American Journal of Cardiovascular Drugs (2022) 22:475–496
https://doi.org/10.1007/s40256-022-00529-6

REVIEW ARTICLE

Atrial Fibrillation Management: A Comprehensive Review with a Focus on Pharmacotherapy, Rate, and Rhythm Control Strategies

Jordan L. Lacoste[1] · Thomas W. Szymanski[1] · Juan Carlo Avalon[2] · Galen Kabulski[1] · Utkarsh Kohli[3] · Nassir Marrouche[4] · Atul Singla[4] · Sudarshan Balla[5] · Arshad Jahangir[6]

Accepted: 24 February 2022 / Published online: 30 March 2022

Abstract
Atrial fibrillation (AF) is an increasingly common arrhythmia encountered in clinical practice that leads to a substantial increase in utilization of healthcare services and a decrease in the quality of life of patients. The prevalence of AF will continue to increase as the population ages and develops cardiac comorbidities; thus, prompt and effective treatment is important to help mitigate systemic resource utilization. Treatment of AF involves two tenets: prevention of stroke and systemic embolism and symptom control with either a rate or a rhythm control strategy. Historically, due to the safe nature of medications like beta-blockers and non-dihydropyridine calcium channel blockers, used in rate control, it has been the initial strategy used for symptom control in AF. Newer data suggest that a rhythm control strategy with antiarrhythmic medications with or without catheter ablation may lead to a reduction in major adverse cardiovascular events, particularly in patients newly diagnosed with AF. Modulation of factors that promote AF or its complications is another important aspect of the overall holistic management of AF. This review provides a comprehensive focus on the management of patients with AF and an in-depth review of pharmacotherapy of AF in the rate and rhythm control strategies.

1 Introduction

Atrial fibrillation (AF) remains the most common cardiac arrhythmia, providing clinical challenges for providers and patients. AF is associated with increased morbidity and mortality due to the increased risk of stroke, systemic embolism, and heart failure [1, 2]. Epidemiologically, AF is more common in the aging population, with the prevalence of AF doubling with each decade of life [3, 4]. As the incidence

Key Points

Atrial fibrillation remains the most common cardiac arrhythmia, posing clinical challenges for providers and patients.

Treatment involves prevention of stroke and systemic embolism and symptom control with a rate or a rhythm control strategy.

Historically, rate control has been the predominant initial strategy, with rhythm control deferred until refractory symptoms.

With advancing technology and patient monitoring, rhythm control-based strategies with or without ablative therapies are gaining popularity.

✉ Jordan L. Lacoste
Jordan.Lacoste.m@wvumedicine.org

1 Department of Pharmacy, WVU Medicine, 1 Medical Center Drive, Morgantown, WV 26505, USA

2 Department of Internal Medicine, West Virginia University School of Medicine, Morgantown, WV, USA

3 Department of Pediatrics, WVU School of Medicine, Morgantown, WV, USA

4 Department of Medicine, Section of Cardiology, Tulane University School of Medicine, New Orleans, LA, USA

5 Department of Cardiovascular and Thoracic Surgery, WVU School of Medicine, Morgantown, WV, USA

6 Center for Advanced Atrial Fibrillation Therapies at Aurora St. Luke's Medical Center, Milwaukee, WI 53215, USA

of AF increases with advancing age, the number of patients with AF is expected to grow in concert with an aging population, with projections estimating that 5–6 million people in the United States will have AF by 2050 as predicted in the ATRIA study [5]. Additional risk factors, such as obesity, hypertension, diabetes, hyperlipidemia, and coronary and valvular heart disease, are also contributory [6]. These conditions and their associated morbidities, such as stroke, have led to substantially increased healthcare costs, ranging from 6 billion to 26 billion dollars annually in the United States [7]. The socioeconomic impact of AF in conjunction with chronic cardiovascular disease cannot be understated, as hospitalization rates for AF and AF-associated complications continue to increase [8].

The diagnosis of AF is suggested by irregularly irregular R-R intervals in the absence of p-waves on a 12-lead electrocardiogram (ECG) [9]. The pathophysiology of AF is multifactorial. Repeated insults to atrial myocytes, through either ischemia or inflammation, lead to reparative fibrosis by activating necrotic and apoptotic signals [10]. Elevated filling pressures due to valvular heart disease or congestive heart failure (CHF) and ensuing chamber dilation also triggers inflammation and fibrosis, leading to atrial chamber remodeling at metabolic, electrical, and structural levels resulting in progression of atrial myopathy and AF. This remodeling disrupts the synchronized electrical signaling, primarily through ion channel dysfunction and myocyte uncoupling, leading to arrhythmogenesis [11]. The long-term effects of AF include increased risk of thromboembolic stroke or systemic emboli, CHF, cognitive dysfunction, and impairment in quality of life [12]. AF is categorized into the following types: paroxysmal (lasting < 7 days), persistent (lasting > 7 days or requiring cardioversion), long-standing persistent (lasting > 1 year), or permanent AF (shared decision made between patient and clinician to cease attempts to restore normal sinus rhythm [NSR]) [9].

