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Effect of beta-blocker therapy on functional status in patients with heart failure — A meta-analysis

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Abstract

Background: The results of randomised control trials (RCTs) evaluating the effect of beta-blockers on functional status in patients with chronic heart failure are conflicting.
Aim: To perform a systematic review and meta-analysis of RCTs evaluating the effect of beta-blockers on New York Heart Association (NYHA) classification and exercise tolerance in chronic heart failure.
Methods and results: We selected 28 RCTs evaluating beta-blocker versus placebo in addition to ACE inhibitor therapy. Combined results of 23 RCTs showed that beta-blockers improved NYHA class by at least one class with odds ratio (OR) 1.80 (1.33–2.43) $p<0.0001$. Meta-analysis of 10 RCTs showed a significant prolongation of exercise time by 44.19 (6.62–81.75) s $p=0.021$. Combining 8 RCTs evaluating the maximal peak oxygen uptake and 9 RCTs evaluating 6-min walk distance showed that beta-blockers had no significant effect compared with placebo, $p=0.484$, and $p=0.730$, respectively. Combined results of the 23 RCTs showed significant reducing effect on all cause mortality with OR=0.69 (0.59–0.82) $p<0.0001$.
Conclusion: Chronic use of a beta-blocker in conjunction with ACE inhibitor therapy improves dyspnoea and prolongs exercise tolerance time, but has no significant effect on 6-min walk test or maximal oxygen uptake in patients with heart failure.

Keywords: Congestive heart failure; Left ventricular dysfunction; Beta-adrenergic blocker; Angiotensin converting enzyme inhibitor

1. Introduction

In addition to life prolongation, patients with chronic heart failure need relevant symptom relief to improve their quality of life. In this context, it is important to clarify and quantify the effect of the pharmacological therapy on symptoms in these patients. Despite the overwhelming documentation on the beneficial effect of beta-blocker therapy on survival, hospitalisation and left ventricular function in patients with heart failure and left ventricular systolic dysfunction (LVSD) [1–4], the results of the studies examining the effect of this therapy on functional status and exercise tolerance variables have been less clear and even conflicting [5,6]. A previous meta-analysis on the effect of beta-blocker therapy on New York Heart Association (NYHA) classification in these patients has shown only a marginal statistically significant effect [7]. Results of studies on exercise tolerance have also been conflicting [8–12]. The varying results demonstrate that any effect of beta-blockers on symptoms is less apparent than effects on survival and left ventricular function. For this reason we have conducted a systematic review and meta-analysis on the effect of beta-blockers on NYHA class and exercise tolerance.

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2. Methods

2.1. Search strategy

We searched the medical literature through MEDLINE, EMBASE, BIOSIS, Cochrane database (issue 3, 2004), CINAHL and OVID databases for all electronically registered clinical trials using the following keywords: beta adrenergic receptors, beta-blocker, congestive heart failure, left ventricular dysfunction, exercise tolerance, exercise capacity, signs and symptoms, dyspnoea, clinical trial, human and in all languages. The search was without time limitation but concentrated on finding trials after 1989; that is after introduction of ACE inhibitors as main treatment in patients with heart failure and LVSD. We examined citations of key articles in Science Citation Index, searched conference proceedings and meetings and screened for abstracts that met the inclusion criteria. Additionally, a manual search of previous meta-analyses and reviews on beta-blockers was performed and all reference lists were screened [5–7,13–18]. Where possible, relevant pharmaceutical companies were contacted and asked for published and unpublished trials on their beta-blocker product.

2.2. Study criteria and selection

2.2.1. Inclusion criteria

Only parallel group, randomised, placebo-controlled trials evaluating the effect of beta-blockers (both selective and non-selective) added to background treatment with an ACE inhibitor, on NYHA class and exercise tolerance [including peak oxygen uptake (PVO_2), exercise tolerance time (ETT) and 6-min walk distance (6MWD)] were considered eligible for inclusion. Eligible studies included patients with an established diagnosis of symptomatic chronic heart failure, documented impaired systolic function with left ventricular ejection fraction (LVEF) $\leq$ 45% and receiving treatment for at least 12 weeks. Included studies had to provide summary data for at least one exercise tolerance variable or changes in NYHA class at the end of study in both treatment arms.

2.2.2. Exclusion criteria

We excluded studies on isolated beta-blocker therapy without background treatment with an ACE inhibitor, and those which were observational, cross-over, withdrawal, or recent acute myocardial infarction studies. In addition, comparative trials without a placebo arm, studies using additional physical training or investigating another drug beside beta-blocker therapy, studies using healthy persons as a control, patients after heart transplantation, patients with predominant diastolic dysfunction, and finally studies of patients with atrial fibrillation were not considered for inclusion.

