Revisiting the clinical evidence of heart rate target in patients with heart failure treated with beta-blockers

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Abstract

Objective: On evaluating the guidelines from previous studies, we found no randomized controlled trials on the use of beta-blockers for heart failure (HF) that employed as evidence for heart rate targets of 60 or 70 beats/min. In this study, we aimed to assess the target heart rate in patients with HF treated with beta-blockers.

Methods: We used the keywords, "heart failure" and "beta-blocker" to search PubMed, Ovid, EMBASE, and Cochrane from 1966 to June 2021. Two authors independently reviewed the results of the search strategy and selected all the studies that reported the effect of beta-blockers on all-cause mortality in patients with HFrEF. We conducted analyses using Review Manager, version 5.0 and Stata version 12.0. Risk of bias was assessed regarding randomization, allocation sequence concealment, blinding, incomplete outcome data, and other biases. Sensitivity analysis was carried out to compare the results of fixed effect model with the results of random effect.

Results: No clinical trial supported the optimal heart rate of 60 beats/min. Risk ratio (RR) and 95% confidence interval (CI) were 0.77 (0.71, 0.83) and 0.86 (0.76, 0.97) in the subgroup with a baseline heart rate >80 beats/min and subgroup with baseline of ≤80 beats/min, respectively. RR and 95% CI were 0.92 (0.82, 1.02) and 0.77 (0.65, 0.92) in 2 subgroups with heart rate controlled ≥70 beats/min and 60–70 beats/min, respectively. Accumulated to MOCHA 1 trial (heart rate controlled 70 beats/min), there was no significant difference in mortality between the experimental group and the control group (RR=0.91, 95% CI 0.82–1.02). Accumulated to SENIORS trial (heart rate controlled 68.8 beats/min), there was a difference in mortality between the experimental and the control groups (RR=0.90, 95% CI 0.82–0.99).

Conclusion: The main effect of beta-blockers in the treatment of HF is achieved by lowering heart rate. The use of beta-blockers did not benefit in people with HFrEF whose heart rate was 77 beats/min before they started the treatment regimen. In patients with HFrEF, the purpose of beta-blockers is to control the heart rate to 65–70 beats min.

Keywords: beta-blocker, heart rate, heart failure, death, ejection fraction, meta-analysis

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Introduction

Beta-blockers are the cornerstone of treatment for heart failure with reduced ejection fraction (HFrEF) (1, 2). Current guidelines (3-5) recommend that patients with stable, symptomatic HF [New York Heart Association (NYHA) class II–IV] should start using beta blockade as early as possible and eventually continue to use it at the maximum tolerable dose. However, there are no specific targets for the use of beta blockers.

Heart rate is an independent risk factor for HF (6). An observational study involving 112,680 people showed that people in the general population with heart rate controlled at approximately 65

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HIGHLIGHTS

- This meta-analysis assesses target heart rate (HR) in patients with heart failure (HF) with reduced ejection fraction (HFrEF) treated with beta-blockers.
- This meta-analysis confirms a clear and specific relationship between HR and beta blockers in the treatment of HF.
- The use of beta-blockers did not significantly benefit people with HFrEF whose HR was 77 beats/min before the use of beta-blockers.

beats/min have the lowest total mortality rates and cardiovascular mortality rates (7). An observational study of 145,211 patients with HF reported a J-shaped relationship between hospital mortality and heart rate. They found that the mortality rate was the lowest among those with a heart rate of 70–75 beats/min (8). Both the American College of Cardiology/American Heart Association (3, 9) and European Society of Cardiology (5) guidelines recommend that patients with a heart rate higher than 70 beats/min after beta-blocker use should consider using ivabradine. This suggests that the heart rate should be controlled at about 70 beats/min with beta blockers. However, so far, no randomized controlled trials of beta blockers for HF were used as evidence for heart rate targets of 60 or 70 beats/min.

This systematic review of randomized controlled trials of beta-blockers in patients with HFrEF was conducted to assess the target heart rate of patients with HF treated with beta blockers.

Methods

We searched PubMed, Ovid, EMBASE, and Cochrane from 1966 to June 2021. No language restrictions were applied, and only human studies, clinical trials, randomized and controlled trials' publications were considered. "Heart failure" and "beta-blocker" were used as keywords. In addition, we searched recent meta-analyses or reviews of beta-blocker in heart failure and HF guidelines.

Selection and data abstraction

Two authors independently reviewed the results and selected studies that reported the effect of beta-blockers on all-cause mortality in patients with HFrEF. Studies were excluded if they did not report death at the end of the follow-up, used beta-blockers for one month or less, or enrolled less than 50 patients. Trials were excluded if there was no difference in the heart rate between the two groups at the end of the trial.

Two authors independently extracted all outcome data with subsequent discussion of any discrepancies. The outcomes from each study were extracted in intention-to-treat categories rather than per-protocol categories (that is, all outcomes were analyzed by randomization group to avoid bias from excluding patients who dropped out, were withdrawn, or did not adhere to treatment).

Statistical analysis

A meta-analyses and subgroup analysis were conducted using Review Manager, version 5.0 (The Cochrane Collaboration, Copenhagen, Denmark). We did cumulative analyses using Stata version 12.0. Owing to the relatively common outcome of interest, we calculated risk ratios (RRs) and 95% confidence interval (CI). We assessed and quantified statistical heterogeneity for each outcome of interest using the Cochran Q test and the I^2 statistic, respectively. The I^2 statistic quantifies the percentage of statistical heterogeneity due to between-study variability. By convention, values ≤25%, 25% to 50%, and ≥50% are considered to have low, moderate, and high amounts of heterogeneity, respectively. If the heterogeneity was high, the statistical method chose the random effect model.

