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Sacubitril/Valsartan (EntrestoTM) hospital prescribing in patients with symptomatic chronic HF with reduced ejection fraction

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Sacubitril/Valsartan (EntrestoTM) hospital prescribing in patients with symptomatic chronic HF with reduced ejection fraction: a UK multi-centre study

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	Total prescribing of sacubitril/valsartan at the three hospitals was 295 patients, lower than expected compared to the NICE guidance resource tool, which predicted 1,151 eligible patients at the three hospital trusts. Conclusion The prescribing of sacubitril/valsartan at the Trusts generally adhered to NICE guidance, however the prescribing rate was lower than expected compared with the NICE resource tool. Further investigations into the safety and scope of application of sacubitril/valsartan are required to match the prescribing of sacubitril/valsartan with eligible patients who could benefit from the medication.
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Sacubitril/Valsartan (Entresto™) hospital prescribing in patients with symptomatic chronic HF with reduced ejection fraction: a UK multi-centre study

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Conflict of interest None declared

Abstract

Background Sacubitril/valsartan (EntrestoTM) is a recently launched combination drug therapy for HF patients that has been shown to reduce mortality and patient hospitalisation.
Aims To explore clinically relevant real-life patient data regarding prescribing of sacubitril/valsartan for heart failure (HF) patients in three United Kingdom hospitals in accordance with national guidelines. To compare prescribing rates with predicted rates calculated using the National Institute for Health and Care Excellence resource tool (a template to calculate the eligible number of patients treated with sacubitril/valsartan) and to describe the characteristics of patients prescribed sacubitril/valsartan at the hospital Trusts.
Methods A retrospective multicentre study in three large UK hospital Trusts based in the West Midlands, an area with a high incidence of patients with HF.
Findings A total cohort of 118 symptomatic chronic HF patients with reduced ejection fraction were included in the study. A high proportion of prescribers adhered to NICE guidelines for treatment with sacubitril/valsartan; 99% (n = 116/118) of patients had a New York Heart Association (NYHA) functional class of at least II; 82% (n = 96/118) had a left ventricle ejection fraction (LVEF) of under 35%; 100% (n= 118/118) received an angiotensin-converting enzyme (ACE) inhibitor or angiotensin II receptor blocker (ARB) before commencing sacubitril/valsartan. The mean age of men and women at the three hospitals was men 65 ± 13, women 59 ± 12. The proportion of men prescribed sacubitril/valsartan was greater than women 80% compared to 20%, respectively. The vast majority of patients on the therapy were White British (65%). Total prescribing of sacubitril/valsartan at the three hospitals was 295 patients, lower than expected compared to the NICE guidance resource tool, which predicted 1,151 eligible patients at the three hospital trusts.
Conclusion The prescribing of sacubitril/valsartan at the Trusts generally adhered to NICE guidance, however the prescribing rate was lower than expected compared with the NICE

resource tool. Further investigations into the safety and scope of application of sacubitril/valsartan are required to match the prescribing of sacubitril/valsartan with eligible patients who could benefit from the medication.

Anonymous manuscript

Sacubitril/Valsartan (Entresto™) hospital prescribing in patients with symptomatic chronic HF with reduced ejection fraction: a UK multi-centre study

Keywords
Entresto, Heart Failure, Sacubitril/Valsartan, Secondary care, Hospital, Prescribing

Introduction

Approximately 1.37% (900,000 people) of the UK population suffer from Heart Failure (HF)[1-3]. HF is a clinical term that encompasses a range of different diseases of the heart which lead to lowered cardiac output and/or high intracardiac pressure and therefore inefficient perfusion to the body[4]. In HF there is a large comorbidity burden including structural or functional heart abnormalities that can exacerbate the syndrome[4]. There are 530,133 people on the UK national heart failure register, including 47,238 from the West Midlands[5]. Five percent of all emergency admissions include adult patients with HF, either as the cause or a complication, with an average length of hospital in-patient stay of 6-9 days in a general medical or cardiology ward, respectively[2]. HF is also associated with various co-morbidities and early death[4]. Therefore, HF causes considerable economic burden on both the patient and the healthcare system, due to extensive health economy costs. Approximately 2% of the NHS budget is used in the standard and hospitalised treatment and aftercare of patients, as well as the reduced number of HF patients that return to full employment[6,7]. Further strain on the individual post-HF results from unemployment, low quality of life and poor prognosis[4].

Treatments for HF, such as beta-blockers, aldosterone blockers, angiotensin-converting enzyme inhibitors (ACEi) and Angiotensin II receptor blockers (ARBs) were developed in the 20th century and have had substantial effects on patients' health, by acting on different targets[8]. In this study, prescribing practices of a recently launched dual drug therapy for HF called Entresto™ (sacubitril/valsartan) were investigated.

The 2014 PARADIGM-HF trial led to a breakthrough in HF treatment[8] with the release of sacubitril/valsartan in January 2016. A NICE guideline, on its use in heart failure with reduced ejection fraction (HFrEF) and a NICE resource tool, on the expected patient uptake, was published in April 2016[1].

