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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

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KEYWORDS
Heart failure;
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Aims We studied the influence of heart rate (HR), systolic blood pressure (SBP), and beta-blocker dose on outcome in the 2599 out of 3029 patients in Carvedilol Or Metoprolol European Trial (COMET) who were alive and on study drug at 4 months after randomization (time of first visit on maintenance therapy).

Methods and results By multivariable analysis, baseline HR, baseline SBP, and their change after 4 months were not independently related to subsequent outcome. In a multivariable analysis including clinical variables, HR above and SBP below the median value achieved at 4 months predicted subsequent increased mortality [relative risk (RR) for HR $>$ 68 b.p.m. 1.333; 95% confidence intervals (CI) 1.152–1.542; $P < 0.0001$ and RR for SBP $>$ 120 mmHg 0.78; 95% CI 0.671–0.907; $P < 0.0013$]. Achieving target beta-blocker dose was associated with a better outcome (RR 0.779; 95% CI 0.662–0.916; $P < 0.0025$). The superiority of carvedilol as compared to metoprolol tartrate was maintained in a multivariable model (RR 0.767; 95% CI 0.663–0.887; $P = 0.0004$) and there was no interaction with HR, SBP, or beta-blocker dose.

Conclusion Beta-blocker dose, HR, and SBP achieved during beta-blocker therapy have independent prognostic value in heart failure. None of these factors influenced the beneficial effects of carvedilol when compared with metoprolol tartrate at the pre-defined target doses used in COMET.

Introduction

Treatment with beta-blockers has been shown to improve survival in patients with chronic heart failure (CHF) and the benefit of the three agents, carvedilol,[1,2] metoprolol,[3] and bisoprolol,[4] has been documented. These agents have important pharmacological differences. Each blocks $beta_1$-adrenergic receptors, but only carvedilol blocks $beta_2$- and $alpha_1$-adrenergic receptors and has further antiproliferative, antioxidant, and anti-endothelin actions.[5,6] Previous studies have shown that carvedilol improves left ventricular (LV) function more than metoprolol,[7–9] and in the Carvedilol Or Metoprolol European Trial (COMET),[10] carvedilol significantly reduced all-cause mortality when compared with metoprolol tartrate. In this trial, carvedilol was associated with a slight, but significantly greater decrease in both heart rate (HR) and systolic blood pressure (SBP) after 4 months of treatment when compared with metoprolol tartrate. Furthermore, not all patients reached the target beta-blocker dose in either study group.[10] As all of these

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factors may influence mortality in CHF patients,[5,11,12] we have analysed their relationships to the outcome, as well as to the differences observed between carvedilol and metoprolol tartrate.

Methods

The COMET design has been published previously.[10,13] In summary, COMET was a multicentre, randomized, double-blind, parallel-group trial comparing the effect on mortality and morbidity of carvedilol and metoprolol tartrate in patients with symptomatic chronic CHF [New York Heart Association (NYHA) class II–IV] associated with LV systolic dysfunction (ejection fraction $\leq$0.35), at least one cardiovascular hospitalization during the 2 years before trial entry, optimal baseline therapy, including the need for diuretic therapy. Among the exclusion criteria were baseline resting HR $<$60 b.p.m. and SBP $<$85 mmHg. COMET was designed as an event-driven study with co-primary endpoints of all-cause mortality and the combined endpoint of mortality or hospitalization for any cause. Patients were randomized to carvedilol or metoprolol tartrate and received initial doses of 3.125 mg or 5 mg twice daily (b.i.d.), respectively. Doses were doubled at 2 week intervals, aiming for target doses of 25 mg b.i.d. of carvedilol and 50 mg b.i.d. of metoprolol tartrate. During up-titration, dosing could be adjusted and, if necessary, delayed by the investigator on the basis of symptoms or intolerance. Therefore, the titration phase could take up to 14 weeks from randomization. When patients reached the target or the maximally tolerated dose, the maintenance phase began. All patients underwent clinical assessment,

