RESEARCH

Cardiovascular Therapeutics

Effect on Mode of Death of Heart Failure Treatment Started with Bisoprolol Followed by Enalapril, Compared to the Opposite Order: Results of the Randomized CIBIS III Trial

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SUMMARY

Background: Mode of death in chronic heart failure (CHF) may be of relevance to choice of therapy for this condition. Sudden death is particularly common in patients with early and/or mild/moderate CHF. β-Blockade may provide better protection against sudden death than ACE inhibition (ACEI) in this setting. **Methods:** We randomized 1010 patients with mild or moderate, stable CHF and left ventricular ejection fraction $\leq$35%, without ACEI, β-blocker or angiotensin-receptor-blocker therapy, to either bisoprolol (n = 505) or enalapril (n = 505) for 6 months, followed by their combination for 6–24 months. The two strategies were blindly compared regarding adjudicated mode of death, including sudden death and progressive pump failure death. **Results:** During the monotherapy phase, 8 of 23 deaths in the bisoprolol-first group were sudden, compared to 16 of 32 in the enalapril-first group: hazard ratio (HR) for sudden death 0.50; 95% confidence interval (CI) 0.21–1.16; P = 0.107. At 1 year, 16 of 42 versus 29 of 60 deaths were sudden: HR 0.54; 95% CI 0.29–1.00; P = 0.049. At study end, 29 of 65 versus 34 of 73 deaths were sudden: HR 0.84; 95% CI 0.51–1.38; P = 0.487. Comparable figures for pump failure death were: monotherapy, 7 of 23 deaths versus 2 of 32: HR 3.43; 95% CI 0.71–16.53; P = 0.124, at 1 year, 13 of 42 versus 5 of 60: HR 2.57; 95% CI 0.92–7.20; P = 0.073, at study end, 17 of 65 versus 7 of 73: HR 2.39; 95% CI 0.99–5.75; P = 0.053. There were no significant between-group differences in any other fatal events. **Conclusion:** Initiating therapy with bisoprolol compared to enalapril decreased the risk of sudden death during the first year in this mild systolic CHF cohort. This was somewhat offset by an increase in pump failure deaths in the bisoprolol-first cohort.

Introduction

The current European guidelines for the diagnosis and treatment of chronic heart failure (CHF) recommend starting therapy for newly diagnosed CHF with an angiotensin-converting-enzyme-inhibitor (ACEI), to be followed by a β-blocker [1]. This order has become the clinical standard because ACEIs were shown to improve survival and morbidity in CHF before β-blockers were investigated in this setting; the beneficial effects of β-blockers on survival and morbidity were therefore shown in addition to ACEI [2–5]. Although the combination of both classes of drugs is recommended standard treatment for CHF, the sequence of initiating these agents may be important. In clinical practice, most patients with CHF do not receive both agents in adequate doses, and the first initiated treatment, that is, an ACEI, is more often given and uptitrated to its target dose, compared to the second agent, that is, a β-blocker [6–9]. Moreover, theoretical considerations suggest that initiation of treatment for CHF with a β-blocker rather than with an ACEI may be more beneficial in terms of survival, especially with regard to sudden death. Sudden death is the most prevalent mode of death in the early course of CHF and in mildly to moderately symptomatic CHF, presenting the major clinical threat to these patients [10–12]. Although there is limited evidence that ACEIs prevent sudden death in CHF patients, β-blockers substantially reduce sudden or other modes of death as add-on therapy to ACEIs [2–5,13–16].

There has been as yet no formal comparison between the two drug classes for sudden death in CHF patients. As the sympathetic nervous system is systemically activated at an earlier stage than the renin–angiotensin–aldosterone system (RAAS) in CHF [17], the concept of early introduction of a β-blocker in CHF is particularly attractive. In addition, there is early sympathetic activation in the damaged heart due to reflexes of cardiac origin [18,19]. β-Blockers effectively inhibit the activation of the sympathetic system and also of the RAAS. Conversely, ACE inhibitors appear to have little direct sympatho-inhibitory effect in CHF patients [20,21].

