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REVIEW

A systematic review of selective and non-selective beta blockers for prevention of vascular events in patients with acute coronary syndrome or heart failure

O.R. de Peuter[1*], F. Lussana[1,2], R.J.G. Peters[3], H.R. Büller[1], P.W. Kamphuisen[1]

[1]Department of Vascular Medicine and [3]Cardiology, Academic Medical Centre, University of Amsterdam, Amsterdam, the Netherlands, [2]Unit of Hematology and Thrombosis, Department of Medicine, Surgery and Dentistry, Ospedale San Paolo, University of Milan, Milan, Italy,
[*]corresponding author: tel.: +31 (0)20-566 75 16, fax: +31 (0)20-566 93 43, e-mail: O.R.dePeuter@amc.uva.nl

ABSTRACT

Background: To assess the influence of β2-receptor suppression on top of selective β1-receptor blockade on the occurrence of vascular events and on all-cause mortality in patients with acute coronary syndrome (ACS) or heart failure (HF).

Methods: Systematic review of studies published since 1980. Randomised controlled trials directly comparing β1 blockers with β1+2 blockers, or comparing the two β blockers with placebo, were included. Studies had a minimum treatment period of three months and total mortality or vascular events as their primary or secondary outcome.

Results: Of the included studies, five directly compared β blockers (3733 patients) and 28 compared β blockers with placebo (30,889 patients). These latter studies were heterogeneous in study population, dose and type of β blockers. In ACS, the only study directly comparing different β blockers was underpowered to detect a difference on mortality, while in HF β1+2 blockers significantly decreased mortality compared with β1 blockers (RR 0.86, 95% confidence interval 0.78 to 0.94). In ACS, β1 blockers in placebo-controlled trials non-significantly reduced total mortality (RR 0.82, 0.67 to 1.01) or vascular events (RR 0.68, 0.42 to 1.11), while β1+2 blockers were associated with a significant decrease in total mortality (RR 0.73, 0.64 to 0.82), and vascular events (RR 0.71, 0.59 to 0.84). In HF, β1 and β1+2 blockers reduced total mortality, while only β1+2 blockers decreased vascular events (RR 0.80, 0.64 to 1.00).

Conclusions: Additional β2-receptor blockade may be more effective than β1-receptor blockade alone in preventing total mortality and vascular events in patients with ACS or, to a lesser extent, HF. However, only a few studies directly compared β blockers, and indirect comparisons were subject to heterogeneity, which weakens firm conclusions.

KEYWORDS

Epidemiology, heart failure, myocardial infarction, pharmacology, prevention

INTRODUCTION

Beta-adrenergic receptor blocking agents (β blockers) are generally recommended for the treatment of patients with acute coronary syndrome (ACS) or heart failure (HF), because of their proven positive effects on life expectancy, risk of sudden cardiac death and left ventricular ejection fraction.[1-4] In patients with HF, β blockers inhibit the adverse effects of an increased sympathetic activity, which has been associated with increased mortality.[2,5]

Beta blockers can be classified as β blockers with a much higher affinity for β1- than for β2-adrenergic receptors (β1 blockers), and β blockers with both β1- and β2-adrenergic receptor blocking properties (β1+2 blockers).[6] Previous meta-analyses have suggested a better effect of β1+2 blockers on total mortality and cardiovascular morbidity in patients with ACS[7] and HF,[8,9] although these parameters were not the primary outcomes in these trials. Furthermore, in the large COMET trial, carvedilol (a β1+2 blocker) significantly

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reduced cardiovascular mortality compared with the β1 blocker metoprolol in patients with HF.[10] Interestingly, the reduction in cardiovascular mortality was largely driven by a difference in vascular events.[11] The underlying mechanism of this effect is unclear. One hypothesis is that sympathetic activity may influence vascular events by increasing the prothrombotic activity.[12,13] This sympathetic activity may be reduced by a specific presynaptic β2-adrenergic inhibitory effect of β1+2 blockers,[14-16] resulting in less activation of platelets and clotting factors.[13] Since patients with HF have an increased sympathetic activation, β blockers with β2-adrenergic inhibitory effects could reduce the associated prothrombotic activity and, consequently, the number of vascular events.

We therefore performed a systematic review of all randomised studies assessing β blockers in patients with ACS and HF to test the hypothesis that suppression of the β2-adrenergic receptor in addition to the β1-adrenergic receptor is more effective in reducing vascular events than a more selective suppression of the β1 receptor.

METHODS

Study selection

To test our hypothesis we divided β blockers into β blockers that antagonise the β1 receptor more selectively (β1 blockers), and β blockers with both β1- and β2-adrenergic receptor blocking capacities (β1+2 blockers). The effects of β1 and β1+2 blockers for secondary prevention in patients with ACS or HF were analysed. The primary outcomes evaluated were 1) all-cause mortality and 2) vascular events, defined as fatal and non-fatal strokes, fatal and non-fatal myocardial infarctions and fatal pulmonary embolisms and other venous thromboembolic events.

