Rate versus rhythm control in atrial fibrillation

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Atrial fibrillation (AF) is the most frequently encountered cardiac arrhythmia, and it becomes more common as people age.[1] Atrial fibrillation is associated with a heightened risk of thromboembolism such as stroke and other cardiovascular events that puts patients at a substantially increased risk of morbidity and mortality. The primary pharmacologic strategy for managing AF includes medications that control either rate or rhythm. However, there is much debate as to whether rate or rhythm control hold specific advantages, and which pharmacologic agents are optimal. Therapy selections should be guided by patient-specific factors, comorbidities, patient preferences, side effects, drug interactions, and cost and convenience.

The objective of this article is to discuss rate- and rhythm-control strategies with the goal of assisting physicians and patients in making informed decisions. Anticoagulation strategies in AF have been discussed previously.[2]

Case description

Mr G.R., a 62-year-old man, presents to you complaining of having had mild palpitations consistently for the past 2 weeks. At times he feels light-headed but he has never fainted. He denies any history of chest pain at rest or with exertion, orthopnea, or paroxysmal nocturnal dyspnea. His past medical history is relevant for mild stable chronic obstructive pulmonary disease (COPD), treated with tiotropium once daily and salbutamol as required. He also has hypertension that is well controlled with 10 mg of ramipril once daily. He quit smoking 20 years ago and has an alcohol intake of 1 to 2 ounces of whisky every week.

On physical examination he is in no obvious distress. His blood pressure is 126/78 mm Hg, and his pulse is 110 beats per minute (BPM). He has no pedal edema, jugular venous distension, or heart murmur on auscultation. There is no audible bruit, and his extremities are warm with palpable bilateral peripheral pulses. Results of his recent blood tests reveal normal complete blood count, thyroid and renal function, liver enzymes, and fasting blood glucose. He has no history of bleeding involving transfusion or a decrease in hemoglobin greater than 20 g/L.

Electrocardiogram confirms AF with a heart rate of 120 BPM.

Bringing evidence to practice

The following step-wise approach can be used to tailor rate or rhythm control for new-onset AF.

Step 1: Determine the type of AF (paroxysmal, persistent, or permanent). Newly diagnosed AF usually falls within the categories of paroxysmal or persistent AF (**Table 1**).[1,3] It is important to identify the type of AF, as management differs among the classifications. Patients who are diagnosed with permanent AF are at higher risk of adverse outcomes, and some treatment strategies are not appropriate.

Application to Mr G.R.: Mr G.R. has been experiencing mild palpitations consistently for the past 2 weeks. He is likely experiencing persistent AF.

Table 1. Identification of type of AF

TYPE OF AF	DEFINITION
Paroxysmal	Terminates spontaneously within 7 d
Persistent	Lasts longer than 7 d or is terminated pharmacologically or electrically
Permanent	Does not terminate, even with cardioversion attempts

AF—atrial fibrillation.
Data from Gillis et al[1] and Sanoski and Bauman.[3]

Step 2: Identify and correct (if possible) underlying causes of AF. There are several potential underlying causes of AF that must be investigated before treatment is initiated with a rate- or rhythm-control strategy. **Table 2**[1,3,4] illustrates the most common risk factors for the development of AF from both

Table 2. Underlying causes of AF

CARDIOVASCULAR CAUSES	NONCARDIOVASCULAR CAUSES
Hypertension	Hyperthyroidism*
Valvular heart disease	Autonomically mediated (vagal) causes
Coronary artery disease	Alcoholism ("holiday heart")* or alcohol withdrawal
Heart failure* or cardiomyopathy	Obstructive sleep apnea* or obesity*
Genetic or familial causes	Pharmacologic agents (stimulants, digoxin toxicity, illicit drugs)
Post cardiac surgery	Neurologic insult
Congenital heart disease*	Excessive physical exertion*
Sick sinus syndrome	Sepsis
Pacemaker*	Pulmonary disease (chronic obstructive pulmonary disease)

AF—atrial fibrillation.
*Management of these risk factors prevents development or recurrence of AF.
Data from Gillis et al,[1] Sanoski and Bauman,[3] and Jin and Kosar.[4]

cardiovascular and noncardiovascular causes.[1,3,4] Ruling out and correcting possible causes of AF will also make the referral process (if necessary) more efficient for the patient.

