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Effect of β1 blockade with atenolol on progression of heart failure in patients pretreated with high-dose enalapril

Barbara Sturm, Richard Pacher, Jeanette Strametz-Juranek, Rudolf Berger, Bernhard Frey, Brigitte Stanek*

Department of Cardiology, University of Vienna, Währinger Gürtel 18-20, A-1090 Vienna, Austria

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Abstract

Background: The survival benefit of β-blocker treatment in patients with heart failure has been established in recent trials. Yet, the impact of β-blockers added on high dose angiotensin converting enzyme inhibitors has not been reported. *Aims:* To investigate the effect of atenolol, a hydrophilic, selective β1-adrenergic antagonist, added on enalapril 40 mg/day in patients with advanced left ventricular dysfunction in a double-blind placebo-controlled trial. *Methods:* One hundred and nineteen patients with class II or III heart failure, left ventricular ejection fraction $\leq 25\%$ and treatment with 40 mg enalapril daily were given an initial challenge dose of atenolol 12.5 mg. One hundred patients (54 with idiopathic, 28 with ischemic, 18 with other dilated cardiomyopathy) tolerated challenge and were randomized to atenolol (maintenance dose 89 ± 11 mg/day, range 50–100 mg/day) or placebo. The primary endpoint was combined worsening heart failure or death within 2 years, the secondary endpoint was hospitalization for cardiac events. *Results:* After 395 ± 266 days interim analysis revealed a significant difference between the atenolol and placebo group (log rank $P < 0.01$) and the trial was concluded. Twenty-seven patients had developed worsening heart failure (8 in the atenolol group vs. 19 in the placebo group) and 13 patients had died (5 in the atenolol vs. 8 in the placebo group). Overall there were 23 hospitalizations for cardiac events (6 in the atenolol group vs. 21 in the placebo group, $P = 0.07$); 17 hospitalizations were due to worsening heart failure (5 in the atenolol group, 12 in the placebo-group, $P = 0.05$) and 10 due to arrhythmias (1 in the atenolol group vs. 9 in the placebo group, $P < 0.01$) *Conclusions:* The data suggest that in patients with advanced left ventricular dysfunction, β-blockers can provide substantial benefits supplementary to that already achieved with high dose enalapril treatment.

Keywords: Heart failure; Advanced left ventricular dysfunction; High-dose enalapril; β-Blockade; Progression of disease

* Corresponding author. Tel.: +431-40400-4616; fax: +431-4081148.
E-mail address: etanzl@pop3.kard.akh-wien.ac.at (B. Stanek).

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1. Introduction

The impact of neurohumoral antagonists for the treatment of patients with chronic heart failure is now well established [1]. β-Adrenergic antagonists have shown potent effects to reverse left ventricular systolic dysfunction, to retard progression of the underlying myocardial disease, and to prolong life when added to angiotensin converting enzyme (ACE) inhibitors [2]. It should be emphasized, however, that few studies investigated how to use ACE-inhibitors. Our own previous single center study suggested that a high enalapril dose produces a greater symptomatic benefit than a low dose [3]. A recent study reported that benefits from increased ACE-inhibitor dosages are indeed related to enalaprilat trough levels in individual patients [4]. Particularly in advanced heart failure the point of using these drugs at higher doses appears critical to avoid frequent decompensations and adverse outcomes due to insufficient treatment [5,6].

These recommendations are based on evidence as far as the target dosages used in CONSENSUS (40 mg enalapril per day) and in SOLVD (20 mg enalapril per day) are concerned and have been substantiated by the results of the ATLAS study which indicated that the use of high doses instead of low doses of the ACE-inhibitor lisinopril reduces the risk of major clinical events in patients with chronic heart failure [7–9]. Thus, despite the success of β-blockers, the role of high-dose ACE-inhibitors should not be underestimated in the treatment of heart failure. Importantly, more intense ACE-inhibition is generally well tolerated also in previously 'resistant' patients who have regained a safe hemodynamic profile after intravenous therapy using nitrates [10] or milrinone [11] and may contribute to the progressive further improvement seen in those patients probably by mechanisms involving structural changes. On the other hand, attention has also extended to include β-blockers in this critical situation [12]. Even a very low ejection fraction does not exclude the consideration of β-blocker therapy as these patients also have the potential to gain from such treatment [13,14].

