



Differences between bisoprolol and carvedilol in patients with chronic heart failure and chronic obstructive pulmonary disease: a randomized trial

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KEYWORDS

Bisoprolol;
Carvedilol;
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Summary

Background: Chronic obstructive pulmonary disease (COPD) frequently coexists in patients with chronic heart failure (CHF) and is a key factor for beta blocker underprescription and underdosing. This study compared effects of bisoprolol and carvedilol in patients with both conditions.

Methods: This was a randomized open-label study, of bisoprolol and carvedilol during initiation and uptitration to target or maximal tolerated dose. Pulmonary function testing, 12-lead electrocardiogram, and N-terminal pro brain natriuretic peptide were measured at baseline and follow-up.

Results: We randomized 63 elderly patients (73 ± 9 years, 81% men, left ventricular ejection fraction $33 \pm 7\%$) with mild to moderate CHF (54% New York Heart Association class II) and moderate to severe COPD (76% Global initiative for chronic Obstructive Lung Disease stage 2). Target dose was tolerated by 31 (49%) patients and 19 (30%) patients experienced adverse events during follow-up (19% bisoprolol, 42% carvedilol, $p=0.045$). Study medication had to be withdrawn in 8 (13%) patients (bisoprolol: 2 due to hypotension, 1 due to bradycardia; carvedilol: 2 due to hypotension and 1 due to wheezing, dyspnoea, and oedema, respectively). Forced expiratory volume in 1st second significantly increased in bisoprolol (1561 ± 414 ml to 1698 ± 519 ml, $p=0.046$) but not carvedilol (1704 ± 484 to 1734 ± 548 , $p=0.44$) group. Both agents reduced heart rate (bisoprolol: 75 ± 14 to 68 ± 10 , $p=0.007$; carvedilol 78 ± 14 to 72 ± 12 , $p=0.016$) and had no effect on N-terminal pro brain natriuretic peptide.

Conclusions: Beta blockers frequently caused adverse events, and thus 49% of patients could tolerate the target dose. Bisoprolol induced demonstrable improvement in pulmonary function and caused less adverse events.

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Introduction

Co-morbidities have recently received increasing research and clinical interest in patients with chronic heart

failure (CHF).^{1,2} Landmark randomized controlled trials established beta blockers as mainstay therapy in CHF with reduced left ventricular ejection fraction.³ Translation to clinical practice, however, remains suboptimal due to many

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reasons. Chronic obstructive pulmonary disease (COPD) is present in about one third of CHF patients and is among key factors for underprescription and underdosing of beta blockers.⁴⁻⁶ Although concern about precipitating respiratory deterioration exists, clinical significance remains poorly determined.

Among the pharmacologically distinct agents carvedilol, bisoprolol, metoprolol, and nebivolol, some differences in side effect profile due to cardioselectivity exist.⁷ Most large-scale CHF trials excluded patients with COPD,⁸ thus safety and efficacy data is largely derived from observational studies which suggest that beta blockers are beneficial.^{9,10} Only few studies evaluated pulmonary function in patients with CHF and even less compared effects of different beta blockers in coexisting COPD.¹¹⁻¹⁴ It was shown that bisoprolol causes reduction in pulmonary function test parameters but without change in symptoms and quality of life.¹⁵ Further studies suggest differences in pulmonary effects between selective and non-selective beta blockers^{9,12} but the results are not conclusive.

No study prospectively evaluated effects of selective and non-selective beta blockers, titrated to target or maximal tolerated dose in patients with coexisting CHF and COPD. In this randomized study, pulmonary and cardiovascular effects of bisoprolol and carvedilol were compared in beta blocker naïve patients.