2.3. Data characteristics and extraction

Three reviewers contributed to the search process and evaluated all potentially eligible studies, data characteristics and performed data extraction. In exercise tolerance studies that compared high versus low dose treatment arms of the same beta-blocker [8,19,20], only the highest dose arm was chosen. In the studies not providing the exact numbers of patients changing NYHA class, the numbers of patients shifting to either NYHA class I or IV were considered as numbers who improved or deteriorated in each arm, respectively [21–23]. One study with two treatment arms randomised to two different beta-blockers was analysed separately versus the same placebo arm [23]. One study examined patients with renal failure on dialysis therapy [24]. The available data on sub-maximal exercise tolerance or trials reporting 9-min walk test were found insufficient for a meta-analysis [8,25,26]. As the included studies did not provide full statistical data to make a comparison with the baseline in exercise tolerance studies, only the data at the end of studies were used for the meta-analyses.

2.4. Statistics

The summary data of studies examining the effect on NYHA class were pooled as numbers of patients that improved or did not improve (unchanged and worsened) in each treatment arm. To obtain an overall treatment effect by combining the effects estimated as improvement and

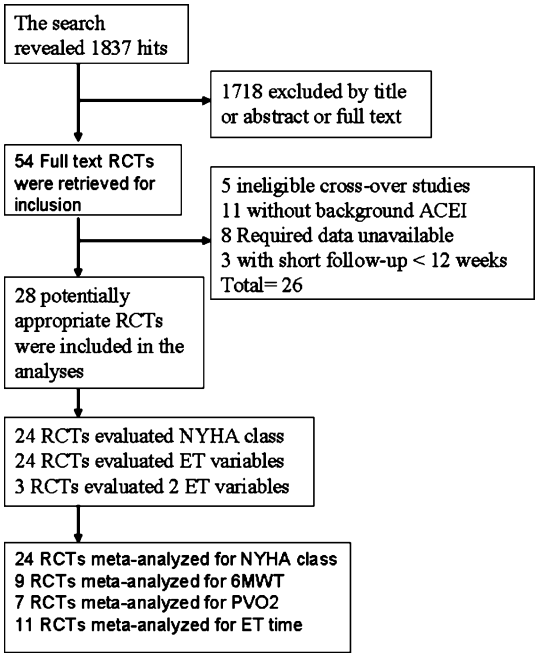


Fig. 1. Trial flow and identification of the randomised controlled trials (RCT). RCT=randomised controlled trial, NYHA=New York Heart Association class, ET=exercise tolerance, PVO_2=peak oxygen consumption.

deterioration, we excluded the population with unchanged NYHA class (not in risk to change either direction) and ran the analysis comparing only the number of patients who improved and those who deteriorated on beta-blocker versus the placebo arm. This analysis provided a higher estimate of odds ratio for the overall improvement produced by beta-blockers. DerSimonian–Laird method was used for random effects model as appropriate, Peto–Yusuf method for fixed effects model and Chi Squared test was used for between study heterogeneity. Survival versus mortality was analysed by the same methods. The measured mean value of exercise tolerance variables (PVO_2, ETT and 6MWD) at study-end were compared between the beta-blocker and placebo arm. This meta-analytic comparison of the continuous data provided the mean weighted difference of the changes observed in the magnitude of exercise tolerance. All standard errors were converted to their standard deviations and thus all values were analysed as means and standard deviations. All p-values <0.05 and z scores >2 were considered significant. The analyses were performed using software package STATA-8 (Stata Corporation, Lakeway Drive, College Station, Texas, USA).

3. Results

3.1. Results of the search

The trial flow is illustrated in Fig. 1. The meta-analysis included 28 studies, study characteristics are shown in Table 1. All studies were published in English except two; one was published in Turkish [22] and one in Russian [27].