Management of AF revolves around two basic principles: rate control or rhythm control and stroke prevention. The goal of rate control in AF is to slow the ventricular rate, while rhythm control aims to terminate AF and maintain NSR by modulating the substrate and triggers for AF by either pharmacological or ablative approaches. Stroke prevention with anticoagulant medications aims to prevent the formation of thrombi that increase the risk of stroke or systemic emboli. Each AF management strategy, however, carries a risk, as patients may have concomitant precluding comorbidities or preferences for a specific therapeutic strategy. Patients deemed at high risk for bleeding, or with a recent serious bleeding event, or contraindications to anticoagulation may be considered for mechanical methods of AF-related thrombus prevention, such as left atrial appendage (LAA) occlusion devices. These devices isolate the LAA from the systemic circulation, being a site where 90% of cardiogenic thrombi have been identified in AF patients. Our review focuses on the most up-to-date literature regarding pharmacological and interventional management of AF.

2 Assessment of Stroke and Bleeding Risk

AF increases the risk of ischemic stroke five times over that of patients in NSR [2]. The risk of stroke can be assessed by calculating the CHA_2DS_2-VASc score, which is currently recommended as the preferred risk stratification tool [13]. Compared with the previously recommended $CHADS_2$ score, the CHA_2DS_2-VASc score includes additional risk factors and improves risk prediction, particularly for patients at lower risk of thromboembolic complications [14, 15].

The CHA_2DS_2-VASc score assigns 1 point each to CHF, hypertension, diabetes mellitus, history of vascular disease, age ≥ 65, and female sex and 2 points each to age ≥ 75 and history of stroke or transient ischemic attack (TIA) [16, 17]. A risk score of 2 or greater in men and ≥ 3 in women identifies a high-risk group that benefits from long-term oral anticoagulation. Risk scores can also help quantify the risk of bleeding in patients with AF. The HAS-BLED score assigns 1 point to each of the following characteristics: hypertension, abnormal liver function or renal function, history of stroke, history of bleeding, labile international normalized ratio (INR), age > 65 years, and concomitant antiplatelet or non-steroidal anti-inflammatory drug (NSAID) use or alcohol use. A score ≥ 3 indicates a high risk for bleeding and a need for close monitoring of the patient, but should not be used as an absolute cutoff to withhold anticoagulation [13, 18].

2.1 Anticoagulation

Anticoagulation is recommended around the time of cardioversion regardless of the CHA_2DS_2-VASc score or method [9, 19]. For AF with a duration of < 48 h, administration of heparin or a direct-acting oral anticoagulant (DOAC) as soon as possible prior to cardioversion followed by long-term anticoagulation is recommended. For AF of 48 h duration or longer, warfarin or a DOAC is recommended at least 3 weeks before and at least 4 weeks after the cardioversion. Alternatively, transesophageal echocardiography can be performed to rule out left atrial thrombus before cardioversion. If immediate cardioversion for hemodynamic instability is required, anticoagulation with heparin, low-molecular-weight heparin, or a DOAC should be initiated as soon as possible prior to cardioversion and continued for at least 4 weeks [13]. The decision to prescribe long-term anticoagulation involves shared decision-making and consideration of the relative risks of stroke and bleeding. For patients with a CHA_2DS_2-VASc score of ≥ 2 in men or ≥ 3 or greater in women, long-term oral anticoagulation is recommended.

Current guidelines recommend DOACs, including dabigatran, rivaroxaban, apixaban, and edoxaban, as preferred agents over warfarin in DOAC-eligible patients [13]. Phase 3 randomized controlled trials that led to the approval of DOACs for AF showed non-inferiority or superiority of DOACs for the efficacy endpoints with fewer hemorrhagic events than vitamin K antagonists [20–23]. However, patients with valvular AF, defined as patients with AF with concomitant mechanical heart valve or moderate-severe mitral stenosis, should still receive warfarin in preference to DOACs. Patients who receive warfarin should have a target INR between 2 and 3. An in-depth discussion of oral anticoagulants used in AF is beyond the scope of this review.

3 Rate Control Strategy

Rate control is often the initial strategy for patients with AF due to familiarity and safety of the drugs. Rate control is preferred in those who have minimal symptoms when the ventricular rate is controlled. The initial rate control strategy involves a gradual titration of beta-blockers or non-dihydropyridine calcium channel blockers (non-DHP CCB) until the heart rate (HR) is adequately controlled. Beta-blockers and non-DHP CCB are equally efficacious at acutely controlling HR [24]. Beta-blockers are preferred in patients with a history of heart failure with reduced ejection fraction (HFrEF); non-DHP CCB are avoided in this population due to their negative inotropic effects. In patients with heart failure with preserved ejection fraction (HFpEF), a strategy of either diltiazem or beta-blockers is acceptable. These agents are initiated during the episode of AF in a hospital or ambulatory care setting. Hemodynamically unstable patients with AF and rapid ventricular rate response should undergo emergent synchronized direct-current cardioversion to restore NSR [31]. Rate control in a hospital setting can be complicated by hypotension or heart failure, precluding the use of a high dose of beta-blockers or non-DHP CCB, in which case, the use of intravenous (IV) amiodarone or digoxin is a reasonable approach. A combination of the agents can be used to achieve adequate rate control.