Application to Mr G.R.: Advancing age, COPD, and hypertension are Mr G.R.'s risk factors for the development of AF. Caution Mr G.R. about limiting his alcohol intake and ensure his COPD and hypertension are well controlled.

Step 3: Determine patient-specific factors that influence the choice between rate-control and rhythm-control strategies. The 2010 Canadian Cardiovascular Society (CCS) AF guidelines[1] suggest that certain patient factors favour rate control over rhythm control (**Table 3**).[1] In terms of mortality, however, several meta-analyses suggest that there are no significant differences between treatment strategies in most patient groups (**Table 4**).[5-16] Rate-control strategies showed fewer embolic events (including stroke) in patients with heart failure (HF),[5] fewer hospitalizations, and fewer adverse events.[6] In patients who are more symptomatic, rhythm control might be more desirable.[1]

When a patient possesses factors that favour both rate control and rhythm control, patient preference, quality of life, comorbidities, side effects, and drug interactions with concomitant medications might also help to guide choice of therapy.

Application to Mr G.R.: Mr G.R. has the following patient factors.

- Favouring rhythm control:
  - -newly detected AF;
  - -age younger than 65 years; and
  - -no previous antiarrhythmic drug failure
- Favouring rate control:
  - -less symptomatic;
  - -hypertension;
  - -no history of HF; and
  - -persistent AF

Overall, the above patient factors favour rate control. The benefits of rate control are explained to Mr G.R., including the lower risk of adverse events and fewer hospitalizations (**Table 4**).[5-16] He agrees to this treatment.

Table 3. Factors favouring rate versus rhythm control

FAVOURING RATE CONTROL	FAVOURING RHYTHM CONTROL
Persistent AF	Paroxysmal AF or newly detected AF
Less symptomatic	More symptomatic
Age ≥ 65 y	Age < 65 y
Hypertension	No hypertension
No history of HF	HF clearly exacerbated by AF
Previous failure of antiarrhythmic drug	No previous failure of antiarrhythmic drug
Patient preference	Patient preference

AF—atrial fibrillation, HF—heart failure.
Data from Gillis et al.[1]

Table 4. Rate versus rhythm control meta-analyses summary

META-ANALYSIS	STUDIES INCLUDED	PATIENTS	KEY FINDINGS
Caldeira et al,[5] 2012	8 RCTs (PIAF,[9] RACE,[10] AFFIRM,[11] STAF,[12] HOT CAFE,[13] AF-CHF,[14] J-RHYTHM,[15] CAFE-II[16])	N = 7499 participants with AF, mean age 68 y, mostly men (63.4%-82%); HTN (42.8%-64.3%), valvular disease (4.9%-17%), CAD (7.4%-43.5%), HF (3.6%-70%); mean follow-up 2.9 y (range 1-3.5 y)	No significant difference between rate and rhythm control in all-cause mortality, CV mortality, arrhythmia or sudden death, ischemic stroke or embolic events, or serious bleeding; there were significantly fewer systemic embolic events in the rate-control group in trials where more than 50% of patients reported HF (RR = 0.43, 95% CI 0.21-0.89)
Cordina and Mead,[6] 2005	2 RCTs (PIAF,[9] AFFIRM[11])	N = 4312 participants > 18 y with acute, paroxysmal, or sustained AF or atrial flutter, of any duration and any cause (most patients were > 60 y with considerable CV risk factors)	No difference in mortality or quality of life between rate- or rhythm-control strategies; hospitalization (P < .001) and adverse events (P < .05) were significantly higher in the rhythm-control group
De Denus et al,[7] 2005	5 RCTs (PIAF,[9] RACE,[10] AFFIRM,[11] STAF,[12] HOT CAFE[13])	N = 5239 participants with first or recurrent AF, mean age 65.1 y, mostly men (65.3%); CAD (29.9%), HTN (52.7%); mean duration of follow-up 1.9 y	Rate control was significantly better for the combined end point of all-cause death and thromboembolic stroke (NNT = 50); however, for single end points of death and stroke individually, the difference between rate and rhythm strategies was non-significant; differences in serious bleeding (intracranial and extracranial) and systemic embolism were also not significant
Kumana et al,[8] 2005	5 RCTs (PIAF,[9] RACE,[10] AFFIRM,[11] STAF,[12] HOT CAFE[13])	N = 5239 participants with persistent or recurrent AF	Rate control was significantly better (P < .01) than rhythm control for preventing hospitalizations (NNH = 35 for rhythm control); differences in death, non-CNS bleeding, and ischemic stroke were non-significant