Table 1 Baseline characteristics of COMET patients by status at 4 months

	Alive on trial medication ($n = 2599$)	Dead ($n = 111$)	Alive, stopped trial medication ($n = 319$)	*P*-value
Age (years)	61.6 $\pm$ 11.3	63.9 $\pm$ 12.4	64.6 $\pm$ 11.4	$<$0.0001
Gender (% male)	79.7	82.0	79.9	0.8382
Body mass index (Kg/m^2)	26.9 $\pm$ 4.4	26.1 $\pm$ 4.7	26.3 $\pm$ 4.5	0.0119
SBP (mmHg)	126.8 $\pm$ 19.2	114.5 $\pm$ 17.1	123.9 $\pm$ 20.9	$<$0.0001
DBP (mmHg)	77.5 $\pm$ 10.7	72.2 $\pm$ 10.6	75.8 $\pm$ 11.9	$<$0.0001
HR (b.p.m)	81.2 $\pm$ 13.4	82.0 $\pm$ 13.6	79.7 $\pm$ 13.1	0.1192
NYHA class (%)				
II	51.4	24.3	32.0	$<$0.0001
III	45.7	63.1	59.9	
IV	2.9	12.6	8.2	
CHF duration (months) mean/median	40.5/19.0	60.5/35.0	51.7/30.0	$<$0.0001
Aetiology (%)				
Ischaemic Heart Disease	50.9	60.4	63.0	0.0001
Hypertension	17.7	15.3	18.5	0.7513
Dilated cardiomyopathy	45.7	34.2	32.6	$<$0.0001
Previous valve surgery	2.4	1.8	3.1	0.6665
LV EF (%)	26.1 $\pm$ 7.1	24.1 $\pm$ 7.4	26.4 $\pm$ 7.6	0.0148
NT-proBNP (pg/mL) median	1149	2350	1600	0.0001
Associated diagnosis (%)				
Previous MI	39.9	52.8	51.3	$<$0.0001
CAD (by angiography)	56.7	73.5	71.9	$<$0.0001
Current angina	20.7	30.3	26.5	0.0049
Hypertension	37.1	30.3	37.6	0.3389
Diabetes	23.5	24.5	29.5	0.0635
Stroke	7.1	5.5	7.5	0.7631
ECG findings (%)				
Sinus rhythm	76.0	60.4	68.0	$<$0.0001
Atrial fibrillation/flutter	19.2	26.1	22.6	0.0851
Paced rhythm	5.7	11.7	11.6	$<$0.0001
Concomitant medication at randomization (%)				
Diuretics	98.7	100.0	98.1	0.3107
ACE inhibitors	91.7	86.5	90.3	0.1248
Angiotensin receptor antagonists	6.4	7.2	7.5	0.7099
Digitalis	59.3	66.7	57.7	0.2433
Antiarrhythmics	11.0	20.7	18.2	$<$0.0001
Nitrates	31.5	44.1	39.2	0.0007
Aldosterone antagonists	10.6	16.2	10.7	0.1723
Beta-blockers (before study started)	4.7	1.8	1.6	0.0131
Anticoagulants	45.7	51.4	44.2	0.4237
Aspirin	36.2	36.0	42.3	0.1005
Lipid lowering agents (statins)	21.3	16.2	21.0	0.4349

P-value refers to significance of differences between the patients alive on trial medication vs. the patients who died or those who stopped the trial medication, considered together.

CAD, coronary artery disease; LVEF, left ventricular ejection fraction; MI, myocardial infarction; %, percent of patients.

including HR and blood pressure measurements at 4 months after randomization when they were receiving a stable beta-blocker regimen. As this was the first visit during the maintenance phase after completion of beta-blocker up-titration, this visit was used to classify patients according to their HR and SBP response and study medication dose.

Statistical analysis

Results are expressed as mean $\pm$ SD unless otherwise specified. Differences were assessed by *t*-tests for continuous variables and by the χ^2 test for categorical data. Kaplan–Meier survival estimates were also calculated. To assess the impact on mortality of SBP, HR, and dose at baseline and at 4 months, we fitted multivariable Cox regression models. These models included 10 baseline factors shown to be important for prognostic assessment in previous studies:[11,12,14] age, gender, NYHA classification, ischaemic aetiology, left ventricular ejection fraction, diabetes, digitalis, haemoglobin, serum sodium and creatinine, and randomized therapy. For dose, comparisons were made between those patients who were on target doses (carvedilol 25 mg b.i.d. or metoprolol tartrate 50 mg b.i.d.) and those on lower doses 4 months after randomization. To assess the best functional form to use for the HR and SBP variables, we calculated Martingale residuals from fitted Cox regression models. These residuals suggested that cutting these variables below and above the median not only made interpretation easier, but also matched the functional form of the predictors very well. Hence, throughout this manuscript the majority of results are presented using these splits. We also performed sensitivity analyses, reported in the text, both splitting the data into quartiles and treating these variables as continuous factors. To assess the proportional hazards assumption, we plotted the rescaled Scoenfeld residuals over time for each parameter and examined the resulting plots.[15]

Results are based on available data with no attempt to replace missing values. All hypothesis tests reported are two-sided and use a *P*-value <0.05 as significant. Although multiple analyses are presented, the purpose is to better understand the differences observed in mortality between carvedilol and metoprolol for which the type I error was well controlled. These analyses are therefore exploratory and no adjustment for the multiple assessments is necessary.

Results

Patient population

In COMET, 3029 patients were randomized to carvedilol (1511 patients) or to metoprolol tartrate (1518 patients). Median study duration was 58 months (interquartile range 54–64). Five patients were lost to follow-up and 28 patients withdrew their consent during the trial. All other patients were followed until death or study end.[10] During the first 4 months of beta-blocker therapy, 111 patients died (53 on carvedilol and 58 on metoprolol tartrate) and 319 patients (161 on carvedilol and 158 on metoprolol tartrate) were withdrawn from study medication. The present analyses, except for baseline, include the remaining 2599 patients alive and on study medication at 4 months. Their characteristics are compared with those of the patients who died or were discontinued during the first 4 months (*Table 1*).