The sequence of initiating therapy with an ACEI or a β-blocker was investigated by the third Cardiac Insufficiency Bisoprolol Study (CIBIS III) [22,23]. In CIBIS III, 1010 patients with stable, mild/moderate, systolic CHF were randomized to monotherapy with either bisoprolol or enalapril for 6 months, followed by their combination for 6–24 months [22]. During a mean follow-up of 1.2 years, the two strategies were similar in terms of combined all-cause mortality or all-cause hospitalization [23]. In this analysis, we compared the two strategies with regard to mode of death.

Methods

Study Design and Patients

The study was approved by the regional ethics committees of the participating centers and was conducted in accordance with the Declaration of Helsinki. All subjects gave informed consent. The study methods have been described in detail previously [22,23]. In essence, CIBIS III was a multicenter, parallel group trial utilizing blinded endpoint evaluation to compare randomized, open-label initial monotherapy with bisoprolol (initial dose 1.25 mg once daily, target dose 10 mg once daily) or enalapril (initial dose 2.5 mg twice daily, target dose 10 mg twice daily) for 6 months, followed by their combination for 6 to 24 months.

At the start of the combined therapy phase, the uptitration of the complementary drug was similar to the first up-titration of that drug. Patients were at least 65 years of age and had mildly or moderately symptomatic CHF, corresponding to New York Heart Association (NYHA) class II or III, and left ventricular ejection fraction $\leq$35%. CHF was clinically stable for at least 7 days before randomization. Patients were essentially ACEI, β-blocker, and angiotensin-receptor blocker naïve.

During the 6-month monotherapy phase, initiation of an angiotensin-receptor blocker or an aldosterone antagonist was not permitted, whereas continued preexisting aldosterone antagonist therapy was. Early introduction of the second drug was allowed, for example, due to poor control of CHF. The two strategies were compared with regard to the combined primary endpoint of all-cause mortality or hospitalization, and each of these components individually. In addition, subcategories of causes for mortality and hospitalization were assessed, as well as safety and tolerability parameters. In this analysis, we assessed mode of death through blinded evaluation and adjudication.

Sudden death was a cardiovascular death defined according to the following criteria:

(1) Death occurring within 1 h of the occurrence of new symptoms or without symptoms.
(2) Death at night during sleep (patient found dead in bed) without other cause.
(3) Death in odd places (e.g., toilet room, parking lot, etc) without other cause.
(4) Death within 28 days after resuscitation from cardiac arrest in the absence of preexisting circulatory failure or other causes of death.
(5) Unwitnessed death in the absence of preexistence progressive circulatory failure or other causes of death.

The blinded adjudication of mode of death was performed by the endpoint committee and three members of the steering committee (RW, DJvV, and FF). Adjudication was based on all five criteria in accordance with previous landmark CHF trials [4,24–28].

Criteria for progressive pump failure death were death in the context of worsening of heart failure, defined as: newly occurring or worsening of previously existing symptoms such as dyspnoea on exertion in the absence of new pulmonary disease, paroxysmal nocturnal dyspnoea or orthopnoea, or signs of venous congestion. In addition, need for new or increased specific treatment for heart failure was required.

Statistical Analysis

Prior to study start, we planned to assess mortality, including mode of death, and hospitalization during the monotherapy phase and during the entire study duration [22]. Prior to data analysis, it was decided to assess mode of death also at 1 year, because this was the minimum time of follow-up for all patients.

Assessment of mode of death was therefore performed: (1) during the monotherapy phase according to the protocol definition (from randomization to the end-of-monotherapy-visit at 157–230 days after randomization), regardless of whether or not some patients had received the second drug earlier than at the end-of-monotherapy-visit; (2) during actual monotherapy up to 6 months, censoring patients when they were given combined therapy prior to the end-of-monotherapy-visit, due to a medically legitimate reason as judged by the blinded endpoint committee; (3) during actual monotherapy, irrespective of how long this phase was, that is, including patients in whom the second drug was not introduced or introduced later than after 6 months; (4) after 1 year of treatment; and (5) during the entire study period. Event-related hospitalizations were unplanned hospitalizations necessitated by clinical events, as judged by the blinded endpoint committee.

All analyses were performed by intention-to-treat using the SAS statistical software. Events were analyzed via a Cox proportional hazards model with treatment as a single factor. Treatment effects were estimated via the hazard ratio (HR) and its corresponding 95% confidence interval (CI). Survival curves were calculated using Kaplan–Meier estimates. Between-group differences in mean study drug doses and other continuous variables were analyzed by Student's *t*-test and expressed as mean (standard deviation, SD). A two-tailed $P < 0.05$ indicated statistical significance.

