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Efficacy and safety of high-dose lisinopril in chronic heart failure patients at high cardiovascular risk, including those with diabetes mellitus

Results from the ATLAS trial

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Aims An analysis was designed to determine whether chronic heart failure patients at high cardiovascular risk benefited to the same extent from high-dose lisinopril as the whole ATLAS population.

Methods and Results A retrospective analysis was performed on high-risk heart failure patients in the Assessment of Treatment with Lisinopril And Survival (ATLAS) trial (total number of patients 3164) comparing high-dose (32·5–35 mg . day^{-1}) vs low-dose (2·5–5 mg . day^{-1}) lisinopril for a median of 46 months. These high-risk patients included those with hypotension, hyponatraemia, compromised renal function, the elderly and patients with diabetes mellitus at baseline. In the whole study population, high-dose lisinopril led to a trend in risk reduction of all-cause mortality (primary end-point $P=0{\cdot}128$) and a significant risk reduction in all-cause mortality plus hospitalization (principal secondary end-point $P=0{\cdot}002$). Subgroup analyses were performed for these end-points. There were no consistent interactions between age, baseline sodium, creatinine or potassium values, and treatment effect. Diabetics showed a beneficial response to high-dose therapy that was at least as good as that in non-diabetics. The underlying higher morbidity/mortality rates in diabetics mean that high-dose lisinopril has potential for a larger absolute clinical impact in these patients.

Conclusion Long-term high-dose lisinopril was as effective and well-tolerated in high-risk patients, including those with diabetes mellitus, as for the ATLAS study population as a whole.

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Key Words: Heart failure, ACE inhibitor, mortality, hospitalization, lisinopril, diabetes mellitus.

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Introduction

The beneficial effects of angiotensin-converting enzyme (ACE) inhibitors on morbidity and mortality in patients with chronic heart failure have been well documented in several major clinical trials (Cooperative New Scandinavian Enalapril Survival Study [CONSENSUS][1], Vasodilator Heart failure Trial I [V-HeFT I][2], Studies of Left Ventricular Dysfunction [SOLVD] treatment[3], Acute Infarction Ramipril Efficacy study [AIRE][4]). However, the doses of ACE inhibitors used in these trials were considerably higher than those routinely prescribed in clinical practice[5,6]. Hence, the Assessment of Treatment with Lisinopril And Survival (ATLAS) trial examined whether the long-term administration of a 'high', trial-based dose of the ACE inhibitor lisinopril would confer additional benefits to those seen with a 'low' dose more typical of clinical practice. This study showed that patients receiving high-dose lisinopril compared with low-dose lisinopril had an 8% reduction in the risk of all-cause

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mortality ($P=0{\cdot}128$), a 12% lower risk for the combined end-point of death or hospitalization for any reason ($P=0{\cdot}002$), and a 15% lower risk for mortality or hospitalization for heart failure ($P<0{\cdot}001$)[7]. Although the overall frequency of adverse events was similar between treatment groups, patients in the high-dose group had somewhat more hypotension and renal insufficiency than those in the low-dose group; these were usually managed by therapy adjustments and seldom led to withdrawal. The number of patients withdrawn from the study was similar in the two treatment groups (data on file).

There are several groups of heart failure patients at high cardiovascular risk[8,9], including those unable to tolerate pharmacological therapy, the elderly, and those with hypotension, hyponatraemia or compromised renal function[10–13]. Management of these subjects, particularly during upward dose titration, requires careful monitoring. It is reasonable to believe that physicians may be particularly hesitant to prescribe these patients high-dose ACE inhibitors, because of the perceived likelihood of adverse effects. Additionally, diabetes mellitus is present in about one-third of patients with heart failure[14], and is associated with increased renal dysfunction, higher mortality and an increased rate of hospitalizations.

The ATLAS database offers a unique opportunity to examine the efficacy and tolerability of high-doses of lisinopril in clinically relevant subgroups of heart failure patients, including those with diabetes, to provide useful information for the practising physician in charge of a mixed population of heart failure patients.

Materials and methods

Detailed descriptions of the ATLAS trial and its patient population have been given elsewhere[7,15,16]. In brief, the ATLAS trial recruited 3793 patients with New York Heart Association (NYHA) Class II-IV heart failure. Patients intolerant to ACE inhibitors or with serum creatinine $>2{\cdot}5\ \text{mg} \cdot \text{dl}^{-1}$ ($221\ \mu\text{mol} \cdot \text{l}^{-1}$) were not included. Patients were titrated over 4 weeks to an open-label dose of 12·5 or 15 mg lisinopril. The 3164 patients who completed this initial phase were randomized to low-dose ($2{\cdot}5$ or $5{\cdot}0\ \text{mg} \cdot \text{day}^{-1}$) or high-dose ($32{\cdot}5$ or $35\ \text{mg} \cdot \text{day}^{-1}$) lisinopril and followed up for a minimum of 36 months (median 46 months).

The primary study end-point was all-cause mortality, with secondary end-points of combined all-cause mortality and all-cause hospitalization (principal secondary end-point), cardiovascular mortality, combined all-cause mortality and cardiovascular hospitalization, combined cardiovascular mortality and cardiovascular hospitalization and combined myocardial infarctions (fatal and non-fatal) plus hospitalization for unstable angina.

Subgroups analysed are shown in Figs 1, 2 and 3. Those considered to be at high cardiovascular risk or having reduced tolerability to high doses of an ACE inhibitor included patients with; hypotension, hyponatraemia, compromised renal function, diabetes mellitus at baseline (defined as concurrent use of antidiabetic medication) and the elderly[10–13].

Statistical methods

Subgroup analyses were performed for the pre-specified primary and principal secondary end-points only: all-cause mortality, and all-cause mortality plus all-cause hospitalizations. These were considered to provide an overall measure of treatment effect.