Methods

Study design and patients

This randomized open-label study was conducted at the Department of Internal Medicine, General Hospital Murska Sobota, and at the Division of Cardiology, University Clinic or Respiratory and Allergic Diseases Golnik, both in Slovenia. Eligible patients with established CHF (LVEF $\leq 40\%$) and COPD according to guidelines^{3,16} were included if clinically stable and beta blocker naïve. Principal exclusion criteria were cardiovascular contraindications to beta blocker therapy (atrioventricular block greater than 1st degree without a pacemaker, bradycardia <60 beats per minute, hypotension defined as systolic blood pressure <100 mmHg, symptomatic peripheral obstructive artery disease at rest, acute heart failure), and those with history of asthma. After baseline investigations, patients were randomly assigned to bisoprolol and carvedilol in a 1:1 fashion. Beta blocker was uptitrated by doubling the dose every 2-4 weeks and patients were titrated to target or maximal tolerated dose, followed by a 4-6 weeks maintenance phase. Study protocol was approved by the national Ethics Committee; study subjects received written and verbal information about the study and signed informed consent form prior to any study related procedure.

Investigations and data collection

Baseline investigations prior to beta blocker initiation and after the maintenance phase included demographic characteristics, patient history, physical examination, 12-lead electrocardiogram, laboratory investigations, 6-minute walk test, echocardiography, and pulmonary function testing. Echocardiography was performed according to Heart Failure Association guidelines.³ At titration visits,

patient history, physical examination, and 12-lead electrocardiogram were performed routinely. At follow-up visit, pulmonary function testing and laboratory investigations were added. Laboratory investigations included NT-pro brain natriuretic peptide (NT-proBNP), haemoglobin, creatinine, and potassium. Spirometry was performed in accordance with guidelines¹⁶ and following parameters were measured: the forced expiratory volume in 1st second (FEV1), vital capacity (VC), and peak expiratory flow (PEF).

Statistical analysis

Continuous variables are presented as mean value \pm standard deviation or as median (interquartile range). Categorical variables are presented as absolute number and percentages. Primary outcome measure was FEV1, and secondary outcome measures were other measures of pulmonary function, heart rate from resting 12-lead electrocardiogram, and NT-proBNP. To evaluate the differences between patients treated with bisoprolol and carvedilol, the Student's t-test, chi-square test, and Mann Whitney U test were used as appropriate. Baseline and follow-up results were compared with paired t-test. Statistical analyses were performed on SPSS for Windows version 16.0 (SPSS Inc., Chicago, IL) and Prism 5 for Windows (GraphPad Software, Inc., San Diego, CA).

Results

Patient characteristics

We included 63 elderly patients (73 ± 9 years), who were predominantly male (81% men). Important co morbidities included ischemic heart disease and arterial hypertension, patients had average left ventricular fraction of $33 \pm 7\%$, and were in NYHA class II (54%) or III (46%). According to GOLD, pulmonary function was moderately (76%) or severely (24%) impaired with a FEV1 of 1631 ± 452 ml ($60 \pm 13\%$ of predicted). At baseline, there were no significant differences between patients randomized to bisoprolol (N=32) and carvedilol (N=31) - Table 1.

Pulmonary and cardiovascular outcomes

Table 2 and Figure 1 present pulmonary function parameters at baseline and at follow-up. FEV1 significantly increased in the bisoprolol (1561 ± 414 ml to 1698 ± 519 ml, $p=0.046$) but not in the carvedilol (1704 ± 484 to 1734 ± 548 , $p=0.44$) group - Table 2 and Fig. 1. FEV1 increased in 66% and 48% of patients receiving bisoprolol and carvedilol, and 7 patients (3 bisoprolol, 4 carvedilol) had at least 12% reduction of FEV1. Differences in other pulmonary function parameters were not significant (Table 2). Bisoprolol (75 ± 14 to 68 ± 10 beats/minute, $p=0.007$) and carvedilol (78 ± 14 to 72 ± 12 beats/minute, $p=0.016$) significantly reduced the heart rate but the difference between agents was not significant (Fig. 2).

No significant difference from baseline to follow-up and between the agents was observed for systolic and diastolic blood pressure. An increase in NT-proBNP concentration was detected in 52% and 63% of patients receiving bisoprolol (1210 ± 1256 to 1259 ± 1463 pg/mL, $p=0.86$) and carvedilol (1340 ± 1296 to 1531 ± 1507 pg/mL, $p=0.24$) but the differences were not significant (Fig. 3).