Results

The main results of CIBIS III have been published previously [23]. Mean follow-up of the 1010 patients enrolled was 1.22 (0.42) years, varying from 1.0 to 2.1 years. Four subjects did not take any study medication and five patients were lost to follow-up (Fig. 1). Baseline characteristics were similar in the two groups (Table 1). Mean age of the patients was 72 years and 32% were female. Ischemic heart disease was considered the etiology of CHF in 62% and hypertension in 37%. Mean left ventricular ejection fraction was 29% and patients were evenly distributed between NYHA classes II and III (due to stratified randomization). Two thirds of the patients had a history of hypertension, almost 50% had a history of acute myocardial infarction and around 20% had a history of

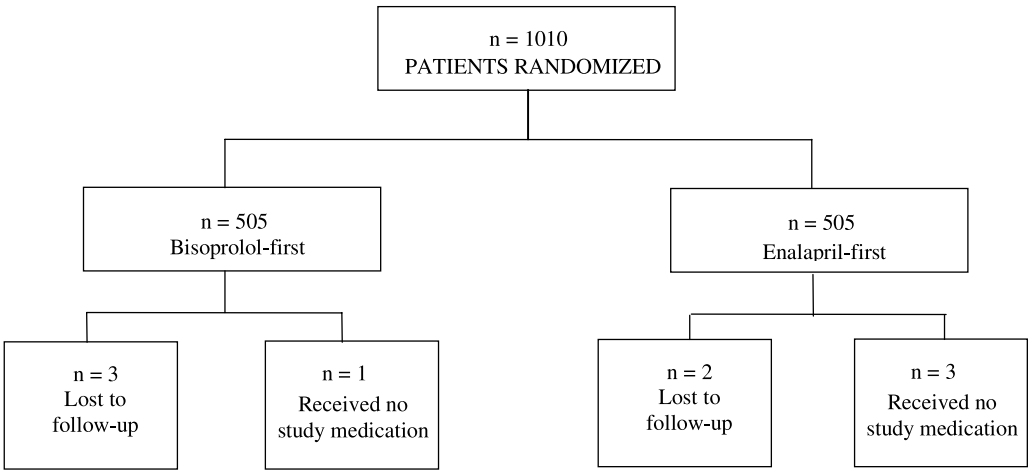

Figure 1 Study flow diagram.

Table 1 Baseline data

	Bisoprolol-first (n = 505)		Enalapril-first (n = 505)	
	Mean/n	%/SD	Mean/n	%/SD
Age (years)	72.4	5.8	72.5	5.7
Females	172	34.1	149	29.5
NYHA class II/III	245/260	48.5/51.5	250/255	49.5/50.5
Left ventricular ejection fraction (%)	28.8	4.8	28.8	5.2
Heart rate (beats per minute)	78.8	13.8	79.5	13.2
Systolic BP (mm Hg)	134.5	17.0	133.7	16.5
Etiology[a]				
Coronary artery disease	309	61.2	321	63.6
Hypertension	197	39.0	172	34.1
Valvular heart disease	11	2.2	15	3.0
Primary cardiomyopathy	49	9.7	51	10.1
Other	68	13.5	50	9.9
History of hypertension	354	70.1	314	62.2
History of myocardial infarction	254	50.3	243	48.1
History of diabetes	95	18.8	113	22.4
Baseline pacemaker use	38	7.5	33	6.5
Baseline diuretic treatment	430	85.1	421	83.4
Baseline aldosterone antagonists	72	14.3	62	12.3
Baseline cardiac glycoside treatment	166	32.9	155	30.7

NYHA, New York Heart Association; CHF, chronic heart failure; BP, blood pressure.
[a]More than one etiology may be given for each patient.

diabetes. Baseline cardiovascular medication was similar in the two groups, and 84% were on diuretic treatment (mostly a loop diuretic), 13% received an aldosterone antagonist, and 32% had a cardiac glycoside. At baseline, only one patient (in the bisoprolol-first group) had an internal cardiac defibrillator.

During follow-up, the use of aldosterone antagonists and digoxin changed very little, and only around 2% in both groups received an angiotensin-receptor blocker. During the study, three patients received a biventricular pacemaker and no patient received an internal defibrillator. In the bisoprolol-first group, 7.7% of the patients received the second drug before the 6-month time point, as compared with 7.3% in the enalapril-first group, but only 0.8% and 0.4%, respectively, due to poor control of CHF.