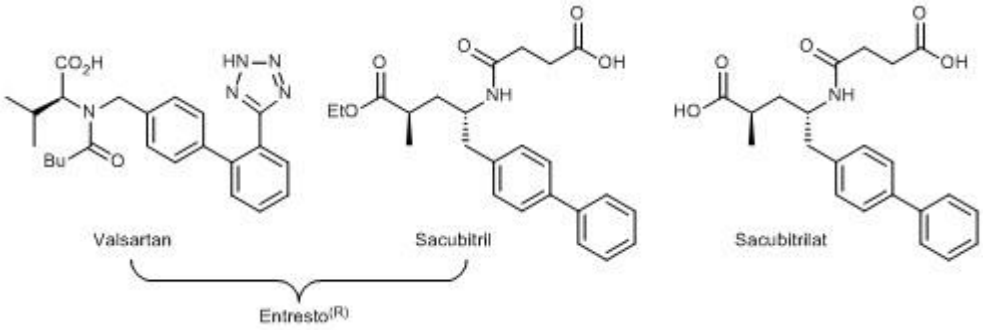
Mode of action of sacubitril/valsartan

Sacubitril/valsartan (Entresto™) is a sodium salt complex (see Figure 1) and the first medication of a new class; combining an angiotensin II type-1 receptor antagonist (Angiotensin receptor blocker, ARB), valsartan, and a neprilysin inhibitor (NEPi), sacubitril, which together is known as a new class of ARNi (Angiotensin receptor-neprilysin inhibitor).

Valsartan acts on the renin-angiotensin-aldosterone system. The mode of action of this molecule is to compete with angiotensin II by binding to the type-1 angiotensin II receptor (AT1R). This therefore prevents the effects of angiotensin II (Ang II), which include vasoconstriction, increased fibrosis, sodium retention, cell proliferation and oxidative stress. Upon oral dosing, Entresto™, via dissolution and absorption, delivers systemic exposure to valsartan and sacubitril. Sacubitril is an inactive pro-drug that is enzymatically cleaved after absorption (at the ethyl ester position to form the carboxylic acid), delivering Sacubitrilat, the active metabolite which inhibits neprilysin. Neprilysin is a metalloprotease, usually membrane-bound that when released from the membrane acts as a catalytic enzyme that degrades natriuretic peptides (atrial natriuretic peptide ANP) and

(brain natriuretic peptide BNP) as well as bradykinin. By blocking this action, sacubitrilat allows these molecules to continue to have their effects of natriuresis, vasodilation and reducing fibrosis on the body.

Figure 1- Entresto™ (sacubitril/valsartan) combination and active metabolite.



Combination of valsartan and sacubitril

When valsartan is combined with sacubitril studies have determined that the plasma concentration of valsartan is 40% higher than when delivered without Sacubitril [8-13]. However, the mechanism of this increase in bioavailability of valsartan remains unclear as valsartan is known to be excreted largely as the unchanged compound and is minimally metabolized in human and this is most likely an effect of the co-crystallised formulation in Entresto™ versus valsartan alone[14]. Among the cytochrome P450 (CYP) enzymes, CYP2C9 is the only CYP isoform responsible for 4-position hydroxylation of valsartan in human liver microsomes (HLMs)[15,16].

In summary, Entresto™ inhibits neprilysin and blocks angiotensin II type-I receptor. Sacubitril increases the levels of peptides that are normally degraded by neprilysin. Valsartan inhibits the effects of angiotensin II by blocking the AT_1 receptor and by inhibiting the release of angiotensin II-dependent aldosterone.

Clinical Evidence for sacubitril/valsartan

The PARADIGM-HF study, conducted in 2014 on 8442 subjects, found that sacubitril/valsartan significantly improved patient outcomes. The medication reduced deaths from cardiovascular causes from 16.5% to 13.3% (P-value <0.001), and rehospitalisation by 21% (P<0.001), when compared to enalapril the current first line therapy[17].

Sacubitril/valsartan has been available for treating HF patients through the NHS since January 2016, via the early access to medicines scheme (EAMS).

Within the NICE recommendations[18] for the use of sacubitril/valsartan, there are three criteria for which patients to select for treatment; those with:

1. An NYHA functional class of II or above
2. A LVEF of 35% or below
3. Stabilised on an ARB or ACE inhibitor

This guideline set a standardised approach to therapy, based on clinical evidence and would lead to optimal treatment of HF patients[18]. Although healthcare providers have a duty to exercise their own judgement according to individual patient needs, an understanding of the NICE recommendations is expected[18]. NICE released a resource impact tool in April 2016, demonstrating the cost-effectiveness and expected prescribing rates of sacubitril/valsartan over the 5 year period following its publication[18]. The NICE resource tool, a template to calculate the eligible number of patients treated with sacubitril/valsartan per year, found that within the UK 108,000 people met the NICE criteria for treatment for sacubitril/valsartan, described above, however as this drug is relatively new, the expected prescribing rate is estimated to be 64,500 by 2020/21 [18]. The NICE resource tool also calculated that annual treatment of sacubitril/valsartan for one patient would cost £1,194 which was a better health economic proposition than hospitalisation which was estimated to cost £2,698 [18].

Aims and Objectives

To explore prescribing practices of sacubitril/valsartan at three UK hospitals in accordance with national guidelines.

Specific objectives:

- To determine adherence to NICE guideline (TA388) when prescribing sacubitril/valsartan therapy.
- To compare prescribing rates of sacubitril/valsartan at three hospitals to the predicted prescribing rates calculated when using the NICE resource tool.
- To explore differences and variations between the Trusts regarding their prescribing of sacubitril/valsartan.
- To describe the characteristics of patients prescribed sacubitril/valsartan.

Methods

A multicentre retrospective study was conducted over a 6 month period of the use of sacubitril/valsartan at three large and well established cardiac centres in the West Midlands area with a high proportion of HF patient admissions. The study proforma was adapted from NICE guidelines[1]. After ethical approval of all relevant bodies including The University of Birmingham and the respective hospitals, the study was carried out by a researcher under supervision of the stakeholders (supervising specialist pharmacist and heart failure team's at each hospital Trust) on the hospital premises. Hospital databases were accessed to gather information, from the initiation of prescribing sacubitril/valsartan (first prescription issued for a patient) up until the end date of the study which was January 2018 at each individual hospital.

