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CHAPTER 6

Beta-blockers and Outcome in Heart Failure and Atrial Fibrillation: A Meta-Analysis

Michiel Rienstra
Kevin Damman
Bart A. Mulder
Isabelle C. Van Gelder
Dirk J. Van Veldhuisen
John J. Mc Murray

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Summary

Background

Beta-blockers are widely used in patients with heart failure (HF) and atrial fibrillation (AF). Recommendation for these drugs in current HF guidelines, however, is based on populations in which the majority had sinus rhythm. Whether beta-blockers are as useful in atrial fibrillation (AF) is uncertain. We assessed the effect of beta-blockade on outcome in patients with HF and AF.

Methods

For this meta-analysis we used Medline to identify randomised controlled studies. Information about study design, sample characteristics, and outcome (HF hospitalization and mortality) was extracted.

Findings

We identified 4 studies which enrolled 8680 patients with HF and reduced systolic left ventricular function, and 1677 of them had AF (19%; mean age 69 years, 30% women); there were 842 patients treated with beta-blockers, and 835 with placebo. In patients with AF, beta-blockade did not reduce mortality (odds ratio (OR) = 0·86 (0·66-1·13), *P* = 0·28), while in patients with sinus rhythm there was a significant reduction (OR 0·63 (0·54-0·73), *P*<0·0001). There was a significant difference in the effect of beta-blocker therapy in AF versus sinus rhythm (*P* = 0·046). By meta-regression analysis we did not find confounding by all relevant covariates. When looking at HF hospitalizations in these studies, beta-blocker therapy was not associated with a reduction in patients with AF (OR 1·11 (0·85-1·47), *P* = 0·44), in contrast to those with sinus rhythm (OR 0.58 [0.49-0.68] *P*<0.0001) (*P* = 0·01 for difference in beta-blocker therapy effect between AF and sinus rhythm).

Interpretation

The effect of beta-blockers on outcome in HF patients who have AF is different than in those who have sinus rhythm. This finding may have implications for the place of these drugs in patients with AF and HF.

Funding

None.

Introduction

Beta-blockers are a cornerstone in the treatment of patients with heart failure (HF).[1] Large scale trials with carvedilol (US Carvedilol Study[2] and COPERNICUS[3,4]), metoprolol (MERIT-HF[5]), bisoprolol (CIBIS-II[6]), and nebivolol (SENIORS[7]) have shown that these drugs reduce morbidity and mortality in HF. As a result, they are now widely used and have received a class IA recommendation in current HF guidelines.[1] Atrial fibrillation is common in HF, and depending on the severity of HF, occurs in up to 30-40% of all patients.[8] The large HF trials that led to the recommendations also included a significant proportion of patients with AF.In current guidelines for HF[1] the recommendation for beta-blockers is not restricted to patients with sinus rhythm, and indeed includes all HF patients, i.e. also those with AF, but it is unknown whether beta-blockers are equally effective and safe in these patients, as they are in those with sinus rhythm.

In patients with sinus rhythm with and without HF, lower heart rate is associated with a better outcome,[9-11] and reduction of heart rate (by beta-blockers) probably plays an important role in the beneficial effect of these drugs. In patients with AF, with or without HF, lower heart rate, however, is not associated with a better outcome as was shown recently.[12]

Although patients with AF were included in the large HF trials, the absolute number of patients with AF in each individual study was rather limited.[13-16] The aim of the present meta-analysis was therefore to assess the effect of beta-blockade on outcome (i.e. mortality and hospitalization for HF) in patients with both HF and AF.

Methods

Literature Search

We searched MEDLINE using search tools provided by Pubmed (http://www.ncbi.nlm.nih.gov/pubmed/clinical; used April 1st 2012) and via OVID. These search tools have been validated by Haynes et al. to optimize retrieval.[17] We also used keywords including atrial fibrillation, heart failure, beta-blocker therapy, beta-blockade, medical therapy and a combination of these, and included papers published in English language. Furthermore, we reviewed reference lists from eligible studies, used the “see related articles” feature for key publications in PubMed, consulted the Cochrane Library, and searched

the ISI Web of Knowledge http://scientific.thomson.com/webofknowledge) for publications that cited key publications.