Sudden Death

Overall mortality results are shown in Table 2 and sudden death plot is shown in Figure 2(a). During the protocol-defined monotherapy phase, applying sudden death definition, comparing bisoprolol with enalapril, the HR for sudden death, was 0.50, 95% CI 0.21–1.16, $P = 0.107$ (Figure 2a). There were no significant between-group differences in any of the other fatal events. By analysis of the monotherapy phase, censoring patients when they were legitimately put on combined therapy prior to 6 months after randomization, there were nine sudden deaths in the bisoprolol-first group versus 18 in the enalapril-first group: HR 0.51; 95% CI 0.23–1.13; $P = 0.098$. The result was also similar analyzing the actual monotherapy, irrespective of how long this phase was: 9 versus 18 sudden deaths; HR 0.51; 95% CI 0.23–1.14; $P = 0.103$.

During the first year, comparing bisoprolol with enalapril, HR for sudden death was 0.54, 95% CI 0.29–1.00, $P = 0.049$ (Figure 3a). There were no significant between-group differences in any of the other fatal events.

During the entire trial, comparing bisoprolol with enalapril, HR for sudden death was 0.84, 95% CI 0.51–1.38, $P = 0.487$ (Figure 3a). There were no significant between-group differences in any of the other fatal events.

Disregarding sudden deaths occurring more than 14 days after the last dose of study medication did not change the level of sudden death risk reduction for bisoprolol-first at any time point during the study.

Progressive Pump Failure Death

Progressive pump failure deaths are shown in Table 2 and summarized in Figure 2(b). During the monotherapy phase, applying the death due to pump

Table 2. Mode of death during different phases of CIBIS III

	Bisoprolol-first, n = 505		Enalapril-first, n = 505	
	n	%	n	%
Monotherapy phase				
All deaths	23	4.6	32	6.4
Sudden deaths	8	1.6	16	3.2
Nonsudden CV deaths	12	2.4	5	1.0
Pump failure deaths	7	1.4	2	0.4
Myocardial infarction deaths	2	0.4	3	0.6
Stroke deaths	2	0.4	0	0.0
Other CV deaths	1	0.2	0	0.0
Non-CV deaths	2	0.4	10	2.0
Unclassifiable deaths	1	0.2	1	0.2
At 1 year				
All deaths	42	8.3	60	11.9
Sudden deaths	16	3.1[a]	29	5.8
Nonsudden CV deaths	19	3.8	15	3.0
Pump failure deaths	13	2.6	5	1.0
Myocardial infarction deaths	2	0.4	6	1.2
Stroke deaths	3	0.6	2	0.4
Other CV deaths	1	0.2	2	0.4
Non-CV deaths	5	1.0	14	2.8
Unclassifiable deaths	2	0.4	2	0.4
At study end				
All deaths	65	12.8	73	14.5
Sudden deaths	29	5.7	34	6.7
Nonsudden CV deaths	26	5.1	18	3.6
Pump failure deaths	17	3.4	7	1.4
Myocardial infarction deaths	3	0.6	6	1.2
Stroke deaths	5	1.0	2	0.4
Other CV deaths	1	0.2	3	0.6
Non-CV deaths	8	1.6	19	3.8
Unclassifiable deaths	2	0.4	2	0.4

[a] HR 0.54, 95% CI 0.29–1.00, $P = 0.049$. All other between-group differences were nonsignificant.

failure/worsened heart failure definition, comparing bisoprolol with enalapril, the HR was 3.43, 95% CI 0.71–16.53, $P = 0.124$ (Figure 3b). During the first year, comparing bisoprolol with enalapril, HR for pump failure death was 2.57, 95% CI 0.92–7.20, $P = 0.073$ (Figure 3b). During the entire trial, comparing bisoprolol with enalapril, HR for pump failure death was 2.39, 95% CI 0.99–5.75, $P = 0.053$ (Figure 3b).

Other Modes of Death

Other causes of death, that is, other nonsudden CV deaths (myocardial infarction, stroke, other) are listed in Table 2. These were relatively few in number over the course of the CIBIS III study and therefore no further interpretation was made regarding the impact of bisoprolol versus enalapril on these events.

