Possible clinical implications of the Cardiac Insufficiency Bisoprolol (CIBIS) III trial

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Abstract

The mainstay of heart failure management is angiotensin-converting enzyme inhibitor therapy initially as a vasodilator, followed by beta blockade at a varying time interval, based on clinical judgement. Early beta blockade has theoretical advantages in terms of possible protection against dysrhythmia or disease progression, although there may be short-term concerns regarding a possible deterioration in cardiac function and aggravation of heart failure.

The Cardiac Insufficiency Bisoprolol (CIBIS) III trial examined the optimum paradigm of initiating treatment for chronic heart failure (CHF). A large cohort of 1,010 systolic CHF patients, at least 65 years of age, with stable, mild-to-moderate symptomatic disease, were followed-up for a mean of 1.25 years. Patients were randomly allocated to initial monotherapy with bisoprolol for six months, followed by the addition of enalapril, or the opposite sequence. Efficacy and safety of the bisoprolol-first strategy versus the enalapril-first strategy was similar in terms of the combined primary end point of mortality or all-cause hospitalisation (hazard ratio 0.94, 95% confidence interval 0.77–1.16, non-inferiority p=0.02). The two approaches also showed similar safety. The bisoprolol-first strategy showed a 28% mortality reduction after the monotherapy phase (p=0.24) and a 31% borderline-significant mortality reduction during the first year (p=0.06), but was associated with a 25% increase in worsening of CHF events (p=0.23). This paper highlights important features of the study design and patient population. Both the clinical perspective and possible clinical implications of CIBIS III are discussed.

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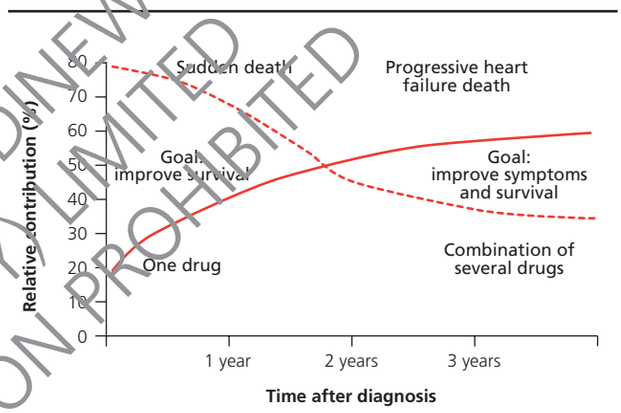
Figure 1. Early versus late stages of chronic heart failure (CHF). In the early phase of CHF, the majority of deaths are due to sudden cardiac death, especially related to activation of the sympathetic nervous system. The predominant cause of death in later stages of CHF is death from progressive CHF. Since not all drugs can be initiated at once, it is reasonable to choose an initial CHF therapy that is aimed at reducing sudden cardiac death, whereas therapy in later stages has several purposes and consists of multiple drugs



Key words: heart failure, beta blockers, bisoprolol, enalapril.

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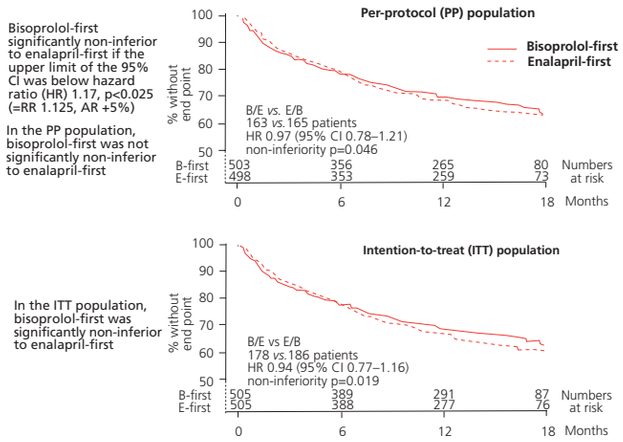
Introduction

The Cardiac Insufficiency Bisoprolol (CIBIS) III trial addressed a clinically important issue: whether we can initiate therapy for chronic heart failure (CHF) with a beta blocker rather than with an angiotensin-converting enzyme (ACE) inhibitor.[1] Thus, CIBIS III examined the importance of the initial strategy for treating patients with CHF with neurohormonal activation blockers. In the early phase of CHF, the majority of deaths are due to sudden cardiac death, particularly related to activation of the sympathetic nervous system, whereas the predominant cause of death in later stages of CHF is death from progressive CHF (figure 1).[2-4] It seems reasonable, therefore, that the choice of initial CHF therapy should be aimed at reducing sudden cardiac death. Since beta-blocking drugs are known to be effective in preventing sudden cardiac death, whereas ACE inhibitors are not well documented in this respect, it was reasonable to hypothesise that

