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Effects of low-dose oral enoximone administration on mortality, morbidity, and exercise capacity in patients with advanced heart failure: the randomized, double-blind, placebo-controlled, parallel group ESSENTIAL trials

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Aims Use of inotropic agents in patients with heart failure (HF) has been limited by adverse effects on outcomes. However, administration of positive inotropes at lower doses and concomitant treatment with beta-blockers might increase benefit–risk ratio. We investigated the effects of low doses of the positive inotrope enoximone on symptoms, exercise capacity, and major clinical outcomes in patients with advanced HF who were also treated with beta-blockers and other guideline-recommended background therapy.

Methods and results The Studies of Oral Enoximone Therapy in Advanced HF (ESSENTIAL) programme consisted of two identical, randomized, double-blind, placebo-controlled trials that differed only by geographic location (North and South America: ESSENTIAL-I; Europe: ESSENTIAL-II). Patients with New York Heart Association class III–IV HF symptoms, left ventricular ejection fraction $\leq$30%, and one hospitalization or two ambulatory visits for worsening HF in the previous year were eligible for participation in the trials. The trials had three co-primary endpoints: (i) the composite of time to all-cause mortality or cardiovascular hospitalization, analysed in the two ESSENTIAL trials combined; (ii) the 6 month change from baseline in the 6 min walk test distance (6MWTD); and (iii) the Patient Global Assessment (PGA) at 6 months, both analysed in each trial separately. ESSENTIAL-I and -II randomized 1854 subjects at 211 sites in 16 countries. In the combined trials, all-cause mortality and the composite, first co-primary endpoint did

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not differ between the two treatment groups [hazard ratio (HR) 0.97; 95% confidence interval (CI) 0.80–1.17; and HR 0.98; 95% CI 0.86–1.12, respectively, for enoximone vs. placebo]. The two other co-primary endpoints were analysed separately in the two ESSENTIAL trials, as prospectively designed in the protocol. The 6MWTD increased with enoximone, compared with placebo, in ESSENTIAL-I ($P = 0.025$, not reaching, however, the pre-specified criterion for statistical significance of $P < 0.020$), but not in ESSENTIAL-II. No difference in PGA was observed in either trial.

Conclusion Although low-dose enoximone appears to be safe in patients with advanced HF, major clinical outcomes are not improved.

Keywords Advanced heart failure • Inotropic agents • Enoximone

Introduction

Current treatment of heart failure (HF) with the administration of neurohormonal antagonists and the use of implantable cardioverter–defibrillators (ICDs) and/or cardiac resynchronization devices has increased patient survival.[1,2] The administration of neurohormonal antagonists may delay, but usually does not halt, the progression of HF.[3,4] ICDs prevent sudden cardiac death, an event often occurring at the early stages of the disease, but do not change, or may even increase,[5] the proportion of patients who develop worsening HF. Many patients therefore progress to a stage of advanced chronic HF (ACHF), characterized by high mortality, frequent hospitalizations, marked limitation of exercise capacity, poor quality of life, and haemodynamic impairment.[6] Impaired left ventricular (LV) pump function likely plays a pivotal role in ACHF, as shown by the independent prognostic value of haemodynamic variables, by intolerance to neurohormonal antagonists for haemodynamic reasons and by poor exercise capacity.[6–11]

These data support the potential usefulness of agents having direct positive inotropic and lusitropic effects to improve clinical outcomes, symptoms, and exercise capacity of ACHF patients.[7,12,13] Enoximone is a non-glycoside, non-catecholamine, imidazolone derivative that selectively inhibits sarcoplasmic-reticulum-associated type IIIa and IIIb phosphodiesterase, leading to increased levels of intracellular cAMP.[14] Similar to other type III phosphodiesterase inhibitors (PDEIs),[15,16] long-term administration of enoximone at high doses ($\geq$100 mg t.i.d.) has been associated with increased mortality in placebo-controlled trials.[14,17,18] These trials were, however, performed before the introduction of beta-blockers in the treatment of HF. Beta-blockers can counteract untoward effects of PDEIs (tachyarrhythmias, tachycardia, excessive increase in myocardial work, and oxygen consumption) but maintain or even enhance, through improved intracellular calcium homeostasis, their beneficial inotropic and lusitropic effects.[12,19–22] Both the adverse effects and the increased mortality observed with enoximone administration are dose dependent, and were absent in trials in which enoximone was administered at doses $<$100 mg t.i.d.[14] These lower doses are associated with an improvement in haemodynamic parameters and increased exercise tolerance, as shown by placebo-controlled trials.[14,23,24]

We hypothesized that the administration of low doses of enoximone in conjunction with optimal neurohormonal blockade could have a favourable impact on outcome, symptoms, and exercise capacity in patients with ACHF. To test this hypothesis, the Studies of Oral Enoximone Therapy in Advanced Heart Failure (ESSENTIAL) were designed and conducted.

Methods

ESSENTIAL encompassed two trials, with identical protocols differing only by geographical location: ESSENTIAL-I was conducted in North and South America, and ESSENTIAL-II in Europe. ESSENTIAL-I and ESSENTIAL-II were multicentre, randomized, double-blind, placebo-controlled, parallel group trials. The target enrolment was 900 patients in each trial, designed to deliver at least 825 first co-primary endpoints and 350 deaths in the two trials combined.

Patients

Inclusion criteria were: age $>$18 years; HF caused by ischaemic or non-ischaemic cardiomyopathy; LV systolic dysfunction shown by an ejection fraction (EF) $\leq$30%, detected on radionuclide ventriculography, two-dimensional echocardiography, or nuclear magnetic resonance imaging; an echocardiographically determined LV end-diastolic diameter $>$3.2 cm/m^2 or $\geq$6.0 cm; symptoms of dyspnoea or fatigue at rest or at minimal exertion [New York Heart Association (NYHA) class III–IV] for $>$2 months; at least one hospitalization or two outpatient visits requiring intravenous diuretic or vasodilator therapy within 12 months before screening; and optimal medical therapy including diuretics, beta-blockers, and angiotensin-converting enzyme (ACE)-inhibitors or angiotensin receptor blockers (ARBs) unless intolerant or contraindicated. Exclusion criteria were an acute myocardial infarction in the previous 90 days, cardiovascular surgery in the previous 60 days, symptomatic ventricular arrhythmias or ICD firing in the previous 90 days, serum potassium $<$4.0 or $>$5.5 mEq/L, digoxin levels $>$1.2 ng/mL, magnesium levels $<$1.0 mEq/L, serum creatinine $\geq$2.0 mg/dL, and serum bilirubin $>$3.0 mg/dL.

