HEART FAILURE

Use of Bisoprolol in Heart Failure. The BISOCOR Observational Study

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Introduction and objectives. The benefits of beta blockers in heart failure are highly dependent on dosage. This study aimed to analyze the degree of concordance between targeted (CIBIS II) and achieved doses of bisoprolol in a group of patients with stable heart failure on conventional treatment. We also evaluated functional parameters, adverse effects and the reasons for withdrawal or drop-out.

Patients and method. The study group consisted of 334 patients with stable systolic heart failure who were receiving conventional treatment. Treatment with bisoprolol was initiated according to current guidelines (starting dose 1.25 mg/day, with weekly increments to 5 mg/day, and then increments every four weeks to a targeted dosis of 10 mg/day). The main endpoint was the comparison between targeted dose and dose reached at each follow-up. Secondary endpoints were quality of life assessment (Minnesota Living with Heart Failure Questionnaire), functional status (New York Heart Association), ejection fraction change, and side effects during the 9-month follow-up period.

Results. Thirty-four (10%) patients did not finish the study: 1 because of sudden death, 2 because of surgery, and 31 because of side effects. 63% of the patients attained the maximum targeted dose; the mean dose at the end of follow-up was 8.5 mg. Functional status, quality of life and ejection fraction improved significantly between the beginning and the end of the study. Only 4 patients had severe adverse effects.

Conclusions. This is the first study in Spain to show that bisoprolol can be used effectively at the maximum recommended doses, for the outpatient treatment of heart failure.

Empleo de bisoprolol en la insuficiencia cardíaca. Resultados del estudio BISOCOR

Introducción y objetivos. La eficacia clínica y pronóstica de los bloqueadores beta en la insuficiencia cardíaca depende de la dosis. Este estudio prospectivo de observación pretendió comparar las dosis de bisoprolol alcanzadas en pacientes con insuficiencia cardíaca con las recomendadas (CIBIS II). También se evaluaron los parámetros funcionales, los efectos adversos y las causas de abandono del tratamiento.

Pacientes y método. Se incluyeron 334 pacientes con insuficiencia cardíaca sistólica estable con tratamiento habitual. Iniciaron tratamiento ambulatorio con bisoprolol con la dosificación progresiva recomendada (inicio con 1,25 mg/día, aumentos semanales en la misma cuantía hasta los 5 mg/día y, después, incrementos de 2,5 mg/día cada 4 semanas hasta 10 mg/día). El seguimiento máximo fue de 9 meses. La variable principal fue la comparación del promedio de la dosis tomada en cada visita con la esperada. La calidad de vida se analizó con el cuestionario Minnesotta.

Resultados. Hubo 34 retiradas (10%): un paciente por fallecimiento súbito, dos por cirugía y 31 por efectos adversos. Del grupo total de pacientes, el 64% alcanzaron la dosis máxima al final del estudio; la dosis media final fue de 8,5 mg/día. El grado funcional, las puntuaciones de calidad de vida y la fracción de eyección mejoraron significativamente entre el inicio y el final del estudio. Sólo hubo cuatro reacciones adversas graves.

Conclusiones. El estudio confirma la factibilidad de introducir el bisoprolol en el tratamiento ambulatorio de la insuficiencia cardíaca crónica en las dosis máximas recomendadas.

INTRODUCTION

Various beta-blockers (BB) have consistently been shown to improve the clinical status and course of patients with chronic heart failure caused by moderate to severe systolic dysfunction.[1-3] According to current international guidelines, these drugs should be prescribed, unless contraindicated, in all patients with heart failure who are also receiving angiotension-converting enzyme inhibitors and diuretics.[4-7]

Despite the overwhelming evidence, however, the present use of BB for this condition reported in clinical studies (above 60%)[8,9] differs markedly from the findings of observational studies (5% to 30%).[10-12] The reasons for this disparity are diverse. Firstly, clinical trials enroll carefully selected patients and are conducted by highly motivated investigators. Moreover, the trial protocol recommends the «best» treatment for heart failure, specifically mentioning BB. Secondly, the assumption that «real» patients are more likely to have contraindications or concomitant conditions advising against the use of BB is largely untrue, since it is estimated that up to 80% of the patients seen for symptomatic systolic dysfunction can tolerate BB.[13] Lastly, there are 2 subjective reasons. The most important is the disparity in expertise between professionals who treat these patients. The other is the presumed difficulty of this therapy, which requires close monitoring, may involve worsening of the patient's condition, and requires gradual increases in the dosage.

