ELSEVIER

European Journal of Heart Failure 9 (2007) 901–909

The European Journal of Heart Failure

www.elsevier.com/locate/ejheart

Should beta-blocker therapy be reduced or withdrawn after an episode of decompensated heart failure? Results from COMET ☆

Marco Metra [a,*], Christian Torp-Pedersen [b], John G.F. Cleland [c], Andrea Di Lenarda [d], Michel Komajda [e], Willem J. Remme [f], Livio Dei Cas [a], Philip Spark [g], Karl Swedberg [h], Philip A. Poole-Wilson [i] for the COMET investigators [1]

[a] *Section of Cardiovascular diseases; Department of Experimental and Applied Medicine, University of Brescia, Italy*
[b] *Department of Cardiology, Bispebjerg University Hospital, Copenhagen, Denmark*
[c] *Department of Cardiology, University of Hull, Kingston upon Hull, UK*
[d] *Department of Cardiology, Ospedale di Cattinara, Trieste, Italy*
[e] *Department of Cardiology, La Pitié-Salpétrière Hospital, Paris, France*
[f] *Sticares Cardiovascular Research Foundation, Rhoon, The Netherlands*
[g] *Nottingham Clinical Research Group, Nottingham, UK*
[h] *Department of Emergency and Cardiovascular Medicine, Sahlgrenska Academy, Göteborg University, Göteborg, Sweden*
[i] *National Heart and Lung Institute, Imperial College London, UK*

Received 30 December 2005; received in revised form 4 February 2007; accepted 16 May 2007
Available online 19 June 2007

Abstract

Background: It is unclear whether beta-blocker therapy should be reduced or withdrawn in patients who develop acute decompensated heart failure (HF). We studied the relationship between changes in beta-blocker dose and outcome in patients surviving a HF hospitalisation in COMET.
Methods: Patients hospitalised for HF were subdivided on the basis of the beta-blocker dose administered at the visit following hospitalisation, compared to that administered before.
Results: In COMET, 752/3029 patients (25%, 361 carvedilol and 391 metoprolol) had a non-fatal HF hospitalisation while on study treatment. Of these, 61 patients (8%) had beta-blocker treatment withdrawn, 162 (22%) had a dose reduction and 529 (70%) were maintained on the same dose. One-and two-year cumulative mortality rates were 28.7% and 44.6% for patients withdrawn from study medication, 37.4% and 51.4% for those with a reduced dosage (n.s.) and 19.1% and 32.5% for those maintained on the same dose (HR,1.59; 95%CI, 1.28–1.98; $p<0.001$, compared to the others). The result remained significant in a multivariable model: (HR, 1.30; 95%CI, 1.02–1.66; $p=0.0318$). No interaction with the beneficial effects of carvedilol, compared to metoprolol, on outcome was observed ($p=0.8436$).
Conclusions: HF hospitalisations are associated with a high subsequent mortality. The risk of death is higher in patients who discontinue beta-blocker therapy or have their dose reduced. The increase in mortality is only partially explained by the worse prognostic profile of these patients.

Keywords: Decompensated heart failure; Trials; Beta-blockers

1. Introduction

Randomised clinical trials have shown the beneficial effects of beta-blockers in the treatment of patients with relatively stable, symptomatic chronic heart failure (HF) due to left ventricular (LV) systolic dysfunction [1–6]. Despite

☆ Source of funding: COMET was supported by F Hoffmann La Roche and GlaxoSmithKline.
* Corresponding author. Cattedra di Cardiologia, c/o Spedali Civili, P.zza Spedali Civili, 25123 Brescia, Italy. Tel.: +39 030 3995572; fax: +39 030 3700359.
E-mail address: metramarco@libero.it (M. Metra).
[1] The COMET investigators are listed in a previous paper (1).

1388-9842/$ - see front matter © 2007 European Society of Cardiology. Published by Elsevier B.V.
doi:10.1016/j.ejheart.2007.05.011