Figure 2. Kaplan-Meier plot of patients without the combined primary end point (death or all-cause hospitalisation) in the per-protocol sample and in the intention-to-treat sample



Key: E = enalapril; B = bisoprolol; CI = confidence interval

Adapted from Willenheimer R *et al*.[1]

Figure 3. Kaplan-Meier plot of patients without all-cause hospitalisation throughout the study duration in the intention-to-treat sample

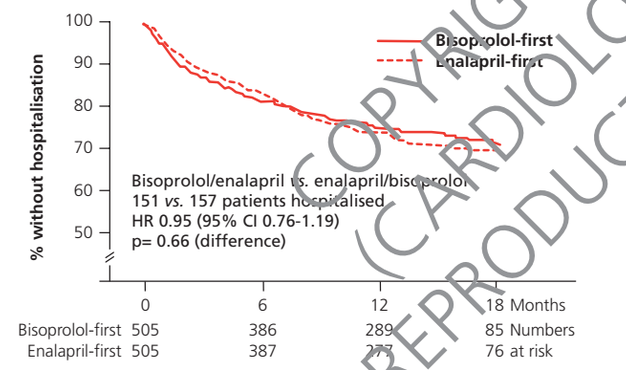
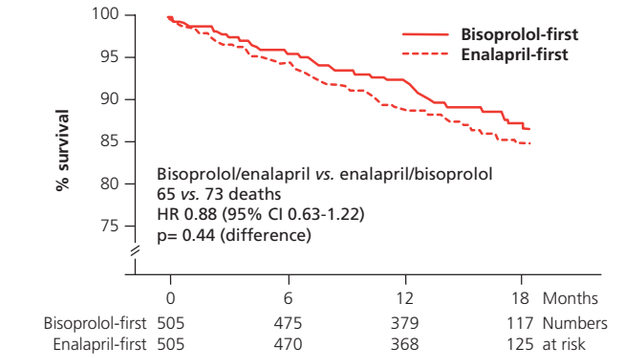
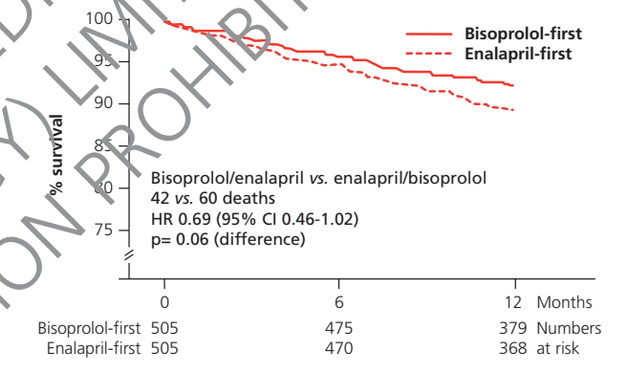


Figure 4. Kaplan-Meier plot of survival throughout the study duration in the intention-to-treat sample



Adapted from Willenheimer R *et al*.[1]

Figure 5. Kaplan-Meier plot of survival at one year in the intention-to-treat sample

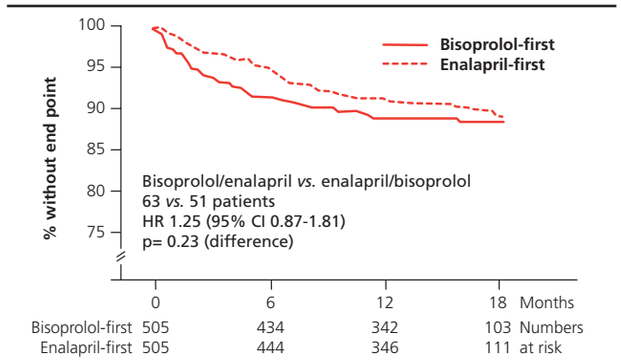


initial beta blockade, followed by the addition of an ACE inhibitor, would be as effective and safe as the alternative approach.[5-12] In CIBIS III, initial six-month monotherapy with bisoprolol (target dose of 10 mg once daily) to which enalapril was subsequently added (target dose 10 mg twice daily) was compared with the opposite sequence of treatment initiation in 1,010 patients at least 65 years of age, with stable, mild-to-moderate symptomatic, systolic CHF.[1,13]

