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The effect of beta-blockers on mortality in patients with heart failure and atrial fibrillation: A meta-analysis of observational cohort and randomized controlled studies

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Abstract

Background: *Beta-blockers (BB) are the cornerstone of therapy for heart failure (HF); however, the effects of these drugs on the prognosis of patients with concomitant atrial fibrillation (AF) remain controversial. The objective of this meta-analysis was to evaluate the efficacy of BB on mortality in HF coexisting with AF.*

Methods: *A systematic search of PubMed, Embase and the Cochrane Library databases was conducted. Observational cohort studies and randomized controlled trials reporting outcomes of mortality or HF hospitalizations for patients with HF and AF, being assigned to BB treatment. A non-BB group was also included.*

Results: *A total of 8 clinical studies (5 randomized controlled trials and 3 observational cohort studies) involving 34197 patients were included in the analysis. The pooled analysis demonstrated that BB treatment was associated with a 22% reduction in relative risk of all-cause mortality in patients with HF and AF (RR: 0.78; 95% CI 0.71–0.86; $p < 0.00001$; $I^2 = 27\%$). The pooled analysis of 5 studies reported the outcome of HF hospitalization (2774 patients) which showed that BB therapy was not associated with a reduction of HF hospitalizations (RR: 0.94; 95% CI 0.79–1.11; $p = 0.46$; $I^2 = 38\%$).*

Conclusions: *Meta-analysis suggests the potential mortality benefit of BB in patients with HF and AF. It was concluded herein that it is premature to deny patients with AF and HF to receive BB therapy considering current evidence.* (Cardiol J 2019; 26, 6: 744–752)

Key words: beta-blocker, atrial fibrillation, heart failure, mortality

Introduction

Heart failure (HF) and atrial fibrillation (AF) are two burdensome cardiovascular epidemics of the 21st century [1–3]. Patients with concomitant AF and HF have even higher mortality and hospital admission rates [1–5]. Thus, the importance of concomitant AF and HF cannot be overstated.

Among the many therapies available for HF and AF, beta-blockers (BB) are a cornerstone of management [5–8]. Based on several large randomized clinical trials, BB are strongly recommended (IA) for heart failure with reduced ejection fraction (HFrEF) by both American and European guidelines [5–8]. However, no randomized trials have been performed specifically to investigate the

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efficacy of BB in HF patients with AF. Post-hoc analyses of randomized trials designed to assess BB in HF suggest no benefit of BB in HF patients with AF [9–13]. Furthermore, two recent meta-analyses have failed to show clearly the mortality and morbidity benefit of BB in patients with HF and concomitant AF [14, 15]. Of note, the AF group comprised only 17–21% of the whole patient cohort, and the obtained meta-analyzed results might reflect an under-powered analysis; in addition, the randomized controlled trials (RCTs) included in the previous meta-analyses were published more than 10 years ago, which was different from the current real world. Recently, several large well-designed observational cohort studies examining the prognostic effect of BB in HF and AF has been published after these meta-analyses were performed [16–18].

Given the limited evidence and uncertain effects of BB in HF with coexisting AF, the aim was to conduct an updated meta-analysis of RCTs and observational cohort studies (OCSs) on the effect of BB on outcome in HF and AF.

Methods

Search strategy

Electronic searches were conducted in the PubMed, Embase and the Cochrane Library databases. Search terms included "beta-blocker", "heart failure", "atrial fibrillation", and their variations. There was no language restriction placed on the searches. Each database was searched from inception to June 2017. Additionally, reference lists in the articles chosen for inclusion, and the reference lists of previous reviews were screened to identify other potentially eligible trials.

Inclusion criteria

Trials with the following characteristics were included:

- Population: Adult patients diagnosed as AF and HF (including both heart failure with reduced ejection fraction [HFrEF] and heart failure with preserved ejection fraction [HFpEF]).
- Intervention: The intervention group included patients who received BB treatment.
- Control: The control group included patients who did not receive BB treatment.
- Outcomes: The all-cause mortality or HF hospitalizations had to be the outcome reported, and the duration of follow-up was at least 6 months.
- Types of study: The studies had to be RCTs or OCSs.

Study selection and data extraction

Two authors independently screened titles and abstracts. They obtained full articles that met the inclusion and exclusion criteria and after an independent review.

Information about the study and patient characteristics, methodological quality, intervention strategies, and clinical outcomes was systematically extracted separately by two reviewers. Disagreements were resolved by consensus.