Inclusion Criteria: patients with symptomatic chronic HF with reduced ejection fraction prescribed sacubitril/valsartan.

The following patient information was collected: NYHA functional class, LVEF, and prior HF medication. Furthermore, data on sacubitril/valsartan treatment was gathered: this included side effects, re-admission, discontinuation, and patient demographic data. In addition, blood pressure data, heart rate, eGFR, potassium and sodium levels as well as patients' baseline medication (beta-blockers, mineralocorticoid antagonists, diuretics) and devices (implantable cardioverter-defibrillator (ICD), cardiac resynchronization therapy (CRT) and pacemakers (PPM)) were collected. All data was anonymised, in line with NHS information governance protocols to protect patient confidentiality and adherence to hospital policies, and then compiled for analysis, which was conducted by using Microsoft Excel and further processed and analysed with IBM Statistical Package for Social Science (SPSS) 24.

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n_1=number of included patients in hospital 1, n_2=number of included patients in hospital 2, n_3=number of included patients in hospital 3, n_t= total (t) number of patients on Entresto™

Results

The study was conducted over a period of six months and the data collection period was from 23/10/17 to 20/1/2018 at the three different UK hospital trusts:

Sample

A total cohort of 118 patients were included in the study (Tables 1 & 2); 20 patients from hospital 1 (n_1), 37 patients from hospital 2 (n_2) and 61 patients from hospital 3 (n_3). The mean age of men and women from the combined findings at the three hospitals was women 59 ± 12, men 65 ± 13 all 64 +13. At the time of the study 198 patients were prescribed sacubitril/valsartan at hospital 3, however, only raw data for 61 patients was available to the researcher to collect and analyse within the time frame of the study.

The majority of patients were within the age ranges of 61 to 70 years and those over 70 years old, 31% and 30% respectively (see figure 2 below). The proportion of men was greater than women 80% compared to 20%, respectively. The vast majority of patients prescribed sacubitril/valsartan therapy were white British (65%), followed by South Asians (10%) then other white backgrounds (9%). Fewer were undocumented (6%), black Caribbean (4%), or either mixed white and black Caribbean or black African background (3% both).

Adherence to NICE guideline

Determining adherence to NICE guidelines for use of sacubitril/valsartan for treating symptomatic chronic HF patients with reduced ejection fraction, three criteria were reviewed: NYHA of II or above, LVEF of 35% or below, and stabilisation on an ACE inhibitor or ARB. Data below details adherence to guidelines for each criteria mentioned in the NICE guideline[1] for all three hospitals combined. Adherence to the NICE guideline was high overall.

<u>New York Heart Association classification (NYHA):</u>

In all three hospitals the majority of patients were within the NYHA class II category 65% (n_1=20), 65% (n_2=37), 44% (n_3=61), with NYHA class III being the next most common 30% (n_1=20), 27% (n_2=37), 31% (n_3=61). There were no patients with NYHA class II-III at hospital 1, 5% (n_2=37), 15% (n_3=61) in hospital 2 and 3 respectively. NYHA class III-IV was only encountered at hospital 3 (n_3=4). Two cases of contraventions of the NICE guidelines were found. In hospital 1, a patient was treated despite having a NYHA function class I and in hospital 3 one patient's NYHA class was not documented.

<u>Left Ventricle Ejection Fraction:</u>

In combined findings from the three hospitals the majority of patients fell under the 20-30% LVEF range (30%, (n_1=20); 38%, (n_2=37); 31%, (n_3=61). There were few patients with no identified LVEF

14% (n_t=17/118) or an LVEF of over 35% (4%, n_t =5/118), which is not in-line with NICE guidelines. Hospital 2 treated two patients with a LVEF over 35% and three with unknown LVEF. Hospital 3 treated two patients with a LVEF over 35% and 14 withunknown LVEF (23%, n_3=61). Hospital 1 complied with the NICE guidelines regarding LVEF.

Prior use of ACE inhibitors or ARB:

The last criteria reviewed was prior stabilisation of the HF patients on an ACEi or ARB. The study showed that in total 71% (n_t=83/118) of the patients in the Trusts were already stabilised on an ACE inhibitor, ramipril (44%), perindopril (24%), lisinopril (2%), and enalapril (1%), and 29% (n_t=35/118) were already stabilised on an ARB, valsartan (1%), losartan (15%) and candesartan (13%), prior to prescribing sacubitril/valsartan.

Side effects

The main side effects mentioned in NICE guideline include hypotension, hyperkalaemia and renal impairment. On average 65% (n_t= 76/118) of patients within this study experienced one of the following side effects dizziness, hypotension, renal impairment and fatigue and were noted in all Trusts. There was a large disparity in the documentation of side effects and their prevalence between the three Trusts.

Rehospitalisation

The rate of re-hospitalisation in hospital 1 was 5% (n_1=20) compared with hospital 2 3% (n_2=37). Difficulties in breathing, shortness of breath, orthopnoea and paroxysmal nocturnal dyspnoea where reported reasons responsible for re-hospitalisation in hospital 1. A case in hospital 2 led to discontinuation of sacubitril/valsartan, the patient was hospitalised due to shortness of breath, chest pain and development of acute kidney injury (AKI). At hospital 3, 28 patients were seen in Accident and Emergency during sacubitril/valsartan treatment. However only 15 cases could be identified to be categorically caused by HF presenting complaints such as chest pain, shortness of breath and decompensated HF.