Baseline HR and SBP

The number of patients in the carvedilol and metoprolol tartrate groups for HR and SBP are shown in *Figure 1*. The

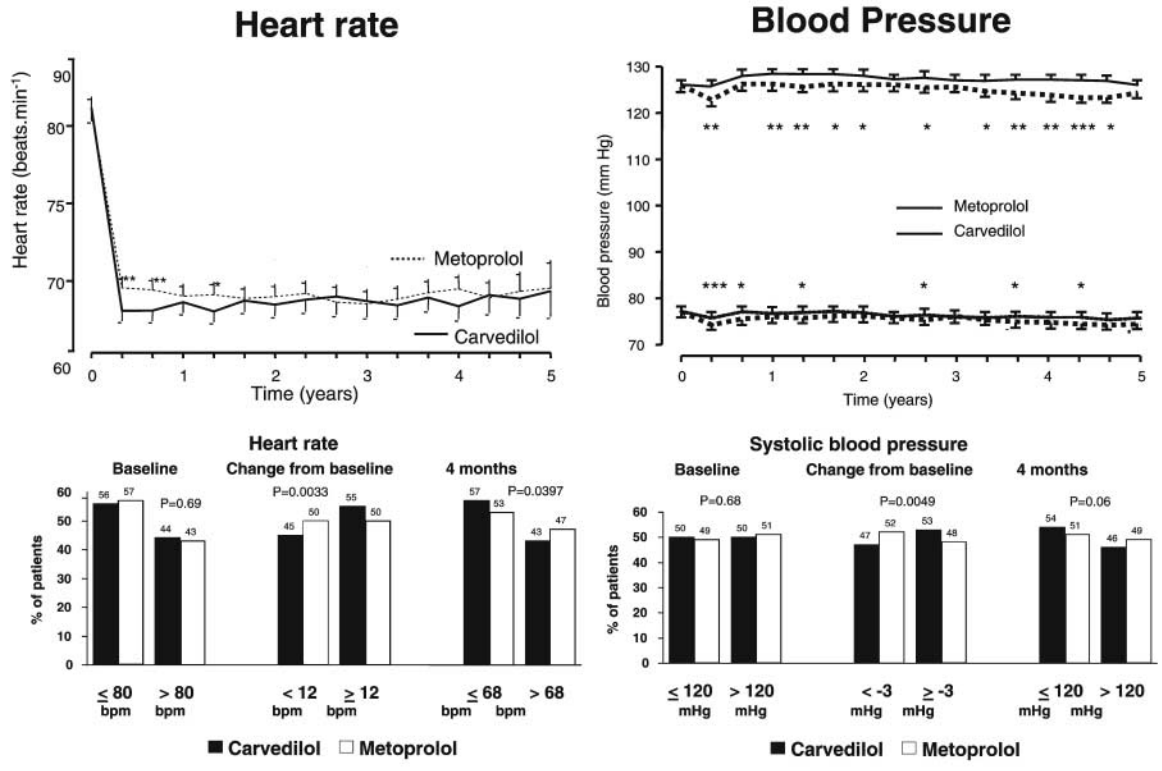

Figure 1 Time course of HR and BP in patients randomized to carvedilol and metoprolol tartrate. Upper graphs show all patients who were on treatment at the time of measurement. Lower graphs show per cent of patients on carvedilol and metoprolol tartrate in subgroups according to median HR and SBP at baseline, after 4 months, and by change from baseline at 4 months. $^{*}P < 0.05$, $^{**}P < 0.01$ and $^{***}P < 0.001$ for comparison between the patients on carvedilol versus those on metoprolol tartrate.

Table 2 Baseline patient characteristics by HR, SBP, and study drug dose subgroups