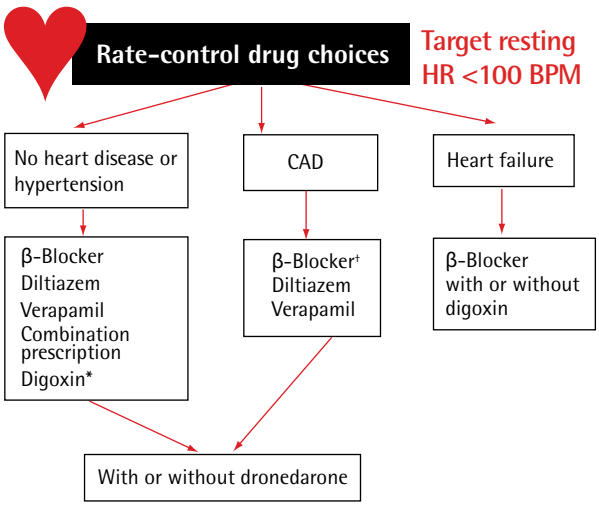
AF—atrial fibrillation, CAD—coronary artery disease, CNS—central nervous system, CV—cardiovascular, HF—heart failure, HTN—hypertension, NNH—number needed to harm, NNT—number needed to treat, RCT—randomized controlled trial, RR—relative risk.

Step 4: Choose an appropriate pharmacologic agent, considering patient-specific factors and comorbidities.[1,4] Algorithms for AF treatment strategies based on patient-specific factors such as comorbid conditions are provided in **Figure 1**[4] (rate control) and **Figure 2**[4] (rhythm control). **Table 5**[1,4,17-19] provides an overview of usual dosing, advantages, disadvantages, and cost for selected drug therapies. The discussion below will highlight important treatment considerations.

Rhythm-control considerations

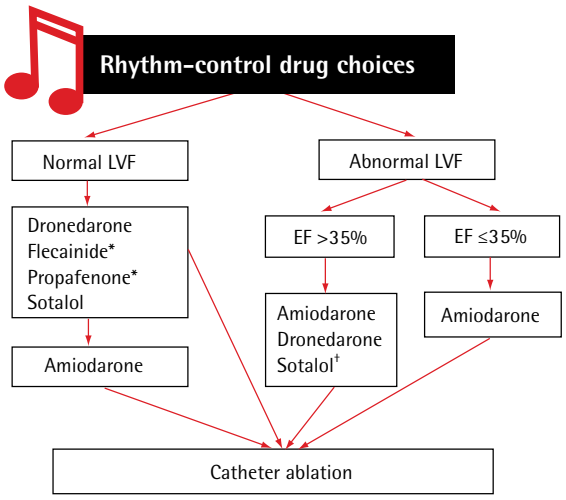
A "pill-in-the-pocket" rhythm-control treatment strategy is acceptable as initial therapy for patients who are quite symptomatic with new-onset paroxysmal AF and no structural heart disease.[1] This strategy involves a larger, 1-time dose of a class I antiarrhythmic (propafenone or flecainide). A fast-acting atrioventricular nodal blocking agent such as metoprolol should be used in conjunction to prevent concealed conduction that can progress to ventricular tachycardia or fibrillation. First-time administration requires observation and is usually performed by a cardiologist. Pill-in-the-pocket dosing for flecainide and propafenone can be found in **Table 5**.[1,4,17-19]

