Beta-blocker treatment in heart failure patients with atrial fibrillation: challenges and perspectives

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ABSTRACT Heart failure (HF) and atrial fibrillation (AF) are common conditions that share similar clinical phenotype and frequently coexist. The classification of HF in patients with preserved ejection fraction (> 50%, HFP EF), mid-range reduced EF (40%–49%, HFr EF) and reduced EF (< 40%, HFr EF) are crucial for optimizing the therapeutic approach, as each subgroup responds differently. Beta-blocker constitutes an important component of our pharmacological regimen for chronic HF. Beta-blocker administration is recommended in patients with HF with reduced ejection fraction in stable sinus rhythm, due to improvement of symptoms, the better long-term outcome and survival. The beneficial role of beta-blocker use in patients with preserved EF still remains unclear, as no treatment showed a positive impact, regarding morbidity or mortality reduction. The presence of AF in HF patients increases as the disease severity evolves and is associated with a higher rate of cardiovascular morbidity and mortality. But more question is the use of beta-blocker in HF patients irrespective of EF and concomitant AF. There are many conflicting data and publications, regarding the beta blocker benefit in this population. Generally, it is supported an attenuation of beta-blockers beneficial effect in HF patients with AF. A design of more randomised trials/studies with HF patients and concomitant AF may improve our clinical approach of beta-blockers use and identify the patients with HF, who mostly profit from an invasive approach.

Atrial fibrillation (AF) and heart failure (HF) with or without systolic dysfunction constitute common cardiac conditions, that frequently coexist and overlap.¹ These entities share multiple risk factors such as age, hypertension, diabetes, obesity, as well as cardiac substrates as valvular, ischemic, and non ischemic structural heart disease.¹,² Their coexistence can be partially explained by the presence of the common risk factors.³

The definition of heart failure revised in 2016, based on the measurement of left ventricular ejection fraction (EF).⁴ Especially, HF can be divided in three groups: heart failure with preserved EF (> 50%, HFP EF), mid-range reduced EF (40%–49%, HFr EF) and reduced EF (< 40%, HFr EF).⁴ Interestingly, up to 50% of chronic HF patients present normal or only mildly impaired left ventricular EF.⁴ The prevalence of AF in HF patients increases as the disease severity evolves.⁶ Specifically, in patients with New York Heart Association (NYHA) I–II is typically about 5%, NYHA III approximately 26% and NYHA IV is presented up to 50%.⁶ According to the data from randomized clinical trials and registries, the presence of AF in HFP EF patients ranges between 15% and 41%.⁷ Patients with HFr EF are more likely to demonstrate prevalent AF or AF at any time up to twice, compared with those with HFr EF.⁷ Data from the nationwide Swedish heart failure registry reported the prevalence of AF among LVEF ranges, specifically 53% in HFr EF, 60% HFr EF, and 65% in HFP EF.⁸ The presence of AF in HFr EF patients was 27% in an analysis of ESC-HF long term registry.⁹ Notably, AF occurs in 24%–44% of patients in the setting of acute HF and in one third of those with chronic HF.¹⁰,¹¹ Atrial fibrillation is also found in more than half (57%) of patients with new onset of HF.¹¹ Furthermore, HF is present in 33%, 44% and 56% of ambulatory patients with paroxysmal, persistent and permanent AF, respect-
ively and in more than one third (37%) of those with new onset AF.\textsuperscript{[12, 13]}

**PHENOTYPIC RANGE OF HEART FAILURE PATIENTS**

The above HF classification is crucial, as each HF group demonstrates different underlying aetiologies, demographics, clinical phenotype, co-morbidities, response to therapies, all-cause and cardiovascular mortality, as well as HF hospitalizations. Patients with HFpEF tend to be older, more often women, with higher AF rates compared with HFrEF patients.\textsuperscript{[14, 15]} On the contrary, HFpEF patients present less commonly a history of previous myocardial infarction.\textsuperscript{[16]} Notably, patients with HFmrEF demonstrate similar characteristics such as age, ischemic heart disease (IHD) to patients with HFrEF and HFpEF.\textsuperscript{[17]} The baseline co-morbidities such as hypertension, diabetes, and AF are more frequent presented in patients with HFmrEF than in those with HFrEF but less frequently in patients with HFpEF.\textsuperscript{[17]} In conclusion, HFmrEF category seem to display a position between the two previous established categories.\textsuperscript{[17]}