Hospitalization

Table 3 shows event-related first hospitalizations at the various study time points. Only the primary reason for the first hospitalization was considered for those patients with multiple event-related hospital admissions. There were no statistically significant between-group differences with regard to type of hospitalization at different time points during the study. There was a non-significant excess of patients with a first hospitalization for worsening of CHF during the protocol-defined monotherapy phase in the bisoprolol group (HR 1.56; 95% CI 0.94–2.58; between-group difference $P = 0.083$).

Bisoprolol-first was similar to enalapril-first in the combined endpoint of all-cause death or hospitalization for worsening of CHF: at the end of the monotherapy phase, HR 1.20; 95% CI 0.83–1.73; between-group difference $P = 0.323$; at 1 year HR 0.93, 95% CI% 0.69–1.26, $P = 0.65$; at study end HR 0.98, 95% CI% 0.74–1.29, $P = 0.89$. One patient in the bisoprolol-first group and two in the enalapril-first group had either documented nonlethal ventricular tachycardia/fibrillation or an internal cardiac defibrillator discharge.

Study Drug Dose

The mean dose of bisoprolol used at 1 year was 8.4 (2.7) mg/day in the bisoprolol-first group, as compared with 7.4 (3.3) mg/day in the enalapril-first group ($P < 0.0001$). The mean dose of enalapril used at 1 year was 17.1 (5.4) mg/day in the bisoprolol-first group, as compared with 18.6 (5.0) mg/day in the enalapril-first group ($P = 0.14$).

Discussion

The present analysis suggests choice of starting therapy may influence mode of death for systolic CHF. In patients with mildly or moderately symptomatic, stable CHF and left ventricular ejection fraction 35% or less, starting treatment for CHF with the β-blocker bisoprolol halved sudden deaths during the first approximately 6 months of monotherapy, as compared with beginning with the ACEI enalapril, although the difference was not statistically significant. After 1 year, that is, after 6 months of combined therapy in both treatment groups, bisoprolol-first showed a sudden death hazard reduction of similar magnitude, which was statistically significant compared to enalapril-first.

The Kaplan–Meier curves illustrate how sudden death was postponed by starting with bisoprolol rather than with enalapril. The number of patients dying a sudden death in the enalapril-first group during the first 6 months of monotherapy was equal to that in the