Table 1
Patient baseline characteristics

	Bisoprolol (N = 32)	Carvedilol (N = 31)	p
Age [years]	72±8	73±9	0.77
Men	25 (78%)	26 (84%)	0.56
Body mass index [kg/m ²]	27.8±3.9	26.8±5.4	0.38
Heart rate [beats/min]	75±15	78±13	0.66
Systolic blood pressure [mmHg]	134±19	134±20	0.43
Diastolic blood pressure [mmHg]	80±12	78±11	0.61
6-minute walk distance [m]	303±71	302±110	0.26
New York Heart Association class II/III	17/15 (53%/47%)	17/14 (55%/45%)	0.89
Left ventricular ejection fraction [%]	33±7	32±8	0.27
Global Obstructive Lung Disease stage II/III	24/8 (75%/25%)	24/7 (77%/23%)	0.82
Forced expiratory volume in 1 st second [ml]	1561±414	1704±484	0.20
Vital capacity [ml]	2630±715	2819±608	0.12
Current/Ex smoker	26 (81%)	26 (84%)	0.78
Ischemic heart disease	23 (72%)	20 (65%)	0.53
Arterial hypertension	26 (81%)	23 (74%)	0.50
Diabetes mellitus	10 (31%)	11 (35%)	0.72
Atrial fibrillation	7 (22%)	5 (16%)	0.56
Haemoglobin [g/L]	141±11	137±16	0.24
Creatinine [μmol/L]	114±36	118±33	0.80
Potassium [mmol/L]	4.5±0.5	4.5±0.4	0.91
Cardiovascular therapy			
Angiotensin converting enzyme inhibitors	28 (88%)	26 (84%)	0.68
Loop diuretics	22 (69%)	18 (58%)	0.38
Spironolactone	13 (41%)	9 (29%)	0.33
Pulmonary inhalative therapy			
Short acting beta agonist	29 (91%)	29 (94%)	0.67
Long acting beta agonist	20 (62%)	18 (58%)	0.72
Inhaled corticosteroids	19 (59%)	18 (58%)	0.92
Anticholinergic agent	21 (66%)	19 (61%)	0.72

Data are presented as mean±standard deviation, or number (percentage).

Table 2
Respiratory function outcomes

	Bisoprolol (N = 32)	Carvedilol (N = 31)	p
Forced expiratory volume in 1 st second [%]			
Baseline	58±12	62±14	0.36
Follow-up	65±16	64±18	0.74
p	0.01	0.29	
Vital capacity [%]			
Baseline	75±16	78±14	0.59
Follow-up	81±19	77±16	0.28
p	0.13	0.47	
Peak expiratory flow [ml/s]			
Baseline	438±179	430±178	0.72
Follow-up	465±195	454±220	0.54
p	0.24	0.15	

Data are presented as mean±standard deviation.

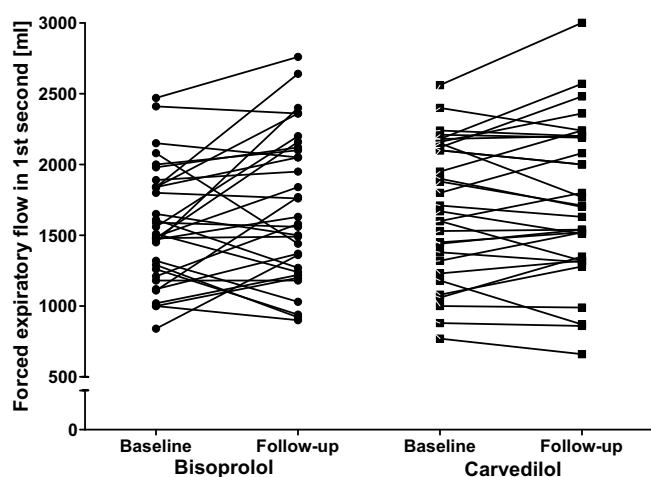


Fig. 1. Forced expiratory volume in 1st second at baseline and at follow-up.