Quality assessment

The quality of random control trial included was assessed by the Jadad quality scale [19]. The quality of the observational study was evaluated by the Newcastle-Ottawa Scale tool (available at: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp).

Statistical analysis

The relative risks (RRs) and 95% confidence intervals (95% CI) were used as the common measure across the studies. The hazard ratios (HRs) were considered equivalent to RRs [20, 21]. If the effect estimates were not available in the studies included, RRs were calculated by using the following formula: RR = Probability of events given treatment/Probability of events given no-treatment. If the studies provided the adjusted estimations, they were directly used in the meta-analysis. Statistical heterogeneity across studies was assessed by using the Q statistic with its p value and I^2 statistic. The I^2 statistic is used to quantify the proportion of total variation in the effect estimation that is due to between study variations. An I^2 value greater than 50% indicates significant heterogeneity [22]. Clinical heterogeneity could not be excluded, so the pooled RR was calculated with the random-effects model [23].

Results

Search and selection of studies

The initial search yielded 680 unique titles and abstracts from PubMed, Embase and the Cochrane Library, and approximately potentially relevant articles identified. Of these articles, 5 RCTs [9–13] and 3 OCSs [16–18] fulfilled the eligibility criteria and were included in the present meta-analysis. The details of study selection flow diagram were described in Figure 1.

Characteristics and quality of study included

The characteristics of the studies included are presented in Table 1. In all 8 studies included,

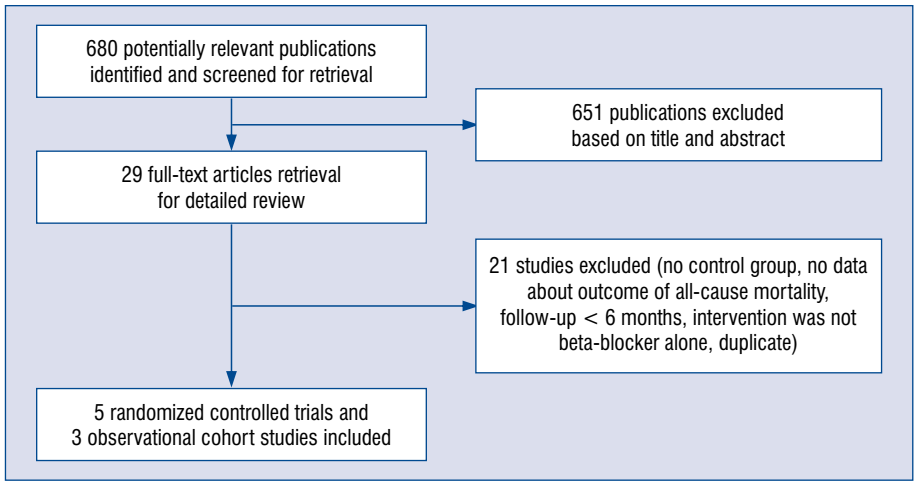

Figure 1. Selection process for articles included in meta-analysis.

5 studies were randomized controlled design and 3 studies were observational cohort design. All the 5 RCTs were specific AF sub-studies of the large HF randomized trials that compared the effect of BB with those of placebo. Among the 3 OCSs, propensity score (PS) analysis was performed with PS matching in 2 studies (AF--CHF study and Danish nationwide registry), and multivariable-adjusted Cox regression analysis was performed in 1 study (Swedish HF Registry). Of the 8 studies, patients with HFrEF were included in the 6 studies (US-Carvedilol, CIBIS-II, MERIT-HF, BEST, Swedish HF Registry and AF-CHF); patients with both HFrEF and HFpEF were included in 2 studies (SENIORS and Danish nationwide registry). A total of 34197 patients were enrolled, including 20235 patients treated with BB and 13962 without BB. The mean follow-up duration ranged from 6 months to 3.1 years. For the 5 RCTs, study quality was scored as "good" for all but one (the US-Carveilol study), which was scored as "fair" by using the Jadad quality scale. For the 3 OCSs, study quality was scored as good (7–9 scores) by using Newcastle-Ottawa Scale tool.

