Heart Rate and Cardiac Rhythm Relationships With Bisoprolol Benefit in Chronic Heart Failure in CIBIS II Trial

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Background—β-Blockade–induced benefit in heart failure (HF) could be related to baseline heart rate and treatment-induced heart rate reduction, but no such relationships have been demonstrated.

Methods and Results—In CIBIS II, we studied the relationships between baseline heart rate (BHR), heart rate changes at 2 months (HRC), nature of cardiac rhythm (sinus rhythm or atrial fibrillation), and outcomes (mortality and hospitalization for HF). Multivariate analysis of CIBIS II showed that in addition to β-blocker treatment, BHR and HRC were both significantly related to survival and hospitalization for worsening HF, the lowest BHR and the greatest HRC being associated with best survival and reduction of hospital admissions. No interaction between the 3 variables was observed, meaning that on one hand, HRC-related improvement in survival was similar at all levels of BHR, and on the other hand, bisoprolol-induced benefit over placebo for survival was observed to a similar extent at any level of both BHR and HRC. Bisoprolol reduced mortality in patients with sinus rhythm (relative risk 0.58, $P<0.001$) but not in patients with atrial fibrillation (relative risk 1.16, P=NS). A similar result was observed for cardiovascular mortality and hospitalization for HF worsening.

Conclusions—BHR and HRC are significantly related to prognosis in heart failure. β-Blockade with bisoprolol further improves survival at any level of BHR and HRC and to a similar extent. The benefit of bisoprolol is questionable, however, in patients with atrial fibrillation. **(*Circulation*. 2001;103:1428-1433.)**

Key Words: heart failure ■ bisoprolol ■ receptors, adrenergic, beta ■ fibrillation ■ heart rate

The benefit of treatment with β-blockers in heart failure is now well established, in view of the concordant results of several clinical trials with different compounds.[1–4] The amplitude of benefit may vary, however, according to the baseline characteristics of patients and the pharmacological properties of β-blockers, as suggested by the results of the BEST trial with bucindolol.[5] Possible relationships between heart rate change, left ventricular function improvement, and prognosis were suggested by the first CIBIS trial.[6,7] Experimental data have shown that the β-blocker–induced benefit for left ventricular function in heart failure could depend on only heart rate reduction.[8]

To further study the mechanism of β-blockade benefit in heart failure and to identify the best responders to such therapy, we studied the relationships between baseline parameters (including the level and nature of cardiac rhythm: sinus rhythm or atrial fibrillation), bisoprolol-induced hemodynamic changes with time (especially heart rate changes), and outcomes (survival and hospitalization for heart failure) in CIBIS II.[3]

Methods

Population and Studied Parameters

Demography and the main results of the CIBIS II trial have been published.[3] Patients could be divided at inclusion into 3 groups according to the nature of their cardiac rhythm: sinus rhythm, atrial fibrillation, and a third, small group including patients not in sinus rhythm but with supraventricular arrhythmias other than atrial fibrillation or with pacemakers. The third, much smaller group of other cardiac rhythms, 108 patients in CIBIS II (4%), was excluded from this analysis. These patients behaved similarly to patients in sinus rhythm.

Heart rate was measured at baseline and during follow-up visits by pulse rate measurement (especially in atrial fibrillation) or on ECG recording at rest in the supine position. Each recorded value of heart rate and blood pressure was the mean of 3 measurements at each visit. Blood pressure was measured by use of a sphygmomanometer.