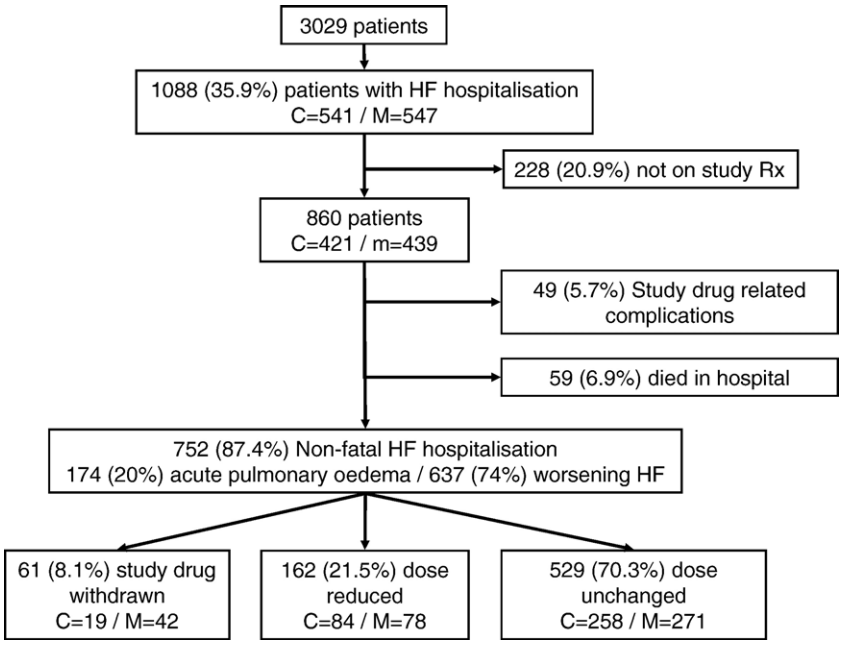

Fig. 1. Flow chart showing number of patients, follow-up and changes in study drug dosages for patients hospitalised for heart failure in COMET. Abbreviations: C = carvedilol; M = metoprolol; HF = heart failure.

the benefits of medical treatment many patients progress to advanced HF and are hospitalised for HF decompensation. When this occurs, beta-blockers are often reduced or discontinued [7–9] as it is thought that this will improve worsening dyspnoea, fatigue and/or hypotension, which may be exacerbated by the short-term negative inotropic effects of beta-blockade [10,11]. On the other hand, randomised controlled trials have shown that the beneficial effects of beta-blockers also occur among patients with severe HF. [2,12–15] Randomised trials, however, include selected patient populations. Even the patients included in the Carvedilol Prospective Randomized Cumulative Survival Study (COPERNICUS) had to be clinically stable with no need of i.v. therapy for at least 4 days before randomisation. We therefore have no definitive results about the effects of beta-blocker therapy on outcome in patients who have been recently hospitalised for decompensated HF.

In the Carvedilol or Metoprolol European Trial (COMET), 3029 patients with chronic HF were randomised to carvedilol or metoprolol tartrate and followed up for a median of 58 months [16]. This trial represents a unique possibility to assess the effects on outcome of a change in beta-blocker therapy after an episode of HF hospitalisation. In the present study we assessed the prognostic role of a change in the beta-blocker dose after a HF hospitalisation in the COMET patients.

2. Methods

The COMET design has been published [16,17]. In brief, COMET was a multicenter, randomised, double-blind, parallel-group trial comparing the effect on mortality and morbidity of carvedilol and metoprolol tartrate in patients with symptomatic chronic HF (NYHA class II–IV), LV ejection fraction (EF) ≤ 35%, at least one cardiovascular hospitalisation during the 2 years before trial entry, optimal baseline therapy, including the need for diuretic therapy. COMET was designed as an event-driven study with the co-primary endpoints of all-cause mortality and the combined endpoint of mortality or hospitalisation for any cause. Patients were randomised to carvedilol or metoprolol tartrate and received initial doses of 3.125 mg or 5 mg twice daily (bid) respectively. Doses were doubled at 2 week intervals, aiming for target doses of 25 mg bid of carvedilol and 50 mg bid of metoprolol tartrate. When patients reached the target or the maximally tolerated dose, the maintenance phase began. During this phase, every patient underwent clinical assessment every 4 months.

Hospitalisations were defined as any admission that required at least one overnight stay in the hospital [17,18]. The causes of admission were classified by the investigator on the case report form. Hospitalisations were differentiated as cardiovascular or non-cardiovascular. Causes of cardiovascular hospitalisations included HF, unstable angina, suspected myocardial infarction, stroke, or others. Three clinical presentations of HF hospitalisations were considered: worsening HF, acute pulmonary oedema and complications of drug treatment. Since this last category included only a few events (49 patients, 5.7%), unrelated to HF (hypotension, dizziness, bradycardia), we excluded them from data analysis.

To assess the prognostic significance of the change in the beta-blocker dose after a HF hospitalisation, we compared the dose of beta-blocker administered at the visit following

Table 1
Baseline characteristics of COMET patients hospitalised for heart failure according to changes in study drug doses

