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McMurray, J. J. V. et al. (2014) *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)*. *European Journal of Heart Failure*, 16 (7). pp. 817-825. ISSN 1388-9842

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Deposited on: 26 August 2014

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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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Received 18 March 2014; accepted 2 April 2014; online publish-ahead-of-print 3 June 2014

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 $29 \pm$ 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.^{1,2} More recently, it has been suggested that natriuretic peptides also have favourable metabolic actions, including improvement of glucose tolerance and reduction in adipocyte growth.^{1,2}

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 neprilysin].^{2,3} There have been several attempts to determine whether inhibition of NEP is of benefit in patients with cardiovascular disease.^{2,4–6}

Because NEP also degrades angiotensin II, NEP inhibition must be combined with an angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB).^{2,3,7} 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.^{3,7,8} 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.^{3,7,9}

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).⁷ 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).⁹ 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.⁷ 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.⁷ 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.⁷ 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).⁹ 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.¹⁰ 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.^{11–25}

Table 1 Design of SOLVD-T, PARADIGM-HF and other, recent, large randomized controlled trials in heart failure and reduced ejection fraction (HF-REF)

	SOLVD-T, N = 2569	CHARM-Added ¹⁰ , N = 2548	HEAAL ¹¹ , N = 3834	RAFT ¹² , N = 1798	SHIFT ¹³ , N = 6505	EMPHASIS-HF [§] , N = 2737	PARADIGM-HF [§] , N = 8442
Inclusion criteria							
Age (years)	21–80	≥18	≥18	≥18	≥18	≥55	≥18
NYHA class	II–IV	II–IV	II–IV	II–III ^d	II–IV	II	II–IV
LVEF (%)	≤35%	≤40%	≤40%	≤30%	≤35%	≤30% ^f	≤40% ^g
HF hospitalization	No	Yes ^b	No	No	Yes ^e	Yes ^b	Yes ^h
Other	–	–	–	Sinus rhythm QRS ^d ≥120 ms	Sinus rhythm ≥70 bpm	–	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	–	≥90	–	≥85	≥85	≥95
Potassium, mmol/L	–	<5.5	≤5.7	–	–	<5.0	≤5.4
Run-in							
Placebo/control	Yes	No	No	No	Yes	No	Yes
Active	Yes	No	Yes ^c	No	No	No	Yes
Baseline treatment	–	Beta-blocker ACEi	Beta-blocker	Beta-blocker ACEi or ARB	Beta-blocker ACEi or ARB	Beta-blocker ACEi or ARB	Beta-blocker MRA as indicated
Comparison	Placebo Enalapril 10 mg b.i.d.	Placebo Candesartan 32 mg q.d.	Losartan 50 mg q.d. Losartan 150 mg q.d.	MRA as indicated ICD CRT–ICD	MRA as indicated Placebo Ivabradine 7.5 mg b.i.d.	Placebo Eplerenone 50 mg q.d.	Enalapril 10 mg b.i.d. LCZ 696 200 mg b.i.d.
Recruitment period	1986–1989	1999–2001	2001–2005	2003–2009	2006–2009	2006–2010	2009–2012 ⁱ

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 I₁-inhibitor Ivabradine Trial; EMPHASIS-HF, Eplerenone in Mild Patients Hospitalization And Survival study in Heart Failure; PARADIGM-HF, Prospective comparison of ARNI (angiotensin receptor 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.
^aSOLVD 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.
^bin CHARM-Added, cardiac hospitalisation within 6 months if NYHA class II; in EMPHASIS-HF cardiovascular hospitalization within 6 months (or BNP ≥250 pg/ml or NT-proBNP ≥500 pg/ml in men and 750 pg/ml in women).
^coptional in patients already taking an ARB.
^dNYHA class III excluded after 2006.
^ewithin 12 months.
^f≥30–35% if QRS duration >130 ms.
^gchanged to ≤35% December 2010.
^hand 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.
ⁱthe 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).¹¹ 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_f Inhibitor Ivabradine Trial, which mandated a heart rate of ≥ 70 bpm for inclusion) and SOLVD-T.^{9,13}