We conducted a comprehensive literature search of Medline, EMBASE and the Cochrane Central Register of Controlled Trials library from 1981 to June 2009. In Medline text and Cochrane library keywords were "randomised controlled trial", "acute coronary syndrome" (in Cochrane "myocardial ischemia") or "congestive heart failure" and "adrenergic beta-antagonists", using Medical Subject Heading Terms. In EMBASE text keywords were "randomised controlled trial", and "heart muscle ischemia" or "heart failure", and "beta adrenergic receptor blocking agent". The results of the searches were limited to studies of humans and were not restricted to English language. In addition a review of references from primary or review articles was performed to identify any additional relevant studies.

The list of articles was reviewed by two authors, who independently evaluated all articles for possible inclusion. Disagreement was resolved by consensus and if necessary by the opinion of a third reviewer. When multiple papers for a single study had been published, we used the publication with the data that best corresponded to our objectives and supplemented it, if necessary, with data from the other publications. To assess the agreement between reviewers for study selection, we used the kappa (κ) statistic, which measures agreement beyond chance.[17]

We included randomised controlled or active controlled trials that directly compared β1 and β1+2 blockers. Since there were only a few trials comparing these compounds directly, we also assessed randomised placebo-controlled trials. Patients with systolic heart failure were included regardless of the underlying cause of heart failure or cardiac rhythm. Only studies with prespecified outcomes of mortality or vascular events were included. To assess the long-term effects of β-blocker treatment only studies with at least three months of treatment were considered. Studies assessing β-blockers with intrinsic sympathicomimetic, class-III antiarrhythmic or partial agonist activity, were excluded. The oldest trial with β1 blockers was published in 1981.[18] To facilitate a balanced comparison between the different β blockers, only studies published since that time were included.

Data extraction and quality assessment

Using a data extraction form, two authors independently extracted the following baseline characteristics for all included studies: first author, year of publication, source of publication, country of origin, study design, inclusion and exclusion criteria, type of β blocker used and dosage, concomitant medication, duration of follow-up, cause of heart failure, NYHA classification and left ventricular ejection fraction, number, mean age and gender of the study patients. The following outcomes were retrieved: all-cause mortality and number of strokes, myocardial (re)infarctions, or venous thromboembolic events (all fatal and non-fatal events). Since the numbers of reported events were relatively small, we analysed these events as a composite endpoint. For each study the number of patient-years was calculated by multiplying the total number of patients with the mean follow-up period.

Study quality was evaluated as described by Jadad *et al.*[19] Studies using adequate treatment allocation sequence, proper concealment, blinding of both patient and investigator, and completeness of follow-up, were considered to reflect higher methodological quality. Since not all studies provided information on these quality criteria, we also assessed the effect of including only trials with adequate concealment and loss to follow-up <20%.

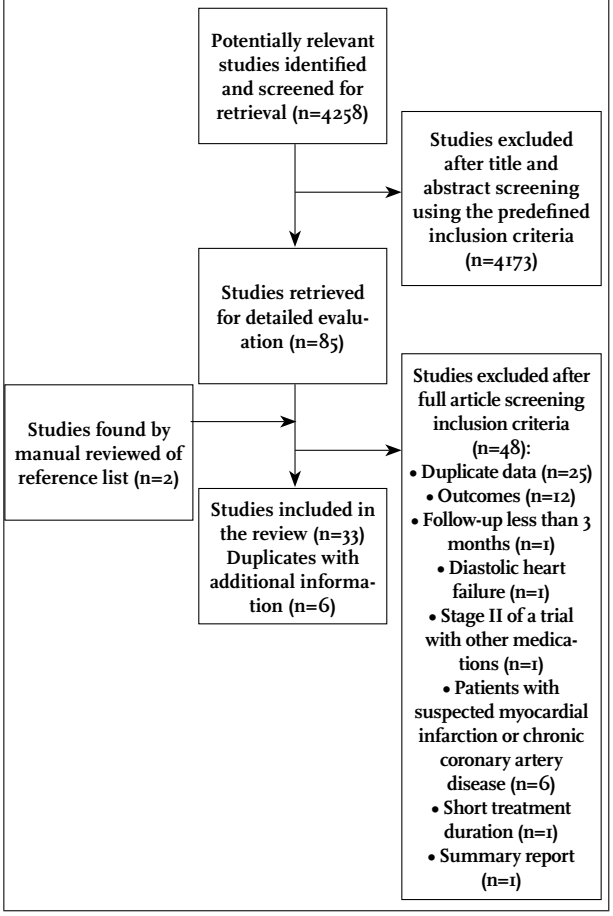
Statistical analysis

There were only a few studies that directly compared β1 and β1+2 blockers. Therefore, despite potential biases of comparisons between different studies, the effects of β1 and β1+2 blockers were indirectly analysed by pooling the results of placebo-controlled studies. Relative risks (RR)

and 95% confidence intervals (95% CI) were calculated using the DerSimonian and Laird random-effects model[20] with the Review Manager developed by the Cochrane Collaboration, version 4.2.10 for Windows. A random-effects model was chosen since results with this model are more conservative. Statistical heterogeneity between studies was evaluated using the χ^2 and I^2 test, for each of the outcomes separately, with a p value <0.05 considered as heterogeneous.