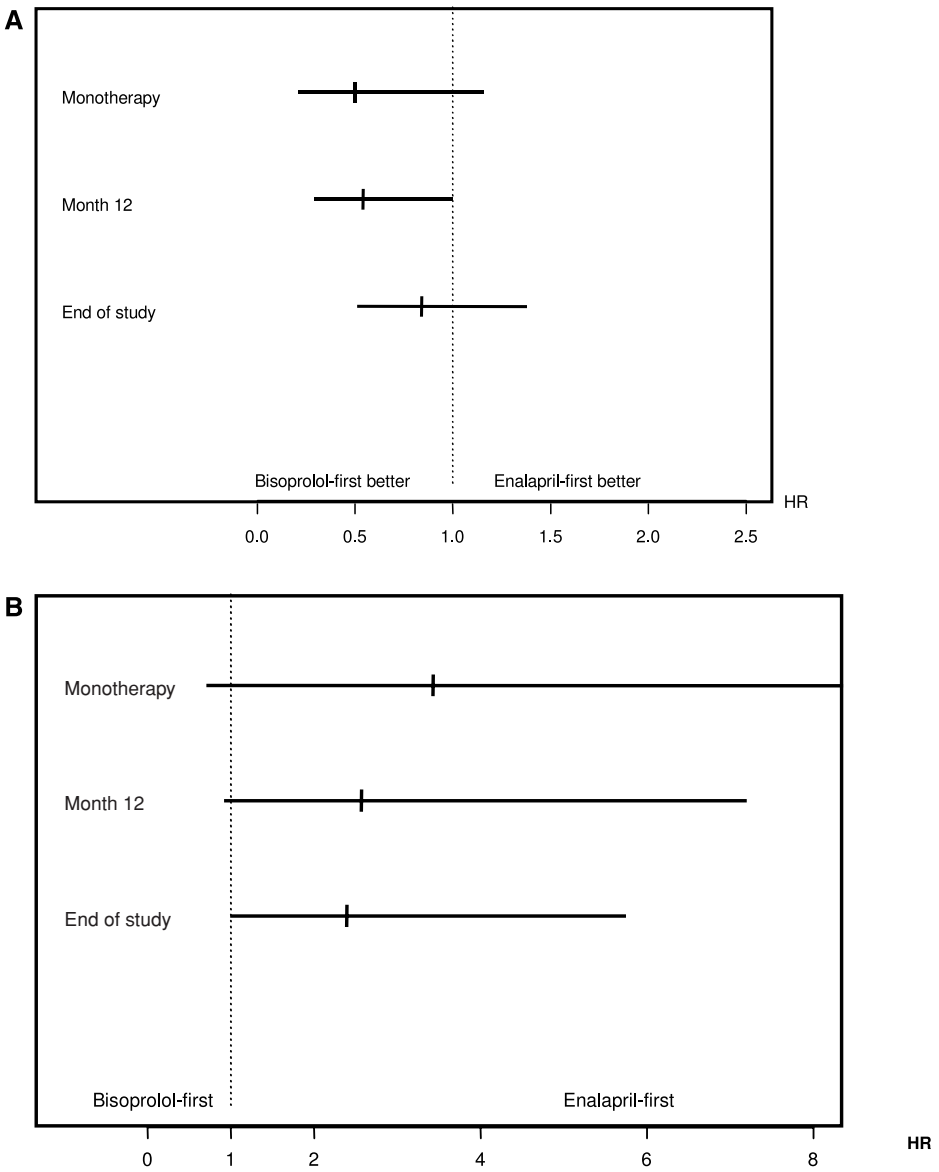

Figure 2 (**a**) Plot showing point estimates and 95% confidence intervals for sudden death at various study time points during the trial, comparing bisoprolol-first and enalapril-first. HR, hazard ratio. (**b**) Plot showing point estimates and 95% confidence intervals for pump failure death at various study time points during the trial, comparing bisoprolol-first and enalapril-first. HR, hazard ratio.

bisoprolol-first group during the entire first year. Thus, although a limited number of patients suffered a sudden death, the early between-group difference was rather substantial and statistically significant at 1 year. After some time of combined therapy, the difference between the two treatment regimens gradually leveled out, and at study end there was no difference.

In contrast, there was a nonstatistically significant increase in progressive pump failure deaths in patients who first received bisoprolol compared to enalapril monotherapy. This difference persisted beyond the monotherapy period.

Prior to the CIBIS III trial, a β-blocker and an ACEI in monotherapy or as first CHF treatment were never directly compared with regard to the effects on sudden death (or all-cause death or hospitalization) in patients with CHF. However, assessment of the effects of ACEIs versus placebo (on top of a diuretic with or without digitalis) and of β-blockers versus placebo (on top of an ACEI and diuretics with or without digitalis) indicates that