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TABLE 1. Baseline Characteristics of Patients From CIBIS II Study

	Placebo (n=1268)		Bisoprolol (n=1271)	
	Sinus Rhythm (n=1004)	Atrial Fibrillation (n=264)	Sinus Rhythm (n=1014)	Atrial Fibrillation (n=257)
Age, y†	61 (22–80)	62 (30–79)	60 (26–80)	63 (27–79)
Male sex	803 (80%)	216 (82%)	809 (80%)	216 (84%)
NYHA class III	844 (84%)	211 (80%)	854 (84%)	206 (80%)
NYHA class IV	160 (16%)	53 (20%)	160 (16%)	51 (20%)
Documented ischemic heart disease†	559 (55%)	67 (25%)	571 (56%)	67 (26%)
Idiopathic dilated cardiomyopathy	118 (11.7%)	33 (12.5%)	113 (11.1%)	34 (13.2%)
Valvular disease†	12 (1.2%)	14 (5.3%)	13 (1.3%)	15 (5.8%)
Hypertension	151 (15%)	42 (15.9%)	165 (16.3%)	45 (17.5%)
LV ejection fraction	27.5% (6)	27.3% (6)	27.5% (6)	27.3% (6)
LV end-diastolic diameter, cm*	6.8 (0.9)	6.6 (0.9)	6.7 (1)	6.6 (0.9)
LV end-systolic diameter, cm	5.7 (0.9)	5.7 (0.85)	5.7 (1)	5.7 (0.9)
LV fractional shortening*	15.8% (5.8)	15% (5.1)	15.7% (5.8)	14.7% (5.3)
Systolic blood pressure, mm Hg*	129.9 (19.5)	132.2 (19.6)	128.8 (18.6)	130.8 (20.7)
Diastolic blood pressure, mm Hg*	79.8 (10.8)	81.5 (11.5)	79.2 (11)	80.4 (12.3)
Heart rate, bpm‡	78.8 (13.4)	89.7 (19.2)	78.8 (13.4)	85.3 (17.8)
Comedication				
Diuretic*	998 (99.4%)	262 (99.3%)	1001 (98.7%)	248 (96.5%)
ACE inhibitor	974 (97%)	253 (95.9%)	977 (96.3%)	246 (95.7%)
Digoxin†	419 (41.7%)	227 (86%)	452 (44.5%)	213 (82.8%)
Amiodarone†	144 (14.3%)	50 (18.9%)	122 (12%)	47 (18.3%)
Anticoagulants†	262 (26.1%)	128 (48.5%)	246 (24.3%)	128 (49.8%)
Antiplatelet agents†	468 (46.6%)	68 (25.7%)	458 (45.2%)	62 (24.1%)
Calcium antagonist	15 (1.5%)	6 (2.2%)	21 (2%)	2 (0.8%)

LV indicates left ventricular. Continuous variables are expressed as mean (SD).
Categorical variables are expressed as absolute numbers (%).
*$P<0.05$, †$P<0.001$, ‡$P<0.0001$, comparison between sinus rhythm and atrial fibrillation groups.

Heart rate and blood pressure changes were those recorded between baseline and 2 months after inclusion. A similar delay was used previously in the CIBIS I study.[7] In CIBIS II, the bisoprolol dose was started at 1.25 mg and increased by 1-week steps to 2.5, 3.5, and 5 mg and by 1-month steps to 7.5 and 10 mg.

Multivariate Analyses

Relationships between baseline parameters, heart rate change, blood pressure change, and outcomes (all-cause mortality, cardiovascular mortality, and hospitalization for heart failure worsening) were studied. Such multivariate analysis, using heart rate and blood pressure changes recorded at 2 months among covariates, therefore excluded patients who died within the first 2 months after inclusion.

Study of Hemodynamic Changes Over Time

Heart rate and blood pressure were recorded during each follow-up visit. In both study treatment groups, we compared heart rate and blood pressure changes between baseline and 2 months after inclusion in patients in sinus rhythm and in atrial fibrillation.

Statistical Analysis

Comparisons of baseline variables between groups were performed with Student's t tests for continuous variables and χ^2 tests for categorical variables. The level of significance was set at a value of $P<0.05$.

Kaplan-Meier survival curves were calculated for the placebo and bisoprolol groups in patients with sinus rhythm and atrial fibrillation.

Univariate and multivariate analyses were computed with Cox's proportional-hazards regression model. The variables that were included in the multivariate analysis were those related to survival in the univariate analysis at value of $P<0.10$.