The study conformed to the Good Clinical Practice guidelines and followed the recommendations of the Declaration of Helsinki. The protocol was approved by each participating centre's Ethics Review Board. Written informed consent was obtained from all patients before enrolment.

Procedures and design

Randomization was preceded by a screening visit occurring 2 to 10 days before entry. Screening included a clinical visit, blood sample analysis for laboratory examinations (see inclusion and exclusion criteria), a 6 min walk test, and a Patient Global Assessment (PGA) questionnaire. Patients were randomized 1:1 to enoximone or placebo

within each trial. Initial study drug dose was 25 mg three times daily. Patients were re-evaluated at 1 and 2 weeks after randomization. During this second visit, the study drug dose was up-titrated to 50 mg three times daily in patients weighing >50 kg without renal and hepatic dysfunction who had tolerated the lower dose. All patients then underwent follow-up clinical visits at 1, 2, 4, 6, 8, 9, 12 months after randomization and, in the following years, every 4 months until study termination. Each visit included clinical examination and blood sampling for analysis of serum bilirubin, creatinine, and potassium.

The study was designed to be terminated with study drug discontinuation after accumulation of a pre-specified number of events ($n = 956$).[15] After the end of the study, subjects had to be carefully observed for the first 30 days with clinical visits after 7 and 30 days. Blinded study medication could be re-initiated if a subject showed rapid deterioration caused by worsening HF that was documented in a dedicated case report form.

In order to assess the effects of treatment on exercise capacity and symptoms, the 6 min walk test distance (6MWTD) was measured at the screening visit, at randomization, and at 6 and 12 months after study entry, and PGA was measured at 6 and 12 months after study entry. For 6MWTD, the results obtained at randomization were used as baseline, and the test was performed according to the standard protocol.[25] Patient Global Assessment was performed by asking the patients to rank their change in symptoms compared with baseline prior to randomization using a seven-level scale that included categories of marked, moderate, and slight improvement; no change; and slight, moderate, and marked worsening, compared with how they felt prior to the start of treatment.

ESSENTIAL-I and ESSENTIAL-II were multicentre, randomized, double-blind, placebo-controlled, parallel group trials. The investigators and all the centre staff members, the personnel at the sponsoring company, including the Medical Monitor, the personnel at the CROs, as well as the Members of the Morbidity and Mortality Committee and the Members of the Steering Committee, were all blinded to treatment assignment. If safety concerns emerged during the trial, where the knowledge of the treatment received could have influenced future treatment decisions, investigators could be unblinded on a case-by-case basis. Only in the case of an emergency was the investigator allowed to proceed with unblinding without first contacting the sponsoring company Medical Monitor. An unblinded DSMB monitored the progress of the trial. Five pre-defined interim analyses were planned testing for efficacy. The first primary endpoint (time to death or cardiovascular hospitalization) and mortality alone, but not the other two primary endpoints (6MWTD changes from baseline to 6 months and PGA at 6 months), were monitored for the possible early termination of the trial for benefit. The trial could not be stopped for efficacy unless the 95% confidence interval (CI) for the mortality difference, based on pooled data for the two ESSENTIAL trials, excluded a hazard ratio (HR) (enoximone/placebo) >1.30.

Endpoints

ESSENTIAL had three co-primary endpoints for efficacy, plus one major safety endpoint. Efficacy endpoints encompassing major clinical outcomes, submaximal exercise capacity, and symptoms were assessed using the following variables: (i) time from randomization to the composite endpoint of all-cause mortality or cardiovascular hospitalization; (ii) change from baseline to 6 months in the 6MWTD; (iii) PGA at 6 months. Hospitalization was defined as a non-elective hospital admission of >24 h duration or including at least one overnight stay documented by a calendar date change. Cardiovascular hospitalization was defined as an admission for worsening HF, myocardial infarction, stroke, atrial or ventricular arrhythmias, or symptomatic heart block. All potential events were reviewed and classified by an Endpoints Committee blinded to treatment assignment. All-cause mortality was the major safety endpoint. The goal of the mortality analysis was to demonstrate non-inferiority of enoximone compared with placebo, defined as the all-cause mortality HR upper bound 95% CI being <1.30.

Statistical analysis

ESSENTIAL used a novel hybrid statistical design in which the two ESSENTIAL trials were combined for the analysis of the first co-primary endpoint (time to all-cause mortality or cardiovascular hospitalizations) and for safety (all-cause mortality), but were analysed separately for the two other co-primary endpoints (6MWTD and PGA). Efficacy was considered demonstrated if either the analysis of the first co-primary endpoint (time to all-cause mortality or cardiovascular hospitalization) indicated benefit at a two-sided P-value <0.007, or if one of the two other co-primary endpoints (6MWTD and PGA) indicated benefit at a two-sided P <0.02 in both ESSENTIAL-I and ESSENTIAL-II. The different levels of statistical significance were based on negotiations with Food and Drug Administration (FDA) and were derivative of the goal of proving that low-dose enoximone added to optimal medical treatment, including beta-blockade, was safe and efficacious for improving clinical outcomes, exercise capacity, and symptoms.[14] A major clinical outcome accepted by FDA in HF indications is the composite of all-cause mortality and cardiovascular hospitalization. ESSENTIAL was planned as an event-driven trial based on this major clinical endpoint. During the planning phase of the ESSENTIAL trials, FDA's CardioRenal Division informed the sponsor that their regulatory criterion for proof of efficacy in a single trial with a time to event major clinical endpoint is a P-value of <0.007. In order to be able to detect the desired 26% reduction in this endpoint at this critical value, 825 primary events were necessary to achieve 90% power, and 956 primary events were required to achieve 94% power.[14] FDA required that the two other primary endpoints, based on less objective data, achieve significance in two separate trials. Thus, ESSENTIAL-I and ESSENTIAL-II functioned as a single trial with respect to the first primary endpoint, and as two separate trials for the second and third co-primary endpoints. Critical values of 0.02 were assigned to 6MWTD/submaximal exercise and PGA/symptom assessment, in each ESSENTIAL trial. On the basis of these critical values, it was calculated that the randomization of 900 patients in each ESSENTIAL trial would have >90% power to detect a treatment group difference of 23 m in the change from baseline of the 6MWTD, and a 14% absolute difference between groups in the number of subjects moderately or markedly improved by the PGA. For safety, it was calculated that the occurrence of 350 deaths would have a 90% power to rule out a ≥30% increase (upper two-sided 95% confidence limit of 1.30) in the risk of death for enoximone vs. placebo. A conservative stopping rule for excess mortality was defined by the independent Data and Safety Monitoring Board to ensure safety throughout the study.[14]