3.1 Randomized Trials of Rate Control and Target Heart Rate

Uncontrolled ventricular rates during AF may lead to severe symptoms and potentially predispose patients to tachycardia-induced cardiomyopathy. The 2014 guidelines for the management of AF suggested a HR goal of < 80 beats/min (bpm) at rest in symptomatic patients and < 110 bpm at rest in asymptomatic patients [19]. The RACE II study compared two rate control strategies by randomizing 614 patients with permanent AF to either a lenient (resting HR < 110 bpm) or a strict (resting HR < 80 bpm) rate control group in an open-label design. Patients enrolled in the trial had a mean age of 68 years, were 66% male, and had a mean duration of AF of 18 months [26]. The primary composite endpoint consisted of cardiovascular death, hospitalization for heart failure, stroke, systemic embolism, bleeding, and life-threatening arrhythmic events. At a median of 3 years, lenient rate control was non-inferior to strict rate control (12.9% lenient vs 14.9% strict; hazard ratio 0.84, 90% confidence interval [CI] 0.58–1.21; $p < 0.0001$ for noninferiority); neither individual components of the primary outcome nor symptoms differed between groups. Of note, patients in the strict rate control group achieved the resting HR goal less frequently than patients in the lenient rate control group (75.2% strict vs 97.7% lenient; $p < 0.001$), but had more follow-up visits to achieve the target HR (68 bpm strict vs 75 bpm lenient; $p < 0.001$). These results must be applied cautiously in patients with HFrEF as few patients were included. Current guidelines, therefore, recommend a resting HR goal of < 110 bpm for asymptomatic patients with preserved left ventricular systolic function and a target of < 80 bpm for symptomatic patients [19].

3.2 Medications Used for Rate Control

3.2.1 Vaughan-Williams Class II: Beta-Blockers

Beta-blockers antagonize the effect of the sympathetic nervous system and control ventricular rate in patients with AF [27, 28]. Due to the high degree of sympathetic innervation within the sinoatrial (SA) and atrioventricular (AV) nodes, beta-blockers are highly effective at reducing sinus node automaticity and slowing conduction through the AV node. In AF, beta-blockers slow AV nodal conduction velocity and extend the refractory period, thus decreasing the number of atrial stimuli that can be conducted to the ventricles, leading to a reduction in ventricular rate. Several beta-blockers are used in practice, including metoprolol, carvedilol, and esmolol. Generally, beta-blockers are initiated at low doses and are titrated to higher doses to achieve the desired ventricular rate. Beta-blockers' adverse effects include hypotension, masking of hypoglycemia symptoms in patients with diabetes, and worsening of bronchospastic disease in susceptible patients. Dosing and further information are summarized in Table 1. Beta-blockers are preferred agents for rate control and as synergistic agents for rhythm control, most effective in sympathetically mediated AF. Beta-blockers are preferred over calcium channel blocker in patients with HFrEF; however, patients with a history of asthma or reactive airway disease with chronic obstructive pulmonary disease (COPD) should be initiated on a beta-1 receptor cardio-selective beta-blocker to reduce the risk of bronchospasm [29].

3.2.2 Vaughan-Williams Class IV: Calcium Channel Blockers

The non-DHP CCBs, diltiazem and verapamil control ventricular rate in AF by inhibiting the voltage-gated slow calcium channels in the AV node, thereby reducing the number of electrical impulses conducted through the AV node to the ventricles [27]. Verapamil and diltiazem exhibit use-dependence and are therefore more effective at faster HRs. Both medications are negative inotropes and should be avoided in patients with HFrEF [27]. Diltiazem is the most commonly used non-DHP CCB and is available orally and intravenously. IV diltiazem is useful for ventricular rate control in AF with rapid ventricular rate and is given as an IV bolus of 0.25 mg/kg followed by infusion at 5–15 mg/h [30]. Alternatively, diltiazem can be given orally at a dosage of 30 mg every 6 h, titrated to the goal HR and blood pressure, and subsequently switched to a longer-acting preparation. Hypotension is the most common adverse effect of non-DHP CCB; therefore, blood pressure and HR should be monitored during therapy. See Table 1 for detailed information on the use of these agents. Calcium channel blockers may be preferred to beta-blockers in patients with a history of severe bronchospasm with asthma or COPD [31].