Patient characteristics

Patient characteristics of the studies included are presented in Table 2. Included patients were a mean age of 70 years, 76% were men, mean left ventricular ejection fraction was 27.5%, 35% had New York Heart Association (NYHA) functional class for I/II and 65% had NYHA III/IV. Coronary artery disease was common and ranged from 21% to 56%, respectively; hypertension and diabetes were also common and ranged from 8% to 56% and from 13% to 27%, respectively. Baseline medication included angiotensin converting enzyme inhibitor/angiotensin receptor blocker in 84.8% of the patients, digoxin in 70%, diuretics in 90% and oral anticoagulant in 60%. Baseline heart rate of patients was similar among included studies, ranging from 79 bpm to 88 bpm. 5 RCTs reported the heart rate change at the end of follow-up with a mean heart rate reduction of 10.9 bpm.

Effect of beta-blockers on all-cause mortality

All 8 studies reported the outcome of all-cause mortality. The effect estimations of HRs were provided in 5 studies and RRs in 3 studies. The effect of BB on all-cause mortality in HF and AF was shown in Figure 2. In the pooled analysis of 5 RCTs, BB use was associated with non-significant reduced risk for mortality (RR 0.97; 95% CI 0.79–1.19, $p = 0.79$; heterogeneity, $p = 0.55$, $I^2 = 0$). In the pooled analysis of 3 OCSs, BB use was associated with improved survival (RR 0.74; 95% CI 0.71–0.78, $p < 0.00001$; heterogeneity, $p = 0.22$, $I^2 = 0$). Overall, use of BB reduced risk for mortality by 22% (RR 0.78; 95% CI 0.71–0.86, $p < 0.00001$; heterogeneity, $p = 0.26$, $I^2 = 27\%$).

Effect of BB on HF hospitalization

Five studies reported the outcome of HF hospitalization (CIBIS-II, MERIT-HF, SENIORS, BEST and AF-CHF), including 2774 patients. The pooled analysis showed that BB therapy was not associated with a reduction of HF hospitalizations (RR 0.94; 95% CI 0.79–1.11, $p = 0.46$; heterogeneity, $p = 0.17$, $I^2 = 38\%$ (Fig. 3).

Table 1. Characteristics of included studies.

Study	Year	Study design	Method for analysis	Sample size	BB group (n)	No BB group (n)	Definition of HF	Mean follow-up [years]	Endpoints	Estimate effect	Study quality
US-Carvedilol	2001	RCT	–	136	84	52	LVEF ≤ 35%; NYHA II–IV	0.5	All-cause mortality	RR	Fair
CIBIS-II	2001	RCT	–	521	257	264	LVEF ≤ 35%; NYHA III–IV	1.3	All-cause mortality; HF hospitalizations	RR	Good
MERIT-HF	2006	RCT	–	556	274	282	LVEF < 40%; NYHA II–IV	1.0	All-cause mortality; HF hospitalizations	RR	Good
SENIORS	2012	RCT	–	738	361	377	HF admission < 1 year or LVEF ≤ 35%	1.8	All-cause mortality; HF hospitalizations	HR	Good
BEST	2013	RCT	–	303	146	157	LVEF ≤ 35%; NYHA III–IV	2.0	All-cause mortality; HF hospitalizations	HR	Good
Swedish HF Registry	2015	Prospective OCS	Multivariable--adjusted Cox regression analysis	7392	6739	439	LVEF < 40%	2.4	All-cause mortality	HR	Good
Danish AF Registry	2016	Prospective OCS	Propensity score analysis	23896	11948	11948	A previous hospital diagnosis of HF	3.1	All-cause mortality	HR	Good
AF-CHF	2017	Retrospective OCS	Propensity score analysis	655	426	229	LVEF ≤ 35% with HF symptom or LVEF ≤ 25% without HF symptom	3.1	All-cause mortality; HF hospitalizations	HR	Good

BB — beat-blocker; HF — heart failure; HR — hazard ratios; LVEF — left ventricular ejection fraction; NYHA — New York Heart Association; OCS — observational cohort study; RCT — randomized controlled trials; RR — relative risk

Table 2. Patient characteristics.