All randomized subjects were to be followed to the end of the study and included in the analyses of efficacy according to their randomized treatment group, with patients included at the moment they took the first trial tablet (intent-to-treat analysis). The time to an event was calculated using the Kaplan–Meier method, and survival curves were compared using the log-rank test, stratified by trial. The relative risk and 95% CI were estimated with a Cox's proportional hazard model, with treatment as the only covariate. The Wilcoxon rank-sum test was used to compare both the PGA at 6 months and the change from baseline to 6 months in the 6MWTD between treatment groups. Missing values at 6 months were replaced with the last post-randomization

Table 1 Patients' follow-up

Status	ESSENTIAL-I			ESSENTIAL-II		
	All (n = 904), n (%)	Placebo (n = 450), n (%)	Enoximone (n = 454), n (%)	All (n = 950), n (%)	Placebo (n = 478), n (%)	Enoximone (n = 472), n (%)
Completed the study alive[a]	552 (61)	271 (60)	281 (62)	649 (68)	334 (70)	315 (67)
Withdrew prematurely due to LVAD, transplant, or death	242 (27)	126 (28)	116 (26)	201 (21)	96 (20)	105 (22)
Death	212 (23)	111 (25)	101 (22)	187 (20)	92 (19)	95 (20)
LVAD placement	4 (0.7)	2 (0.4)	2 (0.4)	3 (0.3)	1 (0.2)	2 (0.4)
Heart transplant	26 (3)	13 (3)	13 (3)	11 (1)	3 (1)	8 (2)
Withdrew prematurely for other reasons	110 (12)	53 (12)	57 (13)	100 (11)	48 (10)	52 (11)
Consent withdrawn	63 (7)	29 (6)	34 (7)	60 (6)	28 (6)	32 (7)
Non-compliance	11 (1)	6 (1)	5 (1)	8 (1)	4 (1)	4 (1)
Marked deterioration in clinical status	6 (1)	1 (0.2)	5 (1)	3 (0.3)	2 (0.4)	1 (0.2)
Adverse event	13 (1)	8 (2)	5 (1)	12 (1)	3 (1)	9 (2)
Treatment with excluded drug	2 (0.2)	2 (0.4)	0	0	0	0
Other	15 (2)	7 (2)	8 (2)	17 (2)	11 (2)	6 (1)
Lost to follow-up[b]	0	0	0	2	1	1

[a]Summarizes subjects whom investigators indicated as having completed the study at the 'official end of study' as per protocol on the TERM CRF.
[b]These patients were censored at the time of lost to follow-up and kept in the intention-to-treat analysis.

measurement carried forward or assigned worst rank if no previous measurement existed. Changes in the 6MWTD were also analysed by ANCOVA using baseline value as a covariate as well as centre as a covariate, since randomization was stratified by centre.

Pre-specified analyses included subgroup analyses for interactions between baseline variables and outcomes as well as 6MWTD changes from baseline. As part of pre-specified model diagnostics, log cumulative hazard plots were performed to detect changes in HR of enoximone vs. placebo over time, with respect to the primary endpoint or total mortality. When a change in HR over time was detected or suggested, a *post hoc* analysis was performed to compare the HRs in the first half of the study with the last half, using the median follow-up time to designate the two groups.

Prior to the initiation of the study, the contract research organization conducting the study (Inveresk) prepared the double-blind randomization scheme with participants allocated to either enoximone or placebo in a 1:1 ratio, blocked by the study centre. Unique subject numbers were assigned within a centre in the order of randomization (investigators gave the lowest medication kit number received at their site to their first subject, etc.). The random allocation sequence was concealed to the investigators throughout the study.

Results

Patient population

A total of 1854 patients were enrolled (904 patients in ESSENTIAL-I and 950 patients in ESSENTIAL-II). Recruitment took place at 211 sites in 16 countries. The trial began on 1 February 2002 and recruitment ended on 30 May 2004. Follow-up for the primary endpoints and safety was concluded on 1 December 2004. Median follow-up duration was of 16.6 months [inter-quartile range (IQR) 8.9–24.0 months; minimum 0.2 months; maximum 34.1 months].

Of the 1854 patients included, 926 were randomized to enoximone (454 patients in ESSENTIAL-I and 472 in ESSENTIAL-II) and 928 to placebo (450 in ESSENTIAL-I and 478 in ESSENTIAL-II). Two patients were lost to follow-up (one on placebo and one on enoximone). Patients who were prematurely withdrawn from the study because of death, LV assist device implantation, cardiac transplantation, or other reasons are shown in *Table 1*.

Baseline characteristics of the patients enrolled in ESSENTIAL-I, ESSENTIAL-II, and the two trials combined are shown in *Table 2*. Significant differences in baseline characteristics were found between the patients in the two trials. These involved both demographics and characteristics reflecting the severity of HF. The percentages of females, non-Caucasian patients, and patients with ischaemic heart disease were higher in ESSENTIAL-I, compared with ESSENTIAL-II. Regarding HF severity, the patients enrolled in ESSENTIAL-I had longer duration of HF, lower LVEF, larger LV end-diastolic diameter, lower 6MWTD, and systolic blood pressure (SBP), consistent with more advanced HF population. Patients in ESSENTIAL-I also had a lower likelihood to be treated with beta-blockers and renin–angiotensin inhibitors. In both trials, patients randomized to enoximone or placebo were similar with respect to all baseline characteristics.

