

What proportion of patients with chronic heart failure is eligible for sacubitril-valsartan?

Short title:- Eligibility for Sacubitril-Valsartan in Heart Failure

Word count: abstract 250; text: 4226. Number of references: 24.

*Pierpaolo Pellicori MD, FESC, *Alessia Urbinati MD, *Parin Shah, *Alexandra MacNamara, *Syed Kazmi, *Riet Dierckx, FESC, *Jufen Zhang, PhD, *#John GF Cleland MD, FRCP, FESC, FACC, *Andrew L Clark MA, MD, FRCP

*Department of Cardiology, Castle Hill Hospital, Hull York Medical School (at University of Hull), Kingston upon Hull, HU16 5JQ, UK

#National Heart & Lung Institute and National Institute of Health Research
Cardiovascular Biomedical Research Unit, Royal Brompton & Harefield Hospitals,
Imperial College, London

Corresponding author: Dr Pierpaolo Pellicori

Department of Cardiology, Hull York Medical School, Hull and East Yorkshire
Medical Research and Teaching Centre, Castle Hill Hospital, Cottingham, Kingston
upon Hull, HU16 5JQ, UK

Tel: + 44 1482 461811; Fax: +44 1482 461779

Email: pierpaolo.pellicori@hey.nhs.uk

Conflict of interest: The University of Hull has received research grants from Novartis and ALC and JGFC have received honoraria for advisory boards and lectures. The other authors have no conflict of interest to disclose.

Keywords: Sacubitril-Valsartan, LCZ696, chronic heart failure, PARADIGM-HF, eligibility.

Abstract

Background: The PARADIGM-HF trial suggested that sacubitril-valsartan, an angiotensin II receptor blocker (ARB)-neprilysin inhibitor, is more effective than enalapril for some patients with heart failure (HF). It is uncertain what proportion of patients with HF would be eligible to sacubitril-valsartan in clinical practice.

Methods: Between 2001 and 2014, 6,131 patients consecutively referred to a community heart failure clinic with suspected HF were assessed. The criteria required to enter the randomized phase of PARADIGM-HF, including symptoms, amino-terminal pro-brain natriuretic peptide (NTproBNP) and current treatment with or without target doses of angiotensin-converting-enzyme inhibitors (ACE-I) or ARB, were applied to identify the proportion of patients eligible for sacubitril-valsartan. Recognizing the diversity of clinical opinion and guidelines recommendations concerning this issue, entry criteria were applied singly and in combination.

Results: Of 1,396 patients with reduced left ventricular ejection fraction (HFrEF) and contemporary measurement of NTproBNP, 379 were on target-doses of ACE-I or ARB at their initial visit and of these 172 (45%) fulfilled the key entry criteria for the PARADIGM-HF trial. Lack of symptoms (32%) and NTproBNP <600 ng/l (49%) were common reasons for failure to fulfil criteria. A further 122 patients became eligible during follow-up (N=294, 21%). However, if background medication and doses were ignored, then 701 (51%) were eligible initially and a further 137 became eligible during follow-up.

Conclusions: Of patients referred to a clinic such as ours, only 21% fulfilled the PARADIGM-HF randomisation criteria, on which the ESC guidelines are based; this proportion rises to 60% if background medication is ignored.

Introduction

The treatment of chronic heart failure due to reduced left ventricular ejection fraction (HFrEF) with angiotensin-converting-enzyme inhibitors (ACE-I) is well established; for those who are unable to take ACE-I, angiotensin receptor blockers (ARBs) are an alternative (1). Beta-blockers and mineralocorticoid receptor antagonists also comprise part of standard “triple therapy” (1). Recently a new class of agent, angiotensin receptor blocker-neprilysin inhibitors (ARNI), has been developed as an alternative to ACE-I or ARB. In the PARADIGM-HF trial, patients with HFrEF assigned to sacubitril-valsartan (LCZ696), the first compound in this new class, had a substantially lower rate of hospitalization for heart failure and mortality compared to those assigned to enalapril (2, 3). However, patients were only eligible for randomisation if they were stable, symptomatic, had an increased plasma concentration of natriuretic peptide, a systolic blood pressure ≥ 100 mmHg and were able to tolerate both guideline-recommended doses of ACE-I (10 mg enalapril twice daily) and subsequently a target dose of sacubitril-valsartan (200 mg bid) during a run-in period.

As a consequence of the PARADIGM-HF results, the recently updated European Society of Cardiology (ESC)-HF guidelines recommend sacubitril-valsartan as a replacement for an ACE-I only for patients similar to those randomized. Accordingly, we applied the entry criteria for the randomized phase of PARADIGM-HF to unselected patients referred to a community-based heart failure clinic to find out what proportion was appropriate for sacubitril-valsartan. Criteria were applied singly and in combination, recognizing the diversity of clinical opinion about how to apply the guidelines as well as differences amongst guidelines.

Methods

Study Population

Between 2001 and 2014, consecutive referrals to a local hospital clinic, from both primary and secondary care physicians, were enrolled at a single clinic serving a local population of about 500,000 people (The Hull LifeLab). Patients were consented for the use of their medical information prior to investigation. Some patients had no prior diagnosis of heart failure and were treatment naive, therefore requiring initiation of guideline-recommended therapy; others had a pre-existing diagnosis of heart failure and had already been initiated on treatment that might, however, require optimisation.

Patients were reviewed by heart failure specialist nurses and doctors at regular intervals, usually at 4 and 12 months, and then annually, unless an appointment was requested sooner by the patient, physician or specialist nurse. Information on demography, symptoms & signs, haematology and biochemistry profiles (including amino-terminal pro-B-type natriuretic peptide (NTproBNP), electrocardiograms (ECGs) and echocardiograms were systematically recorded at each time-point in a dedicated electronic health record stored on a secure NHS server. Titration of treatment was coordinated by the clinic but often implemented by community heart failure nurses or general practitioners.

For the present analysis, we focused only on patients with heart failure who had a baseline echocardiographic left ventricular ejection fraction (LVEF) $\leq 40\%$ (or moderate, or severe, left ventricular systolic dysfunction by visual estimation if LVEF could not be calculated) and a contemporary measurement of plasma NT-proBNP. We used data from the initial assessment and the 4 and 12 month follow-up visits, at which time we expected titration of medication to be complete.

In PARADIGM-HF, patients had to fulfil selection criteria for both screening and randomization but symptom, natriuretic peptide and LVEF criteria only had to be fulfilled at screening and target doses of ACE-I/ARB only had to be fulfilled prior to randomization. The ESC Guidelines use five criteria to recommend eligibility for sacubitril-valsartan; symptoms, natriuretic peptide and LVEF, estimated glomerular filtration rate (eGFR) (which was measured both at screening and randomization) and ACE-I/ARB dose. We adopted a similar mixed approach to eligibility but also report how each individual criterion affected eligibility criteria.