Study	Mean age [years]	Male [%]	Baseline heart rate [bpm]	Heart rate reduction BB [bpm]	LVEF [%]	NYHA [%]		Types of BB	Combined disease [%]			Medication [%]			
						I/II	III/IV		HTN	DM	CAD	Digoxin	ACEI or ARB	OAC	Diuretics
US-Carvedilol	65	90	87	–13.0	24	42	58	Carvediol	NA	NA	51	99	96	NA	98
CIBIS-II	62	83	88	–8.8	27	0	100	Bisoprolol	17	13	25	85	96	49	98
MERIT-HF	66	86	84	–14.8	28	34	66	Metoprolol	41	24	53	90	91	74	95
SENIORS	77	63	84	–11.0	28	49	51	Nebivolol	56	25	35	70	83	41	92
BEST	65	90	79	–6.9	24	0	100	Bucindolol	54	27	56	95	98	84	NA
Swedish HF Registry	76	73	80	NA	30	48	52	NA	45	22	41	36	71	69	84
Danish AF Registry	78	45	NA	NA	NA	NA	NA	NA	44	17	21	20	47	25	NA
AF-CHF	70	81	79	NA	28	69	31	NA	8	NA	50	64	96	82	74

ACEI — angiotensin converting enzyme inhibitor; ARB — angiotensin receptor blocker; BB — beat-blockers; CAD — coronary artery disease; DM — diabetes mellitus; HTN — history of hypertension; LVEF — left ventricular ejection fraction; NYHA — New York Heart Association; NA — not available; OAC — oral anticoagulant

Sensitivity analysis

Leave-one-out sensitivity analysis on all-cause mortality was performed by omitting one study at a time, and found that none of the individual studies significantly influenced the pooled estimate of all-cause mortality. Subgroup analyses showed that when the pooled analysis of all-cause mortality was performed using fixed-effect model, a similar result was observed.

Discussion

Main findings

Meta-analysis of 8 studies involving 34197 patients revealed that BB were associated with a 22% reduction in all-cause mortality. Although the finding was limited to observational studies and trends favored BB for HF hospitalization did not reach statistical significance. Overall, results supported current evidence-based recommendations to pursue BB in all HF patients with or without AF.

Comparison with other studies

The present observed mortality benefit of BB in HF and AF diverged from two earlier meta-analyses [14, 15]. The latest systematic review conducted by Kotecha et al. [15] was more recent and comprehensive, which was an individual patient-level meta-analysis. However, in the 2 earlier meta-analyses, only RCTs were included and the AF group comprised only 17–21% of the whole patient cohort. Therefore, the obtained meta-analyzed results might reflect an under-powered analysis. In meta-analysis, the number of patients in the included 5 RCTs was 2254 with 407 death-events, which is still low for survival analysis, and the possibility that a lack of power may have played a role could not be excluded. Additionally, it is important to recognize that the included 5 RCTs were not specifically designed to assess the effect of BB in patients with AF and HF. Above all, the benefits of BB for all-cause mortality or HF hospitalizations were not observed in the pooled analysis of 5 RCTs, consistent with the earlier meta-analyses.

Our meta-analysis included recently published 3 observational studies with a low heterogeneity. The 3 observational studies from large registries included were well designed by using PS analysis and multivariable-adjusted Cox regression analysis to reduce the effects of confounders (including age, sex, underlying disease, medications, and NYHA functional class). The mortality benefit associated with BB in this analysis was largely driven by the results of Danish AF Registry [15]. However, the