Based on the concern that no trials to evaluate the impact of β-blockers in heart failure reported effects in patients receiving high-dose ACE-inhibitor treatment a pilot study was undertaken to investigate additional effects of β-blockade on top of high-dose enalapril. Atenolol, a β1 selective β blocker was chosen based on previous experience with this drug in our center [15,16], as well as by others [17–19]. When our study was begun the results of the US carvedilol program had already been presented at the American Heart Association (Anaheim, USA, November 1995) meeting. After the results of the preplanned interim analysis were obtained on 24 March 1999 the current study was stopped prematurely. At that time CIBIS II had already been published [20] and the results of the MERIT-HF trial were just being presented at the American College of Cardiology (New Orleans, USA, March 1999) meeting. Soon thereafter also the COPERNICUS trial broke confirming the safe and efficacious use of β-blockers for stable heart failure patients including those with severe symptoms.

2. Methods

2.1. Patients

Between April 1996 and November 1998 we enrolled 100 patients. Men and women were targeted who were 18–75 years old, ambulatory, and had a left ventricular ejection fraction (LVEF) of $\leq 25\%$ determined by radionuclide ventriculography while treated with enalapril 40 mg/day. Patients who had experienced an episode of heart failure decompensation and/or had needed major modifications of heart failure therapy during the previous 6 weeks were not eligible. Women at child bearing age were only accepted if surgically sterile or using an effective method of contraception. Pretreatment with β-blockers, calcium antagonists, inotropic agents (except digitalis), vasodilator agents (other than ACE-inhibitors and nitrates), or theophylline derivatives was not allowed. Other exclusion criteria were: acute myocardial infarction or unstable angina within 2 months before randomization; significant obstructive cardiac valvular disease; restrictive or obstructive cardiomyopathy; atrioventricular block greater than first degree without a chronically implanted pacemaker; respiratory function $< 65\%$ predicted normal as a result of chronic obstructive pulmonary disease; significant hepatic disease (serum transaminases greater than twofold upper normal limit); significant renal dysfunction (serum creatinine > 2.5 mg/dl or proteinuria > 1.5 g/day); presence of leukopenia or neutropenia; history of collagen vascular or autoimmune disease; recent history of alcohol or drug abuse.

2.2. Design

This was a double-blind placebo-controlled single center study designed to evaluate effects of β-blockade added on background therapy of 40 mg/day enalapril throughout 2 years. The investigation conforms with the principles outlined in the Declaration of Helsinki and all patients had given written informed consent. The trial was supervised by the local ethics committee, which also performed the function of an independent safety committee advised by two international reviewers who made suggestions to im-

prove the protocol. The modified protocol was approved by the ethics committee under the condition that for safety reasons an interim analysis had to be performed and the results should be presented to the institution.

2.3. Protocols

The study was preceded by a challenge test performed at the randomization visit when all patients received 12.5 mg atenolol 2 h after morning medications. One hundred out of 119 patients who remained free of significant symptoms and whose systolic blood pressure remained ≥ 90 mmHg and heart rate ≥ 60 b.p.m. after 5 h were assigned treatment with atenolol ($n = 51$) or placebo ($n = 49$) according to a computer-generated schedule. The code was kept by the study monitor and was not broken until interim analysis. Treatment was performed following predefined titration steps (see Table 1). Patients who presented with systolic blood pressure < 90 mmHg and heart rate < 60 b.p.m. after 1 week were maintained on their previous dose level for another week. Patients who did not tolerate doses up to 50 mg/day were withdrawn. The maximum dose during the uptitration period (predefined range 50–100 mg/day) was continued throughout. Follow-up visits were prescheduled at 3, 6, 12, 18 and 24 months.