It should not be underestimated that the prognosis of HFpEF patients remains poor and is almost similar to that of HFrEF patients.\textsuperscript{[18]} Cardiovascular mortality seems to be lower in HFmrEF than in both HFrEF and HFpEF patients.\textsuperscript{[19]} The higher prevalence of IHD and reduced LVEF in HFrEF and the higher incidence of hypertension, diabetes, and AF in HFpEF patients may also explain partially the higher cardiovascular mortality in these two categories in comparison to HFmrEF.\textsuperscript{[20]}

**IMPACT OF ATRIAL FIBRILLATION IN HEART FAILURE PATIENTS**

AF has an adverse impact on cardiac function deterioration via multiple pathways, such as loss of atrioventricular synchrony, reduced filling time, decreased ejection time and stroke volume in the context of tachycardia and a greater prevalence of right and left biventricular performance impairment.\textsuperscript{[21]} Nevertheless, a condition known as tachycardia-induced cardiomyopathy is evident in 25% to 50% of patients with left ventricular dysfunction and AF.\textsuperscript{[22, 23]} On the other hand, AF remains the most common cause of tachycardia-induced cardiomyopathy.\textsuperscript{[24, 25]} The restoration of sinus rhythm (SR) or appropriate rate control, achieving the elimination of these rapid heart rates, reverses the hemodynamic and clinical manifestations associated with this syndrome.\textsuperscript{[26, 27]} Similarly, HF can increase the risk of AF development in several ways, including elevation of cardiac filling pressures, electrical remodelling, structural alterations with interstitial fibrosis, dysregulation of intracellular calcium, autonomic and neuroendocrine deregulation.\textsuperscript{[28]} Both clinical entities trigger increased mechanical cardiac stress, electrical remodeling and inflammation, leading to cardiac hypertrophy/fibrosis and shortening of the atrial effective refractory period, sequences that support the hypothesis that AF and HF constitute a vicious cycle.\textsuperscript{[28-30]}

Generally, the presence of AF is associated with a higher rate of cardiovascular morbidity and mortality in symptomatic patients with HFrEF or HFpEF, attributable to co-existing AF.\textsuperscript{[31]} The stroke risk seems almost equal in both groups.\textsuperscript{[31]} New onset of AF in HF patients increased significantly the cardiovascular, hospitalisation, fatal and non-fatal stroke, as reported in Charm-Study.\textsuperscript{[32]} Similar results revealed the Comet- and Valiant-studies regarding the relationship of AF adverse events in HF patients.\textsuperscript{[33, 34]} Verma, et al supported, that the coexistence of AF and HF were associated with increased rate of stroke, hospitalization and all-cause mortality.\textsuperscript{[35]} Previous studies demonstrated that the incidence of non-cardiac related hospitalizations in HFpEF was much higher, while the incidence of HF-hospitalizations in HFpEF was lower compared to HFrEF.\textsuperscript{[36, 37]} Furthermore, the group of patients with HFpEF and the presence of AF in the TOPCAT trial was related with a significant increase in the risk for cardiovascular mortality, HF hospitalization, and all-cause mortality compared with patients without AF.\textsuperscript{[38]} Notably, in this study new onset AF in HFpEF patients after enrollment was related with an especially high morbidity and mortality risk (i.e., a 2.2-fold increase in risk in those with either no history of AF or history of AF who were not in AF.\textsuperscript{[39, 40]} Both RELAX- and Lam Study showed that HFpEF patients with AF had poorer exercise capacity, higher NT-proBNP levels, and more dilated left atria compared with those in SR.\textsuperscript{[41, 42]}
All the above findings suggested a more advanced HF stage in patients with coexistence of AF and HF, while HF patients with new onset AF demonstrate worse prognosis regarding cardiovascular outcomes and events.[43]

**BETA-BLOCKER TREATMENT IN PATIENTS WITH HFREF AND SINUS RHYTHM**

The treatment of patients with AF and HF is crucial aiming at the reduction of cardiovascular events and mortality. Current guidelines recommend beta-blockers’ administration in patients with HF irrespective of rhythm disorders. The beta-blockers constitute the cornerstone therapy of patients with HFrEF and stable SR (Class I, Level Evidence: A).[44] The MOCHA investigators reported that beta-blockers (BBs) resulted in a dose-dependent improvement of left ventricular function and decrease in mortality and hospitalization rates in HF patients with reduced EF (HFrEF).[45] Moreover, in CAPRICORN study, beta-blocker therapy has been shown to prevent new onset or recurrent AF in HF patients with impaired left ventricular function after myocardial infarction (5.4% in placebo vs. 2.3% in beta-blocker group), after a mean of 1.3 years, and also in a relatively low-risk mostly hypertensive population.[46]