Main results

The two strategies were similar in terms of the combined primary end point of mortality or all-cause hospitalisation, during a mean follow-up of 1.25 years.[1] By intention-to-treat analysis, 178 patients (35.2%) had a primary end point in the bisoprolol-first group compared to 186 (36.8%) in the enalapril-first group: hazard ratio (HR) 0.94; 95% confidence interval (CI) 0.77–1.16 (figure 2). Since non-inferiority was considered proven if the upper limit of the 95% CI was below 1.17, bisoprolol-first was non-inferior to enalapril-first by intention-to-treat analysis. By per-protocol analysis, the result was quite similar (figure 2) but due to less statistical power in this analysis, bisoprolol-first was only borderline-significantly non-inferior to enalapril-first. In the bisoprolol-first group, 151 patients were hospitalised, compared to 157 in the enalapril-first group (HR 0.95; 95% CI 0.76–1.19; between-group difference p=0.66) (figure 3). There were 65 deaths in the bisoprolol-first group compared to 73 in the enalapril-first group (HR 0.88; 95% CI 0.63–1.22; between-group difference p=0.44) (figure 4). During the monotherapy phase, the two strategies were similar with regard to the primary end point (HR 1.02, 95% CI 0.78–1.33, between-group difference p=0.90) and all-cause hospitalisation (HR 1.08, 95% CI 0.81–1.43, between-group difference p=0.59), while there was a statistically non-significant 28% lower mortality rate in

Figure 6. Kaplan-Meier plot of patients without worsening heart failure requiring hospitalisation or occurring while in hospital in the intention-to-treat sample



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favour of bisoprolol-first (HR 0.72, 95% CI 0.42–1.24, between-group difference p=0.24). The borderline, significant (p=0.06) 31% mortality reduction during the first year favoured the bisoprolol-first strategy (figure 5). The only detectable drawback of the bisoprolol-first strategy was a statistically non-significant 25% higher incidence of worsening of CHF events (HR 1.25 95% CI 0.87–1.81, p=0.23), either occurring while in hospital or causing hospitalisation (figure 6).

Patient population

To assess the clinical relevance of the results, the patient population of the trial needs to be fully considered. CIBIS III included 1,010 patients at least 65 years of age with a left ventricular ejection fraction (LVEF) of 35% or less and symptoms of CHF corresponding to New York Heart Association (NYHA) class II or III. For at least seven days before inclusion, patients had been clinically stable without relevant fluid retention or change in diuretic treatment. Patients were ACE inhibitor- and beta blocker-naive and did not have recent acute coronary syndrome or coronary intervention. Patients had no relative or absolute contraindications to any of the study drugs, e.g. low heart rate (< 60, unless pacemaker treated), low blood pressure (< 100 mmHg systolic), pronounced renal failure (serum-creatinine ≥ 220 µmol/L), second or third degree atrioventricular block without a pacemaker, or obstructive lung disease contraindicating bisoprolol. The two treatment groups were well balanced with regard to all important baseline characteristics (table 1).

Since mean age at study conclusion was around 74 years, this is one of the few morbidity/mortality trials in CHF relevant to patients of ages that are predominantly found in everyday clinical practice. Since all patients had an LVEF below 35%, the results might not be relevant to patients with 'preserved' LVEF. The findings are not necessarily applicable to patients who have severe symptoms (NYHA class IV) and/or clinically relevant fluid retention at the time of starting therapy aimed at blocking neurohormonal activation in CHF. However, 85% of the patients in CIBIS III were on diuretic treatment at baseline (table 1).

Table 1. Baseline data

	Bisoprolol-first (n=505) mean/n	%/SD	Enalapril-first (n=505) mean/n	%/SD
Age, years	72.4	5.8	72.5	5.7
Men	333	65.9	356	70.5
NYHA class II/III	245/260	48.5/51.5	250/255	49.5/50.5
Median duration of CHF, months	20		18	
Left ventricular ejection fraction, %	28.8	4.8	28.8	5.2
Serum creatinine, µmol/L	99.6	26.1	101.9	26.9
Heart rate, beats per minute	78.8	13.8	79.5	13.2
Systolic BP, mmHg	134.5	17.0	133.7	16.5
Aetiology*				
- 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 angina pectoris	259	51.3	255	50.5
History of peripheral vascular disease	37	7.3	56	11.1
History of cerebrovascular disease	52	10.3	49	9.7
History of diabetes	95	18.8	113	22.4
History of renal disease	93	18.4	89	17.6
History of anaemia	10	2.0	8	1.6
Prior PCI	22	4.4	18	3.6
Prior CABG	45	8.9	40	7.9
Pacemaker	38	7.5	33	6.5
Baseline diuretic treatment	430	85.1	421	83.4
- thiazide diuretics	97	19.2	115	22.8
- loop diuretics	361	71.5	338	66.9
- potassium-sparing diuretics	52	10.3	53	10.5
- aldosterone receptor blockers	72	14.3	62	12.3
Baseline antiplatelet medication	345	68.3	334	66.1
Baseline cardiac glycoside treatment	166	32.9	155	30.7
Baseline hypoglycaemic medication	72	14.3	86	17.0