To investigate this last issue, the BISOCOR study, a prospective, observational, multicenter study, was designed to assess the use of a bisoprolol regimen with dose increments based on the recommendations of the Cardiac Insufficiency Bisoprolol Study II (CIBIS-II)[14] in a large group of patients with heart failure who were followed in outpatient cardiology clinics. Additional aims were to determine the effects of this drug on quality of life and on echocardiographic parameters of systolic function, and to determine the profile of adverse events.

PATIENTS AND METHODS

Study design

The BISOCOR study was a prospective, observational, multicenter, Phase IV study with a recruitment period of 4 months and a follow-up of 9 months for each patient. A total of 113 staff physicians at outpatient cardiology clinics in Spain agreed to participate after receiving detailed information on the study objectives and the data collection methods. The study was approved by the Agencia Española del Medicamento, the drug regulatory agency in Spain.

Inclusion and exclusion criteria

The study included consecutive patients with New York Heart Association (NYHA) Class II-IV chronic heart failure seen on an outpatient basis. All met the guidelines for bisoprolol therapy.[2,5] The inclusion criteria were as follows: age over 18 years, no decompensated heart failure in the last 6 weeks, ejection fraction below 0.35 on echocardiography in the 6 weeks before enrollment, and appropriate heart failure therapy with no changes in the 2 previous weeks; this included angiotensin-converting enzyme inhibitors (or another vasodilator in case of intolerance), diuretics and, optionally, digitalis drugs.

The exclusion criteria included acute heart failure, uncontrolled hypertension, acute coronary syndrome in the last 3 months, coronary artery bypass graft in the last 6 months, previous or scheduled heart transplantation, second- or third-degree atrioventricular blocks or sinus node dysfunction without a pacemaker, bradycardia (<60 bpm) or hypotension (systolic blood pressure <100 mm Hg) at study enrollment, severe pulmonary disease, major peripheral vascular disease, metabolic acidosis, untreated pheochromocytoma, severe liver or kidney impairment, hypersensitivity to ingredients, pregnancy or lactation, and BB therapy.

No criteria were specified for the withdrawal of BB therapy because of intolerance, and this decision was left at the discretion of the attending physician.

All patients gave informed consent, in accordance with the official ethical standards for therapeutic clinical trials.

Data collection

The data were collected on a standardized computer form (HP 720) and forwarded electronically to the general database (Byomedical Systems Group, Barcelona, Spain). The form included all baseline, demographic and clinical data, as well as all follow-up data related to the endpoints. Data collection ended on the 11th of June 2002, and the database was monitored and analyzed exclusively by the principal investigators and Byomedical Systems Group.

Treatment and follow-up

All study subjects were prescribed oral therapy with bisoprolol on an outpatient basis, to be added to their current medications. The dosing regimen was progressively increased according to recommendations based on the CIBIS-II study,[14] as summarized in Figure 1.

In addition to the dose adjustment visits (three optional visits the first month and another during the second month), all patients were seen after 1, 3, and 6 months. The final visit took place 9 months after the start of therapy.

Endpoint analysis

The main endpoint was compliance with the bisoprolol doses during the study, with the mean dose for the group compared to the target dose at each visit. The secondary endpoint was improved quality of life, defined as a decrease of at least 5 points in the Minnesota Living with Heart Failure Questionnaire after 6 and 9 months.[15] This questionnaire consists of 21 items related to the patients' impressions on how their heart failure affects their physical, psychological and socioeconomic well-being. All questions are scored from 0 (best) to 5 (worst), then totaled to give an overall score.

