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Rationale and design of the Eplerenone in Mild Patients Hospitalization And SurvIval Study in Heart Failure (EMPHASIS-HF)

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Aims In chronic heart failure (HF), aldosterone antagonists have been shown to improve survival in patients with low ejection fraction and moderate-to-severe symptoms [New York Heart Association (NYHA) classes III and IV]. Efficacy of these agents was also shown when they were administered to patients with left ventricular dysfunction and signs and symptoms of CHF early after acute myocardial infarction. It is not known whether the selective aldosterone antagonist eplerenone can improve outcomes in mildly symptomatic patients. The Eplerenone in Mild Patients Hospitalization And SurvIval Study in Heart Failure (EMPHASIS-HF) was designed to evaluate the effect of eplerenone on mortality and morbidity in patients with chronic systolic HF in NYHA class II.

Methods Approximately 3100 patients with ejection fraction $\leq$30% and estimated glomerular filtration rate $\geq$30 mL/min/1.73 m^2 will be recruited. Patients are randomized 1:1 to double-blind eplerenone or placebo in addition to standard chronic HF therapy. Doses are adjusted from 25 mg every other day to 50 mg daily, depending on serum potassium. The primary endpoint is a composite of time to cardiovascular death or first hospital admission for worsening HF, whichever occurs first.

Conclusion The study will be complete when approximately 813 subjects experience a primary endpoint.
Clinical Trials.gov. NCT00232180.

Keywords Systolic heart failure • Clinical trial • Outcome • Aldosterone antagonist • Eplerenone

Introduction

Aldosterone plays an important role in the pathophysiology of heart failure (HF),[1,2] and mineralocorticoid receptors (MRs) are over-expressed in the myocardium of the failing heart.[3,4] Despite chronic angiotensin-converting enzyme (ACE)-inhibitor (ACE-I) therapy,[5,6] β-blocker therapy,[7] and angiotensin receptor blocker (ARB) therapy,[8] patients with even mild symptoms of HF have elevated plasma aldosterone levels,[9] although combined ACE and ARB therapy was recently reported to give a sustained decrease in aldosterone levels.[10]

In patients with a low left ventricular ejection fraction (LVEF) and severe symptoms [New York Heart Association (NYHA) class III or IV], adding the aldosterone (receptor) blocker (AB) spironolactone 25 mg daily to standard therapy (ACE-I and loop diuretic) resulted in a 30% reduction in the relative risk of all-cause mortality in the placebo-controlled Randomized Aldactone Evaluation Study (RALES). Spironolactone treatment also resulted in a 35% lower frequency of hospitalization for worsening HF.[11] However, RALES only enrolled patients with severe HF and signs of volume overload, and few received β-blocker therapy. In patients with acute myocardial infarction (MI) complicated by left

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† In memoriam.

ventricular systolic dysfunction (LVSD) and HF, adding the more selective AB eplerenone to optimal medical therapy, including ACE-Is and β-blockers, reduced morbidity and mortality in the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS).[12] Consequently, current guidelines recommend ABs in patients with low EF (<35%) and moderate-to-severe (NYHA class III and IV) HF and in selected patients after acute MI.[13]

The efficacy, safety, and tolerability of AB have not been systematically evaluated in a large-scale, prospective, randomized study of patients with LVSD and mild chronic HF.

Although patients with LVSD may be clinically stable showing few, if any, symptoms for long periods of time, their clinical course may be complicated by frequent hospital admissions for worsening HF and a relatively high rate of cardiovascular (CV) mortality, the most frequent mode being sudden cardiac death.[14]

The aim of the Eplerenone in Mild Patients Hospitalization And SurvIval Study in Heart Failure (EMPHASIS-HF) is to investigate the effects of eplerenone vs. placebo added to fully optimized therapy including an ACE-I (or/and an ARB) and β-blocker in patients with mild (NYHA functional class II) chronic HF with low EF.

Study design

EMPHASIS-HF is a multicentre, randomized, double-blind, placebo-controlled study.

The primary objective of this trial is to evaluate the efficacy and safety of eplerenone plus standard HF therapy vs. placebo plus standard HF therapy on the cumulative incidence of the composite endpoint of CV death or HF hospitalization, defined as the first occurrence of either HF hospitalization or CV death. The secondary endpoints are the first occurrence of all-cause mortality or HF hospitalization, all-cause mortality, CV mortality, all-cause hospitalization, HF hospitalization, all-cause mortality or all-cause hospitalization, HF mortality or HF hospitalization, CV hospitalization, fatal/non-fatal myocardial infarction, fatal/non-fatal stroke, days alive and out of hospital at one year, implantation of a cardiac defibrillator, implantation of a resynchronization device, new-onset atrial fibrillation/flutter, new-onset diabetes mellitus, worsening renal function (if it results in hospitalization), and hospitalization for hyperkalaemia. For all events both the total number of patients experiencing the event as well as the total number of events will be analysed.

