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Review

Clarity and controversy around rate control in AF, the orphan child in AF therapeutics

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ABSTRACT

The vast majority of clinical arrhythmia-management research over the past couple of decades has focused on catheter-based therapeutic advances. There has been much less emphasis on rate-control strategies; however, the majority of patients with atrial fibrillation (AF) will require some form of rate-control management, making AF rate-control the single most widely used therapeutic component in AF-patients. While the general principles governing AF rate-control have remained largely unchanged, they are often underappreciated. In addition, a number of important controversies make optimal rate-control therapy sometimes difficult to choose. In this review, we aim to address a number of important areas of controversy in the application of AF rate-control, as well as to discuss aspects that are well understood but often underappreciated. Specific areas of focus include the following: (i) heart rate-targets in patients with preserved left-ventricular ejection fraction and concomitant AF; (ii) the clinical implications of differences in pharmacological mechanisms of action between beta-adrenoceptor and Ca^{2+}-channel blockers; (iii) controversies regarding the safety and use of digoxin in AF; (iv) the implications cardiac resynchronization therapy for rate-control in AF; and (v) controversies surrounding the benefits of rate-control with beta-blockers in patients with reduced left-ventricular ejection fraction and AF.

1. Introduction

Recent advances in atrial fibrillation (AF) rhythm-control, especially the development of catheter-based therapies, have resulted in reduced emphasis on the role of rate control in the management of AF. AF rate-control remains the most widely used arrhythmia-management strategy for patients with AF. Moreover, even when a rhythm-control strategy is adopted, rate-controlling drugs are generally needed to modulate the ventricular response-rate in the event of an AF-episode. Hence, the principles of AF rate-control are relevant across the spectrum of AF-management. It is paramount to keep in mind that the main objective of therapy in AF is the control of arrhythmia-related symptoms and prevention of adverse cardiovascular events, not the maintenance of sinus rhythm per se. This view is supported by multiple large randomized controlled trials comparing rate- vs rhythm-control strategies, both in patients with preserved and reduced left-ventricular (LV) ejection fraction (LVEF), which did not show a benefit of rhythm- over rate-control; a rate-control strategy has also been associated with fewer hospital visits and drug-related adverse events [1,2].

AF rate-control has remained largely unchanged for several decades, as the most dynamic aspects of the AF-management landscape have been dominated by catheter-based therapeutic advances. In this review, we highlight some often overlooked, but clinically important, areas of controversy in the application of AF rate-control. In addition, we discuss aspects that are well understood but often underappreciated. We start by (i) discussing the heart rate (HR)-targets for AF rate-control in patients with preserved left-ventricular ejection fraction, followed by (ii) a description of the differences in pharmacological mechanisms of action between beta-blockers and Ca^{2+}-channel blockers relevant to their practical use in AF rate-control, then move on to (iii) a review of the contemporary data on the use of digoxin in patients with AF, and (iv) a discussion of the interaction between AF and cardiac resynchronization therapy (along with pharmacological and catheter-based atrioventricular-node conduction-suppression), concluding with (v) remarks on the controversy surrounding the benefits of rate-control with beta-blockers in patients with reduced left-ventricular ejection fraction (LVEF) and AF.

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2. What is the optimal heart rate-target in patients with preserved left ventricular systolic function?

Defining the optimal HR-target for AF rate-control is an underappreciated clinical challenge. It is important to emphasize that the primary goal of rate control is to minimize AF-related symptoms and prevent tachycardia-induced cardiomyopathy, not per se to achieve a prespecified HR. Excessively-low HR-targets increase the risks of syncope and pacemaker-implantation, whereas overly-high targets risk AF-associated symptoms and tachycardia-mediated LV-function impairment [3]. Clinical characteristics like age, LV systolic function, presence of structural heart disease and other comorbidities modulate the "optimal" HR in AF. There is likely not a one-size-fits-all ideal HR-target. The desire to restore physiological HRs (i.e. <75–80 bpm) in AF is, to a large extent, based on an implicit extrapolation from the non-AF literature. It is well-documented that elevated resting HRs are associated with adverse cardiovascular outcomes in individuals in sinus rhythm [4]. However, elevated HRs may be a marker of underlying conditions more than a cause per se of poor outcome, as HR-lowering therapies (e.g. beta-blockers and ivabradine) have not been shown to improve outcomes in patients with sinus rhythm and preserved systolic function. For example, the recent Study Assessing the Morbidity-Mortality Benefits of the I_f Inhibitor Ivabradine in Patients with Coronary Artery Disease (SIGNIFY) trial found ivabradine not to improve cardiovascular outcomes and to be associated with an *increased* risk of AF [5].