Results

Study selection and evaluation

Among the 8 citations that we identified in our search, 106 were potentially eligible for inclusion. Consequently, 84 were excluded after a detailed review (Fig. 1).

Studies included in the systematic review

Table 1 shows the features from 22 (10-31) randomized trials. Three trials (13, 17, 28) reported outcome data in subgroups (each of these subgroups is reported as a separate row in Table 1). Therefore, a total of 27 trials or subgroups were included in the statistical analysis. The randomization scheme was used in all the experiments, and loss of follow-up and withdrawal were

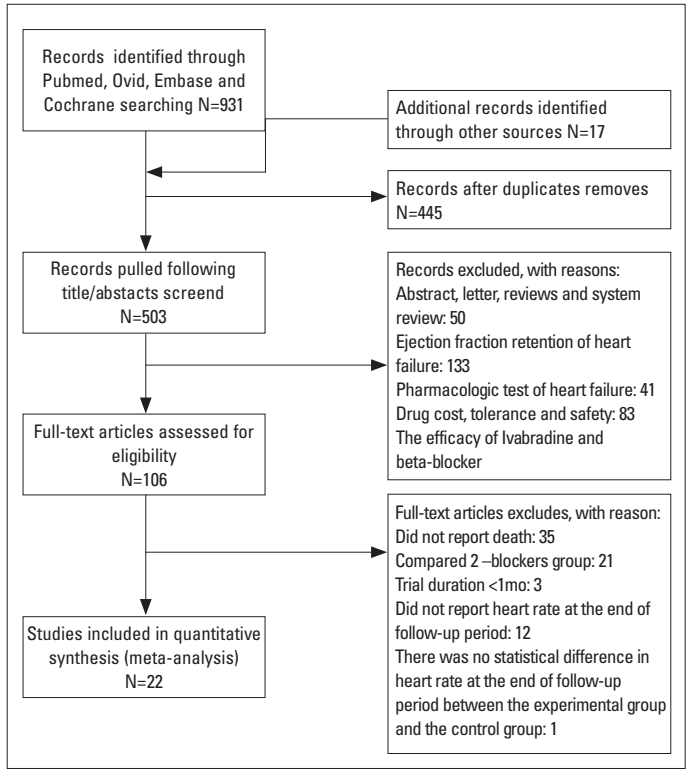

Figure 1. Study flow diagram

Table 1. Characteristics of inclusion trials

Study	Sample size, n beta-blocker vs. control	Mean age, year beta-blocker vs. control	Men, % beta-blocker vs. control	Objects of study	Average follow-up time	Beta-blocker therapy, final dose, mg/day	Baseline heart rate in treatment group, beats/min	Baseline heart rate in control group, beats/min	Baseline systolic pressure in treatment group, mm Hg	Baseline mean LVEF in treatment group	Heart rate in follow-up treatment group	Heart rate in follow-up control group
Anderson, 1985 (10)	25 vs. 25	50±15 vs. 51±13	56 vs. 76	Diagnosis of idiopathic dilated cardiomyopathy made under an approved protocol, LVEF <0.40	19 months	Metoprolol, 61	85	85	—	0.29±0.1	75±12	84±21
MDC, 1993 (11)	194 vs. 189	49±12 vs.49±12	75 vs. 70	Idiopathic dilated cardiomyopathy LVEF <0.40	12 months	Metoprolol, 108±51	91±18	90±17	118±17	0.22±0.08	—	—
Fisher, 1994 (12)	25 vs. 25	63±8 vs. 63±10	100 vs. 92	Chronic heart failure and coronary artery disease LVEF ≤0.40	6 months	Metoprolol, 87 ± 25	82±12	86±12	117±25	0.22±0.08	—	—
Bristow I, 1994 (13) low-dose	38 vs. 34	55±2 vs. 52±2	68 vs. 59	Subjects were required to have heart failure symptoms of at least 1 month's duration, LVEF <0.40,	12 weeks	Bucindolol, 12.5	86±2	87±2	114±3	0.247±0.013	Decreased 6.0±1.2	Increased 1.2±2.6
Bristow II, 1994 (13) medium-dose	32 vs. 34	56±2 vs. 52±2	56 vs. 59		12 weeks	Bucindolol, 50	87±2	87±2	122+4	0.241±0.012	Decreased 5.0±1.4	Increased 1.2±2.6
Bristow III, 1994 (13) high-dose	35 vs. 34	56±1 vs. 52±2	60 vs. 59		12 weeks	Bucindolol 200	88±2	87±2	117±3	0.232±0.011	Decreased 5.0±1.4	Increased 1.2±2.6
CIBIS, 1994 (14)	320 vs. 321	60.1±1.2 vs. 59.2±1.1	82.5 vs. 83	Chronic heart failure of various etiologies, LVEF <0.40	1.9±0.1 years	Bisoprolol, 3.8±0.2	82.8±1.5	82.5±1.6	127.7±1.7	0.250±0.009	Decreased 15.7±1.7	Unchanged
Olsen, 1995 (15)	36 vs. 24	54±2 vs. 50±3	94 vs. 92	Stable heart failure caused by ischemic or idiopathic dilated cardiomyopathy, LVEF <0.35	3 months	Carvedilol, 50 weight <75 kg; 100 weight >75 kg	87±3	83±3	——	0.20 ± 0.0l	67±3	84±3
PRESCISE, 1996 (16)	133 vs. 145	59.3±11.8 vs. 61.2±11.8	74 vs. 73	LVEF ≤0.35	6 months	Carvedilol, 28±13	85±12	83±12	117±18	0.22±0.07	Decreased 16.3	Decreased 1.9
MOCHA I, 1996 (17) low-dose	83 vs. 84	58±11 vs. 60±11	74 vs. 76	Symptomatic heart failure from ischemic or non-ischemic dilated cardiomyopathy, LVEF ≤0.35	6 months	Carvedilol 12.5	86±15	83±16	115±19	0.23±0.08	70±21	80±12

