ORIGINAL RESEARCH ARTICLE

Eligibility of sacubitril–valsartan in a real-world heart failure population: a community-based single-centre study

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Abstract

Aims   This study aims to investigate the eligibility of the Prospective Comparison of Angiotensin Receptor–Neprilysin Inhibitor (ARNI) with ACE inhibitor to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) study to a real-world heart failure population.

Methods and results   Medical records of all heart failure patients living within the catchment area of Umeå University Hospital were reviewed. This district consists of around 150 000 people. Out of 2029 patients with a diagnosis of heart failure, 1924 (95%) had at least one echocardiography performed, and 401 patients had an ejection fraction of ≤35% at their latest examination. The major PARADIGM-HF criteria were applied, and 95 patients fulfilled all enrolment criteria and thus were eligible for sacubitril–valsartan. This corresponds to 5% of the overall heart failure population and 24% of the population with ejection fraction ≤ 35%. The eligible patients were significantly older (73.2 ± 10.3 vs. 63.8 ± 11.5 years), had higher blood pressure (128 ± 17 vs. 122 ± 15 mmHg), had higher heart rate (77 ± 17 vs. 72 ± 12 b.p.m.), and had more atrial fibrillation (51.6% vs. 36.2%) than did the PARADIGM-HF population.

Conclusions   Only 24% of our real-world heart failure and reduced ejection fraction population was eligible for sacubitril–valsartan, and the real-world heart failure and reduced ejection fraction patients were significantly older than the PARADIGM-HF population. The lack of data on a majority of the patients that we see in clinical practice is a real problem, and we are limited to extrapolation of results on a slightly different population. This is difficult to address, but perhaps registry-based randomized clinical trials will help to solve this issue.

Introduction

Heart failure is one of the leading causes of hospital admission and death in elderly people. With a 5 yr survival chance of only 50%, heart failure has a mortality rate similar to that of several cancer diagnoses.[1] Therefore, it is a serious and costly disorder. Standard heart failure therapy is effective and refers to an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB), a beta-blocker, and a mineralocorticoid antagonist.[2] Even though standard

treatment reduces risk of death and heart failure hospitalization by up to 10–37%,[3–9] mortality is high, and many patients suffer from severe symptoms on a daily basis. New and more effective heart failure treatments are needed.

Sacubitril–valsartan, an angiotensin receptor–neprilysin inhibitor, is a new treatment option for heart failure. Sacubitril increases natriuretic peptides, causing vasodilation and diuresis. Valsartan blocks the angiotensin II receptor type 1, reducing vasoconstriction, sodium and water retention, and cardiac hypertrophy. Sacubitril–valsartan was approved by

US Food and Drug Administration (FDA) and European Medicines Agency in 2015, based on the Phase III trial, Prospective Comparison of Angiotensin Receptor–Neprilysin Inhibitor (ARNI) with ACE inhibitor to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF).[10] In PARADIGM-HF, 8442 patients with heart failure and reduced ejection fraction (HFrEF) were randomized to either enalapril or sacubitril–valsartan. Sacubitril–valsartan reduced the primary endpoint cardiovascular death or hospitalizations for heart failure by 20%. The trial was stopped early, after a median follow-up of 27 months, owing to 16% risk reduction in death from any cause. Even though sacubitril–valsartan showed promising results in the PARADIGM-HF trial, it is unknown how applicable the results are to a real-world population.

Similar to most randomized controlled trials (RCTs), PARADIGM-HF used strict enrolment criteria to minimize the risk of confounders, although this strategy reduces the eligibility.[11,12] For example, patients only qualified for randomization if they had stable and symptomatic HFrEF, elevated natriuretic peptide plasma concentration, systolic blood pressure $\geq$ 95 mmHg, and plasma potassium level < 5.4 mmol/L, and tolerated a run-in period of enalapril 20 mg daily and sacubitril–valsartan in target dose.