The Rate Control Efficacy in Permanent Atrial Fibrillation: a Comparison between Lenient versus Strict Rate Control-II (RACE-II) trial sought to define the optimal HR-target for AF rate-control by randomizing 614 permanent-AF patients to a lenient (resting HR <110 bpm) vs a strict (resting HR <80 bpm) HR-target [6]. The lenient-control strategy was non-inferior vs the strict-control strategy and associated with fewer adverse events. More recently, a sub-analysis of the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) study of 2812 permanent-AF patients found a U-shaped relationship between HR and mortality. HRs <65 bpm and > 65 bpm were both associated with adverse events (hazard ratio 1.15 per 5-bpm decrease; 95% CI, 1.01–1.32 and hazard ratio 1.10 per 5-bpm increase; 95% CI, 1.05–1.15, respectively) [7]. The European Society of Cardiology and Canadian Cardiovascular Society AF guidelines recommend lenient HR-targets (<100–110 bpm) whereas the AHA/HRS guidelines suggest a rate-control target <80 bpm [8]. There is clearly uncertainty in this area.

In the RACE-II trial, most patients had preserved left-ventricular ejection fraction (LVEF) and the difference in mean HR between the two groups was small (76 ± 14 bpm vs 85 ± 14 bpm, $\Delta = 9$ bpm), with the lenient-control group almost achieving strict-control targets (85 ± 14 bpm vs <80 bpm); whether higher resting-rate "lenient control" (e.g. at 85–110 bpm) provides satisfactory long-term outcomes was not resolved in RACE-II. Importantly, the RACE-II and ORBIT-AF studies excluded patients with paroxysmal AF. Rate control is particularly challenging in paroxysmal AF. There appears to be adaptation in the ventricular response rate over time as AF is maintained [9], which may account for the resistance to rate-control of recent-onset AF. For example, digoxin is well-documented to be effective in rate-control of persistent AF, but does not significantly reduce ventricular response of acute paroxysms [10]. Adequate rate-control during AF paroxysms may increase the susceptibility to post-conversion pauses and symptomatic sinus bradycardia. In patients with paroxysmal AF and difficult rate-control, a rhythm-control approach (antiarrhythmic drug- and/or catheter-based) may be preferable. A subset of AF patients (e.g. those with severe diastolic dysfunction, ischemic heart disease, mitral stenosis, tachycardia-induced cardiomyopathy) may require more stringent, clinically-driven rate-control targets, or may even fail rate-control and require rhythm-control, whereas others may fare well with a more lenient target. Beyond guideline recommendations, ambulatory Holter HR monitoring should be considered for AF rate-control assessment in patients with deteriorating functional capacity or symptoms attributable to tachy- or bradycardia. The HR-targets for AF rate-control during exercise are even more uncertain than during sinus rhythm and should be individualized to the patients' activity levels.

3. Beta-adrenoceptor vs. Ca^{2+}-channel blocker pharmacology

In patients with preserved LVEF, beta-blockers and non-dihydropyridine Ca^{2+}-channel blockers (diltiazem and verapamil) are first-line agents per American Heart Association/American College of Cardiology and Canadian Cardiovascular Society guidelines [8], and are often used interchangeably. Nevertheless, beta-blockers and Ca^{2+}-channel blockers have different pharmacological mechanisms of action with important clinical implications.

Cells in the atrioventricular node (AVN) are dependent on Ca^{2+} influx through the L-type Ca^{2+} channel for excitation. Several regulatory pathways control L-type Ca^{2+} current (I_{CaL}), with the beta-adrenergic system being a major contributor. Beta-adrenergic agonist binding to the beta-receptor activates an intracellular signal-cascade that increases I_{CaL} with, among other effects, enhanced AVN conduction (positive dromotropic effect). Beta-blockers have a negative dromotropic effect on the AVN by preventing the interaction of endogenous beta-adrenoceptor agonists (principally epinephrine and norepinephrine) from binding to the receptor. Once a very large (near-100%) proportion of beta-receptors has been occupied by a beta-blocker, increasing drug concentrations will not substantially increase receptor-occupancy further, and will have very small additional effects on I_{CaL}; consequently, there will be little incremental effect on the ventricular response rate in AF. Pharmacologically, the dose-response curve for beta-blocker effects on HR is such that it reaches near-maximum at a relatively small drug doses (e.g. the equivalent of 50 mg/day of metoprolol) [11]. In contrast, Ca^{2+}-channel blockers directly block the I_{CaL}-carrying channels and negative dromotropic effects roughly parallel increases in drug concentration throughout the clinically-relevant dose range.