Sensitivity analyses were performed to evaluate the robustness of the results. First, we considered the effect of only including high-quality studies with a double-blind design and with a number of loss to follow-up less than 20%. In addition, the effect of excluding studies one at a time to identify those that may have a disproportionate influence on the summary treatment effect was evaluated. Publication bias was assessed using a funnel plot of effect size versus standard error.[21] In a final analysis the results were adjusted for number of patient-years to assess the influence of duration of study follow-up.

Figure 1. *Results of article search and selection*



RESULTS

Literature search

Figure 1 summarises the process of study selection. A total of 4258 relevant literature citations were identified, of which 4173 were excluded after scanning titles and abstracts, leaving 85 studies for detailed assessment. Two additional studies were identified through a manual review of study bibliographies.[22,23] Of these 87 retrieved articles, 48 were excluded for the following reasons: 12 because total mortality or vascular events were not a prespecified outcome of the study; one study because patients were followed up for less than three months; 25 because of duplicate data, substudies or commentaries; six studies were excluded because of inclusion of patients with suspected myocardial infarction or chronic coronary artery diseases, without documented ACS; one study because it included patients with diastolic heart failure; one because it was the summary report of four randomised trials with carvedilol; another because the treatment with β blockers was the second part of a trial with other medications; and one because treatment duration was only seven days. Hence, of the 39 remaining studies 33 were included in the present systematic review,[10,18,22-52] with a total of 34,360 patients (*table 1*). Six additional studies reported additional information.[11,53-57] The interobserver agreement for study selection was excellent (κ =0.98).

Study characteristics and quality

Table 1 shows the study characteristics of the 33 trials included. Five studies directly compared β1 with β1+2 blockers, one assessing patients with ACS[40] and four patients with HF.[10,37,41,44] Twenty-eight studies compared a β1 or β1+2 blocker with a control group, of which 11 studies enrolled patients with ACS[18,22,23,27,28,35,39,42,45,50,51] and 17 patients with HF.[24-26,29-34,36,38,43,46-49,52] The number of patients among the studies ranged from 50 to 3991. In one study with three treatment arms in different dosages;[29] we only included the group given the target dose used in most other studies. In another study the results from 326 of 764 subjects were excluded, since these patients had no acute myocardial infarction or HF.[23]

Various β blockers were studied: the β1 blockers included metoprolol, nebivolol, bisoprolol, atenolol and betaxol and the β1+2 blockers included carvedilol, bucindolol, propranolol and timolol. In trials that included information on concomitant treatment, on average 91% of the patients received angiotensin-converting enzyme (ACE) inhibitors, 91% diuretics, and 74% digitalis. No information was available on statin use. Twenty-seven studies were reported as double blind,[10,18,22,23,26-39,42-46,48-50,56] 13 had appropriate random allocation of treatment[10,26,30-32,35,38-40,43,49,51,52] and in ten studies information on concealment allocation was adequate.[10,26,30-32,35,38,43,49,51] A description of patient

Table 1. *Study and participant summary characteristics*

	Year	Total (n)	Mean age (years)	Male (%)	Participants	Treatment	Target dose	Main concomitant medication	Average follow-up in months	Patient-years
Patients with ACS; direct comparator β blocker										
CAMIS[40]	2005	232	61	78	Within 24 hours after AMI	Carvedilol/ Atenolol	25 mg bid/ 50 mg bid	Aspirin, statin, vasodilator	18	348
Patients with HF; direct comparator β blocker										
BETACAR[39]	2006	255	57	86	NYHA II-III, LVEF <35%	Carvedilol/ Betaxolol	25 mg bid/ 20 mg od	Vasodilator, diuretic, digitalis, nitrates	8	170
COMET[10]	2003	3029	62	80	NYHA II-IV, LVEF <35%	Carvedilol/ Metoprolol	25 mg bid/ 50 mg bid	Vasodilator, diuretic, digitalis	58	14640
Kukin[41]	1999	67	58	69	NYHA II-IV, LVEF <35%	Carvedilol/ Metoprolol	25 mg bid‡ / 25 mg bid‡	Vasodilator, diuretic, digitalis	6	34
Metra[44]	2000	150	57	91	NYHA II-IV, LVEF <35%	Carvedilol/ Metoprolol	25 mg bid†/ 50 mg bid†	Vasodilator, diuretic, digitalis	14	175
Patients with ACS; β1 blockers										
Goteborg[8]	1983	1395	66% <65 years	76	AMI	Metoprolol	100 mg bid	None reported	3	349
Lopressor[42]	1987	2395	58	83	5-15 days after AMI	Metoprolol	100 mg bid	None reported	12	2395
Manger Cats[22]	1983	553	100% <70 years	?	<1 year after AMI	Metoprolol	100 mg bid	None reported	12	553
Olsson[45]	1985	301	60	81	Within 2 days after AMI	Metoprolol	100 mg bid	Digitalis, diuretics	36	903
Salathia[23]	1985	474	6% <65 years	71	AMI	Metoprolol	100 mg bid	None reported	12	474
Patients with ACS; β1+2 blockers										
BEAT[51]	2002	343	69	83	Within 7 days after AMI, LVEF <35%	Bucindolol	50 mg bid†	Vasodilator, diuretic, digitalis	7.5	214
BHAT[28]	1982	3837	55	84	5-21 days after AMI	Propranolol	60-80 mg 3/day	None reported	25	7994
Basu[27]	1997	151	60	81	AMI	Carvedilol	25 mg bid	Aspirin, heparin, thrombolysis, nitrates	6	76
CAPRICORN[35]	2001	1959	63	74	3-21 days after AMI, LVEF <40%	Carvedilol	25 mg bid	Vasodilator, diuretics, aspirin	16	2612
Hansteen[55]	1982	560	58	85	4 days after AMI	Propranolol	40 mg 4/ day	None reported	12	560
Pedersen[57]	1983	1884	61% <65 years	62	6-27 days after AMI	Timolol	10 mg bid	Diuretics, digitalis	17	2669
Patients with HF; β1 blockers										
Anderson[24]	1985	50	51	66	LVEF <40%, idiopathic	Metoprolol	50 mg bid	Vasodilator, diuretic, digitalis, anticoagulant	19	79
CIBIS-I[31]	1994	641	60	83	NYHA III-IV, LVEF <40%	Bisoprolol	5 mg od	Vasodilator, diuretic, digitalis (in 56% of patients)	23	1229
CIBIS-II[30]	1999	2647	61	81	NYHA III-IV, LVEF <35%	Bisoprolol	10 mg od	Vasodilator, diuretic	16	3529
ENECA[36]	2005	260	72	73	NYHA II-IV, LVEF <35%	Nebivolol	10 mg od	Vasodilator, diuretic, digitalis	8	173
SENIORS[38]	2005	2128	76	63	LVEF <35%	Nebivolol	10 mg od	Vasodilator, diuretic	21	3724
MERIT-HF[43]	1999	3991	64	78	NYHA II-IV, LVEF <40%	Metoprolol*	200 mg od	Vasodilator, diuretic	12	3991
Waagstein[52]	1993	383	49	?	LVEF <40%, idiopathic dilated cardiomyopathy	Metoprolol	100-150 mg 2-3/day	Vasodilator, diuretic, digitalis	12	383