As a complementary analysis, survival curves in the different subgroups defined by the tertiles of baseline heart rate and heart rate change at 2 months were compared between placebo and bisoprolol by use of the log-rank test. One-year survivals were those provided by Kaplan-Meier estimates.

Heart rate and blood pressure changes between baseline and 2 months after inclusion were compared between placebo and bisoprolol groups by Student's t test in patients surviving at 2 months.

All statistical analyses were performed with SAS software.

Results

Demography

The demography of patients according to cardiac rhythm and study treatment group at baseline is presented in Table 1. Few significant differences were found between cardiac rhythm groups (see Table 1). Patients with atrial fibrillation were more often treated with digitalis, amiodarone, and anticoagulants. Among each cardiac rhythm group, no differences were recorded between placebo and bisoprolol groups except for baseline heart rate, which was significantly lower in atrial

TABLE 2. Multivariate Analysis of Predictive Factors of Mortality and Hospitalization for Heart Failure Worsening on CIBIS II Data

	Mortality		Rehospitalization	
Variable	*P*	Risk Ratio	*P*	Risk Ratio
NYHA class (IV vs III)	0.0001	1.725	0.0001	2.408
Age	0.0001	1.031	0.0001	1.024
Baseline systolic blood pressure	0.0001	0.98	0.0001	0.978
Study treatment: bisoprolol vs placebo				
SR patients	0.0003	0.577	0.0005	0.599
AF patients	0.5524	1.161	0.742	0.931
Baseline heart rate	0.0012	1.015	0.0001	1.018
Heart rate reduction (baseline to 2 months)	0.0049	0.988	0.0001	0.982
Sex (men vs women)	0.0117	0.635	0.1258	0.781
LV end-systolic diameter	0.0195	1.167	0.001	1.229
Systolic blood pressure reduction (baseline to 2 months)	0.0394	1.01	0.0001	1.023
Amiodarone	0.0622	1.365	0.0006	1.692
Digoxin	0.094	1.247	0.0001	1.634
Diastolic blood pressure reduction (baseline to 2 months)	0.1075	1.011	0.01611	0.984

SR indicates sinus rhythm; AF, atrial fibrillation; and LV, left ventricular. Risk ratios indicate % change of risk per unit of change of the covariate: For example, risk ratio for mortality of 1.015 for baseline heart rate means an increase of mortality of 1.5% when baseline heart rate increases by 1 bpm. A risk ratio of 0.98 for heart rate reduction means reduction of mortality of 2% when heart rate decreases with time (2 months) by 1 bpm. A risk ratio of 1.725 for NYHA (IV vs III) means a 72.5% increase of risk in NYHA class IV compared to NYHA class III.

fibrillation in patients randomized to bisoprolol than in those randomized to placebo (Table 1).

Mean doses of bisoprolol were similar in patients with sinus rhythm and atrial fibrillation at the different times during the study (2, 6, 12, and 24 months).

Hemodynamic Changes

Two months after inclusion, heart rate decrease (baseline to 2 months) was 0.2±13.7 bpm (placebo) and 9.8±14.7 bpm (bisoprolol), $P<0.0001$; systolic blood pressure reduction was 2.3±16.4 mm Hg (placebo) and 4.1±16.4 mm Hg (bisoprolol), $P=0.001$; and diastolic blood pressure decrease was 0.9±10.9 mm Hg (placebo) and 2.6±10.7 mm Hg (bisoprolol), $P<0.0001$.

Multivariate Analysis

Because patients who died during the first 2 months after inclusion and patients without sinus rhythm or atrial fibrillation were excluded from this multivariate analysis, only 2184 patients were included for this analysis, with 282 deaths during follow-up.