	Baseline HR		HR at 4 months		Baseline SBP		SBP at 4 months		Beta-blocker dose	
	≤80 b.p.m. ($n = 1443$)	>80 b.p.m. ($n = 1136$)	≤68 b.p.m. ($n = 1422$)	>68 b.p.m. ($n = 1160$)	≤120 mmHg ($n = 1236$)	>120 mmHg ($n = 1353$)	≤120 mmHg ($n = 1357$)	>120 mmHg ($n = 1234$)	Below target ($n = 615$)	Target ($n = 1980$)
Age (years)	62.4 ± 10.9	60.5 ± 11.7***	63.1 ± 10.7	59.7 ± 11.7***	60.1 ± 11.5	62.9 ± 10.9***	60.7 ± 11.5	62.5 ± 10.9***	63.6 ± 11.2	61.0 ± 11.2***
Gender (% male)	82.7	76.1***	81.2	77.9*	81.9	77.8**	80.0	79.5	77.8	80.4
Body mass index (Kg/m^2)	26.7 ± 4.0	27.3 ± 4.8***	26.8 ± 4.3	27.2 ± 4.5*	26.2 ± 4.2	27.6 ± 4.5***	26.4 ± 4.3	27.6 ± 4.4***	26.1 ± 4.1	27.2 ± 4.4***
SBP (mmHg)	126 ± 18	127 ± 20	127 ± 19	127 ± 19	111 ± 9	142 ± 13***	118 ± 16	136 ± 18***	122 ± 19	128 ± 19***
Diastolic blood pressure (mmHg)	77 ± 11	79 ± 11***	77 ± 10	78 ± 11**	72 ± 8	83 ± 10***	74 ± 10	81 ± 11***	75 ± 11	78 ± 11***
HR (b.p.m.)	71.7 ± 6.3	93.4 ± 9.7	77.0 ± 11.7	86.4 ± 13.5***	81.4 ± 13.5	81.1 ± 13.2	81.6 ± 13.6	80.8 ± 13.1	79 ± 13	82 ± 13***
NYHA class (%)										
II	54.1	48.3**	52.5	50.5	48.6	54.1**	48.7	54.6**	39.4	54.9***
III	43.6	48.2	44.4	46.9	47.7	43.8	47.8	43.2	54.8	43.1
IV	2.4	3.5	3.1	2.6	3.6	2.1	3.5	2.2	5.8	2.0
CHF duration (months) mean/median	41.7/20.0	39.1/19.0	39.5/19.0	41.7/20.0	42.0/21.0	39.1/18.0	43.0/22.0	37.7/17.0**	45.7/26.0	39.0/17.0*
Aetiology (%)										
Ischaemic heart disease	53.9	47.0***	55.1	45.7***	51.5	50.4	54.0	47.4***	61.4	48.0***
Hypertension	17.6	18.0	17.9	17.5	9.9	25.1***	10.6	25.7***	19.0	17.4
Dilated cardiomyopathy	42.7	49.9***	41.1	51.7***	47.8	44.0	45.3	46.4	35.4	48.6***
Previous valve surgery	2.4	2.2	2.0	2.8	2.8	1.8	2.2	2.4	3.2	2.2
LV EF (%)	26.7 ± 6.9	25.3 ± 7.2***	26.4 ± 7.1	25.7 ± 7.0*	25.0 ± 7.2	27.1 ± 6.8***	25.2 ± 7.2	27.1 ± 6.8***	26.0 ± 7.0	26.2 ± 7.1
NT-proBNP (pg/mL) median	1128	1232	1137	1196	1388	1033	1301	1057	1570	1089*
Associated diagnosis (%)										
Previous MI	44.3	34.2***	45.0	33.7***	41.9	38.1	44.8	34.4***	49.2	37.3
CAD (by angiography)	58.0	54.7	60.3	52.1***	56.1	57.2	59.2	53.5*	65.4	54.1
Current angina	22.7	18.1**	23.5	17.3***	20.0	21.3	21.3	20.0	23.7	20.0
Hypertension	35.6	38.8	36.3	37.9	25.1	47.9***	26.4	48.7***	37.5	36.8
Diabetes	21.7	25.8*	21.2	26.3**	20.0	26.7**	19.6	27.7***	23.7	23.6
Stroke	7.3	6.6	7.7	6.2	6.1	8.1*	7.1	7.1	8.9	6.8
ECG findings (%)										
Sinus rhythm	75.8	76.2	79.0	72.2***	76.4	75.8	74.7	77.6	73.6	76.3
Atrial fibrillation/flutter	17.8	21.0*	17.1	21.8**	17.5	20.7*	19.2	19.1	19.5	19.3
Paced rhythm	7.4	3.4***	4.1	7.7***	6.9	4.6*	6.9	4.3**	7.9	5.2

Continued

Table 2 Continued

	Baseline HR		HR at 4 months		Baseline SBP		SBP at 4 months		Beta-blocker dose	
	≤80 b.p.m. ($n = 1443$)	>80 b.p.m. ($n = 1136$)	≤68 b.p.m. ($n = 1422$)	>68 b.p.m. ($n = 1160$)	≤120 mmHg ($n = 1236$)	>120 mmHg ($n = 1353$)	≤120 mmHg ($n = 1357$)	>120 mmHg ($n = 1234$)	Below target ($n = 615$)	Target ($n = 1980$)
Concomitant medications (%)										
Diuretics	98.3	99.2	98.6	98.9	98.5	98.9	98.6	98.9	98.9	98.7
ACE-inhibitors	90.9	92.6	92.1	91.1	91.9	91.5	92.1	91.2	88.9	92.5*
Angiotensin II Antagonists	6.6	6.2	5.8	7.2	6.3	6.4	6.3	6.5	9.2	5.5
Digitalis	56.7	62.5**	56.9	62.2**	59.8	58.8	58.7	60.0	56.8	60.1
Antiarrhythmics	13.9	7.3***	13.5	7.8***	11.0	11.0	10.7	11.3	15.6	9.7
Nitrates	33.3	29.0*	35.0	26.9***	33.1	29.9	31.8	31.0	37.3	29.8
Aldosterone antagonists	10.1	11.1	9.2	12.2*	14.2	7.2***	13.7	7.1***	15.3	9.2
BB (before study start)	4.2	5.3	3.9	5.6*	3.7	5.5*	4.4	4.9	3.7	5.1
Anticoagulants	44.7	46.7	43.5	48.2*	50.5	41.2***	50.2	40.6***	50.3	44.3
Aspirin	38.6	33.4**	40.6	31.0***	32.9	39.3***	35.0	37.6	38.6	35.7
Statins	23.6	18.7**	21.5	21.2	21.9	20.9	24.1	18.4***	22.8	20.9

BB, beta-blockers. Other abbreviations as shown in *Table 1*.
*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$ for comparison between patients with values above and below the median or on low or on target doses.

baseline characteristics and the differences among the patients in these groups are shown in *Table 2*.

Baseline HR had no relationship to mortality. These results were similar both when we analysed all the 3029 patients randomized in COMET and when our analysis was restricted to only the 2599 patients on study medication at 4 months. In contrast, baseline SBP had a significant relationship to outcome both when all the patients and those on study medication at 4 months were analysed (*Figure 2*). However, the predictive value of baseline SBP was superseded by that of SBP measured at 4 months.