This table continues on the next page.

Table 1. *Continued*

	Year	Total (n)	Mean age (years)	Male (%)	Participants	Treatment	Target dose	Main concomitant medication	Average follow-up in months	Patient-years
Patients with HF; β1+2 blockers										
Aranow[25]	1997	158	81	29	NYHA II-III, LVEF >40%, prior ACS	Propranolol	30 mg 3/ day	Vasodilator, diuretic, digitalis in AF	32	421
Austr/NZ HF[26]	1997	415	67	80	NYHA II-III, LVEF <45%, ischaemic cause	Carvedilol	25 mg bid	Vasodilator, diuretic, digitalis	19	657
BEST[49]	2001	2708	60	78	NYHA III-IV, LVEF <35%	Bucindolol	50-100 mg bid	Vasodilator, diuretic, digitalis	24	5416
CHRISTMAS[32]	2003	387	63	90	NYHA I-III, LVEF <40%, ischaemic cause	Carvedilol	25 mg bid	Vasodilator, diuretic	6	194
COPERNICUS[47]	2001	2289	63	80	LVEF <25%	Carvedilol	25 mg bid	Vasodilator, diuretic, digitalis	10	1908
Cohn[33]	1997	105	60	69	<150 meter on walking test, LVEF <35%	Carvedilol	25 mg bid	Vasodilator, diuretic, digitalis, nitrates	6	53
Colucci[34]	1996	366	54	85	425-550 meter on walking test, LVEF<35%	Carvedilol	25 mg bid‡	Vasodilator, diuretic, digitalis, nitrates	7	214
MOCHA[29]	1996	173	60	77	150-425 meter on walking test, LVEF <35%	Carvedilol	25 mg bid	Vasodilator, diuretic	6	87
Palazzuoli[48]	2005	58	71	66	NYHA III-IV, LVEF <40%	Carvedilol	25 mg bid	Vasodilator, diuretic, digitalis, anticoagulant	12	58
PRECISE[46]	1996	278	60	73	150-450 meter on walking test, LVEF <35%	Carvedilol	25 mg bid‡	Vasodilator, diuretics, digitalis	6	139

ACS = acute coronary syndrome; HF = heart failure; AMI = acute myocardial infarction; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; B = blinding of outcome measure; R = randomisation; bid = twice daily, od = once daily; P = one of our endpoints was a primary outcome. W = description of withdrawals. ‡If bodyweight >85 kg target dose was doubled. †If bodyweight >75 kg target dose was doubled. * Metoprolol CR/XL.

withdrawal was provided in all studies except two.[22,37] Based on Jadad's scale,[19] ten out of 33 (30.3%) studies were rated as high quality.[10,26,30-32,35,38,39,43,49]

Direct comparison of β1 and β1+2 blockers in patients with ACS and HF

For ACS, the only study with direct comparison of different β blockers (n=232) showed no difference on all-cause mortality (RR 0.39, 95% CI 0.08 to 1.95).[40] No data were available on vascular events.