Mortality and mortality or cardiovascular hospitalizations

As prospectively designed, outcome endpoints (e.g. all-cause mortality, as safety endpoint, and all-cause mortality and cardiovascular

Table 2 Patients' characteristics

Parameter	ESSENTIAL-I			ESSENTIAL-II			*P*-value[a] (ESSENTIAL-I vs. -II)
	All (n = 904)	Placebo (n = 450)	Enoximone (n = 454)	All (n = 950)	Placebo (n = 478)	Enoximone (n = 472)	
Age (years)	62 ± 13	62 ± 13	63 ± 13	62 ± 11	62 ± 11	62 ± 11	0.3118
Gender, M/F (%)	74/26	72/28	75/25	86/14	87/13	85/15	<0.0001
Black/Caucasian/Hispanic/other (%)	11/67/18/2	10/66/20/5	11/68/17/4	0/100/00	0/100/00	0/100/0/0	<0.0001
NYHA class, II/III/IV (%)	1/91/8	1/91/9	1/91/8	0/91/9	0/92/8	0/90/10	0.0706
Ischaemic/non-ischaemic aetiology (%)	52/48	48/52	55/45	59/41	61/39	58/42	0.0008
Weight, kg	80 ± 21	79 ± 21	80 ± 22	81 ± 14	81 ± 14	80 ± 14	0.0004
Duration of HF, months	69 ± 65	70 ± 66	67 ± 64	55 ± 55	55 ± 57	55 ± 52	<0.0001
HF hospitalization, last 12 months (%)	90	90	90	87	86	88	0.0179
LV ejection fraction (%)	22.3 ± 5.8	22.6 ± 5.6	22.0 ± 6.0	24.8 ± 4.8	24.9 ± 4.8	24.8 ± 4.7	<0.0001
LV end-diastolic diameter (cm)	6.98 ± 0.78	6.99 ± 0.76	6.96 ± 0.79	6.92 ± 0.70	6.92 ± 0.71	6.92 ± 0.70	0.3124
6 min walk test distance (m)	274 ± 118	278 ± 118	270 ± 118	293 ± 121	294 ± 121	292 ± 121	0.0096
Systolic blood pressure (mmHg)	110 ± 17	109 ± 16	111 ± 18	122 ± 18	122 ± 19	121 ± 18	<0.0001
Heart rate (b.p.m.)	74 ± 11	74 ± 11	74 ± 11	75 ± 12	74 ± 13	75 ± 11	0.1344
Concomitant treatment							
Beta-blockers [n[b] (%)]	754 (83)	376 (84)	378 (83)	857 (90)	433 (91)	424 (90)	<0.0001
Carvedilol	533 (59)			413 (43)			<0.0001
Beta-1 selective	200 (22)			440 (46)			<0.0001
Renin–angiotensin inhibitors	850 (94)	376 (94)	378 (94)	937 (99)	473 (99)	464 (98)	<0.0001
ACE-inhibitors	693 (77)	339 (75)	354 (78)	860 (91)	437 (91)	423 (90)	<0.0001
ARBs	160 (18)	86 (19)	74 (16)	72 (8)	36 (8)	36 (8)	<0.0001
Spironolactone	564 (62)	286 (64)	278 (61)	509 (54)	261 (55)	248 (53)	0.0001
Diuretics	863 (95)	432 (96)	431 (95)	914 (96)	460 (96)	454 (96)	0.4210
Digitalis glycosides	624 (69)	314 (70)	310 (68)	437 (46)	221 (46)	216 (46)	<0.0001
Warfarin	281 (31)			72 (8)			<0.0001
Amiodarone	202 (22)			129 (14)			<0.0001
ICD	189 (21)	101 (22)	88 (19)	47 (5)	24 (5)	23 (5)	<0.0001
Permanent pacemaker	276 (31)	137 (30)	139 (31)	109 (11)	45 (9)	64 (14)	<0.0001

Continuous data expressed as mean values, +/− standard deviation. [a]Significance for ESSENTIAL-I vs. ESSENTIAL-II comparisons. HF, heart failure; LV, left ventricular; ACE, angiotensin-converting enzyme; ARBs, angiotensin receptor blockers; ICD, implantable cardioverter–defibrillator.
[b]Number of patients.

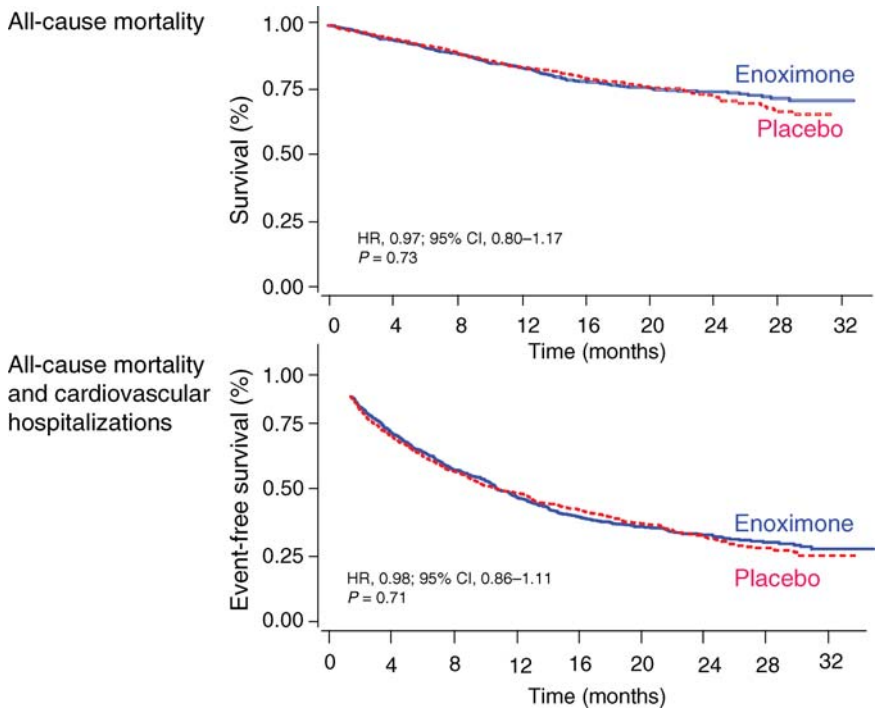

Figure 1 Kaplan–Meier estimates of the time to the safety endpoint of death (up) and to the primary endpoint of death or cardiovascular hospitalization (bottom).

hospitalizations, as first co-primary endpoint) were analysed with the two ESSENTIAL trials combined. Kaplan–Meier estimates of time to all-cause mortality for each treatment (safety endpoint) are shown in *Figure 1*. Of the 926 patients, 196 (21.2%) died in the enoximone group compared with 203 of 928 patients (21.9%) in the placebo group (HR 0.97; 95% CI 0.80–1.17; $P =$ 0.73 for enoximone vs. placebo).