Change in HR and SBP after 4 months

Mean HR decreased from baseline by 13.3 ± 13.4 b.p.m. in the carvedilol group and by 11.7 ± 13.5 b.p.m. in the metoprolol tartrate group at 4 months (−1.6 ± 13.4 b.p.m., 95%CI −2.7 to −0.6 b.p.m.; $P = 0.0022$) for carvedilol vs. metoprolol tartrate. HR was slightly but significantly lower in the carvedilol group when compared with the metoprolol tartrate group also at 8 and 16 months after randomization (−1.7 ± 14.3 b.p.m.; $P = 0.0034$ and −1.8 ± 14.3 b.p.m.; $P = 0.0040$, respectively). No significant differences were observed at further visits during the 5 years after randomization. SBP decreased from baseline by 3.8 ± 17.4 mmHg in the carvedilol group and by 2.0 ±17.7 mmHg in the metoprolol tartrate group ($P = 0.0094$) at 4 months. The difference remained significant during most of the follow-up (*Figure 1*).

There was no relationship between changes in HR or SBP during the first 4 months of treatment and mortality. A HR ≤68 b.p.m. and a SBP >120 mmHg (median values) at 4 months were associated with a better outcome (*Figure 2*). Exclusion of patients with atrial fibrillation and/or those with a permanent pacemaker did not change these results (data not shown).

Beta-blocker dose

The mean daily dose of study drug at entry into the maintenance phase was 41.9 ± 14.7 mg in the carvedilol group and 84.9 ± 29.2 mg in the metoprolol tartrate group. The target doses of 25 mg b.i.d. of carvedilol and of 50 mg b.i.d. of metoprolol tartrate were reached in 75 and 78% of the patients, respectively. Achievement of the target beta-blocker doses was associated with a lower mortality (*Figure 2*).

Multivariable analysis

To assess the impact on mortality of SBP, HR, beta-blocker dose and randomized therapy, these variables were entered in a multivariable model including other baseline factors shown to be important in previous studies.[11,12,14] Variables significantly related to subsequent mortality are shown in *Table 3*. Among the haemodynamic variables, the only ones which had independent prognostic value were the HR and the SBP assessed at 4 months. The beta-blocker dose level administered at 4 months had independent prognostic value as well (*Figure 3*).

Treatment effect

Mortality was lower in the carvedilol group than in the metoprolol tartrate group in each defined group of HR,

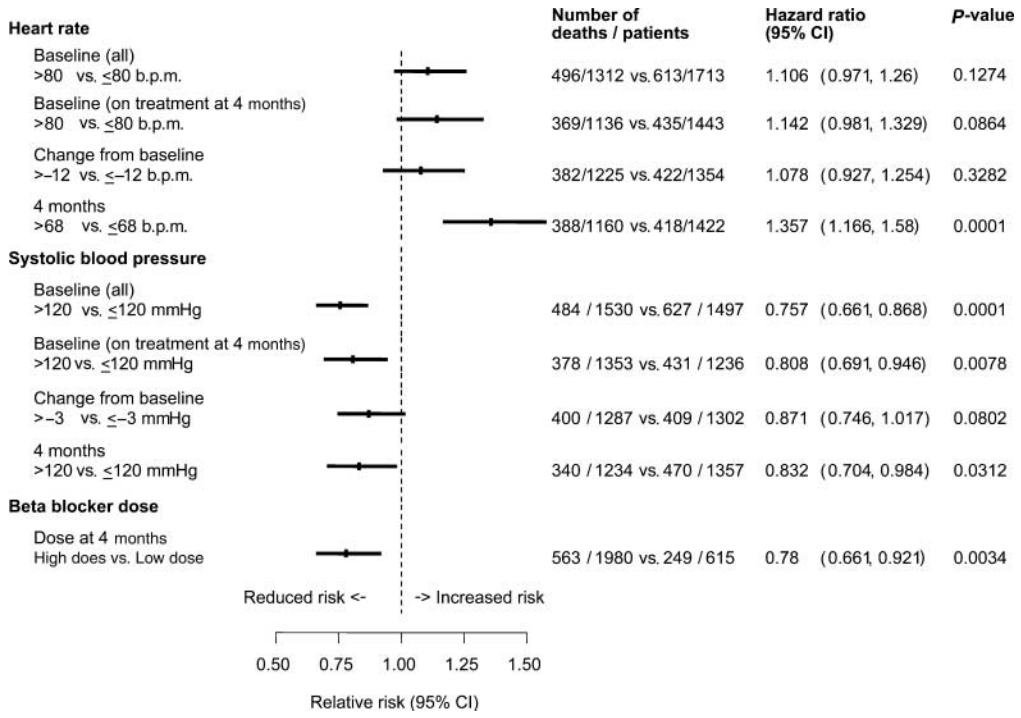

Figure 2 RR of death in subgroups based on median HR and SBP values and by study drug target dose achieved, adjusted for the other baseline variables.