Patients were classified as being “on target dose”, or “not on target dose” of ACE-I or ARB (using the criteria for entering the randomised phase of PARADIGM-HF, consistent with ESC guidelines (i.e., enalapril 20 mg daily, or equivalent; Table 1) (2). In line with eligibility to enter the screening phase of PARADIGM-HF and ESC guidelines, patients who were either asymptomatic (NYHA Class I) or did not have HF_rEF or an elevated NT-proBNP were excluded. PARADIGM-HF allowed inclusion with values of >600ng/L or 400-600ng/L if the patient had been hospitalized for heart failure in the previous year. We did not have such data for this analysis and therefore show data for NT-proBNP using both thresholds. The hospitalization criterion may change during follow-up in clinical practice and therefore it is appropriate to show the more liberal criterion of 400ng/L even in the absence of hospitalization data. Other exclusion criteria at screening were simultaneous prescription of both ACE-I and ARB; systolic blood pressure <100 mmHg; eGFR <30 mL/min/1.73m²; serum potassium >5.2 mmol/L; significant aortic or mitral valve disease; and significant liver disease (see supplementary table 1 for more detailed inclusion and exclusion criteria). We defined “future potential candidates” as those not on target ACE-I or ARB, who might fulfil criteria for eligibility if they were on target doses.

Patients qualifying for randomization had to meet slightly different cut-offs for systolic blood pressure (SBP ≥ 95 mmHg) and serum potassium (≤ 5.4 mmol/L) than those used at screening visit. We therefore also report the proportion of patients meeting these criteria.

We also assessed how many patients might be eligible for sacubitril-valsartan assuming that it might be given regardless of background therapy, including beta-blockers and/or ACE-I or ARB, and regardless of plasma NT-proBNP. We also report the proportion of patients taking doses of ACE-I/ARB required to enter the screening phase (equivalent to 10 mg/day of enalapril) who were otherwise eligible for sacubitril-valsartan.

Echocardiograms and measurements of NT-proBNP, potassium and creatinine were not always repeated at follow-up in which case the most recent test result was used.

For patients not on target dose of ACE-I or ARB at twelve months, medical records were reviewed by three doctors to try to identify reasons for failed up-titration.

The study conformed to the principles outlined in the Declaration of Helsinki and was approved by relevant ethical bodies. All subjects gave their written informed consent for their data to be used for research.

Statistical analysis

Categorical data are presented as number and percentages; normally distributed continuous data as mean \pm standard deviation (SD) and non-normally distributed continuous variables as median and interquartile range (IQR). One-way ANOVA and Kruskal-Wallis tests were used to compare continuous variables between groups depending on the normality of the distribution, and the chi-squared test was used for categorical variables. All analyses were

performed using SPSS (v.22) software. A 2-sided P value < 0.05 was considered statistically significant.

Results

All patients at baseline assessment

Of 6,131 consecutive referrals with suspected heart failure between 2001 and 2014, the diagnosis was confirmed in 3,637, of whom 1,980 had a reduced LVEF (HFrEF). Data were incomplete for 584 patients, mostly because of missing measurements of plasma NTproBNP (Supplementary figure 1), leaving 1,396 patients with HFrEF and a contemporaneous measurement of NTproBNP; of these, 379 (27%) were already on target dose of ACE-I or ARB (Table 2, Figure 1).

Patients on target ACE-I or ARB dose at baseline

Of 379 patients (27%) on target dose of ACE-I or ARB at baseline, just under half (N=172, 45%; 12% of the overall population) fulfilled criteria for sacubitril-valsartan. If the criteria for entering the randomisation phase of PARADIGM-HF are used to define the patient group ($K \leq 5.4$ mmol/L and $SBP \geq 95$ mmHg), then a further 16 patients would have been eligible for sacubitril-valsartan (8 patients had SBP 95-99 mmHg, but 3 had other contraindications, and 15 patients had $K=5.3-5.4$ mmol/L, of whom 4 had other contraindications).

Lack of limiting symptoms (32%) and plasma NTproBNP <600 ng/l (49%) were the commonest reasons for failing to fulfil eligibility criteria; 28% failed for two or more reasons.

Patient characteristics are summarised in table 2.

Patients fulfilling the criteria for sacubitril-valsartan were older, had more clinical signs of congestion, were prescribed higher doses of loop diuretics, had larger left atrial diameter, had a higher heart rate and were less likely to be in sinus rhythm.

Patients not on target ACE-I or ARB dose at baseline

Of 1,017 patients not on target dose of ACE-I or ARB at baseline, 529 (52%) were considered future candidates (38% of the overall population) for sacubitril-valsartan (table 2) if titration of ACE-I/ARB was successful. Of the 529, 178 were on $\geq 50\%$ of target doses of ACE-I or ARB, 351 were taking $< 50\%$ of target dose or were not prescribed these medicines. Those considered future potential candidate were older, more likely to be women, had more peripheral oedema, worse renal function, a higher heart rate and were more likely to be in atrial fibrillation.

Amongst the 488 not thought to be future candidates, absence of limiting symptoms (30%), plasma NTproBNP < 600 ng/l (33%), systolic blood pressure < 100 mmHg (20%) and eGFR < 30 mL/min/1.73m² (16%) were the commonest reasons for classifying the patients as unlikely to be eligible for sacubitril-valsartan even if ACE-I/ARB could be titrated; 25% of patients were excluded for two or more criteria.

Four month assessment

Between the initial and four month assessments, 97 patients died, and 147 did not attend their scheduled visit. Of 1152 who attended, 446 (47%) patients were on target doses of ACE-I/ARB but only 149 fulfilled the eligibility criteria for sacubitril-valsartan (Table 3). Of the 863 patients who had an echo at the 4 month visit, 211 (24%) had an improved LVEF to $> 40\%$. Recovery in LVEF to $> 40\%$ (N=94; 26% of the 355 with an updated echocardiogram;

we assumed LVEF had not changed in 91 patients who had no repeat echocardiogram), lack of limiting symptoms (36%) and plasma NTproBNP <600 ng/l (49%) were the commonest reasons for classifying the patients as ineligible for sacubitril-valsartan; 44% were excluded for two or more reasons.

When we applied the SBP and K criteria used for the randomised phase, the number of patients eligible at this visit increased to 166 (13 patients had SBP 95-99 mmHg, but 5 had other contraindications, and 12 patients had K= 5.3-5.4 mmol/L, of whom 3 had other contraindications).

Patients not on target ACE-I or ARB dose at four month assessment

Of the 706 patients not on target dose of ACE-I or ARB at 4 month follow-up, 278 were still considered to be potential candidates for sacubitril-valsartan (Table 2 supplementary). Absence of limiting symptoms (27%), NTproBNP <600 ng/l (36%), recovery in LVEF to >40% (n=117; 23% of the 508 patients with an updated echocardiogram) and low systolic blood pressure (17%) were other common reasons for not fulfilling criteria for sacubitril-valsartan.

Twelve-month assessment

One hundred and sixty two patients died prior to the 12-month assessment and 196 failed to attend. Of the 979 patients who had an echo either at the 4 month (N=276 carried forward) or 12-month visit (N=703), 304 (31%) had improved their LVEF to >40%, including 6 patients who died after 4 months and 18 who did not attend. Of 1,038 patients who attended, 453 (44%) were on target doses of ACE-I or ARB.

Of the 453 patients titrated to target doses of ACE-I or ARB, only 127 (28%) fulfilled the criteria for sacubitril-valsartan (Table 3).

Recovery in LVEF to >40% (N=134), lack of limiting symptoms (35%) and plasma NTproBNP <600 ng/l (52%) were the commonest reasons for classifying the patients as ineligible for sacubitril-valsartan; 47% were excluded for two or more reasons.