These observations have important clinical implications. It is common clinical practice to initiate beta-blockers for rate control at a low dose and slowly titrate the dose to achieve the desired HR. A limitation of this approach is that, once a significant beta-blocker dose is achieved, small dose increments will have a small additional effect on HR. For example, increasing from metoprolol 25 mg bid to 37.5 mg bid (or equivalent) is not expected to be a sufficient dose up-titration in a patient with a HR far from target. Conversely, once a near-maximal beta-blocker dose is achieved (e.g. metoprolol 50 mg bid or equivalent), further dose increases will have very minor effects on HR and adding another drug-class should be considered. In contrast, the much more linear dose-response characteristics of Ca^{2+}-channel blockers produce appreciable negative dromotropic effect increments across the full therapeutic range. An additional point to consider is the very slow absorption of the commonly-used diltiazem extended-release formulation, which takes over 10 h to achieve maximum blood concentrations. If dose-requirements are unknown and rapid rate-control is sought (e.g. in the emergency room), it makes sense to begin with short-acting regular diltiazem, and converting to the extended-release formulation once the dose-needs are known.

Consistent with these remarks, the RATe control in Atrial Fibrillation (RATAF) study sequentially randomized 60 permanent-AF patients with preserved LVEF to (i) metoprolol SR 100 mg po od, (ii) diltiazem SR 360 mg po od, (iii) verapamil 240 mg po od and (iv) carvedilol 25 mg po od. Ca^{2+}-channel blockers were found to have a more potent effect on HR and larger symptom-burden reduction vs beta-blockers [12]. A more recent study by the same group found Ca^{2+}-channel blockers to be associated with neutral effect on exercise capacity and lower NT-proBNP levels compared to beta-blockers, which decreased exercise tolerance and increased NT-proBNP levels in elderly patients with permanent AF [13]. In patients presenting for emergency care with AF and rapid ventricular response, Ca^{2+}-channel blockers were

found to achieve AF rate-control more rapidly without an increase in adverse event-rates compared to beta-blockers [14]. Given their favorable dose-response characteristics and neutral effects on exercise capacity, Ca^{2+}-channel blockers may be preferable to beta-blockers as first-line agents for AF rate-control in most patients with preserved LVEF.

4. Digoxin and AF rate-control

Digoxin, a cardiac glycoside derived from the Foxglove plant, has been in used in clinical medicine since 1785 [15]. It has a unique and desirable combination of positive inotropic and negative dromotropic properties. Digoxin has been extensively utilized for AF rate-control, but has fallen out of favor over the past decade, following a series of observational studies suggesting harm.

The Digitalis Investigation Group (DIG) trial randomized 6800 heart failure (HF)-patients in sinus rhythm to digoxin vs placebo; digoxin-treated patients showed a significant reduction in hospitalization-rate without effects on mortality [16]. Once the flagship of digoxin use in cardiovascular medicine, the DIG trial is now mostly of historical significance as even for its target population (heart-failure patients), digoxin has largely been supplanted by more effective and safer drugs. The DIG trial excluded patients with AF. Therefore, although it is important as the only large-scale randomized prospective trial of digitalis therapy, extrapolation to the AF-population must be cautious.

A series of observational studies have reported apparent negative effects of digoxin on cardiovascular outcomes in AF-patients [17–20]. For example, Shah et al. analyzed registry data from 140,111 AF-patients and found digoxin-use to be associated with a 14%-increase in all-cause mortality [18]. However, retrospective studies are sensitive to uncontrolled prescription bias effects and even though a variety of statistical methods are applied to control for risk factors, residual confounding is a major issue [21]. As an illustrative example, post-hoc analyses using the same data from the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial found digoxin to be associated with increased mortality [22–24], no change [25] and even decreased mortality [26]. Digoxin is often prescribed to older, frail patients who have HF or are felt to be too hemodynamically fragile to tolerate beta-blockers or Ca^{2+}-channel blockers, introducing major biases in drug-selection. A recent meta-analysis of 28 digoxin-trials (2223 subjects) found no increase in mortality (RR 0.82; adjusted CI 0.02–31.2), serious adverse events, HF or stroke with digoxin vs placebo (Table 1) [27]. Consistent with clinical experience, digoxin was inferior to beta-blockers or Ca^{2+}-channel blockers but superior to placebo for HR-control in AF (Table 1) [27].

