Atrial Fibrillation/Atrial Flutter: Rate and Rhythm Control

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LEARNING OBJECTIVES

1. Apply current evidence on rate versus rhythm control in the treatment of patients with atrial fibrillation (AF).
2. Design a treatment plan for rate control of AF according to current evidence, patient characteristics, and clinical situation.
3. Develop a rhythm control strategy for AF on the basis of current evidence, patient risk factors, and clinical situation.
4. Evaluate current evidence on the use of catheter ablation in patients with AF.
5. Justify the importance of lifestyle interventions to decrease AF recurrence and burden.

ABBREVIATIONS IN THIS CHAPTER

AF	Atrial fibrillation
AFL	Atrial flutter
AV	Atrioventricular
HF	Heart failure
HFrEF	Heart failure with reduced ejection fraction
LVD	Left ventricular dysfunction
LVEF	Left ventricular ejection fraction
LVH	Left ventricular hypertrophy

Table of other common abbreviations

INTRODUCTION

Atrial fibrillation (AF) is an increasingly prevalent cardiac arrhythmia encountered in clinical practice. In 2010, the prevalence of AF in the United States was estimated to affect 5.2 million patients and is projected to increase to 12.1 million by 2030 (Virani 2021). The growing number of AF cases pose a substantial burden on health care and society. Atrial fibrillation is associated with an increased risk of cardiovascular diseases and is an independent risk factor for stroke, worsening or development of new-onset heart failure (HF), and dementia (Michaud 2021). The Framingham Heart Study reported a significant sex difference in all-cause mortality from AF. The risk of mortality increased by a factor of 2.4 in men; in comparison, the risk in women increased by a factor of 3.5 (Benjamin 1998). Additional risk factors for developing AF include obesity, obstructive sleep apnea, alcohol use (particularly in excess), older age, hypertension, diabetes, cardiomyopathy, and family history. Early detection and screening of risk factors are crucial to curb the increasing rate of AF cases.

The underlying pathophysiology of AF is complex and multifactorial. Atrial fibrillation is characterized by a high atrial rate and discordant atrial activity, most commonly triggered by rapid ectopic firing of impulses originating at one or more pulmonary veins. Less commonly, AF can also be triggered by impulses formed outside the pulmonary vein tissues. Mechanisms of the rapid firing may involve automaticity, reentry, or triggered activity. The high atrial rate leads to structural and electrical remodeling of the atria, promoting fibrosis, which ultimately increases the subsequent development of recurrent and persistent AF (hence the phrase, "AF begets AF"). Continuous, long-term episodes of AF impair the ability to restore and maintain normal sinus rhythm. Unlike AF, in atrial flutter (AFL), the electrical activity in the atria is coordinated at 250–300 beats/minute, with around one-third to one-half of these impulses

traveling to the ventricles. The most common symptoms include palpitations, chest pain, dizziness, and reduction in exercise tolerance; however, many patients remain asymptomatic. Both AF and AFL result in irregularity of ventricular contraction, leading to potential hemodynamic changes and decreased cardiac output, tachycardia-induced left ventricular dysfunction (LVD), and cardiomyopathy. Uncontrolled tachycardia can lead to hypotension, syncope, and pulmonary edema requiring emergency management. Thromboembolic changes result from impaired blood flow as well as structural and functional remodeling, ultimately increasing the risk of stroke and systemic arterial thromboembolic disorders (Markides 2003). The cornerstones of AF and AFL management include symptomatic improvement with rate and rhythm control and prevention of thromboembolic complications. In patients with AFL, catheter ablation is preferred to pharmacologic cardioversion for maintenance of sinus rhythm because of its higher success rate compared with that in patients with AF. This chapter focuses on managing AF using rate and rhythm control strategies together with lifestyle interventions to reduce its associated burden and risk of recurrence.

BASELINE KNOWLEDGE STATEMENTS

Readers of this chapter are presumed to be familiar with the following:

- General knowledge of the pathophysiologic mechanisms contributing to AF
- Diagnostic criteria and assessment in AF
- Classification of antiarrhythmic drugs according to the Vaughan-Williams system
- Drug knowledge of the pharmacologic agents used for rate and rhythm control of AF

ADDITIONAL READINGS

The following free resources have additional background information on this topic:

- Atrial Fibrillation: Journal of the American College of Cardiology Council Perspective. J Am Coll Cardiol 2020;75:1689-713 (podcast).
- Atrial Fibrillation Focused Update – 2019. American Heart Association/American College of Cardiology/Heart Rhythm Society Guideline for the Management of Patients with Atrial Fibrillation. J Am Coll Cardiol 2019;74:104-32.
- 2020 European Society of Cardiology guidelines for the diagnosis and management of atrial fibrillation. Eur Heart J 2021;42:373-498.
- American Heart Association. Non-surgical Procedures for Atrial Fibrillation. Last reviewed July 31, 2016.

Table of common laboratory reference values.

Classification

Atrial fibrillation is classified according to the duration of episodes, pattern of recurrence (Table 1) and the presence or absence of moderate or severe mitral stenosis or a mechanical heart valve. In the 2020 update to the American College of Cardiology and American Heart Association (ACC/AHA) clinical performance and quality measures for adults with AF and AFL, valvular AF is defined as AF in the setting of moderate or severe mitral stenosis or a mechanical heart valve (Heidenreich 2021). Of importance, the term *nonvalvular AF* does not necessarily indicate the absence of valvular heart disease and is no longer a preferred term. Instead, AF in the absence of moderate or severe mitral stenosis or a mechanical heart valve is a more appropriate distinction.

Risk Factors for AF Progression

Most patients with newly diagnosed AF present with a paroxysmal pattern, and some AF cases progress to persistent AF within the first year of diagnosis. The percentage of patients whose disease progresses to persistent or permanent AF increases with time from the initial diagnosis (Kerr 2005). Around 20% of patients presenting with persistent AF have recurrence and difficulty maintaining normal sinus rhythm after cardioversion (Michaud 2021). Recurrence of AF or progression to persistent or permanent AF is associated with worsening atrial cardiomyopathy, increased risk of hospitalization from HF, treatment failure, and poor clinical outcomes.

In the Canadian Registry of Atrial Fibrillation (CARAF) study, increased age, significant aortic stenosis, or mitral regurgitation, left atrial enlargement, and cardiomyopathy were independently associated with progression of AF (Kerr 2005). Other predictors of progression include hypertension,

Table 1. Classification of AF

Types of AF	Description
Paroxysmal	Episode terminates spontaneously or with intervention within 7 days of onset
Persistent	Episode lasts > 7 days despite pharmacologic or electrical cardioversion
Longstanding	Continuous episodes lasting > 12 months
Permanent	Ongoing, long-term episodes for which patient and physician jointly decide not to pursue further treatment

AF = atrial fibrillation.

chronic obstructive pulmonary disease, and a history of stroke or transient ischemic attack (de Vos 2010). The Registry on Cardiac Rhythm Disorders Assessing the Control of Atrial Fibrillation (RECORD AF) observational cohort study reported that progression was higher in patients treated with rate control than rhythm control (27.6% vs. 5.8%, p<0.001) (Zhang 2013). Other independent predictors reported in RECORD AF included initial diagnosis of persistent AF compared with paroxysmal, older age, and history of stroke. Progression to persistent or sustained AF can potentially be prevented by early identification and management of risk factors and active treatment approaches.

CURRENT GUIDELINE-DIRECTED CARE ON RATE VS. RHYTHM CONTROL IN AF

Treatment approaches for AF are categorized as rate control (i.e., increasing the refractoriness of conduction through the atrioventricular [AV] node to slow ventricular rate) and rhythm control (i.e., restoring and maintaining normal sinus rhythm). Rate and rhythm control can be achieved through pharmacologic and nonpharmacologic measures. In patients who are hemodynamically stable, rate control is generally considered a sufficient initial approach. Rhythm control can be used to improve quality of life in patients who continue to be symptomatic despite adequate rate control. In patients who are hemodynamically unstable, rhythm control using emergency cardioversion is indicated rather than rate control. Clinical trials have shown no survival advantage of one strategy over the other; however, rate control is associated with a lower risk of adverse events than rhythm control using antiarrhythmic drugs. The 2014 AHA/ACC/Heart Rhythm Society (HRS) and 2020 European Society of Cardiology (ESC) guidelines suggest rate control as first line for AF management (Hindricks 2021; January 2019), particularly in asymptomatic patients.

