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)

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Aim
To describe the baseline characteristics and treatment of the patients randomized in the PARADIGM-HF (Prospective comparison of ARNi with ACEi to Determine Impact on Global Mortality and morbidity in Heart Failure) trial, testing the hypothesis that the strategy of simultaneously blocking the renin—angiotensin—aldosterone system and augmenting natriuretic peptides with LCZ696 200 mg b.i.d. is superior to enalapril 10 mg b.i.d. in reducing mortality and morbidity in patients with heart failure and reduced ejection fraction.

Methods
Key demographic, clinical and laboratory findings, along with baseline treatment, are reported and compared with those of patients in the treatment arm of the Studies Of Left Ventricular Dysfunction (SOLVD-T) and more contemporary drug and device trials in heart failure and reduced ejection fraction.

Results
The mean age of the 8442 patients in PARADIGM-HF is 64 (SD 11) years and 78% are male, which is similar to SOLVD-T and more recent trials. Despite extensive background therapy with beta-blockers (93% patients) and mineralocorticoid receptor antagonists (60%), patients in PARADIGM-HF have persisting symptoms and signs, reduced health related quality of life, a low LVEF (mean 29 ± SD 6%) and elevated N-terminal-proB type-natriuretic peptide levels (median 1608 inter-quartile range 886–3221 pg/mL).

Conclusion
PARADIGM-HF will determine whether LCZ696 is more beneficial than enalapril when added to other disease-modifying therapies and if further augmentation of endogenous natriuretic peptides will reduce morbidity and mortality in heart failure and reduced ejection fraction.

Keywords
Heart failure • Natriuretic peptides • Neutral endopeptidase • Renin–angiotensin system

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Introduction

The role of endogenous natriuretic peptides in protecting against sodium and volume overload is well recognized and this family of peptides is believed to have an range of other beneficial cardiac, vascular, and renal actions. More recently, it has been suggested that natriuretic peptides also have favourable metabolic actions, including improvement of glucose tolerance and reduction in adipocyte growth.

Endogenous concentrations of natriuretic peptides can be increased through inhibition of the enzyme responsible for their degradation [i.e. neutral endopeptidase (NEP), also known as nephrilysin]. There have been several attempts to determine whether inhibition of NEP is of benefit in patients with cardiovascular disease.

Because NEP also degrades angiotensin II, NEP inhibition must be combined with an angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB). The former approach was tested with omapatrilat, but blockade of both NEP and ACE (and probably a third enzyme, aminopeptidase P) resulted in an unacceptable risk of angioedema because each of these enzymes is also involved in the breakdown of bradykinin. The angiotensin receptor blocker-neprilysin inhibitor (ARNi) LCZ696 provides an alternative approach to simultaneously blocking the renin–angiotensin–aldosterone system (RAAS) and augmenting endogenous natriuretic peptides, without increasing bradykinin excessively.

The Prospective comparison of ARNi with ACEi to Determine Impact on Global Mortality and morbidity in Heart Failure trial (PARADIGM-HF) is testing the hypothesis that LCZ696 200 mg b.i.d is superior to enalapril 10 mg bid is reducing mortality and morbidity in patients with heart failure and reduced ejection fraction (HF-REF). Enalapril was chosen as the comparator as the only ACE inhibitor shown to reduce mortality in a broad spectrum of patients with HF-REF in the treatment arm of the Studies Of Left Ventricular Dysfunction (SOLVD-T). A 200 mg b.i.d. dose of LCZ696 was selected because it provides equivalent exposure as valsartan 160 mg b.i.d. (the target dose in heart failure and presumed similar RAAS blockade to enalapril 10 mg b.i.d.), as well as near-complete NEP inhibition. Here we describe the baseline characteristics and treatment of the more than 8400 patients randomized in PARADIGM-HF, comparing these with both SOLVD-T and more contemporary drug and device trials in HF-REF.

Methods

As described previously, PARADIGM-HF is a randomized, double-blind, parallel group, active-controlled, two-arm, event-driven trial comparing the long-term efficacy and safety of enalapril and LCZ696 in patients with chronic symptomatic HF-REF. The key entry criteria are shown in Table 1.

There are four phases in PARADIGM-HF: the rationale for which has been explained previously: (i) screening, (ii) single-blind enalapril run-in, (iii) single-blind LCZ696 run-in, and (iv) randomized, double-blind, treatment. At the screening visit, patient eligibility was assessed including left ventricular ejection fraction (LVEF), New York Heart Association (NYHA) class, BNP or N-terminal pro-brain natriuretic peptide (NT-proBNP), serum potassium, and estimated glomerular filtration rate (eGFR), measured in a central laboratory. Eligible patients then entered a single-blind enalapril run-in followed by a single-blind LCZ696 run-in. Patients tolerating both enalapril 10 mg b.i.d. and LCZ696 200 mg b.i.d. were randomized in a 1:1 ratio to double-blind treatment with either enalapril 10 mg b.i.d. or LCZ696 200 mg b.i.d. Tolerability for randomization was determined as: potassium ≤5.4 mmol/L; eGFR ≥30 mL/min.1.73 m² and no decrease in eGFR of >25% (later amended to >35%) from the screening visit; no symptomatic hypotension, no postural symptoms and systolic blood pressure (BP) ≥95 mmHg; no other adverse events precluding continuation in the trial, according to the investigator's judgement.