The baseline characteristics in PARADIGM-HF were comparable with those of other landmark HFrEF trials.[13] However, these characteristics do not correspond to the real-world heart failure population, which is generally older, consists of ~50% women, and suffer from more co-morbidities.[1,14–18] We therefore sought to investigate if the PARADIGM-HF population is a fair representation of a real-world HFrEF population. We will address the following questions:

- What proportion of a real-world heart failure population is eligible for sacubitril–valsartan according to inclusion and exclusion criteria in the PARADIGM-HF trial?
- How comparable is the PARADIGM-HF population to a real-world heart failure population?

Methods

Study population

In this retrospective study, we included all heart failure patients (10th revision of the *International Statistical Classification of Diseases and Related Health Problems* codes I50.X, I42.X, I11.0), living within the catchment area of Umeå University Hospital, Sweden, and experienced at least one contact with the heart centre or department of internal medicine, between January 2010 and March 2016. The hospital is serving a mixed urban and rural population with ~150 000 residents, and the heart centre represents the only cardiology clinic in the area.

Data collection

We manually abstracted data from the hospital's medical records (NCS Cross), between 1 June 2015 and 31 March 2016, according to a standardized protocol. The protocol consisted of 90 variables per patient, comprising medical history, drug therapy, laboratory data, use of cardiac devices, and echocardiography and electrocardiography parameters.

Selection process

To select patients eligible for sacubitril–valsartan, we applied the main PARADIGM-HF inclusion and exclusion criteria: 18 years and older, left ventricular ejection fraction (LVEF) $\leq$ 35%, ACE inhibitor or ARB in target dose (equivalent to enalapril 20 mg daily), N-terminal pro-B-type natriuretic peptide (NT-proBNP) $\geq$ 600 pg/mL, estimated glomerular filtration rate (eGFR) $\geq$ 30 mL/min, systolic blood pressure $\geq$ 95 mmHg, and serum potassium level < 5.4 mmol/L.[13] We used the Cockroft–Gault equation to calculate eGFR.

As PARADIGM-HF initially included patients with LVEF $\leq$ 40% and pretrial use of ACE inhibitor/ARB in half doses (equivalent to at least enalapril 10 mg daily),[10] we performed a second selection process where we applied the same criteria as described in the first selection, except changing LVEF to $\leq$ 40% and ACE inhibitor/ARB to half dose.

The study was performed according to the principles of the Declaration of Helsinki and approved by the local ethics committee (Umeå, registration number 2015-419-31).

Statistical analysis

Normally distributed continuous variables are reported as means with standard deviations and non-normally distributed continuous variables as medians with interquartile range. Categorical variables are described as frequencies with percentages. We analysed group differences in baseline characteristics using Student t-test for continuous variables and χ^2 test for categorical variables. We considered a P-value < 0.05 to be statistically significant, and we performed all analyses with SPSS version 24.

Results

Between January 2010 and March 2016, 3636 patients in total were treated for heart failure, of whom 2029 were alive in March 2016. Out of these, 1924 (95%) had an echocardiography performed, whereof 622 had LVEF $\leq$ 40% and 401 had LVEF $\leq$ 35% at the latest examination.

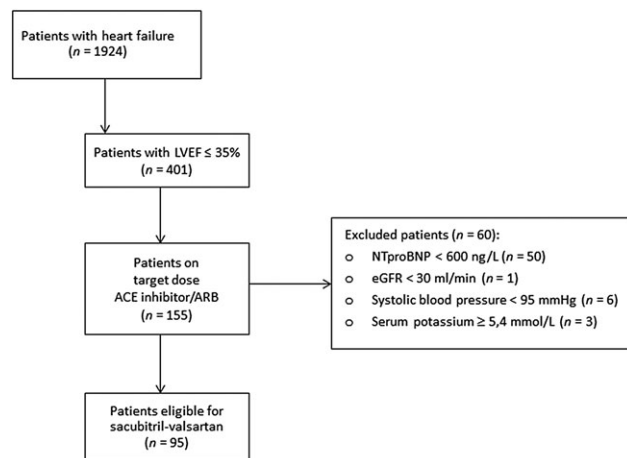We selected patients eligible for sacubitril–valsartan treatment by applying the PARADIGM-HF enrolment criteria