Kaplan–Meier estimates of the time to all-cause mortality or cardiovascular hospitalization for each treatment in the two ESSENTIAL trials combined analysis (first co-primary endpoint) are shown in *Figure 1*. Of the 926 patients, 458 (49.5%) died or had a cardiovascular hospitalization in the enoximone group compared with 465 of 928 patients (50.1%) in the placebo group (HR 0.98; 95% CI 0.86–1.12; $P = 0.71$). Similar results were found with respect to the all-cause mortality or HF hospitalization combined secondary endpoint (HR 0.97; 95% CI 0.84–1.12; $P = 0.68$). No differences between the results of the two ESSENTIAL trials were found when they were analysed separately with respect to outcomes.

Exercise capacity and symptoms

As prospectively designed, the other two co-primary endpoints, changes from baseline in the 6MWTD and the PGA at 6 months, were analysed in the ESSENTIAL-I and ESSENTIAL-II trials separately. In ESSENTIAL-I, median (IQR) change from baseline was 10 m (−60 to 64 m) with enoximone vs. 0 m (−91 to 50 m) with placebo ($P = 0.025$). This did not attain pre-specified criteria for treatment group difference (23 m) and for statistical

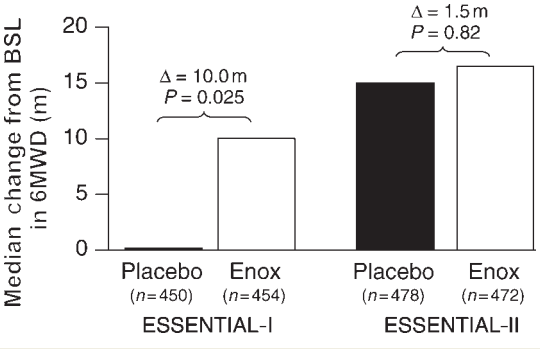

Figure 2 Median change from baseline (BSL) in the 6 min walk distance (6MWD) in the two ESSENTIAL trials.

significance ($P < 0.02$). In ESSENTIAL-II, 6MWTD increased with both enoximone and placebo: 16.5 m (−23 to 60 m) with enoximone vs. 15 m (−20 to 60 m) with placebo ($P = 0.82$) (*Figure 2*). Using ANCOVA, the resulting *P*-values for change in 6MWTD were $P = 0.16$ for ESSENTIAL-I and $P = 0.57$ for ESSENTIAL-II.

Similar changes in PGA were observed in the enoximone and placebo groups in either trial. A moderate or marked improvement in symptoms was observed in 197/454 patients (43%) on enoximone compared with 207/450 patients (46%) on placebo in ESSENTIAL-I ($P = 0.79$) and in 135/472 patients (29%) on

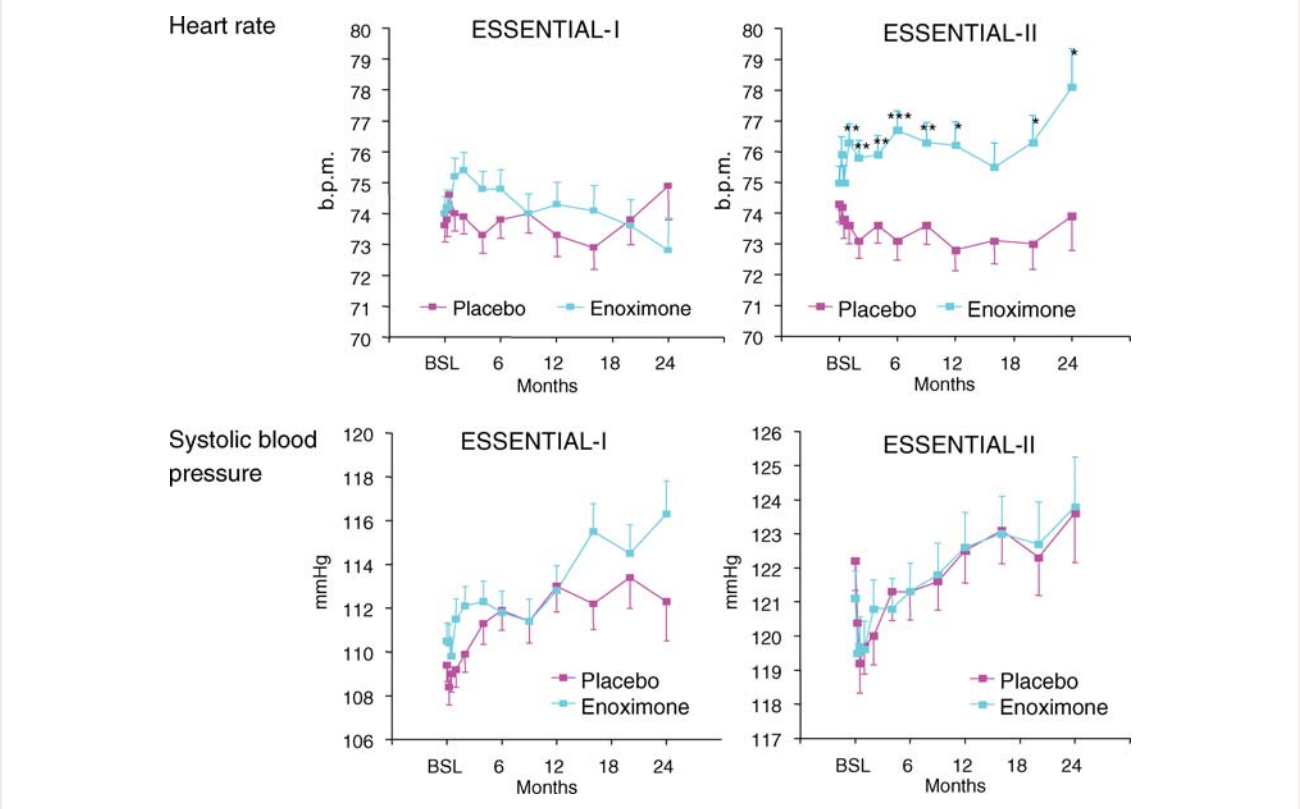

Figure 3 Change from baseline in the heart rate and systolic blood pressure in the two ESSENTIAL trials. Data shown are mean ± standard error. *$P < 0.05$.

enoximone compared with 150/478 patients (31%) on placebo in ESSENTIAL-II ($P = 0.11$).