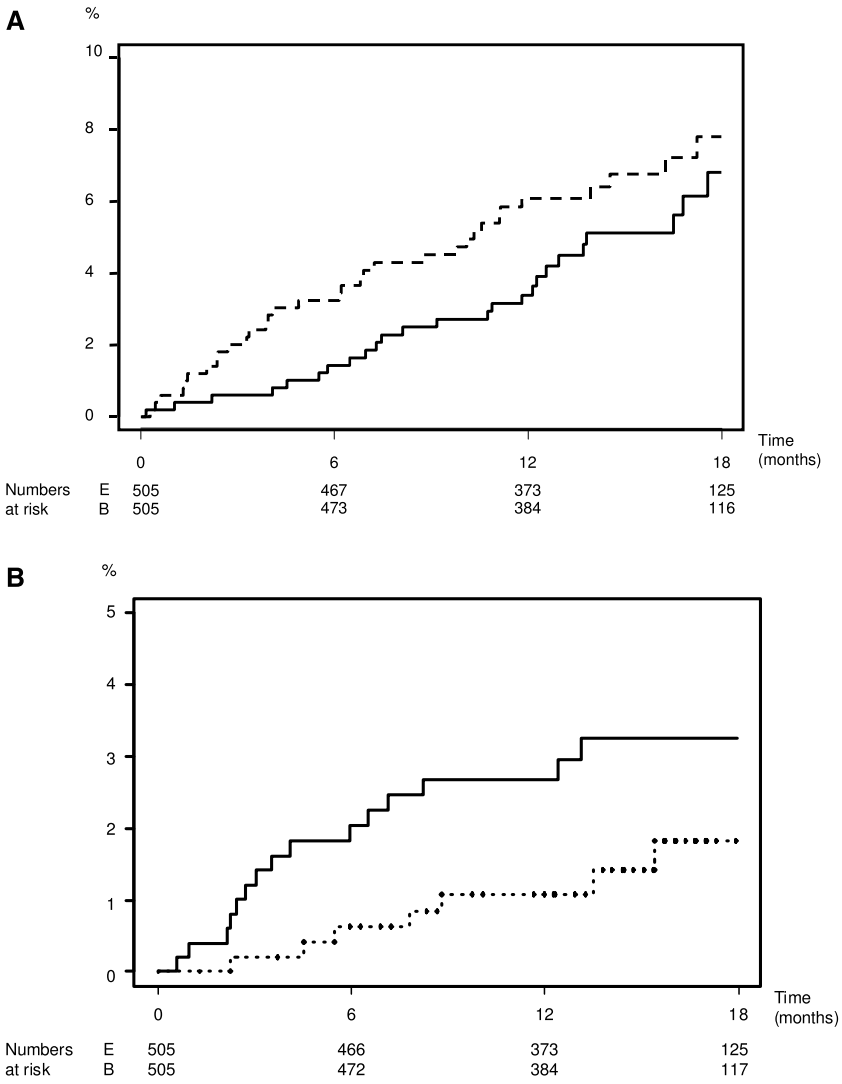

Figure 3 (**a**) Sudden death during the entire study. Broken line, enalapril (E) first, solid line, bisoprolol (B) first. (**b**) Pump failure death during the entire study. Broken line, enalapril (E) first, solid line, bisoprolol (B) first.

β-blockers substantially reduce sudden death, whereas there is no such evidence for ACEIs [2–5,13–16]. The results of the monotherapy phase in CIBIS III constitute the first data on a direct comparison between a β-blocker, bisoprolol, and an ACEI, enalapril, in regard to the effect on sudden death. The results of the entire study represent the first large-scale data comparing a strategy of beginning treatment for CHF with a β-blocker followed by an ACEI with the standard regimen of an ACEI first, followed by a β-blocker. The findings of CIBIS III are in agreement with those of prior trials regarding the superior effects of β-blockers on sudden death [2–5,13–16]. These data suggest that, for patients with mild or moderate symptoms of CHF, the risk of sudden death within the first year is reduced by initial therapy with bisoprolol, as compared with enalapril.

Despite the early reduction in sudden death and a similar, statistically nonsignificant reduction in all-cause mortality, it might be argued that the early increase in hospitalizations for worsening of CHF and for progressive pump failure death in the bisoprolol-first group compared to the enalapril-first group, is a drawback of starting CHF treatment with bisoprolol rather than with enalapril. Because investigators were not blinded to treatment allocation, the nonsignificant increase in hospitalization for worsening of CHF with bisoprolol may, at least partly, be due to unfamiliarity among investigators with starting therapy for CHF with a β-blocker, rather than with an ACEI. Moreover, although we used a titration schedule that is established for bisoprolol as add-on therapy to a regimen including an ACEI, this might be suboptimal when patients are not already on an ACEI. Specifically,

Table 3 Patients with event-related first hospitalizations

	Bisoprolol-first, n = 505		Enalapril-first, n = 505	
	n	%	n	%
Monotherapy phase				
All hospitalizations	84	16.6	73	14.5
CV hospitalizations	58	11.5	48	9.5
Worsening of CHF hospitalizations	39	7.7*	25	5.0
Non-CV hospitalizations	26	5.1	25	5.0
At 1 year				
All hospitalizations	117	23.1	120	23.8
CV hospitalizations	82	16.2	76	15.1
Worsening of CHF hospitalizations	49	9.7	40	7.9
Non-CV hospitalizations	35	6.9	44	8.7
At study end				
All hospitalizations	131	25.9	136	26.9
CV hospitalizations	91	18.0	85	16.8
Worsening of CHF hospitalizations	53	10.5	44	8.7
Non-CV hospitalizations	40	7.9	51	10.1

CV, cardiovascular; CHF, chronic heart failure.
*All between-group differences nonsignificant.

background ACE inhibition may be protective against the risk of worsening of heart failure (contributing to both hospitalization and pump failure death) with the introduction and uptitration of the β-blocker. It is also important to note that, given the absence of a control group, the increased pump failure rate with β-blockers may not necessarily constitute an absolute increase in such events (vs. placebo or no therapy), rather an increase only in comparison to ACE inhibitor.