on the Umeå heart failure population (*Figure 1A*). Of the 401 HFrEF patients (LVEF ≤ 35%), 155 patients (39%) were treated with ACE inhibitor/ARB in target dose. We further excluded 60 patients because of reduced levels of NT-proBNP, eGFR, and systolic blood pressure and elevated serum potassium level. Finally, 95 patients fulfilled all indication criteria and were eligible for treatment with sacubitril–valsartan, which corresponds to 24% of the HFrEF

Figure 1 Selection of patients eligible for sacubitril–valsartan in the Umeå heart failure population when applying major inclusion and exclusion criteria from the PARADIGM-HF trial. (A) First selection including LVEF ≤ 35% and ACE inhibitor or ARB in target dose. (B) Second selection including LVEF ≤ 40% and ACE inhibitor or ARB in half dose. In both (A) and (B) the following exclusion criteria were applied; NTproBNP < 600 pg/mL, eGFR < 30 mL/min, systolic blood pressure < 95 mmHg, and serum potassium level ≥ 5.4 mmol/L. ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PARADIGM-HF, Prospective Comparison of Angiotensin Receptor–Neprilysin Inhibitor (ARNI) with ACE inhibitor to Determine Impact on Global Mortality and Morbidity in Heart Failure.

A

B

population (*n* = 401) and 5% of the overall Umeå heart failure population (*n* = 1924). The most common reasons for exclusion were ACE inhibitor/ARB lower than target dose (*n* = 246, 61%) and NT-proBNP < 600 pg/mL (*n* = 50, 12%).
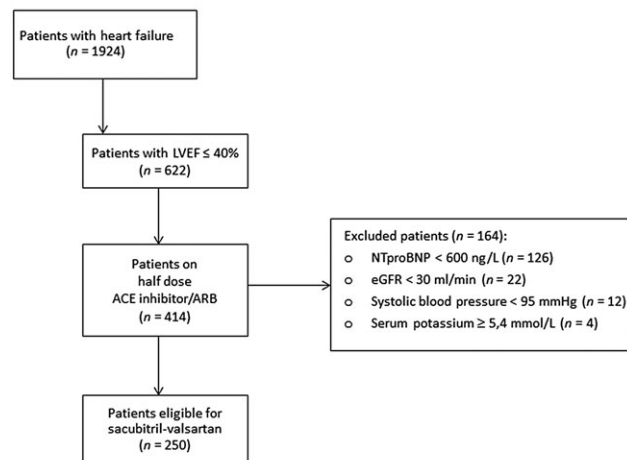
As the entry criteria in PARADIGM-HF were first set to LVEF ≤ 40% and a pre-study dose of ACE inhibitor/ARB equivalent to enalapril 10 mg daily was used, which corresponds to half target dose, we did a second selection process with these criteria (*Figure 1B*). The latest echocardiography showed LVEF ≤ 40% in 622 patients, whereof 414 patients (67%) were treated with ACE inhibitor/ARB in at least half dose. After we had excluded 164 patients owing to NT-proBNP, renal impairment, systolic blood pressure, and potassium level, finally, 250 patients remained eligible for sacubitril–valsartan when applying these alternative criteria. This corresponds to 40% of the HFrEF population (*n* = 622) and 13% of the overall Umeå heart failure population (*n* = 1924).