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Table 1. Characteristics of inclusion trials (Continue)

Study	Sample size, n beta-blocker vs. control	Mean age, year beta-blocker vs. control	Men, % beta-blocker vs. control	Objects of study	Average follow-up time	Beta-blocker therapy, final dose, mg/day	Baseline heart rate in treatment group, beats/min	Baseline heart rate in control group, beats/min	Baseline systolic pressure in treatment group, mm Hg	Baseline mean LVEF in treatment group	Heart rate in follow-up treatment group	Heart rate in follow-up control group
MOCHAII, 1996 (17) medium-dose	89 vs. 84	60±13 vs. 60±11	76 vs. 76			Carvedilol, 25	80±13	83±16	113±16	0.23±0.08	68±12	80±12
MOCHA III, 1996 (17) high-dose	89 vs. 84	60±13 vs. 60±11	78 vs. 76			Carvedilol, 50	84±17	83±16	117±18	0.23±0.08	67±13	80±12
Cohn, 1997 (18)	70 vs. 35	59.7±13.9 vs. 60.6±11.6	54 vs. 66	symptomatic, advanced heart failure, LVEF ≤0.35	6 months	Carvedilol, 50	85	79	117	0.22±0.08	68	81
ANZ, 1997 (19)	207 vs. 208	67	80	chronic stable heart failure due to ischemic heart disease, LVEF <0.45	6 months	Carvedilol, 47 mg	——	——	——	——	——	——
CIBIS II, 1999 (20)	1327 vs. 1320	61 vs. 61	81 vs. 80	symptomatic heart failure, LVEF ≤0.35	1.3 years	Bisoprolol, 5.0-10.0	81.0±15.5	79.9±14.5	129.2±10.2	0.275±0.06	——	——
RESOLVD, 2000 (21)	214 vs. 212	62±12 vs. 61±11	79 vs. 80	LVEF <0.40	17 weeks	Metoprolol CR 156±70	——	——	——	0.28±0.11	——	——
Strum, 2000 (22)	51 vs. 49	51±11 vs. 52±10	86 vs. 90	LVEF ≤0.25	2 years	Atenolol, 125 mg	89±15	91±15	115±18	0.17±0.05	——	——
BEST, 2001 (23)	1354 vs. 1354	60±12.6 vs. 60±12.3	77 vs. 79	NYHA class III or IV heart failure that was due to primary or secondary dilated cardiomyopathy LVEF≤0.35	3 years	Bucindolol 50 weight <75 kg 100 weight >75 kg	82±13.4	81±13.1	117±18.2	0.23±0.074	Decreased 8.6±13.9	Decreased 2.1±13.4
CAPRICORN, 2001 (24)	975 vs. 984	63 vs. 63	73 vs. 74	AMI LVEF ≤0.4	2.5 years	Carvedilol, 12.5-50 mg	77.3± 11.4	77.2±11.3	121.6	0.329	——	——
PACKER, 2001 (25)	1156 vs. 1133	63.4±11.5 vs. 63.2±11.4	79 vs. 80	severe chronic heart failure LVEF <0.25	10.4 months	Carvedilol, 37 mg	83±13	83±12	123±19	0.199±0.040	——	——
MERIT-HF, 2002, (26)	1806 vs. 1845	63.7 vs. 63.6	77.6 vs. 77.2	Symptomatic chronic heart failure, NYHA class II or IV, LVEF ≤0.40	2.4 years	Metoprolol, 192/76	83	83	130	0.28	67	Decreased 0.28

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Table 1. Characteristics of inclusion trials (Continue)

Study	Sample size, n beta-blocker vs. control	Mean age, year beta-blocker vs. control	Men, % beta-blocker vs. control	Objects of study	Average follow-up time	Beta-blocker therapy, final dose, mg/day	Baseline heart rate in treatment group, beats/min	Baseline heart rate in control group, beats/min	Baseline systolic pressure in treatment group, mm Hg	Baseline mean LVEF in treatment group	Heart rate in follow-up treatment group	Heart rate in follow-up control group
CHRISTMAS, 2003 (27)	193 vs. 194	62±9 vs. 63±9	90 vs. 90	Stable chronic heart failure owing to coronary artery disease, NYHA class I–III, LVEF <0.40	6 months	Carvedilol, 12.5-100	77±11	78±13	127	0.30	65±13	81±13
CARMEN I, 2004 (28)	191 vs. 190	61.9 vs. 62.9	77 vs. 84	Stable mild CHF, LVEF <0.40	18 months	Carvedilol, 47.9	77±10.5	78±10.9	129	——	70-75	75-80
CARMEN II, 2004 (28)	191 vs. 190	62.1 vs. 62.9	81 vs. 84			Carvedilol, 48.7	78±10.9	78±10.9	131	——	70-75	75-80
CIBIS III, 2005 (29)	505 vs. 505	72.4±5.8 vs. 72.5±5.7	65.9 vs. 70.5	NYHA class II or III, LVEF ≤0.35	1.22 years	Bisoprolol, 5-10	78.8±13.8	79.5±13.2	134.5±17.0	0.288±0.048	66.7±11.8	67.5±12.7
ENECA, 2005 (30)	134 vs. 126	71.97±5.02 vs. 72.19±5.20	70.15 vs. 76.98	NYHA class II–IV, LVEF ≤0.35	2 months	Nebivolol, 7.4	76.90±10.88	75.29±9.96	134.64±16.57	0.2541±0.0709	67.08±9.21	75.00±9.62
SENIORS, 2005 (31)	1067 vs. 1061	76.1±4.8 vs. 76.1±4.6	61.6 vs. 64.7	A clinical history of chronic heart failure, LVEF ≤0.35	12 months	Nebivolol, 7.7±3.6	79.2±13.6	78.9±13.7	138.6	0.36±0.13	68.8±12.5	77.4±13.5

LVEF - left ventricular ejection fraction; NYHA - New York Heart Association

reported. The other experiments were carried out with a double blind design scheme, except Anderson1985, MDC1993, CIBIS1994, BEST2001, CAPRICORN2001, CARMEN2004. According to the Jadad scoring scale, all included trials were high-quality studies.