Patient enrolment criteria

Inclusion criteria

Male and female patients aged 55 years or over with the following criteria are eligible.

(1) A diagnosis of chronic HF and LVSD of either ischaemic or non-ischaemic aetiology or inoperable valve disease.
(2) Duration of HF must be at least 4 weeks.
(3) Left ventricular ejection fraction ≤30% by echocardiography, contrast ventriculography, magnetic resonance imaging (MRI) or nuclear imaging within 6 months of randomization, or LVEF ≤35% in addition to QRS duration >130 ms. Subjects with LVEF 31–35% must have QRS duration >130 ms to be eligible.
(4) New York Heart Association functional class II at randomization.
(5) Treatment with optimal target or maximal tolerated dose of ACE-I and/or ARB and β-blocker, unless contra-indicated, as well as diuretics if clinically indicated.
(6) Serum potassium (K^+) ≤5.0 mmol/L within 24 h prior to randomization.
(7) Estimated glomerular filtration rate (eGFR), using the Modification of Diet in Renal Disease (MDRD) six-variable formula, ≥30 mL/min/1.73 m^2 within 24 h prior to randomization.
(8) Randomization must occur within 6 months of a hospitalization for CV reasons. In the absence of a history of hospitalization for CV reasons, documented plasma B-type natriuretic peptide (BNP) of at least 250 pg/mL or N terminal proBNP (NT-proBNP) ≥500 pg/mL for males and ≥750 pg/mL for females within 15 days prior to randomization. Cardiovascular hospitalization is defined as hospitalization for HF, acute MI, unstable angina pectoris, cardiac arrhythmia, stroke, or other CV reasons such as peripheral arterial disease or hypotension. Hospitalization for an elective CV procedure does not qualify for entry into this trial except hospitalization for implantation of a cardioverter–defibrillator (ICD) or cardiac resynchronization therapy (CRT) device.
(9) Subjects previously treated with an AB for more than 7 consecutive days must meet the following additional criteria:
   (a) No history of clinically significant hyperkalaemia or renal impairment during previous AB therapy.
   (b) Aldosterone blocker therapy discontinued for at least 3 months prior to randomization. Investigators were instructed not to stop AB in patients just to enter the trial.

Exclusion criteria

Patients are not eligible for enrolment if they present any of the following criteria:

- an indication for AB treatment according to current HF guidelines[13];
- history of stroke, cardiac surgery, or percutaneous coronary intervention within 30 days prior to randomization;
- uncontrolled hypertension [systolic blood pressure (SBP) >180 mmHg and/or a diastolic blood pressure >110 mmHg] or symptomatic hypotension, or an SBP <85 mmHg;
- need for adjunctive potassium-sparing diuretic therapy;
- an intra-aortic balloon pump or any other mechanical assist device;
- scheduled for cardiac transplantation;
- serum potassium >5.0 mmol/L within 24 h prior to randomization;
- estimated glomerular filtration rate <30 mL/min/1.73 m^2 within 24 h prior to randomization;
- following concomitant therapy with potent cytochrome P4503A4 inhibitors or inducers;
- blood haemoglobin <10 g/dL;

- any other pre-existing and ongoing significant co-morbid condition.

Dosing regimen

Subjects are started on eplerenone or matching placebo at doses of 25 mg once daily if eGFR is $\geq$50 mL/min/1.73 m^2, and 25 mg every other day if eGFR is 30–49 mL/min/1.73 m^2. At 4 weeks, provided that serum potassium is $\leq$5.0 mmol/L, the dose of study drug may be increased to 50 mg once daily if eGFR $\geq$50 mL/min/1.73 m^2 and to 25 mg once daily if eGFR is in the range of 30–49 mL/min/1.73 m^2. Study drug dose adjustment or dose maintenance is guided by safety considerations, mainly by changes in serum potassium and eGFR which are monitored at each visit. Investigators are instructed to decrease the dose if potassium is $>$5.5 mmol/L or withhold the dose if potassium is $>$6.0 mmol/L, and to recheck potassium within 72 h and only restart the dose once potassium drops to $<$5.0 mmol/L.