Key: *More than one aetiology may be given for each patient; SD = standard deviation; NYHA = New York Heart Association; CHF = chronic heart failure; BP = blood pressure; PCI = percutaneous coronary intervention; CABG = coronary artery bypass grafting

Adapted from Willenheimer R *et al.*[1]

Current guideline recommendations on treatment initiation

Current European guidelines recommend starting CHF therapy with an ACE inhibitor, which should be up-titrated to target

dose before adding a beta blocker.[14] This recommendation is based on tradition rather than evidence. ACE inhibitors were the first to show an improved survival and reduced morbidity in CHF.[12] The effects on morbidity/mortality of beta blockers were not examined until later.[5-7] For ethical reasons, these trials were performed in CHF patients receiving background therapy including an ACE inhibitor. Subsequently, this order of initiation has been widely accepted as standard. Until CIBIS III, the optimum order in terms of mortality/hospitalisation had not been examined. It could be argued, however, that optimisation of ACE inhibitor therapy over a six to eight week period will reduce symptomatic and objective evidence of CHF. This improved substrate, at the time of initiation of beta-blocking therapy, might lessen the heamodynamic and cardiac function risks associated with the latter therapy.

Timing of initiation of the second drug

There are no data on the optimum time interval between reaching the target dose of an ACE inhibitor and starting a patient on a beta blocker, or the reverse, and guidelines do not specify any time intervals.[14,15] In CIBIS III, the monotherapy phase was six months. Thus, a patient started on bisoprolol received enalapril approximately 3.5 months after having reached the target dose of bisoprolol, which was up-titrated during 2.5 months. Patients who were started on enalapril received the first dose of bisoprolol around five months after reaching the target dose of enalapril, which was up-titrated during one month. However CIBIS III was not designed to assess the optimum time interval between starting the respective drugs and does not allow for any conclusions in this regard. When designing CIBIS III, on the one hand, we wanted a long period of monotherapy to increase the chance of finding any differences between the two strategies, should these exist. On the other hand, the monotherapy phase had to have an ethical justification, which resulted in the six-month monotherapy phase. Most physicians would probably aim to start their patients on the second drug earlier than in CIBIS III. Nevertheless, while there are no reports on the time intervals actually applied in clinical practice, many CHF patients never receive a beta-blocking drug and many patients remain on an ACE inhibitor for extended periods of time.[16-18] Furthermore, those who do receive combined therapy usually receive a beta-blocking dose that is suboptimal.[16-18] So, a definitive answer to the conundrum of the optimum time interval between starting these agents cannot be given.

The open-label study design

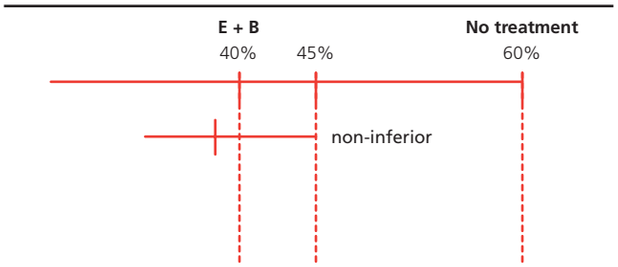
CIBIS III had a prospective, randomised, open-label, blinded end point evaluation (PROBE) design, which could be regarded as a handicap. End points, such as all-cause hospitalisation, might be subject to bias. Studies with a PROBE design are becoming increasingly accepted, however, and can sometimes be considered preferable.[19] Besides CIBIS III, the Cardiac Resynchronisation-Heart Failure study (CARE-HF)[20] and the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT)[21] are other good examples of recent important cardiovascular trials with a PROBE design. A double-blind design would have made it virtually impossible to adjust the doses of the two study drugs separately during the combined study phase, e.g. in response to side effects. Since this might have caused unnecessary discontinuation of both study drugs in response to side effects, it was considered unethical to utilise a blinded strategy. The central telephone randomisation procedure and the blinded end point evaluation by the independent end point committee limited any possible investigator bias.[13] It is not obvious whether any bias would have been in favour of the bisoprolol-first or enalapril-first strategy. It is possible that a fear among some investigators of worsening of CHF during the initial up-titration of bisoprolol might have caused unnecessary hospitalisations of the patients in the bisoprolol-first group. If, indeed, this occurred, it probably reflects clinical reality. The open-label design is especially relevant for beta blocker studies in CHF, where the titration schedule is dependent on individual response to treatment. Individual dose adaptations of beta blockers do not seem to lead to an inferior effect on survival and morbidity, as long as the beta blocker is up-titrated according to true patient tolerability.[22,23]