Data synthesis

Only 19 out of 27 trials or subgroups described end-point heart rate. Except for the CARMEN trial, which controlled the heart rate within the range 70–75 beats/min, the remaining reports described specific heart rate at the end of the trial (Fig. 2). The lowest end-point heart rate was reported in the CHRISTMAS trial, which controlled the heart rate at 65 beats/min. No clinical trial controlled the heart rate at 60 beats/min. Heart rate was controlled at 65–70 beats/min in 12 trials, 70–80 beats/min in 5 trials, and above 80 beats/min in 3 trials. Only MERIT-HF and MOCHA III trials showed that beta-blockers reduced mortality in patients with HF in the 19 trials. The heart rate was controlled at 67 beats/min in both trials.

A total 25/27 trials or subgroups provided baseline heart rate. The lowest baseline average heart rate was 76.90 beats/min in 25 clinical trials or subgroups, and the highest was 91 beats/min. Subgroup analysis was based on the baseline heart rate level (Fig. 3). RR and 95% CI were 0.77 (0.71, 0.83) and 0.86 (0.76, 0.97) in the subgroup with baseline heart rate >80 beats/min and subgroup with baseline ≤80 beats/min, respectively. The use of beta-blockers in the treatment of HF in people with a baseline heart rate >80 beats/min and ≤80 beats/min was beneficial. However, the benefits of beta-blockers decreased in people with heart rate lower than 80 beats/min. It is still unclear whether the benefits of beta-blocker therapy for HF are likely to disappear with a further reduction in baseline heart rate. The lowest baseline heart rate (approximately 77 beats/min) was reported in ENCA, CAPRICORN, CHRISTMAS, and CARMEN I. A meta-analysis of the four trials (Fig. 4) showed that RR and 95% CI were 0.82 (0.67, 1.00), indicating no significant difference in the mortality rate between the beta-blockers and control groups. The sensitivity analysis using the random-effect model yielded significantly similar results.

Furthermore, subgroup analysis was performed according to the heart rate at the end of the trial (Fig. 5). The heterogeneity was low, and the fixed-effect model was used. RR and 95% CI were 0.92 (0.82, 1.02) and 0.77 (0.65, 0.92) in two subgroups with heart rate control ≥70 beats/min and 60–70 beats/min, respectively. These data suggested no significant difference in mortality of patients with HF who used beta-blockers and controlled their heart rate above 70 beats/min compared with placebo therapy. Controlling heart rate at 60–70 beats/min can significantly reduce mortality. We can infer that the benefit of beta-blockers in the treatment of HF mainly occurs through the reduction of heart rate. Beta-blockers are beneficial only when used to

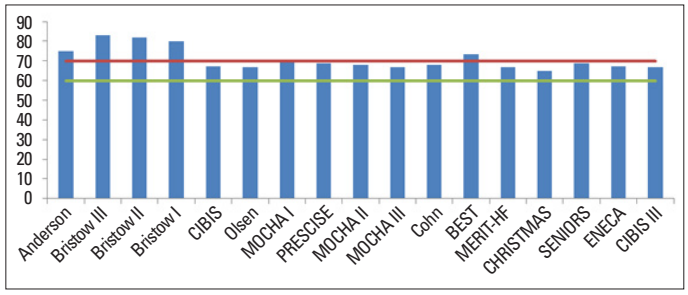

Figure 2. Endpoint heart rate of included trials

reduce heart rate below 70 beats/min. The sensitivity analysis using the random-effect model yielded significantly similar results.

The cumulative meta-analysis was performed according to the end-point heart rate from high to low (Fig. 6). Accumulated to MOCHA I trial, there was no significant difference in mortality between the experimental group and the control group (RR=0.91, 95% CI 0.82–1.02). Accumulated to SENIORS trial (heart rate controlled 68.8 beats/min), there was a difference in mortality between the experimental and the control groups (RR=0.90, 95% CI 0.82–0.99). The end-point heart rate of MOCHA I trial was 70 beats/min and that of SENIORS trial was 68.8 beats/min. The results showed no significant differences in mortality between placebo and beta-blockers in controlling the heart rate to 70 beats/min. The mortality rate was reduced when the heart rate was lowered to 68.8 beats/min by beta-blockers compared with that of the control group. This outcome was consistent with the results of subgroup analysis.

In 27 trials or subgroups, only CIBIS II, MERIT-HF, and MOCHA III showed that the use of beta-blockers reduced the mortality in patients with HFrEF, whereas there was no significant difference in the mortality between the experimental and the control groups in other 24 trials or subgroups. The heterogeneity of the inclusion test was low, and the fixed effect model was adopted. Our meta-analysis (Fig. 7) showed that beta-blocker therapy reduced the mortality in patients with HFrEF (RR=0.79, 95% CI 0.74–0.84).