2.4. Statistical analysis

Data are presented as means $\pm$ S.D. or numbers. The primary endpoint was combined worsening heart failure (including the need of additional treatment) or death at any point during follow-up. A secondary endpoint was frequency of hospitalization due to cardiac events. After 395 ± 226 days when 100 included patients had passed the titration phase of the study the interim analysis of the primary and secondary endpoints was performed on an intention-to-treat basis. The primary endpoints (worsening heart failure or death) were summarized by group and Kaplan–Meier curves were constructed for each treatment curve. The distribution was compared using the log-rank test. A P-value < 0.05 was considered statistically significant. For all statistical analysis SAS version 6 (SAS Institute, Cary, NC, USA) statistical package was used.

3. Results

The two study groups were similar for baseline characteristics including LVEF, heart rate, blood pressure, exercise variables and concomitant therapies (Table 2).

Table 1
Titration schedule of atenolol

	Morning	Noon	Evening
1st level	12.5 mg		12.5 mg
2nd level	12.5 mg	12.5 mg	12.5 mg
3rd level	25 mg		25 mg
4th level	25 mg	25 mg	25 mg
5th level	50 mg		50 mg

Thirty-nine patients in the atenolol group and 46 patients in the placebo group passed the uptitration period. In the atenolol group the main reason of drop was a low heart rate (5 patients), followed by a low systolic blood pressure (2 patients), worsening heart failure (2 patients), non-compliance (2 patients) and vertigo (1 patient). In the placebo group, two patients dropped because of worsening heart failure and one patient because of ventricular tachycardia. The most frequent serious adverse events during the maintenance phase were tachyarrhythmias, resulting in hospitalizations in 10 patients. Minor side effects were sleep disturbance (10 with atenolol and 4 with placebo), depression (5 with atenolol and 4 with placebo) gastrointestinal symptoms (6 with atenolol and 7 with placebo) and impotence (6 with atenolol and 4 with placebo). No adverse effects except arrhythmias were serious enough to discontinue double-blind treatment during the maintenance period.

3.1. Primary and secondary endpoints

At interim analysis 27% of the patients had developed worsening heart failure, 8 in the atenolol group and 19 in the placebo group. Overall mortality was 13%. In the atenolol group five patients had died, with four cardiac deaths (1 from progressive heart failure, 3 sudden) and one non-cardiac death. In the placebo group eight patients had died, with seven cardiac deaths (1 from progressive heart failure and 6 sudden) and one non-cardiac death. Thus, the proportion of patients reaching a primary endpoint (death or worsening heart failure) in the placebo group was twofold compared with that found in the active treatment group (27 out of 49 patients vs. 13 out of 51 patients, $P < 0.01$). Overall there were 23 hospitalizations, six in the atenolol group and 21 in the placebo group ($P = 0.07$ between groups). Seventeen hospitalizations were due to worsening heart failure (5 in the atenolol group, 12 in the placebo-group, $P = 0.05$) and 10 due to arrhythmias (1 in the atenolol group, 9 in the placebo group, $P < 0.01$) (Tables 3 and 4). Kaplan–Meier lifetime analysis showed a significant difference (log-rank $P < 0.01$) between the two study groups with regard to death or worsening heart fail-

Table 2
Patient characteristics[a]