Table 1
Characteristics of the included studies

No.	RCT	No. of patients beta-blocker /placebo	Type of beta-blocker	Follow-up in months	Endpoints: type of exercise tolerance test and NYHA class
1.	Gilbert et al. [37]	13/9	Bucindolol	3	TM/NYHA
2.	Woodley et al. [38]	29/20	Bucindolol	3	TM/NYHA
3.	Waagstein et al. [11]	194/189	Metoprolol	12	BE/NYHA
4.	Fisher et al. [47]	25/25	Metoprolol	6	NYHA
5.	Bristow et al. [19]	105/34	Bucindolol (All doses)	3	TM/6MWT/NYHA
		35/34	Bucindolol (200 mg)		
6.	CIBIS-1 [48]	321/320	Bisoprolol	4–44	NYHA
7.	Metra et al. [26]	20/20	Carvedilol	4	BE (sub-maximal)/NYHA
8.	Eichhorn et al. [32]	15/9	Metoprolol	3	NYHA
9.	Andersson et al. [33]	20/21	Metoprolol	12	BE/NYHA
10.	Olsen et al. [10]	36/24	Carvedilol	4	BE
11.	ANZ [9]	207/208	Carvedilol	6	TM/6MWT/NYHA
12.	Krum et al. [31]	33/16	Carvedilol	3	6MWT/NYHA
13.	Colucci et al. [25]	232/134	Carvedilol	12	9MTM/NYHA
14.	Bristow et al. [8]	261/84	Carvedilol (All doses)	6	6MWT/9MTM/NYHA
		89/84	Carvedilol (25 mg × 2)		
15.	Packer et al. [30]	133/145	Carvedilol	6	6MWT/NYHA
16.	Cohn et al. [49]	70/35	Carvedilol	6	6MWT/TM/NYHA
17.	Sanderson et al. [23]	40/10		3	6MWT/NYHA
	Metoprolol	19/10	Metoprolol 50 mg × 2		
	Celiprolol	21/10	Celiprolol 200 mg × 1		
18.	Goldstein et al. [50]	62/62	Metoprolol	6	NYHA
19.	Witchitz et al. [28]	58/47	Celiprolol	12	BE
20.	Genth-Zotz et al. [29]	26/26	Metoprolol	6	BE/NYHA
21.	Gullestad et al. [12]	1990/2001	Metoprolol	12	NYHA
		43/40		12	BE
22.	Hülsmann et al. [21]	23/20	Atenolol	24	BE/NYHA
23.	Cice et al. [24]	58/56	Carvedilol	12	NYHA
24.	Dubach et al. [35]	13/15	Bisoprolol	12	BE
25.	Brehm et al. [36]	6/6	Nebivolol	3	BE/NYHA
26.	Terzi et al. [22]	28/24	Bisoprolol	3	TM/NYHA
27.	Belenkov et al. [27]	28/21	Bisoprolol	12	6MWT/NYHA
28.	Hori et al. [20]	124/49	Carvedilol (All doses)	6	NYHA
		77/49	Carvedilol 10 mg × 2		
Total		4092/3611	7 types of beta-blocker		

No = number, RCT = randomised controlled trial, TM = treadmill, BE = bicycle ergometer, 6MWT = 6-min walk test, NYHA = New York Heart Association, CIBIS = Cardiac Insufficiency Bisoprolol study, MERIT-HF = Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure, ANZ = Australia-New Zealand Heart Failure Collaborative Group.

Table 2
Baseline characteristics of the meta-analysed data in the included studies

Variable	Value
Mean age (year)	60 (48–64)
Male (sex)	79%
Mean LVEF	23.5 (16–30) %
Use of ACEI	87%
NYHA class I	2%
II	41%
III	54%
IV	3%

ACEI = angiotensin converting enzyme inhibitor, NYHA = New York Heart Association, LVEF = left ventricular ejection fraction.

3.2. Study quality

All the included studies were randomised and placebo-controlled and all described the number of deaths and dropouts. All the included studies were double-blinded except two [22,27]. Only 13 studies clearly stated that the analysis was based on intention to treat or repeated measurements methods [2,9–11,21,25,26,28–33]. The studies were generally of good quality (mean Jadad score=3) [34].

3.3. Characteristics of the analysed data

Characteristics of the meta-analysed data are shown in Table 2. At baseline the total population comprised 7637 patients, 4015 received beta-blockers and 3622 received placebo. The patients were not old (mean age 60 years) and the majority of participants were male and were receiving an ACE inhibitor. The vast majority (98%) were symptomatic (NYHA class II–IV) at baseline. All the included studies specified a LVEF threshold value of $\leq$40% as an inclusion criterion except for two studies that requested a LVEF threshold value of $\leq$45% [9,32]. The aetiology of heart failure was both ischaemic and non-ischaemic. Exercise tolerance data for each study at

Table 3
Data from the randomised controlled trials (RCT) examining the effect of beta-blockers versus placebo on three exercise tolerance parameters