Overall, a systematic review of Imad Abi Nasr et al including different types of beta-blocker (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] showed a clear reduction in 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 associated with no significant reduction of new onset AF in Nebivolol group, fact that may partly be attributed to study design, included elderly patients with higher prevalence of AF at randomisation, and higher proportion (one-third) of HFpEF patients.[53] Clinical trials have shown, that the administration of carvedilol, bisoprolol and metoprolol improved survival and reduced cardiac hospitalizations in patients with HFREF, while nebivolol presented a reduction of cardiovascular hospital admissions but no effect on mortality.[53,54] Also, the above studies revealed a significant reduction of sudden cardiac–heart failure death and HF hospitalization.[53,54] Furthermore, in the Copernicus study patients with more advanced HF with LVEF under 25% and NYHA IV, demonstrated a benefit also from Carvedilol treatment with 35% mortality risk reduction, despite the terminal stage of HF.[55] The benefits of beta-blocker administration and the improvement of survival seem to be dose-related (higher dose better outcomes compared to medium/low dose).[56] Stefania Paolillo supported the theory, that the positive beta-blocker effects were also dependent on heart rate reduction, as demonstrated in the Shift study.[57,58]

Chatterjee, et al. and Paolillo, et al. observed no differences between selective and non-selective -blockers on outcome, although carvedilol demonstrated a tendency on mortality reduction compared with the other beta-blockers.[58,59] Another meta-analysis comparing the effects of carvedilol to metoprolol on LVEF in HF patients revealed that carvedilol lead to greater improvement on LVEF than metoprolol at similar doses.[60] Beta-blockers in patients with HFREF and advanced CKD were independently related with reduced mortality similar as in HFrEF with moderate CKD.[61] However, the above beneficial role of beta-blockers was not presented in patients with HFpEF or HFmrEF with severe CKD and in patients in HFrEF and atrial fibrillation.[61]

In conclusion, there is no doubt of the beneficial impact of beta-blocker treatment in patients with HFREF and SR.

**BETA-BLOCKER TREATMENT IN PATIENTS WITH HFREF AND ATRIAL FIBRILLATION**

The majority of HF patients included in the above clinical trials with BBs were in SR, with only a minor portion of patients with AF, ranged between 11% to 35%.[62]

It remains unclear, if BBs could prevent HF progress and cardiovascular events in patients with AF. There are several hypothesis supported, that the beta-blocker treatment is less effective in HF pa-
patients with AF than in those with SR. In SR BBs act to the sinus node, but in AF these agents target the atrioventricular node. Also, the heart rate drop is different during rest and exercise between patients in AF and SR. In AF patients with loss of atrial contraction, a higher heart frequency may be needed to achieve an adequate cardiac output. Furthermore, a low heart rate under beta-blocker, especially in elderly patients with AF, may unmask an underlying conduction system disorder. AF in patients with HF may constitute a marker of a poorer clinical condition and a sign of a more advanced disease, leading to a worse outcome, less modifiable by beta-blocker treatment. The controversial effect of beta-blockers, regarding survival, mentioned also in the AF treatment guidelines of 2016, where beta-blockers are recommended as a rate control approach in order to reduce the AF-related symptoms but not to improve prognosis. The effect of beta-blockers on outcome in AF patients with HFrEF is reduced compared to those with SR. A subgroup analysis of the four randomized placebo-controlled studies (USCS, MERIT-HF, CIBIS II, Seniors) focused on patients with AF and reduced EF, revealed that beta-blockers did not achieve a positive effect on HF hospitalizations (odds ratio [OR] = 1.11; 95% CI: 0.85–1.47; P = 0.44), or mortality (OR = 0.86; 95% CI: 0.66–1.13; P = 0.28) in comparison to patients with SR. Similarly, Cullington, et al demonstrated that a slower resting ventricular rate is associated with better survival in HFrEF patients in SR but not in AF patients.

