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Sinus rhythm versus atrial fibrillation in elderly patients with chronic heart failure — Insight from the Cardiac Insufficiency Bisoprolol Study in Elderly

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ABSTRACT

Background: It has been suggested that patients with chronic HF and atrial fibrillation (AF) may respond differently to beta-blockers than those in sinus rhythm (SR).
Methods: In this predefined analysis of the CIBIS-ELD trial, a total of 876 chronic HF patients (164 patients with AF) were randomized to bisoprolol or carvedilol. During the 12-week-treatment phase, beta-blockers were doubled fortnightly up to the target dose or maximally tolerated dose, which was maintained for 4 weeks.
Results: Patients with AF had lower left ventricular ejection fraction (LVEF), exercise capacity, self-rated health, quality of life (QoL) scores for both SF36 physical and psychosocial component, and higher NYHA class than those in SR. Beta-blocker titration was associated with clinical improvement in both AF and SR patients: LVEF, 6-minute walk distance, physical and psychosocial components of QoL scores, self-rated health and NYHA class ($p<0.05$, for all). The extent of improvement did not differ between patients with AF and in SR and did not differ between bisoprolol and carvedilol. Heart rate (HR) at baseline was higher in the AF group, and remained higher until the end of the trial. Patients with higher baseline HR had larger reductions in HR, regardless of rhythm. AF patients more frequently reached target beta-blocker dose compared to those in SR ($p<0.005$).
Conclusions: Elderly patients with chronic HF and AF derive comparable clinical benefits from beta-blocker titration as those in SR. Patients with AF tolerate higher beta-blocker doses than those in SR, which appears to be related to higher baseline HR.

1. Introduction

Atrial fibrillation (AF) is the most common rhythm disorder in patients with chronic heart failure (HF), affecting 15–30% of cases, and its proportion increases with age and New York Heart Association (NYHA) functional class [1–3]. Despite the well established beneficial role of beta-blockers in the treatment of both AF and chronic HF, it has been suggested that patients with chronic HF and coexisting AF may not equally benefit from beta-blocker therapy as those in sinus rhythm (SR) [4].

While limited data from previous studies suggested comparable improvement in left ventricular (LV) systolic function with beta-blocker treatment in patients with coexisting chronic HF and AF, exercise capacity and symptoms did not improve to the same extent as in those in SR [5,6].

Further, it is unknown whether different pharmacological characteristics of beta-blockers may influence their clinical effects in

Abbreviations: AF, atrial fibrillation; bpm, beats per minute; CIBIS-ELD, Cardiac Insufficiency Bisoprolol Study in Elderly; HF, heart failure; HR, heart rate; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; QoL, quality of life; SR, sinus rhythm.

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patients with chronic HF and AF. Previous studies suggested that carvedilol's nonselectivity and additional (vasodilatatory) properties may be important in patients with chronic HF [3,7]. On the other hand, it has been shown that beneficial effects of beta-blockers are related to the magnitude of heart rate reduction [8], which favors the selective beta1-adrenoceptor-blocker bisoprolol [9].

Therefore, we prospectively analyzed data from The Cardiac Insufficiency Bisoprolol Study in Elderly (CIBIS-ELD) [9] to compare the response to beta-blocker titration in elderly chronic HF patients with AF versus those in SR. This study is the first head-to-head comparison of carvedilol and bisoprolol in patients with chronic HF and coexisting AF.

2. Methods

The CIBIS-ELD trial was an investigator-initiated, multicenter, double-blind trial, where 876 patients ≥65 years with systolic or diastolic chronic HF (NYHA class II/III) were randomized to receive bisoprolol or carvedilol. Eligible patients had to be beta-blocker naïve or on ≤25% of the recommended target dose. Study design and main results have been published previously [9,10]. Briefly, the beta-blocker dose was doubled fortnightly to reach the target dose (10 mg bisoprolol once daily or 25 mg carvedilol twice daily within 6 weeks) or maximally tolerated dose. Patients weighing >85 kg were scheduled to reach the target dose of carvedilol of 50 mg twice daily within 8 weeks. Investigators were free to delay titration or reduce the dose if clinically indicated. The titration phase was followed by a maintenance period lasting 4 weeks and the final visit was at 10 weeks (12 weeks for patients >85 kg).

The primary endpoint of tolerability of CIBIS-ELD was defined as reaching the target dose through the process of fortnightly doubling with no more than one delayed increase and with the target dose maintained for at least 10 days.

Secondary endpoints included adverse events and clinical parameters of patient status which were measured at baseline, prior to dose titration at each visit, and at follow-up.

Patients with AF were analyzed as a predefined subgroup to determine potential differences in reaching primary endpoint and to compare the effects of beta-blocker titration on exercise capacity (6-minute walk distance — 6MWD), symptoms (NYHA functional class), left ventricular ejection fraction (LVEF), parameters of diastolic function and quality of life (the short-form quality of life health survey) to those in SR. Heart rate and blood pressure changes as well as relationship between heart rate changes and achieved beta-blocker dose in both rhythm groups were also studied.

The effects of beta-blocker titration on additional echocardiographic parameters (LV end-diastolic diameter, LV mass index, left atrial volume index), N-terminal pro b-type natriuretic peptide (NT-proBNP) plasma levels and self-rated health score were also compared between patients with AF versus those in SR.

