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Review Article

BETA BLOCKER AS A TREATMENT OPTION FOR HEART FAILURE WITH ATRIAL FIBRILLATION

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ABSTRACT

Atrial fibrillation (AF) and heart failure (HF) are two diseases with similar clinical phenotypes. The classification of HF is the most important factor for determining the best treatment strategy. Because each subgroup shows different clinical symptoms. These are preserved ejection fraction (> 50 %, HFpEF), mid-range decreased EF (40 % – 49 %, HFmrEF), and reduced EF (< 40 %, HFrEF). Beta-blockers constitute an essential component of our pharmacological treatment plan for chronic HF. Beta-blocker therapy is recommended in patients with HF with low ejection fraction in stable sinus rhythm, because it improves symptoms and leads to a better long-term result. Therapeutic functions of beta-blocker in patients with preserved ejection fraction (EF) is yet unknown. Because till now it fails to improve in reduction of morbidity and mortality rate. The presence of atrial fibrillation (AF) in HF patients rises as the disease progresses, and it is linked to a greater risk of cardiovascular morbidity and mortality. However, irrespective of EF and concurrent AF, the use of beta-blockers in HF patients raises significant questions. There are lots of conflicting research and publications regarding the use and benefit of beta-blocker in patients. Few researches show that beta-blockers have a reduced positive impact in HF patients with AF. In this review, we have discussed the role of beta-blocker as a treatment option for patients who have heart failure with atrial fibrillation.

INTRODUCTION

Heart failure (HF) with or without systolic dysfunction and atrial fibrillation (AF) are the cardiac diseases that commonly coexist and overlap[1]. Age, hypertension, diabetes and obesity all are the risk factors for heart disease [1, 2, 3]. In 2016, the definition of heart failure was updated to include the measurement of the left ventricular ejection fraction (LVEF) [4]. Heart failure can be classified into three categories:

a. Heart failure with preserved EF (> 50 %, HFpEF),
b. Mid-range decreased EF (40 % – 49 %, HFmrEF), and
c. Reduced EF (40 %, HFrEF) [4].

Surprisingly, up to 50 % of chronic heart failure patients have normal or modestly diminished left ventricular EF[5]. As the severity of the illness worsens, the frequency of AF in HF patients rises. Particularly, in patients with New York Heart Association (NYHA) I - III are about 5 %, NYHA III is roughly 26 %, and NYHA IV is presented up to 50 % [6]. The prevalence of AF in HFpEF patients ranges from 15 % - 41 %, according to the data from randomized clinical trials and registries. Patients with HFpEF are more likely to experience prevalent AF or AF at any time up to twice, compared with those with HFrEF[7]. The prevalence of AF was found to be 53 % in HFrEF, 60 % in HFmrEF, and 65 % in HFpEF, according to the data from the Swedish heart failure registry [8]. In an analysis of the ESC-HF long term registry, AF was found 27 % in HFrEF patients[9]. In the case of acute HF, AF affects 24 % - 44 % of patients, and one third of chronic HF patients[10, 11]. Atrial fibrillation is also detected in more than half (57 %) of individuals with new onset HF[12]. Furthermore, HF is seen in 33 %, 44 %, and 56 % of ambulatory individuals with paroxysmal, persistent, and permanent AF, respectively, as well as in more than one third (37 %) of those with new onset AF[12, 13].

Phenotypic Range of Heart Failure Patients

The above HF classification is critical because each HF group has various underlying etiologies, demographics, clinical phenotype, co-morbidities, and cardiovascular mortality. Patients with HFpEF are tend to be older, more common in women, and have greater AF rates than those with HFrEF[14, 15]. Patients with HFpEF are less likely to have a history of prior myocardial infarction[16]. Patients with HFmrEF and patients with HFrEF and HFpEF, have similar features including age and ischemic heart disease (IHD)[17]. Patients with HFmrEF are more likely to have baseline co-morbidities such hypertension, diabetes, and AF than those with HFrEF,

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whereas HFpEF patients are less likely to have them. Finally, the HFmrEF category appears to occupy a position between the two previously identified groups[17]. It is important to note that the prognosis for HFpEF patients is still dismal, and is essentially identical to that of HFrEF patients[18]. Cardiovascular mortality in HFmrEF patients appears to be lower than in HFrEF and HFpEF individuals[19]. The higher frequency of IHD and lower LVEF in HFrEF, as well as the higher incidence of hypertension, diabetes, and AF in HFpEF patients, may help to explain why these two groups had higher cardiovascular mortality than HFmrEF[20].

Impact of atrial fibrillation in heart failure patients

Loss of atrioventricular synchronization, reduced filling time, decreased ejection time and stroke volume in the context of tachycardia all are the factors that contribute to the deterioration of cardiac functions[21]. Tachycardia-induced cardiomyopathy is present in 25 % - 50 % of individuals with left ventricular dysfunction and AF[22, 23]. Atrial fibrillation (AF) is also the leading cause of tachycardia-induced cardiomyopathy [24, 25]. The hemodynamic and clinical signs of this condition are reversed when sinus rhythm (SR) or proper rate regulation is restored, resulting in the removal of these rapid heart rates[26,27]. Elevated heart filling pressures, electrical remodelling, structural abnormalities with interstitial fibrosis, dysregulation of intracellular calcium, and autonomic and neuroendocrine deregulation all are the ways that HF can raise the risk of AF development[28]. Both clinical entities cause increased mechanical cardiac stress, electrical remodelling, and inflammation, which leads to cardiac hypertrophy and shortening of the atrial effective refractory period, supporting the theory that AF and HF are linked with one another[28, 30]. In symptomatic individuals with HFrEF or HFpEF, the presence of AF is associated with a greater incidence of cardiovascular morbidity and mortality[31]. The risk of stroke appears to be equal in both groups[31]. According to the Charm-Study report, new onset of AF in HF patients increased cardiovascular mortality, hospitalization, fatal and nonfatal stroke[32]. The Comet and Valiant-studies found similar results when it came to the association of AF adverse events in HF patients[33, 34]. The coexistence of AF and HF was linked to an increased risk of stroke, hospitalization, and death; according to Verma *et al*[35]. Previous research has shown that non-cardiac related hospitalizations are substantially more common in HFpEF, although HF-hospitalizations are less common in HFpEF than in HFrEF[36, 37]. According to a study, the occurrence of AF in the group of patients with HFpEF was linked to a substantial increase in the risk of cardiovascular mortality, HF hospitalization, and all-cause mortality when compared to individuals without AF[38]. According to this investigation, new onset AF in HFpEF patients after enrolment was associated with an unusually high risk of morbidity and mortality (i.e., a 2.2-fold increase in risk compared to those with no history of AF or a history of AF but not in AF)[39, 40]. HFpEF patients with AF had worse exercise capacity, higher NT-proBNP levels, and more dilated left atria than those in the SR, according to few studies[42, 41]. All of the preceding data pointed to patients with AF and HF coexisting having a more advanced HF stage, whereas HF patients with new onset AF have a poorer prognosis in terms of cardiovascular outcomes and events[43].