Practically speaking, most patients will tolerate and achieve satisfactory rate control with beta-blockers and/or Ca^{2+}-channel blockers. Nevertheless, there are specific clinical situations in which digoxin, alone or in combination with other rate-controlling agents, may be a desirable therapeutic choice. For example, in patients presenting with decompensated HF and AF with a rapid ventricular response, digoxin is a reasonable option to avoid the negative inotropic effects of beta-blockers/Ca^{2+}-channel blockers. Similarly, in patients with reduced LVEF and rapid rates despite maximally-tolerated doses of beta-blockers, digoxin is a viable therapeutic choice (non-dihydropyridine Ca^{2+}-channel blockers are relatively contraindicated in this setting [28]). Other patient-characteristics may deter the use of beta-blockers (e.g. severe bronchospastic pulmonary disease) or Ca^{2+}-channel blockers (reduced LVEF) as first-line agents. Finally, the role of digoxin therapeutic drug-concentration monitoring (TDM) is controversial: no studies have been published that directly investigate whether TDM increases the safety of digoxin use. Data from the available digoxin trials suggest that trough-levels between 0.5 and 0.9 ng/ml might minimize risk while preserving therapeutic efficacy [29]. TDM may be particularly useful in patients at increased risk of digoxin toxicity such as those with impaired renal function and low body weight.

5. AF and cardiac resynchronization therapy

Up to 25% of patients treated with a cardiac resynchronization therapy (CRT) device have coexisting AF [30]; the coexistence of AF and CRT offers unique challenges and opportunities in clinical management. The response to CRT is highly dependent on the percent of time the patient receives effective biventricular pacing (BiV%) [31]. During AF, the irregular and often rapid ventricular-response rates increase the percentage of intrinsically-conducted beats, reducing BiV% and CRT effectiveness. Furthermore, the BiV% reported during routine device interrogation may overestimate true/effective BiV% as fusion and pseudo-fusion beats are common during AF but are counted as resynchronized beats; this is particularly problematic in patients with permanent AF [32].

In sinus rhythm, beta-blockers cause sinus bradycardia and do not directly improve BiV% as their effect on AV conduction is modest; increasing beta-blocker dosage will therefore have only a minor effect on BiV%. During AF, beta-blockers generally have an appreciable effect on the ventricular response-rate. Consequently, pharmacological AVN-blockade reduces the number of intrinsically-conducted beats and can significantly increase BiV% during AF. These observations have important implications for rate control-targets, as the lenient HR-targets recommended for the general AF-population may not be appropriate for AF-patients with a CRT device. For example, a patient with a mean HR of 75 bpm in AF would be considered to have excellent rate control, whereas a comparable patient with a CRT-device would probably have suboptimal BiV% and be receiving less-than-anticipated benefits. In the AF/CRT population, aggressive maximally-tolerated pharmacological AVN blockade should be sought to maximize BiV%.

A subset of patients will maintain excessively rapid ventricular response rates despite maximally-tolerated pharmacological AVN-blockade. AV-junction (AVJ) catheter ablation is a highly-effective and safe but irreversible option for such individuals. In the setting of LV-dysfunction, patients should be preferentially implanted with CRT over VVI devices after AVJ-ablation, as the risk of right ventricular pacing-induced LV-dysfunction is non-trivial in pacing-dependent

Table 1
Meta-analysis of digoxin for AF rate-control, based on results in Sethi et al. [27].