Survival analysis techniques, which account for censoring of data and make use of time-to-event information, were used on an intention-to-treat basis with adjustment for NYHA class and ejection fraction at baseline. In the analysis, cardiac transplantations were considered to be the same as cardiovascular deaths. For each subgroup, a hazard ratio for high-dose lisinopril compared with low-dose lisinopril was computed by including a term for the subgroup and the interaction between the subgroup and treatment in the Cox proportional hazards model. Hazard ratios of less than 1 indicate a risk reduction in the high-dose lisinopril group. 95% confidence intervals and the *P*-value of the interaction were used to identify differences in response.

Results

The total patient population

Of the 3164 randomized patients, 1568 were assigned to high-dose and 1596 to low-dose lisinopril therapy[7]. The target dose of study medication was achieved in more than 90% of patients, with mean daily lisinopril doses of 33·2 mg and 4·5 mg in the high and low-dose groups respectively, at the end of the dose titration period. Median duration of follow-up in surviving patients was 46 months; none were lost to follow-up.

There were 666 deaths (42%) in the high-dose group and 717 (45%) in the low-dose group. This corresponds to an 8% mortality risk reduction with high-dose lisinopril (96·1% confidence interval (CI) -18% to $+3\%$; $P=0{\cdot}128$). The combined risk of mortality and hospitalization for any reason was significantly lower in the high-dose group (1250 events) than in the low-dose group (1338 events; risk reduction 12%, 95% CI$=-5\%$ to -18%, $P=0{\cdot}002$).

Subgroup data

The influence of baseline characteristics and laboratory findings is shown in Fig. 1 and Table 1. There was no

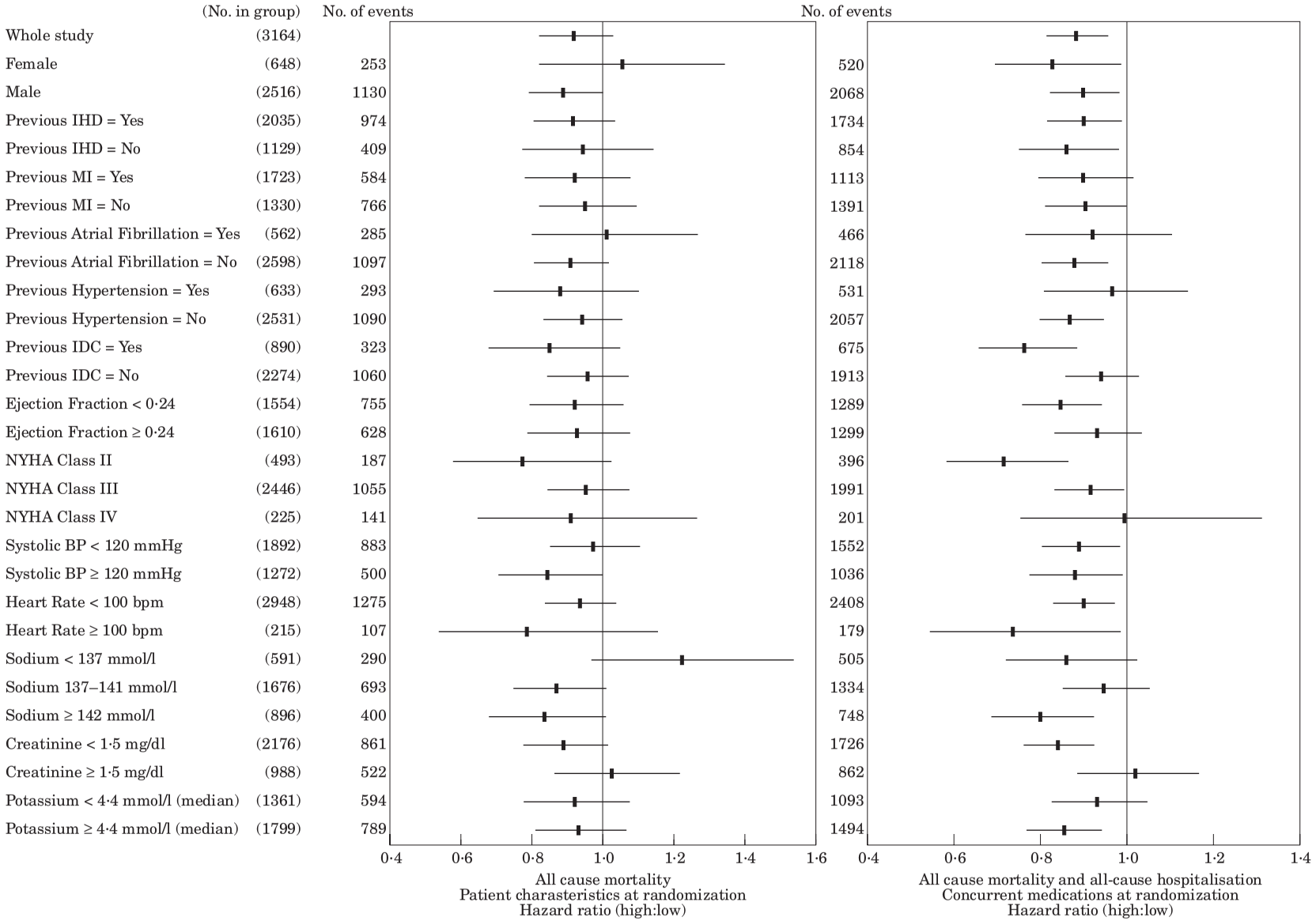

Figure 1 **All-cause mortality and the combined end-point of all-cause mortality and all-cause hospitalization for the whole study populations and subgroups (including number in subgroup and number of events) are shown, with hazards ratio (high dose : low dose) on the vertical axis. Values under 1·0 indicate superiority of high-dose lisinopril over low dose. Vertical bars represent the 95% confidence intervals for hazard ratio, except for the whole study result for all-cause mortality, where the 96·1% confidence interval is shown (as a result of the pre-planned interim analyses performed for this end-point). IHD=ischaemic heart disease; MI=myocardial infarction; IDC=idopathic dilated cardiomyopathy.**

