Rate vs Rhythm Control Strategy for Atrial Fibrillation in 2022

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Abstract
Atrial fibrillation (AF) is a chronic and evolving condition; patients need to be explained that management could require repeated, changing, and combination of interventions. This article is intended to present and emphasize new information that was published last year regarding the suitability of rate vs rhythm control strategy for management of AF.

Keywords
Cardiology, Cardiovascular medicine, Cardiology and cardiovascular research, Clinical cardiology

Atrial fibrillation (AF) is a chronic and evolving condition; patients need to be explained that management could require repeated, changing, and combination of interventions. This article is intended to present and emphasize new information that was published last year regarding the suitability of rate vs rhythm control strategy for management of AF. A discussion on factors influencing the choice of initial treatment strategy is followed by contemporary evidence-based considerations on the 2 strategies and in conclusion is outlined how clinical outcomes are affected.

Factors Influencing Initial Treatment Strategy

A. Timing of initiating AF treatment: EAST-AFNET 4 trial and other investigators have put forth a view that in comparison with rate control of AF, initiating early rhythm control, within 1-year of AF onset, decreases the risk of death from cardiovascular (CV) causes, ischemic stroke, heart failure (HF) admission, or acute myocardial infarction.1,2 Better CV outcomes with rhythm control were due to lower rates of stroke/transient ischemic attack.3 A contrarian view by the AFFIRM sub study is that rather than the timing, benefits of rhythm control were due to refined therapies.4 Data from a large Chinese AF registry that recruited >8,000 patients, wherein progression of AF was lesser in patients who received antiarrhythmic drugs (AAD) and/or catheter ablation (CA), supports this notion.5 In fact, an echocardiographic and hemodynamic reversal of an acute tachycardiomyopathy-induced cardiogenic shock following AF ablation has been documented by 1 small study.6 In patients with nonvalvular AF, the purported clinical benefit of early rhythm control is apparent only after long-years of patient follow-up7 and would likely be influenced by the evolving CHA2DS2-VASc score. A nonsignificant trend in favor of rate control was observed by Kim et al,2 when treatment was initiated late, 2 years after the AF diagnosis.

B. Symptom status decides: In practice, rate control is chosen twice as frequently for AF symptom management vis-à-vis rhythm control, even in highly symptomatic patients (EHRA III-IV), thereby hinting at the need to improve physician’s skills to prescribe symptom-focused treatment.8 Younger patients with less comorbidities appear to be more active and may complain of higher burden of symptoms due to paroxysmal AF during daily activities, these patients more often receive rhythm control. Choice of AAD is often dictated by its availability, thus amiodarone is...
used more frequently, followed by class IC agent (flecainide, propafenone). While one needs to guard against overuse of amiodarone, damning would be to wrongly prescribe class IC drugs in patients with significant structural heart disease (SHD). Less patients with symptomatic paroxysmal AF receive CA due to limited hospitals in our country offering this expertise, direct current cardioversion (DCV) is more often used for persistent asymptomatic AF. Rate control, even for symptomatic paroxysmal AF, is often assigned to elderly with comorbidities; but also to patients who are reluctant, fail, or have contraindications to rhythm control AADs. A lenient rate control in a persistent/permanent AF patient (resting HR < 110/min) may be enough, unless symptoms demand a stricter rate control (resting HR < 80/min, with moderate exertion < 110/min). Beta blockers ± digoxin are mostly preferred. Quality of life (QOL) of HF patients with AF may be better with rhythm control, by employing CA or amiodarone, and needs to be individualized over rate control strategy. Finally, it should be understood that clinical outcomes in AF, all-cause death, CV mortality, and thromboembolic phenomenon, are not entirely determined by symptom status.9