Haemodynamic parameters

Absolute changes from baseline in heart rate and SBP in ESSENTIAL-I and ESSSENTIAL-II are shown in *Figure 3*. Differences were found between the two trials. Heart rate was unchanged in patients receiving enoximone, compared with those on placebo, in ESSENTIAL-I. In contrast, patients receiving enoximone in ESSENTIAL-II showed a higher heart rate compared with those on placebo, at most of the follow-up visits.

No significant difference between patients randomized to enoximone or placebo was found for baseline SBP. However, SBP tended to increase with enoximone compared with placebo, after 12 months, in ESSENTIAL-I, while SBP values in the two treatment groups were virtually superimposable at all time points in ESSENTIAL-II.

Subgroup analyses

Pre-specified subgroup analyses are shown in *Figures 4–6*. There was a statistically significant interaction between baseline LVEF and 6MWTD changes (*Figure 6*; $P = 0.016$), with the greatest treatment effect observed among patients with an LVEF <25% (median value). Overall, the 6MWTD increased from baseline by 15 m with enoximone vs. 0 m with placebo in these patients ($P = 0.007$). Similar responses were found when the two trials were considered separately (change from baseline of 10 m with enoximone vs. −5 m with placebo, $P = 0.004$ in ESSENTIAL-I, and of 20 m with enoximone vs. 8 m with placebo, $P = 0.51$ in ESSENTIAL-II). No other significant interactions in the pre-defined subgroups were observed (*Figure 6*).

A *post hoc* analysis, prompted by inspection of the Kaplan–Meier curves, showed an interaction between follow-up duration and the effects of enoximone on death or cardiovascular hospitalization ($P < 0.01$). The incidence of death or cardiovascular hospitalizations was similar between enoximone and placebo during the first 16.4 months (median value) (420/926 patients, 45.4% vs. 409/928 patients, 44.1%, respectively), whereas it tended to be lower with enoximone during the second half of follow-up (38/303 patients, 12.5%, on enoximone vs. 56/322 patients, 17.4%, on placebo; $P = 0.09$). A trend ($P = 0.16$) for significant interaction by the length of follow-up was also found for all-cause mortality, as enoximone reduced mortality in the second half of the trial (24/447 deaths, 5.4%, on enoximone vs. 41/467 deaths, 8.8%, on placebo; $P = 0.045$).

Adverse events

Most frequently reported adverse events are summarized in *Table 3*. Enoximone administration was associated with a greater incidence of diarrhoea and palpitations. No difference was found with regard to any other adverse events.

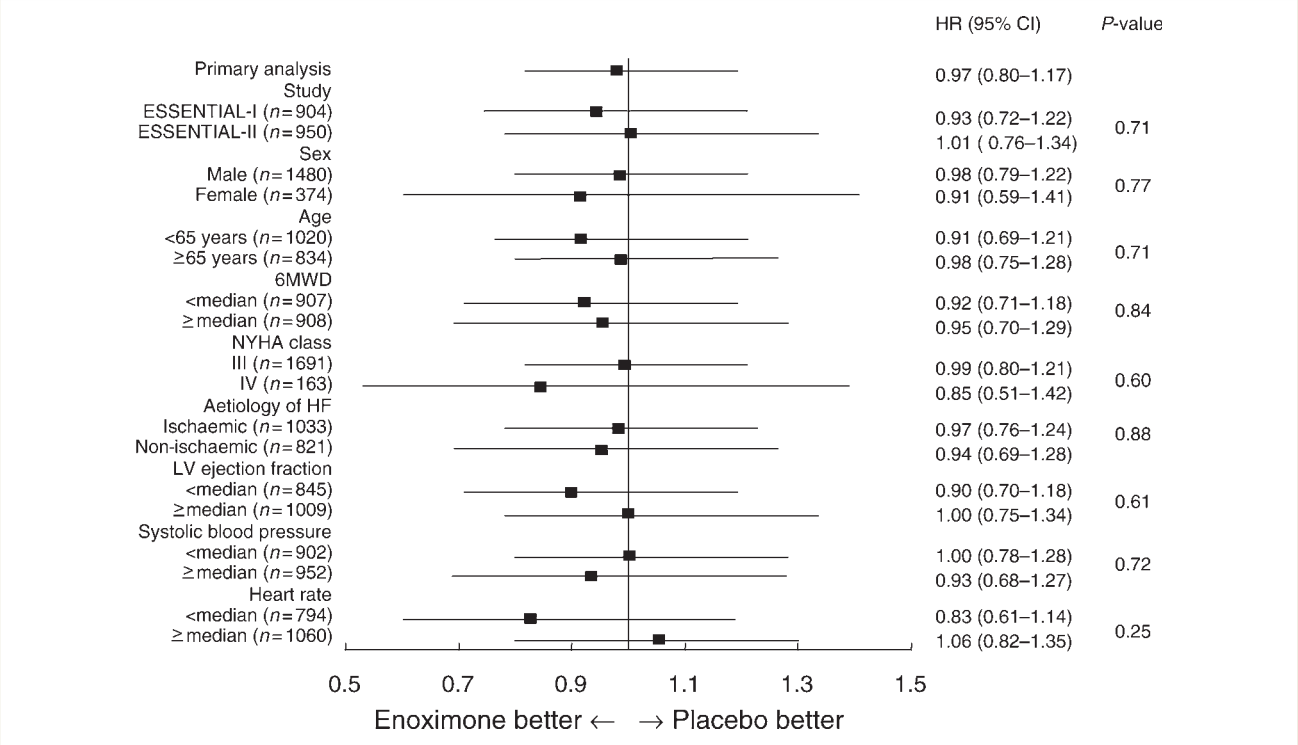

Figure 4 Hazard ratios and 95% confidence intervals for all-cause death, according to the baseline characteristics of the patients. *P*-values are for interaction.