Major Clinical Trials

Two large clinical trials, the Rate Control versus Electrical Cardioversion for Persistent Atrial Fibrillation (RACE) and the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM), evaluated strategies for rate or rhythm control in AF and reported that rhythm control was noninferior to rate control (Van Gelder 2002; Wyse 2002). In the RACE trial, the primary end point, a composite of cardiovascular death, hospital admissions for HF, thromboembolic complications, severe bleeding, pacemaker implantation, and severe adverse effects of therapy, occurred in 17.2% of patients in the rate control arm compared with 22.6% in the rhythm control arm (HR 0.73; 90% CI, 0.53–1.01; p=0.11) (Van Gelder 2002). Findings were similar in the AFFIRM trial, where the primary end point of mortality from any cause occurred in 25.9% of patients in the rate control arm compared with 26.7% in the rhythm control arm (HR 1.15; 95% CI, 0.99–1.34; p=0.08). Even though a trend toward increased mortality was seen in the rhythm control group of the AFFIRM trial, no statistically significant difference was noted between the two treatment strategies (Wyse 2002). According to these findings, an initial rate control strategy is reasonable in most patients with AF; however, certain patient characteristics and underlying comorbidities, such as heart failure with reduced ejection fraction (HFrEF), may favor pursuing early rhythm control using catheter ablation (Hindricks 2021).

Atrial fibrillation predisposes patients to developing LVD, and AF and LVD have common risk factors which precipitate each other, worsening clinical outcomes and patient prognosis. Further challenging AF management in patients with HFrEF is the limited selection of antiarrhythmic agents. Several drugs are contraindicated in underlying HFrEF, such as class IC antiarrhythmic drugs (Hindricks 2021). The Atrial Fibrillation and Congestive Heart Failure (AF-CHF) trial specifically evaluated whether a rhythm control strategy was associated with a reduced rate of cardiovascular mortality compared with rate control in patients with AF and an ejection fraction (EF) of 35% or less (Roy 2008). In the AF-CHF trial, patients enrolled in the rate control group received adjusted doses of a β-blocker and digoxin to achieve a target heart rate of less than 80 beats/minute. If the target heart rate was not achieved with drug therapies, AV nodal ablation with pacemaker implantation was recommended. The rhythm control group received amiodarone, with sotalol and dofetilide as alternative antiarrhythmics. Electrical cardioversion was performed if sinus rhythm was not restored after 6 weeks of initial antiarrhythmic treatment. Patients in the rhythm control group also received maximally tolerated doses of β-blockers for HF management. All eligible study participants received anticoagulation and angiotensin receptor blockers or angiotensin-converting enzyme inhibitors. Catheter ablation was not offered as a treatment option to the rhythm control group. The mean age of the study population was 67 years, and 82% of the patients were men. Most study patients had persistent AF, and more than 50% had previously been hospitalized for HF. The rate of the primary outcome of cardiovascular mortality was similar in the two groups after a mean follow-up of 37 months (27% vs. 25%; unadjusted HR 1.06; 95% CI, 0.86–1.3; p=0.59). Hospitalizations for AF were higher in the rhythm control group than in the rate control group (14% vs. 9%, p=0.001). During the study, 21% of patients from the rhythm control group crossed over to rate control because of the inability to maintain sinus rhythm. This is compared with 10% in the rate control arm who crossed over to rhythm control because of worsening HF (Roy 2008).

Results of the AF-CHF trial corroborated the findings of AFFIRM and RACE and suggest that routine rhythm control does not improve clinical outcomes over rate control, even in patients with concomitant AF and HFrEF (Roy 2008). Of importance, patients with HFrEF have an indication for rate control therapy (i.e., guideline-directed β-blocker) irrespective

of which approach is being considered. A trend toward increased mortality was not observed with rhythm control. This may be attributable to the higher rate of oral anticoagulant use, which, unlike in the AFFIRM trial, was recommended for all patients irrespective of rhythm (Roy 2008; Wyse 2002).

Early Rhythm Control vs. Guideline-Directed Usual Care

EAST-AFNET 4 Study

More recent clinical trials have assessed whether early rhythm control can reduce cardiovascular risk in patients with recently diagnosed AF (Packer 2021). Early rhythm control can prevent the development of AF-induced irreversible atrial damage. The Early Treatment of Atrial Fibrillation for Stroke Prevention Trial (EAST-AFNET 4) compared early rhythm control with evidence-based usual care on cardiovascular outcomes in patients having been given a diagnosis of AF within the past year. The trial enrolled 2789 patients with a diagnosis of AF within the past 12 months with high cardiovascular risk to randomly receive early rhythm control (treatment included antiarrhythmic drug, catheter ablation, or cardioversion) or usual care (initial rate control followed by rhythm control if symptoms persisted). High cardiovascular risk was defined as age older than 75, prior stroke or transient ischemic attack, or two of the following criteria: age older than 65, female, HF, hypertension, diabetes, severe coronary artery disease, chronic kidney disease, and left ventricular hypertrophy (LVH) with a diastolic septal wall width greater than 15 mm. Oral anticoagulation was required in all study participants irrespective of treatment intervention, with 91.2% of patients in the early rhythm control group receiving anticoagulation at baseline compared with 89.7% in usual care. At the 2-year follow-up, 88% of patients assigned to early rhythm control were still taking oral anticoagulants compared with 90.9% in the usual care group (Kirchhof 2020).

The trial was stopped for efficacy after a median of 5.1 years of follow-up per patient. The primary composite end point of death from cardiovascular causes, stroke, or hospitalization for worsening HF or acute coronary syndrome was less common in the rhythm control group than in usual care (3.9 vs. 5.0 per 100 person-years; HR 0.79; 96% CI, 0.66–0.94; p=0.005). The trial showed positive results for the primary composite end point with a small effect size and a modest absolute risk reduction of 1.1% per 100 person-years. The two treatment groups did not differ in the primary composite safety outcomes of death from any cause, stroke, or prespecified serious adverse events (16.6% early rhythm control vs. 16% usual care). The magnitude of change in LVD also did not differ between the two groups at the 2-year follow-up. Serious adverse events related to rhythm control therapy favored usual care (1.4%) over early rhythm control (4.9%). Sinus rhythm was maintained in 82.1% of patients in the early rhythm control group compared with 60.5% in usual care at the 2-year follow-up (Kirchhof 2020).

There are several key distinctions between the EAST-AFNET 4 study and former studies comparing rate and rhythm control, such as RACE and AFFIRM. First, the patient population enrolled in the EAST-AFNET 4 study differed from those enrolled in previous trials. Patients enrolled in the EAST-AFNET 4 study included those with AF diagnosed within 1 year compared with RACE, which included patients with persistent AF, and AFFIRM included patients at high risk of stroke and mortality. Second, treatment strategies differed among the three trials. In the EAST-AFNET 4 study, catheter ablation was used in 19.4% of patients at 2 years in the early rhythm control arm compared with AFFIRM, where 5.2% of patients received ablation after at least two trials of rate control therapy had failed, and in RACE, catheter ablation was not used. Selection of antiarrhythmic drugs in the rhythm control group also differed in the EAST-AFNET 4 study, with class IC antiarrhythmic drugs most commonly used, followed by amiodarone and dronedarone. On the contrary, AFFIRM used primarily amiodarone and sotalol. In RACE, patients in the rhythm control group primarily received sotalol, flecainide, or propafenone after electrical cardioversion. Results of the EAST-AFNET 4 study suggest that early rhythm control is associated with a lower risk of adverse cardiovascular outcomes in patients with high cardiovascular risks and AF diagnosed within 1 year.

RATE CONTROL IN AF

The recommended first-line approach for most patients with AF is ventricular rate control using drug therapy. This approach is sufficient in most patients to improve AF-related symptoms. Rate control can be achieved with drugs that increase the refractoriness of AV node and, as a result, reduce the number of impulses conducting to the ventricles. Rate control can also be achieved with nonpharmacologic measures by performing AV node ablation with pacemaker implantation. Atrioventricular node ablation is recommended in patients who are intolerant of, or unable to achieve symptomatic improvement on, rate and rhythm control pharmacotherapies and who are not eligible for catheter ablation, with the understanding that these patients will become pacemaker-dependent to maintain a normal heart rate (Hindricks 2021; January 2014).

Pharmacotherapies for Rate Control According to Patient Characteristics and Clinical Situation

Pharmacotherapies to achieve rate control include β-blockers, non-dihydropyridine calcium channel blockers (verapamil and diltiazem), digoxin, and amiodarone. Rate control therapy is often selected on the basis of patients' underlying comorbidities, symptom severity, and likelihood of success. β-Blockers and non-dihydropyridine calcium channel blockers are usually considered the initial therapy, depending on patient comorbidities. For example, in patients with underlying cardiovascular diseases such as HFrEF, β-blockers are

preferred, followed by digoxin, whereas in patients with underlying pulmonary disease, such as severe chronic obstructive pulmonary disease or asthma, non-dihydropyridine calcium channel blockers are preferred, and amiodarone and nonselective β-blockers are avoided. Digoxin and amiodarone are generally reserved as add-on therapies if the goal heart rate is not adequately achieved with maximally tolerated doses of first-line therapies.