Discussion

Heart rate is an independent risk factor for HF (6). The resting heart rate has been identified as a particular modifying risk factor for HFrEF (32). Previous evidence (33, 34) suggests that the higher reduction in the heart rate resulted in a better overall prognosis in patients with HF. Therefore, recent guidelines (3, 5) recommend stricter heart rate control with a target of 60 or 70 beats/min. However, there is no sufficient basis for setting these heart rate targets. Observational studies (7) have shown that for the general population, the total mortality and cardiovascular mortality rates were the lowest in people with heart rate of approximately 65 beats/min. For patients with HFrEF, the mortality rate was the lowest when the heart rate was between 70 and 75 beats/min (8). All these results suggest that for patients with HF, heart rate is clearly related to mortality. Not the lower the better, but there is a heart rate range to make mortality the lowest. Subgroup analysis according to baseline heart rate showed that there was no significant benefit from beta-blockers in the population with baseline heart rate of 77 beats/min. In addition, the cumulative meta-analysis showed statistical differences until the end-stage heart rate was below 70 beats/min. The RR values gradually decreased along with the decrease of heart rate, but the decrease range became smaller and smaller. Accumulated to CHRISTMAS trial, RR value was higher than before, which may be related to the sample size of the test itself. It may also be that when the heart rate is controlled to 65 beats/min, the heart rate further decreases without more benefit or even the benefit begins to decrease. This needs further trial confirmation.

Beta-blockers reduce morbidity and mortality in patients with HFrEF (1). Nonetheless, it remain unclear whether the key mechanisms underpinning their benefits are protection of adrenergic receptors from heightened sympathetic activity or reduction in heart rate. It is also uncertain whether the efficacy of beta-blocker is related to dose, reduction in heart rate, or the achieved heart rate (35, 36). Whether clinicians should strive to achieve a target heart rate or a target dose of beta-blocker remains unanswered.

A large retrospective clinical (37) study involving 1,669 patients suggested that the use of beta-blockers to achieve the target dose or target heart rate (50–70 beats per minute) had similar benefits and that controlling the heart rate after reaching the target dose was still beneficial. The new premise was that the aim of using beta blockers is not to achieve the maximum tolerable dose, but to control heart rate (38, 39).

The SHIFT (32) trial is the first trial to specifically test the effect of isolated heart-rate reduction on outcomes in a population with HF. Treatment with ivabradine was associated with an average reduction in heart rate of 15 bpm from a baseline value of 80 bpm, which was largely maintained throughout the course of the study. In the SHIFT population, patients with heart rates higher than the median were at increased risk of an event and received greater event-reducing benefit from ivabradine than did those with heart rates lower than the median. This is consistent with our conclusion.

The relationship between dose and efficacy of beta-blockers was not evaluated in this paper. However, our subgroup analysis confirmed that the use of beta blockers did not reduce mortality in patients with baseline heart rate of 77 beats/min. In the SHIFT (32) trial, 3,181 (56%) patients on beta blockers were treated with at least 50% of the target doses, and 1,488 (26%) were at target doses. The results showed that the use of ivabradine on this basis benefited by lowering the heart rate, which suggests that the dose of the Beytagh blocker is not critical. Compared with placebo treatment, there was no significant difference in mortality among those using beta blockers that controlled heart rate over 70 beats/min. Controlling heart rate at 60–70 beats/min can significantly reduce mortality. The cumulative meta-analysis also showed that there was no significant difference in the mortality between placebo and beta-blocker groups when control-

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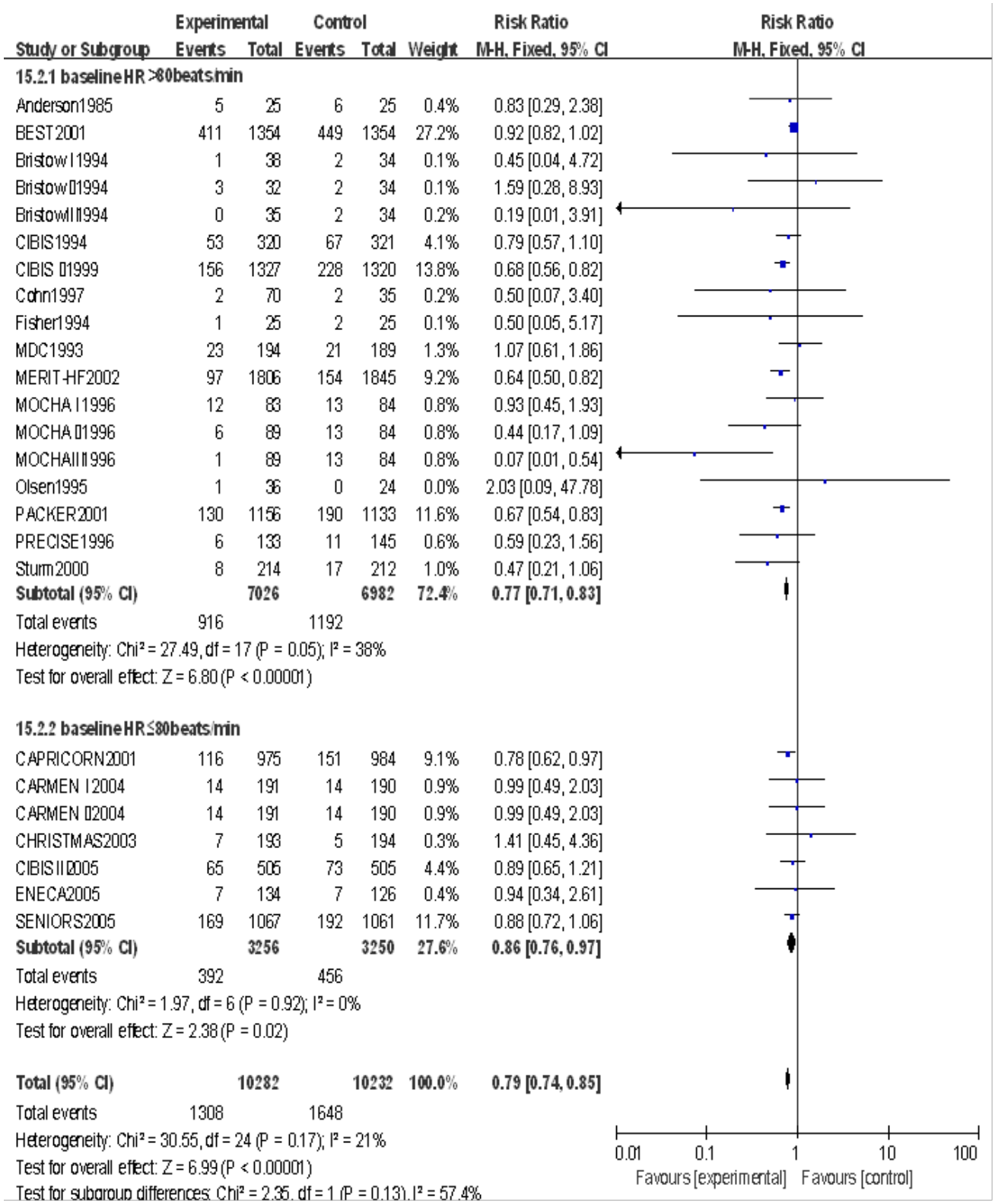