	All $n=752$	Withdrawn or reduced $n=223$	Unchanged $n=529$	p value withdrawn or reduced versus unchanged
Age (years)	64±11	65±10	64±11	0.278
Sex (% male)	76	70	78	0.025
Race (% white)	99	99	99	0.635
Body Mass Index (kg/m^2)	27±4	26±4	27±5	0.220
Systolic BP (mm Hg).	124±20	122±20	124±20	0.062
Diastolic BP (mm Hg)	76±11	75±11	76±11	0.445
Heart rate (bpm)	81±13	83±13	81±13	0.111
NYHA class (%)				
II	40	32	42	0.035
III	56	63	53	
IV	6	5	6	
Duration CHF (months) mean/median	51/32	53/30	51/32	0.574
Aetiology (%)				
Ischaemic heart disease	60	58	60	0.608
Hypertension	18	13	20	0.032
Dilated cardiomyopathy	39	39	39	0.908
Previous valve surgery	4	2	4	0.197
LV ejection fraction (%)	25.1±7.2	24.1±7.0	25.5±7.3	0.018
NT-proBNP (pg/ml) median	1890	2280	1771	0.797
Associated diagnosis (%)				
Previous myocardial infarction	48	49	48	0.948
CAD (by angiography)	65	67	64	0.470
Current angina	25	21	27	0.070
Hypertension	39	38	39	0.711
Diabetes	33	33	32	0.800
Stroke	9	8	9	0.763
ECG findings (%)				
Sinus rhythm	71	69	72	0.294
Atrial fibrillation/flutter	22	23	21	0.554
Paced rhythm	8	9	8	0.563
% LBBB	6	7	6	0.651
Concomitant medications (%)				
Diuretics	99	99	99	0.623
ACE Inhibitors	91	89	92	0.150
ARBs	6	6.7	5.7	0.577
Digitalis	62	66	60	0.097
Antiarrhythmics	14	17	12	0.083
Nitrates	39	35	41	0.010
Aldosterone antagonists	14	17	13	0.154
Beta-blockers	5	4	5	0.408
Anticoagulants	48	46	49	0.367
Aspirin	38	38	38	0.975
Statins	21	18	23	0.172

Abbreviations: % = percentage of patients; BP = blood pressure; CAD = coronary artery disease; CHF = heart failure; LV = left ventricular; LBBB = left bundle branch block; ARBs = angiotensin receptor blockers; BB = beta-blockers; HR = heart rate. Beta-blockers refer to patients receiving beta-blockers before entry into the trial.

the HF hospitalisation with the dose administered at the visit before the HF hospitalisation. Patients were subdivided in three groups: those who received the same dose before and after the HF hospitalisation; those who had a dose reduction of at least one level at the visit after the hospitalisation; and those who were withdrawn from the study drug. Dose levels were the following: 3.125 mg bid, 6.25 mg bid, 12.5 mg bid, and 25 mg bid for carvedilol, and 5 mg bid, 12.5 mg bid, 25 mg bid, and 50 mg bid for metoprolol.

2.1. Statistical analysis

Results are expressed as mean±SD unless otherwise specified. All hypothesis tests reported are two-sided and use a p-value <0.05 as significant. Differences were assessed by t-tests for continuous variables and by chi-squared test for categorical data. Kaplan–Meier survival estimates were calculated.

To assess the impact of the change in beta-blocker dose on mortality after the HF hospitalisation, changes in the beta-

Table 2
Clinical characteristics of the patients at the visit before the heart failure hospitalisation according to changes in study drug doses

	All $n=752$	Withdrawn or reduced dose $n=223$	Unchanged $n=529$	p value withdrawn or reduced versus unchanged
NYHA class (%)				0.044
I	5	3	6	
II	39	34	41	
III	46	53	43	
IV	9	9	9	
Orthopnoea (%)	23	29	21	0.014
Dyspnoea (%)				0.317
Asymptomatic	8	7	9	
Walking upstairs	31	28	31	
Walking normally	32	32	32	
Walking slowly	21	26	19	
At rest	8	7	8	
Angina (%)				0.483
Yes	18	15	19	
No	82	85	81	
Well being (%)				0.039
Very good	4	4	4	
Good	28	21	31	
Average	35	41	33	
Poor	23	23	24	
Very poor	9	11	8	
Pulmonary rales (%)	17	16	18	0.504
Peripheral oedema (%)				0.315
Yes	24	21	25	
No	76	79	75	
Body weight, kg	79±16	76±15	80±16	0.006
Systolic blood pressure, mm Hg	122±21	118±21	124±21	0.001
Diastolic blood pressure, mm Hg	75±11	74±12	75±11	0.653
Study drug dose, (%)				0.008
C, 3.125 mg bid, M 5 mg bid	18	13	20	
C, 6.25 mg bid; M 12.5 mg bid	17	18	16	
C, 12.5 mg bid; M 25 mg bid	16	22	13	
C, 25 mg bid; M 50 mg bid	48	45	49	
Days from randomisation to hospitalisation (%)				0.338
0–74	23	20	25	
75–385	25	28	24	
386–926	25	27	25	
>926	26	25	26	

blocker dose were included in a multivariable Cox regression model including baseline factors, shown to be important by bootstrap methods, as well as variables collected at the visit before the hospitalisation and causes of hospitalisation that differed significantly between the beta-blocker dose groups. The baseline variables included in the model are those retained in ≥70% of the models generated by backward regression from 200 bootstrap samples of the patients in the study, i.e. random samples of 3029 patients with replacement. No data are available regarding patients' symptoms and treatment during the HF hospitalisation. The variables entered into the multivariable model were: age, sex, systolic blood pressure, NYHA class, HF duration, LVEF, serum creatinine, sodium, and haemoglobin levels, cardiac rhythm (sinus, paced, atrial fibrillation), furosemide dose, administration of antiarrhythmics, digitalis, lipid lowering agents, study drug, amongst the variables assessed at baseline; body weight, systolic blood pressure, NYHA class, orthopnoea, well being, study drug dose level, amongst the variables assessed at the visit prior to the HF hospitalisation; acute pulmonary oedema, and worsening HF, amongst the causes of the hospitalisation; and, finally, study drug dose change or withdrawal.