Acute Rate Control

Intravenous β-blockers, such as metoprolol or esmolol, and non-dihydropyridine calcium channel blockers are generally considered first line over digoxin for acute rate control because of their rapid onset of action and lower risk of toxicity. Use of non-dihydropyridine calcium channel blockers is contraindicated in patients with acute myocardial infarction and LVD or HFrEF. De novo initiation of β-blockers should be avoided in patients with HFrEF presenting with acute worsening of HF. Digoxin can be considered as an add-on therapy to first-line treatment, particularly in patients with LVD. Caution should be exercised when using digoxin in patients with renal impairment. Intravenous amiodarone is an alternative drug that may be preferred in patients with existing or worsening LVD. Amiodarone can also be considered if other rate control therapies are contraindicated or ineffective. Combination therapies may be required in patients with an insufficient response to first-line therapy or in patients with underlying comorbidities when drugs with different mechanisms of action may be beneficial.

AF and HF

Treatment of patients with concurrent AF and HF is often challenging, given that both conditions aggravate and worsen the prognosis of each other. Heart rate control is paramount to prevent worsening of HF. Heart failure also increases the risk of thromboembolic disorders in patients with AF. In patients with HFrEF, preferred rate control therapies include β-blockers, digoxin, and amiodarone, whereas in HF with preserved EF, diltiazem and verapamil are viable therapies. In patients presenting with AF and worsening of HF, emergency or immediate electrical cardioversion can be considered.

β-Blockers

β-Blockers are generally considered first line for the long-term management of rate control, particularly in patients with cardiovascular comorbidities (e.g., coronary artery disease or HFrEF). Although chronic use of β-blockers has shown mortality benefit and decreased hospitalizations in HFrEF, a meta-analysis of their use in patients with HF and concurrent AF did not show a reduction in all-cause mortality (HR 0.97; 95% CI, 0.83–1.14; p=0.75); however, chronic β-blocker use showed a benefit in patients with HF and in sinus rhythm (HR 0.73; 95% CI, 0.67–0.80; p<0.001) (Kotecha 2014). In contrast, a subanalysis of the AF-CHF trial, which included 79% of patients with AF and HFrEF receiving a β-blocker at baseline, showed lower overall mortality with β-blocker use (HR 0.721; 95% CI, 0.549–0.945; p=0.0180) (Cadrin-Tourigny 2017). These findings may bring into question the magnitude of benefit of β-blockers in patients with HFrEF and AF, but their role as first-line therapy remains unchanged. The 2020 ESC guidelines for the diagnosis and management of AF recommend the use of β-blockers and digoxin for rate control in patients with HFrEF and reserve the use of amiodarone for the acute setting.

Digoxin

Digoxin is generally used an adjunctive therapy when additional rate control is needed despite optimal use of first-line therapies. Use of digoxin as an initial therapy was evaluated in the Rate Control Therapy Evaluation in Permanent Atrial Fibrillation (RATE-AF) trial. The RATE-AF was an open-label trial with blinded end point assessment comparing the effect of digoxin (dose range 62.5–250 mcg/day; mean dose 161 mcg/day) and bisoprolol (dose range 1.25–15 mg/day; mean dose 3.2 mg/day) on patient-reported quality of life. The RATE-AF enrolled patients 60 and older with permanent AF requiring rate control and symptoms of HF equivalent to New York Heart Association (NYHA) class II and above, irrespective of their baseline left ventricular ejection fraction (LVEF). Quality of life was assessed using the 36-Item Short Form Health Survey Physical Component Summary score. These scores were similar between the two groups at 6 months (adjusted mean difference 1.4; 95% CI, -1.1 to 3.8; p=0.28), but at 12 months, digoxin improved some measures of quality of life. Reduction in heart rate from baseline was similar in both groups at 12 months (adjusted mean difference 0.3; 95% CI, -3.0 to 3.5; p=0.87). Digoxin better improved the median N-terminal pro-brain natriuretic peptide (NT-proBNP) concentration at 12 months than bisoprolol, in which NT-proBNP concentrations were increased (adjusted mean difference 0.77; 95% CI, 0.64–0.92; p=0.005). Findings were similar with NYHA class, with digoxin showing greater reduction in NYHA class than bisoprolol at 12 months (p<0.001). Fewer patients reported treatment-related adverse events as listed in the product's package insert in the digoxin group than in the bisoprolol group (20 vs. 51 patients; p<0.001). Digoxin concentrations were not reported. The overall clinical significance of these findings is unknown because of the trial's design and size. The RATE-AF trial was the first to evaluate digoxin as the initial choice of therapy in patients with AF and HF; however, most of the patients enrolled had an LVEF greater than 50%. The mean LVEFs of study participants at baseline in the digoxin and bisoprolol groups were 56.2% and 57.6%, respectively, with only 17% of patients in the digoxin group and 13% of patients in the bisoprolol group having an LVEF less than 50% (Kotecha 2020).

Targets for Rate Control in AF

Atrial fibrillation with rapid ventricular rate can result in symptoms of palpitations and dyspnea and, if left untreated for a prolonged period, may progress to development of tachycardia-induced cardiomyopathy and HF. Although the optimal heart rate goals in AF remain unclear and may vary depending on underlying comorbidities as well as treatment response, the general recommendations are to aim for a lenient heart rate goal of less than 100–110 beats/minute. If the symptoms persist despite achieving a heart rate goal of less than 100–110 beats/minute, drug therapy can be titrated to achieve a stricter goal of less than 80 beats/minute (Hindricks 2021; January 2014). Strict heart rate control can be considered to reduce AF-related symptoms and improve quality of life and exercise tolerance but can increase adverse events such as bradycardia or syncope.

The RACE II trial showed that lenient rate control was noninferior to strict heart rate targets in patients with permanent AF. β-Blocker monotherapy for rate control was used in 45% of study participants, whereas 17% of study participants received a combination of β-blocker and digoxin. Target heart rate was achieved in 97.7% of patients in the lenient rate control arm compared with 67% of patients in the strict rate control arm ($p<0.001$). Fewer patients achieved the target heart rate in the strict control group because of drug-related adverse events or because target heart rate was difficult to achieve at maximally tolerated doses. The primary composite end point of death from cardiovascular causes, hospitalization for HF,

Patient Care Scenario

A 68-year-old woman presents to her cardiologist's office with palpitation and dyspnea occurring over the past 2 months. Her symptoms are affecting her daily performance. She reports increased shortness of breath when climbing 2 flights of stairs and having to rest often when going on her usual evening walks. Her medical history includes dyslipidemia, HFrEF, and seasonal allergies. Her current medications include furosemide 40 mg 1 tablet orally daily, sacubitril/valsartan 97/103 mg 1 tablet orally twice daily, metoprolol succinate 100 mg 1 tablet orally daily, spironolactone 25 mg 1 tablet orally daily, atorvastatin 40 mg 1 tablet orally daily, and loratadine 10 mg 1 tablet orally as needed for seasonal allergies. She has no known drug allergies. Her vital signs include blood pressure 130/78 mm Hg, heart rate 120–125 beats/minute, and respiratory rate 18 breaths/minute. Her ECG reveals an irregularly irregular rhythm with a narrow QRS complex and a heart rate of 120 beats/minute. An ECHO from last year was notable for an EF of 35%. A repeat ECHO in the office today reveals an EF of 25%–30% with no evidence of myocardial ischemia. Review of systems is notable for fatigue with no chest pain, weight gain, or peripheral edema. Pertinent laboratory results include Na 148 mEq/L, K 4.4 mEq/L, Cl 98 mEq/L, CO_2 26 mEq/L, and SCr 1.1 mg/dL. She is given a new diagnosis of persistent AF. According to a review of the information presented, what is an appropriate treatment plan to manage this patient's AF?