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 m²) 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 ^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	18
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 ²	–	28	27	–	28	28	28
Ischaemic aetiology (%)	71	62	–	67	67	69	60
Medical history (%)							
Hospitalization for HF	–	77	–	25 ^c	100 [†]	53	63 ^k
Hypertension	42	48	60	45	67	66	71
Angina pectoris	37	53	65 ⁱ	–	–	43	27 ^j
Myocardial infarction	66	56	–	–	56	50	43
PCI	N/A	15	–	24	–	22	21
CABG	29 [*]	25	–	34	–	19	15
Atrial fibrillation/flutter	10	26	28	13 ^e	8 ^d	31	37 ⁱ
LBBB ^b	–	31	–	72	–	27	20
Diabetes mellitus	26	30	31	34	31	31	34
Stroke	(8) ^{**}	9	–	–	8	10	9
Current smoker	22	17	–	14	18	–	14
Renal function							
Serum creatinine	106	103	97	–	–	102	99
(μmol/L)	76 ^{***}	71	–	61	75	71	68
eGFR mL/min.1.73m ² (mean)	36 ^{***}	33	–	50	–	33	37
eGFR <60 mL/min.1.73m ² (%)							
Treatment (%)							
Diuretic	85	90	77	85	–	85	80
ACE inhibitor	N/A	100	N/A	–	79	78	N/A ^m
ARB	N/A	N/A	N/A	–	14	19	N/A ^m
ACEi, ARB, or both	N/A	N/A	N/A	97	–	94	N/A ^m
βeta-blocker	8	55	72	90	90	87	93
MRA	–	17	38	42 ^f	60	N/A	60
Digoxin	67	58	42	35	22	27	30 ⁿ
Anticoagulant	16	38	33	34 ^g	–	–	32 ^o
Antiplatelet							
Aspirin	–	51	51	67	–	–	52 ^p
ADP antagonist	N/A	–	–	16	–	–	15 ^q
Any antiplatelet	33	–	–	–	–	–	57
Lipid lowering	–	41	39 ^h	68 ^h	58 ^h	62	56

Table 2 Continued

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

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 I₁Inhibitor Ivabradine Trial; EMPHASIS-HF, Eplerenone in Mild Patients Hospitalization And Survival study in Heart Failure; PARADIGM-HF, Prospective comparison of ARNi (angiotensin receptor neprilysin inhibitor) with ACEi (angiotensin-converting enzyme inhibitor) to Determine Impact on Global Mortality and morbidity in Heart Failure trial; N/A, not applicable; –, not reported; BMI, body mass index; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; LBBB, left bundle branch block; ACE, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; MRA, mineralocorticoid receptor antagonist; ADP, adenosine diphosphate; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter defibrillator; CRT-D, cardiac resynchronization therapy—defibrillator.

^aMedian.

^bNYHA class at randomization—all patients were in NYHA functional class II or greater at entry to the active run-in period.

^cin previous 6 months.

^dcurrent AF excluded.

^epermanent AF at baseline.

^fspironolactone.

^gwarfarin.

^hstatin.

ⁱhistory of AF only.

^jhistory of ischaemic heart disease in HEAAL and of stable or unstable angina in PARADIGM-HF.

^kno time limit.

^lCRT-D or CRT-P.

^mpre-enrolment, 77% were treated with an ACE inhibitor and 22% with an ARB (100% with one, other or both).

ⁿincludes all digitalis derivatives.

^oincludes vitamin K antagonists, rivaroxiban, dabigatran, and apixaban.

^pincludes all aspirin derivatives, alone or in combinations.

^qincludes clopidogrel, prasugrel, ticagrelor, ticlopidine, and their combinations.

^rCABG or PCI.

^{**}Cerebrovascular disease.

^{***}Creatinine clearance (in SOLVD overall, the mean eGFR was 70 mL/min.1.73 m² and 32% of patients had an eGFR <60 mL/min.1.73 m²).

[†]Per protocol, all patients had an admission for worsening heart failure within 12 months.

exception of race because of the much wider geographical reach of PARADIGM-HF.^{7,10}

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

MRA, 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

Table 3 Baseline signs of heart failure in PARADIGM-HF compared with other trials in heart failure and reduced ejection fraction

	SOLVD-T ⁹ , N = 2569	CARE-HF ¹⁵ , N = 813	COMET ¹⁶ , N = 1511	CHARM-Added ¹⁰ , N = 2548	MERIT-HF ¹⁸ , N = 3991	PARADIGM-HF ⁷ , N = 8442
Mean age (year)	61	67	62	64	64	64
NYHA class distribution (%)						
I/II	68	21	48	24	41	75
III	30	64	48	73	56	24
IV	2	10	3	3	3	1
LVEF (%)	25	25*	26	28	28	29
Proportion (%) with						
Rales	12	12	9	15	11	8
S3	23	20	19	18	23	9
JVP elevation	11	18	N/R	11	14	10
Peripheral oedema	17	18	13	23	15	21