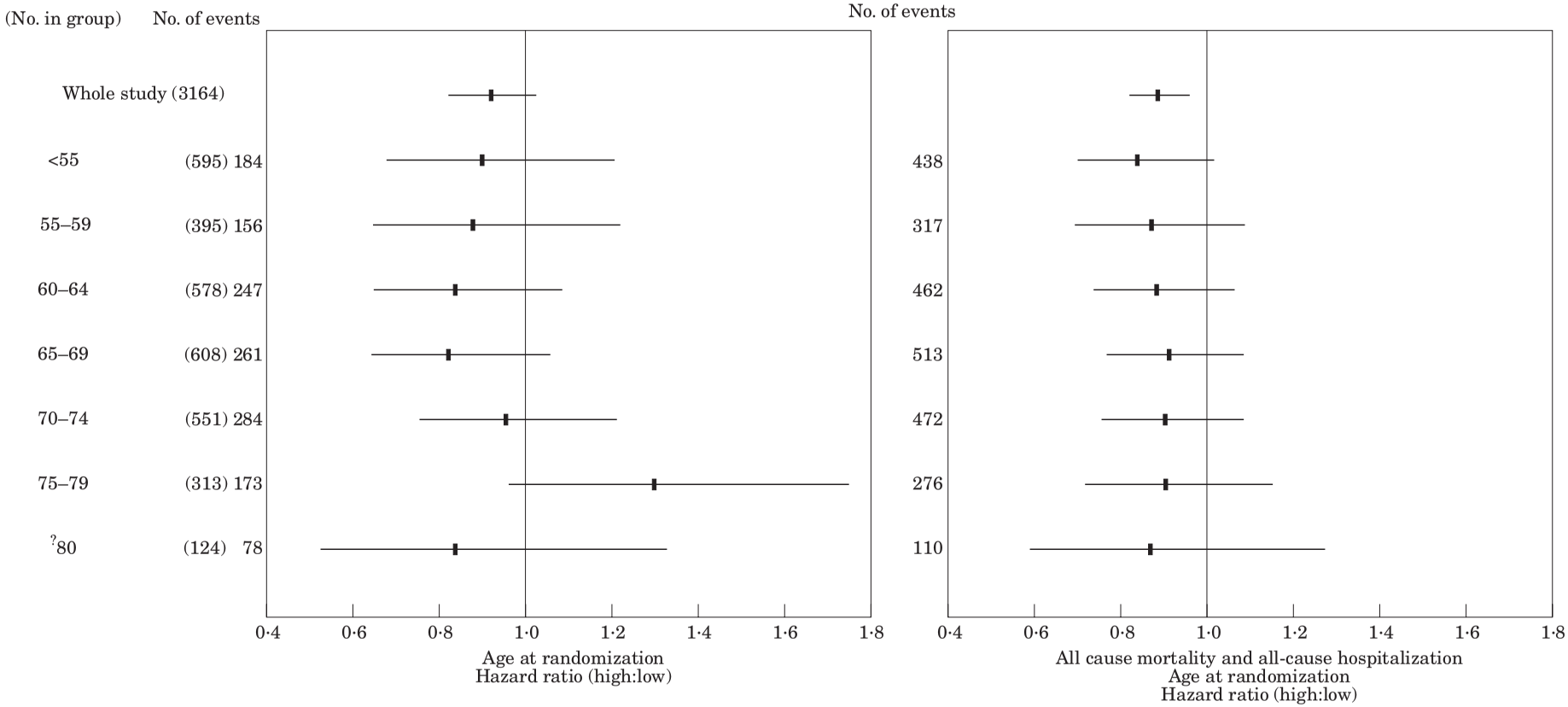

Figure 2 **Treatment effect of high-dose vs low-dose lisinopril for subgroups by age in 5-year bands for all-cause mortality and mortality plus hospitalization. Numbers in brackets indicate number in subgroup; number of events is also shown. Hazard ratios for high-dose vs low-dose and their 95% confidence intervals are shown.**