ANSWER

This patient's initial AF management should include symptom control with drug therapies that slow AV nodal conduction, with a long-term goal of minimizing cardiac complications as a result of uncontrolled heart rate. Ventricular rate in AF is an important determinant of hemodynamic consequences, and as such, therapy is usually warranted to control it. When AF develops, there is a loss of atrial kick, which consequently leads to a decline in cardiac output, particularly in patients with underlying LVD. When selecting an appropriate rate control strategy, patient presentation and comorbidities should be considered. Because this patient is hemodynamically stable, a rate control approach with pharmacotherapy would be preferred. If rate control results in symptomatic improvement, rhythm control is generally not needed. In the absence of contraindications, β-blockers are generally considered first line, with plans to titrate doses as needed to control symptoms. Although meta-analyses on the use of β-blockers in patients with HFrEF and AF have shown them not to affect mortality, they remain an effective therapy in light of the limitations and contraindications with the use of other rate-controlling drugs in this patient. Use of verapamil and diltiazem is contraindicated in a patient with LVD. β-Blocker doses can be titrated to achieve an initial target heart rate. Target heart rate goals for patients with HF remain uncertain. In most patients, a heart rate less than 110 beats/minute is acceptable if symptoms are controlled and ventricular function is preserved. This patient's metoprolol dose can be titrated from 100 mg to 150–200 mg daily. According to the information provided, the patient is not in acute decompensated HF; thus, titrating the β-blocker dose would be acceptable. If the β-blocker is insufficient to achieve the heart rate goal, digoxin can be considered as an add-on therapy to improve rate control. Digoxin would also be acceptable if titrating the β-blocker dose were contraindicated. Finally, amiodarone can also be considered as an alternative in patients with HFrEF. Data on the use of amiodarone as a rate control therapy in persistent AF are limited. Rhythm control is also a justifiable approach if the patient's symptoms progressively worsen or do not improve with rate control, or in an effort to minimize progressive declines in left ventricular function.

1. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation. J Am Coll Cardiol 2014;64:e1-e76.
2. Bunch TJ, Steinberg BA. Revisiting rate versus rhythm control in atrial fibrillation- timing matters. N Engl J Med 2020;383:1383-4.

stroke, systemic embolism, major bleeding, and arrhythmic events – including syncope, sustained ventricular tachycardia, cardiac arrest, life-threatening adverse effects of rate control drugs, and implantation of a pacemaker or cardioverter-defibrillator – was reported in 12.9% of patients in the lenient rate control group compared with 14.9% in the strict rate control group (HR 0.84; 90% CI, 0.58–1.21). Findings were similar between the groups for death from cardiovascular causes: 2.9% of patients in the lenient control group compared with 3.9% in the strict rate control group (HR 0.79; 90% CI, 0.3–1.65). As a result, the study concluded that lenient rate control was easier to achieve with noninferior cardiovascular outcomes compared with the strict rate control strategy at 3 years (Van Gelder 2010). Data supporting the optimal heart rate targets in patients with AF and heart rate goals in certain patient subsets, such as those with HFrEF, continue to remain uncertain. Target heart rate in AF should be individualized on the basis of patient factors, symptoms, concurrent comorbidities, and response to therapy.

RHYTHM CONTROL IN AF

The rhythm control approach in AF aims to restore and maintain sinus rhythm to improve quality of life in symptomatic patients and prevent the recurrence or progression of AF. Rhythm control can be achieved through a combination of pharmacologic and nonpharmacologic approaches, which include the use of antiarrhythmic drugs, electrical cardioversion, catheter ablation with pulmonary vein isolation, or surgery (e.g., MAZE procedure). Even though rate control is generally considered a first-line approach, certain patients may benefit from an initial rhythm control approach to prevent AF progression. Choice of initial rhythm control depends on patient factors, comorbidities, and long-term goals.

In patients who are hemodynamically unstable, rhythm control with synchronized direct current electrical cardioversion is preferred because it can rapidly be employed and yields the greatest success in converting to sinus rhythm. In patients who are hemodynamically stable, either pharmacologic or electrical cardioversion can be performed, with electrical conversion having a higher success rate. Antiarrhythmic drugs may be necessary to maintain normal sinus rhythm after successful electrical cardioversion and can also be used before electrical cardioversion for improved efficacy. Thromboembolic risk must be assessed before attempting non-emergency cardioversion. Therapy goals with the use of antiarrhythmic drugs include reducing AF-related symptoms and complications while balancing the risk of adverse drug effects.

Catheter ablation is another type of rhythm control used in patients with paroxysmal and persistent AF whose treatment with antiarrhythmic drugs has failed. Catheter ablation can also be considered as an initial rhythm control approach in a selected patient subset with underlying HFrEF. Catheter ablation with pulmonary vein isolation prevents the propagation of irritable foci from pulmonary veins, the most common origin of impulses in AF, terminating the abnormal rhythm. Catheter ablation has been the mainstay of ablative procedures; however, alternative ablative strategies have also been explored. Compared with antiarrhythmic drugs, catheter ablation better prevents AF progression and recurrence (Hindricks 2021; January 2014). Box 1 lists general considerations surrounding the indication and selection of antiarrhythmic drugs versus catheter ablation.

Box 1. Rhythm Control Using Pharmacologic Cardioversion vs. Catheter Ablation

Pharmacologic Cardioversion

- Reduces AF-related symptoms refractory to rate control
- Has modest efficacy in maintaining sinus rhythm
- AADs reduce, but do not eliminate, AF recurrence
- If one AAD does not achieve a clinically acceptable response, another AAD can be selected
- Safety and toxicity profile should guide treatment selection
- AADs may enhance the efficacy of electrical cardioversion

Catheter Ablation

- More effective than AADs in maintaining sinus rhythm and reducing AF burden
- Recommended in paroxysmal and persistent AF after unsuccessful treatment with an AAD (class I)[a]
- Can be considered first line in patients with AF and HFrEF to improve QOL and LV function, and potentially mortality (class IIa)[a]
- May be considered first line in selected patients with symptomatic paroxysmal (class IIa)[a] or persistent AF without major risk factors for recurrence (class IIb)[a]
- A reasonable alternative to pacemaker implantation in patients with tachy-brady syndrome (class IIa)[a]
- In asymptomatic AF, considered if patient-physician discussion favors ablation over other treatment plans

[a]Class of recommendation as provided in the 2020 ESC guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery.

AAD = antiarrhythmic drug; AF = atrial fibrillation; HFrEF = heart failure with reduced ejection fraction; LV = left ventricular; QOL = quality of life.

Information from: Calkins H, Hindricks G, Cappato R, et al. 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation. Heart Rhythm 2017;14:e275-e444; Hindricks G, Potpara T, Dagres N, et al. 2020 ESC guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J 2021;42:373-498.

ANTIARRHYTHMIC DRUGS TO RESTORE NORMAL SINUS RHYTHM IN AF

Pharmacologic cardioversion using antiarrhythmic drugs is indicated in patients who are hemodynamically stable and continue to be symptomatic after attempts to control

the ventricular rate. In these patients, antiarrhythmic drugs serve as a valuable option to reduce AF burden and AF-related symptoms; however, none of the antiarrhythmic drugs have shown a reduction in all-cause mortality (Dan 2018). Use of antiarrhythmic drugs should be weighed against any potential risk of toxicities and adverse effects. As such, antiarrhythmic drugs are selected on the basis of several patient- and drug-specific factors, including the presence and severity of cardiovascular diseases (e.g., HF, coronary artery disease, LVH), adverse effect profile, proarrhythmia risk, need for renal dose adjustment, and potential for drug interactions (Table 2).

For pharmacologic cardioversion, flecainide, propafenone, ibutilide, amiodarone, and dofetilide are considered the drugs of choice. Flecainide and propafenone are effective for pharmacologic cardioversion of AF in patients with no underlying structural heart disease (e.g., ischemic heart disease, LVH, and LVD). Use of flecainide and propafenone in patients with structural heart disease, and more specifically in patients with a history of myocardial infarction experiencing frequent premature ventricular contractions, is associated with an increased risk of mortality (Echt 1991). Oral flecainide and propafenone doses can be used for pharmacologic cardioversion in selected outpatients with paroxysmal AF as a pill-in-the-pocket approach, provided the first dose is administered in a monitored setting. The pill-in-the-pocket approach is slightly less effective than in-hospital cardioversion or continuous use of antiarrhythmic drugs, but is more convenient for patients (Dan 2018). Agents that slow AV nodal conduction, such as β-blockers or non-dihydropyridine calcium channel blockers, should be administered at least 30 minutes before class IC antiarrhythmic drugs to protect from 1:1 AV conduction in the event of underlying AFL. Amiodarone, though less effective than flecainide and propafenone for cardioversion, is acceptable in patients with underlying structural heart disease. Conversion to sinus rhythm usually takes much longer with amiodarone than with flecainide or propafenone. Amiodarone can also be initiated before electrical cardioversion in patients who will receive amiodarone long term as maintenance therapy to facilitate successful restoration of sinus rhythm. Similarly, dofetilide can also be used as pretreatment to electrical cardioversion. Dofetilide can be used in patients with structural heart disease and must be initiated in the hospital setting with close monitoring of renal function and ECG because of the increased risk of torsades de pointes. Dose adjustment requires readmission for monitoring (Hindricks 2021; January 2014).