2.1. Electrocardiographic recordings

As per CIBIS-ELD study protocol, an electrocardiogram (ECG) was recorded at baseline, fortnightly at each titration visit, as well as at follow up. The standard 12-lead ECG was recorded after 2 to 3 min of rest in the supine position, at the paper speed of 25 mm/s and standardization of 10 mm/1 mV. Baseline rhythm was used to classify patients as belonging to the AF or the SR group. Fifty-six patients with pacemakers (8 in AF and 48 in SR group) were excluded from the analysis.

2.2. Measurement of left ventricular ejection fraction

Left ventricular ejection fraction was calculated using biplane Simpson's rule, as the mean value of three consecutive cardiac cycles.

2.3. Statistical analysis

Differences in baseline characteristics between patients with AF and SR were analyzed using Student t-test for continuous variables and Fisher's exact test for categorical variables. The difference of rates in reaching the maximum recommended beta-blocker dose between AF and SR group was tested by two-sided Fisher's exact test.

Logistic regression was used to examine the increase of the odds for reaching the target dose associated with AF, baseline heart rate (odds ratio per additional beat/min) and both AF and baseline heart rate combined.

The significance of changes in clinical endpoints was assessed within each group by paired t-test. Comparison across groups was carried out by the analysis of covariance (ANCOVA) with the follow-up measurement as dependent variable, the heart rhythm (AF or SR) at baseline ECG as factor, and the baseline measurement as covariate (or as categorical co-factor in case of NYHA class). When significant differences between groups were observed, additional comparison (bisoprolol vs. carvedilol) was carried out by 2-way ANCOVA, with the type of beta-blocker as cofactor. A separate analysis was done to test the interaction between observed differences and baseline LV systolic function (preserved vs. reduced LVEF). Analyses were performed using SPSS Version 15 (SPSS Inc., Chicago, IL, USA).

The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology [11].

3. Results

Of 876 patients randomized in CIBIS-ELD, 164 (18.6%) had AF at baseline. Demographic and clinical patients' characteristics are summarized in Table 1. Patients with AF were more frequently male, higher resting HR, lower systolic and higher diastolic blood pressure than those in SR.

Patients with AF had lower LVEF, presented with higher NYHA classes, higher NTproBNP levels and lower exercise capacity, as indicated by 6MWD, than those in SR. Left ventricular end-diastolic dimension, LV mass index and left atrial volume index were all significantly larger in the AF group. Patients with AF also had lower quality of life scores (both physical and psychosocial components), higher depression sum scores (Patient Health Questionnaire — PHQ) and more frequently rated their health as poor. Ischemic cardiomyopathy was the most common etiology of chronic HF in both groups (44% in AF and 54% in SR group).

More patients with AF were receiving diuretics, aldosterone receptor antagonists, anticoagulants, cardiac glycosides and anti-arrhythmic drugs at baseline, while there was no difference in angiotensin converting enzyme inhibitors/angiotensin receptor blockers and beta-blocker pre-treatment.

3.1. Heart rate and blood pressure changes

Patients with higher baseline heart rates had larger reductions in heart rate, regardless of rhythm (Fig. 1, negative slope of the solid lines). As baseline heart rates were higher in the AF group, the

Table 1
Baseline characteristics.

	Atrial fibrillation (n = 164)	Sinus rhythm (n = 712)	p Value
Woman, no. (%)	39 (23.8)	290 (40.7)	<0.001
Age, yrs	72.1 ± 5.3	72.4 ± 5.6	0.126
Heart rate, bpm	86 ± 17	71 ± 12	<0.001
Systolic blood pressure, mm Hg	133 ± 18	138 ± 22	0.003
Diastolic blood pressure, mm Hg	82 ± 12	80 ± 12	0.036
LVEF, %	37 ± 11	43 ± 14	<0.001
Preserved LVEF (>45%), no. (%)	25 (15.2)	225 (31.6)	<0.001
NYHA class, no. (%)			0.016
I	3 (1.8)	31 (4.4)	
II	96 (58.5)	479 (67.3)	
III	64 (39.0)	194 (27.2)	
IV	1 (0.6)	8 (1.1)	
6MWD, m	292 ± 106	329 ± 110	<0.001
NTproBNP, median (IQR), pg/ml	1540 (924–2747)	503 (207–1433)	<0.001
Hemoglobin, mean (SD), g/dl	13.6 ± 1.6	13.9 ± 1.7	0.299[a]
FEV1, ml	2218 ± 661	2186 ± 663	0.651
Co-morbidities, no. (%)			
Hypertension	128 (78)	596 (84)	0.087
Diabetes mellitus	40 (24)	183 (26)	0.766
Hyperlipidemia	83 (56)	465 (65)	<0.001
Renal dysfunction [eGFR <60 ml/min/1.73 m^2]	58 (35)	270 (38)	0.592
Cardiovascular medication, no. (%)			
Beta-blocker (pretreatment)	97 (59)	430 (60)	0.791
ACE inhibitor and/or ARB	136 (83)	605 (85)	0.549
Aldosterone receptor antagonist	73 (45)	202 (28)	<0.001
Diuretic	138 (84)	511 (72)	0.001
Cardiac glycoside	72 (44)	57 (8)	<0.001
Antiarrhythmic	28 (17)	67 (9)	0.008
Statin	43 (26)	299 (42)	<0.001
Antiplatelet	86 (52)	495 (70)	<0.001
Anticoagulant	107 (65)	112 (16)	<0.001

6MWD = 6-minute walk distance. ACE = angiotensin converting enzyme. ARB = angiotensin receptor blocker. eGFR = estimated glomerular filtration rate. FEV1 = forced expiratory volume in first second. LVEF = left ventricular ejection fraction. NTproBNP = N-terminal pro b-type natriuretic peptide.

[a] Adjusted for sex.