Table 3 Predictors of death by multivariable analysis

	RR	95% CI	*P*-value
Carvedilol vs. metoprolol	0.767	0.663, 0.887	0.0004
HR at 4 months, >68 b.p.m.	1.333	1.152, 1.542	0.0001
SBP at 4 months >120 mmHg	0.78	0.671, 0.907	0.0013
High dose vs. low dose	0.779	0.662, 0.916	0.0025
Increasing age (years)	1.038	1.03, 1.046	<0.0001
Female vs. male	0.667	0.547, 0.813	0.0001
NYHA class III vs. NYHA class II	1.293	1.11, 1.508	0.001
NYHA class IV vs. NYHA class II	1.703	1.191, 2.437	0.0036
Ischaemic aetiology	1.333	1.138, 1.561	0.0004
Increasing LVEF (%)	0.975	0.965, 0.985	<0.0001
Diabetes	1.328	1.129, 1.562	0.0006
Digitalis	1.523	1.305, 1.778	<0.0001
Increasing haemoglobin (g/dL)	0.896	0.852, 0.941	<0.0001
Increasing sodium (mmol/L)	0.956	0.935, 0.977	<0.0001
Increasing creatinine (μmol/L)	1.002	1.001, 1.003	0.0002

LVEF, left ventricular ejection fraction.

SBP, and study drug dose (*Figures 3* and *4*), and the benefit of carvedilol was similar in each group. Similar models using quartiles and treating the HR and SBP as continuous predictors are shown in *Table 4*. The conclusions were not different.

In the multivariable analysis, the superiority of carvedilol compared with metoprolol tartrate was maintained [relative risk (RR) 0.767; 95% CI 0.663–0.887; $P < 0.0004$], and there was no interaction between study drug and any other variable in the final model (all *P*-values for interaction > 0.10).

Discussion

We have examined the relationships between HR, SBP, achieved beta-blocker dose, and outcomes in COMET and found that the HR and SBP values after 4 months from initiation of beta-blocker therapy and beta-blocker dose have independent prognostic value for subsequent mortality in CHF patients. However, these variables could not explain the differences observed between carvedilol and metoprolol tartrate on reducing mortality in the COMET study.

Heart rate

By multivariable analysis, neither baseline HR nor its change after 4 months of therapy was related to prognosis. These data contrast with some previous studies showing that HR is an independent prognostic factor in CHF.[11,12] Previous studies had also shown that enalapril,[16] amiodarone,[17] and beta-blockers[18,19] may exert greater benefit in the patients with faster HR. In the CIBIS-I trial, the achieved HR after 2 months of therapy was an important prognostic factor.[20] In the CIBIS-II trial, baseline HR and HR change at 2 months predicted outcome. However, this appeared to be related to the adverse prognosis of patients in whom HR had increased, a possible marker of non-compliance with the beta-blocker.[21] Other studies could not establish any relationship between the baseline HR and the efficacy of beta-blocker therapy with either non-selective agents[22,23] or selective agents[24,25]. In the MERIT-HF trial, metoprolol CR/XL significantly reduced mortality and hospitalizations independent of resting baseline HR, achieved HR, and

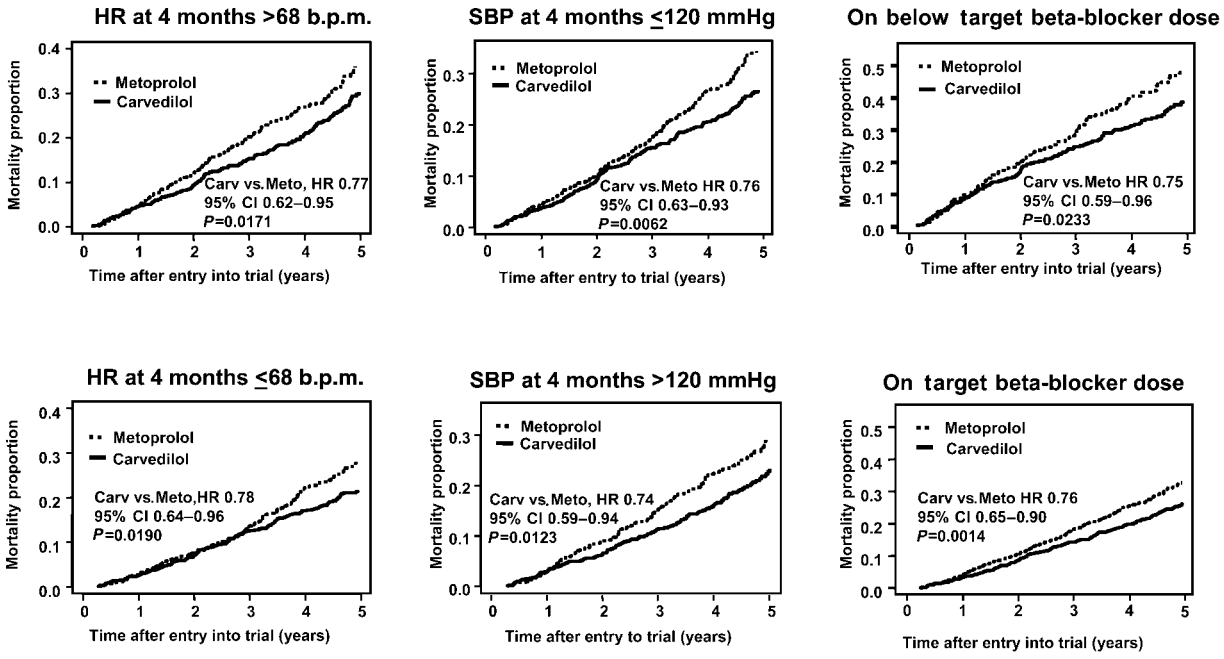

Figure 3 Kaplan–Meier curves of the defined patient subgroups based on 4 months HR, SBP, and achieved beta-blocker dose. Meto indicates metoprolol tartrate and Carv indicates carvedilol.