Non-inferiority

CIBIS III was designed to demonstrate the non-inferiority of bisoprolol-first versus enalapril-first with regard to the combined primary end point of time to first event of mortality or all-cause hospitalisation.[13] In simple terms, this means that the study has to prove statistically that the beta blocker-first approach is no worse than the ACE inhibitor-first strategy – however, it was not an objective and nor was it required to establish that the newer approach was superior. Reasons for this are primarily related to power calculations and sample size – a superiority trial would require a considerably larger patient population. The study then, by design, did not have the statistical power to assess mortality differences between the alternative treatment strategies. The non-inferiority limit was set to HR 1.17, meaning that the upper limit of the 95% CI of the bisoprolol-first versus enalapril-first strategy had to be below HR 1.17 in order to prove non-inferiority.[13] This upper limit corresponds to an absolute risk increase of 5%, and to a relative risk of 1.125, based on an expected combined event rate of 40% in the enalapril-first group.[13] A commonly applied criterion for non-inferiority, usually accepted by regulatory authorities, requires that at least 50% of the efficacy of the comparator be preserved, as indicated by the upper limit of the 95% CI.[24]

Based on data from CIBIS II and the Studies Of Left Ventricular Dysfunction (SOLVD),[5,25] it would be expected that in a patient population such as CIBIS III, who are neither treated with an ACE inhibitor nor a beta blocker, there would be an event rate of combined mortality/all-cause hospitalisation of around 60% during 1.25 years of follow-up (figure 7). Combined treatment with enalapril (first) and bisoprolol (as add-on therapy) decreases the event rate to around 40%, i.e. 20% absolute risk reduction. Allowing a 5% absolute risk increase from 40% to 45% secures the preservation of at least 75% of that benefit, i.e. 15% absolute risk reduction.

Figure 7. Rationale for the non-inferiority definition. In a patient population such as that of CIBIS III, who are neither treated with an ACE inhibitor nor a beta blocker, an event rate of combined mortality/all-cause hospitalisation of around 60% during 1.25 years of follow-up could be expected. Combined treatment with enalapril and bisoprolol decreases the event rate to around 40%, i.e. 20% absolute risk reduction. Allowing a 5% absolute risk increase from 40% to 45%, thus, secures the preservation of at least 75% of that benefit, i.e. 15% absolute risk reduction. Consequently, the non-inferiority limit applied in CIBIS III, easily met the demands of any regulatory authorities



Key: ACE = angiotensin-converting enzyme; E = enalapril; B = bisoprolol

Consequently, assuming the validity of using the data from CIBIS II and SOLVD as a benchmark for an expected event rate, the non-inferiority limit applied in CIBIS III would definitely meet the regulatory demands of competent drug authorities.[24]

Within the CIBIS III Steering Committee, there has been considerable internal debate about the most appropriate type of analysis for a non-inferiority study, between an intention-to-treat and a per-protocol analysis. These considerations were initially prompted by the outcome: the upper limit of the 95% CI for bisoprolol-first versus enalapril was 1.16 in the intention-to-treat sample and 1.21 in the per-protocol sample. Consequently, non-inferiority was formally proven by the intention-to-treat but not by the per-protocol analysis. By design, CIBIS III opted for the per-protocol analysis, since this is traditionally the preferred and most conservative approach for a non-inferiority trial design.[24] However, experience with large, long-term non-inferiority trials is limited and it is possible that the discussion surrounding the CIBIS III trial results may have contributed appreciably to knowledge in this field. Thus, while the per-protocol analysis is clearly the best approach in short-term studies, in trials with a relatively long follow-up, such as CIBIS III, the intention-to-treat analysis becomes increasingly relevant. With increasing duration of follow-up, the per-protocol sample becomes more difficult to define. Despite the best intentions to avoid introduction of any bias in this respect, e.g. by blinded definition of the per-protocol sample by the end point committee, it may be difficult to exclude. Therefore, the intention-to-treat analysis may be just as relevant as the non-inferiority approach.

Overall in CIBIS III, the results in the per-protocol and intention-to-treat samples were quite similar, although, as the number of patients in the per-protocol sample rapidly diminished with time (figure 2), due to various protocol violations and withdrawals, this analysis became increasingly underpowered over time. It is, therefore, reasonable to conclude that the bisoprolol-first strategy was non-inferior to the enalapril-first strategy in relation to the combined primary end point.

Effect on survival

The bisoprolol-first strategy tended to be more favourable in terms of survival: fewer patients died, deaths occurred later, and the HR for mortality was 28% lower at the end of the monotherapy phase and 31% lower at one year (post-hoc analysis), compared to the enalapril-first strategy (figure 5). These differences were not statistically significant, which could be due to a lack of statistical power, since the study was not by design powered to assess any mortality differences between the two strategies. Nevertheless, the mortality difference at one year is of similar magnitude to prior comparisons between adding a beta blocker versus placebo on top of a regimen including an ACE inhibitor,[5-7] and may be of clinical relevance.