Figure 3. Assessment of the effect of beta-blockers on mortality by subgroup analysis grouped according to baseline heart rate in the experimental group

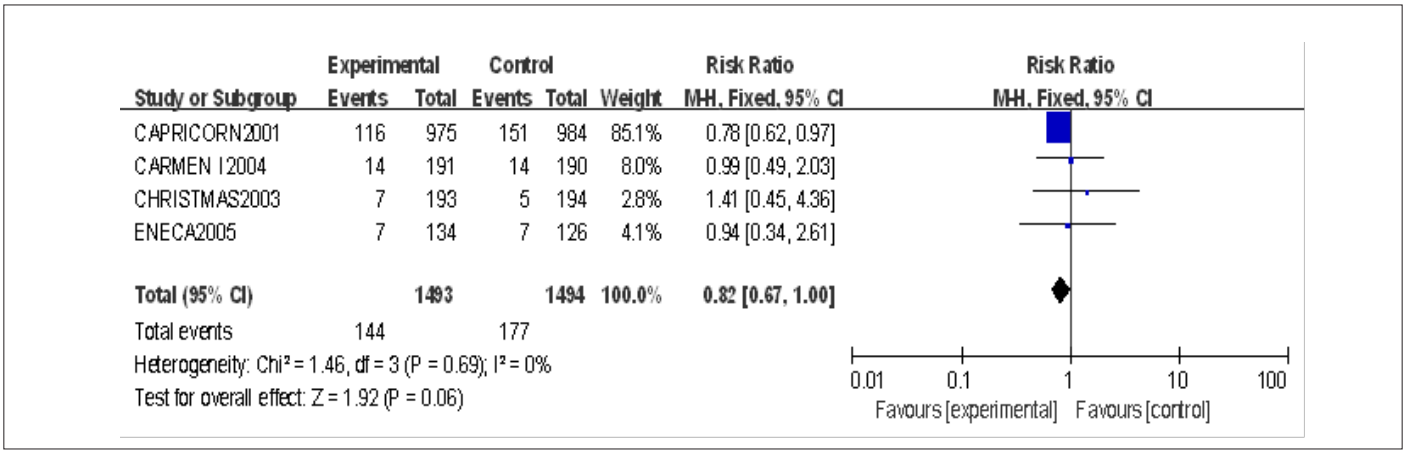

Figure 4. Effect of beta-blockers on mortality in population with a baseline heart rate of 77 beats/min