C. Patient characteristics matter: It seems befitting to prefer rate control in the elderly, as they commonly have persistent or permanent AF with left atrial enlargement, the latter leads to failure of rhythm control AADs to restore sinus rhythm and risks proarrhythmogenicity.10 In fact, rate control is safe in the elderly with a comparable improvement in QOL as with rhythm control, the latter often associated with a higher rate of hospitalization. AF in elderly can incite decompensatory episodes of pre-existing HF, digoxin is an effective rate control agent in this setting. A proactive Korean experience reported that CA in nonfrail elderly patients lowers the risk of all-cause death, CV death, and composite outcomes.11 AF in patients from the lower socioeconomic strata is associated with increased 1-year all-cause and CV mortality; they get offered fewer DCVs, CAs, readmissions, and outpatient visits.12 Again, women despite a higher risk of stroke, death, and worse QOL, less often receive DCV and CA for rhythm control.13 HF and AF have a bidirectional pathophysiological relation. In practice, rate control is initiated first and rhythm control thereafter for resistant HF-AF symptoms.14 Beta-blockers, despite their doubtful mortality benefit, should be the initial monotherapy; digoxin (HFReF-AF) and dihydropyridine calcium channel blockers (CCBs, HfPef-AF) are appropriately added to achieve target rate control. Empirically, optimal rate control would be < 100 to 110 bpm. Aggressive rate control < 70 bpm is associated with poor prognosis and more pacemaker implantations. Inadequate rate control may need addition of amiodarone or subsequently atrioventricular node ablation with permanent pacemaker implantation. In HF-AF, rhythm control is superior to rate control and is better achieved by CA than AADs. Immediate DCV would be indicated for a hemodynamically unstable or life-threatening AF episode, or for a new-onset (< 48 h) AF; plan DCV in persistent AF only after adequate anticoagulation. Amiodarone is the “weapon of choice” to maintain sinus rhythm; dofetilide, though indicated in HFrEF-AF, requires in-hospital initiation to mitigate the risk of torsades de pointes (TdP). In an AF patient, with HFrEF or HfPefEF, CA of AF can substantially reduce AF burden and thereby reduce mortality and HF hospitalizations.15 Benefits also accrue by improvement in left ventricular ejection fraction (LVEF) and consequently VO2max, 6-minute walk distance, and QOL measures. Due to advanced atrial disease, patients may require multiple or “pulmonary vein isolation plus” (PVI + lines + complex fractionated electrograms) CA strategies. Trick here is to recommend CA to young patients with “arrhythmia-induced cardiomyopathy” and a clinical profile wherein recent AF, nonischemic cardiomyopathy, LVEF ≥ 35%, no significant left atrial/LV dilatation or fibrosis, and absence of comorbidities are weighed in.16

D. Health-care setting dictates: Facility-specific variation in AF management abounds. In the contemporary UK general practice, 70% AF patients are prescribed rate control medications and a far lesser number (5%) receive rhythm control medications, probably due to concerns over AAD efficacy and safety and greater availability of CA.17 Patients presenting to the emergency department (ED) with a new/recurrent AF episode and rapid heart rate (HR) may complain of palpitations, shortness of breath, or exercise intolerance. Achieving rate control from 150 to 100 bpm reduces symptoms sufficiently to allow discharge home. Restoration of sinus rhythm would resolve symptoms that triggered the ED visit better and can be achieved by DCV or IV ibutilide (1 or 2 mg). In case of ibutilide, pretreatment with MgSO4 and post-ibutilide rhythm monitoring for 4 to 6 h prior to ED discharge is mandated. Hospitalization would be necessitated when fast HR persists.18 In absence of a protocol for management of AF in the intensive care unit (ICU), termination was often (95%) awaited in hemodynamically stable patients and rhythm control was sought using amiodarone, DCV, beta blockers (not Sotalol), and MgSO4 in that order of preference in hemodynamically unstable patients. Comorbidities kept digoxin and CCBs out of favor in the ICU setting.19 In present-day practice, clinical significance of smartphone-connectable electrocardiogram (ECG)
device detected new AF episode is not convincingly established. However, in patients with recurrent paroxysmal AF, AF burden logged-in by an implantable loop recorder has a greater impact on QOL than the duration and number of AF episodes, and may guide upscaling rhythm control therapy.