Of the 585 patients not on target dose of ACE-I or ARB at the 12 month follow-up visit, 192 (33%) were still considered to be potential candidates for sacubitril-valsartan (Table 3 supplementary). Absence of limiting symptoms (30%), NTproBNP <600 ng/l (41%), recovery in LVEF to >40% (n=146) and low systolic blood pressure (15%) were other common reasons for failing to meet criteria for sacubitril-valsartan.

When the SBP and K criteria for the randomisation phase were applied, the number of patients eligible at this visit increased from 127 to 150 (18 patients had SBP 95-99 mmHg, but 2 had other contraindications, and 8 patients had K= 5.3-5.4 mmol/L, of whom 1 had other contraindications). Thus, there would thus have been 340 (24%), rather than 294 (21%) patients with HFrEF eligible for sacubitril-valsartan.

Missing up-titration

Overall, 625 (45%) patients achieved target doses of ACE-I/ARB on at least one occasion, compared to 27% at the initial visit. Of the 585 not on target ACE-I/ARB at the 12 month visit, there was no obvious reason for failure to up-titrate in 271 cases (46%); up titration was

still ongoing in 100 cases (17%) or had been prevented by symptomatic hypotension (12%) or worsening renal function (12%) (Figure 2).

All patients taking at least 50% of target ACE-I or ARB dose.

Further analysis was done in order to evaluate if, and how, a lower dose of ACE-I/ARB (equivalent to 50% of target dose of enalapril, as required for entry into the PARADIGM-HF trial, rather than the target dose required for the randomization phase of the PARADIGM-HF (2)), would have affected the proportion of patients with HFrEF eligible for sacubitril-valsartan. Of patients prescribed at least 50% of target ACE-I or ARB dose, 350 (25%) patients fulfilled criteria for sacubitril-valsartan at baseline, rising to 504 (36% of surviving attenders) at 4 months and 594 (43% of surviving attenders) by 12 months.

All patients regardless of background therapy and natriuretic peptide plasma levels.

If criteria for eligibility were extended to all 1,396 patients regardless of background treatment, 701 (50%) were potentially eligible for sacubitril-valsartan at baseline (figure 3). During follow-up, the overall number of patients eligible for sacubitril-valsartan decreased, mainly due to improvement in symptoms, LVEF and reductions in NT-proBNP. Ignoring background medication, 838 (60%) unique patients might have been eligible for sacubitril-valsartan on at least one visit.

If neither NTproBNP nor ACE-I/ARB were considered as criteria for eligibility, 877 (63%) patients would have been eligible initially. The number of potentially eligible patients at any time during one year FU was 1139 (81% of the total population); this includes 253 patients who were naïve to, or had not tolerated, ACE-I or ARB at the time of consideration.

One-year mortality

Of patients fulfilling strict criteria for eligibility to sacubitril-valsartan in our analysis, one-year mortality was 8.7%. This compares to 1.5% in those excluded because NT-proBNP was <400ng/L and 2.0 % when NT-proBNP was <600ng/L. For patients excluded because of contraindications, the one-year mortality was 13.3%. When more liberal criteria (eligibility regardless of background therapy, including beta-blockers and ACE-I or ARB) were applied, one-year mortality was 10.8% in patients otherwise eligible for sacubitril-valsartan. This compares to 2.3% in those excluded because NT-proBNP was <400ng/L and 3.0% when NT-proBNP was <600ng/L. For patients excluded because of contraindications, the one-year mortality was 18.2% (figure 4).

Discussion

It could be argued that only patients whose disease has not been controlled by an adequate trial of ACE-I/ARB and who still have a substantial increase in risk should be considered for a new and potentially costly treatment (4). If the entry criteria for the PARADIGM-HF trial are strictly followed, sacubitril-valsartan should be prescribed to fewer than 25% of patients with HFrEF referred to (and followed-up in) a community heart failure clinic. This not only reflects the relatively low proportion of patients who achieve guideline-target doses of ACE-I or ARB in clinical practice due either to problems such as renal dysfunction or hypotension, failure of doctors and nurses to recommend or implement titration or unwillingness of patients to comply, but also the substantial proportion of patients who either have few symptoms or who do not have elevated plasma concentrations of natriuretic peptides once treated.

The evidence for prescribing ACE-I in patients with HFrEF is clear. However, even though prescription rates have improved over the last 15 years, many patients are not titrated up to the target doses advocated in guidelines (5). The Registry to Improve the Use of Evidence-Based Heart Failure Therapies in the Outpatient Setting (IMPROVE-HF) prospectively tested a multi-dimensional, performance-improvement intervention in >15,000 patients with HFrEF in the US (6). Only 38% achieved target doses of ACE-I/ARB in the 24 months after intervention; an improvement of only 2% on the pre-intervention rate (7). In Denmark, a study of >100,000 patients discharged after a first hospitalization for heart failure found that although 79% patients were still on renin-angiotensin inhibitors five years after initiation of treatment, the doses of ACE-I were substantially lower than target and similar to those at the time of discharge (8).

Amongst 5,000 patients with HFrEF in the ESC Heart Failure Long-Term Registry only 28% were receiving target dose of ARBs or ACE-I. Common reasons for not being at target were on-going up-titration and side effects, such as symptomatic hypotension and/or worsening renal function but for many patients there was no obvious reason (9, 10). This is similar to the experience in our own clinic. Whether audit and education can improve implementation any further than in our clinical practice remains to be demonstrated.

A recent retrospective analysis of the PARADIGM-HF study showed that more than 40% of patients had doses of trial medication down-titrated during follow-up but this was not associated with a loss of the advantage of sacubitril-valsartan over enalapril on morbidity and

mortality (11). This suggests that lower dose of sacubitril-valsartan might be superior to lower than target doses of ACE-I/ARB. However, it is important to remember that all these patients passed the initial run-in phase and had thus received target doses of enalapril and sacubitril-valsartan before the doses were subsequently decreased (due, for example, to hypotension or hyperkalemia). There remains some uncertainty whether sacubitril-valsartan is superior to ACE-I in patients unable to tolerate guideline-recommended doses in the first place.

We found that a common reason for not meeting criteria for sacubitril-valsartan was improvement in symptoms, LVEF and NT-proBNP with conventional therapy following initiation of treatment. Data from American and European registries suggest that about 1/3 of patients with HFrEF have a substantial improvement in LV systolic function with guideline-indicated treatments (12-14), especially for patients with dilated cardiomyopathy who are less likely to have extensive myocardial scar (15,16). We do not know if sacubitril-valsartan will be superior to enalapril in patients whose disease is well controlled on current standard treatment. Although patients had to be symptomatic to enter screening, 5% were asymptomatic by the end of run-in but this is too small a sample to provide definitive guidance. Even if the relative benefit is similar in this subgroup of patients, the absolute benefit of treatment is likely to be small and may not be cost-effective.

The PARADIGM-HF trial was designed to prove the concept that ARNIs were superior to ACE-I and was not a pragmatic trial designed primarily to inform clinical practice. If it is accepted that ARNIs are superior to ACE-I then, rather than going to the trouble of titrating patients to full dose ACE-I and then switching to an ARNI, it may be appropriate to initiate

patients on the latter from the outset. HFrEF is fundamentally a malignant disease and it is reasonable to consider that the best treatment should be applied from the point of diagnosis in all patients at increased risk. From this perspective, ARNIs, rather than ACE-I, could be considered to be the first-line treatment for HFrEF. If so, this greatly expands the proportion of patients with HFrEF who are eligible for sacubitril-valsartan.