Antiarrhythmic Drugs to Maintain Normal Sinus Rhythm in AF

After successful cardioversion, antiarrhythmic drugs can be used to reduce the recurrence of AF. As indicated earlier, antiarrhythmic drugs can also be used before electrical cardioversion to improve the success rate of the procedure and increase the likelihood of maintaining sinus rhythm. Selection of an antiarrhythmic drug for the maintenance of sinus rhythm is largely driven by the drug's safety profile and the patient's underlying comorbidities. A common approach used to select an antiarrhythmic drug is to first eliminate drugs with contraindications. Patient characteristics such as age, organ function, and concurrent drug therapies that may potentially alter the pharmacokinetics of the antiarrhythmic drug are considered, together with risk factors for QT prolongation and the drug's toxicity profile. Antiarrhythmic agents indicated for the maintenance of sinus rhythm include flecainide, propafenone, amiodarone, sotalol, dofetilide, and, less commonly, dronedarone. The 2014 AHA/ACC/HRS guidelines recommend dofetilide, dronedarone, or sotalol as first line in patients with coronary artery disease, followed by amiodarone as an alternative antiarrhythmic agent. In patients with underlying HF, amiodarone and dofetilide are recommended. In patients with no structural heart disease, any of the aforementioned antiarrhythmic agents can be used. Amiodarone is an alternative second-line treatment in patients without structural heart disease (January 2014). Amiodarone, though very effective at maintaining sinus rhythm, is generally considered as second line because of its extensive adverse effect profile and need for frequent monitoring. Although dronedarone has an improved toxicity profile over amiodarone, it is less effective than amiodarone and is contraindicated in patients with HF in NYHA class III and IV because of an increased risk of mortality.

Current Guideline Recommendation on the Use of Catheter Ablation in AF

Traditionally, catheter ablation has been reserved as a nonpharmacologic measure in highly symptomatic patients who could not tolerate antiarrhythmic drugs or for whom such therapies had failed or cannot tolerate antiarrhythmic drugs. This recommendation was based on studies showing higher complication rates with first-line ablation than with antiarrhythmic drugs (Morillo 2014; Cosedis Nielsen 2012). However, data on the use of catheter ablation are evolving as ablation techniques improve and complication rates decline. Currently, the 2019 AHA/ACC/HRS guideline update recommends catheter ablation as reasonable in patients with symptomatic AF and HFrEF to lower mortality and hospitalization from HF (class IIb recommendation) (January 2019). The 2020 ESC guidelines recommend catheter ablation as the first-line rhythm control therapy to reverse LVD in patients with paroxysmal or persistent AF with tachycardia-induced cardiomyopathy (class I recommendation) (Hindricks 2021).

Catheter Ablation Clinical Trials

Effect of Catheter Ablation vs. Antiarrhythmic Drugs as Initial Therapy on AF Recurrence

Recent evidence suggests that catheter ablation with radiofrequency or cryotherapy is a safe alternative to antiarrhythmic

Table 2. Comparison of Antiarrhythmic Drugs Used in AF

Vaughn-Williams Class	Drug	Contraindications	Clinical Pearls
IC	Flecainide Propafenone	• LV dysfunction • Ischemic heart disease • Sinus or AV node dysfunction	• Can be used as a "pill-in-the-pocket" approach to terminate out-of-hospital paroxysmal AF • Patient must be observed in a monitored setting before implementing this approach • Must be used with AV nodal blocking agents (e.g., β-blocker). This also applies to the pill-in-the-pocket approach • Not recommended in LVH • The most common adverse effects are hypotension, AFL, and ventricular arrythmia
III	Amiodarone	• Sinus or AV node dysfunction • Cardiogenic shock • Bradycardia without functioning pacemaker	• Associated with reduced AF recurrence compared with sotalol and dronedarone • Associated with several extracardiac adverse effects – pulmonary, hepatic, and thyroid toxicity, including neurologic disturbances, skin discoloration, optic neuritis • The most common noncardiac adverse effect include GI upset • The most common cardiac adverse effect is bradycardia • Least proarrhythmic agent, rarely causes torsades de pointes • Significant drug interactions
III	Dofetilide	• CrCl < 20 mL/min/1.73 m^2 • Prolonged QT interval (QTc > 440 msec) or 500 msec in patients with ventricular conduction abnormalities	• Requires inpatient admission for initiation because of high risk of proarrhythmia • Requires dose adjustment on the basis of renal function • Correct electrolyte abnormalities before and during use • Not recommended in severe LVH • The most common adverse effects include QT prolongation, headache, and dizziness • Significant drug interactions
III	Dronedarone	• Symptomatic HF • Second- or third-degree AV block or sick sinus syndrome • HR < 50 beats/min • QT interval ≥ 500 msec • Permanent or longstanding persistent AF • Severe hepatic impairment	• Lower incidence of thyroid-induced adverse events than amiodarone because of lack of iodine moieties • Less effective than amiodarone for rhythm control • Not evaluated in LVH • The most common adverse effects include bradycardia, GI upset, and QT prolongation • Significant drug interactions
III	Sotalol	• Second- or third-degree AV block • HR < 50 beats/min • QTc interval > 450 msec • CrCl < 40 mL/min/1.73 m^2 • Serum potassium < 4 mEq/L	• Consider initiation in a hospital setting with ECG monitoring in patients with increased risk of arrhythmia or torsades de pointes • Avoid use in patients with asthma or decompensated HF • The most common adverse effects include hypotension and dizziness

AF = atrial fibrillation; AFL = atrial flutter; AV = atrioventricular; HF = heart failure; HR = heart rate; LV = left ventricular; LVH = left ventricular hypertrophy; msec = milliseconds.

Information from: January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation. J Am Coll Cardiol 2014;64:e1-e76.

drugs for symptomatic improvement, maintenance of normal sinus rhythm, and prevention of AF recurrence and may be reasonable as an initial rhythm control strategy in symptomatic patients and patients with LVD (see Box 1) (Hindricks 2021). The Cryoballoon Catheter Ablation in Antiarrhythmic Drug Naive Paroxysmal Atrial Fibrillation (STOP AF First) trial evaluated cryoballoon catheter ablation as an initial choice of therapy compared with class I (flecainide, propafenone) and class III (amiodarone, sotalol, and dronedarone) antiarrhythmic drugs in patients with recurrent symptomatic paroxysmal AF. Patients with an enlarged left atrial diameter greater than 5 cm were excluded from the study, including patients with previous left atrial ablation or surgical procedures and those who had received treatment with class I or III antiarrhythmic drugs in the 7 days before study enrollment. The study participants in the catheter ablation group underwent pulmonary vein isolation within 30 days of randomization and were allowed to continue class I or III (except for amiodarone) antiarrhythmic drugs for up to 80 days after the procedure. In addition, use of β-blockers and non-dihydropyridine calcium channel blockers was permitted in both study groups. The primary end point was treatment success at 12 months. Treatment success was defined as freedom from early postprocedure AF recurrence, subsequent AF-related surgery or ablation, development of atrial arrhythmias, cardioversion, or use of class I or III antiarrhythmic drugs outside the 90-day study blanking period. The percentage of patients with treatment success at 12 months was 74.6% in the cryoballoon catheter ablation group (95% CI, 65–82) compared with 45% in the antiarrhythmic drug group (95% CI, 34.6–54.7) (p<0.001). The rate of serious adverse events was similar in the two groups at 14%. Quality-of-life end points were assessed in the catheter ablation group only and not compared with those of patients receiving antiarrhythmic drugs (Wazni 2021).

The Early Aggressive Invasive Intervention for Atrial Fibrillation (EARLY-AF) trial reported findings similar to STOP AF First. The EARLY-AF trial compared the use of catheter ablation with antiarrhythmic drugs in treatment-naive patients with paroxysmal or persistent AF diagnosed within the past 2 years. Patients with HF and NYHA class III and IV symptoms were excluded from the study. The most commonly used antiarrhythmic drug in the drug treatment group was flecainide. At 12 months, atrial tachyarrhythmia first recurred in 42.9% of patients in the catheter ablation group compared with 67.8% in the antiarrhythmic drug group (HR 0.48; 95% CI, 0.35–0.66; p<0.001). Serious adverse events occurred similarly across the two groups: 3.2% of patients in the catheter ablation group compared with 4% of patients in the antiarrhythmic drug group (Andrade 2021).