Statistical considerations

Sample size determination

The study was initially designed to enrol a total sample size of 2584 randomized subjects (1292 per treatment group) with at least 80% power to detect an 18% risk reduction in the primary efficacy endpoint. This is based on the two-sided log-rank test for between-treatment comparison in the time to first occurrence of CV mortality or hospitalization for HF (a composite endpoint) at a 5% level of significance, assuming an annual event rate of 18% and a 5% annual dropout rate. For a group-sequential trial with three equal interval efficacy looks (two interim analyses and the final analysis at trial completion), an expected annual event rate of 18%, a subject enrolment period of 18 months at most, an endpoint accrual period of 30 months, an assumed exponential dropout rate of 5% per year, and a sample size of 2584 (1292 per treatment group), randomized subjects will be followed until 813 primary events (CV death or HF hospitalization) have occurred.

During the course of the study, a lower than anticipated overall event rate prompted us to amend the protocol by increasing sample size to 3100 patients.

Efficacy analysis

The efficacy analysis will be performed on the intent-to-treat population. The time-to-event distributions will be summarized by treatment group using Kaplan–Meier estimates of cumulative incidence. Cox's proportional hazards regression model will be used for adjusting the following baseline prognostic factors: age, eGFR, LVEF, body mass index, haemoglobin, heart rate, SBP, diabetes, history of hypertension, prior MI, atrial fibrillation, and left bundle branch block (LBBB) or QRS $>$130 ms.

In addition, the primary efficacy endpoint will be analysed on the following pre-specified subgroups for subjects' baseline characteristics: gender, age ($<$65 and $\geq$65 years), region (Western Europe/Australia, Eastern Europe, Asia/Middle East/Africa, and South/North America), baseline SBP and pulse pressure (less than or equal to median and greater than median), heart rate (less than or equal to median and greater than median), eGFR ($\leq$50 and $>$50 mL/min/1.73m^2), LVEF ($\leq$30 and $>$30%), LBBB, atrial fibrillation, diabetes (yes and no), and aetiology of HF (ischaemic and non-ischaemic HF), prior use of triple neurohumoral blockers (β-blocker plus ACE-I plus ARB), prior use of β-blocker, prior use of ACE-I or ARB, history of hypertension, period of prior CV hospitalization ($\leq$180 days and $>$180 days), prior CRT, prior ICD, and QRS $>$130 ms.

Safety analysis

For all subjects who took at least one dose of study medication (eplerenone or placebo), the incidence, severity, and relationship to the study drug of treatment-emergent adverse events will be summarized by body system and treatment groups. In addition, the incidence of adverse events causing study drug discontinuation and serious adverse events will be summarized per treatment group. Incidence of marked abnormalities in the protocol-specified laboratory tests will be summarized per treatment group.

Trial oversight

An independent Executive Steering Committee in conjunction with the sponsor will oversee the conduct of the trial. An independent Endpoint Adjudication Committee will review the documentation on clinical endpoint events and determine whether the events meet the pre-specified criteria. An independent Data Safety Monitoring Committee (DSMC) will monitor the safety and efficacy of the trial and periodically assess whether the trial should continue as planned (Appendix).

Statistical decision rules and interim analyses

All hypothesis tests will be two-sided. Results will be considered statistically significant if a *P*-value $<$0.05 is obtained for primary hypotheses (adjusting for two interim analyses; see the discussion on interim analyses in what follows). Interim analyses examining the primary efficacy endpoint will be performed after a total of approximately 271 and 542 primary endpoint events have occurred. At the accrual of 542 primary endpoints, the DSMC may recommend the trial be terminated if either an overwhelming benefit (two-sided *P*-value $<$0.001 in favour of eplerenone) or an overwhelming harm (two-sided *P*-value $<$0.01 against eplerenone) is observed. In addition, the trial will be recommended for termination in the event of excessive all-cause mortality ascribable to eplerenone treatment (*P*-value $<$ 0.01) at any of the interim looks. Using an adaptation of the Haybittle-Peto stopping criterion, the *P*-value for the final primary analysis will be compared with $\alpha = 0.049$. No adjustment in α will be made for any looks on parameters/endpoints other than the primary composite endpoint.

Current status

EMPHASIS-HF started enrolling patients in March 2006. As of February 2010, it had enrolled 2600 patients in 272 centres and 29 countries distributed across all of the major regions worldwide. Study completion date is estimated at October 2011.