Worsening of CHF

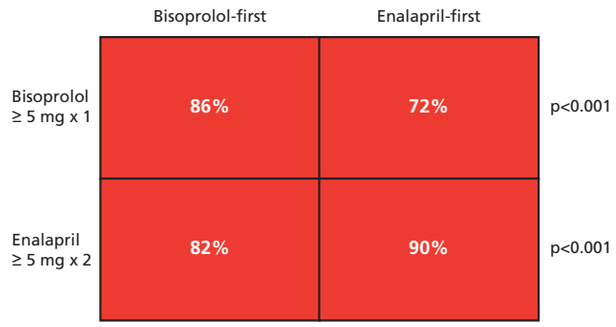
The issue of worsening of CHF is important (figure 6). In contrast to the effects on survival, the bisoprolol-first strategy was associated with a trend towards a higher frequency of this end point, especially during the early course of the study. A patient was judged to have this end point if a worsening of CHF occurred while in hospital or caused a new hospitalisation. We do not know if one or the other reason prevailed, which is of some importance. Although beta blockers have been shown to decrease CHF hospitalisations,[5-7] it is well recognised that their initiation and up-titration may cause minor and temporary deterioration of CHF.[14-15] This is likely to be due to an early and temporary negative inotropic effect, which might appear clinically differently in patients not receiving background ACE inhibition. In clinical practice, this is usually handled by temporarily increasing the diuretic dose, which in some hospitalised patients in CIBIS III might have been sufficient reason for reporting this as an end point. The generally limited prior experience of up-titrating a beta blocker in CHF patients not on an ACE inhibitor may also be of importance. With more experience, it is possible that worsening of CHF during initial up-titration of the beta blocker can be avoided more often.

The issue of competing risks is also important. Since more patients survived in the bisoprolol-first group, more patients were at risk of worsening of CHF. This circumstance alone could actually explain the difference between study groups in relation to worsening of CHF events.

Theoretical support for starting with bisoprolol

There are theoretical considerations which suggest that it may be more beneficial to initiate treatment for CHF with a beta blocker rather than with an ACE inhibitor. The sympathetic system is systemically activated at an earlier stage than the renin-angiotensin-aldosterone system (RAAS) in CHF.[26] Beta blockers effectively inhibit the activation of the sympathetic system and also of the

Figure 8. Last prescribed study drug dose in relation to initiation of therapy. In both study groups, a significantly greater percentage of the patients were last prescribed at least 50% of the target dose of the first initiated drug



RAAS, but ACE inhibitors have a less pronounced sympatho-inhibitory effect.[27,28] Sudden death is the most prevalent cause of death in the early course of CHF (figure 7) and in mildly symptomatic CHF.[2-4] While there is limited evidence that ACE inhibitors prevent sudden death in CHF patients, beta blockers are well documented in this respect.[5-12] An analysis of sudden deaths in CIBIS III is currently being undertaken but given the all-cause mortality findings, the findings of CIBIS III are well in line with these theoretical considerations.

A comparison between two initial treatment strategies

It may be argued that CIBIS III compared two different monotherapies for CHF, i.e. bisoprolol versus enalapril, rather than two treatment initiation strategies. It is reasonable to assume that the CHF therapy that is initiated first stands a better chance of being given at target dose. Indeed, surveys have shown that ACE inhibitors, which are usually started before beta blockers in patients with CHF, are given at substantially higher doses than beta blockers in clinical practice.[16,18] One reason for doing CIBIS III was to test if this would also hold true if therapy were started with a beta blocker. Indeed, irrespective of whether it was bisoprolol or enalapril, whichever drug was initiated first was significantly more often prescribed at 50% or more of the target dose, as compared with the second drug (figure 8). This finding may be important to future morbidity and survival and indicates that CIBIS III was, indeed, a comparison between treatment initiation strategies rather than monotherapies.

Clinical implications of CIBIS III

One of the most important lessons learned from CIBIS III is that beta blockers are at least as important as ACE inhibitors in patients with CHF and these agents should not be withheld from any patient with CHF and depressed LVEF, unless contraindicated.