3.2.3 Vaughan-Williams Class V: Digoxin

Digoxin is a cardiac glycoside and has been used in medicine for hundreds of years. Its pharmacological effect on ventricular rate control is mainly exerted by the stimulation of the parasympathetic nervous system mediated through the vagus nerve, which leads to hyperpolarization of the AV nodal cells, reducing their excitability and conduction with a resultant decrease in ventricular rate [32]. Digoxin has a half-life of 1.5–2 days, so a loading dose is needed when treating AF with a rapid ventricular response. A loading dose of 1 mg is typically given as three separate doses: a single 0.5 mg IV dose followed by two doses of 0.25 mg separated by 6 h [32]. Alternatively, a weight-based regimen of 8–12 mcg/kg can be considered, with 50% of the dose given initially, followed by the remaining 50% given split as two doses separated by 6 h. Control of the ventricular rate is not immediate and may be delayed by up to 6 h following an initial loading dose. Digoxin is hemodynamically neutral, making it an appealing option for hypotensive patients. Due to digoxin's therapeutic effect of increasing parasympathetic tone, it is ineffective when used alone for rate control in situations of high sympathetic stimulation, such as sepsis or during exercise, but with a beta-blocker or calcium channel blocker, it has a synergistic effect in slowing the ventricular rate response. Digoxin is renally cleared, and dose reductions for both the loading and maintenance doses are recommended in patients with renal impairment. Digoxin has a narrow therapeutic index, with serum concentrations > 1.2 ng/mL associated with increased mortality and levels > 2 ng/mL associated with toxicity [33]. Trough levels should be checked at steady-state, generally 5–7 days (4–6 half-lives) after initiation. Early trough levels may be considered in patients with low body weight or renal impairment to ensure supratherapeutic levels are not reached early after a loading dose, knowing that levels will continue to increase as a steady-state concentration is attained. Notably, in patients with renal dysfunction, digoxin does not reach a steady-state concentration for several days to weeks [32]. Toxicity commonly manifests as anorexia, nausea, vomiting, visual disturbances, bradyarrhythmias, frequent ectopy, paroxysmal atrial tachycardia, or ventricular tachyarrhythmias. Chronic digoxin toxicity can often be managed by close observation, supportive measures, and cessation of digoxin [34]. Patients who present with cardiac arrest, life-threatening ventricular arrhythmias, hyperkalemia or are hemodynamically unstable should receive digoxin-specific antibody fragments [34]. Digoxin–antibody complexes will remain in the serum, and subsequent digoxin levels are not indicative of free, circulating digoxin. Re-dosing of digoxin-specific antibody fragments may be considered based on clinical worsening after an initial dose is given. Clinically significant drug–drug interactions with digoxin exist, including with amiodarone, flecainide, propafenone, and inhibitors of P-glycoprotein that necessitate dose reduction of digoxin by up to 50%.

4 Rhythm Control Strategy

Once the decision is made to pursue rhythm control, the patient must first be converted to NSR with direct-current cardioversion or antiarrhythmic medications after appropriate anticoagulation is initiated. The choice of antiarrhythmic drugs to maintain NSR is based upon the patient's underlying comorbidities (Fig. 1). Comorbidities of importance include coronary artery disease (CAD), HFrEF, COPD, renal dysfunction, long-QT syndromes, and age. In patients with CAD, class I antiarrhythmics (sodium channel blockers) are contraindicated due to increased mortality reported in the CAST trials, leaving sotalol, dofetilide, amiodarone, and dronedarone as potential therapeutic options [35, 36]. In patients with HFrEF, sodium channel blockers are also contraindicated due to their negative inotropic properties, proarrhythmic risk, and increased mortality. Dronedarone use has been associated with increased mortality in this population, especially with decompensated heart failure, thus leaving dofetilide, sotalol, and amiodarone as options for the maintenance of NSR [37]. Sotalol also possesses beta-blocking properties and is often avoided in HFrEF to maintain higher doses of beta-blockers as part of guideline-directed medical therapy, thus leaving dofetilide and amiodarone as options in