Figure 1. Rate-control algorithm



BPM—beats per minute, CAD—coronary artery disease, HR—heart rate.
*Digoxin can be considered as monotherapy in sedentary individuals.
†β-Blockers are preferred in CAD.
Data from Jin and Kosar.[4]

Figure 2. Rhythm-control algorithm



AV—atrioventricular, CAD—coronary artery disease, EF—ejection fraction, LVF—left ventricular function.
*Class I agents should be AVOIDED in CAD; they should be combined with AV-nodal blocking agents (eg, β-blocker, digoxin, diltiazem, or verapamil).
†Sotalol should be used with caution with EF 35% to 40%; contraindicated in women >65 y who are taking diuretics.
Data from Jin and Kosar.[4]

Dronedarone has received increased attention as a novel agent for the treatment of arrhythmias in the hope of finding a safer alternative to amiodarone therapy. According to data from the ATHENA[20] (A Placebo-controlled, Double Blind, Parallel-arm Trial to Assess the Efficacy of Dronedarone 400 mg BID for the Prevention of Cardiovascular Hospitalization or Death from any Cause in Patients with Atrial Fibrillation/Atrial Flutter) and PALLAS[21] (Permanent Atrial Fibrillation Outcomes Study Using Dronedarone on Top of Standard Therapy) trials, as well as previous trials,[22-25] dronedarone should be used with great caution and in select patients only. **Table 6**[20,21] provides a summary of the key findings of the ATHENA and PALLAS trials and is available from **CFPlus**.* A detailed trial summary of PALLAS is also available from **CFPlus**.*[26] Dronedarone should not be prescribed for patients with HF or permanent AF owing to increased risk of mortality.[21,24,27] In addition, dronedarone should not be used in patients with hepatic disease, with concomitant use of QT-prolonging agents, or with concomitant use of cytochrome P450 3A4 inhibitors (eg, azole antifungals, macrolide antibiotics, protease inhibitors). Use *might* be considered in patients with paroxysmal or persistent AF for rhythm control if no contraindications are present, or as add-on therapy for inadequate rate control. It should be noted that dronedarone's efficacy approximates 40% for sinus conversion at 1 year,[1] which is inferior to amiodarone, but it is better tolerated.

Consider referral to a cardiologist for radiofrequency catheter ablation (RFCA) as a treatment option in symptomatic patients who are refractory or intolerant to antiarrhythmics.[1,28] A meta-analysis of 8 randomized clinical trials comparing the efficacy and safety of RFCA versus antiarrhythmic drugs found that RFCA therapy was more successful in reducing AF recurrence than antiarrhythmic drugs were (23.2% recurrence for ablation and 76.6% recurrence for antiarrhythmics).[29] A recent study, however, showed that ablation as initial therapy for *paroxysmal* AF is no different than class I or III antiarrhythmic drug therapy in terms of cumulative burden.[30]

Application to Mr G.R.: Mr G.R. prefers rate control. Therapeutic options include β-blockers, nondihydropyridine calcium-channel blockers (verapamil or diltiazem), and digoxin.