Both the STOP AF First and the EARLY-AF trial used an intention-to-treat analysis and reported that catheter ablation using the cryoballoon ablation procedure was superior to the use of antiarrhythmic drugs in patients with symptomatic paroxysmal and early persistent AF. The EARLY-AF trial used an implantable cardiac monitor to capture atrial arrhythmias, potentially capturing more AF episodes than the STOP AF First trial, which used intermittent noninvasive rhythm monitoring. Neither trial was adequately powered to assess cardiovascular outcomes. The type of catheter ablation used in these two trials differed from those used in previous trials, which used radiofrequency ablation and reported similar findings (Cosedis Nielsen 2012; Wazni 2005). Head-to-head trials comparing radiofrequency and cryoballoon ablation reported similar rates in arrhythmia-free survival (Hindricks 2021). Efficacy of first-line catheter ablation beyond 1 year is unknown.

Effect of Catheter Ablation vs. Antiarrhythmic Drugs on Quality of Life

When evaluating the effect of catheter ablation versus antiarrhythmic drugs on quality-of-life measures, the Catheter Ablation compared with Pharmacological Therapy for Atrial Fibrillation (CAPTAF) trial reported significantly improved quality of life as measured by the 36-Item Short Form Health Survey Physical Component Summary score at 12 months in patients treated with catheter ablation versus antiarrhythmic drugs (mean treatment difference 8.9 points; 95% CI, 3.1–14.7; p=0.003) (Blomström-Lundqvist 2019). However, data on the longer-term effect of catheter ablation on cardiovascular outcomes and mortality are not as promising.

Effect of Catheter Ablation vs. Antiarrhythmic Drugs on Mortality

The Catheter Ablation versus Antiarrhythmic Drug Therapy for Atrial Fibrillation (CABANA) trial evaluated the effect of catheter ablation on cardiovascular outcomes and mortality. This intention-to-treat, randomized trial showed that catheter ablation was not superior to antiarrhythmic therapy for the primary composite outcomes of death, disabling stroke, serious bleeding, or cardiac arrest at 5 years in patients with new-onset or untreated AF requiring treatment (8% vs. 9.2%; HR 0.86; 95% CI, 0.65–1.15; p=0.3). The CABANA trial reported that compared with antiarrhythmic drugs, catheter ablation was associated with lower rates of first AF recurrence (52.1% vs. 70.8%; HR 0.52; 95% CI, 0.45–0.60; p<0.0001), concordant with the findings of STOP AF First (Packer 2019). Recent findings indicate that at 12 months, catheter ablation is associated with improved quality of life and freedom from treatment failure; however, evidence is still lacking for a reduction in all-cause mortality, stroke, or major bleeding in the general patient population with AF treated with catheter ablation.

In the patient subset with AF and HF, use of catheter ablation has reduced all-cause mortality and AF recurrence, making it a reasonable rhythm control option in these patients (see Box 1). A recent subgroup analysis of the CABANA trial evaluated the effect of catheter ablation in patients with AF and HF in which 9.3% of patients had an EF of less than 40%. The primary composite end point was significantly reduced

with ablation (9% vs. 12.3%; HR 0.64; 95% CI, 0.41–0.99), as was all-cause mortality (6.1% vs. 9.3%; HR 0.57; 95% CI, 0.33–0.96) and AF recurrence (37% vs. 58%; HR 0.56; 95% CI, 0.42–0.74). No reductions in cardiovascular mortality or HF hospitalization were observed. Study participants in this subgroup analysis had NYHA class II–IV symptoms, and most had a preserved EF (Packer 2021).

The Catheter Ablation versus Standard Conventional Therapy in Patients with Left Ventricular Dysfunction and Atrial Fibrillation (CASTLE AF) trial compared the effect of catheter ablation with standard rate or rhythm control treatment specifically in patients with HFrEF. The primary composite end point of death from any cause or hospitalization for HF was reduced with catheter ablation (28.5% vs. 44.6%; HR 0.62; 95% CI, 0.43–0.87; p=0.007). The HF-related hospital admission rate was 20.7% in the catheter ablation group versus 35.9% in the medical therapy group (HR 0.56; 95% CI, 0.37–0.83; p=0.004) (Marrouche 2018). Findings from the CABANA subgroup analysis and CASTLE AF challenge the current recommendations that rate control is the appropriate strategy in patients with AF and HF and show that catheter ablation may be beneficial in selected patients with LVD where LVD may be a result of AF.

Place of Catheter Ablation in Current Practice

Data supporting catheter ablation over antiarrhythmic drugs as initial therapy in patients with symptomatic paroxysmal or persistent AF continue to evolve. The risk of AF recurrence and its associated burden, complications associated with catheter ablation, and cost of the procedure must be weighed against the potential benefits of the procedure. Of importance, catheter ablation reduces AF burden but is not curative. Patients with a significant cardiovascular history, duration of persistent AF longer than 2 years, severe mitral stenosis or regurgitation, untreated obstructive sleep apnea, and a large left atrium have a lower success rate with catheter ablation (Parikh 2010; Berruezo 2007). Risk of AF recurrence is highest in the first 3 months after pulmonary vein isolation, with recurrence rates of 20%–50%. A strong association between AF recurrence and time from AF diagnosis to ablation has also been reported. The recurrence rate is higher with increasing time from AF diagnosis to ablation, likely because of the progressive nature of AF when atrial inflammation and fibrosis make it increasingly difficult to maintain sinus rhythm (Chew 2020). Use of antiarrhythmic drugs temporarily for 6 weeks after catheter ablation has been shown to temporarily reduce AF recurrence; however, 6 months after ablation, patients who received antiarrhythmic drugs versus those who did not for 6 weeks had similar rates of AF recurrence (Leong-Sit 2011). For patients with recurrent AF after first catheter ablation, further management options consist of antiarrhythmic drugs or a subsequent ablation procedure, depending on a patient-physician discussion of the risk-benefit. Although catheter ablation may reduce the symptomatic burden in selected patients, it has not been shown to reduce the risk of stroke. Patients who undergo catheter ablation benefit from continued use of anticoagulants because of high rates of AF recurrence.

LIFESTYLE INTERVENTIONS

Obesity

Risk factor modification includes assessment and management of underlying conditions that may precipitate AF development or progression. Obesity is associated with increased left atrial volume, fibrosis, and inflammation, which increases the risk of AF progression and recurrence. Weight reduction with intensive risk factor management compared with general advice in patients with obesity resulted in fewer AF-related symptoms and lower AF recurrence (Abed 2013). The Long-Term Effect of Goal Directed Weight Management in an Atrial Fibrillation Cohort: A 5-Year Follow-Up Study (LEGACY) enrolled patients with a BMI of 27 kg/m^2 or greater and evaluated the impact of weight and risk factor management on AF burden, with optional participation in a dedicated physician-led weight management clinic or self-managed weight-loss program. The LEGACY trial excluded patients with significant cardiac valvulopathy, LVD, active malignancy, autoimmune or systemic inflammatory diseases, severe renal or hepatic failure, and less than 24 months of follow-up. Sustained weight loss was associated with a dose-dependent reduction in AF burden and maintenance of sinus rhythm. Weight fluctuation of over 5% was independently associated with the recurrence of AF symptoms (Pathak 2015).

Both the 2019 AHA/ACC/HRS guideline update and the 2020 ESC guidelines give a class I recommendation for weight loss and risk factor modification in overweight patients and patients with obesity with AF (Hindricks 2021; January 2019). For the overweight and obese population with AF, a 10% reduction in weight through routine exercise, together with management of diabetes, hyperlipidemia, and moderation of alcohol consumption, helps reduce AF burden (Chung 2020). Patients who lost and maintained over 10% of their baseline weight had a 6-fold greater likelihood of being arrhythmia free than those who lost less than 3% or gained weight. Bariatric surgery in patients with a BMI over 40 kg/m^2 before catheter ablation was associated with a 3-fold reduction in the risk of AF recurrence (Donnellan 2019). Physical activity with moderate-intensity exercise is recommended over excessive endurance exercise, which has been shown to promote AF, especially in patients older than 50 (Hindricks 2021).

Alcohol

Excessive alcohol consumption is associated with an increased risk of AF. A randomized trial of patients (n=140) with symptomatic paroxysmal or persistent AF showed that abstention from alcohol (defined as average consumption of 2 or fewer drinks per week) compared with consumption of

more than 10 alcoholic drinks per week was associated with reduced AF burden. At 6 months, recurrence of AF of more than 30 seconds' duration was reported in 53% of patients in the abstinence group compared with 73% in the control group that consumed more than 10 drinks per week. Time to AF recurrence was longer in the abstinence group than in the control group (HR 0.55; 95% CI, 0.36–0.84; p=0.005) (Voskoboinik 2020).