	Number of trials providing information	Number of patients	RR (CI)
All-cause mortality	6	522	0.82 (0.02–31.2)
Serious adverse events	13	1210	1.65 (0.24–11.5)
Heart failure	4	462	1.05 (0.00–1414.8)
Stroke	3	325	2.27 (0.0–7887.3)
Conversion to SR within 6 h vs placebo	4	453	1.39 (0.33–5.91)
Conversion to SR between 6 and 24 h vs placebo	6	484	1.15 (0.59–2.27)
			Mean difference
HR control within 6 h vs placebo	4	306	−12.0 (−17.3 to −6.8) bpm
HR control between 6 and 24 h vs placebo	1	123	−25.0 (−37.9 to −12.1) bpm

Overall, digoxin-therapy was not associated with increased all-cause mortality, serious adverse events, heart failure or stroke. Digoxin is not effective for conversion to sinus rhythm (SR) but had a significant effect on heart rate (HR) vs placebo. RR, risk ratio; CI, confidence interval.

patients. Alternatively, in patients with a CRT-device implant for primary HF indications who subsequently develop AF, there is observational evidence that AVJ-ablation may be associated with improved outcomes vs. pharmacological rate-control. A meta-analysis of 6 studies including 768 AF-patients with CRT devices found AVJ-ablation to be associated with lower all-cause and cardiovascular mortality and greater NYHA-class improvement vs. pharmacological rate-control [33]. The benefits of AVJ-ablation are thought to be primarily mediated by improvements in BiV% beyond that achievable with medical therapy [32]. More recently, the Cardiac Resynchronization Therapy in Atrial Fibrillation Patients Multinational Registry (CERTIFY), a prospective study of 7384 consecutive patients undergoing CRT-implantation, found cardiovascular outcomes to be similar in patients with AF + AVJ ablation vs. in sinus rhythm (HR for total mortality 0.93; 85% CI 0.74–1.67). Outcomes were worse in patients with AF and pharmacological rate control (HR for total mortality 1.52; 95% CI 1.26–1.82), independent of baseline clinical characteristics [34].

6. Beta-blockers, HFrEF and AF

Beta-blockers, along with angiotensin-converting enzyme inhibitors and mineralocorticoid receptor antagonists, form the backbone of pharmacological therapy for patients with HF and reduced LVEF (HFrEF). A meta-analysis including several of the landmark randomized clinical trials of patients with HFrEF found that every beta-blocker-mediated 5 beats/min reduction in resting HR was associated with an 18% reduction in mortality (CI, 6%–29%); the absolute dose used had no bearing on outcomes [35]. Importantly, most trials excluded patients with AF and those that did include AF-patients had only a very small number.

However, a sizeable fraction of patient with HFrEF also has coexisting AF. Whether beta-blockers are beneficial in patients with HFrEF and AF is controversial. A recent prospective study of 2039 patients with HF and systolic dysfunction found HR-lowering with beta-blockers to be associated with improved survival in patients in sinus rhythm but not for those in AF [36]. Conversely, a retrospective study of 46,217 Medicare beneficiaries found a statistically significant association between resting HR at discharge and mortality in patients with AF (hazard ratio per 10 bpm increment 1.05; 95% CI 1.01–1.08); the effect size was nevertheless smaller than in patients in sinus rhythm (hazard ratio per 10 bpm increment 1.15; 95% CI 1.12–1.20) [37]. Kotecha et al. sought to explore the relationship between HFrEF, AF and beta-blocker therapy by meta-analyzing 10 randomized controlled trials stratified by baseline rhythm [38]. They reported a significant effect of beta-blockers on all-cause mortality in patients in sinus rhythm (hazard ratio 0.73; CI 0.67–0.80) but not in patients in AF (hazard ratio 0.97; CI 0.83–1.14) [38]. An important limitation of the Kotecha meta-analysis is that the rhythm attribution was based solely on the initial surface electrocardiogram; this may have misclassified a large number of patients with paroxysmal AF in the sinus-rhythm group. An individual-patient data meta-analysis of 11 trials showed beta-blockers to have no mortality benefit in patients with HFrEF in sinus rhythm but not those in AF [39]. More recently, in another study using the same database, beta-blockers were shown to improve LVEF in patients with AF and LV systolic dysfunction but without improvement in cardiovascular outcomes [40]. These observations call into question the extrapolation of generally-accepted mortality benefits of beta-blockers in HFrEF-patients based on studies including mostly sinus-rhythm patients to those with AF [38]. A recent propensity-matched post-hoc analysis of the AF-CHF trial found beta-blockers to reduce mortality by 28% in patients with HFrEF and AF, regardless of burden (low vs high) or AF pattern (paroxysmal vs persistent) [41]; rhythm attribution (sinus rhythm vs AF) was re-evaluated at each visit, minimizing but not eliminating misclassification errors. Of note, no patients in this study had permanent AF. The benefits of beta-blockers in patients with AF and coexisting HFrEF are thus controversial. In the absence of evidence for harm from beta-blockers in AF-patients with HFrEF, it seems reasonable to maintain the recommendation for beta-blocker use. Furthermore, beta-blockers are the "default" choice for AF rate-control in patients with HFrEF, as Ca^{2+}-channel blockers are contra-indicated, digoxin mono-therapy often insufficient and amiodarone associated with a major risk of extracardiac toxicity.