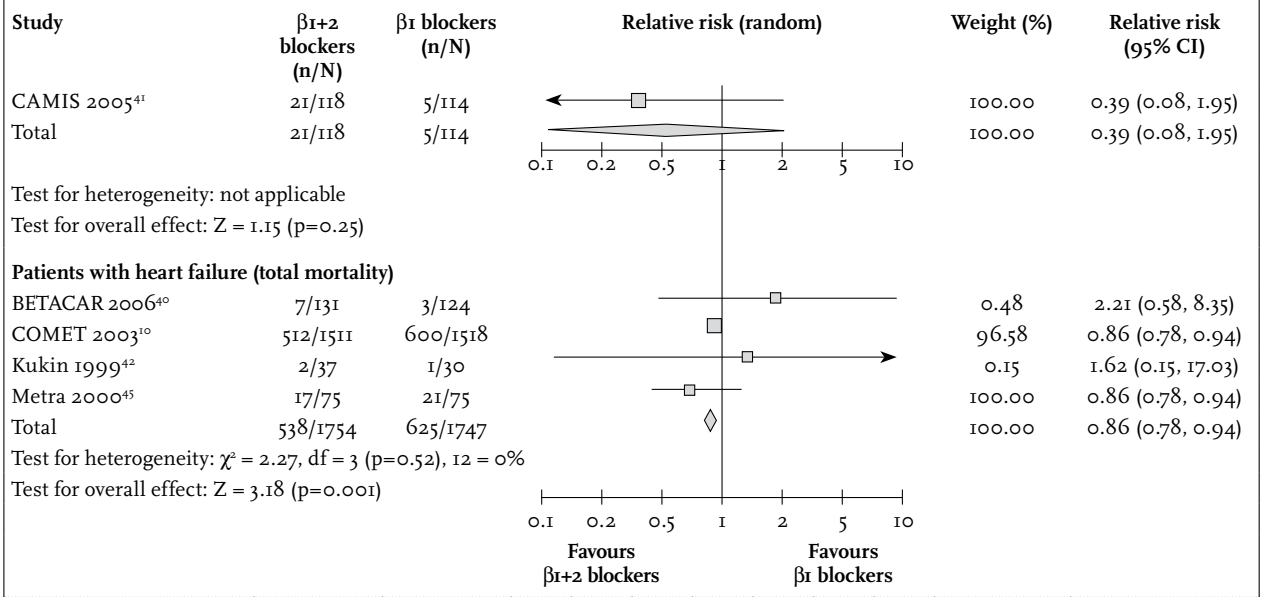
In four studies that directly compared the effects of β1 and β1+2 blockers on total mortality in patients with HF,[10,37,41,44] β1+2 blockers significantly decreased total mortality compared with β1 blockers (RR 0.86, 95% CI 0.78 to 0.94) (*figure 2*). It should be noted that the COMET trial[10] contributed to more than 96% of these results. Only the COMET trial reported vascular mortality and morbidity,[11] showing a significantly better effect of the β1+2 blocker carvedilol in reducing fatal and non-fatal myocardial infarction and death from stroke (HR 0.70, 95% CI 0.50 to 0.99, and HR 0.33, 95% CI 0.18 to 0.62, respectively).

Indirect comparison of β1 and β1+2 blockers in ACS

In the five studies on β1 blockers,[18,22,23,42,45] treatment resulted in a non-significant reduction of all-cause mortality compared with placebo (RR 0.82, 95% CI 0.67 to 1.01) (*figure 3*). Information on vascular events was available in three of the five studies.[18,42,45] Fifty-six of the 2047 (3%) patients with β1 blockers and 81 of 2044 (4%) patients in the control group had vascular complications, without a statistical significant difference between the two groups (RR 0.68, 95% CI 0.42 to 1.11) (*figure 3*). There was no clear heterogeneity across studies for both outcomes (I^2=31.4 %, p=0.20 and I^2=0 %, p=0.61, respectively).

Compared with placebo, β1+2 blockers reduced total mortality in patients with ACS, (RR 0.73, 95% CI 0.64 to 0.82).[27,28,35,39,50,51] In addition, β1+2 blockers also lowered the risk of vascular events by 29% (RR 0.71, 95% CI 0.59 to 0.84), occurring in 395 of 4361 (9%) patients with β blockers and in 545 of 4373 (12%) patients with placebo (*figure 3*). This effect was consistent in all studies except one.[39] There was no significant statistical heterogeneity among the studies (I^2=0%, p=0.79).

Figure 2. *Direct comparison of β1 and β1+2 blocker treatment on total mortality*



95% CI = 95% confidence interval; n = number of events; N = number of included patients.

Indirect comparison of β1 and β1+2 blockers in HF

In seven studies that assessed all-cause mortality in patients with heart failure,[24,30,31,36,38,43,52] 558 of 5057 patients (11%) who received β1 blockers died compared with 736 of 5043 patients (15%) in the control group, resulting in a reduction in mortality (RR 0.76, 95% CI 0.68 to 0.84) (*figure 4*). Data on vascular events were available in three placebo-controlled trials,[30,31,52] involving 3671 patients. In these studies, β1 blockers did not protect patients against vascular events, as compared with placebo (RR 1.33, 95% CI 0.86 to 2.04) (*figure 4*). There was no significant heterogeneity for both outcomes (I^2=0 %, p=0.38 and I^2=19.3 %, p=0.28, respectively) (*figure 4*).