Beta-blocker as a treatment option for the patients with HFREF and Sinus Rhythm

The management of AF and HF is critical in patients as it leads to several cardiovascular events. Beta-blockers are currently recommended for all patients with HF, regardless of whether or not they have a rhythm abnormality. Beta-blockers constitute the cornerstone treatment for the patients with HFrEF and stable SR (Class I, Level Evidence: A)[44]. A group of researchers found that beta-blockers improve left ventricular function, reduce mortality and hospitalization rates in HF patients with impaired EF in a dose-dependent manner[45]. A study found that beta-blocker therapy preventes new onset or recurrent AF in HF patients with impaired left ventricular function after myocardial infarction after a mean of 1.3 years, and also in a relatively low risk mostly hypertensive population[46]. Imad Abi Nasr et al conducted a systematic analysis of several kinds of beta-blockers (CAPRICORN with carvedilol[46], CIBIS I with bisoprolol[47], MERIT HF with metoprolol[48], BEST bucindolol[49], COPERNICUS with carvedilol[50], Waagstein with metoprolol[51], Seniors with Nebivolol[52], found a significant decrease in the incidence of new AF in patients with HFrEF, from 39 to 28 per 1000 patient-years (relative risk reduction 27 %; 95 % CI: 14 - 38, P < 0.001)[53]. The only exception was the seniors study, which found no significant reduction in new onset AF in the Nebivolol group, a finding that could be explained in part by the study design, which included elderly patients with a higher prevalence of AF at randomization and a higher proportion (one-third) of HFpEF patients [53]. Clinical studies have indicated that administering carvedilol, bisoprolol, and metoprolol to individuals with HFrEF enhanced survival and reduced cardiac hospitalizations, whereas nebivolol reduced cardiovascular hospital admissions but had no impact on death [53, 54]. In addition, the trials found a substantial decrease in sudden cardiac–heart failure mortality and HF hospitalization [54,53]. Furthermore, despite the terminal state of HF, patients with more advanced HF with LVEF less than 25% and NYHA IV showed a benefit from Carvedilol medication with a 35 % mortality risk decrease in the Copernicus research[55]. The advantages of beta-blocker administration, as well as the improvement in survival, appear to be dose-related manner (larger doses provide better results than medium or low doses) [56]. Stefania Paolillo agreed with the hypothesis that, as proved in the Shift trial, the favourable beta-blocker effects were also reliant on heart rate lowering [57,58]. A composite result of CV mortality, urgent heart transplantation, or LVAD installation demonstrated the favourable impact of beta-blocker therapy [58]. Although carvedilol showed a propensity to reduce mortality compared to the other beta-blockers, Chatterjee et al. and Paolillo *et al*. found no changes in outcome between selective and non-selective-blockers[58, 59]. Another meta-analysis compared the effects of carvedilol and metoprolol on LVEF in HF patients and found that at similar dosages, carvedilol improved LVEF more than metoprolol[60]. Beta-blockers were linked to lower mortality in individuals with HFrEF and advanced CKD, just as they were in those with HFrEF and intermediate CKD[61]. However, in patients with HFpEF or HFmrEF with severe CKD, as well as in patients with HFrEF with atrial fibrillation, the aforesaid positive impact of beta-blockers was not demonstrated[61]. Finally, there is no question that beta-blocker therapy is advantageous in patients with HFrEF and SR.

Beta-blocker treatment in patients with HFREF and Atrial Fibrillation

The majority of HF patients with beta-blockers in the aforementioned clinical studies were in SR, with just a small percentage of patients having AF, ranging from 11% to 35 % [62]. It is still uncertain that beta-blockers can prevent HF progression and cardiovascular events in AF patients or not. According to several studies, beta-blocker is less successful in HF patients with AF than in those with SR[63]. Beta-blockers act on the sinus node in SR, and atrioventricular node in AF [63, 64]. Patients with AF and SR have differing heart rate drops during rest and activity[64]. To generate an appropriate cardiac output in AF patients with loss of atrial contraction, a greater heart frequency may be required[64, 65]. As a result, it is probable that increasing the dose of beta-blockers will cause an increase in heart rate, aggravating the underlying HF[65]. Furthermore, a low heart rate when using a beta-blocker may hide an underlying conduction system issue, especially in older individuals with AF[66, 67]. In individuals with HF, AF may be a symptom of a worsening clinical state and a more advanced illness, resulting in a worse prognosis that is less modifiable by beta-blocker therapy[68]. The disputed impact of beta-blockers on survival is also highlighted in the 2016 AF treatment guidelines, where beta-blockers are indicated as a rate-control method to alleviate AF-related symptoms but not to enhance prognosis [69]. In AF patients with HFrEF, the effect of beta-blockers on outcome is lower than in those with SR[69]. In comparison to patients with SR, a subgroup analysis of the four randomised placebo–controlled studies (USCS, MERIT-HF, CIBIS II, Seniors) focused on patients with AF and reduced EF revealed that beta-blockers had no positive effect on HF hospitalizations (OR = 1.11; 95 % CI: 0.851.47; P = 0.44), or mortality (OR = 0.86; 95 % CI: 0.661.13; P = 0.28) [70]. Cullington *et al*. found that a lower resting ventricular rate is linked to increased mortality in HFrEF patients in SR but not in AF patients[71]. Kotecha, *et al.* [72] evaluated data from ten randomised controlled trials including 18,254 symptomatic patients with HFrEF who were treated with beta-blockers vs placebo, with 26.8% of them having AF. In patients with SR (HR = 0.73; 95 % confidence interval [CI]: 0.670.80; P 0.001), but not in AF (HR = 0.97; 95 % confidence interval [CI]: 0.831.14; P = 0.73), the beta-blockers treated group was linked with significantly decreased mortality[72]. "Beta-blockers should not be administered preferentially over other rate-control drugs and should not be considered as standard treatment to enhance prognosis in patients with simultaneous HF and AF" – according to the research[72]. When the composite endpoint of mortality or hospitalization was examined, there was a trend of a favorable impact in beta-blocker medication (HR = 0.89, P = 0.06) [72]. According to propensity-matched sub-analyses of the AF-CHF Study, beta-blockers were linked with a substantial decrease in all-cause mortality (28 %) but not in hospitalization or cardiovascular mortality in HFrEF patients with concurrent AF [73]. Regardless of the kind or duration of AF, beta-blockers had a favourable effect[73]. The high proportion of AF-related hospitalizations (i.e., 20 %) may be due to the AF-CHF trial design, which was predicated on an aggressive approach to preserve SR[73]. The AF-CHF subgroup research has limitations because it was not a randomized comparison and there is the possibility of confounding[73]. The same findings were seen in the Swedish Heart Failure Registry and a countrywide cohort trial, with mortality reductions of 29 % and 25 % [74,75]. In compared to Kotecha and Rienstra's findings, the aforementioned results are different [70, 71, 72, 73, 74,75]. Differences in methodology, patient demographics, HF stage and type, drugs (beta-blocker type-or target dose), heart rate target, or follow up period may explain some of the discrepancies. Overall, because to the heterogeneity of the trials, no strong conclusions about the impact of beta-blockade in AF patients with HFrEF can be reached. The study from Kotecha publication was particularly criticized because only one electrocardiogram was used to classify baseline patient rhythm. As a result, several of the SR patients may have paroxysmal AF. The reported prevalence of AF (17 %) in a group with HFrEF was consistent with a possible misclassification mistake, as this proportion was significantly lower than the prevalence of AF (41 %) in HF patients from the Swedish registry[72,74]. Furthermore, patients in Kotecha's research had more advanced HF stages, were taking more diuretics and aldosterone antagonists, and had a prevalence of NYHA functional class III or IV symptoms of roughly 70 % vs. 30 % in the AF-CHF trial[72, 73]. In the Swedish HF-registry, almost 50 % of the patients had a NYHA class I/II HF stage [74]. Furthermore, in Kotecha's study, only 58 % of patients were given oral anticoagulants, whereas in the AF-CHF study, up to 82 % of patients were given oral anticoagulants [72,73]. Another difference was that the Kotecha study had a higher proportion of patients on digoxin therapy (83 %) than the AF-CHF and Swedish HF studies, which had 65 % and 36 % of patients on digoxin therapy [72-74]. A more aggressive beta-blocker target dose was reported in Kotecha's trial, with 72.1 % of patients receiving the maximum dose of beta-blockers compared to 28.1 % in the Swedish HF-study[72, 74]. Another difference between Kotecha's study and the Peter Brnnum Nielsen Nationwide Cohort Study in Denkmark is that Kotecha's study included patients with stable or permanent AF, whereas the Peter Brnnum Nielsen Nationwide Cohort Study in Denkmark included patients with a first-time hospital AF diagnosis, showing a mortality reduction with beta-blocker therapy in AF patients with concomitant HF. As previously stated, new onset AF in HF patients is associated with a greater mortality rate, which helps to explain why beta-blocker improves survival in new onset AF patients compared to persistent AF patients [72, 75]. Based on published evidence, it is commonly recognised that the combination of beta-blocker and digoxin has contentious consequences[76]. Digoxin is mostly used in elderly and fragile AF patients, with a more neutral long-term result, according to the SCAF research (The Stockholm Cohort of Atrial Fibrillation SCAF study) [77]. The Registry of Information beta-blockers, digoxin, and atrial fibrillation and Swedish Heart Intensive Care Admissions (RIKS-HIA) found that digoxin-treated patients with AF without coexisting HF had a higher overall mortality, but there was no significant difference in patients with HF[78]. After adjusting for comorbidities and propensity scores, AF patients on digoxin had increased all-cause mortality, independent of the presence or absence of underlying HF, according to a sub-analysis of the AFFIRM study[79]. In contrast, another post-hoc analysis from the AFFIRM trial found that digoxin can help HFrEF patients with AF[80]. Furthermore, regardless of AF load (permanent or non-permanent) or HF phenotype (maintained or lowered LVEF), beta-blockers alone or in