Sacubitril-valsartan might be well-tolerated in those naïve to the drug (17, 18) but, during the run-in phase of PARADIGM-HF, 10% of patients did not tolerate the target dose of sacubitril-valsartan even amongst patients who tolerated enalapril 10 mg bd (2). Moreover, patients had to be on stable medication for up to two months before randomization. The safety of initiating sacubitril-valsartan in ACE-I naïve patients or those with recent decompensation, including those with incident heart failure, is uncertain.

Previous and current European guidelines do not recommend routine treatment with ACE-I in patients with HFrEF and impaired renal function (creatinine >221 $\mu\text{mol/l}$ or $\text{eGFR} \leq 30 \text{ mL/min/1.73 m}^2$) (1, 19); whether sacubitril-valsartan is safe and effective in this scenario also requires further investigation.

Three major regulatory authorities (FDA, EMA and NICE) have not suggested that initiation of sacubitril-valsartan should be restricted to patients with an elevated NT-proBNP. We believe this is a mistake. Natriuretic peptides are powerful prognostic markers. Low values will identify patients at low risk in whom sacubitril-valsartan is unlikely to be cost-effective. Even if the relative reduction in risk is similar, patients at low risk of events will have a small absolute reduction in risk.

The PARADIGM-HF trial mostly included patients who were very stable. Patients and their doctors may be reluctant to change therapy when symptoms are mild and the patient has had no recent events. Most patients with mild symptoms won't notice much difference after changing therapy; the doctor knows this. Some patients will have adverse events after changing therapy, which will be blamed on the new treatment whether or not it is the reason; the doctor knows this. Prescribing inertia, which is associated with short-term safety but long-term risk, must somehow be overcome. Educating doctors and patients to change prescriptions is likely to be facilitated by a test indicating that although the patient appears symptomatically to be 'doing quite well' their underlying disease is not yet under control. The cost of measuring natriuretic peptides is similar to that of a few days' treatment with sacubitril-valsartan. In our opinion, measuring plasma natriuretic peptides would be a simple, effective and probably cost-effective strategy that would reduce prescriptions of sacubitril-valsartan for patients who had little to gain and greatly increase them in those who had much to gain. We predict that this would lead to an overall increase in sacubitril-valsartan use but, importantly, a greater increase in what we consider appropriate use.

Limitations

The analysis should be considered a snapshot at three time intervals, and not a complete picture of the natural history of the disease in this group of patients.

Some might argue about the representativeness of our cohort and generalizability of our findings: however, our heart failure clinic accepts consecutive referrals from multiple sources, without any exclusion criteria (thus, for example, patients with previous or current diagnosis of cancer, with severe renal failure or undergoing renal dialysis are all accepted).

Our study was conducted in secondary care; patients managed solely in primary care are likely to differ but, in our region, are unlikely to receive the diagnostic tests that would qualify them for sacubitril-valsartan. The population enrolled in our study was much older than that enrolled in PARADIGM-HF, and is thus for more representative of “real world” clinical practice. However, as in PARADIGM-HF, the population we serve is predominantly of European descent with few people of Asian, African or American origin.

For the purpose of the analysis we used patients with a complete baseline data-set, including NTproBNP and echocardiography; the proportion of eligible patients might have been different in those with incomplete data. Data collection was also incomplete during follow-up visits, reflecting current clinical practice; some patients did not attend all clinical visits, or did not have NTproBNP or LVEF reassessed at every follow-up. We included patients with an LVEF $\leq 40\%$ but the entry criteria for PARADIGM-HF were changed to include only patients with LVEF $\leq 35\%$ during the course of the study. This change was implemented to try to increase events and because investigators, trying to increase recruitment, introduce some bias in their measurement of LVEF (20). There is no similar reason for bias in our cohort as all referred patients are enrolled regardless of LVEF. Restriction of sacubitril-valsartan only to patients with an LVEF $\leq 35\%$ would have further reduced the proportion eligible (for instance, from 172 to 107 of those eligible at baseline).

We started enrolment of this cohort in 2001. Since then there have been changes in recommended treatments for HFrEF, including cardiac resynchronization therapy when QRS duration is prolonged, ivabradine for those in sinus rhythm with higher heart rates despite the use of beta-blockers, and extension of the indication for mineralocorticoid receptor antagonists to patients with mild symptoms (1, 19). Such treatment applied to patients from the earlier part of our cohort might increase the number of patients with improved LV

function, fewer symptoms, and lower natriuretic peptides, thus decreasing the proportion of patients eligible for sacubitril-valsartan.

Conclusions

Sacubitril-valsartan is an important advance in the management of patients with HFrEF. Some preliminary reports give widely differing views on the proportion of patients eligible for sacubitril/valsartan (21, 22), which might reflect the criteria applied and the lack of detailed patient information. Our highly granular data emphasises the importance of showing more than one scenario. If the selection criteria for PARADIGM-HF are strictly applied, fewer than 25% of patients with HFrEF might be eligible for switching to sacubitril-valsartan. The proportion of patients with HFrEF eligible for sacubitril-valsartan increases substantially if it is considered an agent of first choice in preference to an ACE-I for patients with HFrEF and an adverse risk profile, and increases even further if natriuretic peptide plasma levels are not considered, with up to 81% of patients with HFrEF potentially eligible at some point. If the prevalence of heart failure is considered to be 1% and half of these patients have HFrEF (23,24) then, assuming our data are representative of other regions, somewhere between 65,000 (conservative estimate) and 200,000 (liberal estimate) patients in the UK (population ~65 million) might be eligible for sacubitril-valsartan, between 500,000 and 1.5 million in current European Union countries (population ~500 million) and between 320,000 and ~1million in the United States of America (population ~320 million).

Acknowledgments

The author P. Pellicori was receiving a research grant from Societa' Italiana di Cardiologia (Borsa di studio SIC e MSD Italia-Merck Sharp & Dohme Corporation) whilst involved in this research paper.

References

1. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, González-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; Authors/Task Force Members; Document Reviewers. 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 J Heart Fail.* 2016 May 20. doi: 10.1002/ejhf.592.
2. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau JL, Shi VC, Solomon SD, Swedberg K, Zile MR; PARADIGM-HF Investigators and Committees. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med.* 2014 ;371:993-1004.
3. Clark AL, Pellicori P. Clinical trials update from the European Society of Cardiology meeting 2014: PARADIGM-HF, CONFIRM-HF, SIGNIFY, atrial fibrillation, beta-blockers and heart failure, and vagal stimulation in heart failure, *ESC Heart Failure* 2014; 1:82–86
4. Crespo-Leiro MG, Anker SD, Maggioni AP, Coats AJ, Filippatos G, Ruschitzka F, Ferrari R, Piepoli MF, Delgado Jimenez JF, Metra M, Fonseca C, Hradec J, Amir O, Logeart D, Dahlström U, Merkely B, Drozd J, Goncalvesova E, Hassanein M, Chioncel O, Lainscak M, Seferovic PM, Tousoulis D, Kavoliuniene A, Fruhwald F, Fazlibegovic E, Temizhan A, Gatzov P, Erglis A, Laroche C, Mebazaa A; Heart Failure Association (HFA) of the European Society of Cardiology (ESC). *European*