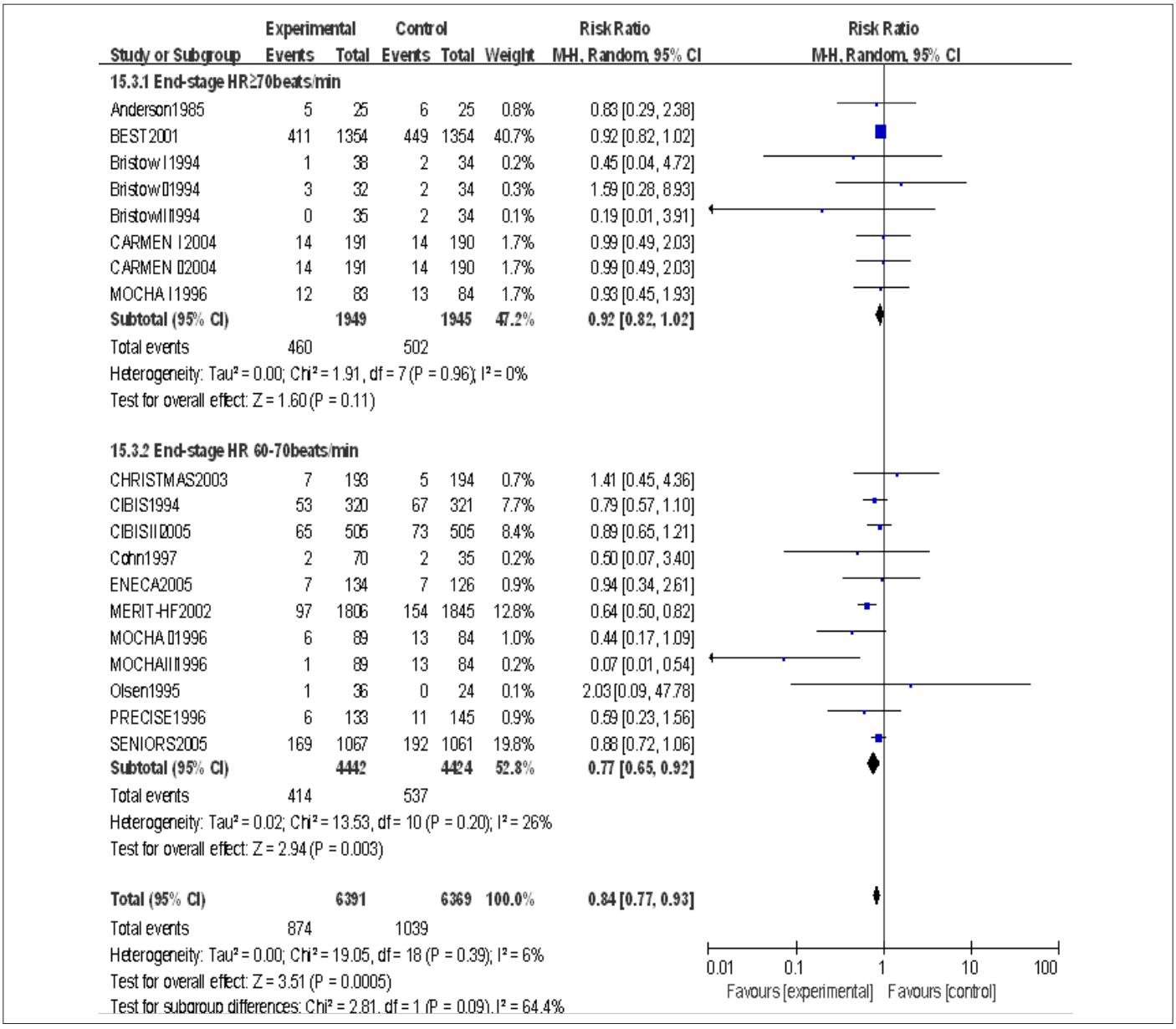

Figure 5. Assessment of the effect of beta-blockers on mortality by subgroup analysis grouped according to end-stage heart rate in the experimental group

Anatol J Cardiol 2021; 25: 762-73
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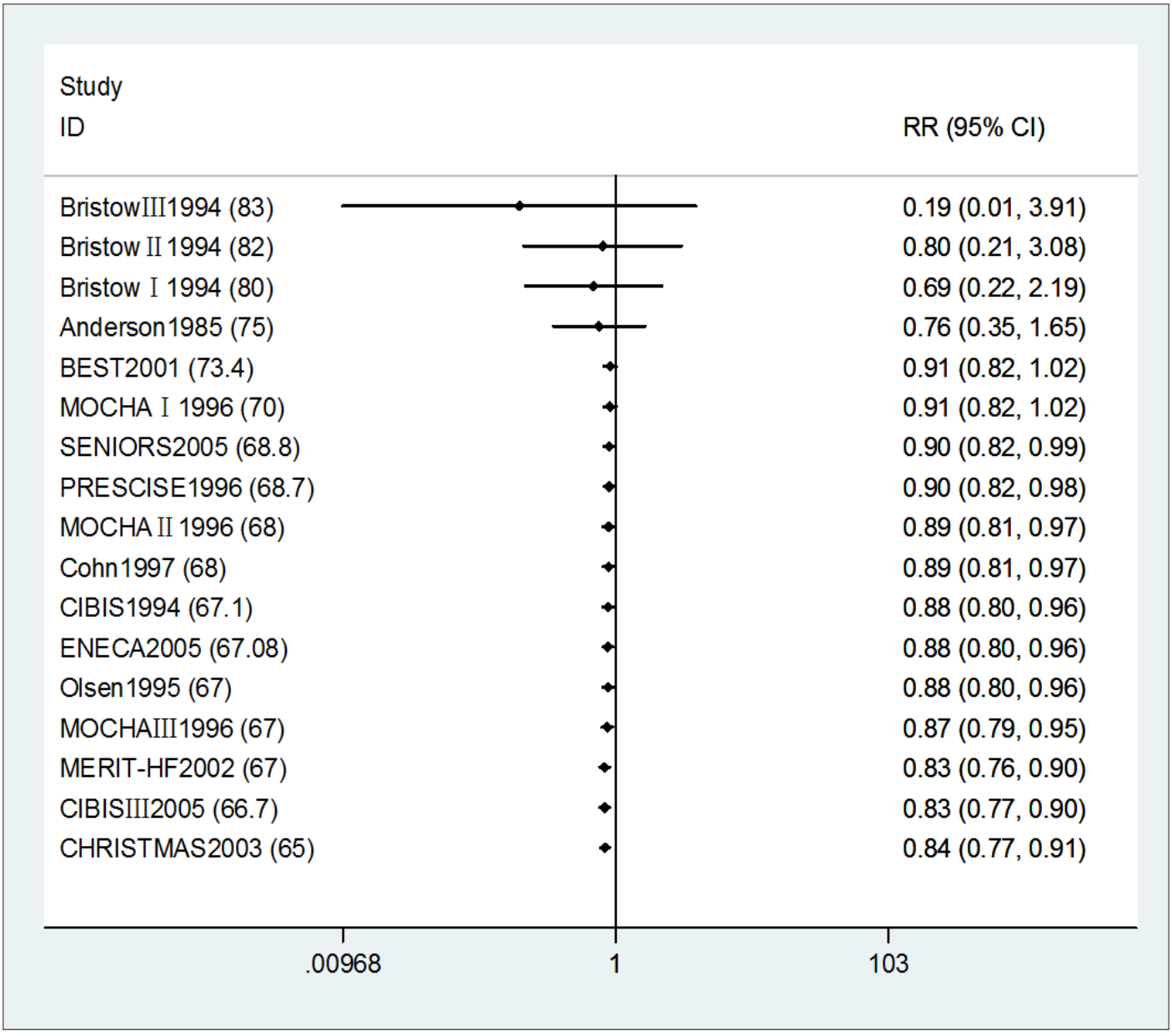

Figure 6. Cumulative meta-analysis based on end-point heart rate

ling the heart rate above 70 beats/min. The use of beta-blockers lowered the heart rate to 68.8 beats/min and reduced the mortality compared with that in the control groups. Our findings suggest that beta-blockers can reduce mortality in the treatment of HF depending on the specific heart rate.