In *Table 1*, we compare patients' baseline characteristics from the PARADIGM-HF and Umeå cohort. Patients eligible for sacubitril–valsartan in the Umeå population were more likely to be older (73.2 ± 10.3 vs. 63.8 ± 11.5 years, *P* < 0.001) and have higher systolic blood pressure (128 ± 17 vs. 122 ± 15 mmHg, *P* < 0.001) and higher heart rate (77 ± 17 vs. 72 ± 12 b.p.m., *P* < 0.001) than was the PARADIGM-HF population. In the Umeå cohort, more patients had atrial fibrillation (51.6% vs. 36.2%, *P* = 0.002), mineralocorticoid antagonist treatment (70.5% vs. 54.2%, *P* = 0.002), and devices, such as implantable cardioverter–defibrillator (23.3% vs. 14.9%, *P* = 0.04) and cardiac resynchronization therapy (18.9% vs. 7.0%, *P* < 0.001). Compared with the main selection, the 250 eligible patients identified in the second selection process were slightly older (75.6 ± 9.1 vs. 73.2 ± 10.3, *P* = 0.04) but did not differ significantly in other baseline characteristics.

Discussion

Sacubitril–valsartan is a major breakthrough in heart failure treatment that should be used in patients who fulfil the inclusion criteria in the PARADIGM-HF study. We showed that there is a clear group within the heart failure population that should benefit from this treatment. The limited number of eligible patients in the population will probably not present a major burden on health-care costs. Therefore, the fear of unacceptable rise of financial costs for health-care system is probably not valid. However, only a quarter of the patients with HFrEF in a real-world setting clearly fulfil the inclusion criteria in the PARADIGM-HF trial. For the rest of the 75% of the HFrEF population, data are less clear. Expanding the criteria to slightly higher ejection fraction and trying to titrate

Table 1 Comparison of baseline characteristics between the Umeå cohort and the PARADIGM-HF study population

Characteristics[a]	Umeå cohort (n = 95)	PARADIGM-HF (n = 4187)	*P*-value
Age, year	73.2 ± 10.3	63.8 ± 11.5	<0.001
Female sex, no. (%)	15 (15.8)	879 (21.0)	0.27
Systolic blood pressure, mmHg	128 ± 17	122 ± 15	<0.001
Heart rate, b.p.m.	77 ± 17	72 ± 12	<0.001
Body mass index, kg/m^2	28.4 ± 5.8	28.1 ± 5.5	0.62
Serum creatinine, mg/dL[b]	1.09 ± 0.3	1.13 ± 0.3	0.20
Clinical features of heart failure			
Left ventricular ejection fraction, %	29.8 ± 5.4	29.6 ± 6.1	0.72
NT-proBNP (IQR), pg/mL	1681 (1074–3337)	1631 (885–3154)	—[c]
Medical history, no. (%)			
Hypertension	66 (69.5)	2969 (70.9)	0.85
Diabetes	25 (26.3)	1451 (34.7)	0.11
Atrial fibrillation	49 (51.6)	1517 (36.2)	0.002
Myocardial infarction	42 (44.2)	1818 (43.4)	0.96
Pretrial use of ACE inhibitor	65 (68.4)	3266 (78.0)	0.04
Pretrial use of ARB	32 (33.7)	929 (22.2)	0.01
Treatment at randomization, no. (%)			
Beta-blocker	91 (95.8)	3899 (93.1)	0.42
Mineralocorticoid antagonist	67 (70.5)	2271 (54.2)	0.002
Diuretic	64 (67.4)	3363 (80.3)	0.002
Digitalis	17 (17.9)	1223 (29.2)	0.02
Implantable cardioverter–defibrillator[d]	22 (23.2)	623 (14.9)	0.04
Cardiac resynchronization therapy[d]	18 (18.9)	292 (7.0)	<0.001

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; IQR, interquartile range; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PARADIGM-HF, Prospective Comparison of Angiotensin Receptor–Neprilysin Inhibitor (ARNI) with ACE inhibitor to Determine Impact on Global Mortality and Morbidity in Heart Failure
[a]Plus–minus values are means ± SD. Statistical significance level *P* < 0.05.
[b]To convert the values for creatinine to micromoles per litre, multiply by 88.4.
[c]Standard deviation is missing.
[d]Including patients with cardiac resynchronization therapy defibrillator.

patients with only half dose ACE inhibitor/ARB, we still end up with only 250 patients.