**Rate vs Rhythm Control in 2022: Initial Strategy**

A. **Rhythm control therapy:** Implementation of rhythm control strategy, in patients with significant burden of symptoms, has QOL benefits at the cost of higher utilization of health-care resources, including hospitalizations. Pill-in-pocket approach can be used for acute, symptomatic, infrequent, and non-destabilizing AF episodes, preferably using a class IC AAD, provided no contraindications for the latter preexist, and at best, within a day of recognizing the symptom onset. As a maintenance therapy, aimed at preventing recurrences of paroxysmal and persistent AF, amiodarone is more effective than other AADs, but extracardiac toxic effects are common and increase with time. For this reason, class IC AADs (flecainide, propafenone) should be considered first in patients with no major SHD. Various modifiable (hypokalemia, hypomagnesemia, or coadministered drugs that prolong repolarization), may be modifiable (bradycardia, ventricular hypertrophy, altered drug clearance), and inherited (female sex and specific gene defects) risk factors for drug-induced TdP should be considered, besides a consideration for in-hospital initiation (sotalol, dofetilide) of certain AADs. An eye on the renal function and ECGs on follow-up to check on bradycardia, QRS width (class IC AADs), and QTc (class III AADs) is a necessary exercise. The availability of cryoballoon (CB, Arctic Front Advance, Medtronic) has pushed the envelope of recommending CA early in AAD-naïve symptomatic paroxysmal AF patients; the

![Figure 1. 4S-AF Scheme for Characterization of Patients With Atrial Fibrillation (AF) in Clinical Practice.](source)

**Note:** For colour version of the figure refer to the article online.
findings of EARLY-AF and CRYOFIRST documented lesser AF recurrences and improvement in symptoms and QOL lasting for at least 12 months supporting the notion.\textsuperscript{22,23} This uptick for AF ablation needs to be tempered by experience at other high volume centers that report a higher success rate with paroxysmal vis-à-vis persistent AF (neither reporting >70% procedural success), close to 5% risk of major procedural complications, CB not substantially more effective than radiofrequency CA, and 10% redo procedure rate within a year.\textsuperscript{24}

**B. Rate control therapy:** AF has a higher prevalence in aging population with multiple comorbidities. In one global registry, 50% patients had permanent AF, by definition rhythm control would not be considered in permanent AF patients. Beta blocker use is generally prioritized because of proven better outcomes in other CV conditions, this has not been replicated in AF-HF though. Inadequate HR control may worsen HF. Digoxin is usually a second-line option due to neutral mortality effects in randomized controlled trials of patients with HF. Low-dose digoxin can be used without concerns of toxicity and drug interactions.\textsuperscript{25} A large single-center experience in HF patients, a majority of whom had atrial tachyarrhythmias, suggested that benefits of AV node ablation (followed by a pacemaker implantation) viz. reduction in NYHA class, ED visits, and HF hospitalization, continue over long term.\textsuperscript{26} Considering the possible detrimental effects of right ventricular pacing, current guidelines would recommend biventricular or conduction system pacing.\textsuperscript{27}

### Outcome Studies: How Do We Go About?

**Outcome studies:** The 4S-AF scheme for structured characterization of nonvalvular AF is reproduced in Figure 1. In practice, the rhythm vs rate control choice suggested by this scheme is adopted in only 50% to 60% of patients. The risk of adverse clinical outcome is high when treatment was discordant with the rhythm control suggestion.\textsuperscript{28} When rhythm control strategy is chosen, patient preference and treating physician’s recommendation decide the method employed. Certain AADs have major contraindications that increase the likelihood of adverse events, such as presence of SHD for class IC AADs and advanced chronic kidney disease for sotalol and dofetilide. New onset persistent AF should be considered for DCV. CA is generally recommended for symptomatic patients after failure or intolerance to 1 AAD. Despite intended rhythm control, symptomatic recurrences occur in 40% to 70% patients on AADs and 20% to 50% after CA procedure. More than 1 AAD should be uncommonly used. Rate control may be sufficient to improve AF-related symptoms and is certainly used in patients with permanent AF.\textsuperscript{29} Routine use of amiodarone, sotalol, and dofetilide for rate control is not recommended. The use of nondihydropyridine CCBs in AF-HFrEF is inappropriate.\textsuperscript{30} Finally, appropriate consideration for anticoagulation, lifestyle intervention, and treatment of underlying CV condition is a must.