Kotecha, et al analyzed data from 10 randomized controlled trials of 18,254 symptomatic patients with HFrEF treated with beta-blockers versus placebo, 26.8% of whom were presented with AF. The BBs treated group was associated with significantly lower mortality in patients with SR (HR = 0.73; 95% confidence interval [CI]: 0.67–0.80; P < 0.001) but not in AF (HR = 0.97; 95%CI 0.83–1.14; P = 0.73). The investigators concluded that beta-blockers “should not be used preferentially over other rate-control medications and not regarded as standard therapy to improve prognosis in patients with concomitant HF and AF. Although, there was a trend of beneficial effect in beta-blockers treatment when the composite endpoint of death or hospitalisation was analysed (HR = 0.89, P = 0.06). On the contrary, beta-blockers were associated with significant reduction on all cause mortality (28%) but not hospitalisation or cardiovascular mortality in HFrEF patients and coexisting AF, according to AF-CHF Study propensity-matched sub-analyses. The positive impact of beta-blockers was consistent regardless of the AF type or duration (paroxysmal vs. persistent, high vs slow). Whereas, the high rate of hospitalizations for AF overall (i.e., 20%) might reflect the AF-CHF trial design, based on an aggressive approach to maintain SR. However, the AF-CHF subgroup study displays also limitations as it was not a randomized comparison, and the potential for confounding exists. Same results reported also in the Swedish Heart Failure Registry and in a nationwide cohort study with 29% and 25% reduction of mortality, respectively.

The above results are different in comparison with the respective by Kotecha and Rienstra. The conflicting results may be partly explained by differences in methodology, patient demographics, HF stage and type, medications (beta-blocker type or target dose), heart rate target or follow-up duration. Overall, given the heterogenous nature of different studies, no firm conclusions can be drawn regarding b-blockade impact in AF patients with HFrEF.

Especially, Kotecha publication was criticized as only a single electrocardiogram was used to classify baseline patient rhythm. Thus, many of the patients with SR potentially had paroxysmal AF. The low reported prevalence of AF (17%) in a population with HFrEF was consistent with a potential misclassification error, as this percentage was much lower than the prevalence of AF (41%) in HF patients from the Swedish registry. In addition, Kotecha’s study included patients with more advanced HF stage, receiving more diuretics and aldosterone antagonists, with a prevalence of NYHA functional class III or IV symptoms about 70% vs. 30% of respective patients in the AF-CHF study. While in the Swedish HF-registry, about 50% patients presented with NYHA class I/II HF stage.

Furthermore, only 58% of patients in Kotecha’s study received oral anticoagulants in comparison to AF-CHF study, where up to 82% were under oral
Another difference was the higher proportion of patients on digoxin therapy in the study of Kotecha (83%) in comparison to AF-CHF and Swedish HF-study 65% and 36%, respectively. In Kotecha’s study, a more aggressive beta-blocker target dose was observed, as 72.1% were on maximal dose of beta-blockers vs. 28% of patients in Swedish HF-study. Another point is that Kotecha’s study enrolled stable or patients with permanent AF in comparison to Peter Brønnum Nielsen Nationwide Cohort Study’s in Denmark, that included patients with a first-time hospital AF diagnosis, showing a mortality reduction with beta-blocker therapy in AF patients with concomitant HF. It has been previously mentioned that new onset AF in HF patients is associated with higher mortality rates, explaining partially the positive effect of beta-blocker treatment in survival in new onset AF patients in contrast with permanent AF patients. It is widely known that the combination of beta-blocker and digoxin has controversial effects based on the published data. Digoxin is administrated mainly in elderly and frailer AF patients with more neutral longterm outcome as in SCAF study (The Stockholm Cohort of Atrial Fibrillation SCAF study). The Registry of Information beta-blockers, digoxin and atrial fibrillation and Knowledge about Swedish Heart Intensive Care Admissions (RIKS-HIA) showed a higher overall mortality in digoxin-treated patients with AF without coexisting HF, but not a great difference in patients with HF. A sub-analysis of AFFIRM trial reported that AF patients under digoxin had higher all-cause mortality after adjustment for comorbidities and propensity scores, regardless of the presence or absence of underlying HF. Whereas, another post-hoc analysis from the AFFIRM study demonstrated that digoxin can provide benefits in HFrEF patients with AF. Furthermore, beta-blocker alone or in combination with digoxin irrespective of AF burden (permanent or non) or HF phenotype (preserved or reduced LVEF) associated with neutral and no worse survival compared with a rate control strategy. Similarly, in a recent meta-analysis of observational and controlled data digoxin was associated with a neutral effect on survival and a lower rate of hospitalisation. It still remains not well defined, whether digoxin treatment in combin-
an LVEF improvement without benefit on prognosis. Interestingly, no benefit was seen in patients with preserved LVEF > 50% in SR or AF.\textsuperscript{[90]}

High heart rate predicts poor outcomes in patients with HFrEF and SR. Especially, each standard deviation (12.4 beats/min) increase in heart rate was associated with an 13% increase in risk of cardiovascular death or HF hospitalization ($P = 0.002$), fact that does not apply in AF.\textsuperscript{[91]} Indeed, in I-PRESERVE study, no correlation was observed in HFrEF patients with AF between heart rate and outcomes. Also, beta-blocker administration did not change the heart rate-risk relationship in patients with HFrEF independent of rhythm.\textsuperscript{[91]} Another study showed that, in patients with HFrEF and SR with a heart rate $\geq 70$ beats/min, high dose of beta-blockers was associated with a significantly lower risk of death.\textsuperscript{[92]}