Parameters significantly related to survival in the Cox multivariate analysis are presented in Table 2. The baseline heart rate and heart rate change after the first 2 months of treatment were both significantly related to further survival in both univariate and multivariate analyses. The best prognosis was obtained with the lowest baseline heart rate and with the greatest heart rate reduction. No interaction was found between study treatment and either baseline heart rate or heart rate change, meaning that the benefit of bisoprolol on survival was not influenced by the level of baseline heart rate or by the extent of heart rate reduction. In addition, no interaction was found between heart rate change–related survival improvement and baseline heart rate. The nature of cardiac rhythm at baseline was not related to survival. Survival curves of placebo groups comparing patients in sinus rhythm with those in atrial fibrillation were completely superimposed. Interaction between treatment and rhythm, however, was significant ($P<0.01$): a benefit of bisoprolol was obtained only in patients with sinus rhythm and was questionable in patients with atrial fibrillation (Figures 1 and 2). Results are given in

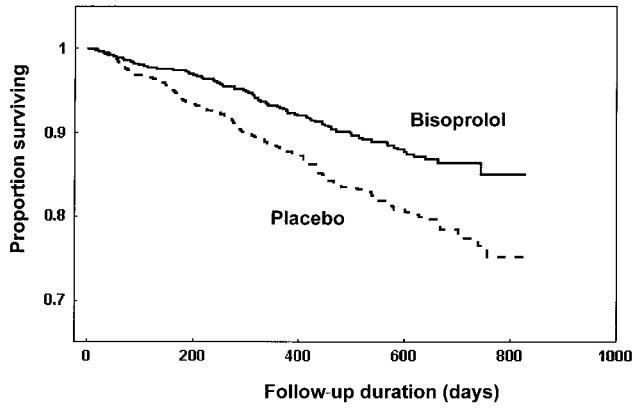

Figure 1. CIBIS II survival curves in patients with sinus rhythm at baseline.

TABLE 3. One-Year Survival and Hospital Admission Rate for Heart Failure Worsening in CIBIS II Trial According to Nature of Cardiac Rhythm

	Placebo		Bisoprolol	
CIBIS II	Sinus Rhythm	Atrial Fibrillation	Sinus Rhythm	Atrial Fibrillation
One-year survival (all-cause deaths)	0.88 (0.01)	0.90 (0.02)	0.94 (0.008)	0.91 (0.02)
One-year survival (cardiovascular deaths)	0.89 (0.01)	0.90 (0.02)	0.94 (0.008)	0.91 (0.02)
One-year hospitalization rate	0.15 (0.01)	0.16 (0.02)	0.07 (0.009)	0.15 (0.02)

Results are expressed as Kaplan-Meier (SD) estimates.

Table 2. For a patient with sinus rhythm, the treatment was beneficial (relative risk 0.58, $P=0.0003$), but conversely, for a patient with atrial fibrillation, bisoprolol did not significantly influence survival compared with placebo (relative risk 1.16).

Similar results were obtained for cardiovascular deaths and hospitalizations for heart failure worsening (Tables 2 and 3), with a similar significant interaction between treatment effect and nature of cardiac rhythm.

The multivariate analysis also showed that the probability of death or hospitalization for heart failure worsening decreased with increasing values of baseline systolic blood pressure but increased when systolic blood pressure decreased at 2 months. A diastolic blood pressure decrease at 2 months, however, was associated with fewer hospitalizations. Digoxin treatment was neutral on mortality but was associated with 39% more hospitalizations ($P<0.001$); amiodarone treatment appeared to be associated with a poorer prognosis ($P=0.06$) and more frequent hospitalizations ($P<0.001$). Patients on digoxin at baseline presented with a more altered left ventricular function, with a higher heart rate, and more often in atrial fibrillation than patients without digoxin treatment. Patients receiving amiodarone had a slightly more severe alteration of left ventricular function than patients without amiodarone treatment. Both digoxin and amiodarone treatments were equally distributed among placebo and bisoprolol groups (Table 1).

Finally, women were at significantly lower risk of death than men.