Study Selection

Studies were included which investigated the effect of placebo-controlled, randomized beta-blocker therapy in patients with AF at baseline, and HF with reduced systolic left ventricular ejection fraction (LVEF < 40%). We restricted our final search to beta-blockers that are registered for HF treatment, i.e. metoprolol, carvedilol, bisoprolol, nebivolol. For this reason one large outcome trial which examined bucindolol (BEST) was not included.[18] One study (SENIORS) included both patients with reduced and preserved left ventricular ejection fraction. For the present analysis we only included patients with LVEF < 35%, since this was the cut-off used in that study, both in the methodology in the main study,[7] and in the separate publication of the 2 groups.[19] The subgroup of patients with AF and HF with a preserved ejection fraction are not presented here since beta-blockers are not recommended in these patients.[1]

The primary and secondary analysis consisted of secondary analyses of randomized controlled trials. Articles were excluded if: a) no data was available for outcome, b) data was only published in abstract form and c) no definition for HF was given: either by combination of symptoms and signs (using New York Heart Association functional class or physical examination), imaging (impaired left ventricular ejection fraction) or a combination of both. The primary outcome measure was defined as all cause mortality. Secondary outcome variable included heart failure hospitalization as reported in the individual reports. Furthermore, we evaluated the beta-blocker effect in both patients with AF and in those with sinus rhythm included in the same studies.

Assessment of quality of studies for inclusion in analysis

The quality of the individual studies was assessed by eleven factors: 1) sufficiently specified inclusion and exclusion criteria, 2) sufficient explanation of sample selection, 3) Specification of clinical and demographic variables, 4) representation of the study sample for the mentioned patient population, 5) specification of outcome measures, 6) definition of AF, 7) assessment of a dose-response relationship between beta-blocker therapy and outcome, 8) adjustment for possible confounders in the analysis, 9) reporting of lost to follow-up rates, 10) study design and 11) duration of follow up. Grading was as follows; good quality: eight-11 criteria, fair quality: five-seven criteria and poor quality: < five criteria.[20]

Statistical Analysis

Meta-analysis was performed using a fixed-effects model to determine risk associated with beta-blocker therapy and all-cause mortality, as measured by combined crude mortality rates. In the secondary analysis, heart failure hospitalizations were studied in a similar matter. For comparison with patients in sinus rhythm, subgroup analysis was carried out by testing of heterogeneity across subgroups. Among studies heterogeneity of risk estimates was examined using a standard chi-square test and I^2 statistic for heterogeneity. I^2 is the percentage of variance that is due to between-study variance. Reasons for diversity in study results were explored using meta-regression analysis. Variables explored included age, sex, hypertension, diabetes, ischemic heart disease, left ventricular ejection fraction, heart rate, blood pressure and medical treatment. Results are presented as odds ratios (ORs) with their 95% confidence intervals (CIs) and p values. Evidence of publication bias was assessed by visual inspection of the Funnel plot. A *P* value of < 0·05 was considered statistically significant. Statistical analyses were performed using Stata 10·0, College Station, Texas and Revman 5·1.[21]

Role of the funding source

No sponsor of any of the individual trials had any role in the study design, data collection, data interpretation, drafting, or review of the report.

Results

Study search and general characteristics

The search retrieved 248 citations, of whom four fulfilled all criteria as they investigated the randomized treatment allocation of beta-blocker therapy in patients with HF and AF (**Figure 1**). All of these studies were specific AF substudies from large HF outcome trials (US-Carvedilol[13], CIBIS II[14], MERIT-HF[15], and SENIORS[16]) that studied the effect of beta-blockers. We were not able to retrieve data from one other large HF beta-blocker study (COPERNICUS), since presence of AF on electrocardiograms at baseline