combination with digoxin were linked with neutral or no poorer survival relative to a rate control approach[81]. Digoxin was also linked to a neutral effect on survival and a decreased risk of hospitalization in a recent meta-analysis of observational and controlled data[82]. It is currently unclear if dixogin medication in conjunction with beta-blockers can help with rate control, and whether the AF profile (permanent or non-permanent), or HF type (HFrEF or HFpEF, ischemic or non-ischaemic aetiology) can influence its effectiveness. The lack of benefit of beta-blockers in individuals with HF and AF might be due to a possible interaction between beta-blockers and digoxin in patients with moderate chronic renal disease [83]. The effect of beta-blocker therapy on heart rate variability should also be considered. A heart rate of more than 100 beats per minute was linked to an elevated risk of death in all HF patients with AF according to Li's research [84,85]. The median heart rate of the patients in Kotecha's trial was 81 beats / min, resulting in more neutral results and probably underestimating the therapeutic impact of beta-blocker medication driven by a rigorous heart rate reduction aim less than 100 beats / min [72, 85]. In conclusion, the higher beta-blocker dose, the more advanced HF, the neutral impact of digoxin usage and the higher beta-blocker dose may have reduced any advantages of beta-blockers on mortality in HF patients with AF.

Beta-blocker therapy in patients with HFPEF and Atrial Fibrillation

In this huge population patients with HFpEF with a wide range of phenotypes and comorbidities, making it even more challenging to identify those who will benefit from beta-blocker medication[86]. There is still some uncertainty about the benefits of beta-blocker therapy in HFpEF patients[87, 88]. In individuals with HFpEF or HFmrEF, no medication has yet been proved to lower morbidity or mortality [87,88]. The optimize HF registry was unable to find a predictive effect of beta-blocker usage [89]. Clenand, *et al*. [90] also found that SR patients with HFmrEF and HFrEF had improved LVEF and had lower cardiovascular mortality, but that there was no statistically significant impact in HFpEF patients with SR. The greater the benefit of beta-blocker is to lower the LVEF [90]. Although the above groups with AF coexistence had a higher LVEF, but this did not show better result [90]. The population with AF and either HFrEF or HFmrEF improved their LVEF without improving their prognosis. Intriguingly, there was no improvement in individuals with maintained LVEF > 50 % in SR or AF[90]. In individuals with HFpEF with SR, a high heart rate predicts poor prognosis. Each standard deviation (12.4 beats / min) increase in heart rate was linked to a 13 % increase in the probability of cardiovascular mortality or HF hospitalisation (P = 0.002), a finding that did not hold true in AF [91]. In fact, in the I-PRESERVE investigation, there was no link between heart rate and outcomes in HFpEF patients with AF. In addition, regardless of rhythm, beta-blocker therapy had no effect on the heart rate-risk association in individuals with HFpEF[91]. Another research found that high doses of beta-blockers were linked with a considerably decreased risk of mortality in individuals with HFpEF and SR with a heart rate of less than 70 beats / min[92]. According to several observational studies, beta-blocker reduce the risk of mortality in HFpEF patients with AF or SR, the fact that was not seen in the SENIORS trial and JDHF study sub-analyses[93,94,95, 96]. The antihypertensive impact, arrhythmic risk reduction, myocardial perfusion and metabolism improvement, ventricular remodelling, and any protection against acute coronary events might all be factors in the positive beta-blocker effect in the HFpEF group[97]. Despite the possibility of a reduction in all-cause mortality, the absence of a reduction in hospitalizations is most likely related to the fact that patients with HFpEF tended to be older and had several non-cardiac or cardiac comorbidities[97]. Another meta-analysis found that beta-blocker therapy reduced all-cause mortality but did not reduce HF in individuals with HFpEF and SR or AF[98]. Despite the paucity of evidence supporting the advantages of beta-blocker medication in HFpEF patients, these drugs are commonly used to treat comorbidities such as hypertension, coronary artery disease, and atrial fibrillation. In a limited number of patients with HFpEF and coexistence of CAD or AF, a meta-regression analysis of randomized controlled trials highlighted the beneficial impact of beta-blockers[99]. In comparison to HFpEF patients who had neither CAD nor AF and were not on beta-blocker medication, the aforesaid subgroup of patients had reduced BNP levels and increased exercise capacity while on beta-blocker therapy. The possible advantages and side effects of beta-blockers in HFpEF patients with AF or CAD should be carefully considered[99]. Beta-blockers reduce left ventricular oxygen consumption and enhance myocardial perfusion via their negative chronotropic effect, but the unmasking of any conduction problems or chronotropic intorelance may have a deleterious impact on this subset of patients[99]. The restricted therapeutic window of beta-blocker action remains difficult to define. Following the exclusion of patients with severe comorbidities, beta-blocker medication in HFpEF patients with AF resulted in a considerably decreased mortality and a minor increase in the chance of re hospitalization due to worsening of HF, according to Yang's retrospective clinical analysis [100]. The results of the preceding study provided a better knowledge of the effect of beta-blockers on HFpEF patients with AF but no other comorbidities[100]. Another subgroup investigation in a Korean registry of patients with HFpEF and AF (30 % of the total population) revealed that beta-blocker medication has a favorable effect[101]. During the 6-month and 1-year follow-up periods, Min-Soo Ahn found a lower risk of re hospitalization in 639 patients with acute HFpEF with AF [102]. Furthermore, angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin-converting enzyme blockers (ARBs), statins, and beta-blockers can prevent individuals with AF from developing HFpEF[103]. In certain subgroups of individuals with HFpEF and AF, beta-blockers may have beneficial benefits.

Rate control in Heart Failure patients with Sinus Rhythm or Atrial Fibrillation

In patients with stable HFrEF and SR, resting heart rate is a significant predictor of prognosis[104]. In this patient population, a lower heart rate is often connected with better results. In SR patients, the amount of heart rate drop with beta-blocker use, but not beta-blocker dosage, was linked to a survival advantage[105]. However, among patients with HFpEF and SR, the aforesaid favorable effect of beta-blocker treatment is ambiguous and contentious. A heart rate of less than 70 beats / min at discharge of patients with HFpEF was found to have a significantly lower risk of the composite end point of HF readmissions or all-cause mortality, but not of

either HF or all-cause readmissions individually, when compared to those with a heart rate of more than 70 beats / min [106]. Another intriguing observation was that in a subgroup of patients with coronary artery disease, past myocardial infarction, and coronary revascularization, a discharge prescription of beta-blockers or other heart rate-lowering medicines would be useful[107]. According to a small retrospective analysis of the US Carvedilol Heart Failure Trial, beta-blockers may both control the ventricular response of AF and improve survival in patients with HF and concomitant AF, revealing a trend toward a reduction in the combined end point of death or CHF hospitalization in carvedilol treated patients compared to placebo (RR = 0.35; 95 % CI: 0.121.02; P= 0.055) [109]. Due to patient intolerance of increasing beta-blocker dosages, rigorous heart rate control was shown to be challenging in patients with persistent AF and HFrEF, and it was not related with improved outcomes [110]. In patients with persistent AF and HF, intensive rate control did not offer any benefit, similar to the findings of van Gelder and colleagues [111]. Patients with HFrEF, HFpEF, or AF have a more complicated beta-blocker response. Van Gelder *et al*. [108] found that a lower heart rate is not related with a better prognosis in AF patients with or without HF. The RACE II-Study compared the effects of lenient versus strict rate control in permanent AF patients, finding that lenient rate control (defined as resting HR control 110 beats / min) had similar outcomes to strict rate control (defined as resting HR control 80 beats / min) in terms of cumulative incidence of death from cardiovascular causes, hospitalization for HF, thromboembolic events, bleeding, and life threatening arrhythmia[111]. It is interesting to note that the majority of patients in the RACE II research had an ejection fraction (EF) of 52 %, whereas patients with an EF of less than 40 % made up just 15 % of the entire population[111]. The study clearly showed that tight rate control had no advantage in individuals with maintained ejection and AF[111]. HFrEF patients and AF patients with a mean ventricular rate > 80 beats/min had better outcomes than those with a rate of 72 beats/min in a second prospective randomised investigation of ibopamine's influence on Mortality and effectiveness[112]. Cullington, *et al*.[113] found that HF patients with AF with a ventricular rate of less than 73 beats / minute had a worse survival rate. Despite much greater ventricular rates in AF patients, both AF and SR patients had a comparable prognosis. Miller, *et al*.[114] showed no connection between pre-discharge heart rate and beta-blocker dosage in patients with recent hospitalization for HF with decreased or retained LVEF and AF, implying a more lenient rate control target with no clear benefit of beta-blocker administration. The ideal resting ventricular rate in people with AF and HF is unknown; however it is thought to be between 60 and 100 beats per minute. Independent of HF, the 2016 and 2020 AF ESC recommendations indicate a resting ventricular rate of up to 110 beats / min as the aim for rate control treatment[115, 116]. However, the Task Force and ESC-HF guidelines suggest that a lower rate (60 - 100 beats / min) is desirable for individuals with HF (60 - 100 beats / min at rest and 100 beats / min during activity)[117]. Even though there are few data to support that recommendation, the updated 2011 American College of Cardiology Foundation, American Heart Association, Heart Rhythm Society (HRS) guidelines for the management of AF recommend strict HR control for patients with both conditions, with an HR goal of 60 to 80 beats / min at rest and 90 to 115 beats / min during moderate exercise[118]. The 2009 ACC/AHA recommendations for HF care recommend a more relaxed approach, with a target heart rate of 80 to 90 beats per minute at rest and 110 to 130 beats per minute during moderate activity[119]. In individuals with AF and HF, the aforementioned suggestions lead to inconsistent findings regarding the appropriate heart rate goal. The ideal heart rate for beta-blocker based therapy should be determined individually for each HF patient with AF, taking into consideration heart size, cardiac systolic and diastolic function, concurrent valve function, and any underlying comorbities [120].