The primary objective of the trial is to evaluate the effect of LCZ696 200 mg b.i.d. compared with enalapril 10 mg b.i.d., in addition to conventional heart failure treatment, in delaying time to first occurrence of either cardiovascular (CV) death or hospitalization owing to heart failure. Both components of the composite will also be analysed separately, in accordance with regulatory guidance, and these additional analyses will be considered as part of the primary endpoint and not as secondary outcomes. The trial has 80% power to detect a 15% reduction in cardiovascular mortality once 1229 of these events accrue. Secondary objectives are to test whether LCZ696, compared with enalapril, is superior: (i) in improving the Kansas City Cardiomyopathy Questionnaire (KCCQ) clinical summary score for heart failure symptoms and physical limitations at 8 months; (ii) in delaying the time to all-cause mortality; (iii) in delaying time to new-onset atrial fibrillation; and (iv) in delaying decline in renal function. There are also a number of exploratory objectives. The statistical considerations related to PARADIGM-HF have been described in detail elsewhere.

Briefly, the sample size is based upon CV mortality with 1229 deaths required to give 80% power to detect a relative risk reduction of 15% in the LCZ696 group, compared with the enalapril group, although the trial will continue until at least 2410 patients have experienced CV death, or hospitalization owing to heart failure (meaning it should have >97% power to detect a relative risk reduction of 15% in this primary composite outcome). Hence, PARADIGM-HF was designed as both a mortality trial and a mortality/morbidity trial and the Data Monitoring Committee will only consider early termination at its pre-planned interim analyses if both the primary composite outcome and CV mortality are reduced, in accordance with the pre-specified boundaries.

The present report describes an analysis of the baseline characteristics of the 8442 patients randomized in PARADIGM-HF (this number includes 6 patients found to be incorrectly randomized who had violated the inclusion criteria and who were removed from the trial before receiving study-drug). As described above, the reference comparator in PARADIGM-HF is enalapril 10 mg b.i.d., which was chosen because of the seminal findings of the Treatment Arm of the Studies Of Left Ventricular Dysfunction (SOLVD-T). For this reason we have compared the characteristics of patients in PARADIGM-HF with those in SOLVD-T. The baseline characteristics of the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity-Added (CHARM-Added) trial are also shown as this was used to estimate the rate of the primary outcome in PARADIGM-HF.

Furthermore, to better understand the patients enrolled in PARADIGM-HF in a more contemporary setting, we have compared the patients in PARADIGM-HF with those in a range of recent trials in HF-REF that have reported comparable data.
Table 1 Design of SOLVD-T, PARADIGM-HF and other, recent, large randomized controlled trials in heart failure and reduced ejection fraction (HF-REF)

| Inclusion criteria | SOLVD-T, N = 2569 | CHARM-Added, N = 2548 | HEAAL, N = 3834 | RAFT, N = 1798 | SHIFT, N = 6505 | EMPHASIS-HF, N = 2737 | PARADIGM-HF, N = 8442 |
|-------------------|-------------------|----------------------|----------------|----------------|----------------|----------------------|----------------------|
| Age (years)       | 21–80             | ≥18                  | ≥18            | ≥18            | ≥18            | ≥55                  | ≥18                  |
| NYHA class        | II–IV             | II–IV               | II–IV          | II–III        | II–IV          | II                   | II–IV               |
| LVEF (%)          | ≤35%              | ≤40%                | ≤40%           | ≤30%          | ≤35%           | ≤35%                 | ≤40%                |
| HF hospitalization| No                | Yes^b               | No             | No             | Yes^a          | Yes^b               | Yes                  |
| Other             | –                 | –                   | –              | Sinus rhythm  | Sinus rhythm rate | –                   | BNP, 150 pg/ml (NT-proBNP) ≥600 pg/mL |
| Creatinine, μmol/L| ≤220^a            | <265                | ≤220           | –             | ≤220           | –                   | –                   |
| eGFR, mL/min.1.73 m^b | –             | –                   | –              | –             | ≥30            | –                   | ≥30                  |
| Systolic blood pressure, mmHg | <5.5^a | <5.5                | ≤5.7           | –             | <5.0           | –                   | ≤5.4                |
| Potassium, mmol/L | –                 | –                   | –              | –             | –              | –                   | –                   |
| Run-in            | Placebo/control   | Yes                 | No             | No             | Yes            | Yes                 | Yes                  |
| Active            | Yes               | No                  | No             | No             | No             | No                  | Yes                  |
| Baseline treatment| –                 | Beta-blocker        | Beta-blocker   | Beta-blocker  | Beta-blocker   | Beta-blocker        | Beta-blocker        |
|                   | ACEi              | ACEi or ARB         | MRA as indicated | ACEi or ARB | MRA as indicated | ACEi or ARB         | MRA as indicated   |
| Comparison        | Placebo           | Placebo             | Losartan 50 mg q.d. | ICD          | Placebo        | Placebo             | Enalapril 10 mg b.i.d. |
|                   | Enalapril 10 mg b.i.d. | Canulesartan 32 mg q.d. | Losartan 150 mg q.d. | CRT–ICD     | Placebo         | Eplerenone 50 mg q.d. | LCZ 696 200 mg b.i.d. |
| Recruitment period| 1986–1989         | 1999–2001           | 2001–2005      | 2003–2009     | 2006–2009      | 2006–2010           | 2009–2012^c          |