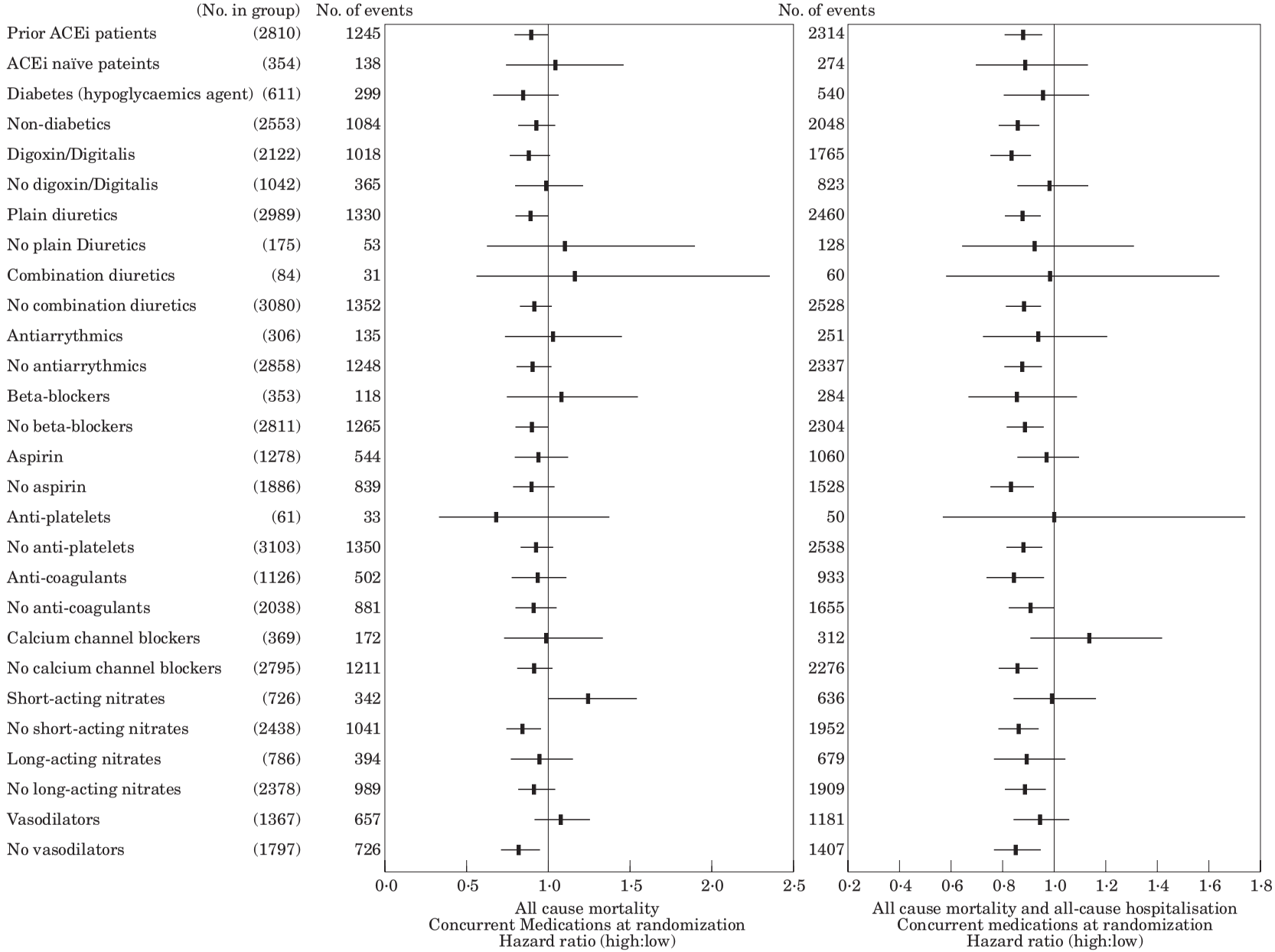

Figure 3 **Treatment effect of high-dose vs low-dose lisinopril for different concurrent treatments at the time of randomization for all-cause mortality, and all-cause mortality and all-cause hospitalization. Numbers in brackets indicate number in subgroup; number of events is also shown.**

Table 1 All-cause mortality and all-cause mortality plus hospitalization: 95% confidence intervals and hazard ratios