The adjusted mortality curves in Fig. 3B are produced from the survivor function of the multivariate Cox regression analysis. The beta-blocker dose variable (reduced/withdrawn versus same dose) is a stratified variable, which results in separately shaped curves (i.e. non-proportional for each).

3. Results

3.1. Follow-up

In COMET, 3029 patients were randomised to carvedilol (1511 patients) or metoprolol tartrate (1518 patients) and followed for a median of 58 months (interquartile range 54 to

Table 3
Reasons for admission and precipitating factors causing heart failure hospitalisation

	Withdrawn	Reduced dose	Same dose	*p* value
	N=61	*N*=162	*N*=529	
Reason for admission				
Acute pulmonary oedema (%)	36.1	20.4	13.6	<0.001
Progressive WHF (%)	78.7	85.2	89.8	0.021
Cause of WHF hospitalisation				
Ischaemia (%)	16.4	19.8	17.2	0.730
Atrial fibrillation (%)	14.8	18.5	11.3	0.057
Infection (%)	3.3	10.5	10.6	0.191
Non-compliance (%)	4.9	6.2	4.5	0.702
Renal dysfunction (%)	9.8	5.6	4.9	0.276
Other (%)	44.3	47.5	49.0	0.768
Alcohol excess (%)	1.6	0.0	0.6	0.318
Dietary salt excess (%)	3.3	5.6	3.6	0.513
Hypertension (%)	3.3	5.6	5.3	0.775
Iatrogenic (%)	11.5	5.6	5.9	0.211

More than one causes could be adjudicated. Abbreviations: WHF = worsening heart failure.

64). Follow-up was complete for all patients except 5 who were lost to follow-up and 28 patients who withdrew their consent during the trial [16]. Patient flow is shown in Fig. 1. Amongst the 3029 patients included in COMET, 1088 (35.9%, 541 on carvedilol and 547 on metoprolol) were hospitalised for HF. Of these, 228 patients (20.9%) were excluded from analysis as they were not on study medication at the time of hospitalisation. The cause of the HF hospitalisation of the remaining 860 patients (421 on carvedilol and 439 on metoprolol) was adjudicated as acute pulmonary oedema, worsening HF and study drug related complications in 174 (20%), 637 (74%) and 49 (6%) patients, respectively. Fifty-nine patients (7%) died during the initial hospitalisation.

Further analysis is limited to the 752 patients who had a non-fatal HF hospitalisation caused by acute pulmonary oedema or worsening HF. Amongst them, 61 patients (8.1%, 19 on carvedilol and 42 on metoprolol) were withdrawn from their study medication, 162 (21.5%, 84 on carvedilol and 78 on metoprolol) had a reduction in their study drug dose, and 529 (70.3%, 258 on carvedilol and 271 on metoprolol) were maintained on the same study drug dose at the visit following the HF hospitalisation, compared to before. Overall, patients receiving carvedilol were less likely to be withdrawn from study medication or have a dose reduction, compared to those on metoprolol ($p=0.018$).

3.2. Clinical characteristics.

The characteristics of the patients' hospitalised for HF, subdivided on the basis of changes in their beta-blocker dose, are shown in Tables 1 and 2. Since there were no differences between patients withdrawn from study medication and those who had the dose reduced, these two groups are shown together. At baseline, the patients withdrawn from study medication or who had a dose reduction were less likely to be males, had more severe symptoms (NYHA class) and more severe LV systolic dysfunction (LVEF), compared to those who had their beta-blocker dose unchanged (Table 1). At the visit prior to the HF hospitalisation, patients withdrawn from study drug treatment or who reduced their beta-blocker dose had more severe symptoms (NYHA class), a higher prevalence of orthopnoea, poorer well being, a lower body weight and a lower systolic blood pressure.