Some observational studies demonstrated, that beta-blocker treatment decreased the all-cause mortality rate in the HFrEF patients with AF or SR,\textsuperscript{[93, 94]} the fact that was not observed in the sub-analysis of SENIORS trial and J DHF trial.\textsuperscript{[95, 96]} A possible explanation of beneficial beta-blocker effect in HFrEF population, might be mainly due to the antihypertensive effect, the arrhythmic-risk reduction, the myocardial perfusion and metabolism improvement, as well as ventricular remodeling, and any protection against acute coronary events.\textsuperscript{[97]} Despite the possible all cause mortality reduction, the lack of hospitalizations’ reduction is probably due to the fact that the patients with HFrEF tended to be elderly and with multiple non-cardiac or/and cardiac comorbidities.\textsuperscript{[97]} Another meta-analysis demonstrated the benefit of the use of beta-blockers for all-cause mortality, but not for HF by beta-blocker use in patients with HFrEF and SR or AF.\textsuperscript{[98]} Although evidence for the benefits of beta-blocker therapy in HFrEF patients is lacking, these agents are used usually for comorbidities’ management such as hypertension, coronary artery disease and AF.

A meta-regression analysis of randomized controlled trials underlined the beneficial role of beta-blockers in HFrEF with coexistence of CAD or AF in a small number of patients.\textsuperscript{[99]} The above subgroup of patients demonstrated lower BNP levels and an increase of exercise capacity on beta-blocker therapy compared to HFrEF with neither CAD or AF treated with betablocker. The use of beta-blockers in HFrEF in patients with AF or CAD should be well balanced between potential benefits and adverse events.\textsuperscript{[99]} On the other hand, beta-blockers provide a reduction of left ventricular oxygen consumption and myocardial perfusion improvement via the negative chronotropic action, but on the other side the unmasking of any conduction disorders or chronotropic intorelance may negatively influence this subgroup of patients.\textsuperscript{[99]} The definition of this narrow therapeutic range/window of beta-blocker effect remains challenging.

The beta-blocker therapy in HFrEF patients with AF according to the retrospective clinical study of Yang, resulted in a significantly lower mortality and a slight increase of the rehospitalization risk due to worsening of HF, post exclusion of patients with severe comorbidities compared with those without beta-blocker treatment.\textsuperscript{[100]} The above analysis offered a better understanding of beta-blocker effect on HFrEF patients with AF but without other comorbidites.\textsuperscript{[100]} Another subgroup analysis of patients with HFrEF and AF (30% of the whole population) in a Korean registry showed that the beta-blocker treatment has eventually a beneficial role with regard to efficacy.\textsuperscript{[101]}

It should be highlighted that the majority of meta-analysis or studies enrolled patients with stable HFrEF. Another interesting point was the effect of beta-blockers in acute setting of HFrEF and AF.\textsuperscript{[102]} Min-Soo Ahn reported a reduced rehospitalization rate in 639 patients with acute HFrEF and AF during the 6-month and 1-year follow up.\textsuperscript{[102]} Furthermore, ACE-inhibitors or/angiotensin receptor blockers (ARBs), statins and beta-blockers alone or in combination can play a protective role in development of HFrEF among patients with AF.\textsuperscript{[103]} Beneficial effects of betablocker may be present in selected subclasses of patients with HFrEF and AF. Further studies are required to identify those groups.

**RATE CONTROL IN HEART FAILURE PATIENTS WITH SINUS RHYTHM OR ATRIAL FIBRILLATION**

Resting heart rate is an important predictor of outcome in patients with stable HFrEF and SR.\textsuperscript{[104]} Generally, a lower heart rate is associated with bet-
ter outcomes in this patient population. The magnitude of heart rate reduction with beta-blocker usage, but not beta-blocker dose in SR patients was associated with a survival benefit. But the above positive impact of beta-blocker use remains unclear and controversial in patients with HFrEF and SR. Using Propensity score-matched patients and data from Optimise study, a heart rate < 70 beats/min at discharge of patients with HFrEF, showed 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, compared with those with a heart rate above 70 beats/min. Another interesting point was that a discharge prescription of beta-blockers or other heart rate-lowering drugs in a subgroup of patients presented with coronary artery disease, prior myocardial infarction and coronary revascularization might be beneficial.