Discontinuation

None of the patients studied at hospital 1 discontinued their sacubitril/valsartan medication. However, at hospital 2, there were three cases 8% (n_1=37), two cases of hypotension and one of AKI. At hospital 3, there were nine cases 15% (n_2=61) of discontinuation: three were due to death (one death was due to AKI), five from adverse events and one due to a prescriber error. Of those where discontinuation was due to adverse events; one was due to an AKI, one suffered from kidney impairment, two patients had a potential allergic reaction and one patient suffered from recurrent hypotension which led to discontinuation of sacubitril/valsartn.

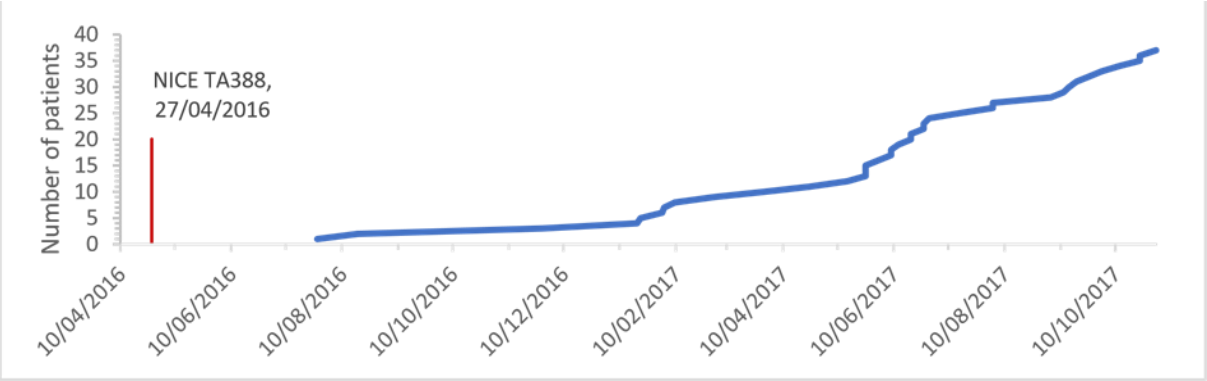
Hospital and prescriber uptake of Entresto

Approximately 12 months after NICE TA388[1], the guideline for the use of sacubitril/valsartan was published (27/04/2016), prescribing at hospital 1 began (Table 3). The prescribing uptake slowly increased from April 2017 with a steady increase in uptake thereafter and there has been further prescribing of sacubitril/valsartan since the completion of this study; 25 patients overall. Prescribers in hospital 2 started prescribing sacubitril/valsartan in July 2016, three months after publication of NICE TA388, after two plateau phases prescribing increased steadily. At the end of the study 52 patients were prescribed sacubitril/valsartan at hospital 2. At hospital 3 the prescribing of sacubitril/valsartan started in February 2016, two months before the NICE TA388 was published. Since September 2016 prescribing has increased and persisted until the end of this study. The NICE resource tool predicted that approximately 404 patients at hospital 1, 253 patients at hospital 2 and 494 patients at hospital 3 would have met the criteria for treatment detailed in NICE TA388 and therefore could have been potential candidates for the treatment of sacubitril/valsartan (Figure 2).

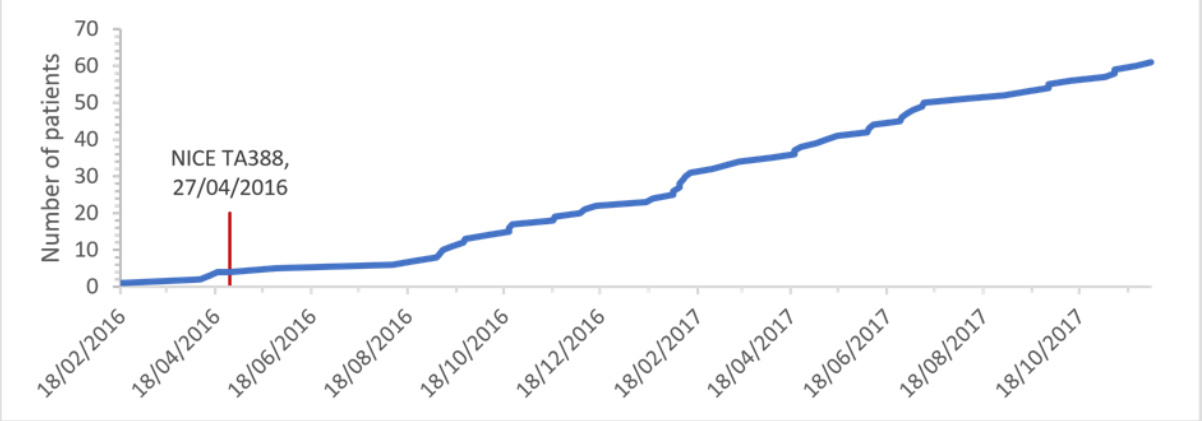
Figure 2 Prescribing uptake onto sacubitril/valsartan at the three hospitals

Prescribing uptake onto sacubitril/valsartan at Hospital 1

Prescribing uptake onto sacubitril/valsartan at Hospital 2



Prescribing uptake onto sacubitril/valsartan at Hospital 3



Discussion

Statement of principal findings

The development of sacubitril/valsartan was preceded by years of research into the pathophysiology of HF. Along with the development of earlier medicines for treatment of HF, for example ACE inhibitors, ARBs and other therapeutic drug classes, this fed directly into the design of this molecule. There is a firm rationale behind the choice of the two molecules that compose Entresto™, which takes advantage of the two different mechanisms of action of valsartan and sacubitril to affect a dual response in treating HF.