Table 1 Medications for ventricular rate control

Class	Drug	Dosing	Renal/hepatic adjustment	Contraindications	Adverse effects	Clinical pearls
Class II: beta-blockers	Metoprolol tartrate	Oral: 12.5–50 mg every 6h–12h Max: total daily dose of 400 mg IV: 2.5–5 mg every 5 min Max: 15 mg total dose	Renal impairment: None Hepatic impairment: Use cautiously, start with a lower dose and titrate gradually	2nd or 3rd degree heart block	Hypotension, bradycardia, masking of hypoglycemia	-Start with a low dose in patients with heart failure with reduced ejection fraction -If q12h dosing is not effective, consider a shorter interval such as q8h -Consider switching to long acting prior to discharge
	Metoprolol succinate	Oral: 50–200 mg every 12h–24h Max: total daily dose 400 mg	Renal impairment: None Hepatic impairment: Use cautiously, start with a lower dose and titrate gradually	2nd or 3rd degree heart block	Hypotension, bradycardia, masking of hypoglycemia	-May exhibit wearing off effect, consider switching to q12h dosing if HR increasing prior to receiving the dose
	Esmolol	IV: 500 mcg/kg loading dose 50 mcg/kg/min continuous infusion Max: 200 mcg/kg/min	Renal impairment: None Hepatic impairment: None	2nd or 3rd degree heart block	Hypotension, bradycardia, fluid overload, hyperkalemia, extravasation	-Large fluid volume required to administer, consider alternative in patients with heart failure -Often causes profound hypotension -Steady state achieved 30 min after titration -Titrate no faster than every 4 min
	Carvedilol	Oral: 3.125–25 mg BID	Renal impairment: None Hepatic impairment: None	2nd or 3rd degree heart block	Hypotension, bradycardia	-Start with a low dose in patients with heart failure with reduced ejection fraction
Class IV: calcium channel blockers	Diltiazem	Oral: IR: 30–60 mg every 6h ER: 120–480 mg every 12h–24h IV: 0.25 mg/kg bolus (may repeat 0.35 mg/kg bolus after 15 min) 5–15 mg/h continuous infusion	Renal impairment: None Hepatic impairment: Extensively metabolized hepatically, accumulates in cirrhosis	2nd or 3rd degree heart block, left ventricular dysfunction	Hypotension, bradycardia, peripheral edema, acute decompensated heart failure	-Avoid use in heart failure with reduced ejection fraction due to negative inotropy; may precipitate exacerbation -May titrate infusion every 15–30 min -Continuous infusion generally used for < 24 h due to drug accumulation -Conversion from IV to PO: -5 mg/h = 180 mg/day -10 mg/h = 200–260 mg/day -15 mg/h = 480 mg/day

Table 1 (continued)

Class	Drug	Dosing	Renal/hepatic adjustment	Contraindications	Adverse effects	Clinical pearls
	Verapamil	Oral: 180–480 mg daily (ER) IV: 0.075−0.15 mg/kg IV bolus over 2 min; may give an additional 10.0 mg after 30 min if no response, then 0.005 mg/kg/min infusion	Renal impairment: None recommended. Accumulates with renal dysfunction Hepatic impairment: 20-30% dose reduction recommended. Extensively metabolized hepatically, accumulates in cirrhosis	2nd or 3rd degree heart block, left ventricular dysfunction	Hypotension, bradycardia, peripheral edema, acute decompensated heart failure	-Avoid use in heart failure with reduced ejection fraction due to negative inotropy; may precipitate exacerbation
Class V: miscellaneous	Digoxin	IV: Empiric strategy: 1 mg IV given as 500 mcg IV followed by two 250-mcg doses every 6 h Individualized strategy: 8–12 mcg/kg (IBW) given as 50% total dose IV followed by 25% of the total dose given every 6 h for 2 doses Oral: Maintenance dose: 62.5–250 mcg daily	Renal impairment: Use cautiously Loading dose: If CrCl < 15 mL/min, reduce total dose by 50% Maintenance dose: CrCl > 60: No adjustment CrCl 45–60: 62.5–125 mcg daily CrCl 30–45: 62.5 mcg daily CrCl < 30: avoid use Hepatic impairment: None	End-stage renal disease	Atrioventricular block, nausea, diarrhea Toxicity: ventricular tachycardia, anorexia, altered mental status, high degree heart block, yellow colored vision	-Hemodynamically neutral; useful in patients with hypotension -Less effective in patients with high sympathetic tone such as sepsis, exercise -Increased mortality with levels > 1.2 ng/mL, levels > 2.0 ng/mL are associated with toxicity

CrCl creatinine clearance, *ER* extended release, *IBW* ideal body weight, *IR* immediate release, *IV* intravenous