	Atenolol	Placebo	*P* value
n	51	49	
Male/female	44/7	44/5	n.s.
Age (years)	51 ± 11	52 ± 10	n.s.
Etiology of CMP			
idiopath/ischem/other	26/16/9	28/12/9	n.s.
LVEF (%)	17 ± 5	17 ± 6	n.s.
NYHA class II/III/IV	40/9/2	38/11/0	n.s.
Sinus rhythm/AF/PM	39/10/2	42/6/1	n.s.
History of hypertension	16	20	n.s.
Diabetes mellitus	7	11	n.s.
Heart rate (b.p.m.)	89 ± 15	91 ± 15	n.s.
Syst. blood pressure (mmHg)	115 ± 18	118 ± 15	n.s.
Diast. blood pressure (mmHg)	77 ± 11	79 ± 10	n.s.
Workload (W)	103 ± 43	96 ± 43	n.s.
Exercise capacity (%)	53 ± 17	52 ± 22	n.s.
Peak V_{O_2} (ml/min/kg)	17.5 ± 4.9	16.2 ± 4.8	n.s.
Treatment			
Enalapril 40 mg per day	51	49	n.s.
Digitalis	51	49	n.s.
Furosemide, mg per day (*n*)	52 ± 31 (24)	44 ± 22 (30)	n.s.
Nitrates	13	20	n.s.
Phenprocoumon	35	37	n.s.
ASA	12	10	n.s.

[a]*Abbreviations:* CMP, cardiomyopathy; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; AF, atrial fibrillation; PM, pace maker; peak V_{O_2}, peak oxygen consumption; ASA, acetylsalicylic acid.

ure in favor of atenolol (Fig. 1). This result was independent of age, gender, etiology or severity of heart failure.

4. Discussion

This placebo-controlled double-blind trial of atenolol, a potent β1 selective adrenergic antagonist, shows substantial clinical benefit of β-blockade in a selected population of heart failure patients with advanced left ventricular systolic dysfunction. Of 100 patients randomized who tolerated initiation of β-blockade without symptoms or decrease in heart rate and/or blood pressure below safety limits 40% reached the combined primary endpoint of worsening heart failure or death at interim analysis after an average 395 days of treatment with Kaplan–Meier curves diverging significantly between atenolol and placebo treatment (log rank $P < 0.01$). Importantly, this treatment benefit was supplementary to that gained with high-dose ACE-inhibitor background therapy alone suggesting that combined vigorous inhibition of two neurohumoral systems (dose of atenolol was 50–100 mg/day, average 89) can produce valuable additive effects in carefully selected patients.

Obviously, the patient selection of the present study

Table 3
Endpoint analysis

	Atenolol	Placebo	*P*-value
Primary endpoint	*n* (%)	*n* (%)	
Combined worsening heart failure or death	13 (26)	27 (55)	$P < 0.01$
Worsening heart failure	8 (16)	19 (39)	n.s.
Death	5 (10)	8 (16)	n.s.
Secondary endpoint			
Hospitalization due to cardiac events	6 (12)	21 (42)	$P = 0.07$
due to worsening heart failure	5 (10)	12 (24)	$P = 0.05$
due to tachyarrhythmia	1 (2)	9 (18)	$P < 0.01$

Table 4
Study completing cohorts

	Atenolol	Placebo
At baseline	51	49
After the titration phase	39	46
After the maintenance phase[a]	28	20

[a] Referring to 395 ± 266 study days.

differs in many aspects from other published trials [2], one (minor) being the greater proportion of patients with idiopathic dilated cardiomyopathy who were also relatively young. However, for this category of patients some evidence is provided by the metoprolol in dilated cardiomyopathy (MDC) trial (mean age 47 years) [21,22]. The major difference is the uniform background therapy with 40 mg/day enalapril in all patients which was associated with only moderate heart failure symptoms despite a low LVEF, as often encountered with this regimen in our center. The mean LVEF at entry to both, CIBIS II [20] and MERIT-HF [23], was 28%, while it was 17% in our study population. It was intriguing, when the study was planned in 1995, to find out if patients who appeared clinically well-treated with high-dose enalapril, as reflected by NYHA class, would benefit further from additional β-blockade.