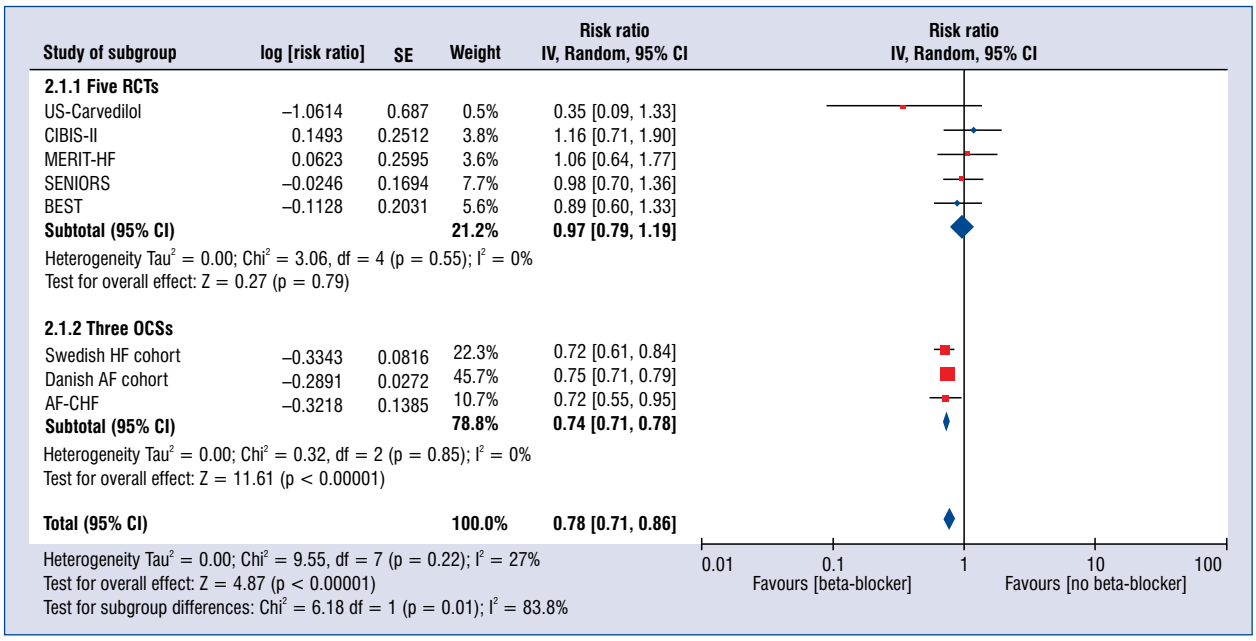

Figure 2. Effect of beta-blockers on all-cause mortality; CI — confidence interval; OCSs — observational cohort study; RCTs — randomized controlled trials.

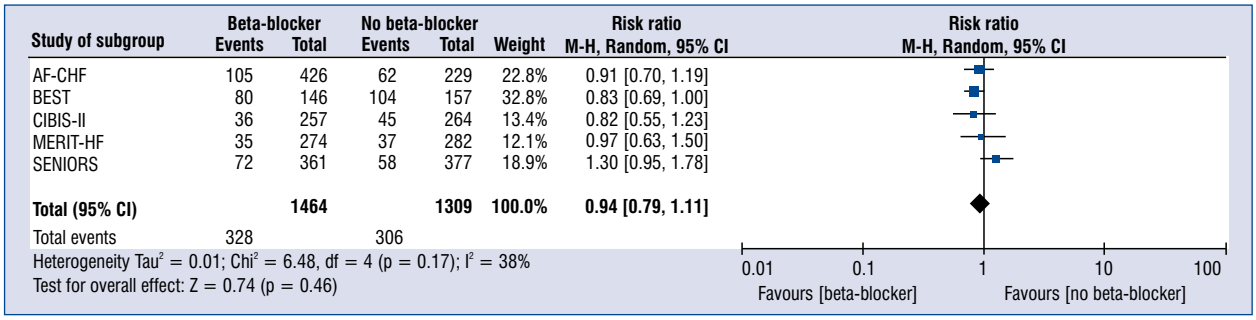

Figure 3. Effect of beta-blockers on heart failure hospitalization.

protective effect still remained after removing this study using the sensitivity analysis. Furthermore, both fixed and random effect models in the pooled analysis shows the significantly similar benefit of BB treatment. Accordingly, the conclusion that the treatment of BB reduces all-cause mortality in patients with HF and AF is fairly reliable.

It must be noted the difference between outcomes in included 5 RCTs and 3 OCSs. The present finding that BB therapy decreased mortality in patients with HF and AF was limited to the 3 observational studies. The controversial results may be partly explained by differences in methodology, patient demographics, HF severity, concomitant medication or follow-up duration. First, baseline characteristics of patients differed in these studies. In 5 RCTs, almost all patients included were symptomatic HF with NYHA II–IV, while in observational studies asymptomatic HF with NYHA I were also included. It seems that patients included in OCSs were at lower risk and had better BB tolerance, which all factors associated with lower mortality. Second, combined treatment was also an important confounder. In 5 RCTs, patients with HF and AF were more commonly treated with digoxin (88%), while in 3 OCSs, only 40% of patients were treated with digoxin. Digoxin had been reported to be associated with increased mortality in AF patients. The potential synthetic adverse effect of digoxin cannot be completely eliminated. Another possible reason as mentioned before was that the small number of patients in the included 5 RCTs was 2254 with 407 death-events which might reflect an under-powered analysis. It was admitted

that a well-designed randomized trial would be of great value according to the highest standards of evidence-based medicine. In RCTs the BB were well defined, with determined type and dose of BB and also heart rate reduction during therapy. While observational studies had inherent limitations including nonuniformly defined variables across studies. The use of BB differed between studies with a different type, dose and course. Based on observational studies, whether the doses and types of BB affect the effects of BB in patients with HF and AF could not be assessed. Until more solid evidence is available, it is premature to deny patients with AF and HF BB therapy considering current evidence.