Other Lifestyle Factors

Unlike alcohol consumption, caffeine intake has not been linked with the development of AF. No evidence indicates that limiting caffeine intake is associated with reduced AF incidence or burden. High caffeine intake may lead to symptoms of palpitations unrelated to AF (Hindricks 2021).

Sleep-disordered breathing is strongly associated with the development of cardiovascular conditions and is common in patients with AF as well as in patients with other cardiovascular conditions such as HF and hypertension. Obesity and male sex are risk factors for sleep-disordered breathing. The severity of sleep-disordered breathing is directly proportional to AF incidence, burden, and response to treatment, with a reduced success rate reported with the use of antiarrhythmic drugs, catheter ablation, and electrical cardioversion. It is important to screen patients with AF for sleep-disordered breathing and the presence of obstructive sleep apnea. In patients with sleep-disordered breathing or obstructive sleep apnea, therapy with continuous positive airway pressure lowers the risk of AF recurrence after catheter ablation (Chung 2020).

CONCLUSION

Atrial fibrillation is associated with a high risk of cardiovascular complications, such as LVD, poor quality of life, and stroke, and an increased risk of hospitalization and mortality. Managing the symptoms and severity of AF includes addressing modifiable risk factors (e.g., weight, alcohol consumption, blood pressure), selecting and evaluating appropriate rate control therapies, and ensuring timely initiation of rhythm control with antiarrhythmic drugs, cardioversion, and/or catheter ablation, depending on patient preferences and symptom severity. Catheter ablation is an important nonpharmacologic treatment to reduce the burden of AF and improve symptoms, and its place in therapy continues to evolve as technology improves and additional data become available. Despite increased use of nonpharmacologic approaches, pharmacotherapy remains a cornerstone in AF management. Pharmacists must be knowledgeable of available therapies and be able to apply new evidence on the use of drug therapies and other interventions to improve the care of patients with AF.

Practice Points

Because of the complex pathophysiology of AF and its associated complications, a multidisciplinary collaborative approach to its management is important. Pharmacists are uniquely positioned to optimize treatment plans for patients with AF regardless of whether in an outpatient or inpatient setting. Pharmacists can discuss drugs for AF, signs and symptoms of drug-related toxicities, and strategies for managing risk factors.

- **Rate control with drugs that slow AV nodal conduction remains the initial approach to reduce the symptomatic burden in most patients with AF.**
- **The precise targets for heart rate in patients with AF are unclear. Clinical trials have evaluated lenient heart rate goals defined as less than 110 beats/minutes and stricter goals of less than 80 beats/minute. Target heart rate should be determined on the basis of symptomatic improvement and achievement of overall clinical outcomes.**
- **Most patients treated with initial rate control have a higher risk of AF recurrence and progression than patients treated with rhythm control.**
- **As an initial approach, rate and rhythm control have similar effects on mortality or quality of life.**
- **Rhythm control is directed to restore and maintain normal sinus rhythm and prevent electrical remodeling and atrial fibrosis. This can be achieved pharmacologically with the use of antiarrhythmic drugs or through electrical cardioversion, catheter ablation, or surgical procedures.**
- **Long-term use of antiarrhythmic drugs is often limited because of their extensive adverse effect profile, monitoring requirements, and high failure rates. Selection of the antiarrhythmic drug is largely based on its toxicity profile rather than its efficacy in maintaining sinus rhythm.**
- **Amiodarone is one of the most effective antiarrhythmic drugs for maintenance of sinus rhythm, but because of its extensive adverse effects, it is often considered a second-line therapy.**
- **Given the limitations and low efficacy of available antiarrhythmic drugs, catheter ablation has become more attractive in symptomatic patients who have not responded to previous attempts to restore sinus rhythm.**
- **New evidence supports the use of catheter ablation as an initial rhythm control approach in patients with AF and HF. In this patient subset, catheter ablation has been shown to improve quality-of-life measures and minimize AF recurrence, but not to improve cardiovascular mortality or reduce hospitalizations from HF.**
- **Risk factor assessment and modification is important in patients with AF. Evidence suggests that weight reduction with intensive risk factor management compared with general advice in patients with obesity results in fewer AF-related symptoms and less recurrence.**

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Self-Assessment Questions

1. According to the EAST-AFNET 4 trial, which one of the following patients would most likely benefit from early rhythm control treatment for atrial fibrillation (AF)?

   A. 56-year-old woman with hypertension and dyslipidemia, and AF diagnosed 2 years ago
   B. 76-year-old man with a history of stroke and AF diagnosed within the past year
   C. 66-year-old man with liver impairment and AF diagnosed within the past year
   D. 48-year-old woman with dyslipidemia and diabetes type II, and AF diagnosed 2 years ago

2. Which one of the following best evaluates the results reported in the landmark AFFIRM and RACE trials?

   A. Rhythm control is associated with significantly higher rates of cardiovascular mortality than rate control.
   B. Rate control is associated with improved quality-of-life measures compared with rhythm control.
   C. Rhythm control does not better reduce the rate of cardiovascular mortality than rate control.
   D. Rate control better reduces the risk of stroke and worsening heart failure (HF) compared with rhythm control.

3. A 78-year-old woman presents to the ED with a 2-day history of low-grade fever and generalized weakness. Her medical history includes hypertension and heart failure with reduced ejection fraction (HFrEF). In the ED, the patient suddenly feels her heart racing, accompanied by difficulty breathing and syncopal feeling. Her vital signs include heart rate 175–180 beats/minute, blood pressure 80/76 mm Hg, Sao_2 96% on room air, and temperature 100.2°C. An ECG reveals AF with a rapid ventricular rate. Which one of the following is best to recommend for this patient?

   A. Initiate intravenous metoprolol.
   B. Initiate intravenous diltiazem.
   C. Discuss with her the need for atrioventricular (AV) node ablation.
   D. Consider emergency direct electrical cardioversion.

4. A 62-year-old man presents to his primary care physician's office with intermittent episodes of heart palpitation and shortness of breath occurring over the past 2 weeks. His medical history includes hypertension, hypothyroidism, and seasonal rhinitis. On presentation, the patient is afebrile, with heart rate 145–160 beats/minute, respiratory rate 18 breaths/minute, blood pressure 140/90 mm Hg, and Sao_2 96% on room air. His current medications include levothyroxine 75 mcg 1 tablet orally daily, amlodipine 10 mg 1 tablet orally daily, and fexofenadine 180 mg 1 tablet orally daily as needed for seasonal allergies. His ECG confirms AF with a rapid ventricular rate. Which one of the following is best to recommend as the patient's initial treatment?

   A. Metoprolol
   B. Amiodarone
   C. Catheter ablation
   D. Emergency direct cardioversion

5. A 58-year-old woman presents to her cardiologist's office for a regular follow-up and reports palpitations and her heart racing for the past 2–3 days. Her medical history consists of HFrEF and hypertension. The patient's current medications include furosemide 40 mg 1 tablet orally daily, lisinopril 20 mg 1 tablet orally daily, metoprolol succinate 50 mg 1 tablet orally daily, and spironolactone 25 mg 1 tablet orally daily, which she has been stable on for around 3 months. Her vital signs include blood pressure 142/88 mm Hg, heart rate 125–130 beats/minute, and respiratory rate 18 breaths/minute. On physical examination, her lungs sound normal, and no edema is observed in her lower extremities. An ECG reveals she is in AF with an irregularly irregular rhythm and a narrow QRS complex. Her EF is 35%. Which one of the following is best to recommend for this patient's newly diagnosed AF?

   A. Increase the metoprolol succinate dose to 100 mg 1 tablet orally daily.
   B. Initiate diltiazem CD 240 mg 1 tablet orally daily.
   C. Initiate sotalol 80 mg 1 tablet orally twice daily.
   D. Initiate amiodarone 200 mg 1 tablet orally twice daily.

6. A 62-year-old woman presents to the ED with shortness of breath that has progressively worsened over the past 2 months. She recently noticed her legs appeared swollen and her shoes felt tight. Her medical history is significant for HFrEF and hypertension. The patient's home drugs include metoprolol succinate, furosemide, losartan, and spironolactone. The patient is afebrile with the following vital signs: blood pressure 144/88 mm Hg, heart rate 130–138 beats/minute, respiratory rate 20 breaths/minute, and Sao_2 94% on room air. Lung examination reveals diffuse rales on auscultation. Examination of the lower extremity reveals 2+ pitting edema, and her jugular vein pressure is elevated. An ECG reveals AF with a rapid ventricular rate. Echocardiography reveals an EF of 25%. Her renal function is stable. In addition to optimizing her volume overload, which one of the following intravenous drugs is best to recommend for managing this patient's new-onset AF?