Distribution of Heart Rate Change, Baseline Heart Rate, and 1-Year Mortality Estimates (Kaplan-Meier)

Patients were split into 3 tertiles of distribution of baseline heart rate and heart rate change at 2 months, obtained in the entire population of patients (both treatment groups). The limits of the tertiles were ≤ 72, between 72 and ≤ 84, and >84 bpm for baseline heart rate and <0 (heart rate increase), ≥ 0 and <11 (moderate heart rate reduction), and ≥ 11 (great heart rate reduction) bpm for heart rate change at 2 months. The distribution of patients according to heart rate change at 2 months according to study treatment is given in Figure 3. As expected, the highest amplitude of heart rate decrease was more often recorded in the bisoprolol group, with no difference in dose between the 3 tertiles. Such results, however, can be obtained even in patients with a low baseline heart rate. The highest heart rate reduction with lowest baseline heart rate occurred in 8.5% of patients in the bisoprolol group and in 1.3% in the placebo group.

Bisoprolol-induced mortality reduction was similar at all levels of heart rate reduction (Figure 4). These results demonstrate that for a given heart rate reduction, bisoprolol treatment further reduced mortality to a similar extent whatever the amplitude of heart rate reduction. Probability values of log-rank tests comparing survival in the 3 tertiles of heart rate change were $P<0.04$ (heart rate reduction ≥ 11 bpm), $P<0.02$ (heart rate reduction between 0 and 11 bpm), and $P<0.04$ for heart rate increase (heart rate change <0 bpm).

Bisoprolol-induced survival improvement was significant and similar whatever the levels of baseline heart rates,

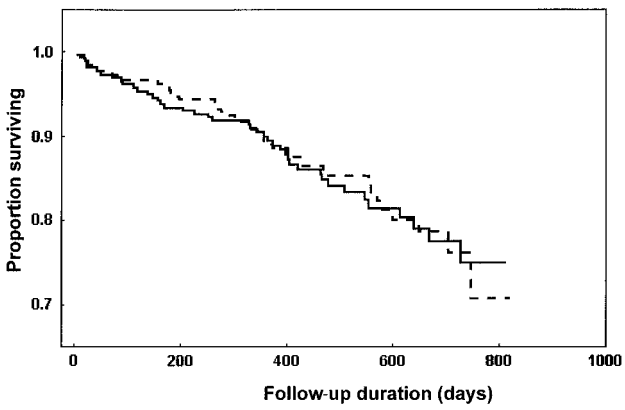

Figure 2. CIBIS II survival curves in patients with atrial fibrillation at baseline. Dashed line indicates placebo; solid line, bisoprolol.

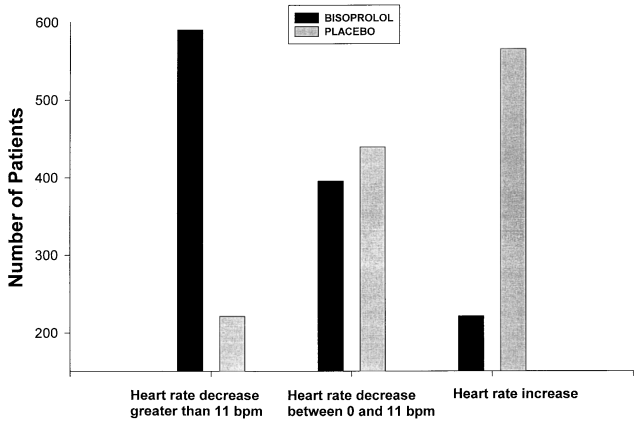

Figure 3. Distribution of patients according to heart rate change after 2 months in CIBIS II trial. Patients were divided into 3 tertiles of distribution of entire population.