RCT	Number of patients		Beta-blockers		Placebo	
	Beta-blocker	Placebo	Baseline	Study-end	Baseline	Study-end
6-min walk test measured as meters						
Bristow et al. [19]	32	34	448±82	449±82	458±81	468±81
Bristow et al. [8]	35	34	356±72	356±72	354±74	356±74
Genth-Zotz et al. [29]	26	16	412±60	452±70	462±102	512±120
Krum et al. [31]	33	16	391±109	444±103	406±92	355±204
Packer et al. [30]	145	133	351±64	368±64	352±70	358±70
Sanderson et al. [23] (M)	17	8	377±16	395±21	425±16	423±22
Sanderson et al. [23] (C)	17	8	361±16	395±21	380±18	423±22
Cohn et al. [49]	70	35	281±81	300±81	250±81	278±81
ANZ [9]	207	208	390±78	396±82	394±69	406±91
Belenkov et al. [27]	27	20	372±44	398±64	377±54	398±62
Total	609	512				
Exercise tolerance time measured as seconds						
Gilbert et al. [37]	13	9	593±184	565±187	436±174	465±180
Woodely et al. [38]	28	19	480±190	456±190	426±157	450±209
Andersson et al. [33]	20	21	588±249	648±249	564±209	539±209
ANZ [9]	207	208	642±267	648±267	618±267	654±267
Olsen et al. [10]	32	23	614±198	624±164	640±177	660±177
Bristow et al. [8]	35	34	511±172	575±172	549±192	537±192
Witchitz et al. [28]	58	47	540±2	540±2	480±2	540±2
Waagstein et al. [11]	194	189	581±287	657±287	567±258	582±258
Dubach et al. [35]	13	15	546±102	681±168	552±120	594±138
Brehm et al. [36]	6	6	486±205	354±114	372±179	330±138
Terzi et al. [22]	26	22	504±240	612±300	378±162	426±210
Total	632	593				
Peak oxygen uptake measured as ml/kg/min						
Olsen et al. [10]	32	23	17.5±4.5	17.5±5	17.3±3.8	17.8±4.3
Hulsmann et al. [21]	23	20	18±5	21±5	17±4	19±7
MERIT-HF [2]	43	40	15.3±3	15.5±3.9	16±5.7	16.2±4.3
Dubach et al. [35]	13	15	18.3±5	21±3.3	18.9±3.6	20.4±3
Genth-Zotz et al. [29]	26	26	13.5±2.8	15.1±2.7	13.6±4.7	14.7±5.1
Gilbert et al. [37]	13	9	20.1±4.7	18.1±4.3	16.4±4.2	16.1±4.5
Woodley et al. [38]	27	19	17.8±4.7	16±4.1	16.3±4.3	16.6±4.8
Total	177	152				

All values are presented as mean±SD.

baseline and study-end are shown in Table 3. Changes in NYHA class and mortality are shown in Table 4.

3.4. Change in NYHA classification

The results of the primary analysis on all patients (not shown as plot) comparing the number of patients who improved (1128 on beta-blocker and 845 on placebo) versus the number who were not improved (unchanged or deteriorated, 2850 on beta-blocker and 2668 on placebo) showed a significant improving effect of beta-blockers; the studies were heterogeneous $p=0.003$ fitting to analysis by a random effects model, OR (odds ratio)=1.5 (1.2–1.9) $p=0.001$. The analysis of the number of patients who deteriorated (336 in beta-blocker and 370 in placebo arm) versus the number who did not deteriorate (3652 in beta-blocker and 3516 in placebo arm) showed that the studies were homogenous $p=0.145$, thus fitting to a fixed effects model that resulted in OR=0.69 (0.54–0.87) $p=0.002$ in favour of the beta-blocker arm. The overall analysis for improvement in treatment effect (combining improvement and deterioration on beta-blocker versus placebo, Table 4) showed an even higher treatment effect in the beta-blocker arm by fixed effects model OR=1.58 (1.32–1.89) $p<0.0001$, heterogeneity $p=0.081$, Fig. 2. The random effects model showed OR=1.80 (1.33–2.43) $p<0.0001$. The difference between the two models indicated the presence of slight heterogeneity between studies; therefore it was relevant to choose the random model. The increase in estimated odds ratio in favour of beta-blocker was compatible with the larger number of patients who improved and less number of patients who deteriorated compared with placebo.