Re-initiation of study drug after end of study

In the month following termination of the trial and study drug withdrawal, study drug was blindly re-initiated for clinical reasons in 171 of 418 patients (41%) who were on enoximone compared with 139 of 423 patients who were on placebo (33%, $P = 0.018$ for comparison between the two treatment groups). The main cause of re-initiation of the study drug was worsening HF occurring in 163/418 patients on enoximone (39%) vs. 130/423 patients on placebo (31%, $P = 0.014$). This was mainly reported as an increase in HF symptoms (34% of patients previously on enoximone vs. 26% of patients on placebo; $P = 0.013$), whereas the incidence of HF hospitalizations or emergency visits was similar. Also, the incidence of other cardiovascular events during the month following trial termination was similar in the two treatment groups.

Discussion

Effects on outcome

ESSENTIAL is the first clinical trial powered to assess an effect on mortality that has demonstrated that a type III PDEI administered at haemodynamically active doses has no untoward effects in patients with HF. Our results differ from those of previous placebo-controlled trials with PDE-Is.[15–18] This difference may be explained by many factors including patient selection, exclusion of patients with low- or high-serum potassium levels or serum digoxin concentrations >1.2 ng/mL, concomitant beta-blocker therapy, and/or the administration of low doses of enoximone in our trial. The results show that oral enoximone may be a safe long-term treatment for appropriately selected patients with ACHF.

Despite the encouraging safety profile, our results did not reveal evidence of efficacy on clinical outcomes in the entire ESSENTIAL cohort. This may be due to either a lack of a favourable effect of enoximone, insufficient follow-up duration, or the study population's characteristics. It is possible, for example, that the inclusion of only patients with more severe haemodynamic impairment would have allowed the detection of a favourable effect on outcomes (*Figures 4* and *5*).

Patients' follow-up in the month following termination of the trial and study drug withdrawal demonstrated a higher re-initiation rate of study drug in the enoximone, compared with the placebo, group. This may be interpreted as evidence of continuous beneficial pharmacological activity of the drug, or as a rebound effect secondary to cardiac function becoming dependent on drug effects. Similar results have been found in digoxin withdrawal studies.[26]

Effects on exercise capacity and symptoms

Enoximone administration was not associated with beneficial effects on symptoms and/or exercise capacity. These results are in contrast with the beneficial effects shown in placebo-controlled trials in which enoximone was administered at doses similar as in ESSENTIAL.[14,23,24] This relatively unexpected finding may be explained by either methodological issues and/or characteristics

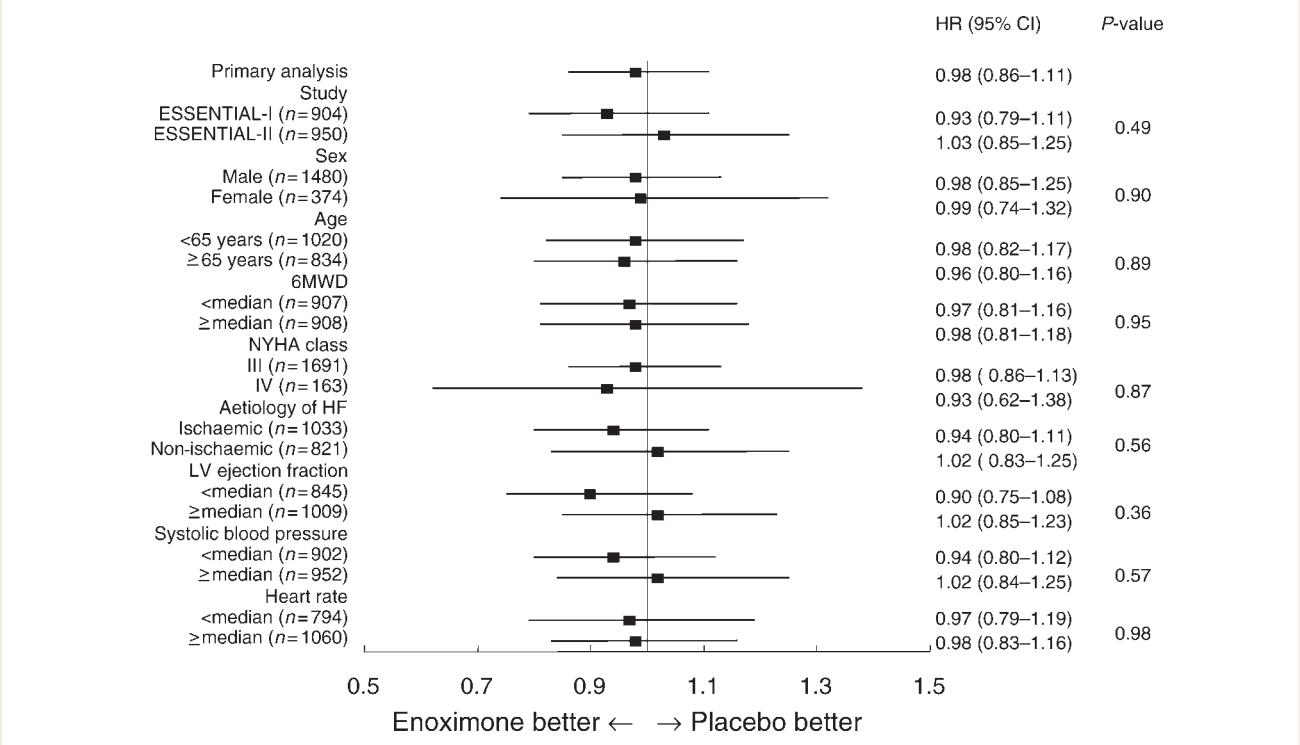

Figure 5 Hazard ratios and 95% confidence intervals for the primary endpoint of all-cause death or cardiovascular hospitalization, according to the baseline characteristics of the patients. *P*-values are for interaction.