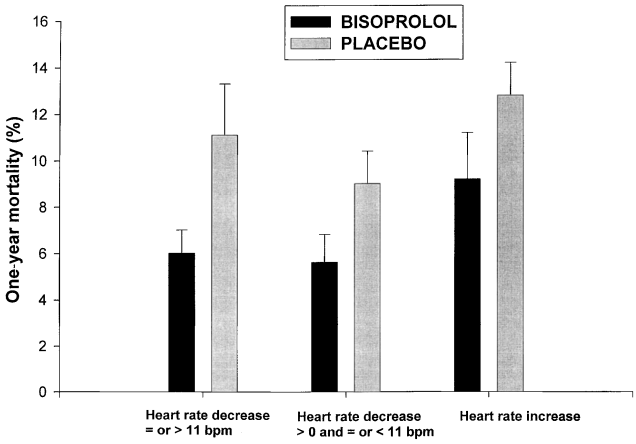

Figure 4. One-year mortality with SD (Kaplan-Meier estimate) according to heart rate change and study treatment group. Patients were divided into tertiles of distribution of heart rate change over entire population. Bars indicate SD.

without interaction between study treatment group and baseline heart rate (tested in the multivariate analysis, Figure 5). Probability values of log-rank tests comparing survival between placebo and bisoprolol were $P=0.01$, $P=0.03$, and $P=0.001$ for the 3 tertiles of baseline heart rate (from highest to lowest baseline heart rate).

Heart Rate and Blood Pressure Changes With Time According to Nature of Cardiac Rhythm at Baseline

Heart rate reduction at 2 months was slightly but significantly lower in the bisoprolol group in patients with atrial fibrillation (-8.8 ± 21.5 bpm) than in patients in sinus rhythm at baseline (-10.6 ± 12.4 bpm, $P=0.02$). The mean blood pressure (systolic and diastolic) decrease at 2 months was similar in patients with atrial fibrillation and in patients with sinus rhythm. In the bisoprolol group, however, patients in atrial fibrillation who later died had a more important systolic blood pressure decrease at 2 months than those who died but who were in sinus rhythm at baseline: -9.9 ± 14.5 versus -4.4 ± 15.9 mm Hg, $P=0.06$ (no such difference was observed in patients of the placebo group).

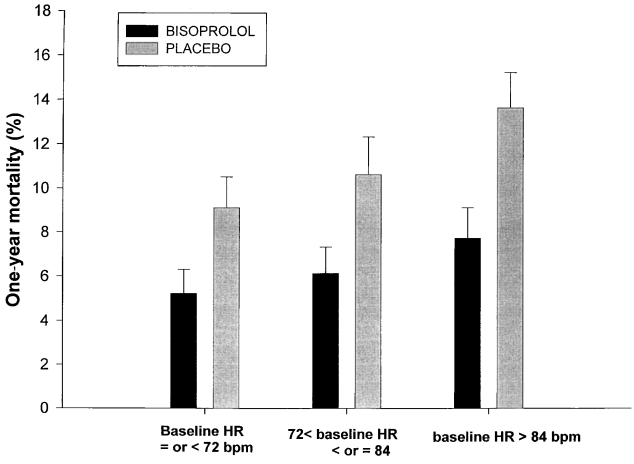

Figure 5. One-year mortality with SD (Kaplan-Meier estimate) according to baseline heart rate and study treatment group. Patients were divided into tertiles of distribution of baseline heart rate over entire population. Bars indicate SD.

Discussion

The major findings reported here in this complementary analysis of the CIBIS II trial are (1) the confirmation of the prognostic value in heart failure of baseline heart rate and of heart rate reduction with time (baseline to 2 months), the latter being more often obtained with β-blockade; (2) the similar benefit of bisoprolol compared with placebo whatever the level of heart rate at baseline and whatever the amplitude of heart rate change with time; and (3) the heterogeneity of bisoprolol effect according to the nature of cardiac rhythm: the benefit of bisoprolol on mortality, cardiovascular mortality, and hospitalization for heart failure was not significant in patients with atrial fibrillation.

Our results therefore confirm that heart rate reduction per se in patients with heart failure is associated with survival improvement. Such an effect was, as expected, more often obtained with β-blockade. For a given heart rate reduction and for any level of baseline heart rate, however, bisoprolol further improved survival compared with placebo. Such results have an important therapeutic impact, because one could have hypothesized that the benefit of β-blockade could have been restricted to heart rate reduction and that such benefit could not be obtained in patients with low baseline heart rate.