Rhythm Control

Few researches (PIAF, STAF, RACE, HOT CAFE, and AFFIRM) found no difference between rhythm control and rate control, regardless of EF, and in HF patients[121-125]. Furthermore, a meta-analysis found a 17 % increase in the incidence of hospitalization in the rhythm control group, but it is important to note that the studies are highly heterogeneous [121-127]. The AFFIRM trial found no survival benefit in the rhythm-control technique for AF patients over the rate-control strategy, however only 23.1 % of patients with HF had HF, and only roughly 9 % had a NYHA functional class of II or higher [128, 129]. In 76 % of AFFIRM patients, LV function was normal[128,129]. A trend for a beneficial impact of rhythm management technique in patients with HF was detected in the subgroup analysis, although it was not statistically significant. It is worth noting that in the rhythm control arm of AFFIRM, SR was maintained in just 63 % of patients throughout a 5-year period, which might explain why the effect of this method has waned[128,129]. The AF-CHF research was the first prospective randomized trial in HF patients to compare the effects of rate versus rhythm management[129, 130]. A total of 1376 patients with AF and HFrEF (mean LVEF, 27 %) were recruited and randomly assigned to rhythm control (usually with amiodarone) or rate control during a three-year period [130]. When compared to rate control, the rhythm control group did not improve mortality, heart failure hospitalization and stroke[130]. Another study in patients with AF and mild to severe HF found that rate control was not inferior to rhythm control in preventing a composite end point of morbidity and death during 2.3 years of follow-up[131]. Another big research of 1,009 individuals with moderate to severe left ventricular failure and AF found no benefit from rhythm control over rate control in terms of overall mortality[132]. However, a research found that SR restoration was linked to a significantly greater survival rate in patients with AF or atrial flutter and an EF of less than 35%.[133] These data back up the idea that rhythm management and SR restoration may be more effective in patients with a higher NYHA stage and severe LV function impairment (LVEF 35 %) than in individuals with mild to moderate HF[133]. When compared to treatment, the randomised Castle AF study found that ablation had a superior result in terms of all-cause mortality, hospitalization, and LVEF improvement in patients with AF with substantial HFrEF (rhythm vs rate control)[134]. Also, among AF patients with a history of HF, a non-significant trend on main endpoint reduction was seen in a prespecified subgroup analysis of the CABANA study [135,136]. It is critical to identify HF patients who have non-ischemic etiology cardiomyopathy, LVEF > 35 % and minimal atrial fibrosis of 10 % or less, since these

individuals may be the major responders to AF ablation[134- 138]. Patients with HFrEF may benefit from ablation, according to Cabana and Castle AF study, since it reduces AF load, improves LVEF, and has a lesser toxicity impact than medication treatment [138,139]. In comparison to the Castle AF study, the AMICA trial looked at patients with more advanced HF and persistent AF who received catheter ablation or stayed on optimum medical treatment [140]. In one year of follow-up, the intrusive technique showed a comparable improvement in EF as the medical group, with no notable advantage of ablation [140]. Taking into account the results of the AMICA trial as well as the neutral effect of ablation in subgroup analyses of the primary end point in CASTLE-AF patients with NYHA III HF symptoms as well as in patients with an LVEF of less than 25 %, who did not show any benefit, AF-ablation is not required in all HFrEF patients[134-136,140].

CONCLUSION

Beta-blocker administration in HF patients with AF is not well established. There are many unanswered concerns and conflicting evidence about their positive impact on this demographic. These are

- Is there a link between the type of beta-blocker and the patient's outcome?
- In this demographic, what is the best targeted medication to control heart rate?
- Are the benefits of beta-blocker usage depending on the amount of EF (reduced versus preserved)?
- Is there a link between beta-blockers and the degree of heart failure (for example, severe low LVEF or diminished right ventricular function with concomitant valve failure)?
- Should it be utilized as a first-line rate control in patients with HF-AF?
- Is there a subset of HF-AF patients and comorbidities that may benefit the most?
- Can the use of a beta-blocker in combination with digoxin or amiodarone impact the patient's prognosis?
- Is AF ablation in conjunction or not with a beta-blocker more effective than medical therapy alone?

More randomized trials and studies are needed to enhance our clinical approach to the use of beta-blockers in heart failure patients with AF. This is the only approach to acquire an evidence based beta-blocker administration that results in improved outcomes and fewer adverse effects for each patient.

References

1. Maisel WH, Stevenson LW Atrial fibrillation in heart failure: epidemiology, pathophysiology, and rationale for therapy. *Am J Cardiol.* 2003; 91:2D–8D.
2. Ozierański K, Kapłon-Cieślicka A, Peller M, et al Clinical characteristics and predictors of one-year outcome of heart failure patients with atrial fibrillation compared to heart failure patients in sinus rhythm. *Kardiol Pol.* 2016; 74:251–261. doi: 10.5603 /KP.a2015.0180.
3. Anter E, Jessup M, Callans DJ Atrial fibrillation and heart failure. Treatment considerations for a dual epidemic. *Circulation.* 2009; 119:2516–2525.
4. Ponikowski P, Voors AA, Anker SD, et al ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Eur J Heart Fail.* 2016; 18:891–975.
5. Lam CS, Donal E, Kraigher-Krainer E, et al Epidemiology and clinical course of heart failure with preserved ejection fraction. *Eur J Heart Fail.* 2011; 13:18–28. doi: 10.1093/eurjhf/hfq121.
6. Batul SA, Gopinathannair R Atrial fibrillation in heart failure: a therapeutic challenge of our times. *Korean Circ J.* 2017; 47:644–662. doi: 10.4070/kcj. 2017.0040.
7. Kotecha D, Lam CS, Van Veldhuisen DJ, et al Heart failure with preserved ejection fraction and atrial fibrillation vicious twins. *J Am Coll Cardiol.* 2016; 68:2217–2228. doi: 10.1016/j.jacc.2016.08.048.
8. Sartipy U, Dahlström U, Fu M, et al Atrial fibrillation in heart failure with preserved, mid-range, and reduced ejection fraction. *JACC Heart Fail.* 2017; 5:565–574. doi: 10.1016/j.jchf.2017.05.001.
9. Barak Zafrir, Lund LH, Laroche C, et al Prognostic implications of atrial fibrillation in heart failure with reduced, mid-range, and preserved ejection fraction: a report from 14 964 patients in the European Society of Cardiology Heart Failure Long-Term Registry. *Eur Heart J.* 2018; 39:4277–4284. doi: 10.1093/ eurheartj/ehy626.
10. Farmakis D, Chrysohoou C, Giamouzis G, et al. The management of atrial fibrillation in heart failure: an expert panel consensus. Heart Fail Rev 2020. Pulished online first: May 28, 2020. Doi: 10.1007/ s10741-020-09978-0.
11. Komajda M, Anker SD, Cowie MR, et al Physicians' adherence to guideline-recommended medications in heart failure with reduced ejection fraction: data from the QUALIFY global survey. *Eur J Heart Fail.* 2016; 18:514–522.
12. Santhanakrishnan R, Wang N, Larson MG, et al Atrial fibrillation be gets heart failure and vice versa: Temporal associations and differences in preserved versus reduced ejection fraction. *Circulation.* 2016; 133:484–492. doi: 10.1161/CIRCULATIONAHA.115.018614.
13. Chiang CE, Naditch-Brûlé L, Murin J, *et a*l Distribution and risk profile of paroxysmal, persistent, and permanent atrial fibrillation in routine clinical practice: insight from the Realise AF international registry. *Circ Arrhythm Electrophysiol.* 2012; 5:632–639. doi: 10.1161/CIRCEP.112.97074 9.
14. Khazanie P, Liang L, Qualls LG, et al Outcomes of medicare beneficiaries with heart failure and atrial fibrillation. *JACC Heart Fail.* 2014; 2:41–48. doi: 10.1016/j.jchf.2013.11.002.
15. Goyal P, Almarzooq ZI, Horn EM, et al Characteristics of hospitalizations for heart failure

with preserved ejection fraction. *Am J Med.* 2016;129:635. e15–26. doi: 10.1016/ j.amjmed.2016.02.007.