So which patients should receive a beta blocker prior to an ACE inhibitor? The CIBIS III results do not really help to address this question. With one exception, subgroup analysis showed

Key messages

- CIBIS III examined the importance of the order of initiating heart failure therapy, with the beta blocker bisoprolol followed by the ACE inhibitor enalapril, or the reverse order
- The results are relevant to clinically stable heart failure patients with systolic heart failure and mild-to-moderate symptoms, whom are on a diuretic but not neurohormonal system blocking therapy
- The two initiation strategies were similarly efficacious with regard to combined mortality or all-cause hospitalisation
- Bisoprolol-first tended to have a better effect on survival
- Enalapril-first tended to result in fewer events of worsening of heart failure
- The findings of CIBIS III support either a bisoprolol-first or enalapril-first initiation of heart failure therapy, which has to be based on the clinician's judgement in the individual patient, rather than evidence
- The bisoprolol-first strategy may allow for more patients to survive the vulnerable initial phase of heart failure, thus enabling more patients to subsequently enjoy the benefits of combined heart failure therapy

nonogeneity across subgroups.[1] In patients with an LVEF below 28%, bisoprolol-first was significantly superior to enalapril-first. There was a trend in the opposite direction among patients with an LVEF between 28 and 35%. In the earlier CIBIS II study, high-risk subgroups of patients had a highly significant protection against premature death by addition of bisoprolol.[29] It could be argued that a low LVEF may define a subset of patients who are particularly at risk from premature, sudden death and, therefore, likely to benefit the most from beta blockade. However, these are precisely the patients in whom clinicians will tend to be cautious with these agents. In CIBIS III, the interaction in relation to LVEF seemed to be explained by an imbalance between treatment groups in non-cardiovascular hospitalisation during the monotherapy phase and may not be of clinical relevance.

The choice remains a decision for the clinician, based on individual judgement in each patient. It may seem particularly attractive to initiate therapy for CHF in clinically stable patients with recently diagnosed CHF, who have ischaemic heart disease and/or tachycardia. However, this decision is not based on evidence from clinical trials but rather on clinical experience. We need to be aware of the differences between the two treatment strategies with regard to survival and worsening of CHF, although these are not statistically significant. In our opinion, a bisoprolol-first strategy is an attractive alternative in any stable patient without clinically relevant fluid retention, with depressed LVEF and NYHA class II or III CHF.

In summary, the CIBIS III findings may change clinical practice for the initiation of therapy for CHF. The results support the initial use of bisoprolol in patients with systolic, mild-to-moderate symptomatic CHF without signs of relevant fluid retention. Clinicians now have an evidence-based choice of initial CHF therapy. Which patients should be started on bisoprolol cannot be based on evidence from morbidity/mortality trials but remains a decision for the clinician. Future investigations will hopefully clarify this issue further.

Conflict of interest

RW and BS served on the Steering Committee of CIBIS III and have received fees for lectures and reimbursement for expenses in connection with CIBIS III meetings from Merck (Germany).