One possible link between heart rate reduction and survival is the left ventricular function improvement secondary to the induced reduction of ischemia, which is present to different degrees in dilated ventricles even in the absence of coronary artery disease.[9]

Our data clearly indicate, however, that heart rate reduction is not the only mechanism responsible for β-blocker–induced benefit in heart failure. Indeed, such benefit was present even without heart rate reduction, and many other different mechanisms have been proposed.[10,11]

No benefit of bisoprolol was observed in patients with atrial fibrillation. This could have been the result of chance only, but a very similar trend was also found in the CIBIS I study. It will be important to see whether this finding is also observed in other studies, such as MERIT[4] and COPERNICUS. There is no obvious explanation of such heterogeneity of the effect of bisoprolol according to cardiac rhythm. The bisoprolol dose was similar in patients in sinus rhythm and in patients with atrial fibrillation. Survival curves of patients in the placebo groups were similar between patients in sinus rhythm and atrial fibrillation, and none of the few baseline differences in recorded parameters between patients in sinus rhythm and atrial fibrillation could explain such a difference of the effect of bisoprolol. Even in the bisoprolol group, patients in atrial fibrillation had a slightly lower baseline heart rate, which should have tended to reduce mortality. Analysis of heart rate reduction with time showed that it was slightly lower at 2 months in the bisoprolol group in patients with atrial fibrillation than in those in sinus rhythm. Such lower heart rate reduction could participate in the loss of efficacy of bisoprolol in patients with atrial fibrillation, but its

amplitude (2 bpm difference) does not appear to be sufficient to reasonably explain such a difference. Such results in heart rate are limited, however, by the poor value of the measure of heart rate in the presence of atrial fibrillation when only pulse rate during patient visit is used, and they should be completed with a 24-hour Holter monitoring study.

The bisoprolol-induced systolic blood pressure decrease could play a more deleterious role in some patients with atrial fibrillation. Indeed, the finding in the bisoprolol group of a more important systolic blood pressure decrease at 2 months in patients with atrial fibrillation who subsequently died suggests that when bisoprolol decreased blood pressure to too great an extent (−10 mm Hg), such a decrease was more deleterious in patients with atrial fibrillation than in sinus rhythm.

In addition to data on heart rate and cardiac rhythm, our analysis provides complementary information:

Women with heart failure have a better prognosis than men, but bisoprolol provides similar benefit (no interaction). This result based on CIBIS II data was presented in detail previously.[12]

Systolic blood pressure, which depends partly on left ventricular function, was at baseline positively associated with a better prognosis and fewer hospital admissions. Both systolic and diastolic blood pressure decreased with time but more importantly in the bisoprolol group than the placebo group. The systolic blood pressure decrease with time was per se deleterious and associated with a poorer prognosis and more hospitalizations, but the decrease of diastolic blood pressure, on the contrary, was beneficial and associated with fewer hospital admissions without impact on mortality. Interpretation of these data is not obvious: β-blockade improves survival but simultaneously decreases both systolic and diastolic blood pressures, which have opposite effects on prognosis or hospitalization. The diastolic blood pressure decrease could be a consequence of sympathetic tone withdrawal (less systemic resistance), which should be beneficial, but too great a systolic blood pressure decrease as an effect of β-blocker could reduce tissue perfusion and/or be a consequence of an altered left ventricular function despite β-blocker treatment. When such alteration of left ventricular function occurred despite bisoprolol treatment in the first CIBIS study, it was found to be associated with a deleterious effect on survival.[7]

Digoxin treatment was not associated with any change of mortality rate but was associated with a markedly increased frequency of hospital admissions for heart failure worsening (63%). This result provided by the multivariate analysis indicates that digoxin per se increased hospitalization rate after adjustment for the other prognostic factors. Similar findings were observed with amiodarone, which increased the probability of death and rehospitalization. These results mean that independently of the higher level of risk of patients receiving either digoxin or amiodarone at baseline, these 2 treatments in this population were associated with deleterious consequences. One cannot exclude other unknown and therefore unstudied risk factors, however, that may have been more frequent in patients treated by digoxin or amiodarone. Here again, comparison and pooling of data from the other trials with β-blocker treatment in heart failure would be very useful to confirm such findings, which appear to be in opposition to those of previous randomized studies testing digoxin or amiodarone in patients with heart failure.