**Notes:**

SOLVD-T: Studies of Left Ventricular Dysfunction Treatment trial; CHARM-Added: Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM)-Added trial; HEAAL: Heart failure Endpoint evaluation of Angiotensin II Antagonist Losartan; RAFT: Resynchronization/Defibrillation for Ambulatory Heart Failure Trial; SHIFT: Systolic Heart Failure Treatment with the I_F inhibitor Ivabradine Trial; EMPHASIS-HF: Eplerenone in Mild Patients Hospitalization And Survival study in Heart Failure; PARADIGM-HF: Prospective comparison of ANII (angiotensin II antagonist) neprilysin inhibitor) with ACEI (angiotensin-converting enzyme inhibitor) to Determine Impact on Global Mortality and morbidity in Heart Failure trial. HF, heart failure; NYHA, New York Heart Association functional class; LVEF, left ventricular ejection fraction; eGFR, estimated glomerular filtration rate.

^a SOLVD Protocol states a creatinine >220 μmol/L at baseline is an exclusion although results manuscript states >177 μmol/L. During run-in patients were to be excluded if creatine increased by 88.4 μmol/L or to 354 μmol/L, potassium increased to 5.5 mmol or greater or the patient developed symptomatic hypotension.

^b In CHARM-Added, cardiac hospitalisation within 6 months if NYHA class II, in EMPHASIS-HF cardiovascular hospitalization within 6 months (or BNP ≥230 pg/ml or NT proBNP ≥500 pg/mL in men and 750 pg/mL in women).

^c optional in patients already taking an ARB.

^d NYHA class III excluded after 2006.

^e within 12 months.

^f ≥30–35% if QRS duration >130 ms.

^g changed to ≤35% December 2010.

^h and BNP ≥100 pg/mL (or NT proBNP ≥400 pg/mL) or BNP ≥150 pg/mL (NT proBNP ≥600 pg/mL) if no heart failure hospitalization within 12 months.

^i the last patient entered the run-in in 2012 but was randomised in 2013.
Results

Between 8 December 2009 and 17 January 2013, 8442 patients were randomized in PARADIGM-HF at 985 sites in 47 countries. The clinical characteristics, baseline treatment, laboratory findings and health-related quality of life are described in Tables 2–5. These tables also show the same findings from SOLVD-T and more recent trials in patients with HF-REF.11–25

Baseline characteristics

The average age of patients in PARADIGM-HF is 64 (SD 11) years, similar to SOLVD-T and the other more recent trials with the exception of EMPHASIS-HF (Eplerenone in Mild Patients Hospitalization And Survival study in Heart Failure) in which patients had a higher average age; however, eligible participants in EMPHASIS-HF had to be 55 years or older (Table 2). Consistent with previous trials, the vast majority (78%) of patients are men. Similarly, as in most trials, the majority of patients are in NYHA class II although this proportion (70%) in PARADIGM-HF was greater than in SOLVD-T (57%). The patients enrolled in PARADIGM-HF are more racially diverse than most previous trials with the exception of HEAAL (Heart failure Endpoint evaluation of Angiotensin II Antagonist Losartan).13 Blood pressure is slightly lower in PARADIGM-HF than in SOLVD-T and LVEF slightly higher, although the entry LVEF threshold is higher in PARADIGM-HF (Tables 1 and 2). Heart rate in PARADIGM-HF is similar to most other studies except SHIFT (Systolic Heart Failure Treatment with the I_1 Inhibitor Ivabradine Trial, which mandated a heart rate of $\geq 70$ bpm for inclusion) and SOLVD-T.9

Medical and surgical history

More patients (71%) in PARADIGM-HF have a history of hypertension than in SOLVD-T (42%) although the proportion in PARADIGM-HF is consistent with most other contemporary trials. Conversely, the proportion of patients in PARADIGM-HF with an investigator-reported ischaemic aetiology is lower than in SOLVD-T (and other trials), and this is in keeping with the smaller proportion in PARADIGM-HF with a history of myocardial infarction and previous coronary revascularization. The proportion of patients with a diagnosis of diabetes is higher in recent trials (at around one-third) compared with SOLVD-T (where about a quarter of patients had diabetes). The proportion with atrial fibrillation also seems higher although trials do not always distinguish between atrial fibrillation at the time of enrolment and history of atrial fibrillation.