7. Conclusions

Rate control is a ubiquitous component of the management of AF and remains the most commonly used arrhythmia-management strategy. Despite largely unchanged fundamentals, contemporary advances in cardiovascular therapeutics make for new challenges and opportunities for AF rate-control. Several areas of substantial controversy (summarized in Table 2) are unlikely to be addressed by new, adequately-powered prospective randomized clinical trials and clinicians are left with an imperfect basis on which to guide practice. A potential algorithm for a clinical approach to rate-control based on the

Table 2
Summary of controversial and unresolved questions surrounding AF rate-control.

Safety of digoxin for AF rate-control
• Methodologically-limited observational data for harm of digoxin-use for AF rate-control.
• Digoxin remains useful as alternative/adjunctive therapy in sedentary patients with HFrEF and unsatisfactory rate-control.
• Monitoring of digoxin levels may increase safety (target level 0.5–0.9 ng/ml), but not prospectively studied.
"Optimal" HR-target for AF rate-control
• HR-target extremes are clearly associated with harm.
• The "optimal" HR-target is likely patient-dependent.
• HR at rest between 70 and 90 bpm are associated with a favorable risk/benefit profile.
Role of beta-blocker therapy in patients with HFrEF and coexistant AF
• Large body of literature supporting the use of beta-blockers in HFrEF patients in sinus rhythm (mortality benefit).
• Conflicting post-hoc analyses on the benefit of beta-blockers in HFrEF patients in AF.
• In practice, beta-blockers are first-line for AF rate-control in patients with HFrEF, irrespective of the presence/absence of HF-related benefits from beta-blocker therapy.
AF rate-control vs catheter-based rhythm-control
• Large body of literature documenting the non-inferiority of rate-control vs pharmacological rhythm-control.
• Advances in AF catheter ablation may increase sinus rhythm-maintenance rates without the antiarrhythmic drug-related side effects.
• The preliminary results of the Catheter Ablation vs Antiarrhythmic Drug Therapy in Atrial Fibrillation (CABANA) trial failed to show a benefit of AF ablation vs medical therapy.
First-line drug for AF rate-control in patients with preserved LVEF
• Beta-blockers and non-dihydropyridine Ca^{2+}-channel blockers are guidelines-supported first-line agents.
• Ca^{2+}-channel blockers have favorable pharmacokinetics, a neutral effect on exercise capacity and on NT-proBNP vs beta-blockers.
• Ca^{2+}-channel blockers may be preferred first-line agents in patients with preserved LVEF.
AF rate-control and CRT
• A significant proportion of patients with an existing CRT device have co-existing AF.
• AF rate-control targets should be more stringent in patients with CRT to maximize BiV%.
• AVJ ablation should be considered in patients with suboptimal (<95%) BiV% on maximally tolerated rate-control drugs.

Abbreviations: AF, atrial fibrillation; HFrEF, heart failure with reduced ejection fraction; HR, heart rate; CRT, cardiac resynchronization therapy; BiV%, biventricular pacing percentage; AVJ, atrioventricular junction; LVEF, left-ventricular ejection fraction.