16. Adamczak DM, Oduah MT, Kiebalo T, et al Heart failure with preserved ejection fraction-a concise review. *Curr Cardiol Rep*. 2020; 22:82. doi: 10.1007/ s11886-020-01349-3.
17. Lopatin Y Heart failure with mid-range ejection fraction and how to treat it. *Card Fail Rev.* 2018; 4:9–13.
18. Chan MM, Lam CS How do patients with heart failure with preserved ejection fraction die? *Eur J Heart Fail.* 2013; 15:604–613. doi: 10.1093/eurjhf/ hft062.
19. Branca L, Sbolli M, Metra M, et al Heart failure with mid-range ejection fraction: pro and cons of the new classification of heart failure by European Society of Cardiology guidelines. *ESC Heart Fail.* 2020; 7:381–399. doi: 10.1002/ehf2.12586.
20. Chioncel O, Lainscak M, Seferovic PM, et al Epidemiology and one-year outcomes in patients with chronic heart failure and preserved, mid-range and reduced ejection fraction: an analysis of the ESC Heart Failure Long-Term Registry. *Eur J Heart Fail.* 2017; 19:1574–1585. doi: 10.1002/ejhf.813.
21. Lee Park K, Anter E Atrial fibrillation and heart failure: A review of the intersection of two cardiac epidemics. *J Atr Fibrillation.* 2013; 6:751.
22. Mohamed HA Tachycardia-induced cardiomyopathy (Tachycardiomyopathy) *Libyan J Med.* 2007; 2:26–29. doi: 10.3402/ljm.v2i1.4688.
23. Redfield MM, Kay GN, Jenkins LS, et al Tachycardia-related cardiomyopathy: A common cause of ventricular dysfunction in patients with atrial fibrillation referred for atrioventricular ablation. *Mayo Clin Proc.* 2000; 75:790–795. doi: 10.4065/75.8.790.
24. Nerheim P, Birger-Botkin S, Piracha L, et al Heart failure and sudden death in patients with tachycardia-induced cardiomyopathy and recurrent tachycardia. *Circulation.* 2004; 110:247–252. doi: 10.1161/01.CIR.0000135472.28234.CC.
25. Calò L, De Ruvo E, Sette A, et al Tachycardia-induced cardiomyopathy: mechanisms of heart failure and clinical implications. *J CardiovascMed (Hager stown)* 2007;8:138–143. doi: 10.2459/01.JCM.0000260841.30415.62.
26. Edner M, Caidahl K, Bergfeldt L, et al Prospective study of left ventricular function after radiofrequency ablation of atrioventricular junction in patients with atrial fibrillation. *Br Heart J.* 1995; 74:261–267. doi: 10.1136/hrt.74.3.261.
27. Van Gelder IC, Crijns HJ, Blanksma PK, et al Time course of hemodynamic changes and improvement of exercise tolerance after cardioversion of chronic atrial fibrillation unassociated with cardiac valve disease. *Am J Cardiol.* 1993; 72:560–566. doi: 10.1016/0002-9149(93)90352-D.
28. Schotten U, Dobrev D, Platonov PG, et al Current controversies in determining the main mechanisms of atrial fibrillation. *J Intern Med.* 2016; 279:428–438. doi: 10.1111/joim.12492.
29. Jalife K, Kaur K Atrial remodeling, fibrosis and atrial Fibrillation. *Trends Cardiovasc Med.* 2015; 25:475-484. doi: 10.1016/j.tcm.2014.12.015.
30. Neuberger HR, Reil JC, Adam O, et al Atrial fibrillation in heart failure: Current treatment of patients with remodeled atria. *Curr Heart Fail Rep.* 2008;5:219-225. doi: 10.1007/s11897-008-0033-x.
31. Kotecha D, Chudasama R, Lane DA, et al Atrial fibrillation and heart failure due to reduced versus preserved ejection fraction: A systematic review and meta-analysis of death and adverse outcomes. *Int J Cardiol.* 2016; 203:660–666. doi: 10.1016/j.ijcard. 2015.10.220.
32. Olsson LG, Swedberg K, Ducharme A, et al Atrial fibrillation and risk of clinical events in chronic heart failure with and without left ventricular systolic dysfunction: Results from the candesartan in heart failure-assessment of reduction in mortality and morbidity (CHARM) Program. *J Am Coll Cardiol.* 2006; 47:1997–2004.doi: 10.1016/j.jacc.2006.01.060.
33. Swedberg K, Olsson LG, Charlesworth A, et al Prognostic relevance of atrial fibrillation in patients with chronic heart failure on long-term treatment with beta blockers: Results from COMET. *Eur Heart J.* 2005; 26:1303–1308. doi: 10.1093/eurheartj/ehi166.
34. Køber L, Swedberg K, McMurray JJ, et al Previously known and newly diagnosed atrial fibrillation: A major risk indicator after a myocardial infarction complicated by heart failure or left ventricular dysfunction. *Eur J Heart Fail.* 2006; 8:591-598. doi: 10.1016/j.ejheart.2005.11.007.
35. Verma A, Kalman JM, Callans DJ Treatment of patients with atrial fibrillation and heart failure with reduced ejection fraction. *Circulation.* 2017; 135:1547–1563.doi: 10.1161/CIRCULATIONAHA.116.026054.
36. Edelmann F, Stahrenberg R, Gelbrich G, et al Contribution of comorbidities to functional impairment is higher in heart failure with preserved than with reduced ejection fraction. *Clin Res Cardiol.* 2011; 100:755-764. doi: 10.1007/s00392-011-0305-4.
37. Oktay AA, Rich JD, Shah SJ The emerging epidemic of heart failure with preserved ejection fraction. *Curr Heart Fail Rep.* 2013; 10:401–410. doi: 10.1007/ s11897-013-0155-7.
38. Silverman DN, Plante TB, Infeld M, et al Association of β-blocker use with heart failure hospitalizations

and cardiovascular disease mortality among patients with heart failure with a preserved ejection fraction. A secondary analysis of the TOPCAT trial. *JAMA Netw Open.* 2019; 2:e1916598. doi: 10.1001/jamanet workopen.2019.16598.