Laboratory investigators

The proportion of patients with chronic kidney disease (estimated glomerular filtration rate <60 mL/min.1.73 m$^2$) is similar in PARADIGM-HF and SOLVD-T, as well as in EMPHASIS-HF.14

Baseline treatment

As expected, the biggest difference between PARADIGM-HF and SOLVD-T is in treatment with a beta-blocker (93 vs. 8%), although the use of this therapy in PARADIGM-HF reflects that in other contemporary trials. Use of mineralocorticoid receptor antagonists (MRAs) is also likely to be quite different, although impossible to quantify as MRA treatment was not recorded in SOLVD-T (as it was not known to be beneficial at the time of that trial). The rate of MRA use in PARADIGM-HF is, however, the joint highest in any trial. Anticoagulant use is also more common in PARADIGM-HF and other recent trials. Conversely, digoxin use is much less in PARADIGM-HF (and other contemporary trials) than in SOLVD-T.

Device use in PARADIGM-HF is greater than in any other recent pharmacological treatment trial but still low.

Signs and symptoms at baseline

With the exception of a third heart sound, the clinical findings described in PARADIGM-HF are broadly consistent with SOLVD-T and in the more recent trials that reported these (Table 3). Notably, in these trials up to one in five patients had peripheral oedema and around one in 10 had an elevated jugular venous pressure.

N-terminal pro B-type natriuretic peptide

Relatively few trials have reported NT-proBNP levels. Those that have are summarized in Table 4. The two trials with the highest levels [CARE-HF (Cardiac Resynchronization in Heart Failure), 1814 pg/mL, and COPERNICUS (Carvedilol Prospective Randomized Cumulative Survival Trial), 1767 pg/mL] by design enrolled more severely symptomatic patients with a particularly low LVEF.15,20 Despite this, the median level in PARADIGM-HF (1608 pg/mL) is only slightly less than in these two trials and higher (or much higher) than in the other trials shown.

Health-related quality of life

Pharmacological therapy and device trials reporting KCCQ Overall Summary Score (OSS) are shown in Table 5 (where a lower score reflects worse quality of life). The OSS in PARADIGM-HF is similar to that in GISSI-HF and MADIT-CRT but higher (better) than in several other recent trials.23,25

Discussion

The PARADIGM-HF trial is the largest, most contemporary and most geographically diverse mortality—morbidity trial in patients with HF-REF. It is testing the hypothesis that the ARNi LCZ696 is superior to enalapril 10 mg twice daily, the ACE inhibitor and dose shown to reduce mortality and hospitalization for heart failure in SOLVD-T.