Events (n)	n	All-cause mortality	Lower 95%	Upper 95%	HR	*P*-value	Interaction
	3164	Whole study*	0·824	1·030	0·921	0·128	
253	648	Female	0·824	1·348	1·054	0·677	0·228
1130	2516	Male	0·793	1·001	0·891	0·053	
974	2035	Previous ischaemic heart disease=Yes	0·807	1·038	0·916	0·170	0·808
409	1129	Previous ischaemic heart disease=No	0·776	1·144	0·942	0·547	
584	1330	Previous myocardial infarction=Yes	0·780	1·080	0·918	0·301	0·742
766	1723	Previous myocardial infarction=No	0·826	1·097	0·952	0·494	
285	562	Previous atrial fibrillation=Yes	0·798	1·270	1·006	0·955	0·425
1097	2598	Previous atrial fibrillation=No	0·804	1·019	0·905	0·100	
293	633	Previous hypertension=Yes	0·695	1·103	0·876	0·260	0·612
1090	2531	Previous hypertension=No	0·832	1·055	0·937	0·281	
323	890	Previous idiopathic dilated cardiomyopathy=Yes	0·680	1·053	0·846	0·134	0·351
1060	2274	Previous idiopathic dilated cardiomyopathy=No	0·844	1·075	0·953	0·431	
755	1554	Ejection fraction <0·24	0·797	1·060	0·919	0·247	0·962
628	1610	Ejection fraction >=0·24	0·790	1·081	0·924	0·322	
187	493	NYHA Class II	0·579	1·028	0·771	0·076	
1055	2446	NYHA Class III	0·844	1·075	0·952	0·433	0·184
141	225	NYHA Class IV	0·652	1·263	0·907	0·564	0·467
883	1892	Systolic BP <120 mmHg	0·850	1·107	0·970	0·651	0·201
500	1272	Systolic BP >=120 mmHg	0·705	1·002	0·840	0·053	
1275	2948	Heart rate <100 beats . min^{-1}	0·836	1·041	0·933	0·216	0·393
107	215	Heart rate >=100 beats . min^{-1}	0·535	1·150	0·784	0·214	
290	591	Sodium <137 mmol . l^{-1}	0·967	1·535	1·218	0·095	
693	1676	Sodium 137–141 mmol . l^{-1}	0·748	1·009	0·868	0·065	0·016
400	896	Sodium >=142 nmol . l^{-1}	0·681	1·010	0·829	0·063	0·013
861	2176	Creatinine <1·5 mg . dl^{-1}	0·775	1·012	0·886	0·075	0·201
522	988	Creatinine >=1·5 mg . dl^{-1}	0·860	1·212	1·021	0·815	
594	1361	Potassium <4·4 mmol . l^{-1} (median)	0·777	1·073	0·913	0·269	0·884
789	1799	Potassium >=4·4 mmol . l^{-1} (median)	0·807	1·067	0·927	0·291	
All-cause mortality and all-cause hospitalization							
	3164	Whole study	0·818	0·955	0·884	0·002	
520	648	Female	0·698	0·985	0·829	0·033	0·410
2068	2516	Male	0·824	0·980	0·899	0·016	
1734	2035	Previous ischaemic heart disease=Yes	0·818	0·988	0·899	0·027	0·595
854	1129	Previous ischaemic heart disease=No	0·752	0·983	0·860	0·027	
1113	1723	Previous myocardial infarction=Yes	0·799	1·011	0·899	0·075	0·944
1391	1330	Previous myocardial infarction=No	0·813	1·004	0·904	0·059	
466	562	Previous atrial fibrillation=Yes	0·766	1·102	0·919	0·359	0·650
2118	2598	Previous atrial fibrillation=No	0·805	0·955	0·877	0·003	
531	633	Previous hypertension=Yes	0·809	1·139	0·960	0·639	0·309
2057	2531	Previous hypertension=No	0·797	0·948	0·869	0·002	
675	890	Previous idiopathic dilated cardiomyopathy=Yes	0·658	0·890	0·765	0·001	0·022
1913	2274	Previous idiopathic dilated cardiomyopathy=No	0·859	1·028	0·939	0·173	
1289	1554	Ejection fraction <0·24	0·756	0·941	0·844	0·002	0·236
1299	1610	Ejection fraction >=0·24	0·831	1·033	0·926	0·169	
396	493	NYHA Class II	0·585	0·867	0·712	0·001	
1991	2446	NYHA Class III	0·835	0·996	0·912	0·040	0·025
201	225	NYHA Class IV	0·754	1·312	0·994	0·970	0·054
1552	1892	Systolic BP <120 mmHg	0·804	0·981	0·888	0·020	0·885
1036	1272	Systolic BP >=120 mmHg	0·777	0·992	0·878	0·037	
2408	2948	Heart rate <100 beats . min^{-1}	0·827	0·971	0·896	0·007	0·204
179	215	Heart rate >=100 beats . min^{-1}	0·546	0·988	0·734	0·041	
505	591	Sodium <137 mmol . l^{-1}	0·721	1·023	0·859	0·088	
1334	1676	Sodium 137–141 mmol . l^{-1}	0·847	1·050	0·943	0·283	0·372
748	896	Sodium >=142 nmol . l^{-1}	0·690	0·920	0·797	0·002	0·515
1726	2176	Creatinine <1·5 mg . dl^{-1}	0·764	0·924	0·840	0·001	0·022
862	988	Creatinine >=1·5 mg . dl^{-1}	0·890	1·164	1·018	0·794	
1093	1361	Potassium <4·4 mmol . l^{-1} (median)	0·823	1·045	0·927	0·214	0·294
1494	1799	Potassium >=4·4 mmol . l^{-1} (median)	0·770	0·944	0·853	0·002	