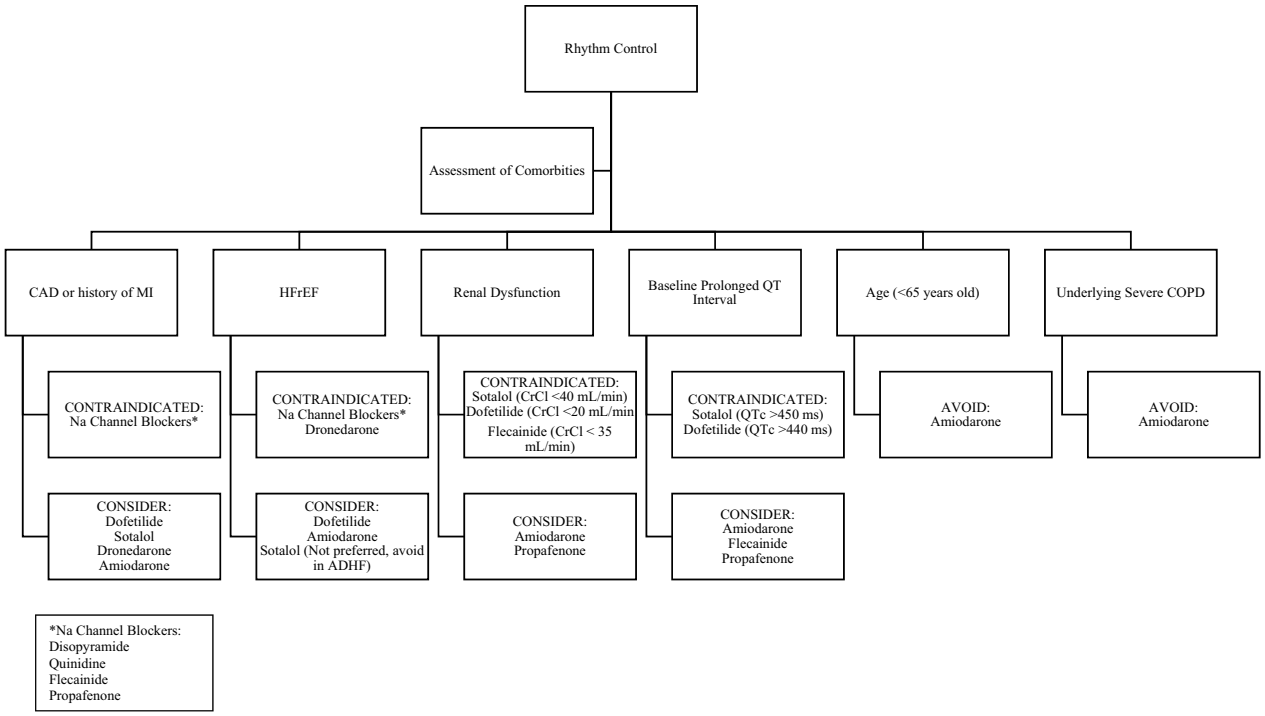

Fig. 1 Rhythm control medication decision tree. *ADHF* acute decompensated heart failure, *CAD* coronary artery disease, *COPD* chronic obstructive pulmonary disease, *CrCl* creatinine clearance, *HFrEF* heart failure with reduced ejection fraction, *MI* myocardial infarction, *QTc* corrected QT

these patients. The choice between dofetilide and amiodarone is based on age, renal function, baseline corrected QT (QTc) interval, and the presence of pulmonary disease. For patients without underlying cardiac comorbidities, sodium channel blockers, particularly the class Ic medications flecainide and propafenone, are commonly used. Once the antiarrhythmic drug is chosen, the patient should be monitored for recurrence of AF and adverse effects. If a patient experiences an adverse event, especially proarrhythmias, the offending agent should be withdrawn and considered a treatment failure if the patient was on an appropriate agent and dose. Consideration of an antiarrhythmic drug from a different class may be considered if contraindications are not present, as can catheter-based or surgical ablation.

4.1 Medications Used for Rhythm Control

4.1.1 Vaughan-Williams Class I: Sodium Channel Blockers

Sodium channel blockers exert pharmacological antiarrhythmic action by inhibition of the voltage-gated sodium channels that slow the rapid upstroke of phase 0 of the propagating action potential in atrial, ventricular, and His-Purkinje fibers [27, 28]. Inhibition of sodium channels leads to a slowing conduction velocity, an extension of the effective refractory period, decreased excitability, and reduced automaticity. This effect is manifested on an ECG as prolongation of the QRS duration. Therefore, excessive QRS prolongation may point to supratherapeutic sodium channel blockade, necessitating dose reduction. Sodium channel blockade builds, and the slowing of phase 0 of depolarization occurs more at faster than slower HRs. This property is known as "use dependence" and is ubiquitous to this class. Sodium channel blockers are a diverse class of medications, and are divided into three distinct subclasses: Ia, Ib, and Ic, based on additional electropharmacological effects on cardiac repolarization and action potential duration by their inhibitory effect on potassium channels.

4.1.1.1 Class Ia Sodium Channel Blockers Class Ia antiarrhythmics have moderate phase 0 sodium channel blockade and potassium channel blockade, leading to inhibition of potassium efflux during phases 3 and 4 of the action potential [27, 38]. Their net effect on the action potential is a slowing of conduction velocity and prolongation of the action potential, leading to both QRS widening and QTc interval prolongation on the ECG [38]. Though class Ia agents are useful for both atrial and ventricular arrhythmias, they have largely fallen out of favor due to poor tolerability [38, 39].