Despite the 23 year gap between the start of recruitment to SOLVD-T and the start of PARADIGM-HF, the baseline demographics of patients in both trials are remarkably similar with the
| Table 2 Baseline characteristics and treatment in SOLVD-T, PARADIGM-HF and other recent heart failure and reduced ejection fraction (HF-REF) trials |
|---------------------------------------------------------------|
| SOLVD-T, N = 2569  | CHARM-Added, N = 2548 | HEAAL\textsuperscript{a}, N = 3834 | RAFT, N = 1798 | SHIFT, N = 6505 | EMPHASIS-HF, N = 2737 | PARADIGM-HF, N = 8442 |
| Age (mean) 61 | 64 | 66 | 66 | 60 | 69 | 64 |
| Female sex (%) 20 | 21 | 30 | 17 | 23 | 22 | 22 |
| NYHA class (%) |
| I 11 | 0 | 0 | 0 | 0 | 0 | 5 |
| II 57 | 24 | 69 | 80 | 49 | 100 | 70 |
| III 30 | 73 | 30 | 20 | 50 | 0 | 24 |
| IV 2 | 3 | 1 | 0 | 2 | 0 | 1 |
| Race (%) |
| White 80 | 92 | 61 | – | 89 | 83 | 66 |
| Black 15 | 5 | 1 | – | – | 2 | 5 |
| Asian – | – | – | 22 | – | 8 | 12 |
| Other 4 | 4 | 16 | – | 3 | 3 | 11 |
| Heart rate (mean) bpm 80 | 74 | 72 | – | 80 | 72 | 72 |
| Blood pressure (mean) mmHg |
| Systolic 125 | 125 | 125 | – | 122 | 124 | 121 |
| Diastolic 77 | 75 | 72 | – | 76 | 75 | 74 |
| LVEF (mean) % 25 | 28 | 33 | 23 | 29 | 26 | 29 |
| QRS duration (mean) ms – | – | – | 158 | – | 122 | 117 |
| BMI (mean) kg/m\textsuperscript{2} – | 28 | 27 | – | 28 | 28 | 28 |
| Ischaemic aetiology (%) 71 | 62 | – | 67 | 67 | 69 | 60 |
| Medical history (%) |
| Hospitalization for HF – | 77 | – | 25\textsuperscript{c} | 100\textsuperscript{t} | 53 | 63\textsuperscript{k} |
| Hypertension 42 | 48 | 60 | 45 | 67 | 66 | 71 |
| Angina pectoris 37 | 53 | 65\textsuperscript{j} | – | 43 | 43 |
| Myocardial infarction 66 | 56 | – | 56 | 50 | 43 |
| PCI N/A 15 | – | 24 | – | 22 | 21 |
| CABG 29\textsuperscript{a} | 25 | – | 34 | – | 19 | 15 |
| Atrial fibrillation/flutter 10 | 26 | 28 | 13\textsuperscript{a} | 8\textsuperscript{d} | 31 | 37\textsuperscript{i} |
| LBBB\textsuperscript{b} – | 31 | – | 72 | – | 27 | 20 |
| Diabetes mellitus 26 | 30 | 31 | 34 | 31 | 31 | 34 |
| Stroke (8)\textsuperscript{m} | 9 | – | – | 8 | 10 | 9 |
| Current smoker 22 | 17 | – | 14 | 18 | – | 14 |
| Renal function |
| Serum creatinine 106 | 103 | 97 | – | – | 102 | 99 |
| (\textmu mol/L) 76\textsuperscript{w} | 71 | – | 61 | 75 | 71 | 68 |
| eGFR mL/min.1.73m\textsuperscript{2} (mean) 36\textsuperscript{m} | 33 | – | 50 | – | 33 | 37 |
| Treatment (%) |
| Diuretic 85 | 90 | 77 | 85 | – | 85 | 80 |
| ACE inhibitor N/A | 100 | N/A | – | 79 | 78 | N/A\textsuperscript{m} |
| ARB N/A | N/A | N/A | – | 14 | 19 | N/A\textsuperscript{m} |
| ACEi, ARB, or both N/A | N/A | N/A | 97 | – | 94 | N/A\textsuperscript{m} |
| \betaeta-blocker 8 | 55 | 72 | 90 | 90 | 87 | 93 |
| MRA – | 17 | 38 | 42\textsuperscript{f} | 60 | N/A | 60 |
| Digoxin 67 | 58 | 42 | 35 | 22 | 27 | 30\textsuperscript{a} |
| Anticoagulant 16 | 38 | 33 | 34\textsuperscript{f} | – | – | 32\textsuperscript{a} |
| Antiplatelet |
| Aspirin – | 51 | 51 | 67 | – | – | 52\textsuperscript{a} |
| ADP antagonist N/A | – | – | 16 | – | – | 15\textsuperscript{a} |
| Any antiplatelet 33 | – | – | – | – | – | 57 |
| Lipid lowering – | 41 | 39\textsuperscript{h} | 68\textsuperscript{h} | 58\textsuperscript{h} | 62 | 56 |
exception of race because of the much wider geographical reach of PARADIGM-HF.\(^5\)\(^6\)

However, NYHA class distribution was somewhat more favourable, and mean LVEF higher in PARADIGM-HF than in SOLVD-T, possibly reflecting greater treatment with disease-modifying drugs (and devices) in the former. The lower heart rate and systolic blood pressure in PARADIGM-HF probably also result from this. In particular, the higher heart rate in SOLVD-T presumably reflects the conduct of the trial before the value of beta-blockers in heart failure was recognized (see below).

The proportion of patients with diabetes is higher in contemporary trials, including PARADIGM-HF, compared with SOLVD-T and this may in part reflect newer and lower diagnostic thresholds for diabetes since the start of enrolment in SOLVD-T.\(^26\) Patients in contemporary trials may also be more obese than in the past but this hypothesis could not be tested as body mass index was not recorded in SOLVD-T.

A more puzzling difference is in the lower proportion of patients with coronary heart disease in PARADIGM-HF. Whether this reflects greater diagnostic accuracy in more contemporary practice, the different racial and geographical mix of patients in the two trials or some other factor is uncertain.