Table 1 Continued

Events (n)	n	All-cause mortality	Lower 95%	Upper 95%	HR	*P*-value	Interaction
Concurrent medications at randomization							
1245	2810	Prior ACE patients	0·812	1·014	0·907	0·086	0·404
138	354	ACE naïve patients	0·755	1·471	1·054	0·759	
299	611	Diabetics (hypoglycaemics at randomization)	0·684	1·076	0·858	0·185	0·502
1084	2553	Non-Diabetics (no hypoglycaemics at randomization)	0·831	1·055	0·936	0·280	
1018	2122	Digoxin/Digitalis at randomization	0·789	1·010	0·893	0·071	0·351
365	1042	No digoxin/digitalis at randomization	0·815	1·228	1·000	0·998	
1330	2989	Plain diuretics at randomization	0·821	1·018	0·914	0·102	0·475
53	175	No plain diuretics at randomization	0·651	1·915	1·117	0·688	
31	84	Combination diuretics at randomization	0·574	2·364	1·165	0·672	0·511
1352	3080	No combination diuretics at randomization	0·824	1·020	0·917	0·110	
135	306	Antiarrhythmics at randomization	0·737	1·449	1·033	0·850	0·487
1248	2858	No antiarrhythmics at randomization	0·815	1·018	0·911	0·098	
118	353	Betablockers at randomization	0·751	1·552	1·079	0·681	0·344
1265	2811	No betablockers at randomization	0·805	1·003	0·898	0·057	
544	1278	Aspirin at randomization	0·799	1·118	0·945	0·511	0·702
839	1886	No aspirin at randomization	0·791	1·038	0·906	0·154	
33	61	Antiplatelets at randomization	0·344	1·368	0·686	0·285	0·398
1350	3103	No antiplatelets at randomization	0·834	1·032	0·928	0·168	
502	1126	Anti-coagulants at randomization	0·782	1·109	0·931	0·425	0·881
881	2038	No anti-coagulants at randomization	0·802	1·045	0·916	0·192	
172	369	Calcium channel blockers at randomization	0·735	1·338	0·992	0·958	0·606
1211	2795	No calcium channel blockers at randomization	0·815	1·021	0·912	0·109	
342	726	Short-acting nitrates at randomization	1·003	1·533	1·240	0·047	0·002
1041	2438	No short-acting nitrates at randomization	0·744	0·949	0·840	0·005	
394	786	Long-acting nitrates at randomization	0·769	1·143	0·937	0·522	0·847
989	2378	No long-acting nitrates at randomization	0·809	1·038	0·916	0·169	
657	1367	Vasodilators at randomization	0·920	1·249	1·072	0·373	0·011
726	1797	No vasodilators at randomization	0·704	0·943	0·815	0·006	
All-cause mortality and all-cause hospitalization							
2314	2810	Prior ACE patients	0·814	0·959	0·883	0·003	0·939
274	354	ACE naïve patients	0·704	1·131	0·892	0·345	
540	611	Diabetics (hypoglycaemics at randomization)	0·811	1·136	0·960	0·632	0·275
2048	2553	Non-diabetics (no hypoglycaemics at randomization)	0·791	0·942	0·863	0·001	
1765	2122	Digoxin/digitalis at randomization	0·764	0·921	0·839	0·001	0·058
823	1042	No digoxin/digitalis at randomization	0·858	1·128	0·984	0·819	
2460	2989	Plain diuretics at randomization	0·815	0·955	0·882	0·002	0·789
128	175	No plain diuretics at randomization	0·655	1·309	0·926	0·663	
60	84	Combination diuretics at randomization	0·594	1·637	0·986	0·956	0·672
2528	3080	No combination diuretics at randomization	0·816	0·954	0·882	0·002	
251	306	Antiarrhythmics at randomization	0·730	1·202	0·937	0·608	0·640
2337	2858	No antiarrhythmics at randomization	0·811	0·955	0·880	0·002	
284	353	Betablockers at randomization	0·674	1·081	0·854	0·189	0·766
2304	2811	No betablockers at randomization	0·817	0·962	0·887	0·004	
1060	1278	Aspirin at randomization	0·858	1·093	0·969	0·604	0·056
1528	1886	No aspirin at randomization	0·752	0·919	0·831	0·001	
50	61	Antiplatelets at randomization	0·572	1·735	0·997	0·991	0·669
2538	3103	No antiplatelets at randomization	0·816	0·954	0·882	0·002	
933	1126	Anti-coagulants at randomization	0·742	0·960	0·844	0·010	0·376
1655	2038	No anti-coagulants at randomization	0·824	0·999	0·907	0·048	
312	369	Calcium channel blockers at randomization	0·907	1·416	1·133	0·270	0·021
2276	2795	No calcium channel blockers at randomization	0·789	0·930	0·857	0·001	
636	726	Short-acting nitrates at randomization	0·850	1·160	0·993	0·929	0·110
1952	2438	No short-acting nitrates at randomization	0·785	0·938	0·858	0·001	
679	786	Long-acting nitrates at randomization	0·765	1·034	0·889	0·128	0·928
1909	2378	No long-acting nitrates at randomization	0·806	0·965	0·882	0·006	
1181	1367	Vasodilators at randomization	0·840	1·056	0·942	0·303	0·188
1407	1797	No vasodilators at randomization	0·764	0·942	0·848	0·002	

Table 1 Continued

No of events	n	Age	HR	Lower 95%	Upper 95%	*P*-value
All-cause mortality						
	3164	Whole Study	0·921	0·824	1·03	
184	595	<55	0·902	0·675	1·205	0·4854
156	395	55–59	0·884	0·642	1·216	0·4489
247	578	60–64	0·838	0·65	1·08	0·1727
261	608	65–69	0·825	0·646	1·053	0·1224
284	551	70–74	0·953	0·754	1·203	0·6838
173	313	75–79	1·298	0·96	1·755	0·0897
78	124	>=80	0·834	0·525	1·325	0·4417
All-cause mortality and all-cause hospitalization						
	3164	Whole Study	0·884	0·818	0·955	
438	595	<55	0·839	0·694	1·014	0·0687
317	395	55–59	0·867	0·692	1·086	0·2128
462	578	60–64	0·883	0·734	1·062	0·1875
513	608	65–69	0·906	0·762	1·078	0·2677
472	551	70–74	0·901	0·752	1·08	0·2592
276	313	75–79	0·902	0·712	1·143	0·3922
110	124	>=80	0·859	0·583	1·267	0·4434

*96·1% CI.

consistent interaction between treatment and gender, cause of heart failure and/or previous ischaemic heart disease, baseline ejection fraction, NYHA class, systolic blood pressure and heart rate at entry, previous myocardial infarction, previous atrial fibrillation, or any other baseline laboratory finding. In most subgroups, the hazard ratios were below 1. The few exceptions occurred in subgroups with relatively few events, and few deviations gave concordant results for the two major end-points, indicating that the treatment effect seen in the whole study was not influenced by any of these subgroups. An exception was seen with serum sodium. Higher levels of serum sodium were associated with decreased risk of death from any cause in the high-dose lisinopril group.

Figure 2 shows the influence of age in 5-year bands on the hazard ratio for high-dose vs low-dose lisinopril for all-cause mortality and mortality plus hospitalization. For all-cause mortality and all-cause hospitalization, there was no effect of age on outcome, with uniform hazard ratios in the different age bands. The hazard ratio for the 75–79 age group was above 1·0 for the all-cause mortality end-point, although this was not statistically significant. Moreover it was not concordant with the findings for patients ≥ 80 years or with the results for death plus hospitalizations in the 75–79 age group. Analysis using age as a continuous covariate also showed no interaction between age and treatment.

The effect of concurrent medications at randomization is shown in Fig. 3. For all subgroups the confidence interval overlaps that for the study as a whole, indicating that none of the subgroups behave differently to the overall study population.