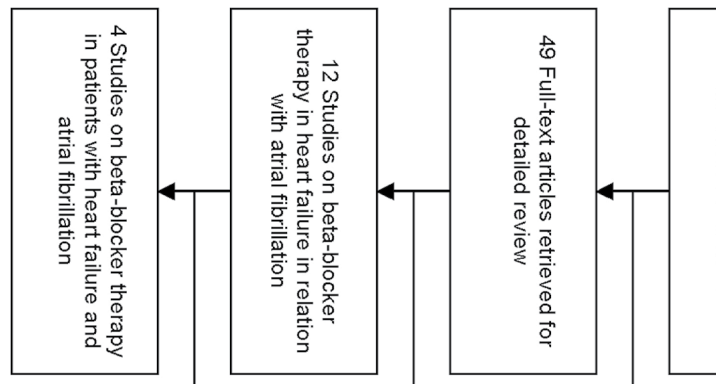

Figure 1. Quality of Reporting of meta-analyses (QUOROM) flow diagram for study selection

was not reported (although new onset AF was documented in one article).[4] Study quality was scored as "good" for all but one, the US-Carvedilol study, which was scored as "fair". All four studies reported the effect on all-cause mortality, and 3 of these 4 also on HF hospitalizations.

The main characteristics of the studies included in the analysis are reported in **Table 1**. Altogether, in the main analysis, 8680 HF patients with reduced systolic left ventricular function were included, 1677 (19%) of them with AF (mean age 69 years, 30% women). Among therapy groups, 842 patients with AF were treated with beta-blocker therapy, and 835 with placebo. Heart rate reduction with beta-blocker therapy was similar in patients with AF versus sinus rhythm. All patients had stable HF with reduced ejection fraction, and most patients were treated with angiotensin converting enzyme inhibitors and diuretics (**Table 2**). In **Table 3** and **Figure 2** the baseline heart rate and change in heart rate of each study are depicted. Heart rate reduction

Table 1. Study characteristics.

First Author	Study	Published	F/U	N (% of total sample)	Type Patients	Endpoints	Major Exclusion Criteria	HR Reduction by beta-blocker (bpm)
Joglar[11]	US-Carvedilol	2001	Max 400 days	136 (12%)	HF LVEF ≤ 35%	All-cause Mortality	Stable HF Heart rate < 68 bpm Class I or III anti-arrhythmic drugs	-13 in AF
Lechat[12]	CIBIS-II	2001	Max 800 days	521 (21%)	HF LVEF ≤ 35% NYHA III-IV	All-cause Mortality HF Hospitalisations	Stable HF Heart rate < 60 bpm Anti-arrhythmic drugs other than amiodarone	- 8.8 in AF - 10.6 in SR
Van Veldhuisen[13]	MERIT-HF	2006	Mean F/U 1 year	556 (14%)	HF LVEF < 40% NYHA II-IV	All-cause Mortality HF Hospitalisations	Stable HF Heart rate < 68 bpm CCB or Amiodarone	- 14.8 in AF - 13.7 in SR
Mulder[14]*	SENIORS	2011	Mean F/U 21 months	464 (22%)	≥ 70 years HF admission < 1 year or LVEF ≤ 35%	All-cause Mortality	Stable HF BBL	- 11 in AF -10.9 in SR

Only patients from SENIORS with LVEF ≤ 35% were included.
Abbreviations: BBL: beta-blocker, bpm: beats per minute, CCB: calcium channel blockers, F/U: follow up, HF: Heart failure, HR: Heart rate, LVEF: Left ventricular ejection fraction, N: number of patients, NYHA: New York heart association, SR: sinus rhythm

was similar for AF and sinus rhythm, although the baseline and end-of-titration heart rate were higher in AF patients. Dosages of beta-blockers were comparable in CIBIS-II, MERIT-HF, and SENIORS (no data of US-Carvedilol).