- β-Blocker (metoprolol or bisoprolol, both β-1 cardioselective):
  -Mr G.R. does not have a history of myocardial infarction, HF, or left ventricular dysfunction (automatic indications for β-blocker therapy).
  -Mr G.R. has mild COPD, which is not an absolute contraindication, but β-blocker therapy might not be the best choice owing to possible bronchoconstriction, and other agents are available.
  -β-Blockers are usually well tolerated but might increase the risk of falls in the elderly. β-Blockers are preferentially avoided in patients older than 60 years.[31]
  -Mr G.R. is already taking ramipril, and his hypertension is well controlled; initiation of β-blocker therapy puts him at risk for hypotension.
- Calcium channel blocker (verapamil or diltiazem):
  -Mr G.R. has COPD, and these agents would pose no risk of bronchoconstriction.
  -Diltiazem might be better tolerated than verapamil (verapamil has a 7% incidence of constipation).
  -Mr G.R. is already taking ramipril, and his hypertension is well controlled; his blood pressure should be monitored closely if calcium channel blockers are initiated, as hypotension puts patients at increased risk of falls.
  -Only nondihydropyridine calcium channel blockers (verapamil and diltiazem) are indicated owing to their atrioventricular node blocking actions. Other calcium channel blockers (amlodipine, nifedipine, and felodipine) are not appropriate, as this is not their main mechanism of action.
- Digoxin:
  -Digoxin is not appropriate for Mr G.R., as it is indicated for sedentary patients because of its poor

*__Table 6__ and the **RxFiles Trial Summary** of PALLAS and RACE II are available at **www.cfp.ca**. Go to the full text of the article online, then click on **CFPlus** in the menu at the top right-hand side of the page.

efficacy in controlling heart rate with exercise or in acute exacerbated COPD.
-Digoxin is usually reserved for add-on therapy for symptom control.
-Digoxin is not as efficacious as β-blocker or calcium channel blocker therapy.

Step 5: Decide on monitoring and follow-up parameters for the patient based on selected therapy. The 2010 CCS guidelines on AF[1] recommend a target resting heart rate below 100 BPM in patients with persistent or permanent AF. This is a change from the previously recommended target of below 80 BPM and is based on the RACE-II (Rate Control Efficacy in Permanent Atrial Fibrillation) trial.[32] RACE-II suggested that in a low-risk population with permanent AF, less stringent (<110 BPM) target heart rate control was not more harmful than, and was as efficacious as, strict (<80 BPM) rate control. Generally, more lenient rate control is easier to achieve with fewer medications, lower doses (less risk for side effects), and fewer physician visits. The guidelines adopted a target of below 100 BPM because the mean heart rate over 3 years in the less stringent group was approximately 100 BPM. A detailed trial summary is available from **CFPlus.***[33]

All patients should be followed regularly to assess the efficacy and safety of their current therapy, regardless of whether a rate- or rhythm-control approach is taken, or of the pharmacologic agent used.

Application to Mr G.R.: Mr G.R. is prescribed 120 mg of controlled-delivery diltiazem a day orally for rate control. His target resting heart rate is 100 BPM (as per the RACE-II trial and the CCS 2010 guideline update). Mr G.R. will require follow-up in 1 to 2 weeks to assess

- efficacy (symptom resolution, heart rate <100 BPM, and dose titration, if required) and
- safety (side effects such as bradycardia, anorexia or nausea, and edema; blood pressure to monitor for hypotension; and decreases in ramipril dose, if necessary).

Patient case continued

Mr G.R. 10 years later: Mr G.R. is now 72 years old and is admitted to hospital with signs and symptoms of HF, which is being exacerbated by his AF. He is taking appropriate anticoagulation therapy (warfarin). His diltiazem is discontinued and replaced with metoprolol to manage both his HF and rate control. However, after a few days of 200 mg of sustained-release metoprolol daily, he remains symptomatic