Summarily, rate vs rhythm control strategy in 2022 should be a holistic decision, accounting for severity of symptoms, documented AF burden, and underlying substrate characteristics. Changes or combination of strategies could be required in the long-term follow-up. Suitable anticoagulation strategy is a prime consideration.

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### References

1. Kirchhof P, Camm AJ, Goette A, et al. EAST-AFNET 4 Trial Investigators. Early rhythm-control therapy in patients with atrial fibrillation. *N Engl J Med*. 2020;383:1305-1316. doi:10.1056/NEJMoa2019422.
2. Kim D, Yang PS, You SC, et al. Treatment timing and the effects of rhythm control strategy in patients with atrial fibrillation: nationwide cohort study. *BMJ*. 2021;373:n991. doi:10.1136/bmj.n991.
3. Tsadok MA, Jackevicius CA, Essebag V, et al. Rhythm versus rate control therapy and subsequent stroke or transient ischemic attack in patients with atrial fibrillation. *Circulation*. 2012;126:2680-2687. doi:10.1161/CIRCULATIONAHA.112.092494.
4. Yang E, Tang O, Metkus T, et al. The role of timing in treatment of atrial fibrillation: an AFFIRM substudy. *Heart Rhythm*. 2021;18(5):674-681. doi:10.1016/j.hrthm.2020.12.025.
5. Yang WY, Du X, Fawzy AM, et al. Chinese Atrial Fibrillation Registry Study Group. Associations of atrial fibrillation progression with clinical risk factors and clinical prognosis: a report from the Chinese Atrial Fibrillation Registry study. *J Cardiovasc Electrophysiol*. 2021;32(2):333-341. doi:10.1111/jce.14826.
6. Volle K, Delmas C, Rollin A, et al. Successful reversal of severe tachycardia-induced cardiomyopathy with cardiogenic shock by urgent rhythm or rate control: only rhythm and rate matter. *J Clin Med*. 2021;10(19):4504. doi:10.3390/jcm10194504.
7. Ionescu-Ittu R, Abrahamowicz M, Jackevicius CA, et al., et al. Comparative effectiveness of rhythm control vs rate control drug treatment effect on mortality in patients with atrial fibrillation. *Arch Intern Med*. 2012;172:997-1004. doi:10.1001/archinternmed.2012.2266.
8. Koziel M, Mihajlovic M, Nedeljkovic M, et al. BALKAN-AF Investigators. Symptom management strategies: rhythm vs
rate control in patients with atrial fibrillation in the Balkan region: data from the BALKAN-AF survey. Int J Clin Pract. 2021;75(6):e14080. doi:10.1111/ijcp.14080.
9. Sgreccia D, Manicardi M, Malavasi VL, et al. Comparing outcomes in asymptomatic and symptomatic atrial fibrillation: a systematic review and meta-analysis of 81,462 patients. J Clin Med. 2021;10(17):3979. doi:10.3390/jcm10173979.
10. Salih M, Abdel-Hafez O, Ibrahim R, Nair R. Atrial fibrillation in the elderly population: challenges and management considerations. J Arrhythm. 2021;37(4):912-921. doi:10.1002/joa3.12580.
11. Yang PS, Sung JH, Kim D, et al. Frailty and the effect of catheter ablation in the elderly population with atrial fibrillation - a real-world analysis. Circ J. 2021;85(8):1305-1313. doi:10.1253/circj.CJ-20-1062.
12. Hagengaard L, Andersen MP, Poleciawtak C, et al. Socioeconomic differences in outcomes after hospital admission for atrial fibrillation or flutter. Eur Heart J Qual Care Clin Outcomes. 2021;7(3):295-303. doi:10.1093/ehjqcco/qcz053.
13. Volgman AS, Benjamin EJ, Curtis AB, et al., and the American College of Cardiology Committee on Cardiovascular Disease in Women. Women and atrial fibrillation. J Cardiovasc Electrophysiol. 2021;32(10):2793-2807. doi:10.1111/jce.14838.