All-cause mortality. Follow up duration of the included studies ranged between a maximum of 13 months in the US-carvedilol study to a mean of 21 months in SENIORS. The crude mortality rates of AF patients with beta-blocker therapy versus those without were 13·5% and 15·7%, respectively, and for sinus rhythm with and without beta-blocker therapy 8·3% and 13·1%, respectively. This resulted in a combined mortality risk for AF patients of OR = 0·86 (0·66 – 1·13), *P* = 0·28 for beta-blocker therapy, versus a combined mortality risk for sinus rhythm patients of OR =0·63 (0·54 – 0·73), *P*< 0·00001 for beta-blocker therapy (**Figure 3**). There was a difference in the effect of beta-blocker therapy in AF versus sinus rhythm (*P* =0·046). There was no heterogeneity observed among the studies with AF included (I^2=0%, *P*= 0·46). We performed meta-regression analysis to determine factors explaining possible confounding. We found no confounding by any of the explored variables. **Figure 4** shows the Funnel plot for the main outcome analysis, which shows no evidence of publication bias.

Heart failure hospitalisations

Three of the four studies investigated the effect of beta-blocker therapy on HF hospitalisations, including 7586 HF patients with reduced systolic left ventricular function (1541 (20%) AF patients).

Table 2. Patient characteristics.

First Author	Age (years)	Men (%)	HTN (%)	DM (%)	IHD (%)	Stroke (%)	LVEF (%)	HR (bpm)	SBP (mmHg)	Digoxin (%)	ACEi (%)	Diuretics (%)
Joglar	65	90	NA	NA	51	NA	24	87	117	99	96	98
Lechat	62	83	17	13	25	12	27	87	131	85	96	98
Van Veldhuisen	66	62	41	24	34	12	28	84	131	90	91	95
Mulder*	77	63	56	25	35	NA	28	84	136	70	83	92

Abbreviations: ACEi: Angiotensin converting enzyme inhibitors, bpm: beats per minute, DM: History of diabetes, HR: Heart rate, HTN: History of hypertension, IHD: Ischemic heart disease, LVEF: Left ventricular ejection fraction, NA: Not available, SBP: Systolic blood pressure.

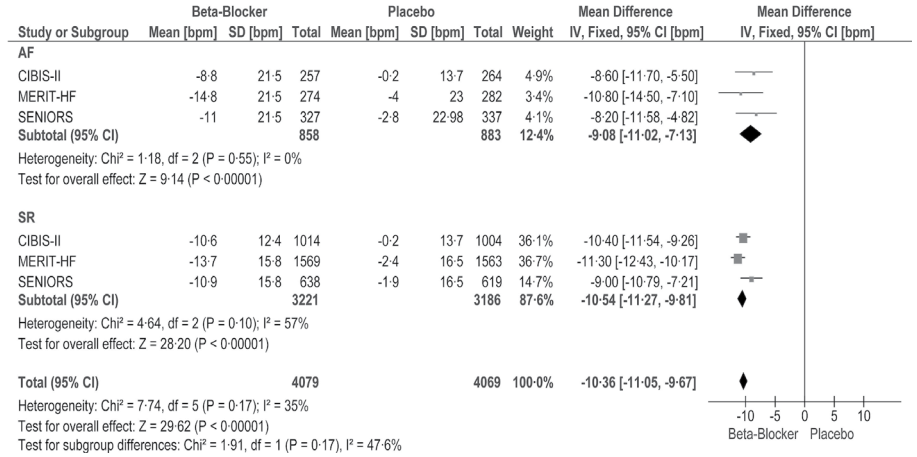

Figure 2. Heart rate and heart rate reduction: Effect of beta-blocker therapy in patients with heart failure and atrial fibrillation, and in patients with heart failure and sinus rhythm

Beta-blocker therapy in AF patients was not associated with a reduction of HF hospitalisations (14·8% versus 16·2% events), resulting in an OR of 1·11 (0·85 – 1·47), *P* = 0·44) (**Figure 5**). In sinus rhythm patients (8·5% versus 14·3% events), beta-blocker therapy was associated with a reduction of HF hospitalisations (OR 0·58 (0·49 – 0·68), *P*< 0·00001). There was a difference in the effect of beta-blocker therapy in AF versus sinus rhythm (*P*<0·001).