This study highlights the central problem of how valid clinical trials are to real-world patients. Clinical trials use strict inclusion and exclusion criteria to increase the chance of showing significant results with a smaller number of patients. This approach was also used in PARADIGM-HF with 20 key exclusion criteria, in addition to the already strict entry criteria.[19] Real-world patients rarely fit into those tight frames,[1,14–18] and we have 75% of our HFrEF population who does not meet the entry criteria, but we still have to give them the best treatment possible. Previous studies have shown that between 10% and 66% of real-world patients managed to fulfil all enrolment criteria from heart failure RCTs.[15,17] A recent study applying the strict PARADIGM-HF main criteria on a heart failure clinic showed that 21% of a HFrEF population was eligible for sacubitril–valsartan.[20] This is similar to the experience from our clinic and confirms the low fraction eligible for sacubitril–valsartan.

Based on our results, the main validity issues of the PARADIGM-HF trial seem to be the LVEF level and ACE inhibitor/ARB doses. We think that LVEF ≤ 35% appears to be too strict, considering that the definition of HFrEF includes LVEF < 40%[2] and that 80% of our patients were excluded in the selection process when applying LVEF ≤ 35% to the overall heart failure population (*Figure 1A*). Further, PARADIGM-

HF only randomized patients who tolerated up-titration of enalapril and sacubitril–valsartan to target doses. This study design ensured study performance with target doses for each drug and reduced study dropout rate. With our second selection process, with LVEF ≤ 40% and ACE inhibitor/ARB in at least half dose (*Figure 1B*), 40% of the patients were eligible for sacubitril–valsartan instead of only 24% in the stricter main selection. Provided that results shown in PARADIGM-HF would persist, we conclude that using less strict criteria, and hence have the opportunity to prescribe sacubitril–valsartan to 40% of a real-world HFrEF population instead of only 24%, would be more appropriate for a landmark study like PARADIGM-HF. However, it is unclear how well a real-world population who has been under up-titration once but does not reach ACE inhibitor/ARB target doses tolerates a second attempt of up-titration.

When we strictly applied the target ACE inhibitor/ARB dose criteria in the main selection process, we had a 61% dropout in the Umeå cohort, which shows that reaching target doses is difficult in an unselected heart failure population. Even in clinical trials, this is problematic; e.g. in the CHARM-Alternative study, 59% of the candesartan group reached target dose.[4] In the PARADIGM-HF trial, 12% of the patients withdrew during the run-in phase owing to adverse events of enalapril or sacubitril–valsartan.[10] A previous study from the Swedish Heart Failure Registry showed

that ~45% of the patients had target dose of ACE inhibitors/ARB and beta-blockers, which is in line with our 39%.[21] Hence, we cannot expect that ACE inhibitor/ARB target dose can be reached with all patients, but before considering sacubitril–valsartan, it is central to try to up-titrate standard therapy as much as possible. It would be of great interest for additional studies to investigate why target doses cannot be reached in more heart failure patients.

Focusing on the overall heart failure population of 1924 patients, only 95 patients (5%) fulfilled all enrolment criteria in the PARADIGM-HF trial. Similar results were shown in a previous study, where 7% of the total heart failure population in a single-centre setting fulfilled the PARADIGM-HF criteria.[20] This highlights the need for studies in heart failure with ejection fraction > 40%.