4.1.1.2 Disopyramide Disopyramide possesses both sodium and potassium channel blocking effects and is mod-

erately effective for both atrial and ventricular arrhythmias [27]. Disopyramide has anticholinergic properties and decreases the impact of the parasympathetic nervous system on the heart, leading to enhanced sinus node activity and AV nodal conduction. Pharmacokinetics of disopyramide are shown in Table 2. Disopyramide is converted to an active metabolite, which may be responsible for its anticholinergic side effects. Disopyramide's half-life is prolonged in patients with renal disease, hepatic disease, and HFrEF [40]. A typical dosage at the initiation of therapy is 100 mg every 8 h, and slow titration is recommended every 3 days. Therapeutic drug monitoring is possible, although not routinely performed. Additional pharmacological properties of disopyramide, notably negative inotropic, anticholinergic, and vasoconstrictive effects, limit its use. Because of its anticholinergic properties, disopyramide may be useful in AF that is vagally mediated. Due to the significant combined negative inotropic and vasoconstrictive effects, decompensation of a previously stable patient with heart failure is possible, and HFrEF is an absolute contraindication to disopyramide therapy [27, 38, 40]. Due to potassium channel blockade, the QTc interval should be monitored as QTc-prolongation and torsades de pointes (TdP) has been reported in patients receiving disopyramide [38, 40]. Additionally, acceleration of atrial flutter to 1:1 conduction and exacerbation of reentrant circuits may occur. Use with an AV nodal blocker, such as a beta-blocker, is recommended to mitigate this risk [27, 38–40]. In addition to the antiarrhythmic effect to suppress AF, the negative inotropic effect of disopyramide is useful in patients with hypertrophic obstructive cardiomyopathy to reduce the dynamic outflow tract obstruction in symptomatic patients [41]

4.1.1.3 Quinidine Originally used as an antimalarial drug, D-quinine (quinidine) has been used for atrial arrhythmias since 1920. Pharmacologically, quinidine is similar to disopyramide, as they both block sodium and potassium channels and have negative inotropic effects [27, 38]. Quinidine also possesses alpha-adrenergic receptor blocking effects, leading to vasodilation and subsequent rebound tachycardia; the overall effect is a net neutral effect on HR. Although effective for the treatment of AF, with more than 50% of patients remaining in NSR at 1 year, quinidine use has largely been replaced by safer and more effective agents [38, 39]. Severe gastrointestinal symptoms, such as nausea, vomiting, and diarrhea, warrant discontinuation because they can cause electrolyte abnormalities that may result in exacerbation of arrhythmias [42]. Acceleration of atrial flutter to 1:1 conduction can also occur, and quinidine should be given with an AV nodal blocker to reduce this risk. Due to the risk of TdP, admission to the hospital is recommended, with ECG monitoring to assess for significant (25–50%) increases in QRS duration or QTc interval, with the initial five doses of quinidine. If an excessive increase in either is noted, an alternative antiarrhythmic is recommended [38, 42]. Due to the modest efficacy and concern regarding safety, quinidine is rarely used as an antiarrhythmic agent for AF control.

4.1.1.4 Procainamide Like disopyramide and quinidine, procainamide blocks sodium and potassium channels, possesses moderate negative inotropic effects. and leads to infusion rate-dependent arteriolar dilation [43]. Potassium channel blockade is primarily mediated by an active metabolite, *N*-acetyl procainamide (NAPA) [38, 43]. Procainamide has found its place as a primary drug for patients presenting with AF with pre-excited ventricular conduction through an accessory bypass pathway [27, 38, 43]. Procainamide is only available as an IV infusion in the United States. Another indication for IV procainamide use is in patients suspected of Brugada syndrome, where the sodium channel blockade of procainamide may help unmask a diagnostic type 1 Brugada ECG pattern. Approximately 30–60% of procainamide is excreted unchanged in the urine, and 6–52% is metabolized via acetylation to NAPA, the primary active metabolite; NAPA itself is cleared renally (85%). Renal impairment, therefore, causes accumulation of NAPA and can result in significant QTc interval prolongation that increases the risk for TdP [43, 44]. A loading dose of procainamide of 10–17 mg/kg, based on ideal body weight, is administered at a rate of 20–50 mg/min. The loading dose is followed by a maintenance infusion of 1–4 mg/min if required [43, 44]. A maximum loading dose of 12 mg/kg should be used in patients with HFrEF due to reduced clearance and negative inotropic effects [45]. An alternative standardized dosing strategy is a loading dose of 1000 mg over 60 min, followed by a continuous infusion [46]. If hypotension occurs during infusion, the rate should first be decreased, then withheld if no improvement is noted. During infusion, patients should be on continuous telemetry, with serial monitoring of the QRS and QTc intervals due to the risk of TdP. If the QRS duration is prolonged by > 50% from baseline, or the QTc interval increases by > 25%, procainamide should be stopped, and an alternative antiarrhythmic is recommended [39, 43]. Doses should be adjusted for renal dysfunction, hepatic dysfunction, and HFrEF (see Table 2). Therapeutic drug monitoring is recommended for patients with adverse effects, HFrEF, and renal or hepatic impairment to guide dosing [43]. A therapeutic serum concentration for procainamide ranges from 4 to 10 mcg/mL for the parent drug and 10–25 mcg/mL for NAPA. Procainamide use is contraindicated in patients with a history of complete heart block, second-degree AV block without a pacemaker, myasthenia gravis, history of systemic lupus erythematous, history of or active TdP, or a baseline prolonged QTc interval [44]. Substantial adverse effects associated with the use of procainamide have led to a decline in its use. Agranulocytosis,