Discussion

The main finding of the present meta-analysis indicates that the effect of beta-blockers in patients with HF and AF is significantly different from the effect of these drugs in patients with HF and sinus rhythm. Indeed, beta-blockers were not found to have a favourable effect of HF hospitalizations or mortality in 1677 AF patients who had been enrolled in placebo-controlled, randomized studies.

This finding is important since most patients with HF and AF receive beta-blocker treatment. Beta-blockade is recommended in the current guidelines for HF and AF, albeit for different indications.[1,22] In the HF guidelines, beta-blockers are recommended for all patients in order to reduce morbidity and mortality, without differentiation regarding rhythm (i.e. sinus rhythm or AF). As such, these drugs are part of the standard medical therapy for all patients with HF with reduced systolic left ventricular ejection fraction. In addition, beta-blocker therapy has been shown to prevent new-onset or recurrent AF in

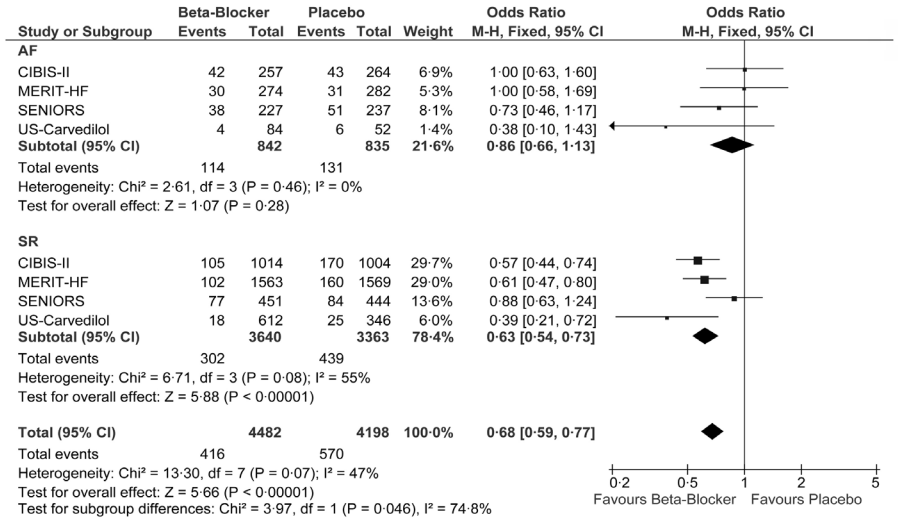

Figure 3. Combined all cause mortality risk: Effect of beta-blocker therapy in patients with heart failure and atrial fibrillation, and in patients with heart failure and sinus rhythm

patients with HF,[15,23] after myocardial infarction,[24] and also in a relatively low risk (most hypertension) population.[25]

In the AF guidelines, however, beta-blockers are recommended for rate control in order to reduce AF-related symptoms, but not to improve prognosis.[22]In line with the latter study are recent data from the CHARM (Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity) Program, which showed no predictive value of higher heart rates in HF patients with AF, in contrast to the observations in sinus rhythm patients.[11]

How can this different effect of beta-blockers between HF patients with AF and sinus rhythm be explained? First, heart rate reduction by beta-blocker therapy may be less effective in patients with AF than in those with sinus rhythm since the mode of action of beta-blockers is different during AF and sinus rhythm. During sinus rhythm, beta-blockers exert their heart-rate lowering effect by targeting the sinus node, whereas during AF their main site of action is the atrioventricular node. In the present analysis, however, we found a similar mean reduction in heart rate for patients with both AF and sinus rhythm with comparable dosages of beta-blockers. Second, heart rates were only measured at rest. Heart rate reduction during (moderate) exercise may have been different between AF and sinus rhythm patients. Indeed, there may be differences in the optimal heart rate at rest and during exercise, and optimal heart rate reduction by beta-blockers between both groups of patients.