3.5. Exercise tolerance

Meta-analysis of the studies on exercise tolerance, which included 2625 patients (1384 assigned to beta-blocker versus 1241 to placebo), demonstrated no significant effect of beta-blockers on PVO_2 or 6MWT but there was a significant effect on exercise tolerance

Table 4
Changes in New York Heart Association (NYHA) class and all cause mortality

No.	RCT	NYHA class (Number of patients)		Mortality (number of patients)	
		Beta-blocker	Placebo	Beta-blocker	Placebo
		Improved/deteriorated	Improved/deteriorated	Dead/survivor	Dead/survivor
1.	Gilbert et al. [37]	NA	NA	0/14	0/9
2.	Woodley et al. [38]	14/2	4/2	0/30	0/20
3.	Waagstein et al. [11]	67/8	52/9	23/171	21/168
4.	Fisher et al. [47]	15/1	6/8	1/24	2/23
5.	Bristow et al. [19]	26/3	15/2	4/101	2/32
6.	CIBIS-1 [48]	68/41	48/35	53/267	67/254
7.	Metra et al. [26]	11/11	8/8	0/20	0/20
8.	Eichhorn et al. [32]	3/0	0/0	0/15	0/9
9.	Andersson et al. [33]	NA	NA	2/19	1/19
10.	Olsen et al. [10]	17/1	10/4	1/35	0/24
11.	ANZ [9]	54/33	58/27	20/187	26/182
12.	Krum et al. [31]	21/5	5/5	3/30	2/14
13.	Colucci et al. [25]	23/27	9/23	2/230	5/129
14.	Bristow et al. [8]	47/44	16/24	12/149	13/71
15.	Packer et al. [30]	35/20	27/45	6/127	11/134
16.	Cohn et al. [49]	10/8	7/5	2/68	2/33
17.	Sanderson et al. [23] (M)	3/0	1/2	0/17	0/8
	Sanderson et al. [23] (C)	2/0	1/2	2/15	0/8
18.	Goldstein et al. [50]	16/6	8/4	1/42	0/19
19.	Witchitz et al. [28]	15/3	11/5	1/61	2/60
20.	Genth-Zotz et al. [29]	NA	NA	2/24	1/25
21.	MERIT-HF [2]	566/119	514/150	145/1845	217/1784
22.	Hulsmann et al. [21]	18/1	11/1	4/23	0/20
23.	Cice et al. [24]	21/0	0/3	0/58	3/56
24.	Dubach et al. [35]	NA	NA	1/12	0/15
25.	Terzi et al. [22]	6/0	2/1	1/27	2/22
26.	Brehm et al. [36]	4/1	4/1	0/6	0/6
27.	Belenkov et al. [27]	14/0	5/2	0/30	2/24
28.	Hori et al. [20]	51/1	23/5	1/76	0/49
Total		1128/335	846/370	287/3723	380/3237
Percents		77/23	69/31	7/93	10.5/89.5

No = number, RCT = randomised controlled trial.