Table 5. Pharmacotherapy options: *A) Rate control; B) Rhythm control.*

A) DRUG	USUAL DOSE	ADVANTAGES	DISADVANTAGES	COST/30 D
β-Blockers (β-1 cardioselective)				
• Metoprolol (Lopresor, regular and SR)	25-200 mg BID or 100-200 mg SR OD to BID	• First-line agents in patients with comorbid conditions such as CAD, HF, or LV dysfunction • Generally well tolerated • Effective for rate control at rest and with exercise, but no remarkable effects on exercise capacity	• Dizziness or fatigue often reported as bothersome side effects • Use cautiously in elderly patients (fall risk) • Can mask hypoglycemia (use cautiously in diabetes)	$10-$33
• Bisoprolol (Monocor)	2.5-10 mg OD			$10-$15
Nondihydropyridine CCBs				
• Diltiazem (Cardizem, regular and CD; Tiazac, regular and XC)	120-480 mg OD	• Preferred for younger patients (less fatigue than with β-blockers) • Preferred in COPD or severe asthma • Less effective for controlling HR during exercise, but might lead to increased exercise capacity	• Constipation is a common side effect for verapamil • Avoid in patients after MI or HF	$25-$60
• Verapamil (Isoptin SR)	120 mg OD to 240 mg SR BID			$22-$52
Other				
• Digoxin (Toloxin)	0.0625-0.25 mg OD	• Can be used as add-on therapy to β-blockers or CCBs if HR is not controlled • Use for sedentary patients or LV dysfunction	• NOT first-line therapy • Less effective than β-blockers or CCBs, especially in nonsedentary patients for exercise tolerance • Serious toxicity or side effects are possible • Considerable amount of drug interactions • Associated with increased risk of all-cause mortality regardless of the presence or absence of HF according to AFFIRM trial follow-up analysis[17] • Use cautiously in renal dysfunction	$15
B) DRUG	**USUAL DOSE**	**ADVANTAGES**	**DISADVANTAGES**	**COST/30 D**
Class III antiarrhythmics				
• Amiodarone (Cordarone)	Loading 800-1600 mg/d for 1-3 wk, then 600-800 mg/d for 1 mo, then 100-400 mg/d; use the lowest effective dose for maintenance	• Efficacy at 1 y 60%-70% (most effective) • CTAF trial[18] showed amiodarone was more efficacious at preventing AF than propafenone or sotalol were • Possesses both rate- and rhythm-control mechanisms • Can be used in patients with renal dysfunction or HF (LVEF ≤ 35%) • Long-term effects known and studied	• Safety: many serious side effects that require judicious monitoring (see **Table 7**) • Considerable drug interactions (especially with warfarin; must decrease warfarin dose) • Loading dose and extensive titrating schedule required • Long half-life (26-107 d)	$31-55
• Dronedarone (Multaq)	400 mg BID	• Efficacy at 1 y 40% • Fewer side effects than amiodarone • Less proarrhythmia than with propafenone or sotalol • No loading dose required	• Should NOT be used in patients with permanent AF (increased CV mortality) • Relatively new drug; limited experience with efficacy and safety • Not covered by provincial formularies (not recommended by CDR)[19]	$150
• Sotalol (Sotacor)	80 mg BID (must adjust dose for renal impairment)	• Efficacy at 1 y 30%-50% • Possesses both rate- and rhythm-control mechanisms	• Possesses proarrhythmic qualities • CI in patients with CrCl < 40 mL/min (renally eliminated) • Bradycardia common in elderly patients • Avoid in women > 65 y who are taking diuretics or who have renal impairment owing to increased risk of torsade de pointes	$16
Class I antiarrhythmics				
• Flecainide (Tambocor)	Usual dose: 50-150 mg BID; pill-in-the-pocket dose: 200-300 mg in 1 dose	• Efficacy at 1 y 30%-50% • Can be used for the pill-in-the-pocket strategy in patients without structural heart disease	• Should be coupled with an AV nodal blocking agent (β-blocker or CCB) owing to concealed conduction and risk of ventricular tachycardia • CI in structural heart disease • Can have serious cardiac side effects (cardiac arrest, arrhythmia, AV node block) • Pill-in-the-pocket strategy: first dose is usually given and observed by a cardiologist	$60-$85
• Propafenone (Rythmol)	Usual dose: 150 mg OD-TID; pill-in-the-pocket dose: 450-600 mg in 1 dose			$21-$45