Diabetic patients

Of the 3164 patients in the study, only the 611 (19%) receiving hypoglycaemic agents (oral or insulin) at baseline were considered as having clinical diabetes mellitus. The mean age of these patients was 65 ± 9 years and 78% were male. The cause of heart failure in this diabetic group was predominately ischaemic heart disease (71%), with dilated cardiomyopathy reported in 23%. Thus the diabetic patients had similar reasons for heart failure as the non-diabetic cohort (ischaemic heart disease 64% and dilated cardiomyopathy 28%). All-cause mortality was 49% among the diabetic patients compared with 42% in the non-diabetic group, while the occurrence of combined end-point of mortality plus need for hospitalization was 88% vs 80%, for the diabetic and non-diabetic groups respectively. Kaplan–Meier survival curves are shown in Fig. 4.

The relative risk reduction in mortality for high-dose vs low-dose lisinopril was 14% for patients with diabetes mellitus and 6% for those without; for mortality plus hospitalization risk reductions were 4% and 14%, respectively. The interaction *P*-values for these subgroups were, however, not significant (mortality, $P=0{\cdot}502$; mortality plus hospitalization, $P=0{\cdot}275$), so diabetic patients responded to high-dose lisinopril as well as non-diabetics.

Diabetic patients were hospitalized more often than non-diabetics as would be expected, but high-dose lisinopril reduced the number of hospitalizations and days in hospital per patient to a greater extent in diabetic than in non-diabetic patients (Table 2). Over one-third of all admissions and days in hospital were for heart failure. High-dose lisinopril was more effective than

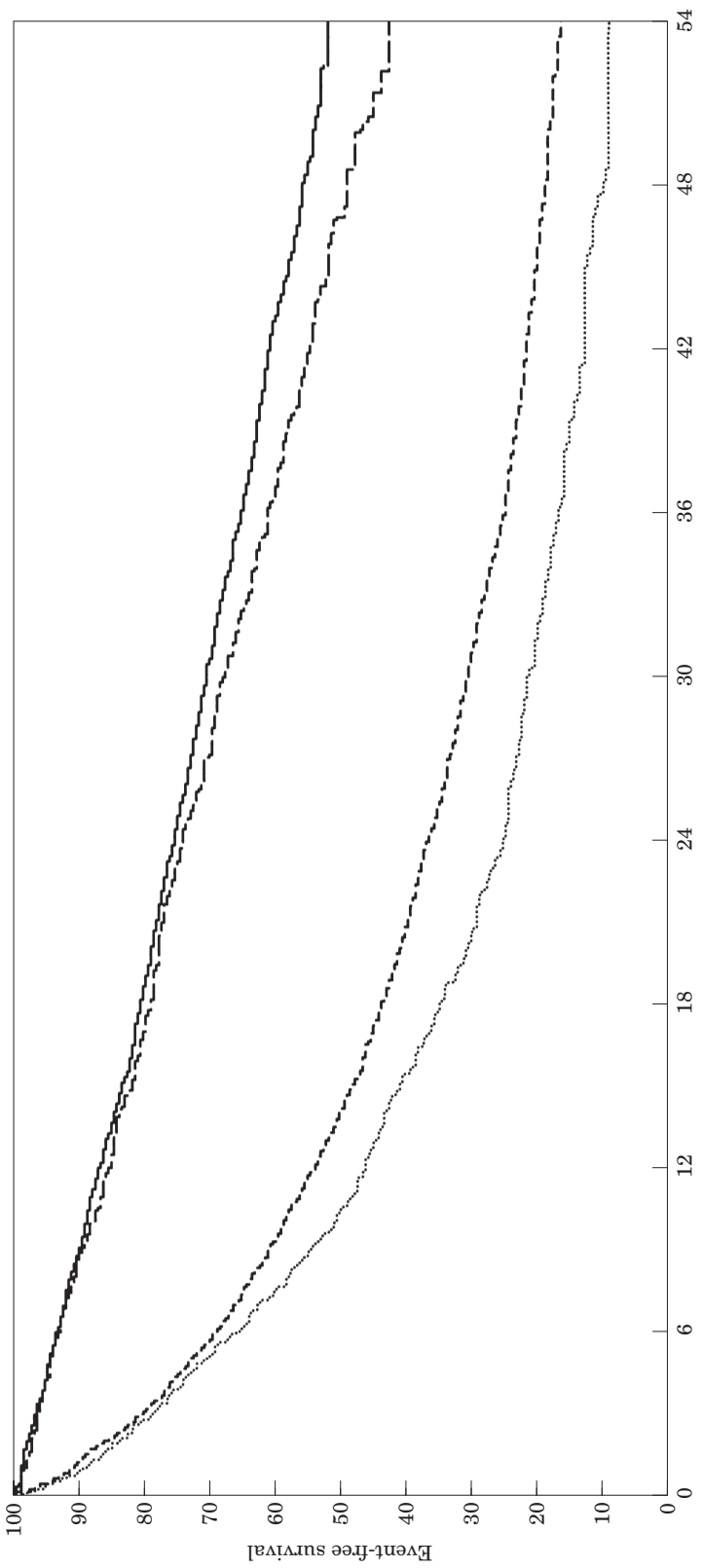

Figure 4 **All-cause mortality and all-cause mortality plus need for hospitalization by any reason in patients with and without diabetes mellitus. ——= All cause mortality/non-diabetic; — — —= all cause mortality/diabetic; – – –= all cause mortality and hospitalization/non-diabetic; . . . = all cause mortality and hospitalization/diabetic.**

Table 2 Number of hospitalizations per patient and days in hospital for patients with or without diabetes receiving high- or low-dose lisinopril

	High-dose lisinopril (n=1568)		Low-dose lisinopril (n=1596)	
	Diabetics	Non-diabetics	Diabetics	Non-diabetics
Total patients n	314	1254	297	1299
Hospitalizations/patient	3·0	2·2	3·5	2·5
Days in hospital/patient	21·4	17·7	29·1	21·0
Hospitalized patients n (%)	254 (81)	874 (70)	239 (80)	958 (74)
Hospitalizations/patient	3·7	3·2	4·3	3·4
Days in hospital/patient	26·5	25·4	36·2	28·5

low-dose in reducing the number of days in hospital for heart failure in diabetic patients (by 27%): high-dose lisinopril was as effective in reducing hospitalizations per patient for heart failure in diabetic patients as in non-diabetic populations (21% vs 24%).