Secondary endpoints for efficacy included changes from baseline to final in shortening fraction and left ventricular ejection fraction, as measured by the echocardiograms performed by their physicians, and in blood pressure and heart rate. Baseline and final NYHA Class was also compared.

The safety endpoints were adverse effects, classified by severity, site and relationship with therapy, as well as withdrawal or dropout due to adverse effects.

Statistical study

The information entered in the original database was then validated and corrected by obtaining the frequency distribution for each variable and eliminating any outliers. The SPSS program for Windows, version 9.0, was used for the statistical analysis.

All quantitative variables are expressed as mean±SD (standard deviation), maximum and minimum values, and number of cases. Correlations between the variables were analyzed by the Student *t*-test for paired data. Categorical variables are expressed as absolute and relative frequencies, number of cases and missing values. The homogeneity tests and comparisons were based on the McNemar test. An alpha level of 5% was used in all cases.[16]

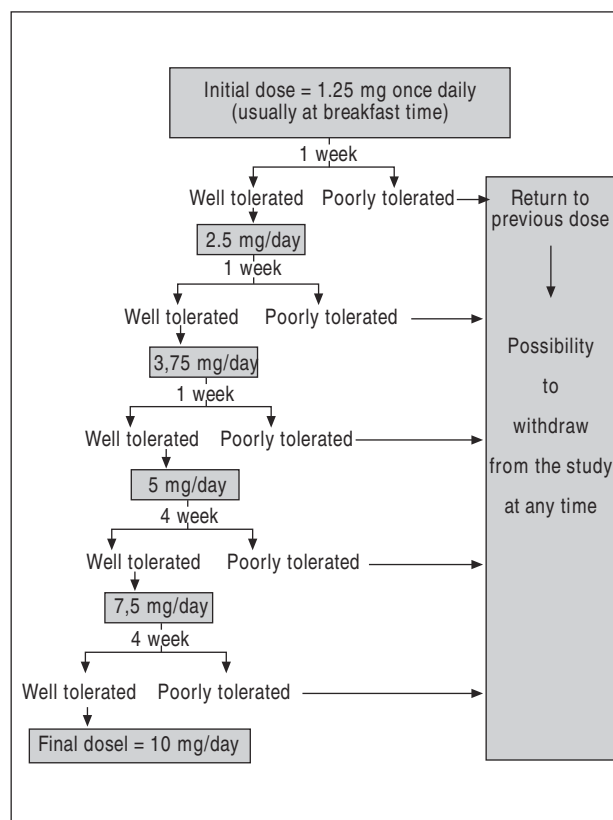For the main endpoint, the comparison of the mean

Fig. 1. Dosing algorithm for bisoprolol in patients with chronic heart failure

versus target dose is presented as a bivariate graph. If applicable, the reasons for maintaining the dose and the withdrawals are also shown.

The quality of life questionnaires were analyzed by adding the scores for the 21 items (range, 0 to 105 points) and computing the difference between the baseline and final scores, along with the 95% confidence interval (95% CI). All questionnaires that were incomplete or contained more than 1 answer in any item were excluded. The same assessment was also performed after separating the data on physical well-being (sum of items 2 to 7, 12 and 13) and psychological well-being (items 17 to 21).[15]

RESULTS

Baseline data

The study included 334 patients (69% men) between 29 and 89 years of age (64 ± 11 years). The main baseline data are shown in Table 1. The background medications were diuretics in 84% of patients, ACE inhibitors in 72%, digoxin in 39%, calcium antagonists in 8% and nitrates in 20%.