AF—atrial fibrillation, AV—atrioventricular, BID—twice daily, CAD—coronary artery disease, CCB—calcium channel blocker, CD—controlled delivery, CDR—Common Drug Review, CI—contraindicated, COPD—chronic obstructive pulmonary disease, CrCl—creatinine clearance, CV—cardiovascular, HF—heart failure, HR—heart rate, LV—left ventricular, LVEF—left ventricular ejection fraction, MI—myocardial infarction, OD—once daily, SR—sustained release, TID—3 times daily, XC—extended release.
Data from Gillis et al[1] and Jin and Kosar[4]

with AF episodes. His left ventricular ejection fraction (LVEF) is 34% and his renal function is decreased (estimated creatinine clearance of 30 mL/min). After baseline thyroid function tests, liver function tests, and chest x-ray examination, the cardiologist decides to load the patient with amiodarone. Upon discharge, Mr G.R. is taking 200 mg a day orally.

Mr G.R. is not achieving adequate control of his AF with rate control therapy alone (metoprolol). He also has heart failure (LVEF of 34%) and reduced renal function. Amiodarone is an appropriate choice of add-on therapy for the following reasons:

- It is the only agent recommended by the CCS guidelines[1] for rhythm control in patients with abnormal LVEF below 35% (**Table 5**[1,4,17-19]).
- Amiodarone does not require dosage adjustment in renal dysfunction, as it is hepatically metabolized.
- Amiodarone possesses the greatest efficacy at 1 year compared with other antiarrhythmic agents (60% to 70%).[1]
- Mr G.R. is elderly (72 years) and therefore his cumulative lifetime exposure to amiodarone will likely be limited, as opposed to if this agent had been initiated at a younger age.

Patients taking amiodarone therapy require judicious monitoring owing to the extensive side effect profile of the medication. Toxicity is related to the cumulative exposure of amiodarone; therefore, the lowest possible dose to control symptoms is recommended, with some patients being managed on as little as 100 mg every other day, taken orally.[34] **Table 7**[4,34,35] provides an overview of important side effects to monitor, including frequency of occurrence, diagnostic procedures to perform, and frequency of follow-up required.

Conclusion

There is no difference between rate and rhythm control in terms of mortality. Underlying factors for AF should be identified and corrected if possible. When deciding whether to control rate or rhythm, patient-specific factors such as type of AF, comorbidities, and patient preference should be considered. In addition, other factors such as side effect profile, pill burden, monitoring intensity, and cost are important to consider when prescribing therapy for AF.

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Table 7. Amiodarone-monitoring parameters

PARAMETER MONITORED	FREQUENCY OF OCCURRENCE, %	WHAT TO ORDER OR PERFORM	HOW OFTEN
CNS (ataxia, dizziness)	4-9	Physical examination	Every follow-up visit
Corneal deposits	4-9	Slit lamp examination	Annually
Optic neuropathy	Unknown	Ophthalmologic examination	Baseline, every 6-12 mo
Pulmonary toxicity	2-17	Chest x-ray scan, pulmonary function tests (and DLCO)	Baseline, every 6-12 mo
Thyroid complications	2-6	Free T4 level, TSH level	Baseline, every 6-12 mo
Photosensitivity	3-10	History, physical examination	Every follow-up visit
Blue discoloration of skin (Smurf or Avatar syndrome)	<9	History, physical examination	Every follow-up visit
GI (nausea, vomiting, anorexia)	4-33	Weight, physical examination, and history	Every follow-up visit
Liver toxicity	4-9	AST, ALT, bilirubin	Baseline, every 6-12 mo

ALT—alanine aminotransferase, AST—aspartate aminotransferase, CNS—central nervous system, DLCO—diffusing capacity of lung for carbon dioxide, GI—gastrointestinal, T4—thyroxine, TSH—thyrotropin.
Data from Jin and Kosar,[4] Siddoway,[34] and Pfizer Canada.[35]

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