Study limitations

This was a meta-analysis. Background therapy of the included trials would have changed since these trials were conducted. In addition, the heart rate was not measured in a standardized fashion. Moreover, different patient study groups and different beta-blockers were used in different trials, which is a major reason for heterogeneity. The degree of heterogeneity is also assessed. A certain degree of heterogeneity does not affect the stability of the results.

Our analysis plan specified that only mortality should be analyzed as an outcome. The benefits of beta-blockers may manifest as improved symptoms, shortened hospitalization times and duration, reduced heart-related events, and so forth. These benefits are not analyzable in this paper.

Conclusion

The main benefit of beta-blockers in the treatment of HF is achieved by lowering heart rate. Patients with HFrEF whose heart rate is approximately 70 beats/min have the lowest mortality rate. In addition, the use of beta-blockers did not significantly benefit patients with HFrEF whose heart rate was 77 beats/min before the use of beta-blockers. In patients with HFrEF with a

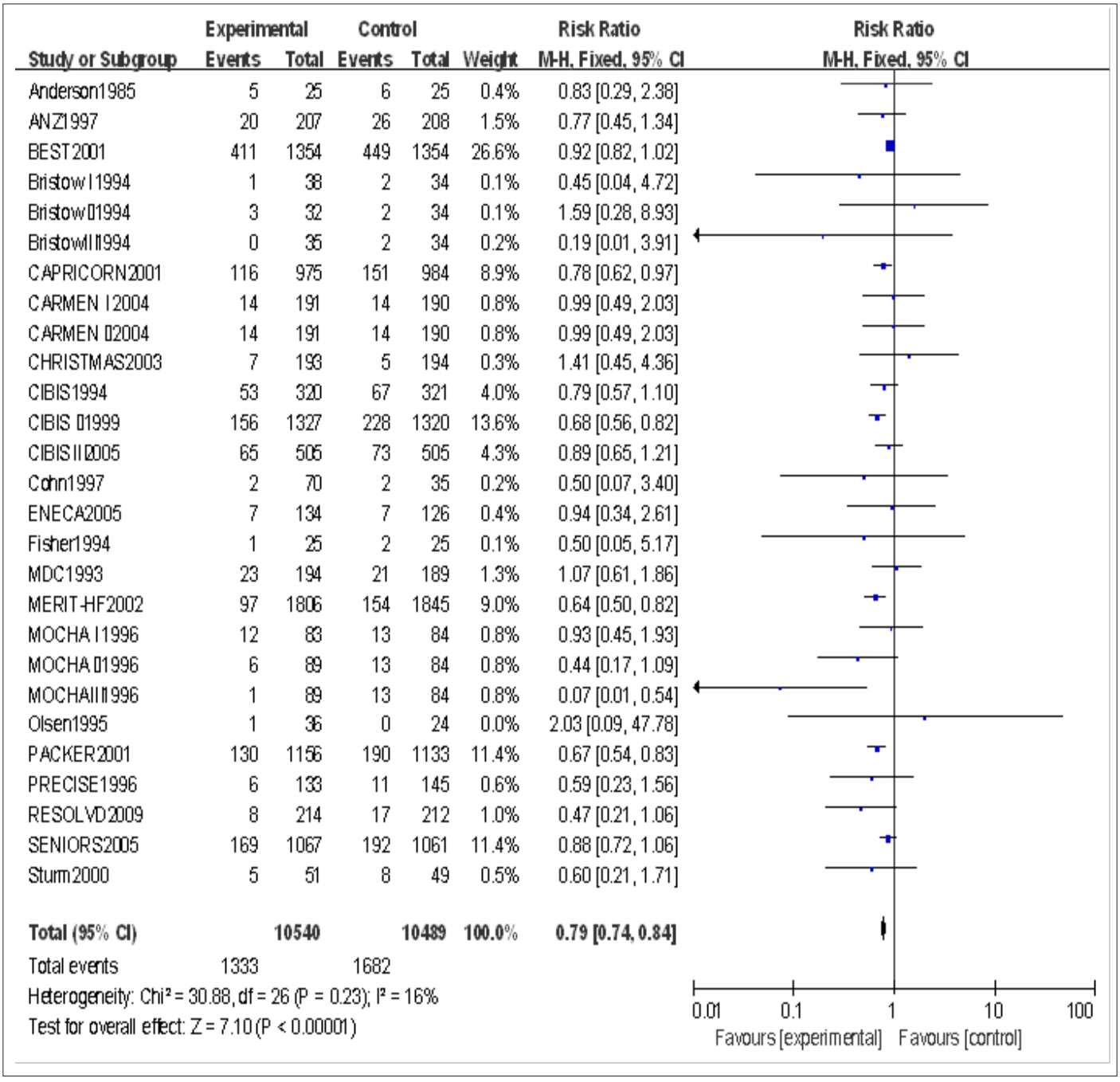

Figure 7. Forest flop for reducing mortality using beta-blockers

higher heart rate, the administration of beta-blockers to control heart rate to 70 beats/min can significantly reduce mortality. Further reduction of heart rate to 65 beats/min may not increase the benefit.

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