The duration of the initial hospitalisation was longer in the patients who were withdrawn or had a dose reduction, compared to the others: 27±53 days; median, interquartile range (IQR), 17, 7–28 days in those withdrawn, 11±9 days,

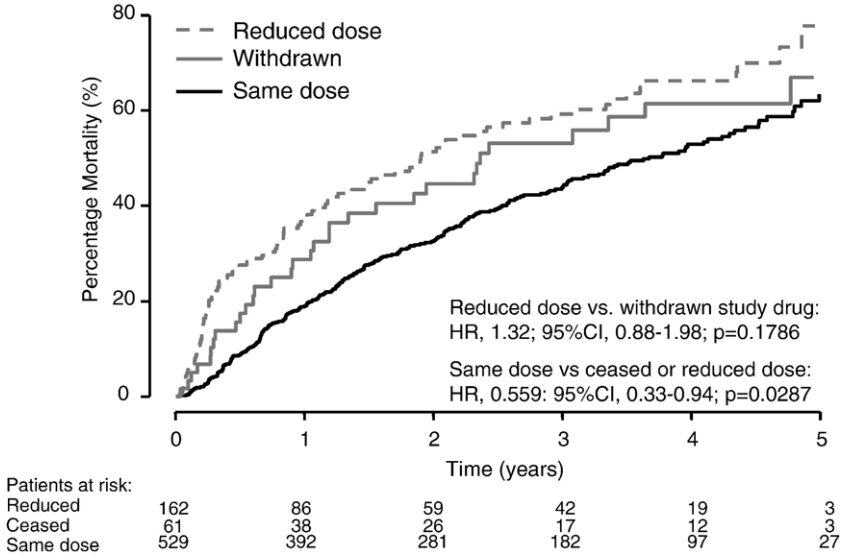

Fig. 2. Kaplan–Meier curves of mortality subsequent to discharge for the patients who had an admission for HF, according to whether study medication was withdrawn, the dose was dose reduced or the dose was left unchanged (same dose).

Table 4
Variables predictive of all cause mortality post heart failure hospitalisation at multivariable analysis

	HR	95% CI	*p*
Baseline variables			
Increasing age (years)	1.035	1.022–1.048	<0.0001
Female versus male	0.749	0.558–1.006	0.0548
Increasing HF duration (months)	1.003	1.001–1.005	0.0006
Increasing LVEF	0.975	0.959–0.99	0.0017
Increasing serum creatinine (μmol/L)	1.003	1.001–1.004	0.0002
Increasing serum sodium (mmol/L)	0.974	0.948–1.000	0.0504
ECG: sinus rhythm versus paced	1.436	0.991–2.08	0.0558
Diuretic dose 81–160 versus ≤40 mg/day	1.591	1.163–2.178	0.0037
Diuretic dose 161–320 versus ≤40 mg/day	1.457	0.945–2.246	0.0885
Antiarrhythmics	1.671	1.217–2.296	0.0015
Digitalis	1.816	1.416–2.328	<0.0001
Lipid lowering medication	0.593	0.435–0.808	0.0009
Prior to hospitalisation			
Increasing systolic blood pressure (mm Hg)	0.984	0.977–0.991	<0.0001
Study drug (beta-blocker) dose change			
Reduced/withdrawn versus same dose	1.302	1.023–1.656	0.0318

median, IQR, 8, 5–14 days in those with dose reduction versus 9±8 days, median, IQR, 7, 4–12 days in those with dose unchanged ($p<0.0001$ versus the others).

The potential causes and precipitating factors of the HF hospitalisations are shown in Table 3. Patients withdrawn from beta-blocker therapy and, to a lesser extent, those who had a reduction in their beta-blocker dose were more likely to be admitted because of acute pulmonary oedema rather than because of progressive HF. The precipitating factors for HF hospitalisation did not differ amongst groups.

3.3. Mortality versus changes in beta-blocker dose

Hospitalisation for HF was associated with high mortality. Mortality was not different between the patients withdrawn from beta-blocker therapy and those who had a dose reduction. Thirty-two of the 61 patients (52.5%) withdrawn from the study drug died and 94 of the 162 patients (58%) who had a dose reduction also died (hazard ratio=1.32; 95% confidence intervals [CI], 0.88–1.98; $p=0.179$). These two groups were therefore combined for the purposes of comparison with patients maintained on the same dose of study drug, of whom 242 of 529 died (45.7%; HR, 1.59; 95% CI, 1.28–1.98; $p<0.0001$ for the comparison) (Fig. 2).

Patients who were maintained on the same dose of the study medication had less severe HF compared to those who had a dose reduction or who were withdrawn. However, their mortality risk remained lower after adjustment for baseline variables and variables collected at the visit before the HF hospitalisation (HR, 1.30; 95%CI, 1.02–1.66; $p=0.0318$; Table 4 and Fig. 3). The other variables which were associated with increased mortality after the HF hospitalisation at multivariable analysis were increasing age, higher serum creatinine, greater HF duration, lower serum sodium, lower LVEF, treatment with higher furosemide doses, antiarrhythmic therapy, digitalis therapy, lack of use of statins, lower systolic blood pressure at the visit prior to hospitalisation (Table 4).

To address the sensitivity of the analyses to high risk patients, they were repeated disregarding patients that died within 4 weeks of hospitalisation (8 patients). The risk of subsequent mortality remained higher in those patients that reduced or withdrew study medication compared to those that were maintained on the same dose (HR, 1.51; 95%CI, 1.22–1.89; $p<0.001$) but an adjusted analysis resulted in a non-significant difference between these groups (HR, 1.25; 95%CI, 0.98–1.60; $p=0.0711$, Table 5).