The efficacy of sacubitril/valsartan, evidenced in the literature shows a definite benefit in patient outcomes to reduce mortality and re-hospitalisation[17]. It is also proven to be within accepted cost-effectiveness limits (<£20,000 per QALY), despite costing significantly more than the current generic treatment available[17].

At the three Trusts in the study it was found that the overall majority of prescribers (93%) adhered to the three main criteria of NICE guidelines: NYHA functional class of II or above, LVEF of 35% or below, and prior stabilisation of an ACEi or ARB. However, a large difference was observed in the prescribing practices of sacubitril/valsartan therapy between the trusts which could be due to a variety of factors including local delays in implementing NICE guidelines.

There were differences in the three hospitals regarding the time of initiation of the first prescription issued for sacubitril/valsartan and the number of patients prescribed the medication. Explanations for this disparity could be due to hospital prescribing policies differing from trust to trust, and prescribing habits, such as inertia to prescribing a new medication among the prescribers, differing between individuals, as well as knowledge of the medication and its use. This study did not take into account the input of prescribers or hospital policy and the influence of Clinical Commissioning Groups with regards to sacubitril/valsartan so a solid conclusion cannot be drawn. Nevertheless, a qualitative study including interviews with prescribers investigating their knowledge of guidelines and local hospital policies, in addition to their experiences with patients when prescribing sacubitril/valsartan would be important to recommend.

Compared to the estimation using the NICE resource tool, in all hospitals there were substantially fewer patients prescribed sacubitril/valsartan than anticipated. The NICE resource tool predicted prescribing uptakes varying from 253 to 494 patients (404, 6%, $n1_t$=25; 253, 21%, $n2_t$=52; 494, 44%, $n3_t$=218), whereby the trusts only had a total uptake which varied from 25 to 218 patients. Therefore, there is potential to improve prescribing practices and recruiting HF patients which meet the criteria for this new medication. This is particularly important as new findings are emerging from recent studies showing a distinct post-sacubitril/valsartan initiation improvement in HF symptoms and a reduction in subsequent hospitalizations [19], which supports the findings from the PARADIGM-HF study[8].

Regarding the sample of patients included in this study the average age for both men and women was similar, at around 60 years old and around 5% (7/118) of patients were below the age of 40 years. However there was variability in the age of the patients on sacubitril/valsartan at the three hospitals regardless of gender. Statistics from the British Heart Foundation in 2017 showed prevalence of HF to be 0.8% regardless of gender. With earlier research showing the prevalence of heart failure in 2013, was slightly higher in men of all ages than women of all ages 1.22% vs. 0.76% [20, 21]. Furthermore, HF is not common in younger people under 50 years and prevalence and incidence increases with age. Population-based studies have shown that the prevalence of HF is 2.2% and increases from 0.7% in persons aged 45 through 54 years to 8.4% for those aged 75 years or older[22], a similar trend was observed in this patient sample.

In this study the proportion of men with HF prescribed sacubitril/valsartan was greater than women 80% compared to 20% respectively. There are several factors which could influence this proportion, such as women being twice as likely as men to develop HF with preserved ejection fraction (HFpEF) making those women ineligible for sacubitril/valsartan treatment[23]. Literature also shows a gender bias in receiving HF treatments, for example ACE inhibitors and beta blockers. Currently, despite a lack of evidence that ACE inhibitors or beta blockers have any less effect in women, they are less likely to receive such therapies in clinical practice, even after correction for age bias[24]. In addition being stabilised on an ARB or ACE inhibitor before commencing treatment on sacubitril/valsartan is an essential criteria for prescribing, this may have also accounted for the discrepancy in the proportion between male and female patients at the studied hospitals.

In this study the largest proportion of patients prescribed sacubitril/valsartan therapy were White British, 65%, followed by South Asian, 10%, then other White backgrounds, 9%. There is limited information available on a link between ethnicity and HF, while there is more research on ethnicity and cardiovascular disease in general, especially South Asian patients having increased risk of developing coronary heart disease. A recent large UK study including a cohort of more than 1 million patients with cardiovascular disease found an expected substantial predominance of coronary heart disease presentations in South Asians and predominance of stroke presentations in Black patients, but no ethnic differences in presentation with heart failure compared to White patients [25]. Furthermore an American study, found that African Americans were more likely than Hispanic, White and Chinese Americans to develop chronic HF, 4.6 compared to 3.5, 2.4 and 1.0 per 1,000 person years respectively, however it was concluded that this was due to the disparity in the incidence of diabetes and hypertension as well as socioeconomic differences rather than race [26]. Studies investigating ethnic differences in the prescribing and response to sacubitril/valsartan in patients with HF in different ethnic groups would be of interest especially since an abundance of previous evidence has shown ethnic differences in the response to ACE inhibitors and ARBs [27].

Regarding the incidence of side effects the sample size in this study was small and no clear conclusion could be made due to inconsistency in the documentation of side effects in the 3 hospital databases. This could be due to different prioritisation of recording of side effects by the differing trusts. Cough as a main side effect was documented by hospital 3 could be caused by HF or sacubitril/valsartan as well as viral or bacterial infection. Due to most of the patients having

comorbidities, other medications could have contributed to side effects recorded. Furthermore, other side effects documented including light-headedness, dizziness and nausea in one hospital were recorded as presyncopal symptoms or vasovagal symptoms in another hospital which made it difficult to analyse and categorise side effects from the collected data.