SOLVD-T, Studies of Left Ventricular Dysfunction Treatment trial; CARE-HF, Cardiac Resynchronization in Heart Failure; COMET, Carvedilol Or Metoprolol European Trial; CHARM-Added, Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM)-Added trial; MERIT-HF, the Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure; 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; S3, third heart sound; JVP, jugular venous pressure; N/R, not reported.

*Median.

Table 4 Plasma N-terminal pro β -type natriuretic peptide (NT-proBNP) concentrations in PARADIGM-HF compared with other trials in heart failure and reduced ejection fraction (HF-REF)

	CARE-HF ¹⁵ , N = 813	COMET ¹⁶ , N = 1511	CORONA ¹⁹ , N = 5011	COPERNICUS ²⁰ , N = 2289	Val-HeFT ²¹ , N = 5010	PARADIGM-HF ⁷ , N = 8442
Mean age (years)	67	62	73	63	63	64
NYHA class distribution (%)						
I/II	21	48	37	0	61	75
III	64	48	62	0	36	24
IV	10	3	2	100**	2	1
Mean LVEF (%)	25*	26	31	20	27	29
AF (%)	0	20 [†]	24 [†]	N/R	12 [†]	24 [†]
NT proBNP, pg/mL*	1814	1242	1497	1767	861	1608

CARE-HF, Cardiac Resynchronization in Heart Failure; COMET, Carvedilol Or Metoprolol European Trial; CORONA, Controlled Rosuvastatin Multinational Trial in Heart Failure; COPERNICUS, Carvedilol Prospective Randomized Cumulative Survival Trial; Val-HeFT, Valsartan Heart Failure Trial. 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; AF, atrial fibrillation.

NT proBNP was measured in 732 patients in CARE-HF, 1559 patients in COMET, 3664 patients in CORONA, 1011 patients in COPERNICUS, 1742 patients in the placebo group of Val-HeFT, and 8394 patients in PARADIGM-HF.

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*Median.

**NYHA class not reported but all patients said to have 'severe' heart failure with symptoms at rest or on minimal exertion.

[†]On baseline electrocardiogram.

median NT-proBNP concentration was almost as high as in the CARE-HF and COPERNICUS trials, which enrolled patients with more severe functional limitation and a very low LVEF.^{15,20} This probably reflects two factors. First, in PARADIGM-HF, patients without a history of hospitalization owing to heart failure within 12 months were required to have either a BNP ≥ 150 pg/mL or NT-proBNP of ≥ 600 pg/mL in order to be enrolled.⁷ Second, the proportion of patients with atrial fibrillation or flutter at baseline was higher in PARADIGM-HF than in any other trial in which NT-proBNP was measured (Table 4). It is anticipated that the high

median NT-proBNP level in PARADIGM-HF will help ensure that the expected rates for CV mortality and hospitalization owing to heart failure will be obtained.⁷

In addition to the primary endpoints of CV death and hospital admission for treatment of worsening heart failure, the first secondary endpoint in PARADIGM-HF is health-related quality of life (HRQL), as assessed by the KCCQ.³⁰ The HRQL in patients with heart failure is associated with many factors, including NYHA class (patients with worse functional class tend to have worse HRQL), age (younger patients on average

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

	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 hospitalization	HF hospitalization past year	Suitable for exercise training	QRS ^d ≥130 ms	Elevated BNP/NT proBNP ± recent HF hospitalization
Intervention	OMT vs. OMT + darbepoetin	OMT vs. OMT + ivabradine	OMT vs. OMT + rosuvastatin [†]	OMT vs. OMT + exercise training	OMT + CRT-D vs. OMT + ICD	OMT + enalapril vs. OMT + LCZ696
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 I₁-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 polyunsaturated 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.

report worse HRQL than older ones), sex (women report worse HRQL than men), and comorbidity.³¹ Differences among trials in these factors may explain why, for example, RED-HF (Reduction of Events With Darbepoetin Alfa in Heart Failure Trial, which had a high proportion of women and in which all patients had anaemia) reported the worst HRQL, and why patients in both SHIFT (high proportion of patients in NYHA class III and IV) and HF-ACTION (Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training; youngest average age) had generally worse HRQL than those in other contemporary trials, including PARADIGM-HF.^{7,15,22,24} Patients in PARADIGM-HF had a KCCQ OSS similar to that of patients in GISSI-HF (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico-heart failure) and MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy), probably reflecting the larger proportion of patients in NYHA class I or II in these trials, as well as age and gender distribution.^{23,25}

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.