39. Shah AM Atrial fibrillation in heart failure with preserved ejection fraction: The TOPCAT. *JACC Heart Fail.* 2018; 6:689–697.doi: 10.1016/j.jchf.20 18.05.005.
40. Zakeri R, Chamberlain AM, Roger VL, et al Temporal relationship and prognostic significance of atrial fibrillation in heart failure patients with preserved ejection fraction: A Community-Based Study. *Circulation.* 2013; 128:1085-1093.doi:10. 1161/CIRCULATIONAHA.113.001475.
41. Lam C, Rienstra M, Tay WT, et al Atrial fibrillation in heart failure with preserved ejection fraction: Association with exercise capacity, left ventricular filling pressures, natriuretic peptides, and left atrial volume. *JACC Heart Fail.* 2017; 5:92–98. Doi:10 .1016/j.jchf.2016.10.005.
42. Zakeri R, Borlaug BA, McNulty SE, et al Impact of atrial fibrillation on exercise capacity in heart failure with preserved ejection fraction: A RELAX Trial ancillary study. *Circ Heart Fail.* 2014; 7:123–130. doi: 10.1161/CIRCHEARTFAILURE.113.000568.
43. Cheng M, Lu X, Huang J, et al The prognostic significanc eof atrial fibrillation in heart failure with a preserved and reduced left ventricular function: insights from a meta-analysis. *Eur J Heart Fail.* 2014; 16:1317–1322. doi: 10.1002/ejhf.187.
44. Van der Meer P, Gaggin HK, Dec GW ACC/AHA Versus ESC Guidelines on Heart Failure: JACC Guideline Comparison. *J Am Coll Cardiol.* 2019; 73:2756-2768.
45. Bristow MR, Gilbert EM, Abraham WT, et al Carvedilol produces dose-related improvements in left ventricular function and survival in subjects with chronic heart failure. *MOCHA Investigators. Circulation.* 1996; 94:2807–2816.
46. McMurray J, Køber L, Robertson M, et al Antiarrhythmic effect of carvedilol after acute myocardial infarction results of the carvedilol post-Infarct survival control in left ventricular dysfunction (CAPRICORN) Trial. *J Am Coll Cardiol.* 2005; 45:525–530. doi: 10.1016/j.jacc.2004.09.076.
47. A randomized trial of beta-blockade in heart failure The Cardiac Insufficiency Bisoprolol Study (CIBIS) *CIBIS Investigators and Committees. Circulation.* 1994; 90:1765–1773.
48. Effect of metoprolol CR/XL in chronic heartfailure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF) Effect of metoprolol CR/XL in chronic heartfailure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF) *Lancet.* 1999; 353:2001–2007. doi: 10.1016/S0140-6736(99)04440-2.
49. Eichhorn EJ, Domanski MJ, Krause-Steinrauf H, al A trial of the beta-blocker bucindolol in patients with advanced chronic heartf ailure (BEST) *N Engl J Med.* 2001;344:1659–1667.doi:10.1056/NEJM2001 05313442202.
50. Packer M, Fowler MB, Roecker EB, et al Effect of carvedilol on the morbidity of patients with severe chronic heart failure: Results of the carvedilol prospective randomized cumulative survival (COPERNICUS) study. *Circulation.* 2002; 106:2194-2199. doi: 10.1161/01.CIR.0000035653.72855.BF.
51. Waagstein F, Stromblad O, Andersson B, et al Increased exercise ejection fraction and reversed remodeling after long-term treatment with metoprolol in congestive heart failure: A randomized, stratified, double-blind, placebo-controlled trial in mild to moderate heart failure due to ischaemic or idiopathic dilated cardiomyopathy. *Eur J Heart Fail.* 2003; 5:679–691. doi: 10.1016/S1388-9842(03)00105-3.
52. Flather MD, Shibata MC, Coats A, et al Randomized trial to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart failure (SENIORS) *Eur Heart J.* 2005;26:215–225. doi: 10.1093/eurheartj/ehi115.
53. Nasr IA, Bouzamondo A, Hulot JS, et al Prevention of atrial fibrillation onset by beta-blocker treatment in heart failure: A meta-analysis. *Eur Heart J.* 2007; 28:457–462. doi: 10.1093/eurheartj/ehl484.
54. Klapholz M Beta-blocker use for the stages of heart failure. *Mayo Clin Proc.* 2009; 84:718–729. doi: 10.4065/84.8.718.
55. Packer M, Coats AJ, Fowler MB, et al Effect of carvedilol on survival in severe chronic heart failure. *N Engl J Med.* 2001; 344:1651–1658. doi: 10.1056/NEJM200105313442201.
56. Fiuzat M, Wojdyla D, Kitzman D, et al Relationship of beta-blocker dose with outcomes in ambulatory heart failure patients with systolic dysfunction: results from the HF-ACTION (Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training) trial. *J Am Coll Cardiol.* 2012; 60:208-215. doi: 10.1016/j.jacc.2012.03.023.
57. Swedberg K, Komajda M, Böhm M, et al Effects on outcomes of heart rate reduction by ivabradine in patients with congestive heart failure: Is there an influence of beta-blocker dose?: Findings from the SHIFT (systolic heart failure treatment with the I(f) inhibitor ivabradine Trial) study. *J Am Coll Cardiol.* 2012; 59:1938–1945. doi: 10.1016/ j.jacc.2012.01.020.
58. Paolillo S, Mapelli M, Bonomi A, et al Prognostic role of β-blocker selectivity and dosage regimens in heart failure patients. Insights from the MECKI score database. *Eur J Heart Fail.* 2017; 19:904-914.
59. Chatterjee S, Biondi-Zoccai G, Abbate A, et al Benefits of β blockers in patients with heart failure and reduced ejection fraction: Network meta-analysis. *BMJ.* 2013; 346:f55. doi: 10.1136/bmj.f55.

60. Packer M, Antonopoulos GV, Berlin JA, et al Comparative effects of carvedilol and metoprolol on left ventricular ejection fraction in heart failure: Results of a meta-analysis. *Am Heart J.* 2001; 141:899–907. doi: 10.1067/mhj.2001.115584.
61. Fu E, Uijl A, Dekker FW, et al Association between use of beta-blockers and mortality/morbidity in patients with heart failure with reduced, mid range or preserved ejection fraction and advanced chronic kidney disease. *Circ Heart Fail.* 2020; 13:e007180.
62. Ozierański K, KapłonCieślicka A, Balsam P, et al Effect of β blockers on 1year survival and hospitalizations in patients with heart failure and atrial fibrillation: Results from ESC HF Pilot and ESC HF LongTerm Registry. *Pol Arch Intern Med.* 2018; 128:649–657.
63. Carlisle MA, Fudim M, DeVore AD, Piccini JP Heart failure and atrial fibrillation, like Fire and Fury. *JACC Heart Fail.* 2019; 7:447–456. doi:10.1016/j.jchf. 2019.03.005.
64. Camm AJ, Savelieva I, Lip GYet Guideline Development Group for the NICE clinical guideline for the managementof atrial fibrillation. Rate control in the medical management of atrial fibrillation. *Heart.* 2007; 93:35–38.
65. Daoud EG, Weiss R, Bahu M, Knight BP Effect of an irregular ventricular rhythm on cardiac output. *Am J Cardiol.* 1996; 78:1433–1436. doi:10.1016/S0002-9149(97)89297-1.
66. Fauchier L, Laborie G, Clementy N, et al Beta-blockers or Digoxinfor Atrial Fibrillation and Heart Failure? *Card Fail Rev.* 2016; 2:35–39. doi: 10.15420 /cfr.2015:28:2.
67. Goyal P, Rich MW Electrophysiology and heart rhythm disorders in older adults. *J Geriatr Cardiol.* 2016; 13:645–651.
68. Kotecha D, Piccini JP Atrial fibrillation in heart failure: What should we do? *Eur Heart J.* 2015; 36:3250–3257.
69. Camm AJ, Kirchhof P, Lip GY et al Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC) *Eur Heart J.* 2010; 31:2369–2429. doi:10.1093/eurheartj/ehq 278.
70. Rienstra M, Damman K, Mulder BA, et al Beta-blockers and outcome in heart failure and atrial fibrillation: A meta-analysis. *JACC Heart Fail.* 2013; 1:21–28. doi: 10.1016/j.jchf.2012.09.002.
71. Cullington D, Goode KM, Zhang J, *et al* Is heart rate important for patients with heart failure in atrial fibrillation? *J ACC Heart Fail.* 2014; 2:213–220. doi: 10.1016/j.jchf.2014.01.005.
72. Kotecha D, Holmes J, Krum H, et al Efficacy of β blockers in patients with heart failure plus atrial fibrillation: an individual-patient data meta-analysis. *Lancet.* 2014; 384:2235–2243. doi:10.1016/ S0140-6736(14)61373-8.
73. Cadrin-Tourigny J, Shohoudi A, Roy D, et al Decreased mortality with beta-blockers in patients with heart failure and coexisting atrial fibrillation: An AF-CHF Substudy. *JACC Heart Fail.* 2017; 5:99-106. doi: 10.1016/j.jchf.2016.10.015.
74. Li SJ, Sartipy U, Lund LH, et al Prognostic significance of resting heart rate and use of betablockers in atrial fibrillation and sinus rhythm in patients with heart failure and reduced ejection fraction: Findings from the Swedish Heart Failure Registry. *Circ Heart Fail.* 2015; 8:871–879. doi: 10.1161/CIRCHEARTFAILURE.115.002285.
75. Nielsen PB, Larsen TB, Gorst-Rasmussen A, et al Beta-blockers in atrial fibrillation patients with or without heart failure: Association with mortality in a Nationwide Cohort Study. *Circ Heart Fail.* 2016; 9:e002597.
76. Chamaria S, Desai AM, Reddy PC, et al Digoxin use to control ventricular rate in patients with atrial fibrillation and heart failure is not associated with increased mortality. *Cardiol Res Pract.* 2015; 2015:314041.
77. Rosenqvist M Digoxin in atrial fibrillation: Report from the Stockholm Cohort study of Atrial Fibrillation (SCAF) *Heart.* 2010;96:275–280. doi: 10.1136/hrt.2009.175786.
78. Hallberg P, Lindbäck J, Lindahl B, et al Digoxin and mortality in atrial fibrillation: a prospective cohort study. *Eur J Clin Pharmacol.* 2007;63:959–971. doi: 10.1007/s00228-007-0346-9.
79. Whitbeck MG, Charnigo RJ, Khairy P, et al Increased mortality among patients taking digoxin: Analysis from the AFFIRM study. *Eur Heart J.* 2013; 4:1481–1488.
80. Patel NJ, Hoosien M, Deshmukh A, et al Digoxin significantly improves all-cause mortality in atrial fibrillation patients with severely reduced left ventricular systolic function. *Int J Cardiol.* 2013;69:e84–e86.
81. Fauchier L, Grimard C, Pierre B, et al Comparison of betablocker and digoxin alone and in combination for management of patients with atrial fibrillation and heart failure. *Am J Cardiol.* 2009; 103:48–54.
82. Ziff OJ, Lane DA, Samra M, et al Safety and efficacy of digoxin: Systematic review and meta-analysis of observational and controlled trial data. *BMJ.* 2015; 51:4451.
83. Pérez-Calvo JI, Sánchez-Marteles M, Morales-Rull JL β blockers in patients with heart failure and atrial fibrillation. *Lancet.* 2015; 385:1617–1618.
84. Hori M, Okamoto H Heart rate as a target of treatment of chronic heart failure. *J Cardiol.* 2012; 60:86–90. doi: 10.1016/j.jjcc.2012.06.013.
85. Chen Y, Huang WJ, Huang YL, et al Beta-blockers treatment in heart failure with atrial fibrillation-Who