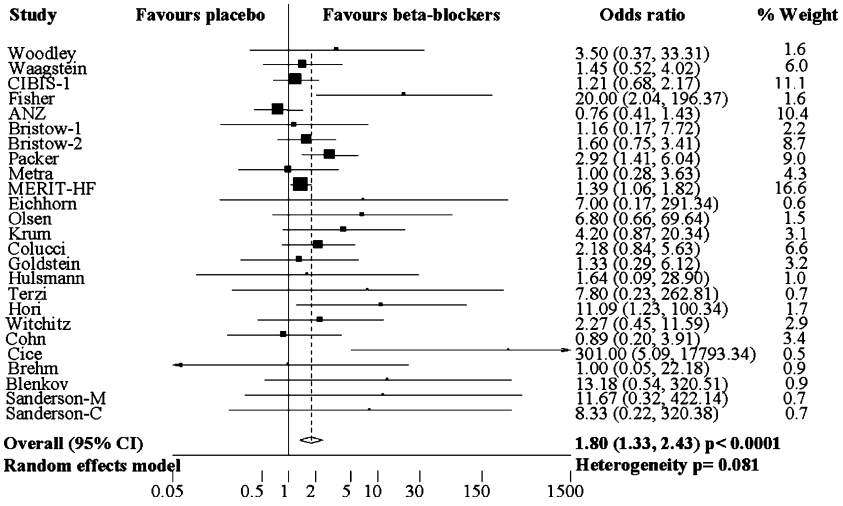


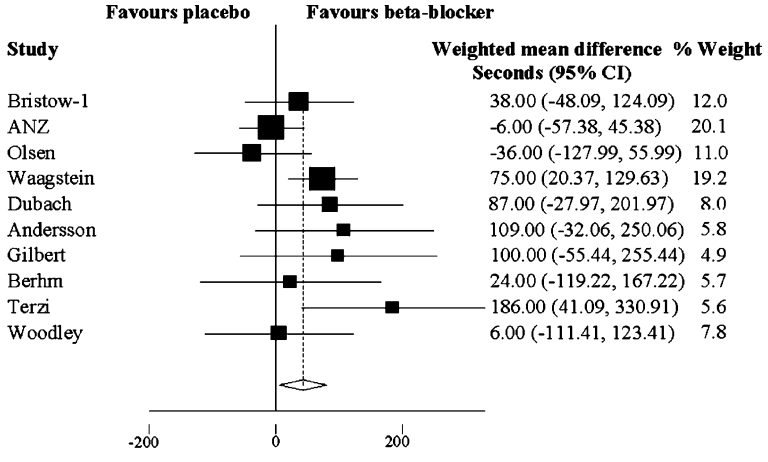
Fig. 2. Meta-analysis of 24 studies showing that beta-blockers had a significant improving effect on New York Heart Association class.

time. The sensitivity analysis showed that the meta-analysis of the studies on exercise tolerance time was characterised by significant heterogeneity due to the study by Wichitz, apparently because of the reported small standard deviations. The combined results of these 11 studies including the study by Wichitz were analysed in a random effects model that showed a significant effect on exercise tolerance time 33.24 (0.77, 65.71) s $p=0.045$, heterogeneity $p=0.020$. By exclusion of the study by Wichitz the remaining 10 studies showed good homogeneity with a pronounced effect on exercise tolerance time of 44.2 (6.62, 81.75) s corresponding to an improvement of 7% compared to placebo, Fig. 3. A subgroup analysis according to type of maximal exercise test used (bicycle ergometer versus Treadmill) revealed a significant improving effect produced by bicycle ergometer test used in 5 studies [10,11,33,35,36] with a weighted mean difference of 50.9 (0.55, 101.3) s $p=0.048$ and $p=0.257$ for heterogeneity between studies, while treadmill test used in 5 studies [9,19,22,37,38] produced an insignificant effect with a weighted mean difference of 42.8 (−17.2, 102.9) s $p=0.162$ and $p=0.125$ for heterogeneity (Fig. 3).

Subgroup analysis according to the type of beta-blocker, particularly carvedilol, did not show an improving effect in any of the analyses, Figs. 3–5.

3.6. Mortality

As previously demonstrated in large scale studies, beta-blockers had a significant reducing effect on all cause mortality, Fig. 6.



Random effects model: 44.19 (6.62, 81.75) seconds p=0.021, heterogeneity p= 0.134.
Fixed effects model: 38.66 (10.96, 66.36) seconds p=0.006, heterogeneity p= 0.134.
Five studies using bicycle ergometer: 50.9 (0.55, 101.3) seconds p= 0.048 heterogeneity p= 0.257
Five studies using treadmill : 42.8 (-17.2, 102.9) seconds p= 0.162 heterogeneity p= 0.125

Fig. 3. Meta-analysis of 10 exercise tolerance studies showing that beta-blockers had significant prolonging effect on exercise tolerance time.

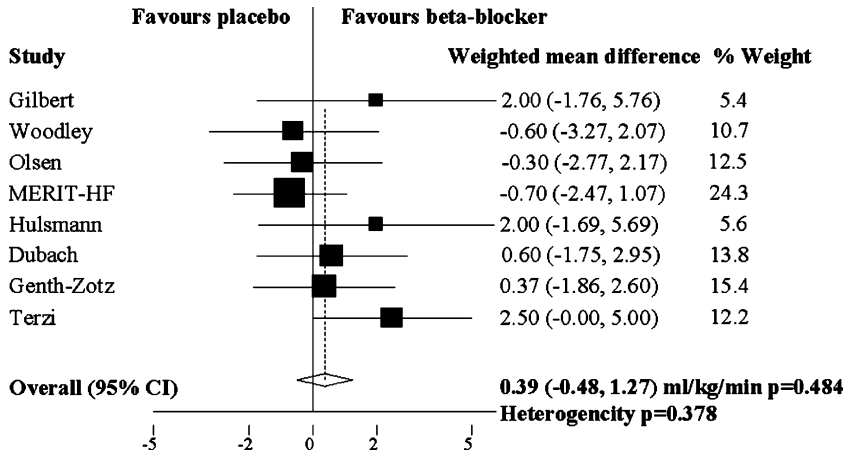


Fig. 4. Meta-analysis of 8 exercise tolerance studies showing that beta-blockers had no significant effect on maximal peak oxygen uptake (ml/kg/min).

3.7. Test for publications bias

Begg's and Egger's tests showed no significant publications bias, $p=0.138$ and $p=0.469$, respectively.