Patients with HFrEF For HFrEF and AF consist a more complex field of beta-blocker impact. Van Gelder et al. demonstrated that in AF patients, with or without HF, the lower heart rate is not associated with a better outcome. On the contrary, beta-blockers may both control the ventricular response of AF and improve survival in patients with HF and concomitant AF based on a small retrospective analysis of the US Carvedilol Heart Failure Trial, revealing a trend toward a reduction in the combined end point of death or CHF hospitalization in carvedilol treated patients compared with placebo (RR = 0.35; 95% CI: 0.12–1.02; P = 0.055).

An intensive heart rate control was proven difficult in patients with chronic AF and HFrEF due to patient intolerance of increasing doses of beta-blockade, and it was not associated with improved outcomes. Similarly to the study by van Gelder and colleagues, an aggressive rate control in patients with chronic AF and HF did not add any benefit. The RACE II-Study evaluated the lenient versus strict rate Control in permanent AF-patients, and showed that lenient rate control (defined as resting HR control < 110 beats/min) led to similar outcomes, regarding cumulative incidence of death from cardiovascular causes, hospitalization for HF, thromboembolic events, bleeding and lifethreatening arrhythmia; as strict rate control (defined as resting HR control < 80 beats/minute). It should be emphasized that the majority of patients enrolled in RACE II study demonstrated a mean ejection fraction (EF) of 52%, while patients with an EF < 40% presented only 15% of the total population.

It is obvious that the study revealed no benefit of strict rate control in patients with preserved ejection and AF.

In a second prospective randomised study of ibopamine’s effect on Mortality and efficacy study, HFrEF patients and AF with mean ventricular rate > 80 beats/min presented better outcomes than those with < 72 beats/min. On the same line, Cullington et al. showed a worse survival in HF patients with AF and ventricular rate < 73/min. Especially, AF or SR patients had a similar prognosis, despite substantially higher ventricular rates in AF patient.

A study of Miller et al. found no relationship between predischarge heart rate or BBs dose/titrating dose in patients with recent hospitalisation for HF with reduced or preserved LVEF and AF, suggesting a more lenient rate control goal with no obvious effect of beta-blocker administration.

The optimal resting ventricular rate in patients with AF and HF is uncertain but may be ranged between 60–100 beats/min. AF ESC guidelines of 2016 and 2020 recommend a resting ventricular rate of up to 110 beats/min as the target for rate control therapy independent of HF. However, the Task Force and the guidelines of ESC-HF support that a lower rate for patients with HF may be preferable (60–100 beats/min), specifically 60–100 beats/min at rest and < 100 beats/min at exercise. The updated 2011 American College of Cardiology Foundation/American Heart Association/Heart Rhythm Society (HRS) guidelines for management of AF recommend a strict HR control for patients with both conditions, with a HR goal of 60 to 80 beats/min at rest and 90 to 115 beats/min during moderate exercise, even though there are few outcomes/data to support that recommendation. The 2009 ACC/AHA guidelines for management of HF advocate a somewhat more lenient approach, with the HR goal of < 80 to 90 beats/min at rest and < 110 to 130 beats/min during moderate exercise. The above recommendations lead to conflicting evidence regarding the optimal heart rate target in patients with AF and HF.
The optimal heart rate of beta-blocker driven therapy should be for each HF patient with AF individualised, taking into account the heart size, cardiac systolic and diastolic function and the concomitant valve function and any underlying comorbidities.\textsuperscript{120}

**RHYTM CONTROL**

A plethora of studies (PIAF, STAF, RACE, HOT CAFE and AFFIRM) demonstrated no superiority of rhythm control against rate control approach, irrespective of EF and mostly in underpowered HF population.\textsuperscript{[121–125]} Besides, a meta-analysis documented a 17\% increase in the risk of hospitalisation in the rhythm control group, but it must be highlighted the significant heterogeneity of the studies.\textsuperscript{[121–127]}

AFFIRM study demonstrated no survival advantage in rhythm-control approach of AF patients over the rate-control strategy, however the patients with HF presented only 23.1\%, and about 9\% had an NYHA functional class of II or greater.\textsuperscript{[128, 129]} LV function was normal in 76\% of AFFIRM patients.\textsuperscript{[128, 129]} In the subgroup analysis, a trend was found for positive impact of rhythm control strategy in patients suffering from HF, but statistically not significant. It must be highlighted, that SR was maintained in only 63\% of patients in the rhythm control arm of AFFIRM in a period of 5 years, that may be the reason for the benefit attenuation of this approach.\textsuperscript{[128, 129]}