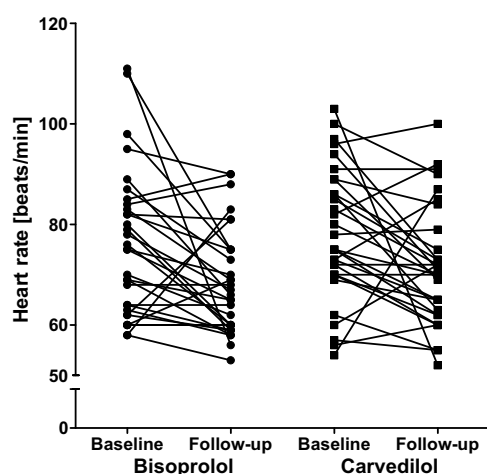


Fig. 2. Heart rate at baseline and at follow-up.

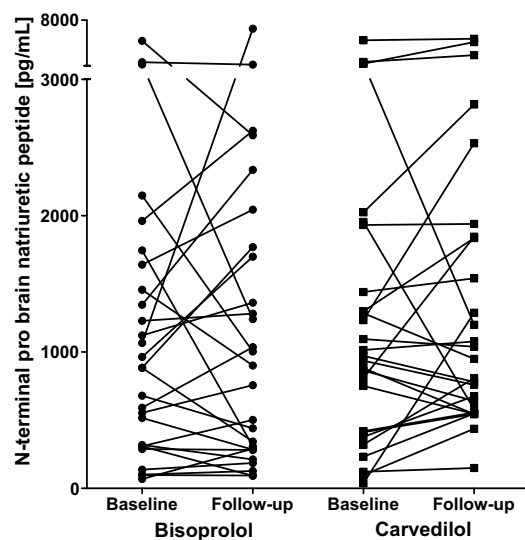


Fig. 3. N-terminal brain natriuretic peptide at baseline and at follow-up.

Titration and adverse events

The mean daily dose of bisoprolol and carvedilol at follow-up was 6.4 and 47mg, respectively. Target dose was tolerated by 49% of patients (56% bisoprolol, 42% carvedilol). During follow-up, 24 adverse events in 19 (30%) patients were reported: 6 (19%) on bisoprolol and 13 (42%) on carvedilol ($p=0.045$). Most of them were mild and transient and no measures were needed. Study medication had to be withdrawn in 8 (13%) patients (bisoprolol: 2 due to hypotension, 1 due to bradycardia; carvedilol: 2 due to hypotension and 1 due to wheezing, dyspnoea, and oedema, respectively). During titration, study drug dose had to be reduced in 10 (16%) patients and titration was temporarily interrupted in 19 (30%) patients.

Discussion

Initiation and uptitration of beta blockers in patients with coexisting CHF and COPD to target or maximal tolerated dose was possible in 87% of patients and 49% reached target dose. Adverse events and study medication withdrawal were more frequent in carvedilol group. Cardiovascular effects were similar; however, bisoprolol had more favorable effects on pulmonary function and caused less pulmonary adverse events.

Airway obstruction during treatment with beta blockers is mediated through interference with β_2 -receptor mediated bronchodilatation⁷ and remains a valid concern. Due to pharmacological properties, such events are more frequent but not limited to non-selective agents (e.g. carvedilol), which are up to 120 times less selective for β_1 - than β_2 -receptor than selective agents (e.g. bisoprolol).¹⁷ Indeed, in patients with CHF and moderate to severe COPD, bisoprolol significantly reduced FEV1 when compared to placebo.¹⁵ However, no symptom deterioration, quality of life reduction, or drug discontinuation was needed, which again suggests individual evaluation of side effects. In a recent trial that included 35 patients with coexisting COPD and CHF, carvedilol caused significant FEV1 reduction which was well tolerated.¹¹ Bisoprolol, on the other hand, induced FEV1 increase and the difference between agents was also significant (mean difference 150 ml, 95% CI +40 to +260 ml, $p < 0.01$). Long acting beta agonists like salbutamol, are COPD mainstay therapy, and were prescribed to 60% of our patient cohort. In this context, study by Agostoni et al. is relevant.¹⁸ Response to salbutamol was tested in 53 CHF patients on background beta blocker therapy and it was significantly higher in patients on bisoprolol when compared to carvedilol ($p=0.04$). We share the observations with previous studies about pulmonary test findings and pulmonary adverse events. Bisoprolol increased FEV1 whereas carvedilol induced no significant changes but the clinical relevance should be assessed individually. In many cases, the benefits could outweigh risks and patients should not be withheld this life saving therapy.¹⁹ Even in reversible airway obstruction, this could be the case: according to Kotlyar et al.,²⁰ 50% of asthma patients tolerated non-selective beta blockade with carvedilol.