As expected, background therapy in PARADIGM-HF is quite different than in SOLVD-T, with greater use of beta-blockers and MRAs, oral anticoagulants (and presumably statins, which were not available during SOLVD-T), in keeping with the accrual of new evidence of treatment effectiveness and evolution of guidelines to reflect this.\(^27\)\(^28\) Even among contemporary trials, the patients in PARADIGM-HF are particularly well treated, with the highest rate of use of beta-blockers (93%) and the joint highest rate (60%) of MRA use along with SHIFT (60%), even though SHIFT had a higher proportion of NYHA class III/IV patients (52%) than PARADIGM-HF (25%). Consequently, PARADIGM-HF will test the value of LCZ696 in addition to the best pharmacological standard of care. The lower use of digoxin in PARADIGM-HF, compared with SOLVD-T presumably reflects changed perceptions of the value of this agent and newer alternative therapies of proven effectiveness.\(^29\)

Despite strong evidence of effectiveness, device use remains low in contemporary trials, especially those with a large proportion of patients enrolled in regions other than North America and Western Europe, where there is greater uptake of cardiac resynchronization therapy (CRT) and, in particular, implantable cardioverter defibrillators (ICDs).\(^13\)\(^14\)\(^17\)\(^27\)\(^28\) In this respect, patients in PARADIGM-HF had similar rates of device use as those in EMPHASIS-HF and more than in SHIFT.\(^13\)\(^14\)

Although the majority of patients in PARADIGM-HF were in NYHA functional class II or III at the time of randomization, the

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### Table 2 Continued

| SOLVD-T, CHARM-Added, HEAAL\(^2\), RAFT, SHIFT, EMPHASIS-HF, PARADIGM-HF, N = 2569, N = 2548, N = 3834, N = 1798, N = 6505, N = 2737, N = 8442 |
|---|---|---|---|---|---|---|
| CRT N/A | N/A | – | N/A | 1 | 2 | 7\(^1\) |
| ICD N/A | 4 | – | 100 | 4 | 13 | 15 |
| CRT-D N/A | N/A | – | N/A | – | 6 | 5 |

\(^1\)NYHA class at randomization—all patients were in NYHA functional class II or greater at entry to the active run-in period.
\(^2\)in previous 6 months.
\(^3\)current AF excluded.
\(^4\)permanent AF at baseline.
\(^5\)spironolactone.
\(^6\)warfarin.
\(^7\)history of AF only.
\(^8\)history of ischaemic heart disease in HEAAL and of stable or unstable angina in PARADIGM-HF.
\(^9\)no time limit.
\(^10\)CRT-D or CRT-P.
\(^11\)pre-enrolment, 77% were treated with an ACE inhibitor and 22% with an ARB (100% with one, other or both).
\(^12\)includes all digitalis derivatives.
\(^13\)includes vitamin K antagonists, rivaroxaban, dabigatran, and apixaban.
\(^14\)includes all aspirin derivatives, alone or in combinations.
\(^15\)includes clopidogrel, prasugrel, ticagrelor, ticlopidine, and their combinations.
\(^16\)CABG or PCI.
\(^17\)Cerebrovascular disease.
\(^18\)Creatinine clearance (in SOLVD overall, the mean eGFR was 70 mL/min 1.73 m\(^2\) and 32% of patients had an eGFR <60 mL/min 1.73 m\(^2\)).
\(^19\)Per protocol, all patients had an admission for worsening heart failure within 12 months.

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NT-proBNP was measured (was higher in PARADIGM-HF than in any other trial in which proportion of patients with atrial fibrillation or flutter at baseline NT-proBNP of without a history of hospitalization owing to heart failure within probably reflects two factors. First, in PARADIGM-HF, patients with other trials in heart failure and reduced ejection fraction (HF-REF) median NT-proBNP concentra...
Table 5 Kansas City Cardiomyopathy Questionnaire (KCCQ) Overall Summary Score (OSS) in heart failure and reduced ejection fraction trials—a higher score means better quality of life

| Intervention               | RED-HF 22, N = 2278 | SHIFT 13, N = 6558 | GISSI-HF 23, N = 4574 | HF-ACTION 24, N = 2331 | MADIT-CRT 25, N = 1820 | PARADIGM-HF 7, N = 8442 |
|----------------------------|----------------------|---------------------|-----------------------|------------------------|-------------------------|------------------------|
| Mean age (years)           | 70                   | 60                  | 68                    | 59*                    | 64                      | 64                     |
| Female sex (%)             | 41                   | 23                  | 23                    | 28                     | 25                      | 22                     |
| NYHA class                 |                      |                     |                       |                        |                         |                        |
| I/II                       | 35                   | 49                  | 62                    | 63                     | 100†                    | 75                     |
| III                        | 63                   | 50                  | 35                    | 36                     | 0                       | 24                     |
| IV                         | 2                    | 2                   | 3                     | 1                      | 0                       | 1                      |
| LVEF                       | 30                   | 29                  | 33                    | 25‡                    | 24                      | 29                     |
| Other variables            | Anaemia              | Recent HF hospital- | HF hospitalization    | Suitable for exercise training | QRS < 130 ms            | Elevated BNP/NT         |
|                           |                     | ization past year  | past year             | exercise training       | proBNP† recent          | Hospitalization         |
|                           |                     |                     |                       |                        |                         |                        |
| Intervention               |                     |                     |                       |                        |                         |                        |
|                           | OMT vs.              | OMT vs.             | OMT vs.               | OMT vs.                | OMT + CRT-D vs.         | OMT + ICD vs.           |
|                           | darbepoetin          | OMT +         | OMT +               | OMT + exercise training | OMT + CRT-D vs.         | OMT + LCZ696 vs.        |
|                           |                     | ivabradine         | rosvastatin†         | exercise training       |                         |                        |
|                           |                     |                     |                      |                        |                         |                        |
| KCCQ OSS                   | 56                   | 65                  | 73                    | 66                     | 76                      | 73                     |