should we believe? *Int J Cardiol.* 2016; 203:60–61. doi: 10.1016/j.ijcard.2015.10.096.

86. Wintrich J, Kindermann I, Ukena C, et al Therapeutic approaches in heart failure with preserved ejection fraction: past, present, and future. *Clin Res Cardiol.* 2020; 109:1079–1098. doi: 10.1007/s00392-020-01633-w.
87. Xu X, Wang DW The progress and controversial of the use of betablockers in patients with heart failure with a preserved ejection fraction. *Int J Cardiol Heart Vasc.* 2019; 26:100451.
88. Borlaug BA, Redfield MM Diastolic and systolic heart failure are distinct phenotypes within the heart failure spectrum. *Circulation.* 2011;123:2006–2013. doi: 10.1161/CIRCULATIONAHA.110.954388.
89. Fonarow GC, Stough WG, Abraham WT, et al Characteristics, treatments, and outcomes of patients with preserved systolic function hospitalized for heart failure: A report from the OPTIMIZE-HF Registry. *JAm Coll Cardiol.* 2007; 50:768–777. doi: 10.1016/j.jacc.2007.04.064.
90. Cleland J, Bunting KV, Flather MD, et al Beta-blockers for heart failure with reduced, mid-range, and preserved ejection fraction: An individual patient-level analysis of double-blind randomized trials. *Eur Heart J.* 2018; 39:26–35. doi:10.1093/eurheartj/ehx564.
91. Böhm M, Perez AC, Jhund PS, et al Relationship between heart rate and mortality and morbidity in the irbesartan patients with heart failure and preserved systolic function trial (I-Preserve) *Eur J Heart Fail.* 2014; 16:778–787. doi: 10.1002/ejhf.85.
92. Lam PH, Gupta N, Dooley DJ, et al Role of High-Dose Beta-Blockers in Patients with Heart Failure with Preserved Ejection Fraction and Elevated Heart Rate. *Am J Med.* 2018; 131:1473–1481. doi: 10.1016/j.amjmed.2018.07.008.
93. Dobre D, van Veldhuisen DJ, DeJongste MJ, et al Prescription of beta-blockers in patients with advanced heart failure and preserved left ventricular ejection fraction. Clinical implications and survival. *Eur J Heart Fail.* 2007; 9:280–286. doi: 10.1016/j.ejheart.2006.07.008.
94. El-Refai M, Peterson EL, Wells K, et al Comparison of beta-blocker effectiveness in heart failure patients with preserved ejection fraction versus those with reduced ejection. *J Card Fail.* 2013 Feb;19:73–9. doi: 10.1016/j.cardfail.2012.11.011.
95. Crijns HJ Effect of nebivolol on outcome in elderly patients with heart failure and atrial fibrillation: Insights from SENIORS. *Eur J Heart Fail.* 2012; 14:1171–1178. doi: 10.1093/eurjhf/hfs100.
96. Yamamoto K, Origasa H, Hori M, J-DHF Investigators Effects of carvedilol on heart failure with preserved ejection fraction: The Japanese Diastolic Heart Failure Study (J-DHF) *Eur J Heart Fail.* 2013; 15:110–118. doi: 10.1093/eurjhf/hfs141.
97. Liu F, Chen Y, Feng X, et al Effects of beta-blockers on heart failure with preserved ejection fraction: A Meta-Analysis. *PloS One.* 2014; 9:e90555. doi:10.1371/journal.pone.0090555.
98. Bavishi C, Chatterjee S, Ather S, et al Beta-blockers in heart failure with preserved ejection fraction: A meta-analysis. *Heart Fail Rev.* 2015;20:193–201. doi: 10.1007/s10741-014-9453-8.
99. Fukuta H, Goto T, Wakami K, et al Effect of beta-blockers on heart failure severity in patients with heart failure with preserved ejection fraction: A meta-analysis of randomized controlled trials. *Heart Fail Rev.* 2021; 26:165–171. doi: 10.1007/s10741-020-10013-5.
100. Yang Y, Guo S, Wakami K, et al Decreased mortality with beta-blocker therapy in HFpEF patients associated with atrial fibrillation. *Cardiol Res Pract.* 2020; 2020:3059864.
101. Kim SH, Yun SC, Park JJ, et al Beta-blockers in patients with heart failure with preserved ejection fraction: Results from the Korea acute heart failure (KorAHF) Registry. *Korean Circ J.* 2019;49:238–248. doi: 10.4070/kcj.2018.0259.
102. Ahn MS, Yoo BS, Son JW, et al Beta-blocker therapy at discharge in patients with acute heart failure and atrial fibrillation. *J Korean MedSci.* 2020; 35:e278. doi: 10.3346/jkms.2020.35.e278.
103. Kumar A, Saluja AK, Adnan Khan, et al Protective role of medications on atrial fibrillation and heart failure with preserved ejection fraction. *J Card Fail.* 2014; 20:S121.
104. Castagno D, Skali H, Takeuchi M, et al Association of heart rate and outcomes in a broad spectrum of patients with chronic heart failure: Results from the CHARM (candesartan in heart failure: Assessment of Reduction in Mortality and morbidity) program. *J Am Coll Cardiol.* 2012; 59:1785–1795. doi:10.1016/j.jacc.2011.12.044.
105. McAlister FA, Wiebe N, Ezekowitz JA, et al Meta-analysis: beta-blocker dose, heart rate reduction, and death in patients with heart failure. *Ann Intern Med.* 2009; 150:784–794. doi: 10.7326/0003-4819-150-11-200906020-00006.
106. Lam PH, Dooley DJ, Deedwania P, et al Heart rate and outcomes in hospitalized patients with heart failure with preserved ejection fraction. *J Am Coll Cardiol.* 2017; 70:1861–1871. doi:10.1016/j.jacc.2017.08.022.
107. Dézsi CA, Szentes V The real role of β-blockers in daily cardiovascular therapy. *Am J Cardiovasc Drugs.* 2017; 17:361–373. doi: 10.1007/s40256-017-0221-8.
108. Van Gelder IC, Wyse DG, Chandler ML, et al Does intensity of rate-control influence outcome in atrial fibrillation? An analysis of pooled data from the RACE and AFFIRM studies. *Europace.* 2006; 8:935–942. doi: 10.1093/europace/eul106.