Acknowledgement

The authors thank Dr Paola Di Giulio for providing information about the OSS for the KCCQ in the GISSI-HF trial.

Funding

J.M.'s employer, Glasgow University, has received monies for his time spent as Co-Principal Investigator of PARADIGM-HF from Novartis. A.S.D. and S.D.S. have received research support from Novartis. K.S. received research support from Amgen, Novartis, Pfizer and Servier.

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

research sponsored by Novartis. M.P.L., V.C.S. and A.R.R. are full-time employees of Novartis. J.R., M.P. and M.R.Z. serve as consultants to Novartis. SDS has received consultancy fees from Novartis. K.S. is a Consultant to Amgen, Novartis, Roche, Servier and Vifor.

References

- Mangiafico S, Costello-Boerrigter LC, Andersen IA, Cataliotti 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.
- von Lueder TG, Sangaralingham SJ, Wang BH, Kompa AR, Atar 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.
- Vardeny O, Tacheny T, Solomon SD. First-in-class angiotensin receptor neprilysin inhibitor in heart failure. *Clin Pharmacol Ther* 2013;**94**:445–448.
- Newby DE, McDonagh T, Currie PF, Northridge DB, Boon NA, Dargie HJ. Candoxatril improves exercise capacity in patients with chronic heart failure receiving angiotensin converting enzyme inhibition. *Eur Heart J* 1998;**19**:1808–1813.
- 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.
- 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.
- McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau J, Shi VC, Solomon SD, Swedberg K, Zile 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.
- Fryer RM, Segreti J, Banfor PN, Widomski DL, Backes BJ, Lin CW, Ballaron SJ, Cox BF, Trevillyan 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.
- 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**:293–302.
- McMurray JJ, Ostergren J, Swedberg K, Granger CB, Held P, Michelson EL, Olofsson B, Yusuf S, Pfeffer MA; CHARM Investigators and Committees. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors: the CHARM-Added trial. *Lancet* 2003;**362**:767–771.
- Konstam MA, Neaton JD, Dickstein K, Drexler H, Komajda M, Martinez FA, Riegger GA, Malbecq W, Smith RD, Guptha S, Poole-Wilson PA; HEAAL Investigators. 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.
- Tang AS, Wells GA, Talajic M, Arnold MO, Sheldon R, Connolly S, Hohnloser SH, Nichol G, Birnie DH, Sapp JL, Yee R, Healey JS, Rouleau JL; Resynchronization–Defibrillation for Ambulatory Heart Failure Trial Investigators. Cardiac-resynchronization therapy for mild-to-moderate heart failure. *N Engl J Med* 2010;**363**:2385–2395.
- Swedberg K, Komajda M, Böhm M, Borer JS, Ford I, Dubost-Brama A, Lerebours G, Tavazzi L; SHIFT Investigators. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. *Lancet* 2010;**376**:875–85.
- Zannad F, McMurray JJ, Krum H, van Veldhuisen DJ, Swedberg K, Shi H, Vincent J, Pocock SJ, Pitt B; EMPHASIS-HF Study Group. Eplerenone in patients with systolic heart failure and mild symptoms. *N Engl J Med* 2011;**364**:11–21.
- Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L, Tavazzi L; Cardiac Resynchronization–Heart Failure (CARE-HF) Study Investigators. The effect of cardiac resynchronization on morbidity and mortality in heart failure. *N Engl J Med* 2005;**352**:1539–1549.
- Poole-Wilson PA, Swedberg K, Cleland JG, Di Lenarda A, Hanrath P, Komajda M, Lubsen J, Lutiger B, Metra M, Remme WJ, Torp-Pedersen C, Scherhag A, Skene A. Carvedilol Or Metoprolol European Trial Investigators. Comparison of carvedilol and metoprolol on clinical outcomes in patients with chronic heart failure in the Carvedilol Or Metoprolol European Trial (COMET): randomised controlled trial. *Lancet* 2003;**362**:7–13.