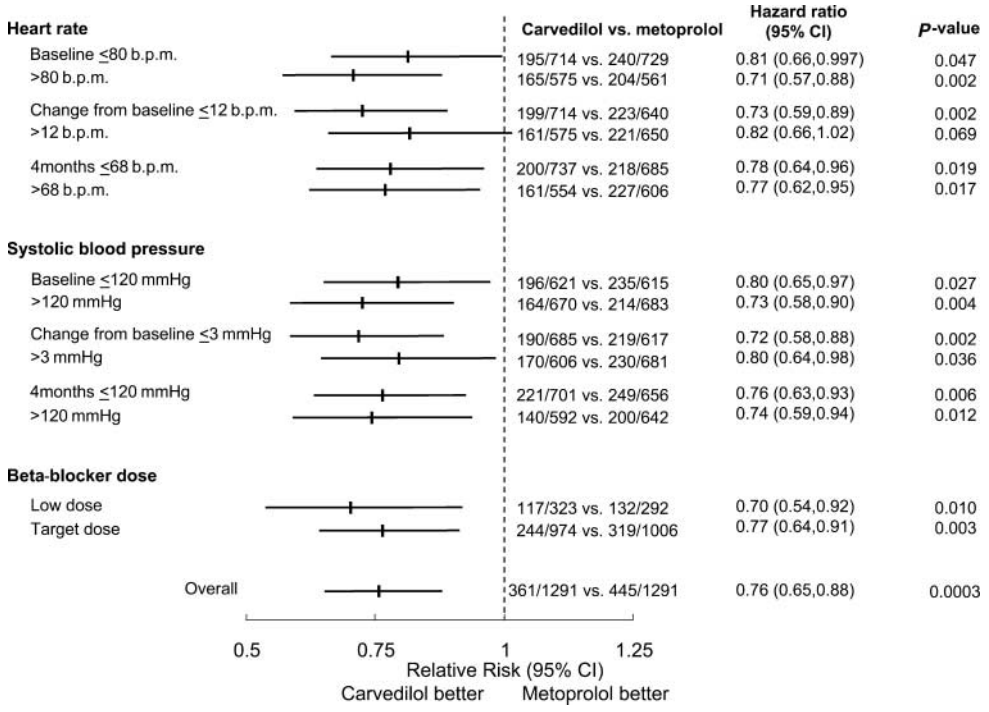

Figure 4 RR of death in subgroups based on median HR and SBP values and by study drug dose achieved, according to treatment group (carvedilol or metoprolol tartrate).

change in HR.[25] The reduction in mortality with bisoprolol, when compared with placebo, was not influenced by HR changes in CIBIS-II as well.[21] It is likely that beta-blocker therapy may counteract the deleterious effects of tachycardia in the failing heart so that this variable loses its prognostic significance.

Another difference between CIBIS-II and COMET is the role of cardiac rhythm. In CIBIS-II, the coexistence of atrial fibrillation was associated with a lack of difference in mortality between bisoprolol and placebo.[21] In contrast, baseline atrial fibrillation did not influence the results of COMET and of other trials.[26] The CIBIS-II findings on atrial fibrillation were therefore possibly due to chance.

In contrast to baseline data, the HR assessed at 4 months after the initiation of beta-blocker therapy had an independent prognostic value for subsequent outcome. Although

Table 4 Predictors of death by multivariable analysis—alternative models

	RR	95% CI	*P*-value
Splitting HR and SBP into quartiles			
Carvedilol vs. Metoprolol	0.767	0.663, 0.888	0.0004
HR at 4 months, <60 b.p.m.	Reference		
HR at 4 months, 60–68 b.p.m.	1.019	0.834, 1.245	0.8529
HR at 4 months, 68–76 b.p.m.	1.349	1.102, 1.651	0.0038
HR at 4 months, >76 b.p.m.	1.339	1.089, 1.645	0.0055
SBP at 4 months, <110 mmHg	Reference		
SBP at 4 months, 110–120 mmHg	0.92	0.754, 1.121	0.4069
SBP at 4 months, 120–140 mmHg	0.723	0.601, 0.871	0.0006
SBP at 4 months, >140 mmHg	0.826	0.656, 1.04	0.1045
High dose vs. low dose	0.777	0.66, 0.915	0.0025
Treating HR and SBP as continuous predictors			
Carvedilol vs. metoprolol	0.765	0.661, 0.885	0.0003
Increasing 4 months HR (b.p.m.)	1.008	1.002, 1.013	0.0114
Increasing 4 months SBP (mmHg)	0.994	0.99, 0.998	0.0038
High dose vs. low dose	0.781	0.663, 0.919	0.0029

RRs are calculated using as reference the lowest quartile (e.g. HR <60 b.p.m. and SBP <110 mmHg).

peak exercise HR provides a more accurate assessment of the degree of beta$_1$-blockade,[27] resting HR is the variable most frequently used to assess the level of beta-blockade in clinical practice. Our findings emphasize the importance of achieving adequate beta-blockade and/or HR lowering in CHF patients.