- Society of Cardiology Heart Failure Long-Term Registry (ESC-HF-LT): 1-year follow-up outcomes and differences across regions. *Eur J Heart Fail.* 2016;18:613-25.
5. Cleland JG, Cohen-Solal A, Aguilar JC, Dietz R, Eastaugh J, Follath F, Freemantle N, Gavazzi A, van Gilst WH, Hobbs FD, Korewicki J, Madeira HC, Preda I, Swedberg K, Widimsky J; IMPROVEMENT of Heart Failure Programme Committees and Investigators. Improvement programme in evaluation and management; Study Group on Diagnosis of the Working Group on Heart Failure of The European Society of Cardiology. Management of heart failure in primary care (the IMPROVEMENT of Heart Failure Programme): an international survey. *Lancet.* 2002;360:1631-9.
 6. Fonarow GC, Albert NM, Curtis AB, Stough WG, Gheorghiade M, Heywood JT, McBride ML, Inge PJ, Mehra MR, O'Connor CM, Reynolds D, Walsh MN, Yancy CW. Improving evidence-based care for heart failure in outpatient cardiology practices: primary results of the Registry to Improve the Use of Evidence-Based Heart Failure Therapies in the Outpatient Setting (IMPROVE HF). *Circulation.* 2010;122:585-96.
 7. Gheorghiade M, Albert NM, Curtis AB, Thomas Heywood J, McBride ML, Inge PJ, Mehra MR, O'Connor CM, Reynolds D, Walsh MN, Yancy CW, Fonarow GC. Medication dosing in outpatients with heart failure after implementation of a practice-based performance improvement intervention: findings from IMPROVE HF. *Congest Heart Fail.* 2012;18:9-17.
 8. Gislason GH, Rasmussen JN, Abildstrom SZ, Schramm TK, Hansen ML, Buch P, Sørensen R, Folke F, Gadsbøll N, Rasmussen S, Køber L, Madsen M, Torp-Pedersen C. Persistent use of evidence-based pharmacotherapy in heart failure is associated with improved outcomes. *Circulation.* 2007;116:737-44.

9. Maggioni AP, Anker SD, Dahlström U, Filippatos G, Ponikowski P, Zannad F, Amir O, Chioncel O, Leiro MC, Drozd J, Erglis A, Fazlibegovic E, Fonseca C, Fruhwald F, Gatzov P, Goncalvesova E, Hassanein M, Hradec J, Kavoliuniene A, Lainscak M, Logeart D, Merkely B, Metra M, Persson H, Seferovic P, Temizhan A, Tousoulis D, Tavazzi L; Heart Failure Association of the ESC. Are hospitalized or ambulatory patients with heart failure treated in accordance with European Society of Cardiology guidelines? Evidence from 12,440 patients of the ESC Heart Failure Long-Term Registry. *Eur J Heart Fail.* 2013;15:1173-84.
10. Maggioni AP, Dahlström U, Filippatos G, Chioncel O, Leiro MC, Drozd J, Fruhwald F, Gullestad L, Logeart D, Metra M, Parissis J, Persson H, Ponikowski P, Rauchhaus M, Voors A, Nielsen OW, Zannad F, Tavazzi L; Heart Failure Association of ESC (HFA). EURObservational Research Programme: the Heart Failure Pilot Survey (ESC-HF Pilot). *Eur J Heart Fail.* 2010;12:1076-84.
11. Vardeny O, Claggett B, Packer M, Zile MR, Rouleau J, Swedberg K, Teerlink JR, Desai AS, Lefkowitz M, Shi V, McMurray JJ, Solomon SD; Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) Investigators. Efficacy of sacubitril/valsartan vs. enalapril at lower than target doses in heart failure with reduced ejection fraction: the PARADIGM-HF trial. *Eur J Heart Fail.* 2016 Jun 10. doi: 10.1002/ejhf.580.
12. Doughty RN, Whalley GA, Gamble G, MacMahon S, Sharpe N. Left ventricular remodeling with carvedilol in patients with congestive heart failure due to ischemic heart disease. Australia-New Zealand Heart Failure Research Collaborative Group. *J Am Coll Cardiol.* 1997;29:1060-6.
13. Konstam MA, Rousseau MF, Kronenberg MW, Udelson JE, Melin J, Stewart D, Dolan N, Edens TR, Ahn S, Kinan D, Howe D, Kilcoyne L, Metherall J, Benedict C,

- Yusuf S, Pouleur H. Effects of the angiotensin converting enzyme inhibitor enalapril on the long-term progression of left ventricular dysfunction in patients with heart failure. SOLVD Investigators. *Circulation*. 1992;86:431-8.
14. Cicoira M, Zanolla L, Rossi A, Golia G, Franceschini L, Brighetti G, Marino P, Zardini P. Long-term, dose-dependent effects of spironolactone on left ventricular function and exercise tolerance in patients with chronic heart failure. *J Am Coll Cardiol*. 2002;40:304-10
15. Wilcox JE, Fonarow GC, Yancy CW, Albert NM, Curtis AB, Heywood JT, Inge PJ, McBride ML, Mehra MR, O'Connor CM, Reynolds D, Walsh MN, Gheorghiade M. Factors associated with improvement in ejection fraction in clinical practice among patients with heart failure: findings from IMPROVE HF. *Am Heart J*. 2012;163:49-56.e2.
16. Merlo M, Pyxaras SA, Pinamonti B, Barbati G, Di Lenarda A, Sinagra G. Prevalence and prognostic significance of left ventricular reverse remodeling in dilated cardiomyopathy receiving tailored medical treatment. *J Am Coll Cardiol*. 2011;57:1468-76.
17. Pellicori P, Clark AL. Clinical trials update from the European Society of Cardiology-Heart Failure meeting 2015: AUGMENT-HF, TITRATION, STOP-HF, HARMONIZE, LION HEART, MOOD-HF, and renin-angiotensin inhibitors in patients with heart and renal failure. *Eur J Heart Fail*. 2015;17:979-83.
18. Senni M, McMurray JJ, Wachter R, McIntyre HF, Reyes A, Majercak I, Andreka P, Shehova-Yankova N, Anand I, Yilmaz MB, Gogia H, Martinez-Selles M, Fischer S, Zilahi Z, Cosmi F, Gelev V, Galve E, Gómez-Doblas JJ, Nociar J, Radomska M, Sokolova B, Volterrani M, Sarkar A, Reimund B, Chen F, Charney A. Initiating sacubitril/valsartan (LCZ696) in heart failure: results of TITRATION, a double-blind,

- randomized comparison of two uptitration regimens. *Eur J Heart Fail.* 2016 May 12. doi: 10.1002/ejhf.548. [Epub ahead of print]
19. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Böhm M, Dickstein K, Falk V, Filippatos G, Fonseca C, Gomez-Sanchez MA, Jaarsma T, Køber L, Lip GY, Maggioni AP, Parkhomenko A, Pieske BM, Popescu BA, Rønnevik PK, Rutten FH, Schwitter J, Seferovic P, Stepinska J, Trindade PT, Voors AA, Zannad F, Zeiher A; Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology, Bax JJ, Baumgartner H, Ceconi C, Dean V, Deaton C, Fagard R, Funck-Brentano C, Hasdai D, Hoes A, Kirchhof P, Knuuti J, Kolh P, McDonagh T, Moulin C, Popescu BA, Reiner Z, Sechtem U, Sirnes PA, Tendera M, Torbicki A, Vahanian A, Windecker S, McDonagh T, Sechtem U, Bonet LA, Avraamides P, Ben Lamin HA, Brignole M, Coca A, Cowburn P, Dargie H, Elliott P, Flachskampf FA, Guida GF, Hardman S, Iung B, Merkely B, Mueller C, Nanas JN, Nielsen OW, Orn S, Parissis JT, Ponikowski P; ESC Committee for Practice Guidelines. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail.* 2012;14:803-69.
20. McGowan JH, Cleland JG. Reliability of reporting left ventricular systolic function by echocardiography: a systematic review of 3 methods. *Am Heart J.* 2003;146:388-97.
21. Lainscak M, Coats AJ. The PARADIGM of ARNI's: Assessing reasons for non-implementation in heart failure. *Int J Cardiol.* 2016 ;212:187-9.