Coexisting COPD in patients with CHF has important therapeutic and prognostic implications. Although not a valid contraindication, clinicians frequently withhold beta blockers in patients with COPD due to concern of pulmonary

and other deteriorations. Beta blockers induce worsening of clinical symptoms and signs in most patients but this frequently is mild and transient event. Natriuretic peptides seem to follow the clinical course of transient increase in serum concentration,²¹ a pattern not too different as observed with our baseline and follow-up measurement. Guideline translation in frail and high-risk patients may therefore be prolonged and more caution should be taken in titration decisions. Crucial step seems to be therapy initiation which is less likely to be performed by inexperienced personnel. Once started on the beta blocker, titration intervals and daily dose can be adjusted to the patient. Due to the system capacity, which outside of specialized settings like heart failure clinics may not allow for two week titration visits,²² titration interval is prolonged which may in fact be beneficial for the patients. The SATELLITE survey²³ tried to resemble clinical practice: 531 physicians (61% cardiologist, 38% internists) started carvedilol in 3721 CHF patients (mean age 65 years, 60% men), and up-titration decisions were left to the attending physician. At 6 months the mean daily dose of carvedilol was 31 ± 11 mg whereas 50 mg and 25 mg were prescribed to 26% and 35%, respectively. During study period of 6 months, 11% reported adverse events but withdrawal or substitution for another agent was needed only in 1.4% of patients.

Limitations

This study has to be interpreted in view of some limitations. It was an open label study in a relatively small number of patients which however is not different from previous studies.⁶ We also cannot entirely exclude contribution of left ventricular dysfunction and CHF deterioration to pulmonary function results. This however may be unlikely in view of few adverse events due to heart failure deterioration and no apparent differences in NT-proBNP.

Conclusions and clinical implications

Patients with CHF due to left ventricular systolic dysfunction and coexistent COPD should not be withheld life saving therapy with beta blockers. Our study, along with previous reports, demonstrates that these patients are able to tolerate beta blockers. In clinical practice, a slower titration with more frequent follow-up visits and additional considerations about beta blocking agent selection is warranted. In this particular patient subgroup, pulmonary function testing and, in some cases, referral to pneumologist may be necessary to individually tailor guideline suggested management.

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Conflict of interest statement

The authors declare that they have no competing interest.