Clinical implications of our results are as follows: Patients with heart failure in sinus rhythm with the initial lowest heart rate and the greatest heart rate reduction with time (2 months) will have the best prognosis. Bisoprolol-induced benefit over placebo is obtained to a similar extent, however, whatever the level of baseline heart rate and whatever the amplitude of heart rate reduction with time even when heart rate does not decrease. The best results for survival will then be obtained with β-blocker treatment when heart rate reduction reaches the highest level, whatever the baseline heart rate (>10 bpm reduction), without marked systolic blood pressure decrease. To obtain such results for a given patient, dose adjustment may be required. If heart rate reduction >10 bpm is obtained with a low dose level, however, such dosage should be sufficient to improve survival and could be kept low, especially if systolic blood pressure has decreased.

Additional experiments will be needed to understand the reduction of the long-term benefit of bisoprolol in patients with atrial fibrillation. It could be partly related to the deleterious consequences of a too marked systolic blood pressure decrease when it occurs under β-blockade in such patients. A definite therapeutic strategy for β-blocker treatment in these patients will depend on the results of the other large-scale clinical trials.

References

1. Lechat P, Packer M, Chalon S, et al. Clinical effects of β-adrenergic blockade in chronic heart failure: a meta-analysis of double-blind, placebo-controlled, randomized trials. *Circulation*. 1998;98:1184–1191.
2. The CIBIS II scientific committee. Design of the Cardiac Insufficiency Bisoprolol Study II (CIBIS II). *Fund Clin Pharmacol*. 1997;11:38–42.
3. CIBIS II Investigators and Committees. The Cardiac Insufficiency Bisoprolol Study II (CIBIS II): a randomised trial. *Lancet*. 1999;353:9–13.
4. MERIT-HF study group. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). *Lancet*. 1999;353:2001–2007.
5. The BEST steering committee. Design of the Beta-blocker Evaluation Survival Trial. *Am J Cardiol*. 1995;75:1220–1223.
6. CIBIS investigators and committees. A randomized trial of β-blockade in heart failure: the cardiac insufficiency bisoprolol study (CIBIS). *Circulation*. 1994;90:1765–1773.
7. Lechat P, Escolano S, Golmard JL, et al, on behalf of CIBIS investigators. Prognostic value of bisoprolol-induced hemodynamic effects in heart failure during the Cardiac Insufficiency BIsoprolol Study. *Circulation*. 1997;96:2197–2205.
8. Nagatsu M, Spinale FG, Koide M, et al. Bradycardia and the role of β-blockade in the amelioration of left ventricular dysfunction. *Circulation*. 2000;101:653–659.
9. Unverferth DV, Magorien RD, Lewis RP, et al. The role of subendocardial ischemia in perpetuating myocardial failure in patients with nonischemic congestive cardiomyopathy. *Am Heart J*. 1983;105:176–179.
10. Bristow MR. β-Adrenergic receptor blockade in chronic heart failure. *Circulation*. 2000;101:558–569.
11. Eichhorn EJ, Bedotto JB, Malloy CR, et al. Effects of β-adrenergic blockade on myocardial function and energetics in congestive heart failure: improvements in hemodynamic, contractile, and diastolic performance with bucindolol. *Circulation*. 1990;82:473–483.
12. Simon T, Mary-Krausse M, Funck-Brentano, et al. Sex differences in the prognosis of congestive heart failure: results from the Cardiac Insufficiency Bisoprolol Study (CIBIS II). *Circulation*. 2001;103:375–380.