The mortality rate after hospitalisation in each group was lower amongst the patients receiving carvedilol, compared to those on metoprolol (data not shown). No interaction between the changes in dose after the HF hospitalisation and the

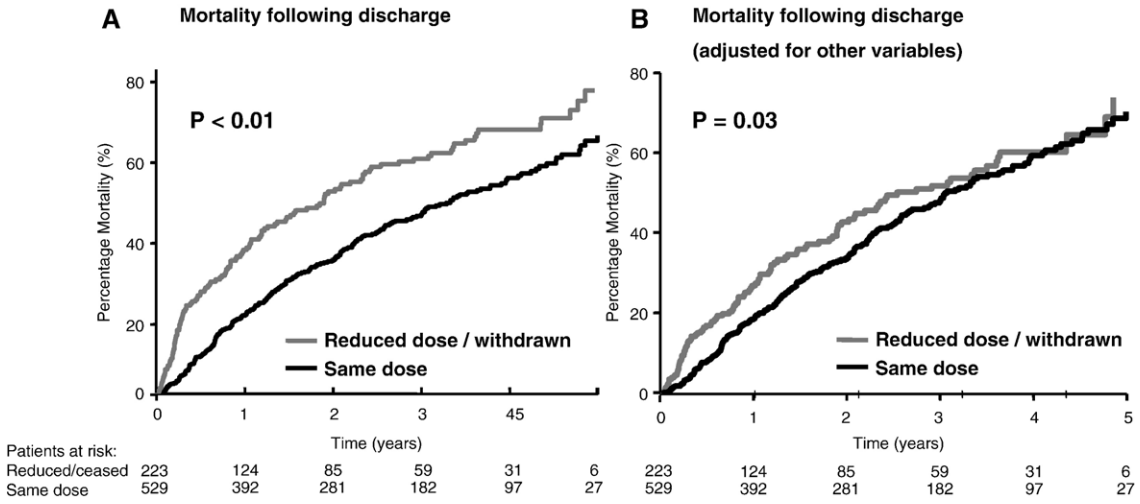

Fig. 3. Kaplan–Meier mortality curves for the patients withdrawn from study medication or who had the dose reduced compared to those who had no dose change. Mortality curves were unadjusted (3A) or adjusted (3B) for other variables related to mortality at multivariable analysis.

Table 5
Variables predictive of all cause mortality post heart failure hospitalisation at multivariable analysis after excluding subjects who died within 4 weeks of admission

Baseline variables	HR	95% CI	*p*
Increasing age (years)	1.035	1.022, 1.048	<0.0001
Female versus male	0.764	0.568, 1.028	0.0758
Increasing HF duration (months)	1.003	1.001, 1.005	0.0006
Increasing LVEF	0.973	0.958, 0.989	0.0009
Increasing serum creatinine (μmol/L)	1.003	1.001, 1.005	0.0001
Increasing serum sodium (mmol/L)	0.973	0.947, 1.000	0.0468
ECG: sinus rhythm versus paced	1.468	1.008, 2.137	0.0451
Diuretic dose 81–160 versus ≤40 mg/day	1.576	1.15, 2.161	0.0047
Antiarrhythmics	1.627	1.178, 2.249	0.0032
Digitalis	1.859	1.447, 2.39	<0.0001
Lipid lowering medication	0.593	0.434, 0.811	0.0011
Prior to hospitalisation			
Increasing systolic blood pressure (mm Hg)	0.984	0.977, 0.991	<0.0001
Study drug (beta-blocker) dose change			
Reduced/withdrawn versus same dose	1.253	0.981, 1.601	0.0711

beneficial effect on mortality of carvedilol, compared to metoprolol, was found ($p=0.8436$).

4. Discussion

4.1. Background and previous studies

Lack of prescription and use of low doses of beta-blockers may adversely affect the outcome of HF patients [19–22]. However, the prognostic significance of a dose reduction and/or withdrawal of beta-blocker therapy may differ in the patients recently hospitalised for worsening HF. In these patients, beta-blockade may theoretically have adverse effects on outcome because of its short-term negative inotropic effects. [10,11] Accordingly, symptoms of worsening HF and low cardiac output (weight gain, fatigue, hypotension) are amongst the most common reasons of discontinuation of beta-blocker therapy in clinical practice [7,8,23,24]. However, there is little information on the impact of changes in beta-blocker therapy after hospitalisation for worsening HF. A retrospective analysis of the Outcomes of the Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF) study [25] reported that, amongst 212 patients treated with beta-blockers at the time of the admission for decompensated HF, the 47 patients who permanently stopped the beta-blocker had a worse outcome [25]. The 268 of 432 patients receiving beta-blockers at the time of hospitalisation in the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization (ESCAPE) had a shorter length of stay and lower 6-month mortality rate and beta-blocker therapy remained independently associated with lower mortality at multivariable analysis [26]. The Organized Program to Initiate Lifesaving Treatment in Hospitalized patients with Heart Failure (OPTIMIZE-HF) showed that carvedilol use at the time of discharge after a HF hospitalisation is well tolerated and associated with a reduction in mortality at 60 and 90 days. [27].