It might be argued that the order of initiating a β-blocker and an ACEI in patients with CHF does not matter, because both should be given to patients with CHF and impaired left ventricular systolic function. However, surveys have shown that the second agent is most often not started soon after the first drug and is frequently not given at all, and when it is prescribed it is usually given in a low dose [6–9]. Even under the clinical trial conditions of CIBIS III, where investigators were forced to uptitrate both study drugs according to protocol unless they had a very good reason for not doing so, the mean dose of bisoprolol at 1 year was significantly higher in the bisoprolol-first group compared to the enalapril-first group. However, there was no statistically significant between-group difference in the enalapril dose. This is in line with previous findings of a small study [29] and may be relevant to the observation of a significantly lower risk of sudden death at 1 year in the bisoprolol-first group. Indeed, a better effect on mortality with higher doses of a β-blocker has been observed in some but not all studies [3,30,31,32]. Furthermore, even if one were to give patients both treatments, the observation of an early sudden death reduction in the bisoprolol-first group indicates the need to give CHF patients a β-blocker as soon as possible. However, irrespective of which drug was given first, after a mean time of follow-up of 1.2 years, around 13–14% of the patients in both groups had died and about 6% in both groups had died a sudden death, indicating that there is substantial room for improvement of therapy. These data support the contention that long-term therapy should ultimately include both drug classes, irrespective of which agent is commenced first.

The reasons for the gradual leveling out of the between-group difference in sudden (and all-cause) deaths after 1 year are unclear. It seems that there was a catch-up phenomenon regarding sudden deaths among patients in the bisoprolol-first group, beginning after more than 6 months of combined treatment. Alternatively, the reason may be that the addition of bisoprolol in the enalapril-first group, after some delay prevented some extra sudden deaths, as compared with the addition of enalapril in the bisoprolol-first group. Possibly, some patients who are prone to die of sudden death will do so irrespective of combined therapy with bisoprolol and enalapril, further indicating that there is room for improved therapy in these patients, for example, an internal cardiac defibrillator.

By study design, the monotherapy phase was around 6 months in duration (157–230 days). The reasons for this have been discussed previously [22,23,33]. In clinical practice, many physicians would likely aim for combined treatment within a shorter time period, although surveys rather show the opposite in reality [7–9]. The CIBIS III results do not constitute a recommendation about the time interval between initiating the first and the second drug. However, even if this time interval were to be shorter than in CIBIS III, the between-group difference in sudden death is likely to be present to some degree.

The main limitation in this analysis is that of inadequate statistical power with which to assess mode of death. The 1-year time point was the only one prespecified by the study protocol in which there was a significant between-group difference favoring bisoprolol. Furthermore, events tracked (nonsignificantly) in the opposite direction for pump failure death, with even smaller numbers. Thus, interpretation of these trends should be necessarily made with caution and any mechanistic interpretation be considered hypotheses-generating only. Clearly, adequately powered randomized trials are needed to definitively test these hypotheses, although there appears little chance that these will be performed.

In conclusion, in patients at least 65 years of age with mildly or moderately symptomatic, stable CHF and left ventricular ejection fraction 35% or less, initiating CHF

therapy with bisoprolol was significantly superior to initiating therapy with enalapril in terms of sudden deaths during the first year. The hazard reduction was similar at the end of the monotherapy phase, although not statistically significant. The difference between the two treatment strategies did not level out until after more than 6 months of combined treatment. The reduction in sudden death for bisoprolol-first was accompanied by a nonsignificant reduction in all-cause death of similar magnitude, although a nonsignificant increase in progressive pump failure death was observed at these time points. The early reduction of sudden death was also balanced by a nonsignificant increase in hospitalizations for worsening of CHF. These results suggest early treatment with a β-blocker may reduce early sudden death in patients with CHF, although at the cost of increased heart failure hospitalizations and pump failure deaths.

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Disclosures

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Conflict of Interests

The authors have no conflict of interest.

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