Hypotension, fatigue and renal impairment were the main side effects identified among the patient population included in this study. Similar results were reported in a recent pharmacovigilance study in France (including 8845 patients)[28] showing that patients on sacubitril/valsartan had common side effects including hypotension, renal impairment and shortness of breath. The results of this study are in agreement with this large pharmacovigilance study and also with side effects reported from NICE guidelines[18].

Unanswered questions and future research

There are many avenues for the future research on sacubitril/valsartan as this medication is new and its use is emerging within HF patient treatment but there are many gaps in the field, where additional studies could aid in the safe administration of the product. For example, the ongoing trials of its efficacy in HF preserved ejection fraction, chronic kidney disease (CKD) and preventing HF events after MI; PARAGON-HF[29], UK HARP-III [30] and PARADISE-MI[31] respectively, are examples.

This study could be expanded to include UK-HF population and enable comparisons to be made between regions. There is scope to expand further and incorporate partners internationally. A study with a longer duration could be attempted to compare prescribing uptake against the 5-year NICE prediction with the resource tool.

Conclusions

The prescribing of sacubitril/valsartan at the sample trusts generally adhered to NICE guidance, however prescribing rates were lower than expected compared with the predictions from the NICE resource tool. Further investigations into the safety and scope of application of sacubitril/valsartan are required to increase the appropriate prescribing of sacubitril/valsartan; to meet the predicted number of patients who could potentially benefit from this medication in accordance with the NICE resource tool.

Key points

- First multicentre study of sacubitril/valsartan in the West Midlands, investigating prescribing practices and adherence to NICE guideline TA388 [1].
- Study criteria were developed through discussion with Consultants at the West Midland Cardiac Pharmacists Group (WMCPG) and patient and public involvement in education at the University of Birmingham.

- The results add significantly to the limited data regarding prescribing practices of sacubitril/valsartan.
- Relatively limited sample size of 118 patients.
- Documentation differed from Trust to Trust, this influenced data collection.

Reflective questions

What is already known about this subject?

Sacubitril/valsartan is a recently launched combination drug therapy for HF patients that has been shown to reduce mortality and patient hospitalisation based on the PARADIGM-HF clinical study.

What does this study add?

This study adds to the very limited data on sacubitril/valsartan and provides new insight into hospital prescribing practices, patterns and clinical characteristics of patients on sacubitril/valsaratan. Furthermore, this is the first multi-centre study that also compares uptake to the NICE resource tool and NICE clinical guidelines.

How might this impact on clinical practice?

As can be seen from the study prescribing of sacubitril/valsartan was lower than expected despite the clinical benefit mainly reduction in patient hospitalisations and mortality. The study may impact on physicians prescribing habits by providing information of current prescribing and prescriber uptake.

Acknowledgements

The authors would like to thank the hospital trusts involved with this study and also Dr Chris Curtis for his valuable guidance and input into the write-up of this manuscript.

Data statement

The underlying patient datasets that enabled this study are retained by the respective hospitals. All other data and analysis is provided in the manuscript and associated supplementary information.

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Author contributions Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; S Cabdi, Z Jalal, AM Jones, N Khan, N Gill, F Toner. Drafting the work or revising it critically for important intellectual content; S Cabdi, Z. Jalal, AM Jones, M Dorsch, N Gill. Final approval of the version to be published; S Cabdi, Z Jalal, AM Jones, M Dorsch, N Khan, N Gill, F Toner. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved; Z Jalal, AM Jones.

Funding Statement

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Competing interests None declared

Patient consent Not required.

Patient involvement The development of the research question was informed by discussions with an advisory group made of senior clinical pharmacists working in the field of cardiovascular diseases. Patients from Patient and Public Involvement in Education (PPIE) at University of Birmingham were involved in the early design of the study. Results will be disseminated through publication, presentation at conferences and back to the PPIE patients.

Ethics approval This study is approved by the University of Birmingham Ethics Committee and site approval by each participant hospital trust's research and development body. SC was granted honorary status in each hospital trust to enable data processing on-site and supervised by consultants NK, NG and FT respectively.

Supporting information Data collection tool for the retrospective study of the use of sacubitril/valsartan in heart failure (Table 4).

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Table 1 – Demographic Data of all patients included into the study

		Hospital 1 (n_1=20)	Hospital 2 (n_2=37)	Hospital 3 (n_3=61)	Total 3 hospitals
Age [years]	< 40	3	2	2	Mean (n1-3) 63.78
	40 - 50	1	7	2	
	51 - 60	7	10	13	

	61 - 70	6	13	17	Standard deviation (n1-3) 13.27
	> 70	3	5	27	
Gender	Male	15	32	48	
	Female	5	5	13	
Ethnicity					% Total 3 hospitals
	White British	17	23	37	65%
	South Asian	1	2	9	10%
	Mixed White&Black Caribbean	1	2	0	3%
	Black Carribbean	1	3	0	4%
	Black African	0	3	0	3%
	White Other	0	4	7	9%
	Not documented	0	0	7	6%
Comorbidities	Previous Stroke/TIA	1	3	8	
	COPD	3	3	5	
	Hypertension	4	15	31	
	Diabetes	4	15	22	
	VHD	5	1	12	
	Nonvalvular AF	7	10	27	
	Previous Myocardial Infarction	9	10	18	
	CHD	16	29	38	
Baseline	Systolic BP [mmHg]	118±15	126±15	126±21	
average	Diastolic BP [mmHg]	70±11	76±10	77±11	
measurements	Heart rate [beats/min]	71±10	70±10	73±12	
	eGFR [mL/min/1.72]	75±15	68±15	n/a	
	Potassium level	4.4±0.4	4.6±0.5	4.3±0.5	
	Sodium level	138±2	138±2	139±4	
Baseline	Implant. cardioverter-defibrillator	7	19	19	
Medication and Devices	Cardiac resynchronization therapy	4	4	4	
	Pacemaker	0	1	1	
	Beta-blockers	20	36	61	
	Diuretics	16	27	51	