14. Tsigkas G, Apostolos A, Despotopoulos S, et al. Heart failure and atrial fibrillation: new concepts in pathophysiology, management, and future directions. Heart Fail Rev. 2021. doi:10.1007/s10741-020-09978-0.
15. Deisenhofer I. Atrial fibrillation in heart failure: prime time for ablation! Heart Rhythm O. 2021;2(6Part B):754-761. doi:10.1016/j.hrto.2021.10.011.
16. Farmakis D, Chrysohou C, Giamouzis G, et al. The management of atrial fibrillation in heart failure: an expert panel consensus. Heart Fail Rev. 2021;26(6):1345-1358. doi:10.1007/s10741-020-09978-0.
17. Phillips K, Subramanian A, Thomas GN, et al. Trends in the pharmacological management of atrial fibrillation in UK general practice 2008-2018. Heart. 2021. doi:10.1136/heartjnl-2021-319338.
18. Kea B, Warton EM, W Ballard D, et al. Predictors of acute atrial fibrillation and flutter hospitalization across 7 U.S. emergency departments: a prospective study. J Arr Fibrillation. 2021;13(5):2355. doi:10.4022/jafib.2355.
19. Wetterslev M, Moller MH, Granholm A, et al. AFIB-ICU collaborators. Management of acute atrial fibrillation in the intensive care unit: an international survey. Acta Anaesthesiol Scand. 2021. doi:10.1111/aas.14007.
20. Reifel JA, Capucci A. “Pill in the pocket” antiarrhythmic drugs for orally administered pharmacologic cardioversion of atrial fibrillation. Am J Cardiol. 2021;140:55-61. doi:10.1016/j.amjcard.2020.10.063.
21. Reifel JA. Antiarrhythmic drugs for atrial fibrillation: selected features of ventricular repolarization that facilitate proarrhythmic torsades de pointes and favor inpatient initiation. J Innov Card Rhythm Manag. 2021;12(7):4600-4605. doi:10.19102/icrm.2021.120704.
22. Andrade JG, Wells GA, Deyell MW, et al. EARLY-AF investigators. Cryoablation or drug therapy for initial treatment of atrial fibrillation. N Engl J Med. 2021;384(4):305-315. doi:10.1056/NEJMo2029980.
23. Pavlovic N, Chierchia GB, Velagic V, et al. Cryo-FIRST investigators. Initial rhythm control with cryoballoon ablation vs drug therapy: impact on quality of life and symptoms. Am Heart J. 2021;242:103-114. doi:10.1016/j.ahj.2021.08.007.
24. Numminen A, Penttilä T, Arola O, et al. Treatment success and its predictors as well as the complications of catheter ablation for atrial fibrillation in a high-volume centre. J Interv Card Electrophysiol. 2021. doi:10.1007/s10840-021-01011-0.
25. Garg J, Gopinathann R, Lakkireddy D. Digoxin vs bisoprol for heart rate control in atrial fibrillation. JAMA. 2021;325(16):1680-1681. doi:10.1001/jama.2021.2673.
26. Manuel AM, Almeida J, Fonseca P, et al. Long-term outcomes after radiofrequency catheter ablation of the atrioventricular node: the experience of a Portuguese tertiary center. Rev Port Cardiol (Engl Ed). 2021;40(2):95-103. doi:10.1016/j.repc.2020.05.016.
27. Brugada J, Katritsis DG, Arbelo E, et al. 2019 ESC Guidelines for the management of patients with supraventricular tachycardia: The Task Force for the management of patients with supraventricular tachycardia of the European Society of Cardiology (ESC). Eur Heart J. 2020;41(5):655-720. doi:10.1093/eurheartj/ehz467.
28. Malavasi VL, Vitolo M, Colella J, et al. Rhythm- or rate-control strategies according to 4S-AF characterization scheme and long-term outcomes in atrial fibrillation patients: the FAMo (Fibrillazione Atriale in Modena) cohort. Intern Emerg Med. 2021. doi:10.1007/s11739-021-02890-x.
29. Fabritz L, Crijns HJGM, Guasch E, et al. Dynamic risk assessment to improve quality of care in patients with atrial fibrillation: the 7th AFNET/EHRA Consensus Conference. Europace. 2021;23(3):329-344. doi:10.1093/europace/eua279.