By comparing patient characteristics, we showed that the HFrEF Umeå cohort was nearly 10 years older than the PARADIGM-HF population. More patients in the Umeå cohort also suffered from elevated systolic blood pressure and atrial fibrillation, probably a consequence of the higher mean age. Likewise, the higher heart rate among the Umeå patients can probably be explained by the increased prevalence of atrial fibrillation. Looking at other recent major heart failure studies, we can easily observe that the population is younger than our population. The SHIFT study had a mean age of 60.4 years,[22] and the ATMOSPHERE study had a mean age of 63.3 years.[23] Overall, few clinical trials include persons > 80 years,[18,24,25] and there is a general problem with clinical studies where patients need to be selected for appropriateness by the individual investigator. This leads to a higher threshold to include fragile patients with co-morbidities who are not as mobile or who are believed to have difficulties fulfilling the requirements of a clinical trial. This can probably explain the age difference between the PARADIGM-HF population and the Umeå cohort formally eligible for the trial.

Further, a retrospective subgroup analysis of the PARADIGM-HF study has shown that sacubitril–valsartan was in favour of enalapril across age categories.[26] Nevertheless, with the age difference between eligible real-world HFrEF patients and the PARADIGM-HF study, one cannot exclude the hypothesis that frail patients were chosen as study subjects to a lesser degree. Frailty increases with age, and it is still unknown how this can impact the drug pharmacodynamics. In addition, heart failure treatment in elderly people is often complicated by age-related cardiovascular changes, polypharmacy, and multi-morbidity.[27] It is quite possible that if the PARADIGM-HF population had been older, the absolute effects would have been greater, reducing the number needed to treat, as older patients in general have a higher mortality risk.

Both FDA and European Medicines Agency have approved sacubitril–valsartan on a wider indication than have

the PARADIGM-HF trial inclusion criteria. This was, e.g. shown in a real-world study where 149 of 210 (71%) hospitalized HFrEF patients meet the FDA criteria for sacubitril–valsartan but only 54 of 210 (26%) patients fulfilled the PARADIGM-HF criteria.[28] To improve the external validity in RCTs, patients who represent the real-world population need to be included to a higher extent. Other study designs, such as registry-based randomized trials or observational studies on real-world patients, may be desirable to complement RCTs and increase eligibility. By using registry-based studies to a higher extent, it might be possible to increase the knowledge of novel drugs effect and safety in elderly patients before they are approved for an unselected and often more fragile population. In the sacubitril–valsartan case, it will be essential to perform real-life (Phase IV) studies to find out how the heart failure patients we meet in clinical practice actually respond.

Limitations

The single-centre study design can limit the generalizability of our results; in the meantime, our hospital represents the only cardiology clinic in the community, which enabled us to study the total heart failure population within the Umeå hospital region and consequently include patients irrespective of renal function, cognitive function, and other co-morbidities that are often excluded in RCTs.

Medical record-based data have limited ability to address explanatory factors, and sometimes, data were incomplete. To minimize this, we only collected parameters when patients were in stable heart failure condition and used the journal entry closest to index or follow-up date.

New York Heart Association functional class information was not available from medical records, which could have excluded some additional patients in our study population if said information was available. On the other hand, PARADIGM-HF included patients with New York Heart Association Functional Class II–IV, which most of our patients fulfilled.

The statistical analysis for comparing NT-proBNP between the Umeå and PARADIGM-HF population could not be performed owing to no access to original data from the Phase III trial.

We used the *International Statistical Classification of Diseases and Related Health Problems* codes to identify patients with heart failure in hospital medical record system and have not validated the heart failure diagnosis on patients with ejection fraction > 50% or where echocardiography was missing. This means that the percentage of patients in the total heart failure population eligible for sacubitril–valsartan is slightly higher.

Conclusions

Only 24% of our real-world HFrEF population was eligible for sacubitril–valsartan, and the real-world HFrEF patients were significantly older than the PARADIGM-HF population. The lack of data on a majority of the patients that we see in clinical practice is a real problem, and we are limited to extrapolation of results on a slightly different population. This is difficult to address, but perhaps registry-based randomized clinical trials will help to solve this issue.