   A. Esmolol

B. Amiodarone
C. Propafenone
D. Diltiazem

7. A 68-year-old man with persistent AF and hypertension presents to his cardiologist's office with concerns for intermittent dyspnea on exertion, fatigue, and dizziness, despite being on maximally tolerated rate control therapies. The patient's current regimen includes metoprolol succinate 100 mg 1 tablet orally daily, diltiazem CD 240 mg 1 tablet orally daily, and rivaroxaban 20 mg 1 tablet orally with the evening meal. On presentation, he is afebrile with heart rate 78–85 beats/minute, respiratory rate 18 breaths/minute, blood pressure 128/72 mm Hg, and SaO_2 94% on room air. An ECHO reveals an EF of 65% with left atrium moderately enlarged and left ventricular wall thickness of 1.6 cm consistent with hypertrophic cardiomyopathy. An ECG reveals irregularly irregular rhythm. If rhythm control to restore sinus rhythm is selected, which one of the following is best to recommend for this patient?

   A. Propafenone
   B. Flecainide
   C. Dronedarone
   D. Amiodarone

8. A 69-year-old woman with symptomatic persistent AF whose medical history is significant for HFrEF and hypertension presents to her cardiologist's office for further management of her AF symptoms. The patient is adequately rate controlled with metoprolol tartrate 50 mg 1 tablet twice daily and digoxin 250 mcg 1 tablet orally daily, but she continues to experience dyspnea upon exertion and fatigue. She takes warfarin 7 mg 1 tablet orally daily with an INR of 2.6 today. Her other medications include furosemide 40 mg 1 tablet orally daily and lisinopril 40 mg 1 tablet orally daily. Her vital signs are heart rate 70–76 beats/minute, blood pressure 118/72 mm Hg, respiratory rate 16 breaths/minute, and temperature 98.8°C. An ECG reveals an irregularly irregular rhythm with a ventricular rate of 74 beats/minute and QTc of 480 milliseconds. If pharmacologic cardioversion is considered as a next step for managing her AF symptoms, which one of the following is best to recommend for this patient?

   A. Amiodarone
   B. Dofetilide
   C. Sotalol
   D. Propafenone

9. A 66-year-old man presents to his cardiologist with continued symptoms of AF despite adequate rate control. His medical history includes chronic obstructive pulmonary disease, pulmonary fibrosis, HFrEF (NYHA class III), and coronary artery disease. The patient is tolerating his anticoagulant therapy with no signs or symptoms of bleeding or thromboembolism. His vital signs on presentation include heart rate 70 beats/minute, blood pressure 120/78 mm Hg, respiratory rate 14 breaths/minute, and temperature 98.6°C. He is willing to start antiarrhythmic therapy for better control of his AF symptoms. His laboratory test results are within normal limits. His ECHO reveals an EF of 35%, and the left ventricular wall measures 1.2 cm. An ECG reveals irregularly irregular rhythm with a QTc of 410 milliseconds. Which one of the following is best to recommend for this patient?

   A. Dronedarone
   B. Amiodarone
   C. Sotalol
   D. Dofetilide

10. A 45-year-old woman with no contributory medical history and a recent diagnosis of paroxysmal AF reports experiencing palpitations once or twice a year. Each episode lasts about 3–5 hours. The patient underwent successful cardioversion with flecainide in the hospital and is being discharged with flecainide 300 mg at the onset of AF symptoms. Her provider prescribes flecainide using the pill-in-the-pocket approach. Which one of the following is best to recommend for this patient?

   A. Flecainide 300 mg is sufficient to control her symptoms.
   B. Flecainide 300 mg should be combined with metoprolol succinate administered 30 minutes prior to flecainide.
   C. Flecainide 300 mg should be combined with low-dose digoxin taken orally daily.
   D. Flecainide is inappropriate and should be changed to amiodarone.

Questions 11 and 12 pertain to the following case.

D.P., a 65-year-old man with paroxysmal AF, underwent catheter ablation with pulmonary vein isolation last month. Today, he presents to the ED with acute mental status changes and severe palpitations. D.P.'s family member reports he was symptom free until yesterday. Since then, his symptoms have progressively worsened. His medical history also includes hypertension. D.P.'s current regimen includes metoprolol succinate 50 mg 1 tablet orally daily, losartan 50 mg 1 tablet orally daily, and rivaroxaban 20 mg 1 tablet with the evening meal. His vital signs include heart rate 130–140 beats/minute, blood pressure 82/70 mm Hg, and respiratory rate 19 breaths/minute. He is in acute renal failure. An ECG reveals an irregularly irregular rhythm with a narrow QRS complex and rapid ventricular rate. An ECHO reveals left ventricular hypertrophy (LVH) with a left ventricular ejection fraction (LVEF) of 55%.

11. Which one of the following is best to recommend to manage D.P.'s AF symptoms?

    A. Another catheter ablation
    B. Intravenous diltiazem
    C. Direct electrical cardioversion
    D. Oral dofetilide

12. After successful restoration of sinus rhythm, D.P. is symptom free. His renal function has normalized to baseline. Which one of the following is best to recommend for D.P. for optimal management of his AF?

    A. Discontinue rivaroxaban because his risk of thromboembolic disorders is low after successful catheter ablation.
    B. Discharge him on his home drugs with no additional medications needed after a successful catheter ablation.
    C. Initiate flecainide using a pill-in-the-pocket approach that the patient can use at the onset of AF symptoms.
    D. Initiate dofetilide to minimize the recurrence of AF in the short term until the success of ablation can be evaluated.

13. Given the findings of the AF-CHF and CASTLE AF trials, which one of the following best assesses use of the rhythm control approach in patients with AF and HF?

    A. Rhythm control with antiarrhythmic drugs or electrical cardioversion is associated with a statistically significant improvement in cardiovascular mortality compared with rate control.
    B. Rhythm control with antiarrhythmic drugs or electrical cardioversion is associated with a statistically significant decrease in hospitalization for AF compared with rate control.
    C. Rhythm control with catheter ablation is associated with a statistically significant reduction in death or hospitalization for worsening HF compared with rate or rhythm control with medical therapy.
    D. Rhythm control with catheter ablation is associated with a statistically significant increase in HF-related hospitalization compared with rate or rhythm control with medical therapy.

14. A 45-year-old man (height 62 inches, weight 102 kg) is scheduled to undergo catheter ablation for paroxysmal AF. His medical history includes hypertension and dyslipidemia. His current regimen includes metoprolol succinate 100 mg 1 tablet orally daily and rosuvastatin 20 mg 1 tablet orally daily. Which one of the following is best to recommend for this patient scheduled for catheter ablation?

    A. He is not a candidate for catheter ablation unless he reduces his weight by 10%.
    B. Bariatric surgery should be discussed before performing catheter ablation.
    C. If catheter ablation is successful, he should reduce his weight by 10% to prevent recurrence of AF.
    D. Success of catheter ablation is not affected by body weight, and he need not make any changes.

15. A 56-year-old woman (height 66 inches, weight 79 kg) whose medical history includes hypertension and persistent AF is referred to your clinic for risk assessment and management of her cardiovascular conditions. She reports worsening dyspnea and fatigue over the past 2 months. She has not tolerated antiarrhythmic drugs and almost always reverts to an irregularly irregular rhythm after a few months of treatment. Her current medications include carvedilol 6.25 mg 1 tablet orally twice daily and lisinopril 20 mg 1 tablet orally daily. She self-discontinued dofetilide because of adverse events. The patient plans to discuss catheter ablation with her cardiologist at her next appointment. She is a nonsmoker, believes she eats healthily, drinks 1 cup of coffee every morning and afternoon, and enjoys drinking 2 or 3 beers every night with her partner. Her vital signs include heart rate 78 beats/minute, blood pressure 132/82 mm Hg, respiratory rate 14 breaths/minute, and temperature 98.6°C. The patient's laboratory values are within normal limits, and her physical examination is unremarkable. Which one of the following is best to recommend for this patient to reduce her risk of complications from catheter ablation and recurrence of AF?

    A. Referral to a bariatric surgeon to discuss weight loss surgery.
    B. Limit caffeine to 1 cup of coffee every day.
    C. Limit alcohol consumption to no more than 2 drinks/week.
    D. Start high-intensity interval training to expedite weight loss before the procedure.