22. Fonarow GC, Hernandez AF, Solomon SD, Yancy CW. Potential Mortality Reduction With Optimal Implementation of Angiotensin Receptor Neprilysin Inhibitor Therapy in Heart Failure. *JAMA Cardiol.* 2016 Jun 22. doi: 10.1001/jamacardio.2016.1724.
23. Roger VL. Epidemiology of heart failure. *Circ Res.* 2013;113:646-59.
24. Pellicori P, Cleland JG. Heart failure with preserved ejection fraction. *Clin Med (Lond).* 2014;14 Suppl 6:s22-8.

Legend to Figures.

Figure 1. Venn diagram showing the number of patients eligible for sacubitril-valsartan following the strict criteria used in the PARADIGM-HF trial. The orange box shows cumulative, unique patients.

Figure 2: Diagram showing reasons for missing up-titration in patients not at target ACE-I or ARB at the 12 month visit.

Figure 3. Venn diagram showing the number of patients eligible for sacubitril-valsartan following the strict criteria used in the PARADIGM-HF trial, regardless of background therapy. The orange box shows cumulative, unique patients.

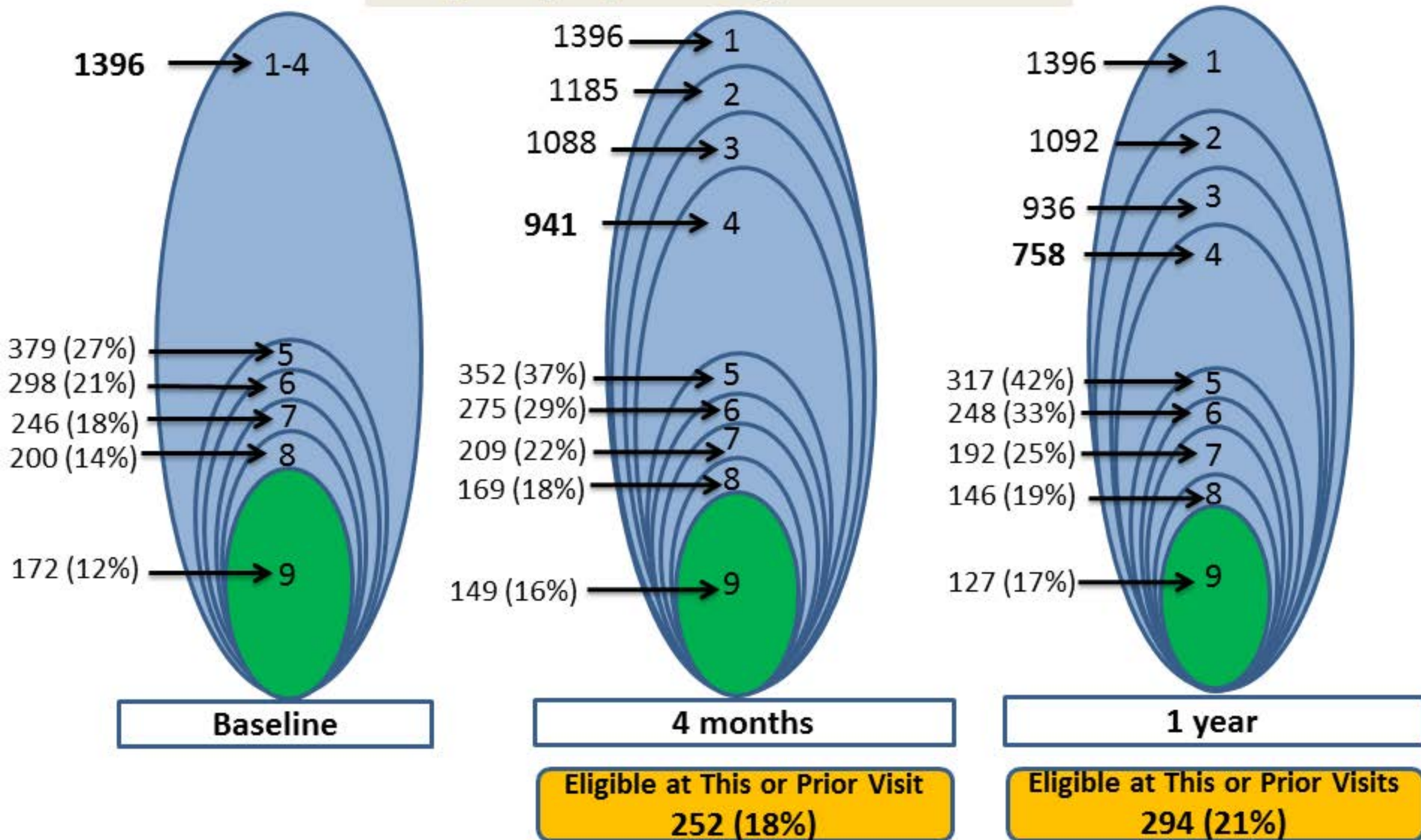
Figure 4. Histograms showing the one-year mortality of patients considered eligible for sacubitril-valsartan, of those with low NTproBNP (<400 ng/l and 600 ng/l) and of those considered to have contraindications to sacubitril-valsartan use. Two clinical situations have been considered, the first in patients who were at target dose of ACE-I or ARB (panel A, on the left), the second in patients regardless of background HF therapy (panel B, on the right). Contraindications include: significant valvular disease, systolic blood pressure <100 mmHg, ALT>2 times normal value, K>5.2 mmol/l, concurrent prescription of ACE-I/ARB, eGFR<30 ml/min/1.73m²

Supplementary figure 1. Consort diagram showing the number of patients with suspected heart failure referred to our clinic between 2001 and 2014. For the purpose of the present analysis, we focused only on patients with heart failure who had a left ventricular ejection fraction (LVEF) \leq 40% or equal to, or worse than, moderate left ventricular systolic dysfunction (LVSD) at visual assessment on echocardiography, who had complete data available.