For β1+2 blockers, ten trials assessed all-cause mortality,[25,26,29,32-34,46-49] 625 of 3546 (18%) HF patients who received β1+2 blockers died, compared with 762 of 3391 (22%) patients in the control group, with a statistically significant reduction in mortality (RR of 0.75, 95% CI 0.61 to 0.92) (*figure 4*). For this latter outcome there was some heterogeneity across the studies (I^2=41%, p=0.04).

Six trials reported vascular events in HF.[25,26,29,46,47,49] Compared with placebo, β1+2 blockers were associated with a 20% decrease in vascular events (RR 0.80, 95% CI 0.64 to 1.00).

All trials reported fatal or non-fatal events of worsening heart failure; β1 and β1+2 blockers equally decreased these events (RR 0.77, 95% CI 0.61 to 0.97, and RR 0.82, 95% CI 0.70 to 0.95 respectively, data not shown).

Sensitivity analysis

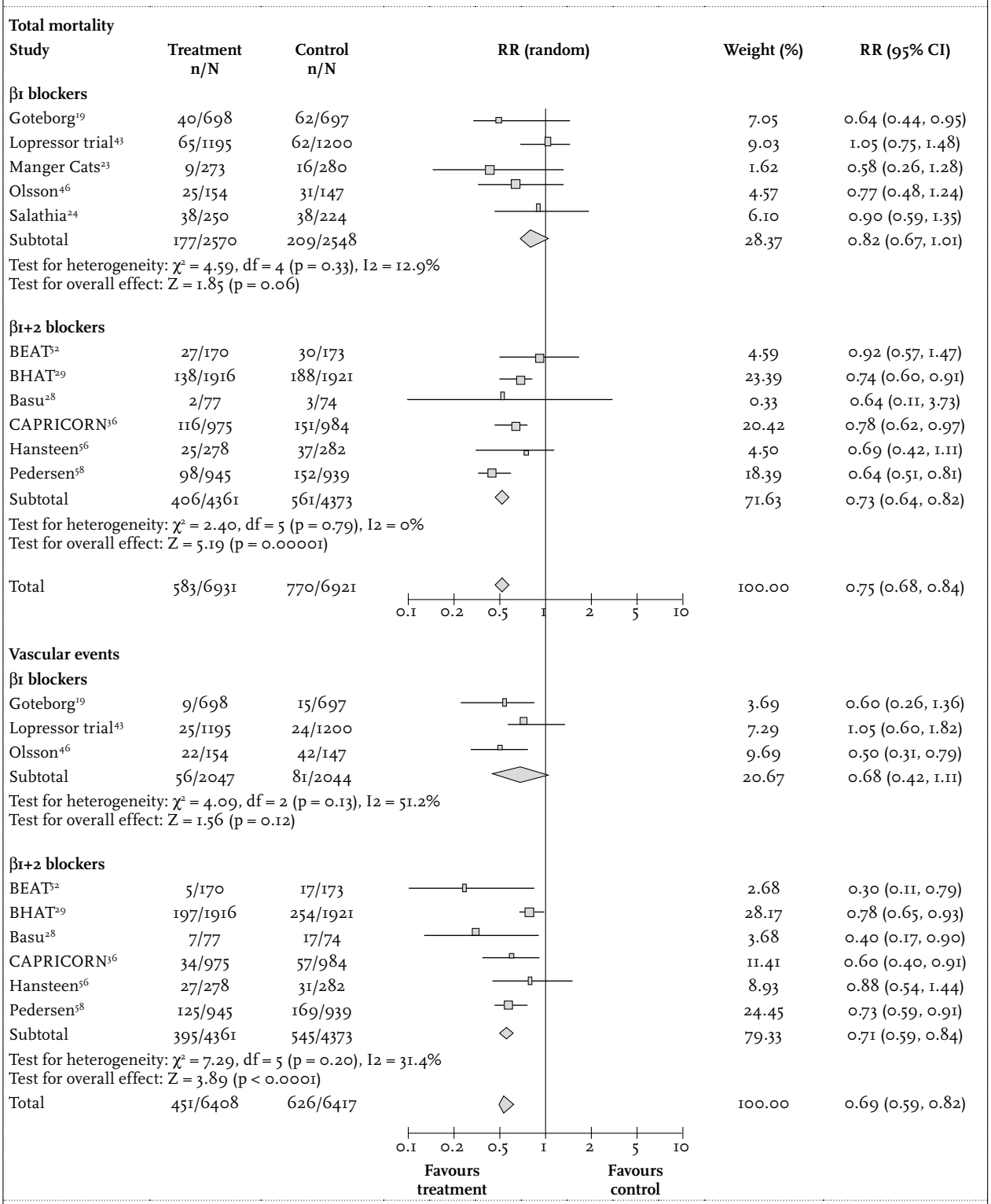
The results of our primary analyses were unaffected by removing individual studies one by one or by analysing the effect of different β blockers. Assessing various factors in Jadad's scale did not affect the significant associations in the results. Moreover, including only higher quality studies, results were virtually the same (*table 2*). When we analysed the long-term effects of β-blocker treatment among studies that had a follow-up of at least 12 months, the overall results on total mortality and on fatal and non-fatal vascular events did not change. Due to the low number of reported events, separate analysis for myocardial infarction and stroke was not possible.