	Mineralocorticoid antagonists	14	28	45
New York Heart Association classification	NYHA I	1	0	0
	NYHA II	13	24	27
	NYHA II - III	0	2	9
	NYHA III	6	10	19
	NYHA III - IV	0	0	4
	NYHA IV	0	1	1
	Unknown	0	0	1
Left Ventricle Ejection Fraction	LVEF <20%	5	12	9
	LVEF 20-30%	6	14	19
	LVEF 31-35%	9	6	17
	LVEF >35%	0	2	2
	Unknown	0	3	14
Prior use of ACE inhibitor or ARB	Candesartan	3	6	7*
	Enalapril	0	0	1
	Lisinopril	0	0	3
	Losartan	2	2	13
	Perindopril	2	16	11
	Ramipril	13	12	27*
	Valsartan	0	1	0
*one patient in hospital 3 was on Ramipril and Candesartan				

Table 2 –Summary of results of the study

		Hospital 1 (n_1=20)	Hospital 2 (n_2=37)	Hospital 3 (n_3=61)
Readmission	Total readmission	1	1	28
	Readmission caused by HF	1	1	15
Discontinuation		0	3	9
Prescriber uptake	Study 10/2017	25	52	218
	NICE Resource tool[1]	404	253	494

[1]NICE Resource tool gives an estimated number of eligible patients for sacubitril/valsartan each year

Table 3 - Number of people eligible for treatment in each of the three trusts provider population, adapted from NICE Resource impact report: Sacubitril/valsartan for treating symptomatic chronic heart failure with reduced ejection fraction (TA388) 2016.

Population	**Proportion (percentage from hospital 1,2,3 respectively)**	**Hospital 1 (2011)**	**Hospital 2 (2014)**	**Hospital 3 (2011)**
Total catchment population	-	847,433a	530,000b	1,037,004a
People with heart failure	0.76%	6,440	4,028	7,881
People with heart failure with reduced ejection fraction	72.00%	4,637	2,900	5,674
People with heart failure with reduced ejection fraction and NYHA class II to III symptoms	71.00%	3,292	2,059	4,029
People with heart failure with reduced ejection fraction and NYHA class II to III symptoms with a left ventricular ejection fraction of 35% or less	59.50%	1,959	1,225	2,397
People with heart failure with reduced ejection fraction and NYHA class II to III symptoms with a left ventricular ejection fraction of 35% or less and taking an ACE inhibitor or ARB	85.95%	1,684	1,053	2,060
People having sacubitril/valsartan from year 2	24.00%	404	253	494

This table is adapted from the NICE Resource Tool for guideline TA388 (NICE, 2016b)
a Value taken from National Clinical Analysis and Specialised Application Team NATCANSAT (2012)
b Value taken from CQC -Care Quality Commission (2014)

Supplementary material

Table -4- Data collection tool for the retrospective study of the use of valsartan/sacubitril in heart failure

Hospital:	Anonymised Patient ID:	Age:
Gender:	Ethnicity:	

Tick the relevant box and/or fill out the information needed under Details.

No.	Questions:	Yes	No	Details:
	NICE Guidelines			
1.	What was the NYHA classification of the patient prior to initiation of Entresto?	-	-	
2.	What was the LVEF classification of the patient prior to initiation of Entresto? (%)	-	-	
	Refer to question 5 for ACE inhibitor/ARB use			
	Patient Medical History			
3.	Does the patient have any comorbidities?			
4.	If so, specify which of the following the patient has:	-	-	
A	Diabetes			
B	Previous Myocardial Infarction (MI)			
C	Non-valvular Atrial Fibrillation (NVAF)			
D	Valvular Heart Disease (VHD)			
E	Previous Stroke or Transient Ishaemic Attack (TIA)			
F	Hypertension			
G	Device e.g. CRT-D/ICD			
H	Coronary Heart Disease (CHD)			
I	Chronic Obstructive Pulmonary Disease (COPD)			
J	Other (Please state)	-	-	
5.	Was the patient on an ACE inhibitor/ARB prior to initiation of Entresto? Document drug and dose			
6.	Was the patient on a Beta-blocker (BB) prior to initiation of Entresto? Document drug and dose			
7.	Was the patient on a diuretic prior to initiation of Entresto? Document drug and dose	-	-	
8.	Was the patient on a Mineralocorticoid Receptor Antagonist (MRA) prior to initiation of Entresto? Document drug and dose			
9.	If the patient wasn't prescribed an MRA, which of the following reasons was the cause:	-	-	

A	Hyperkalaemia			
B	Hypotension			
C	Renal function			
D	Sexual side effects/gynaecomastia			
E	Other (please state)	-	-	
F	No reason stated			
	Entresto Therapy			
10.	Date of initiation of Entresto	-	-	
11.	How long has the patient been on Entresto? Date of initiation to date of audit or date of discontinuation			
12.	Date of discontinuation (if applicable) Document reason and alternative prescribed	-	-	
13.	How did the dose of Entresto change over time? Dose on initiation: date Dose on optimisation: date Dose when stabilised: date	-	-	
14.	What was the NYHA classification of the patient while on Entresto?	-	-	
15.	How many follow-up appointments did the patient have with the HF team?	-	-	
16.	At each point of contact, what was the patient's CrCl (ml/min)? K? Na? BP?	-	-	

Figure (i.e. diagram, illustration, photo)
Click here to access/download;Figure (i.e. diagram, illustration, photo);fig1.docx

Figure 1- Entresto™ (sacubitril/valsartan) combination and active metabolite.