Possible mechanisms for findings

The optimal heart rate target in AF patients is unclear. Moreover, there is limited evidence for lenient rate control for AF patients with HF. Previous studies have mainly examined sinus rhythm, and whether a higher heart rate is associated with worse outcomes in HF with concomitant AF has not been adequately studied. The lack of a relationship between heart rate and outcomes in patients with HFrEF and concomitant AF has previously been described [24–27]. In Rate Control Efficacy in Permanent Atrial Fibrillation: A Comparison between Lenient versus Strict Rate Control II (RACE II) trial, lenient rate control (< 110 bpm) did not yield worse outcomes than strict rate control (< 80 bpm) overall or in the subgroup of patients with HF [28, 29]. Potential mortality benefit of BB in HF coexisting with AF has been observed in the present meta-analysis. However, this meta-analysis does not provide the possible mechanisms for the survival benefit of BB in those patients without specific initial data on heart rate and heart rate change during BB treatment. The Swedish HF Registry [18] included in the present meta-analysis is the only study to assess an association of heart rate strata and BB use with all-cause mortality in patients with HF in AF. The study showed that higher resting heart rate was associated with increased mortality in AF, which was true only if heart rate > 100 bpm. Furthermore, BB use was associated with reduced mortality in patients with AF, and a lower heart rate was associated with reduced mortality in AF only for those with heart rate ≤ 100 bpm. In our meta-analysis, baseline heart rate of patients were similar among included studies, ranging from 79 bpm to 88 bpm (< 100 bpm); only 5 RCTs had reported the heart rate change for BB treatment at the end of follow-up, with a mean heart rate reduction of 10.9 bpm. However, in the pooled analysis of 5 RCTs, BB use was associated with non-significant reduced risk for mortality. Except for small sample size of an under-powered analysis, another possible explanation is that patients included in the trials benefit less from BB use with a baseline heart rate < 100 bpm. Patients with a higher heart rate may possibly benefit from BB treatment according to the results of Swedish HF Registry.

Implications for clinical practice

Considering the current controversies and challenges, more studies on BB in patients with HF and AF are still needed. Randomized controlled trials on BB for HF with concomitant AF may not be feasible because of ethical reasons. Thus, well designed and analyzed cohort studies from large registry will be more expected, which can give us more information from the real world. Future investigation should also help determine which patients with AF and HF will derive the greatest benefit from BB therapy, including those with HFrEF or HFpEF, older or younger, baseline heart rate. Additionally, the potential benefit of BB and their potential mechanisms beyond HR reduction in HF coexisted with AF also require further study.

Limitations of the study

The present analysis has several limitations that must be taken into consideration when interpreting the results. First, observational studies were included in the analysis and the mortality benefit was largely driven by those OCSs. Because of the observational nature of the cohort study and lack of randomization, the effect of unmeasured or residual confounding could not be ruled out. Although 3 observational studies from large registries were well designed by using PS analysis and multivariate regression analysis to reduce the effects of confounders, it would be specially mentioned that not all the studies adjusted for all covariates, so combined results should be interpreted with caution. Even though a very low heterogeneity was showed in the present analysis, clinical heterogeneity could not be underestimated. Therefore, a random-effect model was used in the meta-analysis and sensitivity analysis was also used to explore possible study characteristics that might have influenced the pooled estimates. Inherent limitations of pooled analysis of studies include the limited availability of confounding variables, including the type and dose of BB, the course of

treatment. Also, in the present analysis, the effects of different BB therapies were pooled and thereby assumed a class effect. However, specific differences in pharmacologic profiles may have added to the heterogeneity of the cohort and thereby the results. Finally, this analysis pooled study group estimates and did not assess individual patient data, which limits the possibility of adjustment for individual patient characteristics.

Conclusions

In summary, the present meta-analysis suggested the potential mortality benefit of BB in HF coexisting with AF, and supported current evidence-based recommendations to pursue BB for those patients. It was concluded that it is premature to deny patients with AF and HF beta-blocker therapy considering current evidence.

Conflict of interest: None declared

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