The funnel plots for the studies with patients with ACS were symmetrical, indicating no publication bias. There was some asymmetry in the funnel plots for β blockers in patients with HF, indicating a possible publication bias. Because of its low power and relatively small number of included trials (maximum of ten included studies per group), we did not perform an Egger's regression analysis. Correcting the results for number of patient-years provided similar pooled relative risks for all figures (data not shown).

DISCUSSION

This systematic review confirms the beneficial effects of β blockers on total mortality, as reported previously.[8,9,58] We specifically assessed the beneficial effect of β2-adrenergic receptor blockade on vascular events in patients with ACS or HF. Beta blockers with β2-adrenergic inhibitory effects could reduce sympathetic activation and the associated prothrombotic activity, and, consequently, the number of vascular events. Indeed, our results suggest a somewhat

Figure 3. *Effects of β1 and β1+2 blocker treatment on total mortality and vascular events in patients with acute coronary syndrome*



RR = relative risk; 95% CI = 95% confidence interval; n = number of events; N = number of included patients.

Figure 4. *Effects of β1 and β1+2 blocker treatment on total mortality and vascular events in patients with heart failure*

Total mortality

Study	Treatment n/N	Control n/N	RR (random)	Weight (%)	RR 95% CI)
β1 blockers					
Anderson[25]	5/25	6/25		1.10	0.83 (0.29, 2.38)
CIBIS-I[32]	53/320	67/321		7.64	0.79 (0.57, 1.10)
CIBIS-II[31]	156/1327	228/1320		13.17	0.68 (0.56, 0.82)
ENECA[37]	7/134	7/126		1.16	0.94 (0.34, 2.61)
MERIT-HF[44]	145/1990	217/2001		12.57	0.67 (0.55, 0.82)
SENIORS[39]	169/1067	192/1061		13.19	0.88 (0.72, 1.06)
Waagstein[53]	23/194	19/189		3.27	1.18 (0.66, 2.09)
Subtotaal	558/5057	736/5043		52.11	0.76 (0.68, 0.87)
Test for heterogeneity: χ^2 = 7.44, df = 6 (p = 0.28), I2 = 19.3%					
Test for overall effect: Z = 4.24 (p = <0.0001)					
β1+2 blockers					
Aronow[26]	44/79	60/79ww		11.07	0.73 (0.58, 0.93)
Austr / NZ HF[27]	20/207	26/208		3.51	0.77 (0.45, 1.34)
BEST[50]	411/1354	448/1354		17.37	0.92 (0.82, 1.02)
CHRISTMAS[33]	8/193	6/194		1.12	1.34 (0.47, 3.79)
COPERNICUS[48]	130/1156	190/1133		12.24	0.67 (0.54, 0.83)
Cohn[34]	2/70	2/35		0.34	0.50 (0.07, 3.40)
Colucci[35]	2/232	5/134		0.47	0.23 (0.05, 1.17)
MOCHA[30]	1/89	13/84		0.31	0.07 (0.01, 0.54)
PRECISE[47]	6/133	11/145		1.28	0.59 (0.23, 1.56)
Palazzuoli[47]	1/33	1/25		0.17	0.76 (0.05, 11.53)
Subtotal	625/3456	762/3391		47.89	0.75 (0.61, 0.92)
Test for heterogeneity: χ^2 = 18.05, df = 9 (p = 0.03), I2 = 50.1%					
Test for overall effect: Z = 2.78 (p = 0.005)					
Total	1183/8603	1498/8434		100.00	0.77 (069, 0.86)
Test for heterogeneity: χ^2 = 1.95, df = 2 (p = 0.38), I2 = 0%					
Test for overall effect: Z = 1.29 (p = 0.20)					
			0.01 0.1 1 10 100		
Vascular events					
β_1 blockers					
CIBIS-I[32]	10/320	11/321		7.93	0.91 (0.39, 2.12)
CIBIS-II[31]	38/1327	24/1320		16.55	1.57 (0.95, 2.61)
Waagstein[53]	0/194	1/189		0.67	0.32 (0.01, 7.92)
Subtotal	48/1841	36/1830		23.15	1.33 (0.86, 2.04)
Test for heterogeneity: χ^2 = 5.45, df = 5 (p = 0.36), I2 = 8.2%					
Test for overall effect: Z = 1.98 (p = 005)					
Aranow[26]	3/79	5/79		3.27	0.60 (0.15, 2.43)
Austr / NZ HF[27]	25/207	34/208		17.64	0.74 (0.46, 1.19)
BEST[50]	79/1354	78/1354		27.15	1.01 (0.75, 1.37)
COPERNICUS[48]	52/1156	76/1133		24.68	0.67 (0.48, 0.95)
MOCHA[30]	1/89	3/84		1.33	0.31 (0.03, 2.97)
PRECISE[47]	0/133	3/145		0.78	016 (0.01, 299)
Subtotal	160/3018	199/3003		74.85	0.80 (0.64, 1.00)
Total	208/4859	235/4833		100.00	0.87 (0.67, 1.14)
			0.01 0.1 1 10 100		
			Favours treatment	**Favours control**	

RR = relative risk; 95% CI = 95% confidence interval; n = number of events; N = number of included patients.