109. Joglar JA, Acusta AP, Shusterman NH, et al Effect of carvedilol on survival and hemodynamics in patients with atrial fibrillation and left ventricular dysfunction: Retrospective analysis of the US carvedilol heart failure trials program. *Am Heart J*. 2001; 142:498–501. doi: 10.1067/mhj.2001.117318.

110. Silvet H, Hawkins LA, Jacobson AK Heart rate control in patients with chronic atrial fibrillation and heart failure. *Congest Heart Fail.* 2013; 19:25–28. doi: 10.1111/j.1751-7133.2012.00309.x.

111. Van Gelder IC, Groenveld HF, Crijns HJ, et al Lenient versus strict rate control in patients with atrial fibrillation. *N Engl J Med*. 2010; 362:1363–1373. doi: 10.1056/NEJMoa1001337.

112. Rienstra M, Van Gelder IC, Van den Berg MP, et al A comparison of low versus high heart rate in patients with atrial fibrillation and advanced chronic heart failure: effects on clinical profile, neurohormones and survival. *Int J Cardiol*. 2006; 109:95–100. doi:10.1016/j.ijcard.2005.05.054.

113. Ehrlich JR, Ovsyshcher E Slowing down the heart rate in permanent atrial fibrillation. *Eur Heart J*. 2014; 35:480–481. doi: 10.1093/eurheartj/eht476.

114. Miller RJ, Howlett JG, Chiu MH, et al Relationships among achieved heart rate, β-blocker dose and long-term outcomes in patients with heart failure with atrial fibrillation. *Open Heart*. 2016 23; 3:e000520. doi: 10.1136/openhrt-2016-000520.

115. Kirchhof P, Benussi S, Kotecha D, et al 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J*. 2016; 37:2893–2962. doi:10.1093/eurheartj/ehw210.

116. Hindricks G, Potpara T, Dagres N, et al 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European association for Cardio-Thoracic Surgery (EACTS) *Eur Heart J*. 2021;42:373-498. doi:10.1093/eurheartj/ehaa612.

117. Ponikowski P, Voors AA, Anker SD, et al 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2016; 37:2129-2200. doi: 10.1093/eurheartj/ehw128.

118. Fuster V, Rydén LE, Cannom DS, et al 2011 ACCF/AHA/HRS focused updates incorporated into the ACC/AHA/ESC 2006 Guidelines for the management of patients with atrial fibrillation: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines developed in partnership with the European Society of Cardiology and in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. *J Am Coll Cardiol.* 2011; 57:e101–e198.

119. Wann LS, Curtis AB, January CT, *et al* 2011 ACCF/AHA/HRS focused update on the management of patients with atrial fibrillation (updating the 2006 guideline): A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation.* 2011; 123:104–123. doi: 10.1161/CIR.0b013e3181fa3cf4.

120. Okumura T, Kimura Y, Murohara T Heart rate control using beta-blockers for heart failure with atrial fibrillation: More than enough is too much. *Hypertens Res.* 2019; 42:1826–1827. doi: 10.1038/s41440-019-0303-x.

121. Hohnloser SH, Kuck KH, Lilienthal J Rhythm or rate control in atrial fibrillation-Pharmacological Intervention in atrial fibrillation (PIAF): a randomised trial. *Lancet.* 2000; 356:1789–1794. doi:10.1016/S0140-6736(00)03230-X.

122. Carlsson J, Miketic S, Windeler J, et al Randomized trial of rate-control versus rhythm-control in persistent atrial fibrillation: The strategies of treatment of atrial fibrillation (STAF) study. *J Am Coll Cardiol.* 2003; 41:1690–1696. doi:10.1016/S0735-1097(03)00332-2.

123. Rienstra M, Vermond RA, Crijns HJ, et al Asymptomatic persistent atrial fibrillation and outcome: Results of the RACE study. *Heart Rhythm.* 2014; 11:939-945. doi: 10.1016/j.hrthm.2014.03.016.

124. Opolski G, Torbicki A, Kosior DA, et al Rate control vs rhythm control in patients with nonvalvular persistent atrial fibrillation: The results of the polish how to treat chronic atrial fibrillation (HOT CAFE) Study. *Chest.* 2004; 126:476486. doi:10.1378/chest.126.2.476.

125. Planning and Steering Committees of the AFFIRM Study forthe NHLBI AFFIRM Investigators Atrial fibrillation follow-up investigation of rhythm management—the AFFIRM study design. *Am J Cardiol.* 1997; 79:1198–1202.13. doi:10.1016/S0002-9149(97)00082-9.

126. Vora A, Karnad D, Goyal V, et al Control of heart rate versus rhythm in rheumatic atrial fibrillation: A randomized study. *J Cardiovasc Pharmacol Ther*. 2004; 9:65-73. doi: 10.1177/107424840400900201.

127. Kotecha D, Calvert M, Deeks JJ, et al A review of rate control in atrial fibrillation, and the rationale and protocol for the RATE-AF trial. *BMJ Open.* 2017; 7:e015099. doi: 10.1136/bmjopen-2016-015099.

128. Wyse DG, Waldo AL, DiMarco JP, et al A comparison of rate control and rhythm control in patients with atrial fibrillation. *N Engl J Med.* 2002; 347:1825–1833. doi: 10.1056/NEJMoa021328.

129. Anter E, Jessup M, Callans DJ Atrial fibrillation and heart failure: treatment considerations for a dual epidemic. *Circulation.* 2009; 119:2516–2525. doi: 10.1161/CIRCULATIONAHA.108.821306.

130. Roy D, Talajic M, Nattel S, et al Rhythm control versus rate control for atrial fibrillation and heart failure. *N Engl J Med.* 2008; 358:2667–2677. doi: 10.1056/NEJMoa0708789.

131. Hagens VE, Crijns HJ, Van Veldhuisen DJ, et al Rate control versus rhythm control for patients with persistent atrial fibrillation with mild to moderate heart failure: Results from the rate control versus electrical cardioversion (RACE) study. *Am Heart J.* 2005; 149:1106–1111. doi:10.1016/j.ahj.2004. 11.030.

132. Al-Khatib SM, Shaw LK, Lee KL, et al Is rhythm control superior to rate control in patients with atrial fibrillation and congestive heart failure? *Am J Cardiol.* 2004; 94:797–800. doi:10.1016/j.amjcard. 2004.06.009.

133. Pedersen OD, Bagger H, Keller N, et al Efficacy of dofetilide in the treatment of atrial fibrillation-flutter in patients with reduced left ventricular function: a Danish investigations of arrhythmia and mortality on dofetilide (diamond) substudy. *Circulation.* 2001; 104:292–296. doi: 10.1161/01.CIR.104.3.292.

134. Marrouche NF, Brachmann J, Andresen D, et al Catheter ablation for atrial fibrillation with hear tfailure. *N Engl J Med.* 2018; 378:417–427. doi: 10.1056/NEJMoa1707855.

135. Asad ZUA, Yousif A, Khan MS, et al Catheter ablation versus medical therapy for atrial fibrillation: A systematic review and meta-analysis of randomized controlled trials. *Circ Arrhythm Electrophysiol.* 2019; 12:e007414.

136. Providencia R, Adragão P Science deserves justice: The results of the CABANA trial are positive and support catheter ablation of atrial fibrillation for reducing mortality and hospitalizations. *Rev Port Cardiol.* 2019; 38:245–250. doi: 10.1016/j.repc .2019.05.002.

137. Dagres N, Varounis C, Gaspar T, et al Catheter ablation for atrial fibrillation in patients with left ventricular systolic dysfunction. A systematic review and meta-analysis. *J Card Fail.* 2011; 17:964–970. doi: 10.1016/j.cardfail.2011.07.009.

138. Prabhu S, Taylor AJ, Costello BT, et al Catheter ablation versus medical rate control in atrial fibrillation and systolic dysfunction: The CAMERA-MRI Study. *J Am Coll Cardiol.* 2017; 70:1949–1961. doi: 10.1016/j.jacc.2017.08.041.

139. Willems S, Meyer C, de Bono J, et al Cabins, castles, and constant hearts: rhythm control therapy in patients with atrial fibrillation. *Eur Heart J.* 2019; 40:3793-3799. doi: 10.1093/eurheartj/ehz782.

140. Kuck KH, Merkely B, Zahn R, et al Catheter ablation versus best medical therapy in patients with persistent atrial fibrillation and congestive heart failure: The randomized AMICA Trial. *Circ Arrhythm Electrophysiol.* 2019; 12:e007731.

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