4. Discussion

The principal result of this study is that a comprehensive meta-analysis on the available randomised controlled trials demonstrated that beta-blocker therapy is associated with a significant improvement in cardiac functional class and exercise tolerance time in patients with heart failure, but not with any improvement in exercise tolerance measured by 6-min walk test or maximal oxygen uptake.

The increase in exercise tolerance time is in concordance with the improvement in NYHA class and the well known favourable effect of beta-blockers on survival. However, the lack of a positive exercise response using 6-min walk test and maximal oxygen consumption conflicts with these positive findings, but is not surprising. Beta-blockers reduce maximal heart rate during exercise and would be expected perhaps even to reduce maximal exercise capacity [39]. Also, methodological difficulties with the equipment and the expertise required for measurement of maximal oxygen consumption, particularly in the multi-centre studies, may make the results of this test difficult to interpret. Whether a sub-maximal exercise test such as the 6-min walk test is more reliable and reproducible has not been determined. Conversely, finding a positive effect on exercise time and not on the other exercise tolerance variables does not make the measurement of exercise tolerance time a more reliable and consequently a valid method, but it is possible that this measurement was more sensitive at detecting changes in exercise capacity.

On the other hand, despite the crudeness of measurement of dyspnoea by NYHA classification, the substantial and consistent effect demonstrated by beta-blockers in several studies including a meta-analysis suggests a real clinical

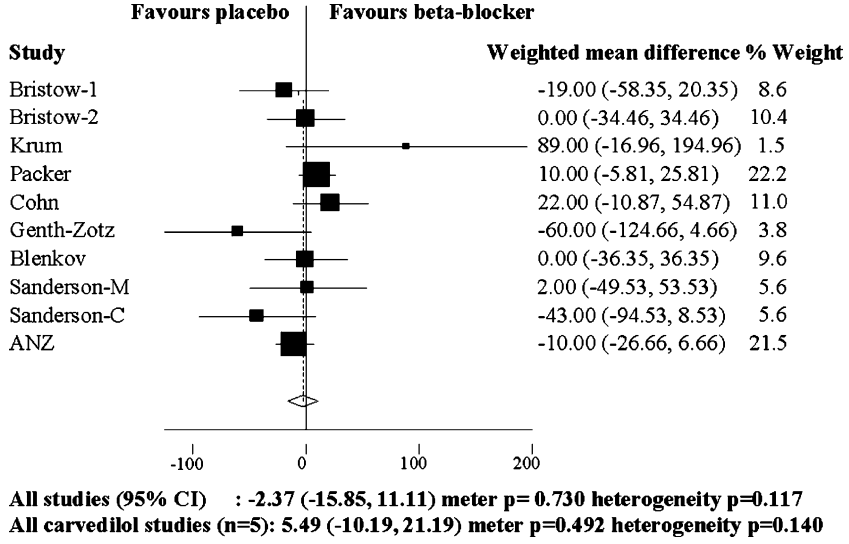


Fig. 5. Meta-analysis of 9 exercise tolerance studies showing that beta-blockers had no effect on 6-min walk distance.

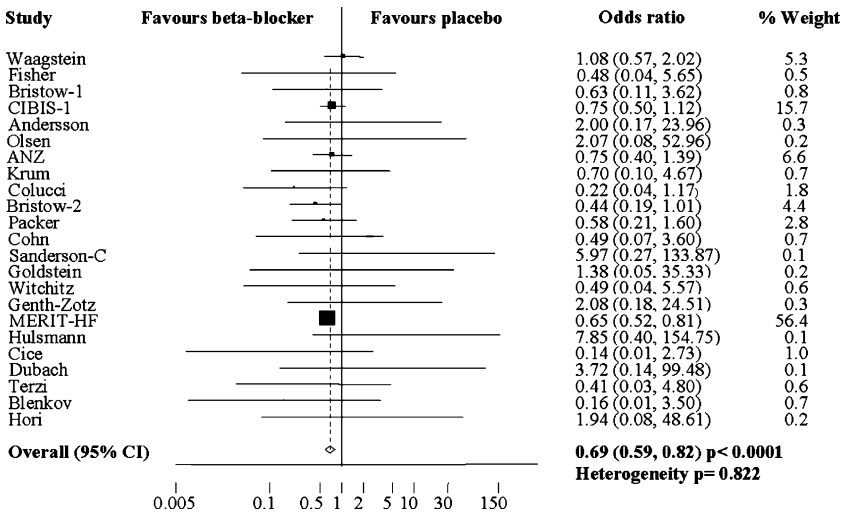


Fig. 6. Meta-analysis of 23 studies showing a significant reduction in all-cause mortality. Five studies and one substudy that did not report events in either treatment arm were excluded [23,26,32,36–38].

effect on dyspnoea. It can be argued that this effect, particularly on NYHA class II–III (exertional dyspnoea), in all likelihood might also imply some effect on exercise tolerance, even though this effect was ascertained only by prolonged exercise time and not by 6-min walk test and maximal oxygen consumption.

