potassium is required with Sacubitril/valsartan. In the PARADIGM HF trial more patients in the Enalapril group had creatinine elevation of ≥2.5 mg/dl and potassium elevation of >6 mmol/L (both were statistically significant) compared to the Sacubitril/valsartan group, which is reassuring, but this should not lead to complacency about checking these as the real world experience may differ from trial data. Reassuringly, our own data [7] in a small cohort of patients did not find renal dysfunction or hyperkalaemia to be a significant problem.

5) The drug has an unusual dose combination that may feel strange and unfamiliar to most physicians. For example, the standard doses are 49/51 mg and 97/103mg (which, added together actually make up to 100mg and 200mg respectively). The lowest dose is 24/26mg (50 mg dose). Hospital physicians not yet familiar with Sacubitril/valsartan should ideally involve the hospital’s heart failure team if they wish to make changes in dosage.

6) Stopping Sacubitril/valsartan temporarily for acute kidney injury or for a drop of BP due to an unrelated cause (sepsis for example) should be done in the same way as with an ACE/ARB with the plan to reinstate Sacubitril/valsartan when it is safe to do so. If Sacubitril/valsartan is not tolerated at all, but an ACE or ARB was tolerated, it would be sensible to switch back to the ACE/ARB, but before abandoning the significantly greater benefits of Sacubitril/valsartan physicians must be sure that the drug was truly not tolerated.

7) As with any new drug a lot of education is still needed. Hospital and community pharmacists need to play an important role in disseminating knowledge about the drug. Area Prescribing Committees have in many cases helped to set up a shared care agreement or a similar arrangement for GPs to continue prescribing the drug after specialist initiation.

In conclusion, it is still early days for this exciting new drug in HFREF. Early experience in the real world seems promising but there is still some way to go before an adequate amount of awareness of the drug filters into the medical community dealing with heart failure patients.

Declarations of Interest
The author has received honoraria from Novartis.

Acknowledgements
The authors state that they abide by the “Requirements for Ethical Publishing in Biomedical Journals [8].”

References
8. Shewan LG, Coats AJS, Henein M. Requirements for ethical publishing in biomedical journals. International Cardiovascular Forum Journal 2015;2:2 DOI: 10.17987/icfj.v12i0.464