Our study shows that the difference in mortality, observed between carvedilol and metoprolol tartrate in COMET, was independent of baseline HR, its values after 4 months of treatment, and its changes. These results are important for the interpretation of the mortality results of COMET.[10] Some authors have suggested that these results may just reflect the different levels of beta$_1$-receptor blockade achieved with the doses of carvedilol and metoprolol tartrate administered in this trial. The difference in the 4 month resting HR between the two treatments has been used as evidence of this.[28,29] It is known that resting HR is only weakly related to beta$_1$-receptor stimulation as it is influenced by many other factors, such as beta$_2$-receptors stimulation, vagal activity, and epinephrine levels, so that the level of beta$_1$-receptor blockade is better predicted by peak exercise HR or mean 24 h HR.[9,27,30] However, neither of these variables was assessed in COMET. Hence, our analysis is not optimal for assessing whether similar levels of beta$_1$-receptor blockade were achieved with carvedilol and metoprolol tartrate in COMET. However, as far as the level of beta$_1$-receptor blocking is reflected in the resting HR, we have shown that having adjusted for this, the significance and, more importantly, the magnitude of the mortality benefit of carvedilol vs. metoprolol tartrate remained unchanged. We can therefore state that the small difference in the 4 month resting HR was not responsible for the mortality difference seen in COMET. These results are consistent with the specific pharmacological characteristics of carvedilol, such as its tighter binding to the beta$_1$-receptors,[31,32] beta$_2$-receptor blockade,[27,33] or increased beta$_2$-receptor coupling with the Gi proteins.[34]

Systolic blood pressure

Baseline SBP was related to prognosis by univariate analysis. The patients with a baseline SBP $\leq$120 mmHg had a 24% higher risk of death when compared with those with a SBP >120 mmHg ($P = 0.0001$). This is in agreement with previous studies.[11,12,21] It is likely that patients with lower SBP have poorer LV systolic function and hence a poorer outcome. A correlation between SBP and a greater benefit from beta-blocker therapy has been found in previous studies.[21,22,24] A recent analysis of the COPERNICUS study, which, unlike other beta-blocker trials, included patients with a SBP as low as 85 mmHg, showed that the absolute benefit from carvedilol, when compared with placebo, is maintained and even greater in patients with the lowest SBP (85–95 mmHg) because of their highest risk.[35] When assessed in a multivariable model including the variables measured 4 months after the initiation of beta-blocker therapy, the SBP at 4 months replaced the baseline measurements which lost their predictive value. This may reflect the profound effects of beta-blockers on both the haemodynamic variables and their prognostic value, so that they have a greater significance when measured during therapy. The correlation between a higher SBP value, during beta-blocker treatment, and a better outcome contradicts the hypothesis that the beneficial effects of carvedilol were related to its greater hypotensive action in COMET. Moreover, similar to HR, the effects of carvedilol on mortality were not influenced by SBP.

Beta-blocker dose

Treatment with less than target doses of either carvedilol or metoprolol tartrate was a strong and independent predictor of a poor prognosis in COMET. The patients receiving reduced doses at 4 months had signs of more advanced CHF. They were also older, more likely to have ischaemic

heart disease and not to tolerate an ACE-inhibitor. The prognostic value of the beta-blocker dose remained significant after adjustment for the other baseline variables. These data confirm previous studies showing that intolerance of target beta-blocker doses is associated with more severe symptoms and a worse prognosis.[36,37] Intolerance to beta-blocker therapy had similar consequences for metoprolol tartrate and carvedilol and these results shed no light on the question of whether the differences in mortality between carvedilol and metoprolol have any bearing on dose. Multivariable analysis found no interaction between high and low achieved doses of metoprolol tartrate and carvedilol and the beneficial effects of carvedilol, when compared with metoprolol tartrate, on outcome.

Limitations of the study

This is a *post hoc* analysis focusing on events which occurred later than 4 months after randomization. Focusing on post-randomization changes creates a risk of bias as it excludes the patients who died or who discontinued the study medication during the first 4 months. We therefore had to exclude 430/3029 patients (15%). However, the inclusion of the haemodynamic measurements at 4 months is important as, at this time interval, most patients were titrated to their final beta-blocker doses and, thus, the role of the changes in HR or SBP caused by the two beta-blockers could be assessed. Accordingly, the 4 months changes in HR and SBP were the focus of the controversy regarding the magnitude of the $beta_1$-receptors blockade achieved with the two beta-blockers.[28,29]

Conclusions

Our results show that the survival of patients with CHF on long-term beta-blocker treatment is related neither to their HR nor to their SBP before the initiation of beta-blocker therapy or to their subsequent changes. In contrast, the HR and SBP achieved on maintenance beta-blocker therapy and beta-blocker dose have independent prognostic value. The beneficial effects of carvedilol, when compared with metoprolol tartrate, at the pre-defined target doses of each compound, on mortality could not be explained by the differences in BP and HR observed after 4 months of study treatment or by patients not achieving target study drug levels.

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