In patients with sinus rhythm, it has been proven that a pronounced reduction in heart rate is associated with improved morbidity and mortality independent of the dose of the used beta-blocker, or by additive therapy with selective *If*-channel blockade.[9,10]For patients with permanent AF, it was recently demonstrated, that a more strict rate control was not superior to a lenient rate control.[12] Third, due to loss of the atrial kick and the irregularity in ventricular response during AF, patients with AF may need a higher heart rate to maintain a similar cardiac output, possibly even more so during heart failure.[26] Fourth, a low heart rate in patients with AF may be an expression of an underlying conduction disorder, which may be associated with impaired outcome itself. Finally, AF in patients with HF may be a marker of a poorer hemodynamic situation leading to a worse outcome.[27]

In addition to these potential explanations, we also cannot exclude the fact that the present findings could apply to some but not all beta-blockers, as differences in the pharmacological profiles of beta-blockers may have played a role. Metoprolol and bisoprolol are selective beta-1 receptor antagonists, and carvedilol and nebivolol are beta-blockers with additional vasodilating properties. A subanalysis of the COMET trial (in which there were 600 patients with AF) demonstrated that carvedilol had a

Table 3. Baseline heart rate and change in heart rate.

First Author	Study	Assessment of baseline HR	Baseline HR (bpm)	Absolute HR reduction Beta-Blocker (bpm)	Relative HR reduction Beta-Blocker (%)	Beta-Blocker dose during study
Joglar	US-Carvedilol	Unclear	AF: 87 SR: 84*	AF: - 13.0 SR: - 12.6*	AF: - 14.9 SR: - 15.0*	Unclear
Lechat	CIBIS-II	ECG	AF: 88 SR: 79	AF: - 8.8 SR: - 10.6	AF: - 10.1 SR: - 13.5	Similar in both groups
Van Veldhuisen	MERIT-HF	ECG	AF: 84 SR: 82	AF: - 14.8 SR: - 13.7	AF: - 17.6 SR: - 16.7	Similar in both groups
Mulder	SENIORS	ECG	AF: 84 SR: 77	AF: - 11.0 SR: - 10.9	AF: - 13.1 SR: - 14.2	Similar in both groups

* Mean heart rate reduction in main study population. Abbreviations: AF: atrial fibrillation, HR: heart rate, ECG: electrocardiogram, SR: sinus rhythm

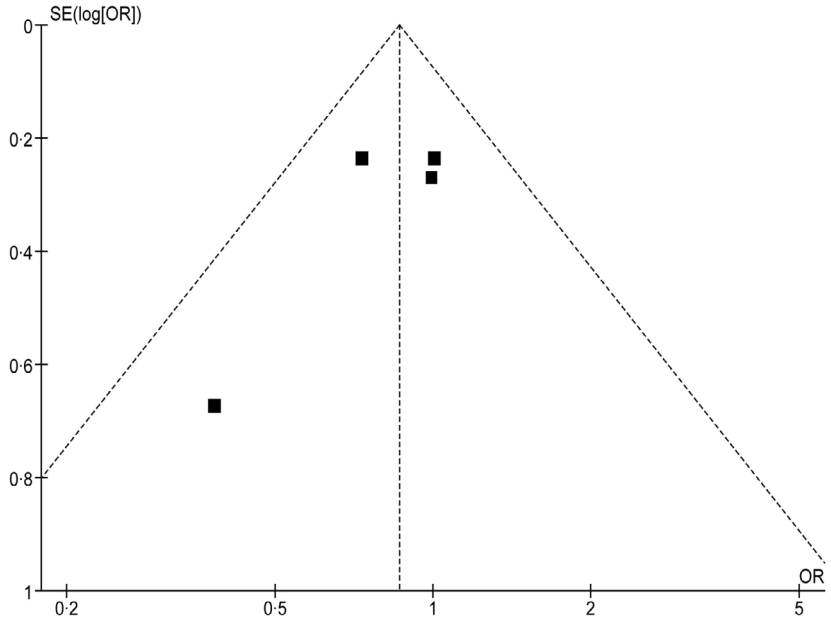

Figure 4. Funnel plot for the main analysis

better effect on outcome than metoprolol.[28] The main COMET study (which compared carvedilol to metoprolol) has been criticized because the dose of the 2 drugs (carvedilol and metoprolol) might not have been equal, since they lowered heart rate to a different extent. However, given the absence of a relation between heart rate lowering and outcome in AF patients, this criticism may be less relevant in this subpopulation of AF patients. Clearly, these beta-blockers have other properties, and for example carvedilol causes inhibition of apoptosis, antioxidant effects, and free radical scavenging, which may also lead to electrophysiological effect.[29] It must be noted, that carvedilol had a relatively favourable effect in the present analysis in the AF patients in the US Carvedilol study,[13] but these were patients had milder disease than in the other studies, which also may have affected the results. Data on carvedilol in AF in more advanced HF were unfortunately not available (as reported above).