Conflict of interest

Krister Lindmark has received lecture grants from Novartis. Helena Norberg and Ellinor Bergdahl declare that they have no conflict of interest.

Funding

References

1. Zarrinkoub R, Wettermark B, Wandell P, Mejhert M, Szulkin R, Ljunggren G, Kahan T. The epidemiology of heart failure, based on data for 2.1 million inhabitants in Sweden. *Eur J Heart Fail* 2013; **15**: 995–1002.

2. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, Gonzalez-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GM, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2016; **37**: 2129–2200.

3. SOLVD Investigators, Yusuf S, Pitt B, Davis CE, Hood WB, Cohn JN. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *N Engl J Med* 1991; **325**: 293–302.

4. Granger CB, McMurray JJ, Yusuf S, Held P, Michelson EL, Olofsson B, Ostergren J, Pfeffer MA, Swedberg K. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the CHARM-Alternative trial. *Lancet* 2003; **362**: 772–776.

5. Konstam MA, Neaton JD, Dickstein K, Drexler H, Komajda M, Martinez FA, Riegger GA, Malbecq W, Smith RD, Guptha S, Poole-Wilson PA. Effects of high-dose versus low-dose losartan on clinical outcomes in patients with heart failure (HEAAL study): a randomised, double-blind trial. *Lancet* 2009; **374**: 1840–1848.

6. Packer M, Fowler MB, Roecker EB, Coats AJ, Katus HA, Krum H, Mohacsi P, Rouleau JL, Tendera M, Staiger C, Holcslaw TL, Amann-Zalan I, DeMets DL. Effect of carvedilol on the morbidity of patients with severe chronic heart failure: results of the carvedilol prospective randomized cumulative survival (COPERNICUS) study. *Circulation* 2002; **106**: 2194–2199.

7. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. *Lancet* 1999; **353**: 9–13.

8. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, Palensky J, Wittes J. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. *N Engl J Med* 1999; **341**: 709–717.

9. Zannad F, McMurray JJ, Krum H, van Veldhuisen DJ, Swedberg K, Shi H, Vincent J, Pocock SJ, Pitt B. Eplerenone in patients with systolic heart failure and mild symptoms. *N Engl J Med* 2011; **364**: 11–21.

10. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau JL, Shi VC, Solomon SD, Swedberg K, Zile MR, Investigators P-H, Committees. Angiotensin–neprilysin inhibition versus enalapril in heart failure. *N Engl J Med* 2014; **371**: 993–1004.

11. Yandrapalli S, Aronow WS, Mondal P, Chabbott DR. Limitations of sacubitril/valsartan in the management of heart failure. *Am J Ther* 2017; **24**: e234–e239.

12. Vaduganathan M, Desai AS. Angiotensin–neprilysin inhibition as a paradigm for all? *Curr Cardiol Rep* 2016; **18**: 115.

13. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz M, Rizkala AR, Rouleau JL, Shi VC, Solomon SD, Swedberg K, Zile MR, Investigators P-HC. Baseline characteristics and treatment of patients in prospective comparison of ARNI with ACEI to determine impact on global mortality and morbidity in heart failure trial (PARADIGM-HF). *Eur J Heart Fail* 2014; **16**: 817–825.

14. Maggioni AP, Orso F, Calabria S, Rossi E, Cinconze E, Baldasseroni S, Martini N. The real-world evidence of heart failure: findings from 41 413 patients of the ARNO database. *Eur J Heart Fail* 2016; **18**: 402–410.

15. Masoudi FA, Havranek EP, Wolfe P, Gross CP, Rathore SS, Steiner JF, Ordin DL, Krumholz HM. Most hospitalized older persons do not meet the enrollment criteria for clinical trials in heart failure. *Am Heart J* 2003; **146**: 250–257.