4.2. Beta-blocker withdrawal or dose change in the present study

COMET is one of the largest and longest trials of patients with chronic HF on optimal medical treatment. This, therefore, allows an assessment of the relation between the changes in beta-blocker treatment and subsequent outcome. Our results show that either discontinuation or a reduction in the dose of the beta-blocker after a HF hospitalisation is associated with a worse outcome. Though stopping beta-blockers or reducing their dose was associated with more severe HF, it remained significantly and independently associated with increased mortality after adjustment for baseline variables and for variables obtained at the visit before the HF hospitalisation. Our results are consistent with recent analyses from trials [25,27] and registries [20,26] and show, in addition, that even a reduction in the beta-blocker dose may be associated with an increase in mortality.

When the patients who died in the first 4 weeks after the initial hospitalisation were excluded, discontinuation or dose reduction in beta-blockers remained associated with increased mortality at univariable but not multivariable analysis ($p=0.0711$). These results show the role of changes in beta-blocker therapy for short-term outcome. The lower significance of dose changes at multivariable analysis may be explained by the reduction in the number of events so that the power of the model to detect significant changes was reduced as well.

We did not find any difference in outcome between the patients who had beta-blocker therapy withdrawn and those who had a dose reduction. This may reflect the relatively low number of patients who were completely withdrawn from beta-blocker therapy (61 patients, 8%). On the other hand, the association between reduction in beta-blocker dose and adverse outcome is consistent with post-hoc analysis of this and other trials [19,21,22]. However, no trial has adequately, prospectively assessed whether the dose of beta-blocker has an important effect on clinical outcome.

4.3. Carvedilol versus metoprolol tartrate comparison

The COMET trial showed that carvedilol administration is associated with a lower mortality, compared to metoprolol tartrate, in patients with HF. Carvedilol did not reduce the rate of HF hospitalisation, compared to metoprolol, but its effect on mortality was observed whether or not such a hospitalisation had occurred. Our present study shows that patients assigned to carvedilol were less likely to be withdrawn from beta-blockade or have a reduction in their beta-blocker dose. This mechanism, though occurring in a relative minority of patients, is consistent with the beneficial effects on outcome of carvedilol, compared to metoprolol tartrate.

4.4. Limitations of the study

The present study is a retrospective *post-hoc* analysis of the patients who had a HF hospitalisation in COMET. In a non-randomised analysis it is not possible with certainty to distinguish between the effects of reducing beta-blockade and the reasons for which the beta-blocker was discontinued or the dose reduced. We adjusted for available variables that are markers for disease severity, but this adjustment may be incomplete. Lastly, no data regarding the clinical course and treatment during the HF hospitalisation were collected in COMET. This hinders any inference regarding the possible effects of in-hospital treatment on subsequent outcome.

5. Conclusions

We have analysed the relationship between the changes in beta-blocker dose and outcome of the HF patients studied in COMET. Hospitalisations for HF were associated with a high mortality. The patients who were withdrawn from beta-blocker therapy or who had a dose reduction had a higher mortality compared with those who had their dose unchanged, independent of prognostic variables assessed at baseline and at the visit before hospitalisation.