RED-HF: Reduction of Events With Darbepoetin Alfa in Heart Failure Trial; SHIFT: Systolic Heart Failure Treatment with the I, Inhibitor Ivabradine Trial; GISSI-HF: Gruppo Italiano per lo Studio della Sopravvivenza nell’Infarto miocardico-heart failure; HF-ACTION, Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training; MADIT-CRT, Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy; PARADIGM-HF, Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial. NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; OMT, optimum medical treatment.

†Median NYHA class II 15%.

‡OMT vs. OMT + omega-3 polysaturated fatty acids; 10% of patients had a LVEF > 40%; KCCQ was recorded in 1699 patients in MADIT-CRT, 1465 in GISSI-HF; 2330 in HF-ACTION, 1944 in SHIFT, 2210 in RED-HF and 496 in STICH. The mean age, NYHA class distribution and LVEF are those reported in the main trial.

As with all analyses of this type, there are limitations, the principal one of which is that the explanations for many of the differences observed are speculative and cannot be proven. However, this report does provide a quarter-century perspective on the evolution of trials in HF-REF and, in particular changes in therapy over time.

In summary, our findings show that while the basic demographics of the selected patients with HF-REF enrolled in PARADIGM-HF differ little from those in SOLVD-T, the potential benefit of LCZ696 over enalapril is being tested in addition to two additional disease-modifying drugs in the majority of patients in PARADIGM-HF. Despite these treatments, patients in PARADIGM-HF have persisting symptoms and signs, reduced HRQL, a chronically low LVEF and elevated levels of B-type natriuretic peptides. PARADIGM-HF will test whether further augmentation of the endogenous protective natriuretic peptide and other vasoactive systems will reduce morbidity and mortality in HF-REF.

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Conflict of interest: J.M. has worked as Co-Principal Investigator of PARADIGM-HF from Novartis, who make LCZ696. A.S.D has received honoraria from Novartis. J.G. holds stock in and conducts
References

1. Mangafico S, Costello-Boerrigter LC, Andersen IA, Castiliano A, Burnett JC Jr. Neutral endopeptidase inhibition and the natriuretic peptide system: an evolving strategy in cardiovascular therapeutics. Eur Heart J 2013;34:886–893c.

2. von Lueder TG, Sangaralingham SJ, Wang BH, Kompa AR, Aatar D, Burnett JC Jr, Krum H. Renin-angiotensin blockade combined with natriuretic peptide system augmentation: novel therapeutic concepts to combat heart failure. Circ Heart Fail 2013;6:594–605.

3. Vardeny O, Tacheny T, Solomon SD. First-in-class angiotensin receptor neprilysin inhibitor in heart failure. Clin Pharmacol Ther 2013;94:445–448.

4. Newby DE, McDonagh T, Currie PF, Northridge DB, Boon NA, Dargie HJ. Can- doxatril improves exercise capacity in patients with chronic heart failure receiving angiotensin converting enzyme inhibition. Eur Heart J 1998;19:1808–1813.

5. Packer M, Califf RM, Konstam MA, Krum H, McMurray JJ, Rouleau JL, Swedberg K. Comparison of omapatrilat and enalapril in patients with chronic heart failure: the Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events (OVERTURE). Circulation 2002;106:920–926.

6. Kostis JB, Packer M, Black HR, Schmieder R, Henry D, Levy E. Omapatrilat and enalapril in patients with hypertension: the Omapatrilat Cardiovascular Treatment vs. Enalapril (OCTAVE) trial. Am J Hypertens 2004;17:103–111.

7. McMurray JJ, Packer M, Desai AS, Gong J, Levkowitz MP, Rizkalla AR, Rouleau J, Shi VC, Solomon SD, Swedberg K, Thompson MR. PARADIGM-HF Committees and 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.