References

1. von Haehling S, Lainscak M, Doehner W, Ponikowski P, Rosano G, Jordan J, et al. Diabetes mellitus, cachexia and obesity in heart failure: rationale and design of the Studies Investigating Co-morbidities Aggravating Heart Failure (SICA-HF). *J Cachexia Sarcopenia Muscle* 2010;1:187-94.
2. von Haehling S, Anker SD. Cachexia as a major underestimated and unmet medical need: facts and numbers. *J Cachexia Sarcopenia Muscle* 2010;1:1-5.
3. Dickstein K, Cohen-Solal A, Filippatos G, McMurray JJ, Ponikowski P, Poole-Wilson PA, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the diagnosis and treatment of acute and chronic heart failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). *Eur J Heart Fail* 2008;10:933-89.
4. Flu W-J, van Gestel YRBM, van Kuijk J-P, Hoeks SE, Kuiper R, Verhagen HJM, et al. Co-existence of COPD and left ventricular dysfunction in vascular surgery patients. *Respir Med* 2010;104:690-6.
5. Lainscak M, Cleland JG, Lenzen MJ, Follath F, Komajda M, Swedberg K. International variations in the treatment and comorbidity of left ventricular systolic dysfunction: data from the EuroHeart Failure Survey. *Eur J Heart Fail* 2007;9:292-9.
6. Hawkins NM, Petrie MC, Jhund PS, Chalmers GW, Dunn FG, McMurray JJV. Heart failure and chronic obstructive pulmonary disease: diagnostic pitfalls and epidemiology. *Eur J Heart Fail* 2009;11:130-9.
7. Matera MG, Martuscelli E, Cazzola M. Pharmacological modulation of β -adrenoceptor function in patients with coexisting chronic obstructive pulmonary disease and chronic heart failure. *Pulm Pharm Ther* 2010;23:1-8.
8. Hawkins NM, Petrie MC, MacDonald MR, Jhund PS, Fabbri LM, Wikstrand J, et al. Heart failure and chronic obstructive pulmonary disease: the quadrangy of beta-blockers and beta-agonists. *J Am Coll Cardiol* 2011;57:2127-38.
9. Gottlieb SS, McCarter RJ, Vogel RA. Effect of beta-blockade on mortality among high-risk and low-risk patients after myocardial infarction. *N Engl J Med* 1998;339:489-97.
10. Sin DD, McAlister FA. The effects of beta-blockers on morbidity and mortality in a population-based cohort of 11,942 elderly patients with heart failure. *Am J Med* 2002;113:650-6.
11. Jabbour A, MacDonald PS, Keogh AM, Kotlyar E, Mellekmjaer S, Coleman CF, et al. Differences between beta-blockers in patients with chronic heart failure and chronic obstructive pulmonary disease. *J Am Coll Cardiol* 2010;55:1780-7.
12. Galatius S, Gustafsson F, Atar D, Hildebrandt PR. Tolerability of beta-blocker initiation and titration with bisoprolol and carvedilol in congestive heart failure—a randomized comparison. *Cardiology* 2004;102:160-5.
13. Maack C, Elter T, Nickenig G, et al. Prospective crossover comparison of carvedilol and metoprolol in patients with chronic heart failure. *J Am Coll Cardiol* 2001;38:939-46.
14. Düngen HD, Apostolovic S, Inkrot S, Tahirovic E, Töpper A, Mehrhof F, et al.; on behalf of the CIBIS-ELD investigators and Project Multicentre Trials in the Competence Network Heart Failure. Titration to target dose of bisoprolol vs. carvedilol in elderly patients with heart failure: the CIBIS-ELD trial. *Eur J Heart Fail* 2011;13:670-80.
15. Hawkins NM, MacDonald MR, Petrie MC, Chalmers GW, Carter R, Dunn FG, et al. Bisoprolol in patients with heart failure and moderate to severe chronic obstructive pulmonary disease: a randomized controlled trial. *Eur J Heart Fail* 2009;11:684-90.
16. Rabe KF, Hurd S, Anzueto A, Barnes PJ, Buist SA, Calverley P, et al.; for the Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management,

- and prevention of chronic obstructive pulmonary disease: GOLD executive summary. *Am J Respir Crit Care Med* 2007;176:532-55.
17. Bristow MR. Changes in myocardial and vascular receptors in heart failure. *J Am Coll Cardiol* 1993;22:61A-71A.
 18. Agostoni P, Contini M, Cattadori G, Apostolo A, Sciomer S, Bussotti M, et al. Lung function with carvedilol and bisoprolol in chronic heart failure: is beta selectivity relevant? *Eur J Heart Fail* 2007;9:827-33.
 19. Salpeter S, Ormiston T, Salpeter E. Cardioslective beta-blockers for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2005;CD003566.
 20. Kotlyar E, Keogh AM, Macdonald PS, Arnold RH, McCaffrey DJ, Glanville AR. Tolerability of carvedilol in patients with heart failure and concomitant chronic obstructive pulmonary disease or asthma. *J Heart Lung Transplant* 2002;21:1290-5.
 21. Davis ME, Richards AM, Nicholls MG, Yandle TG, Frampton CM, Troughton RW. Introduction of metoprolol increases plasma B-type cardiac natriuretic peptides in mild, stable heart failure. *Circulation* 2006;113:977-85.
 22. McDonagh TA, Blue L, Clark AL, Dahlström U, Ekman I, Lainscak M, et al.; on behalf of Heart Failure Association Committee on Patient Care. European Society of Cardiology Heart Failure Association Standards for delivering heart failure care. *Eur J Heart Fail* 2011;13:235-41.
 23. Lainscak M, Moullet C, Schön N, Tendera M. Treatment of chronic heart failure with carvedilol in daily practice: the SATELLITE survey experience. *Int J Cardiol* 2007;122:149-55.