Table 2. *Sensitivity analysis by methodological criteria, defined as double blind and loss to follow-up less than 20%*

Group of patients and outcomes	β1 blockers RR (95% CI)	β1+2 blockers RR (95% CI)
Acute coronary syndrome: total mortality	0.84 (0.67-1.05)	0.72 (0.63-0.81)
Acute coronary syndrome: vascular events	0.68 (0.42-1.11)	0.74 (0.66-0.84)
Heart failure: total mortality	0.75 (0.66-0.85)	0.74 (0.56-0.96)
Heart failure: vascular events	1.34 (0.82-2.18)	0.79 (0.61-1.03)

RR = relative risk; CI = confidence interval.

better, and at least a more consistent, reduction of vascular events and total mortality of additional β2-receptor blockade compared with β1-receptor blockade alone in patients with ACS. In patients with HF, β1 and β1+2 blockers both reduced total mortality, but only β1+2 blockers had an effect on vascular events.

Our analysis was hampered by the few trials that directly compared β1 and β1+2 blockers, including a limited number of patients. For ACS one trial directly compared β blockers, but was underpowered to detect a difference on mortality. For HF, four trials directly compared β blockers, but these results were dominated by the large COMET trial, in which the dosages and formulation of metoprolol tartrate have been heavily debated.[59] The remaining three trials included only 472 patients and were not powered to detect a difference on mortality. The results of the COMET trial point to beneficial effects of carvedilol on reducing vascular events, which could also be explained by antiadrenergic effects.[60]

Consequently, we extended our analysis to placebo-controlled trials assessing the efficacy of the different β blockers, a method prone to potential biases. These studies have different designs and are heterogeneous, which impairs comparing these studies. Different types and dosages of β blockers were assessed, the study subjects differed, and clinical outcomes were not clearly reported in every trial. In addition, the β1 blocker trials were in general older than the studies assessing the β1+2 blockers. However, β1+2 blockers studies showed far more consistency compared with β1 blockers, with a reduction of vascular events in all except one trial. Furthermore, the validity of our findings is supported by the absence of heterogeneity among studies for the major outcomes, and by the sensitivity analysis, where the better efficacy of β1+2 blockers remained in high-quality studies. In addition, removing individual trials or analysing different types of β blockers did not affect our main results. Five out of six studies that investigated the efficacy of β1+2 blockers in patients with ACS, including the three largest studies involving almost 8000 patients, found a reduction in vascular events.[28,35,57]

Our aim was to assess the influence of β2-receptor blockade in addition to β1-receptor blockade. We therefore compared β1 versus β1+2 blockers. Due to this classification we also included third-generation β blockers (such as carvedilol and nebivolol) in both groups. These third-generation β blockers have additional effects such as α-receptor blocking properties, antioxidative effects and NO-releasing capacities and have a more favourable metabolic profile.[61,62] These additional effects on our outcome parameters cannot be totally ruled out. However, the third-generation β1 blocker nebivolol showed no clear effect on mortality and vascular events. Furthermore, the beneficial effect of β1+2 blockers on vascular events could have been influenced by α1-receptor blocking properties of the β1+2 blockers carvedilol and bucindolol. However, propranolol and timolol,[28,55,57] not affecting the α1 receptor, also reduced all-cause mortality and vascular events in the ACS trials (RR 0.63, 95% CI 0.55 to 0.74, and RR 0.77, 95% CI 0.67 to 0.88, respectively). In addition, specific α1-receptor blockers are not effective in patients with HF, also when combined with β1 blockers.[63]

Previous studies have suggested that the release of norepinephrine is partly regulated by prejunctional β_2-adrenergic receptors. This implies that β1+2 blockers have a specific sympathoinhibitory effect that is less prominent in more selective β1 blockers. Indeed, β1+2 blockers reduce norepinephrine levels more effectively compared with selective β1 blockers.[14-16] Furthermore, increased (nor)epinephrine plasma levels enhance coagulation activity by increased platelet activity and thrombin generation,[13,64] and these prothrombotic effects can be blocked by the β1+2 blocker propranolol but not by metoprolol or phentolamine, which points to a specific β2-adrenergic receptor mediated effect.[13] Thus β1+2 blockers not only reduce sympathetic activity more effectively, but also the associated platelet activation and increments in coagulation factors.[13,64-66] The net result could be a reduced prothrombotic state, thereby reducing both arterial as venous thrombotic events.

In conclusion, this systematic review suggests that suppression of the β2-adrenergic receptor in addition to the β1 receptor may be more effective in reducing vascular events in patients with ACS and HF. The current literature is too heterogeneous to draw firm conclusions. Nevertheless, the presumed antithrombotic effect of β2-adrenergic receptor blockers may call for additional studies assessing the beneficial effect of β1+2 blockers in patients with ACS or HF.

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