Discussion

The combination of an ACE-I and a β-blocker forms the core basis of therapy for patients with HF and low LVEF. These drugs have been proved to decrease morbidity and mortality in patients with HF across the full spectrum of symptoms (NYHA classes II–IV).[15,16]

To date, the efficacy of ABs has only been proved in patients with severe symptoms (NYHA classes III and IV) and in patients with low LVEF and clinical evidence of HF (or diabetes) after acute MI.[11,12]

Patient population

Patients with visibly 'mild' symptoms may nevertheless present severe underlying ventricular dysfunction, and the prognosis outcome over a 2-to-3-year period after initial diagnosis may be poor. The event rate in such patients is usually high, though relatively lower than for patients with moderate-to-severe symptoms.[14] Apart from the now-dated Studies Of Left Ventricular Dysfunction (SOLVD) prevention study,[17] no large-scale studies have focused exclusively on patients with mild symptoms at the time of randomization. EMPHASIS-HF will therefore provide important information on the contemporary natural history of these patients as well as on the impact of ABs in this setting.

A low event rate is a challenging feature in any outcome trial, requiring a large population sample size. In EMPHASIS-HF, in order to spare sample size, we elected to enrich the event rate by selecting patients aged >55 years. In addition, we restricted enrolment to patients with a history of recent CV hospitalization or a high BNP value. Data from the SOLVD[17,18] study as well as from the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) trial[19] underline that a recent history of HF hospitalization is consistently reported to be associated with a subsequently higher event rate.

Since LVEF is inversely associated with the outcome, we also set the inclusion LVEF at the relatively low level of <30%, whereas for patients with an LVEF ranging 30–35%, we added the additional risk factor requirement of QRS duration >130 ms. This was prompted by the fact that QRS prolongation is associated with a worse outcome in HF patients.[20]

Aldosterone blockers in patients with chronic mild heart failure

Current HF guidelines do not recommend the use of ABs in patients with mild symptoms of HF. European Society of Cardiology HF guidelines state that, unless contra-indicated or not tolerated, ABs should be considered in patients with low LVEF (<35%) and moderate-to-severe symptoms, i.e. NYHA classes III and IV, in the absence of hyperkalaemia and significant renal dysfunction (Class of recommendation I, Level of Evidence B).[13]

Few studies have investigated the effect of ABs specifically in patients with chronic mild-to-moderate systolic HF, and those that have been published enrolled a small number of patients and investigated the effect of ABs on surrogate endpoints. None was adequately powered to investigate mortality and morbidity outcomes.[9,21–24] All are covered in the systematic review by Ezekowitz and McAlister.[25] One relatively large study, the Anti-remodelling effect of canrenone in patients with mild chronic heart failure (AREA IN-CHF), was a randomized, double-blind, parallel-group comparison of canrenone (up to 50 mg/day), the active metabolite of spironolactone, against placebo in mild stable HF.[9] The primary endpoint was change in echocardiographic LV end-diastolic volume over 12 months. Patients had NYHA class II HF, LVEF ≤45%.[21] Left ventricular end-diastolic volume was similarly reduced in both arms, but LVEF increased more ($P < 0.04$) in the canrenone arm (from 40 to 45%) than in the placebo arm (from 40 to 43%). B-type natriuretic peptide decreased more in the canrenone arm (37%) than in the placebo arm (8%; $P < 0.0001$). The composite endpoint of cardiac death and hospitalization was significantly lower in the canrenone arm (8 vs. 15%; $P < 0.02$). The authors concluded that canrenone on top of optimal treatment for HF did not have additional effects on LVEDV but increased LVEF.[21] However, the number of clinical events in this study was relatively small ($n = 382$) and it was therefore unlikely to influence current guidelines and clinical practice.

The Reversal of Cardiac Remodelling with Eplerenone trial (REMODEL) investigated the effects of eplerenone compared with placebo on ventricular remodelling assessed by radionuclide ventriculography in 226 patients presenting with mild-to-moderate HF and left ventricular dysfunction. Eplerenone did not provide any additional benefit on LV remodelling in these patients over the 9-month duration of the study.[26]

Study endpoints

The primary endpoint of EMPHASIS-HF is the cumulative incidence of the composite endpoint of CV death or hospitalization for HF. This cause-specific endpoint is the most frequently used primary endpoint in recent and ongoing HF trials. All-cause mortality as a primary endpoint would have been more integrative and more robust. However, eplerenone is not expected to have any effect on non-CV deaths, and this endpoint might lead to a dilution of the expected benefit together with a loss of power, requiring an even larger sample size.