8. Fryer RM, Segreti J, Banfor PN, Widomska DL, Backes BJ, Lin CW, Balzaroso J, Cox BF, Trevillian JM, Reinhart GA, von Geldern TW. Effect of bradykinin metabolism inhibitors on evoked hypotension in rats: rank efficacy of enzymes associated with bradykinin-mediated angioedema. Br J Pharmacol 2008;153:947–955.

9. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. The SOLVD Investigators. N Engl J Med 1991;325:393–402.

10. McMurray JJ, Ostergren J, Swedberg K, Granger CB, Held P, Michelson EL, Olofsson B, CHARM Investigators and Committees. Clinical features and contemporary management of patients with low and preserved ejection fraction heart failure: baseline characteristics of patients in the Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity (CHARM) programme. Eur J Heart Fail 2003;5:261–270.

11. Hjalmarson A, Goldstein S, Fagerberg B, Wedel H, Waagstein F, Kjekshus J, Wikström J, El Alf Al A, Vitovce J, Aldershult J, Halin M, Dietz R, Neuhaus KL, Jäkoni A, Thorgeirsson G, Dunsellman PH, Gullstedt L, Kuch J, Herlitz J, Rickenbacher P, Ball S, Gottlieb S, Deedwania P. Effects of controlled-release metoprolol on total mortality, hospitalizations, and well-being in patients with heart failure: the Metropolol CR/XL Randomized Intervention Trial in con- gestive heart failure (MERIT-HF); MERIT-HF Study Group. JAMA 2000;283:1295–1302.

12. Kjekshus J, Apetrei E, Barrios V, Böhm M, Ciglai J, Currie PF, Krum H, McMurray J, Ruppel J, Schaefferberger M, Vanhaecke J, van Veldhuisen DJ, Wedel H, Wikström J, CORONA Group. Rosuvastatin in older patients with systolic heart failure. N Engl J Med 2007;357:2248–2261.

13. Packer M, Coats AJ, Fowler MB, Katus HA, Krum H, Mohacsi P, Rouleau JL, Tendera M, Castaigne A, Roeger EB, Schultz MK, DeMets DL. Carvedilol Prospective Randomized Cumulative Survival Study Group. Effect of carvedilol on survival in severe chronic heart failure. N Engl J Med 2001;344:1651–1658.

14. Cohn JN, Tognoni G; Vasartlan Heart Failure Trial Investigators. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. N Engl J Med 2001;345:1667–1675.

15. Swedberg K, Young JB, Anand IS, Cheng S, Desai AS, Diaz R, Maggioni AP, McMurray JJ, O’Connor C, Pfeffer MA, Solomon SD, Sun Y, Tendera M, van Veldhuisen DJ, RED-HF Investigators. Treatment of anemia with darbepoetin alfa in systolic heart failure. N Engl J Med 2013;368:1210–1219.

16. Gissi-HF Investigators, Tavazzi L, Maggioni AP, Marchioli R, Maggioni AP, Parkhomenko A, Pieske BM, Popescu BA, Rønnevik PK, Rutten FH, Schmitter J, Seferovic P, Stepinska J, Trindade PT, Voors AA, Zannad F, Zannad K, Foonia P, IL; MADIT-CRT Trial Investigators. Efficacy and safety of exercise training in patients with chronic heart failure: HF-ACTION randomized controlled trial. JAMA 2010;303:139–149.

17. Moss AJ, Hall WJ, Cannom DS, Klein H, Brown MW, Daubert JP, Estes NA 3rd, Foster E, Greenberg H, Higgins SL, Pfeffer MA, Solomon SD, Wilber D, Zareba W; MADIT-CRT Trial Investigators. Cardiac-resynchronization therapy for the prevention of heart-failure events. N Engl J Med 2009;361:1329–1338.

18. Epidemiological considerations related to the new diagnostic criteria for diabetes mellitus. The European Diabetes Epidemiology Group (EDEG). Diabetologia 1998;41:51–52.

19. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Böhm M, Dickstein K, Falk V, Filippatos G, Fonseca C, Gomez-Sanchez MA, Jaarsma T, Kober L, Lip GY, Maggioni AP, Parkhomenko A, Pieske BM, Popescu BA, Rønnevik PK, Rutten FH, Schmitter J, Seferovic P, Stepinska J, Trindade PT, Voors AA, Zannad F, Zehir A. Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Eur J Heart Fail 2012;14:83–89.

20. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Drazner MH, Fonarow GC, Geraci SA, Horwich T, Januzzi JL, Johnson MR, Kasper EK, Levy WC, Masoudi FA, McBride PE, McMurray JJ, Mitchell JE, Peterson PN, Riegel B, Sam F, Stevenson LV, Tang WH, Tsai EJ, Wilkoff BL. American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. 2009 focused updated guideline for the management of patients with heart failure. J Am Coll Cardiol 2009;53:e69–e203.

21. American Diabetes Association. Clinical practice recommendations of the American Diabetes Association. Diabetes Care 2003;26(suppl 1):S1–S88.