Table 3 Adverse events

Event	Placebo (n = 928), n (%)	Enoximone (n = 926), n (%)	*P*-value[a]
Worsening heart failure	364 (39)	360 (39)	0.8782
Dizziness	102 (11)	115 (12)	0.3390
Hypotension	94 (10)	113 (12)	0.1563
Diarrhoea	62 (7)	110 (12)	0.0001
Chest pain	90 (10)	82 (9)	0.5316
Nausea	64 (7)	77 (8)	0.2412
Palpitations	47 (5)	74 (8)	0.0107
Hyperkalaemia	64 (7)	57 (6)	0.5183
Hypokalaemia	65 (7)	69 (7)	0.7101
Increased serum creatinine	62 (7)	61 (7)	0.9355
Cough	64 (7)	61 (7)	0.7907
Headache	54 (6)	59 (6)	0.6190
Sudden death unexplained	54 (6)	57 (6)	0.7601
Atrial fibrillation	48 (5)	43 (5)	0.5982

[a]Differences between placebo and enoximone.

of the patients studied. Exercise capacity was assessed in ESSENTIAL by 6MWTD. This method has the advantages of being easy to perform, suitable for use in multicentre trials, and similar to everyday physical activity. However, its reproducibility and accuracy in detecting an improvement in exercise performance may be significantly reduced in large multicentre trials.[27,28] It may also be that enoximone has more favourable effects on maximal, rather than submaximal, exercise performance.[23,24]

Our results were influenced by the characteristics of the patients studied. This is shown by the comparison between the two ESSENTIAL trials. The patients enrolled in ESSENTIAL-I, who had more advanced HF compared with those in ESSENTIAL-II, showed an improvement in their 6MWTD with enoximone, compared with placebo. Second, subgroup analysis indicated interaction between the changes from baseline in the 6MWTD and LVEF at entry into the study. The study suggests that enoximone may favourably affect exercise capacity when administered to patients with severe impairment of LV systolic function. Patients with less severe impairment of LV function are more likely to be limited by peripheral, skeletal muscle-dependent, mechanisms rather than by an abnormal haemodynamic response to exercise.

Both with respect of outcomes and of 6MWTD changes, our results did not show a worse response to enoximone administration in the patients with more advanced HF (e.g. those with a lower LVEF, low SBP, NYHA class IV). These results are in contrast with those obtained with chronic milrinone treatment, showing a worse outcome compared with placebo, in patients with more advanced HF.[15] Drug characteristics, use of lower dosages, and ongoing beta-blocker treatment may explain these differences.

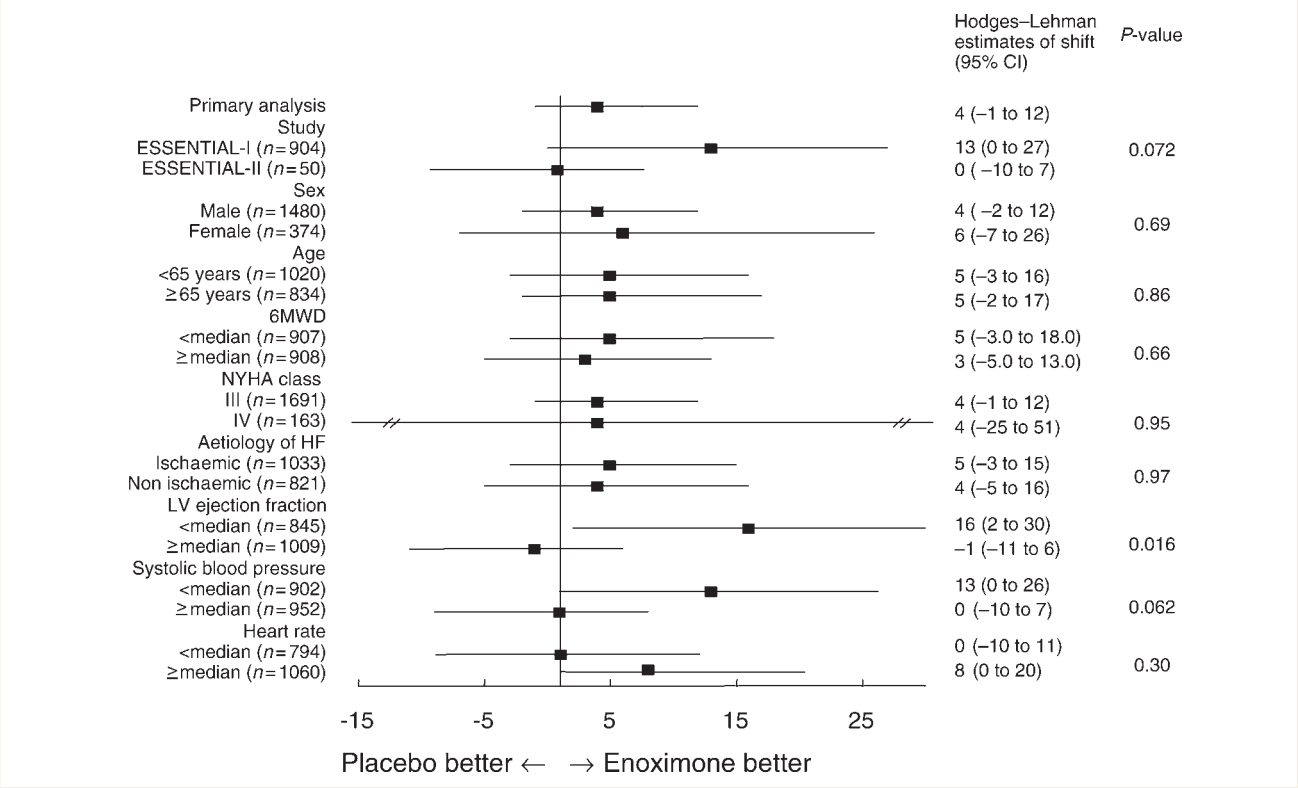

Figure 6 Changes from baseline in the 6 min walk distance (Hodges–Lehman estimates of shift and 95% confidence intervals), according to the baseline characteristics of the patients. *P*-values are for interaction.

Conclusions

The ESSENTIAL-I and -II trials indicate that low-dose enoximone added to contemporary medical therapy is safe, but does not produce favourable effects on the three primary endpoints as defined in the statistical analysis plan. Further studies of inotropic agents in advanced HF may want to take these observations into consideration.

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Conflict of interest: Authors of the study have occasionally received honoraria and reimbursements for presentations at meetings and/or attendance at advisory boards from pharmaceutical companies involved in cardiovascular reasearch. M.G. and M.B. were employees of Myogen Inc. at the time of the research and J.L. and J.S. are employees of Gilead Inc. Gilead Inc. currently owns enoximone.

Appendix

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