Several new secondary pre-specified endpoints are included in the protocol with the aim of generating new hypotheses. Given the potential effects of ABs on cardiac remodelling and electrophysiology, the study will investigate the effect of eplerenone on the implantation of cardiac defibrillators and/or resynchronization device implantation and of new-onset atrial fibrillation/flutter. New-onset diabetes mellitus will also be recorded in an attempt to investigate the possible metabolic effects of eplerenone.

Safety issues

EMPHASIS-HF is also designed to investigate whether the risk–benefit ratio of adding eplerenone is acceptable in mild-to-moderate HF. Spironolactone, even at modest doses, has undesirable side effects, particularly gynaecomastia, which is not observed with the more selective MR-blocker eplerenone. Both have hyperkalaemia as an obligate adverse effect, reflecting the renal tubular effects of MR blockade. Previous trials with eplerenone show that, with careful titration, there appears to be only a very modest increase of <0.3 mmol/L in plasma potassium, even at high doses (200 mg).[27] Similar to the RALES and EPHESUS trials, the carefully set inclusion/exclusion criteria for EMPHASIS-HF are intended to minimize the risk of hyperkalaemia and worsening renal function. Furthermore, the investigators are instructed to use a pre-defined dose titration algorithm based on serum potassium and creatinine levels measured at each visit. However, there is still a real risk of hyperkalaemia in elderly patients and/or diabetic patients with a low eGFR, particularly at higher doses and/or when potassium supplementation is used.[28]

Specific serious safety concerns over hyperkalaemia and renal function will be closely monitored. Hospitalization for worsening renal function and/or hyperkalaemia will be prospectively documented and adjudicated.

In patients with mild HF receiving optimal therapy including β-blockers, the balance between risk and benefit might not be as favourable as in the RALES and EPHESUS trials due to the patients' lower absolute risk of a CV event and likely lower absolute reduction of CV risk with eplerenone. However, a subgroup analysis of the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM)-Added trial has shown that in HF patients already taking spironolactone as well as an ACE-I and β-blocker, the addition of the ARB candesartan appeared to provide added benefit at acceptable risk.[29]

Conclusion

Heart failure with low LVEF but mild symptoms is a frequent condition that is still associated with poor outcome. Few trials have exclusively enrolled patients with this profile. If positive, the results of EMPHASIS-HF would extend the use of AB in HF with low LVEF. They would provide more safety data and expand the range of patients with low LVEF eligible for an AB, as well as provide additional safety information that should be of value in guiding clinical practice.

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Conflict of interest: F.Z. reports receiving consulting honoraria from Servier, AstraZeneca, Pfizer, Boehringer Ingelheim, Novartis, Abbott, Relypsa, Resmed, Merck, Daiichi Sankyo, Takeda, Boston Scientific, Medtronic, and Otsuka. J.J.V.M. and D.J.V.V. are members of the EMPHASIS-HF Executive Committee, which is supported by Pfizer. H.K. reports no conflicts. K.S. has received research support from the sponsor but has no other financial conflicts. H.S. is an employee of Pfizer. J.V. is currently employed by Pfizer and owns stock in Pfizer, Inc., the makers of eplerenone. B.P. is a consultant for Pfizer (eplerenone), Merck, Bayer, Novartis, Takeda, AstraZeneca, Sankyo, ONO, EZ Healthcare, and Forrest Laboratories, is a consultant, and holds stock options in Relypsa, BG Medicine, and Nile Therapeutics, and has received grants from Medtronic, Bayer, Novartis, and Abbott.

Appendix

Executive Steering Committee: Helmut Drexler (Hannover) (deceased), Dirk J. van Veldhuisen (Groningen), Henry Krum (Melbourne), Bertram Pitt (Ann Arbor) (Co-Chairman), Faiez Zannad (Nancy) (Co-Chairman), John McMurray (Glasgow), Karl Swedberg (Göteborg). Endpoint Adjudication Committee: Willem J. Remme (Rhoon) (Chair), Jan Hein Cornel (Schoorl), Per Hildebrandt (Frederiksberg), Jaromir Hradec (Prague), Vlacheslav Mareev (Moscow), K. Srinath Reddy (New Delhi), Andrew Sindone (Eastwood), Felipe Martinez (Córdoba), Angeles Alonso Garcia (Madrid). Data Safety Monitoring Committee: Lars Wilhelmsen (Göteborg) (Chair), Henry J. Dargie (Glasgow), Luigi Tavazzi (Pavia), Stuart Pocock (London), Alain Liezorovic (Lyon).

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