In the analysis of exercise tolerance time we combined results of studies using two different exercise tolerance protocols namely bicycle ergometer and treadmill tests (Fig. 3). The choice of exercise protocol depends upon the tradition of the country that conducts the study and there is no evidence demonstrating superiority of either of these methods. Hence the European and American guidelines for exercise testing in patients with heart failure recommend that the exercise protocol should be individualised so that a given test duration can be targeted [40–42]. Accordingly, it is justified to combine the results of the studies using bicycle and treadmill tests examining exercise time. The insignificant heterogeneity between the studies ($p=0.134$, Fig. 3) supports the concept that the data can be combined. Although our analysis showed a statistically significant effect produced by bicycle but not by treadmill test, it is unrealistic to conclude – due to the small number of studies and the inclusion of a predominant large population study in each subgroup – that the bicycle ergometer protocol was more reproducible. The overall combined result is therefore well represented and valid.

Several factors might have confounded the results of this meta-analysis. Use of excessive concomitant drugs like diuretics and digoxin in the placebo arm might have flawed the results particularly in the long-term studies. These drugs have a significant symptomatic effect and probably due to more frequent hospitalisation of patients on placebo, further prescriptions and increasing doses of diuretics might have led to more symptom relief in the placebo arm and thus minimised the difference in the outcome. A confounding effect by ACE inhibitors is not likely as the majority of the patients received this therapy at baseline, although a slight effect cannot be excluded.

The manner in which the studies reported changes in NYHA class only allowed inclusion of the studies that reported the number of patients changing their class to better, worse or unchanged. The consequence was that patients in NYHA class I and IV were not able to become better or worse, respectively, and the final results might therefore primarily have reflected the changes in NYHA class II–III. However, the low numbers of patients in

Table 5
Summary of current and previous meta-analyses investigating the effect of angiotensin converting enzyme (ACE) inhibitors and beta-blockers in patients with heart failure

Endpoint	Effect of ACE inhibition	Effect of adjuvant beta-blocking
Exercise tolerance [43]	Prolonged exercise time (30 s) $p=0.0008$, corresponding to 5% compared with placebo	Prolonged exercise time (44 s) $p=0.021$, corresponding to 7% compared with placebo
NYHA class [44]	OR=0.875 (0.811–0.943), $p=0.0005$	OR=0.64 (0.53, 0.76) $p<0.0001$
NYHA class IV [44]	OR=0.70 (0.56–0.87), $p=0.001$	NA
Remodeling [46]	Decrease ventricular volumes and improve pump function	Decrease ventricular volumes and improve pump function
Death or readmission [15,51]	OR=0.74 (0.69–0.80), $p<0.0001$	OR=0.68 $p<0.00001$
Death or re-infarction [51]	OR=0.77 (0.72–0.84) $p<0.0001$	NA
Sudden death [13,52]	OR=0.80 (0.70–0.92) p=NA	RR=0.70(0.54–0.89) p=NA

OR = odds ratio, RR = risk ratio, NA = not available, NYHA = New York Heart Association.

NYHA class I and IV, only 2% of the whole population, most likely did not affect the results significantly.

Compared to ACE inhibitors, beta-blockers produced a similar effect on NYHA class and exercise tolerance time [43,44]. It has also been shown that both agents improve left ventricular function [45,46]. This demonstrates that contemporary heart failure therapy is in general associated with significant and substantial symptomatic improvement (Table 5). This underscores the need for optimisation of therapy in all patient groups to obtain maximal symptomatic benefit, particularly in severe symptomatic patients who are likely candidates for further interventions and in elderly patients in whom symptomatic relief is clinically more meaningful. Furthermore, it is important for the patients who are put on long-term therapy with ACE inhibitors and beta-blockers, that they can be motivated not only by the effect on future events but also symptomatic relief in their daily lives.

Finally, it should be mentioned that although the current meta-analysis included a large number of randomised controlled trials, some limitations and publication bias are possible; therefore the results should be interpreted cautiously. It should also be mentioned that the study results have short-term implication as the majority of the included studies were characterised by short-term follow-up.

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