Beta-blockers are standard therapy for HF. Other drugs that are generally recommended for HF are angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers, and aldosterone receptor blockers (or mineralocorticoid anatagonists). It is at least remarkable that all these classes of drugs have been shown to be at least as effective in patients with AF, as they are in patients with sinus rhythm in similar analyses as the present study.[27,30]

Limitations

Although the number of AF patients in the included randomized studies was 1677, this is still rather low for survival analysis, and we cannot exclude the possibility that lack of power may have played a role. Nevertheless, although this number may have been small to detect an effect in the group of AF patients alone, there was a significant difference with regard to this (beta-blocker) treatment effect between AF and sinus rhythm patients, which further supports our findings. Also, in present analysis we pooled the effects of different beta-blocker therapies and thereby assumed a class-effect. However, specific differences in pharmacologic profiles may have added to the heterogeneity of our cohort and thereby results. Inherent limitations of pooled analysis of studies include the limited availability of confounding variables, including history of AF, duration of AF, pattern of AF (paroxysmal vs. persistent/permanent AF), new onset AF, dose response and tolerability of the drugs.

Conclusion

The present analysis shows that the effect of beta-blockade in HF patients with AF with regard to outcome is different than in HF patients with sinus rhythm. This may affect the place of these drugs in patients with AF and HF. Clearly, prospective randomized controlled trials in HF specifically aiming at AF patients are warranted to study the prognostic effects of beta-blockers in this population.

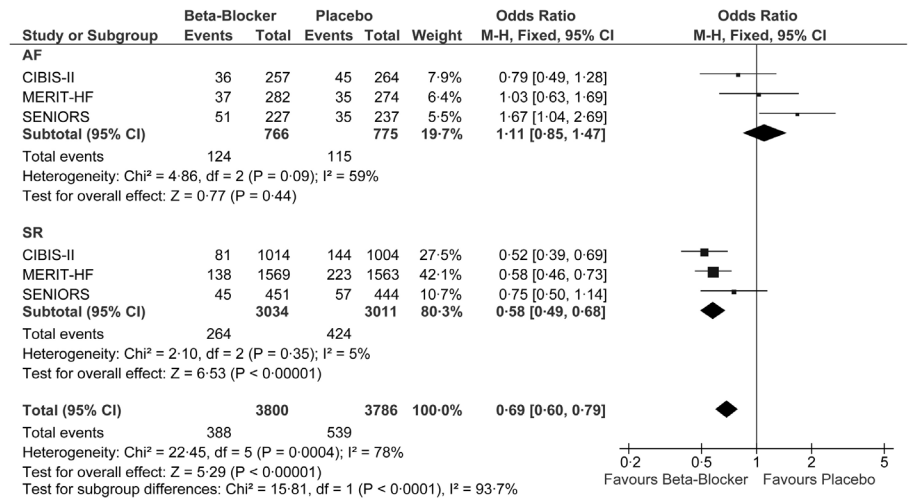

Figure 5. Combined HF hospitalisation risk: Effect of beta-blocker therapy in patients with heart failure and atrial fibrillation, and in patients with heart failure and sinus rhythm

Conflicts of interest

Drs. Rienstra, Damman, and Mulder report no disclosures. Dr. Van Veldhuisen served on the Steering Commitees of MERIT-HF and SENIORS, but has no financial conflicts of interest to report. Dr. Van Gelder received lecture fees from Bayer, Biotronik, Boehringer Ingelheim, BMS, Medtronic and Pfizer, and grant support from Medtronic and Biotronik.

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