The AF-CHF study was the first prospective randomized study to assess the effect of rate versus rhythm control in HF patients.\textsuperscript{[129, 130]} A total of 1376 patients, with AF and HFrEF (mean LVEF, 27\%) were enrolled and randomized to rhythm control (typically with amiodarone) versus rate control in a mean follow-up of 3 years.\textsuperscript{[130]} The rhythm control group did not improve mortality, heart failure hospitalization, or stroke compared with rate control.\textsuperscript{[130]} Another recent subanalysis of the RACE study in patients with AF and mild to moderate HF supported also that rate control was not inferior to rhythm control in the prevention of a combined end point of morbidity and mortality during 2.3 years of follow-up.\textsuperscript{[133]} Another large study of 1,009 patients with moderate to severe left ventricular dysfunction and AF similarly demonstrated no benefit on overall mortality of rhythm compared with rate control.\textsuperscript{[132]}

However, a subgroup analysis of Diamond study showed that the SR restoration was associated with a significant higher survival rate in patients with AF or atrial flutter and EF < 35\%.\textsuperscript{[133]} These findings, support the theory, that the rhythm control and SR restoration could be more beneficial in patients with more advanced NYHA stage and more significant LV function impairment (LVEF < 35\%) in comparison with mild to moderate HF patients.\textsuperscript{[133]}

The randomized Castle AF trial in patients with AF and significant HFrEF demonstrated a better outcome in the risk of all cause death or hospitalization and LVEF improvement of ablation compared with medical therapy (rhythm vs rate control).\textsuperscript{[134]} Also, in a prespecified subgroup analysis of CABANA trial exhibited a non significant trend on primary endpoint reduction among AF patients with a history of HF.\textsuperscript{[135, 136]} It is crucial to identify HF patients with factors such as non ischemic aetiology cardiomyopathy, LVEF > 35\% and limited extension of atrial fibrosis of 10\% or less, who may be the mainly responders of AF ablation.\textsuperscript{[134–138]} Cabana and Castle AF emphasized that patients with HFrEF may benefit from ablation, leading to a AF burden reduction, improvement of LVEF and lower toxicity effect in comparison to medical therapy.\textsuperscript{[138, 139]}

Recently, the AMICA trial studied also patients with more advanced HF compared to Castle AF study and persistent AF who underwent catheter ablation or remained only in optimal medical therapy.\textsuperscript{[140]} The invasive approach showed a similar improvement of EF in one year follow up as in the medical group and no significant benefit of ablation.\textsuperscript{[140]} AF-Ablation is not imperative in all HFrEF patients, taking into consideration the result of AMICA trial and also the neutral effect of ablation by subgroup analyses of the primary end point in CASTLE-AF in patients with NYHA III HF symptoms as well as in patients with an LVEF< 25\%, who did not show any benefit.\textsuperscript{[134–136, 140]}

**CONCLUSION**

The administration of beta-blockers in HF patients with AF is not well defined. There are many questions and controversial data regarding their beneficial effect in this population. Are the type or dose of beta-blocker crucial for a better patients’ outcome? Which is the optimal heart rate target in
this specific population? Are the advantages of beta-blocker use dependent on EF (reduced vs preserved)? Is it any association of beta-blocker and HF type and severity (for example in extreme low LVEF or reduced right ventricular function, and concomitant valve failure)? Should be used as first line rate control in HF-AF patients? Are specific subgroups of HF-AF patients and comorbidities, who mostly may benefit? The combined treatment of beta-blocker with digoxin or amiodarone can affect the patient prognosis? Is there a favourable outcome of AF ablation in combination or not with beta-blocker vs medical treatment alone?

We need more randomised trials/studies to improve our clinical approach of beta-blockers’ use in heart failure patients accompanied with AF. This is the only way to achieve an evidence based beta-blocker administration, achieving an individual targeted therapy with better outcomes and lower adverse/side effects.

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] Ozierniski K, Kaplon-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.

[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.

[6] Batul SA, Gopinathannair R. Atrial fibrillation in heart failure: a therapeutic challenge of our times. *Korean Circ J* 2017; 47: 644–662.

[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.

[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.

[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.

[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. Published 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.

[13] Chiang CE, Naditch-Brûlé L, Murin J, *et al.* 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.

[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.

[15] Goyal P, Almarzooq ZI, Horn EM, *et al.* Characteristics of hospitalizations for heart failure with preserved ejection fraction. Am J Med 2016; 129: e15–e26.

[16] Adamczak DM, Oduah MT, Kiebalo T, *et al.* Heart failure with preserved ejection fraction-a concise review. *Curr Cardiol Rep* 2020; 22: 82.