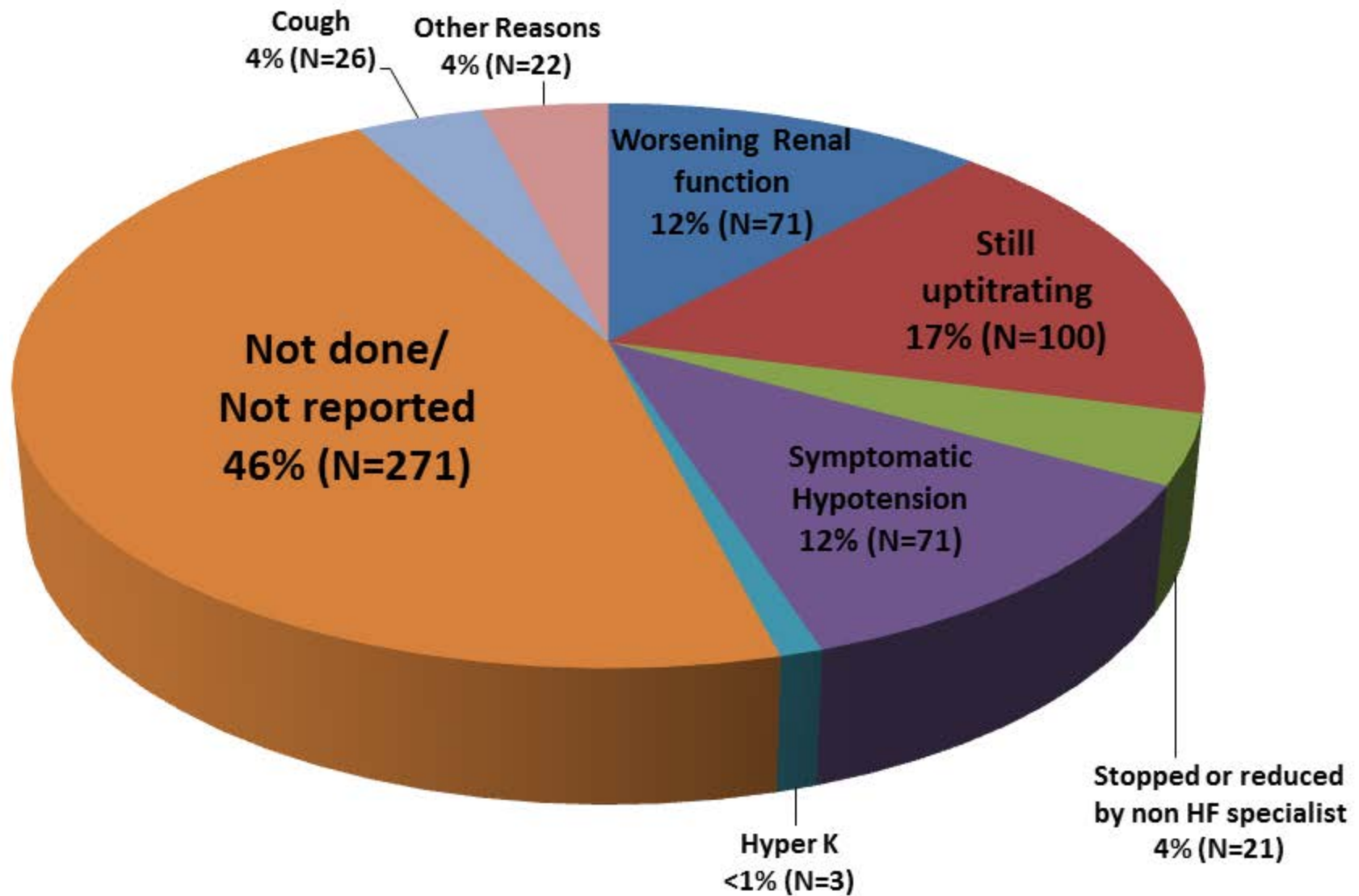
1- LVEF \leq 40% at initial visit
 2 - LVEF \leq 40% at FU
 3 - alive at FU
 4 - attended at FU
 5- on target doses of ACE-I or ARB

6 - No contraindication
 7 - Symptomatic
 8 - NT-proBNP >400 ng/l
 9 - NT-proBNP >600 ng/l

Eligibility in pts on target ACE-I or ARB



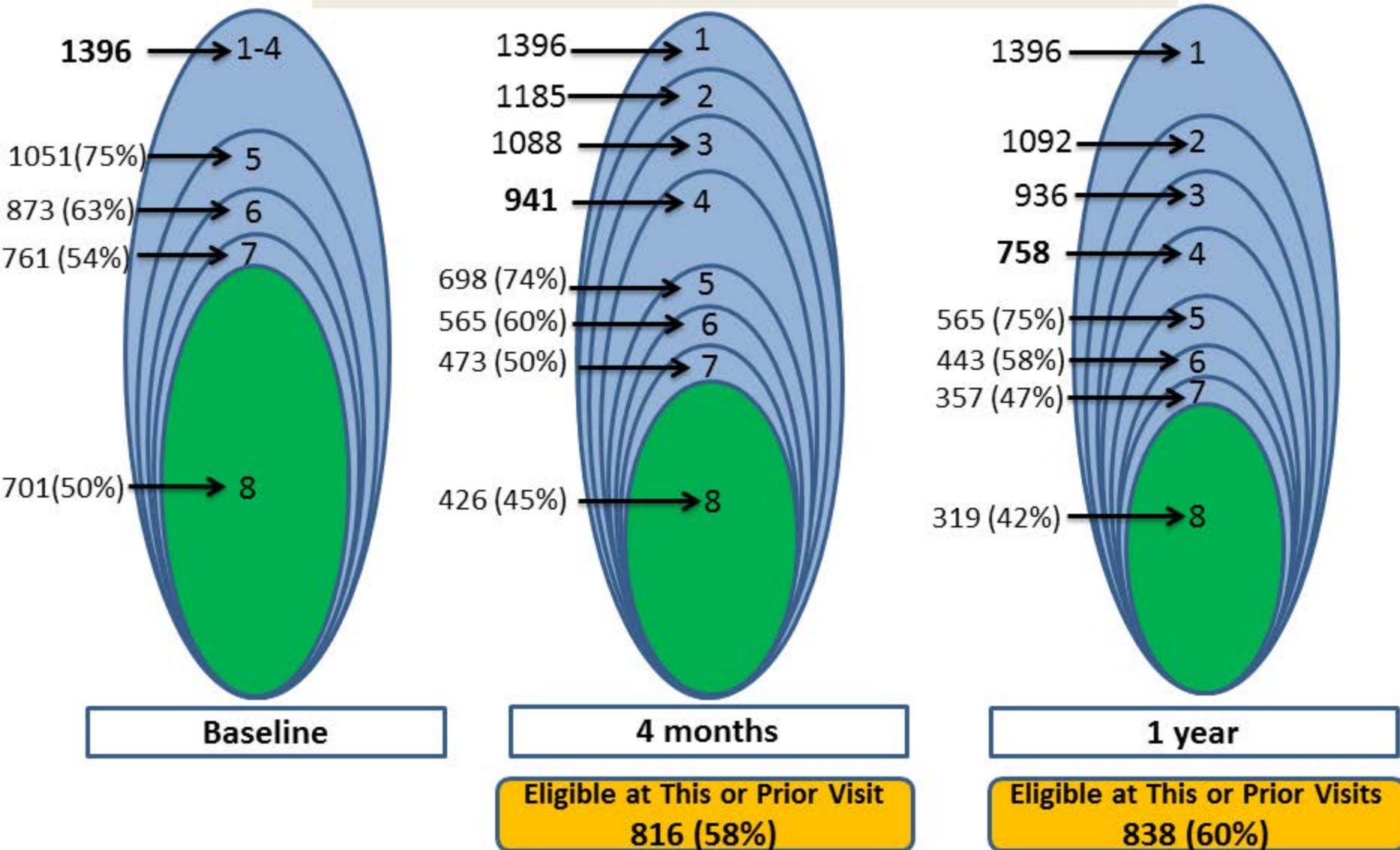
Reasons for not being on target ACE-I/ARB at the 12 months visit (N=585)