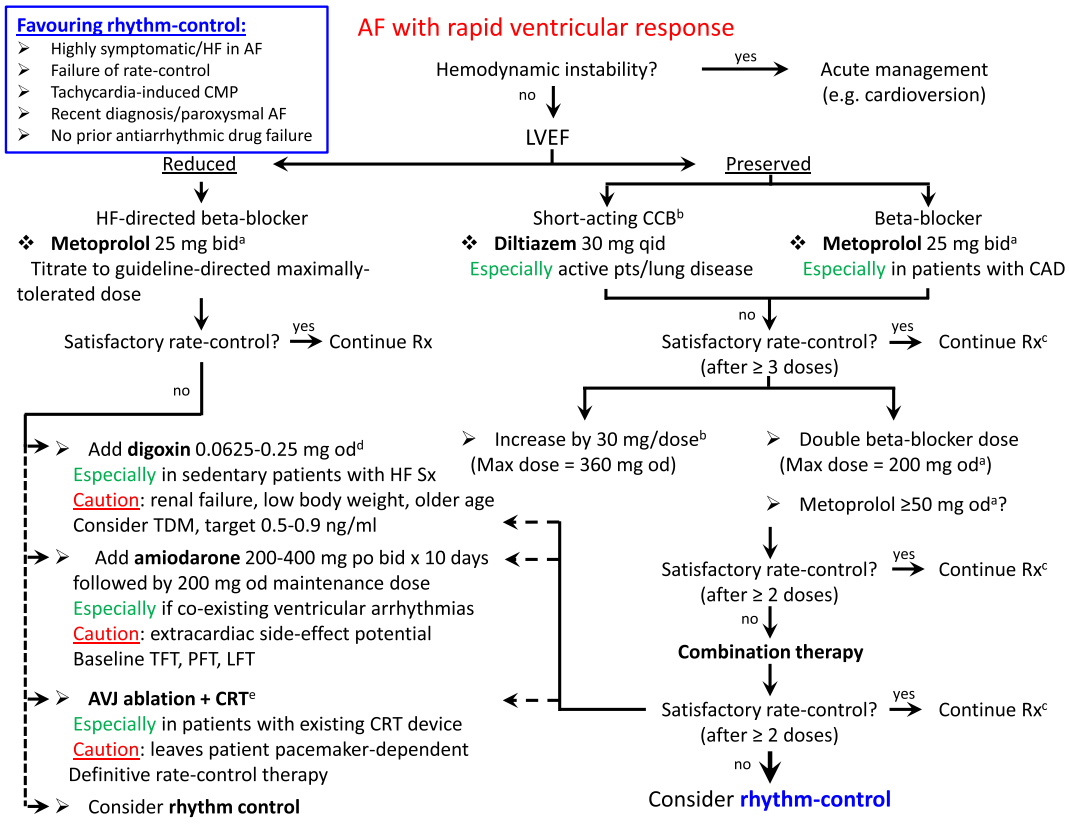

Fig. 1. Practical algorithm for atrial fibrillation (AF) rate-control. Patients in AF with a rapid ventricular response rate and hemodynamic instability should be managed as per the advanced cardiac life support (ACLS) algorithms. In hemodynamically stable patients, a rhythm-control strategy should be considered based on the patient's clinical characteristic (box) and preferences. In patients with reduced left-ventricular ejection fraction (LVEF), heart failure (HF)-directed beta-blockers are first-line and should be titrated to the maximally-tolerated dose as per the HF guidelines. If rate-control is inadequate, alternative/adjunctive options include digoxin, amiodarone, atrioventricular junction (AVJ) ablation with cardiac resynchronization therapy (CRT) and AF rhythm-control. In patients with preserved LVEF, Ca^{2+}-channel blockers (CCBs) and beta-blockers are adequate first-line options per American Heart Association/American College of Cardiology and Canadian Cardiovascular Society guidelines [8], although CCBs may be preferred as detailed in the text. At dose of metoprolol succinate ≥50 mg od, combination therapy should be considered, as further beta-blocker uptitration would not expected to have a significant effect on the ventricular response rates. If rate control remains unsatisfactory, rhythm-control should be strongly considered. Alternative/adjunctive options include digoxin, amiodarone and AVJ ablation with pacemaker implantation. Rate-control should be re-assed periodically. [a]or equivalent beta-blocker dose; [b]in the outpatient setting, the extended-release formulation may be more convenient; [c]convert short-acting CCB to the equivalent dose of extended-release CCB; [d]adjust digoxin dose per renal function, patient size, clinical response and (in selected individuals) plasma concentration; [e]in patients with preserved LVEF, right ventricular pacing is likely equivalent to CRT. CMP, cardiomyopathy; TDM, therapeutic drug monitoring.

principles discussed in this paper is provided in Fig. 1. Despite its apparent simplicity, optimizing rate-control therapy requires a detailed clinical assessment and the balancing of risks and benefits for each patient.

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Disclosures

None.

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