- McMurray JJ, Ostergren J, Pfeffer M, Swedberg K, Granger CB, Yusuf S, 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.
- Hjalmarson A, Goldstein S, Fagerberg B, Wedel H, Waagstein F, Kjekshus J, Wikstrand J, El Allaf D, Vitovec J, Aldershvile J, Halinen M, Dietz R, Neuhaus KL, Jánosi A, Thorgeirsson G, Dunselman PH, Gullestad 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 Metoprolol CR/XL Randomized Intervention Trial in congestive heart failure (MERIT-HF); MERIT-HF Study Group. *JAMA* 2000;**283**:1295–1302.
- Kjekshus J, Apetrei E, Barrios V, Böhm M, Cleland JG, Cornel JH, Dunselman P, Fonseca C, Goudev A, Grande P, Gullestad L, Hjalmarson A, Hradec J, Jánosi A, Kamenský G, Komajda M, Korewicki J, Kuusi T, Mach F, Mareev V, McMurray JJ, Ranjith N, Schaefelberger M, Vanhaecke J, van Veldhuisen DJ, Waagstein F, Wedel H, Wikstrand J; CORONA Group. Rosuvastatin in older patients with systolic heart failure. *N Engl J Med* 2007;**357**:2248–2261.
- Packer M, Coats AJ, Fowler MB, Katus HA, Krum H, Mohacs P, Rouleau JL, Tendera M, Castaigne A, Roecker 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.
- Cohn JN, Tognoni G; Valsartan 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.
- 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 Committees; RED-HF Investigators. Treatment of anemia with darbepoetin alfa in systolic heart failure. *N Engl J Med* 2013;**368**:1210–1219.
- Gissi-HF Investigators, Tavazzi L, Maggioni AP, Marchioli R, Barlera S, Franzosi MG, Latini R, Lucci D, Nicolosi GL, Porcu M, Tognoni G. Effect of rosuvastatin in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial. *Lancet* 2008;**372**:1231–1239.
- O'Connor CM, Whellan DJ, Lee KL, Keteyian SJ, Cooper LS, Ellis SJ, Leifer ES, Kraus WE, Kitzman DW, Blumenthal JA, Rendall DS, Miller NH, Fleg JL, Schulman KA, McKelvie RS, Zannad F, Piña IL; HF-ACTION Investigators. Efficacy and safety of exercise training in patients with chronic heart failure: HF-ACTION randomized controlled trial. *JAMA* 2009;**301**:1439–1450.
- 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.
- Epidemiological considerations related to the new diagnostic criteria for diabetes mellitus. The European Diabetes Epidemiology Group (EDEG). *Diabetologia* 1998;**41**:51–52.
- 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, Schwitler 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. *Eur J Heart Fail* 2012;**14**:803–869.
- Yancy CV, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Drazner MH, Fonarow GC, Geraci SA, Horwitz T, Januzzi JL, Johnson MR, Kasper EK, Levy WC, Masoudi FA, McBride PE, McMurray JJ, Mitchell JE, Peterson PN, Riegel B, Sam F, Stevenson LW, Tang WH, Tsai EJ, Wilkoff BL; American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2013;**62**:e147–e239.
- Gheorghiadu M, Patel K, Filippatos G, Anker SD, van Veldhuisen DJ, Cleland JG, Metra M, Aban IB, Greene SJ, Adams KF, McMurray JJ, Ahmed A. Effect of oral digoxin in high-risk heart failure patients: a pre-specified subgroup analysis of the DIG trial. *Eur J Heart Fail* 2013;**15**:551–559.
- Green CP, Porter CB, Bresnahan DR, Spertus JA. Development and evaluation of the Kansas City Cardiomyopathy Questionnaire: a new health status measure for heart failure. *J Am Coll Cardiol* 2000;**35**:1245–1255.
- Lewis EF, Lamas GA, O'Meara E, Granger CB, Dunlap ME, McKelvie RS, Probstfeld JL, Young JB, Michelson EL, Halling K, Carlsson J, Olofsson B, McMurray JJ, Yusuf S, Swedberg K, Pfeffer MA; CHARM Investigators. Characterization of health-related quality of life in heart failure patients with preserved versus low ejection fraction in CHARM. *Eur J Heart Fail* 2007;**9**:83–91.