References

[1] Packer M, Bristow MR, Cohn JN, et al. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. U.S. Carvedilol Heart Failure Study Group. N Engl J Med 1996;334:1349–55.
[2] Packer M, Coats AJ, Fowler MB, et al. Effect of carvedilol on survival in severe chronic heart failure. N Engl J Med 2001;344:1651–8.
[3] MERIT-CHF Study Group. Effect of metoprolol CR/XL in chronic heart failure: metoprolol CR/XL randomised intervention trial in congestive heart failure (MERIT-CHF). Lancet 1999;353:2001–7.
[4] CIBIS-II Investigators and Committees. The cardiac insufficiency bisoprolol study II (CIBIS-II): a randomised trial. Lancet 1999;353:9–13.
[5] Swedberg K, Cleland J, Dargie H, et al. Guidelines for the diagnosis and treatment of chronic heart failure: executive summary (update 2005): the task force for the diagnosis and treatment of chronic heart failure of the European Society of Cardiology. Eur Heart J 2005;26:1115–40.
[6] Hunt SA, Abraham WT, Chin MH, et al. ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult—summary article a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure). J Am Coll Cardiol 2005;46:1116–43.
[7] Macdonald PS, Keogh AM, Aboyoun CL, Lund M, Amor R, McCaffrey DJ. Tolerability and efficacy of carvedilol in patients with New York Heart Association class IV heart failure. J Am Coll Cardiol 1999;33:924–31.
[8] Krum H, Ninio D, MacDonald P. Baseline predictors of tolerability to carvedilol in patients with chronic heart failure. Heart 2000;84:615–9.
[9] Gardner RS, Martin W, Carter R, McDonagh TA. Importance of beta blockade in the treatment of advanced heart failure. Heart 2003;89:1442–4.
[10] Metra M, Nardi M, Giubbini R, Dei Cas L. Effects of short- and long-term carvedilol administration on rest and exercise hemodynamic variables, exercise capacity and clinical conditions in patients with idiopathic dilated cardiomyopathy. J Am Coll Cardiol 1994;24:1678–87.
[11] Kukin L, Mannino MM, Freudenberger RS, Kalman J, Buchholz-Varley C, Ocampo O. Hemodynamic comparison of twice daily metoprolol tartrate with once daily metoprolol succinate in congestive heart failure. J Am Coll Cardiol 2000;35:45–50.
[12] Krum H, Roecker EB, Mohacsi P, et al. Effects of initiating carvedilol in patients with severe chronic heart failure: results from the COPERNICUS Study. JAMA 2003;289:712–8.
[13] Erdmann E, Lechat P, Verkenne P, Wiemann H. Results from post-hoc analyses of the CIBIS II trial: effect of bisoprolol in high-risk patient groups with chronic heart failure. Eur J Heart Fail 2001;3:469–79.
[14] Goldstein S, Fagerberg B, Hjalmarson A, et al. Metoprolol controlled release/extended release in patients with severe heart failure: analysis of the experience in the MERIT-HF study. J Am Coll Cardiol 2001;38:932–8.
[15] Bouzamondo A, Hulot JS, Sanchez P, Lechat P. Beta-blocker benefit according to severity of heart failure. Eur J Heart Fail 2003;5:281–9.
[16] Poole-Wilson PA, Swedberg K, Cleland JG, et al. Comparison of carvedilol and metoprolol on clinical outcomes in patients with chronic heart failure in the Carvedilol or Metoprolol European Trial (COMET): randomised controlled trial. Lancet 2003;362:7–13.
[17] Poole-Wilson PA, Cleland JG, Di Lenarda A, et al. Rationale and design of the carvedilol or metoprolol tartrate European trial in patients with chronic heart failure: COMET. Eur J Heart Fail 2002;4:321–9.
[18] Torp-Pedersen C, Poole-Wilson PA, Swedberg K, et al. Effects of metoprolol and carvedilol on cause-specific mortality and morbidity in patients with chronic heart failure-COMET. Am Heart J 2005;149:370–6.
[19] Metra M, Torp-Pedersen C, Swedberg K, et al. Influence of heart rate, blood pressure, and beta-blocker dose on outcome and the differences in outcome between carvedilol and metoprolol tartrate in patients with chronic heart failure: results from the COMET trial. Eur Heart J 2005;26:2259–68.
[20] Komajda M, Lapuerta P, Hermans N, et al. Adherence to guidelines is a predictor of outcome in chronic heart failure: the MAHLER survey. Eur Heart J 2005;26:1653–9.
[21] Wikstrand J, Hjalmarson A, Waagstein F, et al. Dose of metoprolol tartrate CR/XL and clinical outcomes in patients with heart failure: analysis of the experience in metoprolol tartrate CR/XL randomized intervention trial in chronic heart failure (MERIT-CHF). J Am Coll Cardiol 2002;40:491–8.
[22] Simon T, Mary-Krause M, Funck-Brentano C, Lechat P, Jaillon P. Bisoprolol dose-response relationship in patients with congestive heart failure: a subgroup analysis in the cardiac insufficiency bisoprolol study (CIBIS II). Eur Heart J 2003;24:552–9.
[23] Parameswaran AC, Tang WH, Francis GS, Gupta R, Young JB. Why do patients fail to receive beta-blockers for chronic heart failure over time? A “real-world” single-center, 2-year follow-up experience of

beta-blocker therapy in patients with chronic heart failure. Am Heart J 2005;149:921–6.
[24] Butler J, Khadim G, Belue R, et al. Tolerability to beta-blocker therapy among heart failure patients in clinical practice. J Card Fail 2003;9:203–9.
[25] Gattis WA, O'Connor CM, Leimberger JD, Felker GM, Adams KF, Gheorghiade M. Clinical outcomes in patients on beta-blocker therapy admitted with worsening chronic heart failure. Am J Cardiol 2003;91:169–74.
[26] Butler J, Young JB, Abraham WT, et al. Beta-blocker use and outcomes among hospitalized heart failure patients. J Am Coll Cardiol 2006;47:2462–9.
[27] Fonarow GC, Abraham WT, Albert NM, et al. Carvedilol use at discharge in patients hospitalized for heart failure is associated with improved survival: an analysis from Organized Program to Initiate Lifesaving Treatment in Hospitalized patients with Heart Failure (OPTIMIZE-HF). Am Heart J 2007;153:82e1–82e11.