Therefore, in this trial all patients who met the inclusion criteria of clinical stability while on high-dose enalapril, were challenged with an open 12.5 mg atenolol test dose. This test revealed that 84% of the pretested patients had neither signs (low blood pressure or heart rate) nor symptoms of β-blocker intolerance. In CIBIS II patients were not pretested, and there were 15% permanent withdrawals in each arm, similar to MERIT-HF. In both studies, however, systolic blood pressure at inclusion was 100 mmHg. In the present study 12 patients were permanently withdrawn in the atenolol group during uptitration, again the majority due to the safety threshold of 90 mmHg systolic blood pressure and 60 b.p.m. heart rate in response to atenolol. In the light of growing experience with β-blockers in the treatment of heart failure it appears questionable, if the safety thresholds of 90 mmHg systolic blood pressure and 60 b.p.m. heart rate in response to β-blockade, as used in the current study, are still valid.

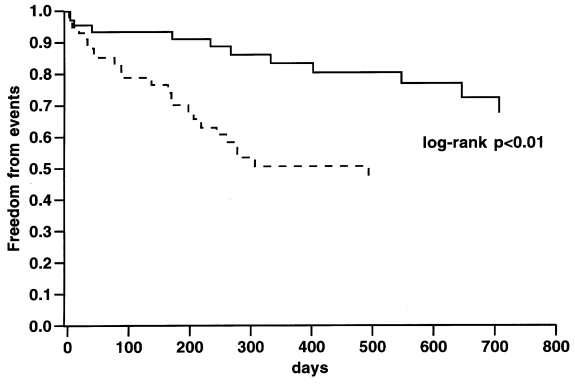

Fig. 1. Kaplan–Meier analysis showing cumulative rates of event-free survival regarding freedom from worsening heart failure or death in 51 patients treated with atenolol (solid line) and 49 patients treated with placebo (dashed line). The difference between the two groups was significant (log rank $P < 0.01$).

Evidence is accumulating that β-blockers can reverse or slow the process of left ventricular remodeling and induce a beneficial structural change [24]. Drugs that affect the underlying neurohumoral disorder may not always produce immediate symptomatic benefits, however. It is well recognized that clinical responses to β-blockers are generally delayed and may require 2–3 months to become apparent [25]. In the present study worsening heart failure during the first or second month was observed in four patients in the atenolol group but only in two patients in the placebo group. In the maintenance phase of the trial this trend was reversed with subsequent decreased incidence of worsening heart failure or death in patients allocated to atenolol. Twenty-seven patients had to be hospitalized for cardiac events, but only six of those received active treatment with atenolol. The majority of hospitalizations in both groups was due to worsening heart failure, as expected, but nine patients experienced tachyarrhythmias on placebo compared with only one patient on atenolol ($P < 0.01$), possibly due to its antiarrhythmic actions.

There are limitations of our study that have to be addressed. Nineteen patients who did not respond to the initial open atenolol challenge as desired, were not included. Accordingly, the study population is rigorously selected and confined to patients who tolerate 40 mg/day enalapril as well as additional 12.5 mg atenolol. We cannot provide any information concerning whether patients who do not tolerate a β-blocker in addition to high dose enalapril, would possibly have tolerated a β-blocker in addition to a lower enalapril dose. It remains unclear whether such patients will benefit from a reduction in enalapril dose to facilitate titration of β-blockers. When the trial was planned in 1995 the use of β-blockers in heart failure was still controversial, while the strategy to use ACE-inhibitors at high doses was already established in our center [3] and is recommended for general use now [9].

5. Conclusion

The findings of this trial provide information regarding safety and tolerability of the combination of ACE-inhibitors and β-blockers in addition to previous

studies. It is remarkable that in spite of the high withdrawal rate in the atenolol group, there was still an important beneficial effect in patients already receiving high-dose enalapril. To define the relative risks and benefits in this specific patient group further information from adequately designed studies is required.

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