TABLE 1. **Baseline data of enrolled patients (n=334)**

History, n (%)	
Hypertension	170 (50.9)
Dyslipidemia	136 (40.7)
Type 2 diabetes	96 (28.7)
Previous infarction	95 (28.4)
Coronary artery bypass graft	28 (8.4)
Previous angioplasty	77 (23.1)
Stroke	21 (6.3)
Previous valvular surgery	20 (6.0)
Etiology of heart failure, n (%)	
Idiopathic dilated cardiomyopathy	121 (36.2)
Ischemia	109 (32.6)
Hypertension	62 (18.5)
Valve disease	20 (6.1)
Other	22 (6.6)
Initial NYHA functional class, n (%)	
II	188 (56.3)
III	128 (38.3)
IV	18 (5.4)
Ejection fraction, mean ± SD	0.29±0.5
Systolic blood pressure (mm Hg), mean ± SD	129.7±15.8
Diastolic blood pressure (mmHg), mean ± SD	76.9±10.5
Heart rate (bpm), mean ± SD	80.1±11.1
Heart rate, n (%)	
Sinus	249 (74.6)
Atrial fibrillation/flutter	66 (19.7)
Pacemaker	19 (5.7)

NYHA indicates New York Heart Association.

Bisoprolol dose

Thirty-four (10%) patients did not finish the study: 1 because of sudden death in the second month of treatment, 31 because of adverse effects attributable to the therapy and 2 because of surgery (1 heart transplantation and 1 valvular surgery).

Table 2 contains the raw data for the main endpoint (actual versus target dose of bisoprolol for each follow-up visit). Figure 2 shows the evolution of the mean doses of bisoprolol targeted for each visit. The final dose achieved on average by the group was 8.5 mg a day, with 64% of patients reaching the target dose of 10 mg a day by the end of the study.
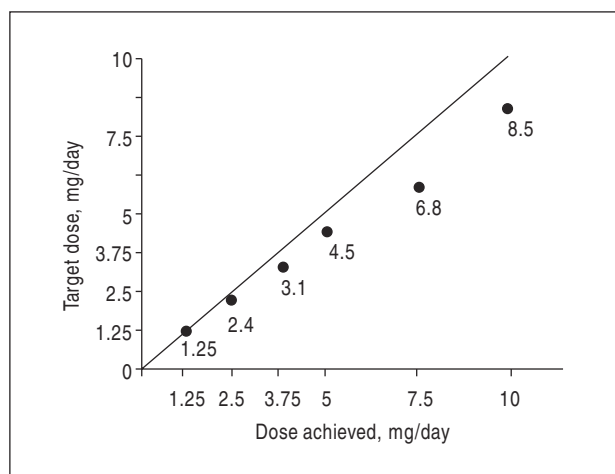

Fig. 2. Actual versus target dose of bisoprolol at each follow-up visit

Clinical response

Figure 3 shows baseline versus final functional class: Class I was attained by 70 patients (20.9%), Class II by 22 (66.5%), Class III by 31 (9.3%) and Class IV by 10 (3.3%). The 31 patients who withdrew because of adverse effects were included in the analysis, being assigned to the same group in which they started the study. The 2 operated patients were assigned to Class IV. The differences between the first and last visits were significant ($P<.001$). Additionally, there were significant decreases in systolic blood pressure (129.7 vs 120.7 mm Hg; $P<.01$), diastolic blood pressure (76.9 vs 71.3 mm Hg; $P<.05$) and heart rate (80 vs 66.1 bpm; $P<.001$), but no change in average weight (75.1 kg in both visits).

Table 3 contains the results of the quality of life assessments (Minnesota questionnaires) at each visit, with the total possible score between 0 (best score possible) and 105 (worst score possible). The subjective improvement between the initial (48.2±18.8) and final results (32.4±20.1) was significant ($P<.0001$). The scores for physical and psychological well-being also gradually improved over the study.