References

1. Willenheimer R, van Veldhuisen DJ, Silke B *et al.* Effect on survival and hospitalization of initiating treatment for chronic heart failure with bisoprolol followed by enalapril, as compared with the opposite sequence. Results of the Randomized Cardiac Insufficiency Bisoprolol Study (CIBIS) III. *Circulation* 2005;**112**:2426-35.
2. Uretsky BF, Sheahan RG. Primary prevention of sudden cardiac death in heart failure: Will the solution be shocking? *J Am Coll Cardiol* 1997;**30**: 1589-97.
3. Huirkuri HV, Castellanos A, Myerburg RJ. Sudden death due to cardiac arrhythmias. *N Engl J Med* 2001;**345**:1473-82.
4. Lane RE, Cowie MR, Chow AW. Prediction and prevention of sudden cardiac death in heart failure. *Heart* 2005;**91**:674-80.
5. CIBIS II Investigators and Committees. The Cardiac Insufficiency Bisoprolol Study II (CIBIS II): a randomized trial. *Lancet* 1999;**353**:9-13.
6. MERIT-HF Study group. Effect of metoprolol CR/XL in chronic heart failure: metoprolol CR/XL randomized intervention trial in congestive heart failure (MERIT-HF). *Lancet* 1999;**353**:2001-07.
7. Packer M, Coats AJ, Fowler MB *et al.* Carvedilol Prospective Randomized Cumulative Survival Study Group. Effect of carvedilol on survival in severe chronic heart failure. *N Engl J Med* 2001;**344**:1651-8.
8. Krum H. ß-adrenoceptor blockers in chronic heart failure - a review. *Br J Clin Pharmacol* 1997;**44**:111-18.
9. Heidenreich PA, Lee TT, Massie BM. Effect of beta-blockade on mortality in patients with heart failure: a meta analysis of randomized clinical trials. *J Am Coll Cardiol* 1997;**30**:27-34.
10. Lechat P, Packer M, Chalon S, Cucherat M, Arab T, Boissel JP. Clinical effects of beta-adrenergic blockade in chronic heart failure. A meta-analysis of double blind, placebo controlled, randomized trials. *Circulation* 1998;**98**:1184-91.
11. Cleland JG, Massie BM, Packer M. Sudden death in heart failure: vascular or electrical? *Eur J Heart Fail* 1999;**1**:41-5.
12. Garg R, Yusuf S. Overview of randomized trials of angiotensin-converting enzyme inhibitors on mortality and morbidity in patients with heart failure. Collaborative Group on ACE inhibitor Trials. *JAMA* 1995;**273**:1450-6.
13. Willenheimer R, Erdmann E, Follath F *et al.* on behalf of the CIBIS-III investigators. Comparison of treatment initiation with bisoprolol versus enalapril in chronic heart failure patients: rationale and design of CIBIS-III. *Eur J Heart Fail* 2004;**6**:493-500.
14. Swedberg K, Cleland J, Dargie H *et al.* Task Force for the Diagnosis and Treatment of Chronic Heart Failure of the European Society of Cardiology. Guidelines for the diagnosis and treatment of chronic heart failure: executive summary (update 2005). *Eur Heart J* 2005;**26**:1115-40.
15. Hunt SA, Baker DW, Chin MH *et al.* American College of Cardiology (ACC)/American Heart Association (AHA) Task Force on Practice Guidelines (Committee to Revise the 1995 Guidelines for the Evaluation and Management of Heart Failure); International Society for Heart and Lung Transplantation; Heart Failure Society of America. ACC/AHA Guidelines for the Evaluation and Management of Chronic Heart Failure in the Adult: Executive Summary A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1995 Guidelines for the Evaluation and Management of Heart Failure): Developed in Collaboration With the International Society for Heart and Lung Transplantation; Endorsed by the Heart Failure Society of America. *Circulation* 2001;**104**:2996-3007.
16. Cleland JG, Cohen-Solal A, Aguilar JC *et al.* IMPROVEMENT of Heart Failure Programme Committees and Investigators. Improvement programme in evaluation and management; Study Group on Diagnosis of the Working Group on Heart Failure of The European Society of Cardiology Management of heart failure in primary care (the IMPROVEMENT of Heart Failure Programme): an international survey. *Lancet* 2002;**360**:1631-9.
17. Davies M, Hobbs F, Davis R *et al.* Prevalence of left-ventricular systolic dysfunction and heart failure in the Echocardiographic Heart of England Screening study: a population based study. *Lancet* 2001;**358**:439-44.
18. Komajda M, Lapuerta P, Hermans N *et al.* Adherence to guidelines is a predictor of outcome in chronic heart failure: the MAHLER survey. *Eur Heart J* 2005;**26**:1653-9.
19. Neutel J, Smith DH. Evaluation of angiotensin II receptor blockers for 24-hour blood pressure control: meta-analysis of a clinical database. *J Clin Hypertens* (Greenwich) 2003;**5**:58-63.
20. Cleland JG, Daubert JC, Erdmann E *et al.* Cardiac Resynchronization-Heart Failure (CARE-HF) Study Investigators. The effect of cardiac resynchronization on morbidity and mortality in heart failure. *N Engl J Med* 2005;**352**:1539-49.
21. Dahlof B, Sever PS, Poulter NR *et al.* ASCOT Investigators. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial – Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomised controlled trial. *Lancet* 2005;**366**:895-906.
22. Vikstrand J, Hjalmarson A, Waagstein F *et al.* MERIT-HF Study Group. Dose of metoprolol CR/XL and clinical outcomes in patients with heart failure: analysis of the experience in metoprolol CR/XL randomized intervention trial in chronic heart failure (MERIT-HF). *J Am Coll Cardiol* 2002;**40**:491-8.
23. Simon T, Mary-Krause M, Funck-Brentano C, Lechat P, Jaillon P. Bisoprolol dose-response relationship in patients with congestive heart failure: a subgroup analysis in the Cardiac Insufficiency Bisoprolol Study (CIBIS II). *Eur Heart J* 2003;**24**:552-9.
24. D'Agostino RB Sr, Massaro JM, Sullivan LM. Non-inferiority trials: design concepts and issues - the encounters of academic consultants in statistics. *Stat Med* 2003;**22**:169-86.
25. Anonymous. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. The SOLVD Investigators. *N Engl J Med* 1991;**325**:293-302.
26. Packer M. Pathophysiology of heart failure. *Lancet* 1992;**340**:88-95.
27. Campbell DJ, Aggarwal A, Esler M, Kaye D. Beta blockers, angiotensin II, and ACE inhibitors in patients with heart failure. *Lancet* 2001;**358**:1609-10.
28. Teisman AC, van Veldhuisen DJ, Boomsma F *et al.* Chronic beta blocker treatment in patients with advanced heart failure. Effects on neurohormones. *Int J Cardiol* 2000;**73**:7-14.
29. Erdmann E, Lechat P, Verkenne P, Wiemann H. Results from post-hoc analyses of the CIBIS II trial: effect of bisoprolol in high-risk patient groups with chronic heart failure. *Eur J Heart Fail* 2001;**3**:469-79.