16. Hernandez AF, Mi X, Hammill BG, Hammill SC, Heidenreich PA, Masoudi FA, Qualls LG, Peterson ED, Fonarow GC, Curtis LH. Associations between aldosterone antagonist therapy and risks of mortality and readmission among patients with heart failure and reduced ejection fraction. *JAMA* 2012; **308**: 2097–2107.

17. Kennedy-Martin T, Curtis S, Faries D, Robinson S, Johnston J. A literature review on the representativeness of randomized controlled trial samples and implications for the external validity of trial results. *Trials* 2015; **16**: 495.

18. Lazzarini V, Mentz RJ, Fiuzat M, Metra M, O'Connor CM. Heart failure in elderly patients: distinctive features and unresolved issues. *Eur J Heart Fail* 2013; **15**: 717–723.

19. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau J, Shi VC, Solomon SD, Swedberg K, Zile MR, Committees P-H, Investigators. Dual angiotensin receptor and neprilysin inhibition as an alternative to angiotensin-converting enzyme inhibition in patients with chronic systolic heart failure: rationale for and design of the Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial (PARADIGM-HF). *Eur J Heart Fail* 2013; **15**: 1062–1073.

20. Pellicori P, Urbinati A, Shah P, MacNamara A, Kazmi S, Dierckx R, Zhang J, Cleland JGF, Clark AL. What proportion of patients with chronic heart failure are eligible for sacubitril–valsartan? *Eur J Heart Fail* 2017; **19**: 768–778.

21. Thorvaldsen T, Benson L, Dahlstrom U, Edner M, Lund LH. Use of evidence-based therapy and survival in heart failure in Sweden 2003–2012. *Eur J Heart Fail* 2016; **18**: 503–511.

22. Swedberg K, Komajda M, Böhm M, Borer JS, Ford I, Dubost-Brama A, Lerebours G, Tavazzi L. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. *The Lancet* 2010; **376**: 875–885.

23. McMurray JJ, Krum H, Abraham WT, Dickstein K, Kober LV, Desai AS, Solomon SD, Greenlaw N, Ali MA, Chiang Y, Shao Q, Tarnesby G, Massie BM. Aliskiren, enalapril, or aliskiren and enalapril in heart failure. *N Engl J Med* 2016; **374**: 1521–1532.

24. Cherubini A, Oristrell J, Pla X, Ruggiero C, Ferretti R, Diestre G, Clarfield AM, Crome P, Hertogh C, Lesauskaite V, Prada GI, Szczerbinska K, Topinkova E, Sinclair-Cohen J, Edbrooke D, Mills GH. The persistent exclusion of older patients from ongoing clinical trials regarding heart failure. *Arch Intern Med* 2011; **171**: 550–556.

25. Konrat C, Boutron I, Trinquart L, Auleley GR, Ricordeau P, Ravaud P. Underrepresentation of elderly people in randomised controlled trials. The example of trials of 4 widely prescribed drugs. *PloS one* 2012; **7**: e33559.

26. Jhund PS, Fu M, Bayram E, Chen CH, Negrusz-Kawecka M, Rosenthal A, Desai AS, Lefkowitz MP, Rizkala AR, Rouleau JL, Shi VC, Solomon SD, Swedberg K, Zile MR, McMurray JJ, Packer M. Efficacy and safety of LCZ696 (sacubitril–valsartan) according to age: insights from PARADIGM-HF. *Eur Heart J* 2015; **36**: 2576–2584.

27. Forman DE, Ahmed A, Fleg JL. Heart failure in very old adults. *Curr Heart Fail Rep* 2013; **10**: 387–400.

28. Perez AL, Kittipibul V, Tang WHW, Starling RC. Patients not meeting PARADIGM-HF enrollment criteria are eligible for sacubitril/valsartan on the basis of FDA approval: the need to close the gap. *J Am Coll Cardiol HF* 2017; **5**: 460–463.