TABLE 2. **Number of patients with each dose at each follow-up visit**

Follow-up (target dose in mg/day)	Actual dose (mg/day)						Withdrawals
	1.25	2.5	3.75	5	7.5	10	
1 week (1.25)	318	—	—	—	—	—	16
2 weeks (2.5)	51	236	28	—	—	—	3
3 weeks (3.75)	38	77	195	—	—	—	5
4 weeks (5)	10	9	79	206	—	—	6
8 weeks (7.5)	10	8	3	133	45	103	2
12 weeks (10)	10	8	3	57	21	202	1
Final at 9 months	10	8	3	48	18	213	1
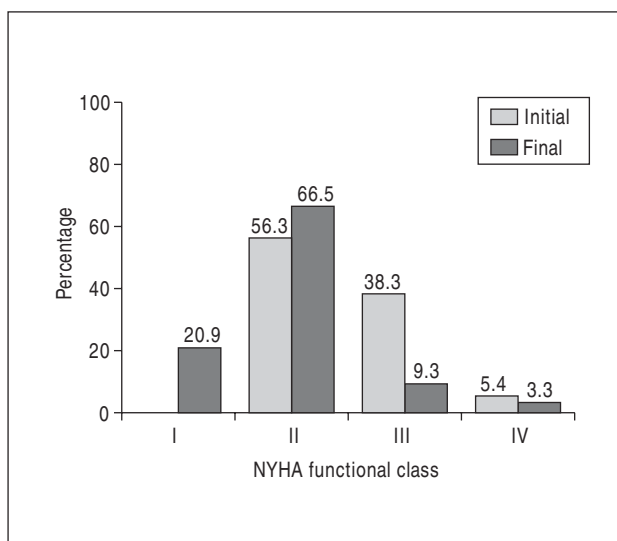
Fig. 3. Initial and final New York Heart Association (NYHA) functional class, expressed as percentage of total (final class for the 2 patients who underwent surgery: Class IV; final class for 32 withdrawals because of adverse effects: same as baseline).

Echocardiographic parameters

Mean left ventricle ejection fraction was 0.29 (0.05) at the start of treatment and 0.35 (0.08) at the end (*P*<.0001). End-systolic and end-diastolic diameters, as well as shortening fraction, also showed significant differences.

Adverse effects

Among the 334 patients studied, there was 1 death, 2 patients who underwent surgery and 31 who withdrew from the study because of adverse effects: 18 before the first month, 9 between the first and third month and 4 between the third and sixth month. The causes for these withdrawals were hospitalization in 4 patients (2 for acute pulmonary edema, 1 for unstable angina and 1 for severe hypotension), worsening of dyspnea in 10 patients, asthenia in 9, electrocardiographic abnormalities (atrioventricular blocks, slow atrial fibrillation or marked sinus bradycardia) in 5 patients, erectile dysfunction in 3 cases, intermittent claudication in 2 and depression in 2.

A total of 75 adverse reactions were recorded; among these 4 were considered serious and 24 moderate. These reactions developed in 50 patients and, apart from those leading to withdrawal, were limited to asthenia, dizziness and increased dyspnea.

TABLE 3. **Results of quality-of-life assessments**

	Initial visit (n=334)	6-month visit (n=239)	Final visit (9 months) (n=330)
Total score	48,2±3	5,2±21	32,4±20,1*
Physical well-being	21,3±8,0	14,5±7,9	13,6±7,6*
Psychological well-being	11,9±6,1	8,8±5,8	8,0±5,8*

Lower scores indicate better qualify of life in each dimension assessed.
Values expressed as mean ±DE.
*P<.0001 with respect to initial visit.

DISCUSSION

Importance of BB therapy

There is a close prognostic correlation between neurohumoral activation and mortality in patients with chronic heart failure, and only the drug groups interfering with neurohumoral activation have been shown to improve survival in this type of patient.[17] The BB are included in these drug groups. Three types of BB have been studied in heart failure to date: *a)* selective blockers of beta-1 receptors (metoprolol and bisoprolol); *b)* blockers of both types of beta receptors (propranolol and bucindolol), and *c)* blockers of both beta and alpha-1-adrenergic receptors (carvedilol). Various clinical trials have demonstrated the favorable impact of BB on morbidity and mortality in this type of patient.[1] In the case of bisoprolol, the CIBIS II study[14] found a 34% decrease in all-cause mortality (*P*<.0001), a 44% decrease in sudden deaths (*P*<.0001) and a 20% reduction in all-cause hospitalization (*P*=.0006) for heart failure patients.

Importance of dose

The beneficial effects of BB in heart failure depend on their proper use. This includes low initial doses (one-fourth or one-fifth of the final target dose) and increments every 1-2 weeks. The apparent complexity of this process is one of the main reasons why few patients with heart failure are adequately treated with BB.