1 – LVEF \leq 40% at initial visit
 2 – LVEF \leq 40% at FU
 3 – alive at FU
 4 – attended at FU

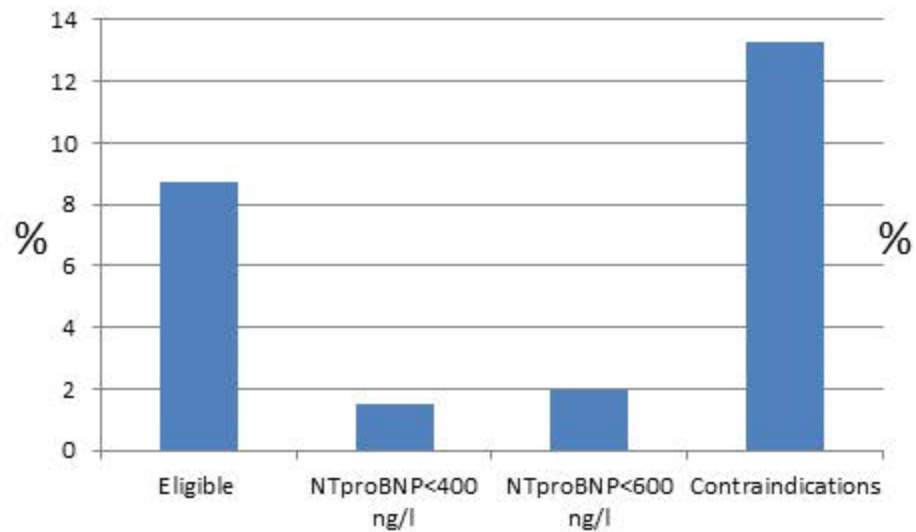
5 – No contraindication
 6 – Symptomatic
 7 – NT-proBNP >400 ng/l
 8 – NT-proBNP >600 ng/l

Eligibility regardless of background HF therapy

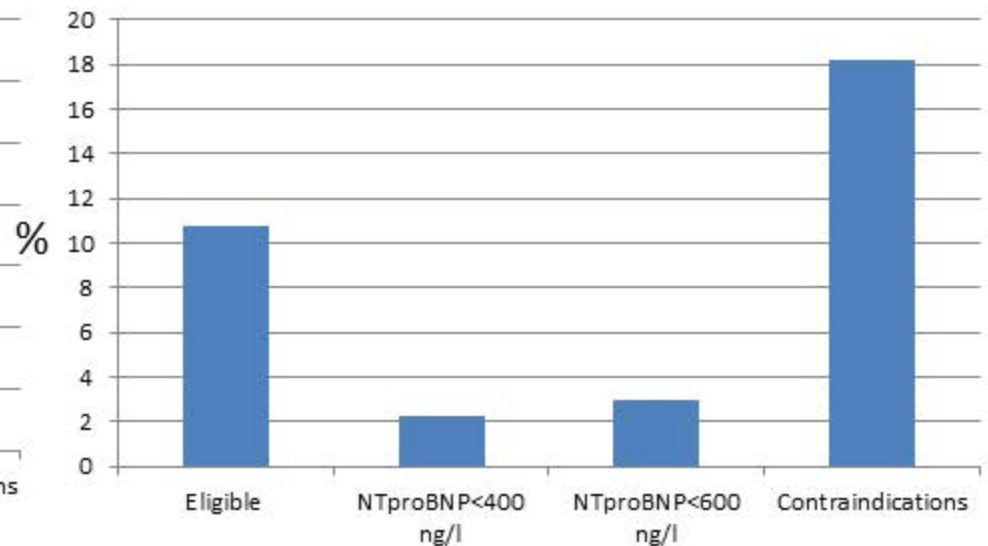


1-year mortality of patients with HFrEF who fulfilled or not criteria for eligibility for sacubitril/valsartan

A – only patients prescribed target doses of ACE-I/ARB



B – regardless of background therapy



Contraindications include: significant valvular disease, systolic blood pressure <100 mmHg, ALT >2 times normal value, K >5.2 mmol/l, concurrent prescription of ACE-I/ARB, eGFR <30 ml/min/1.73m²

Ace-I	Daily dose
Enalapril	20 mg
Captopril	200 mg
Cilazapril	5mg
Fosinopril	40 mg
Lisinopril	20 mg
Moexipril	15 mg
Perindopril	8 mg
Quinapril	40 mg
Ramipril	10 mg
Trandolapril	4 mg
Zofenopril	60 mg
ARBs	Daily dose
Candesartan	32 mg
Eprosartan	800 mg
Irbesartan	300 mg
Losartan	100 mg
Olmesartan	20 mg
Telmisartan	80 mg
Valsartan	320 mg

Table 1. Target dose of ARB or ACE-I considered as a target dose for the purpose of the study. They are the double dose of the minimum required pre-study daily doses of commonly prescribed ACEIs and ARBs considered for eligibility in the PARADIGM-HF trial.

Significant MR no. (%)	0	NA	9 (3)	NA	0	NA	9 (3)	NA
Significant AS no. (%)	0	NA	5 (2)	NA	0	NA	2 (<1)	NA
Significant AR no. (%)	0	NA	0 (0)	NA	0	NA	0 (0)	NA
SBP < 100 mmHg no. (%)	0	NA	27 (9)	NA	0	NA	37 (11)	NA
ALT > 2 times normal value no. (%)	0	NA	2 (1)	NA	0	NA	1 (<1)	NA
eGFR < 30 mL/min/1.73 m ² no. (%)	0	NA	20 (7)	NA	0	NA	25 (8)	NA
K > 5.2 mmol/hour no. (%)	0	NA	37 (13)	NA	0	NA	28 (9)	NA
On ACEi and ARB- no (%)	0	NA	10 (3)	NA	0	NA	7 (2)	NA
Summary								
NYHA I as only exclusion criterion no. (%)	0	NA	34 (11)	NA	0	NA	35 (11)	NA
Only one criterion for exclusion no. (%)	0	NA	166 (56)	NA	0	NA	173 (53)	NA
Two criteria for exclusion no. (%)	0	NA	107 (36)	NA	0	NA	109 (33)	NA
Three or more criteria for exclusion no. (%)	0	NA	24 (8)	NA	0	NA	44 (14)	NA

Table 3 patients at four (4M) and twelve (12M) month visits who were at target-ACE/ARB Abbreviations used: ACE: Angiotensin converting enzyme inhibitor, ARB: Angiotensin Receptor Blocker, MRA: mineral corticoid antagonist, NYHA: New York Heart Association, SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure, NT pro BNP: N Terminal prohormone Brain Natriuretic Peptide, eGFR: estimated Glomerular Filtration Rate, ALT: Alanine Aminotransferase, MR: Mitral Regurgitation, AS: Aortic Stenosis, AR: Aortic Regurgitation, K: Potassium, NA: not applicable (used for classification, therefore statistical comparison is inappropriate).