[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.

[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.

[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.

[21] Lee Park K, Anter E. Atrial fibrillation and heart failure: A review of the intersection of two cardiac epidermics. *J Atr Fibrillaton* 2013; 6: 751.

[22] Mohamed HA. Tachycardia-induced cardiomyopathy (Tachycardiomyopathy). *Libyan J Med* 2007; 2: 26–29.

[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.

[24] Nerheim P, Birger-Botkin S, Piracha L, *et al.* Heart fail-
ure and sudden death in patients with tachycardia-induced cardiomyopathy and recurrent tachycardia. *Circulation* 2004; 110: 247–252.

[25] Calò L, De Ruvo E, Sette A, et al. Tachycardia-induced cardiomyopathy: mechanisms of heart failure and clinical implications. *J CardiovascMed (Hagerstown)* 2007; 8: 138–143.

[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.

[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.

[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.

[29] Jalife K, Kaur K. Atrial remodeling, fibrosis and atrial Fibrillation. *Trends Cardiovasc Med* 2015; 25: 475–484.

[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.

[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.

[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.

[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.

[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.

[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.

[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.

[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.

[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.

[39] Shah AM. Atrial fibrillation in heart failure with preserved ejection fraction: The TOPCAT. *JACC Heart Fail* 2018; 6: 689–697.

[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.

[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.

[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.

[43] Cheng M, Lu X, Huang J, et al. The prognostic significance of 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.

[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.

[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 heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). *Lancet* 1999; 353: 2001–2007.

[49] Eichhorn EJ, Domanski MJ, Krause-Steinrauf H, et al. A trial of the beta-blocker bucindolol in patients with advanced chronic heart failure (BEST). *N Engl J Med* 2001; 344: 1659–1667.

[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.

[51] Waagstein F, Stromblad O, Andersson B, et al. Increased exercise ejection fraction and reversed remod-
eling 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.

[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.

[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.

[54] Klaholz M. Beta-blocker use for the stages of heart failure. Mayo Clin Proc 2009; 84: 718–729.

[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.

[56] Fiuza 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.

[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.

[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.

[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.

[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, KaplanCieslicka 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.

[64] Camm AJ, Savelieva I, Lip GY. Guideline Development Group for the NICE clinical guideline for the management of 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.

[66] Fauchier L, Laborie G, Clementy N, et al. Beta-blockers or Digoxin for Atrial Fibrillation and Heart Failure? Card Fail Rev 2016; 2: 35–39.

[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.

[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.

[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.

[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.

[73] Cadrn-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.

[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.

[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] Rosenberg M. Digoxin in atrial fibrillation: Report from the Stockholm Cohort study of Atrial Fibrillation (SCAF). Heart 2010; 96: 275–280.

[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.

[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 JL, Sánchez-Martalete 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.

[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.

[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.

[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.

[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. *J Am Coll Cardiol* 2007; 50: 768–777.

[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.

[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 (l-Preserve). *Eur J Heart Fail* 2014; 16: 778–787.

[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.

[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.

[94] El-Refaï 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.

[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.

[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.

[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.

[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.

[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.

[100] Yang Y, Guo S, Wakami K, *et al.* Decreased mortality with beta-blocker therapy in HFP EF 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.

[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.

[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.

[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.

[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.

[107] Déczi CA, Szentes V. The real role of β-blockers in daily cardiovascular therapy. *Am J Cardiovasc Drugs* 2017; 17: 361–373.

[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.

[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.

[110] Silve H, Hawkins LA, Jacobson AK. Heart rate control in patients with chronic atrial fibrillation and heart failure. *Congest Heart Fail* 2013; 19: 25–28.

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

http://www.jgc301.com; jgc@jgc301.com
to treat chronic atrial fibrillation (HOT CAFE) Study. Chest 2004; 126: 476–486.

[125] Planning and Steering Committees of the AFFIRM Study for the NHLBI AFFIRM Investigators. Atrial fibrillation follow-up investigation of rhythm management—the AFFIRM study design. Am J Cardiol 1997; 79: 1198–1202.13.

[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.

[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.

[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.

[129] Anter E, Jessup M, Callans DJ. Atrial fibrillation and heart failure: treatment considerations for a dual epidemic. Circulation 2009; 119: 2516–2525.

[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.

[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.

[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.

[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.

[134] Marrouche NF, Brachmann J, Andresen D, et al. Catheter ablation for atrial fibrillation with heart failure. N Engl J Med 2018; 378: 417–427.

[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.

[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.

[138] Prabhhu 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.

[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.

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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