The most relevant result of the BISOCOR study is that 64% of a cohort of unselected heart-failure patients treated with bisoprolol achieved the maximum recommended dose (10 mg/day). This figure compares favorably with the 43% obtained in the reference study, CIBIS II,[14] and the data obtained with other BB, such as metoprolol which reached 64%.[18] The mean dose achieved (8.5 mg/day) is similar to the dose in the CIBIS-II study and other studies (Table 4), all performed in groups of similar patients with strict, ongoing follow-up.[14,18-21] In the BISOCOR study, however, the decision to withdraw BB was made by

TABLE 4. **Mean doses achieved in various studies on beta blockers in heart failure**

Study (year) literature reference	Drug	Follow-up (months)	Target dose (mg/day)	Mean dose achieved	Percentage of maximum achieved
MDC (1993)[18]	Metoprolol	14	150	108	72
CIBIS I (1994)[19]	Bisoprolol	23	5	3.8	76
US (1996)[20]	Carvedilol	6.5	50-100	45	-
CIBIS II (1999)[14]	Bisoprolol	15.6	10	8.5	85
MERIT-HF (1999)[17]	Metoprolol	12	200	159	79
BISOCOR (2002)	Bisoprolol	9	10	8.5	85

the physician or the patient, and there were no predefined criteria for withdrawal.

Achieving this figure appears to have therapeutic advantages. The CIBIS II study showed that the favourable effect of bisoprolol in terms of prognosis increases with higher doses.[2] Similar findings were obtained in U.S. studies conducted with carvedilol: the absolute decrease in mortality was 14.4% with 25 mg/12 h and 9.5% with 6.25 mg/12 h.[21]

Functional improvement

The BISOCOR study did not analyze prognostic parameters. However, significant improvement was observed in all the functional parameters analyzed: ejection fraction and other echocardiographic systolic function parameters, NYHA functional class, and the various quality of life components of the Minnesota Living with Heart Failure Questionnaire.

All these beneficial effects have been reported in various placebo-controlled studies.[13,14,18-21] In the meta-analysis of these studies, the average improvement for left ventricular ejection fraction was 0.07,[2] whereas improvement was 0.02 in the respective placebo groups, giving a net improvement of 0.05. In the BISOCOR study, the ejection fraction increased by 0.06 after 9 months of bisoprolol therapy.

Safety and tolerance

The number and type of adverse effects observed in this study is consistent with data from previous studies and confirms the safety of BB therapy, specifically bisoprolol in this case, in patients with stable heart failure. The most frequent adverse effect was fatigue, potentially associated with either the therapy or the heart condition itself, but typically improving over time in the case of the former.

The available studies and guidelines all indicate that the adverse effects of BB on heart failure can be minimized if the patients are properly selected, the doses are increased carefully and gradually, and any effects are managed adequately. Strict adherence to these guidelines was probably the reason why there

were so few withdrawals and adverse effects in the BISOCOR study.

Limitations of the study

BISOCOR was a prospective, observational study that could not be randomized because of the main endpoint. As a result, the conclusions on the secondary endpoints (quality of life and adverse effects) cannot be considered definitive. Nevertheless, the results of the BISOCOR study closely mirror those of the major placebo-controlled studies on BB in heart failure, and therefore, the open assessment of the secondary endpoints probably contains no relevant bias. In a study of this type, some bias in patient selection (those showing better compliance or functional class) by the participating physicians cannot be excluded.

Echocardiographic analysis was not centralized, since it was a secondary endpoint. Differences between the baseline and final studies were computed on the basis of the results obtained at each center.

Finally, the participating physicians were highly motivated to achieve the target dose although this merely stresses the importance of motivation and dedication in achieving the proper dose and beneficial effects of bisoprolol in the majority of patients.

CONCLUSIONS

Bisoprolol can be used for therapy in a high percentage of outpatients with stable chronic heart failure, with acceptable tolerability at the maximum recommended dose. Thus, the proven benefits of BB therapy can probably be extended to many patients for whom this treatment is potentially useful.

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