Tolerability

The tolerability of high-dose lisinopril was similar for patients with and without diabetes with respect to cough (12% and 10% respectively), renal dysfunction (29% vs 22%) and hypotension (35% vs 32%).

High-dose lisinopril was tolerated slightly better than low-dose in both young and elderly patients (Table 3) and although more elderly than younger patients were withdrawn from study treatment, more were withdrawn from low-dose treatment. There was a trend for more hypotension/dizziness and renal dysfunction/hyperkalaemia with high-dose lisinopril (Table 4).

Discussion

In this population of patients with advanced heart failure, high-dose lisinopril reduced overall mortality by 8% and hospitalization by 12%, compared with low-dose lisinopril, as previously reported[7]. The characteristics and numbers of adverse events were similar between treatment groups and typical of ACE inhibitors. In this analysis, findings in high-risk patients were consistent with the overall results, suggesting a reduction in mortality and morbidity with high-dose lisinopril.

In patients with hypotension, and thus more advanced myocardial dysfunction, high-dose lisinopril was as effective as in the overall study population in terms of mortality reduction. In general, patients with an increased mortality risk are those with low serum sodium or increased creatinine at baseline, aged over 70, or with ischaemic heart disease. For all-cause mortality, the hazard ratio for the 75–79 age group appears as a single high outlying value (Fig. 2) with a wide confidence interval which crosses 1·0 and overlaps the confidence intervals for the other groups: there is thus no evidence that these patients respond less well to high-dose lisinopril. Thus age did not influence the effect of treatment. There were no consistent interactions between creatinine or potassium values and treatment effect. The high hazard ratio for baseline sodium <137 mmol $.1^{-1}$ for mortality does not appear to indicate a genuine safety hazard, because the 95% CI overlaps the result for the study as a whole and the hazard ratio for the other end-point of combined

Table 3 Patient withdrawals by lisinopril dose and age group

Age at entry (years)	Percentage of patients withdrawn from therapy	
	High dose	Low dose
<70	24·5	28·8
70–74	33·6	34·7
>75	31·2	35·2
Overall	27·1	30·7

Table 4 Incidence (percentage) of possible dose-related side effects in high-risk subgroups

	High-dose	Low-dose
(A) Hypotension/dizziness		
Receiving hypoglycaemic agents on entry		
yes	34·7	21·2
no	32·2	22·3
Age		
≥70 years	36·8	24·8
<70 years	30·7	21·0
(B) Renal dysfunction/hyperkalaemia		
Receiving hypoglycaemic agents on entry		
yes	28·7	21·2
no	21·5	15·2
Age		
≥70 years	32·2	21·7
<70 years	18·5	15·3

mortality plus hospitalizations is considerably below 1·0. When sodium is treated as a continuous covariate, analysis shows no interaction with treatment.

Thus, none of these factors altered the treatment effect: high-dose lisinopril was still more effective than low-dose lisinopril in these high-risk patients. However, there is a consistent pattern suggesting that for both mortality and mortality plus hospitalization, patients who were not receiving calcium channel blockers, nitrates, vasodilators and beta-blockers (each considered separately) seemed to derive greater benefit from high-dose lisinopril than patients receiving these medications (Fig. 3). This suggests that high-dose lisinopril is even more necessary and beneficial in heart failure patients who cannot, for whatever reason, be treated with other medications.

Patients taking hypoglycaemic medications at baseline were assumed to have clinical diabetes mellitus. It was not possible to distinguish between type I and type II diabetes; however, the vast majority of patients (at least 90%) can be assumed to have type II diabetes. High-dose lisinopril was as effective in these patients as in the overall study population in reducing mortality. The reduction in mortality in patients with diabetes was 14%, compared with 8% in the overall population. However, the confidence intervals were wide and the interaction not significant ($P=0·502$), and therefore high-dose lisinopril is similarly effective in both diabetic and non-diabetic patients.

Although the percentage reductions in the combined end-point of all-cause mortality and all-cause hospitalizations were smaller in the diabetic subgroup than in non-diabetic patients (4% vs 14%), this difference was also not statistically significant. The data in Table 2 show a generally consistent tendency towards greater reductions in various measures of hospitalizations with high-dose lisinopril in diabetic patients. These data show that high-dose lisinopril is more effective than low-dose lisinopril in the diabetic population, as it is in the non-diabetic population and in the overall study population. In addition, since diabetic patients are generally more severely ill than non-diabetic patients, and lisinopril has beneficial effects in diabetic nephropathy[17] and retinopathy[18], the benefits of high-dose treatment may be proportionately greater in diabetic subjects.

As this is a retrospective subgroup analysis, the conclusions that can be drawn from this analysis are limited. However, it can be seen that high-dose lisinopril is as effective in high-risk populations as in the overall study population. In addition, although the criteria for diabetes mellitus were poorly defined (as in most other similar trials), the data show a number of interesting trends, particularly larger reductions in days in hospital for heart failure in these patients.

Conclusion

The results of this subanalysis are of value for the practising physician. They show that in subgroups of heart failure patients at high risk, high-dose lisinopril is well-tolerated and at least as effective as in the overall study population, with significant reductions in mortality and morbidity. The results show that it will generally be advantageous to up-titrate lisinopril in these high-risk patients, to gain the mortality and morbidity benefits seen in the overall population of the ATLAS study.

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