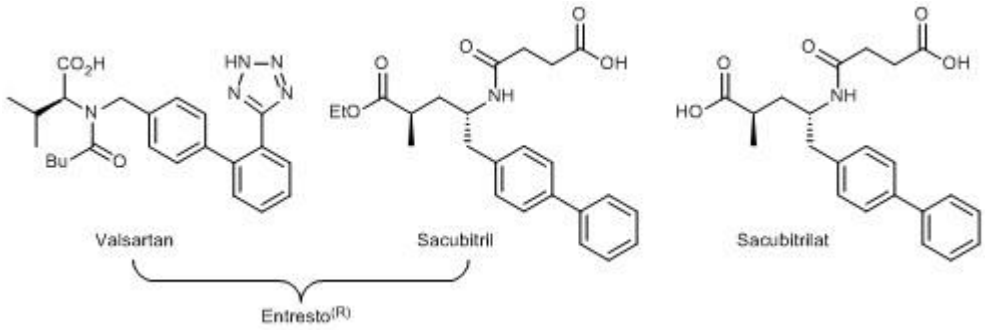
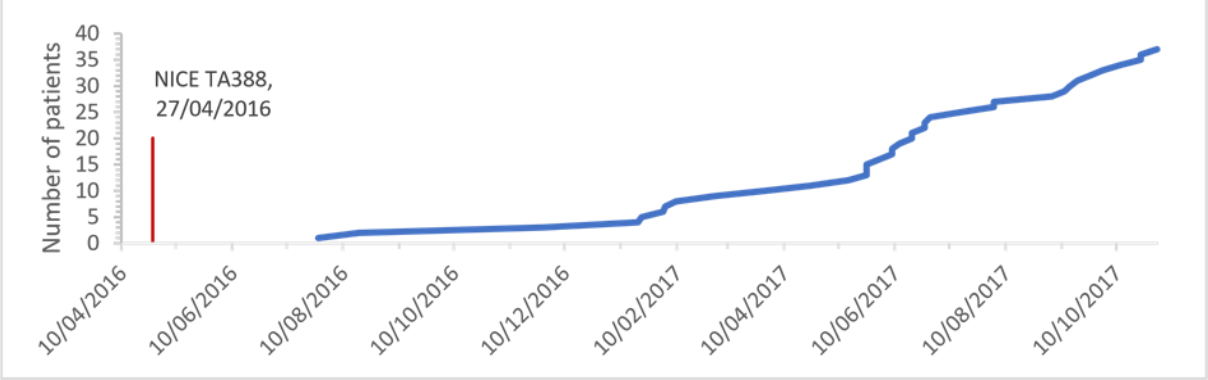


Figure (i.e. diagram, illustration, photo)
Click here to access/download;Figure (i.e. diagram, illustration, photo);fig2.docx

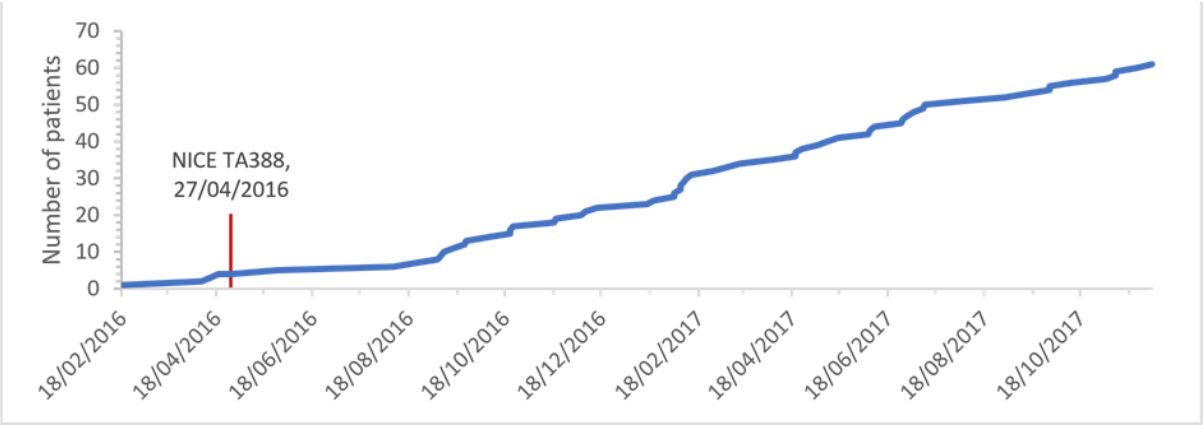
Figure 2 Prescribing uptake onto sacubitril/valsartan at the three hospitals

Prescribing uptake onto sacubitril/valsartan at Hospital 1

Prescribing uptake onto sacubitril/valsartan at Hospital 2



Prescribing uptake onto sacubitril/valsartan at Hospital 3



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Comorbidities	Previous Stroke/TIA	1	3	8	
	COPD	3	3	5	
	Hypertension	4	15	31	
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New York Heart Association classification	NYHA I	1	0	0
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	Perindopril	2	16	11
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	Valsartan	0	1	0
*one patient in hospital 3 was on Ramipril and Candesartan				

Table Click here to access/download;Table;Table 2.docx

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Table 4- Data collection tool for the retrospective study of the use of valsartan/sacubitril in heart failure

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