Table 2 Medications for rhythm control

Class	Drug	Dosing	Pharmacokinetics	Dose adjustments	Contraindications	Adverse effects	Efficacy	Clinical pearls
Class Ia: sodium channel blockers	Disopyramide	Oral: IR: 100–200 mg every 6h CR: 200–400 mg every 12h	Bioavailability: 90–95% Vd: 0.8–2 L/kg $T_{½}$: 6–8 h Metabolism: 40% hepatic to active metabolite Excretion: 60% in urine as unchanged drug	Renal impairment: CrCl > 40: No adjustment, avoid CR formulation CrCl 30–40: 100 mg q8h CrCl 15–30: 100 mg q12h CrCl < 15: 100 mg q24h Hepatic impairment: Use low doses, titrate cautiously	HFrEF, CAD, BPH, urinary retention, glaucoma, myasthenia gravis	Xerostomia, constipation, urinary hesitancy, precipitation of CHF exacerbation, 1:1 atrial flutter, VT, TdP	NSR at 6 months: 67% [96]	-Significant negative inotropic and vasoconstrictive effects -Poorly tolerated due to anticholinergic side effects -Patients should be screened for HFrEF and CAD prior to initiation -Leads to QRS widening and QTc prolongation -Combine with an AV nodal blocker (beta-blocker/non-DHP CCB) to reduce the risk of 1:1 atrial flutter -Useful in AF with comorbid HOCM
	Quinidine	Oral: IR: 400 mg every 6h ER: 648 mg every 8h	Bioavailability: 70% Vd: 2–3 L/kg, 0.5 L/kg in CHF $T_{½}$: 6–8 h, prolonged with hepatic/renal dysfunction, CHF Metabolism: 50–90% hepatic to inactive drug Excretion: 5–20% as unchanged drug	Renal impairment: CrCl > 10: No adjustment CrCl < 10: Administer 75% of the normal dose iHD: Administer doses after dialysis Hepatic impairment: No adjustments but accumulation is possible	HFrEF, CAD, myasthenia gravis	Diarrhea, nausea, vomiting, hypotension, precipitation of CHF exacerbation, 1:1 atrial flutter, VT, TdP, worsening of AV nodal function	NSR at 6 months: 58% [97]	-Increased risk of mortality when used for AF [97] -Significant negative inotropic effects -Poorly tolerated due to nausea, vomiting and diarrhea -Patients should be screened for HFrEF and CAD prior to initiation -If QRS duration of QTc interval prolong greater than 30% from baseline or new onset bundle branch block occur, discontinue quinidine

Table 2 (continued)

Class	Drug	Dosing	Pharmacokinetics	Dose adjustments	Contraindications	Adverse effects	Efficacy	Clinical pearls
	Procainamide	IV: Loading dose: 10–17 mg/kg (IBW) or 1000 mg over 60 min Maintenance dose: 1–4 mg/min	Vd: 2 L/kg, decreased in hepatic dysfunction, CHF $T_{½}$: Procainamide: 2–5 h prolonged in CHF, renal dysfunction NAPA: 6–8 h, up to 42 h in renal dysfunction Metabolism: 6–52% metabolized to NAPA via NAT2 Excretion: Procainamide: 30–60% in urine NAPA: 85% in urine	Renal impairment: CrCl > 50: No adjustment CrCl 10–50: Reduce maintenance dose by 25–50% CrCl < 10: Reduce maintenance dose by 50–75% and monitor procainamide/NAPA levels Hepatic: Child-Pugh 8–10: Reduce initial continuous infusion dose by 25% Child-Pugh > 10: Reduce initial continuous infusion dose by 50% Heart failure: Limit loading dose to 12 mg/kg (IBW) and reduce maintenance dose by 25–50%	History of TdP, myasthenia gravis, baseline prolonged QTc interval, complete heart block	Hypotension, nausea, vomiting, diarrhea, lupus-like syndrome, drug fever, thrombocytopenia, VT, TdP	Acute conversion: 52% after loading dose [98]	-Drug of choice for AF RVR with WPW -Active metabolite NAPA causes QTc prolongation -Causes infusion related hypotension; decrease infusion rate if hypotension occurs -Accumulates in setting of HF, hepatic dysfunction, renal dysfunction -May worsen HF due to negative inotropic effects -If QRS duration increases > 50% or QTc prolongs > 25% or > 500 ms consider discontinuation

Table 2 (continued)

Class	Drug	Dosing	Pharmacokinetics	Dose adjustments	Contraindications	Adverse effects	Efficacy	Clinical pearls
Class Ic: sodium channel blockers	Flecainide	Oral: 50 mg every 12h Max: 400 mg/day Acute cardioversion: single dose of 300 mg (> 70 kg) or 200 mg (< 70 kg)	Bioavailability: 95% Vd: 8.7 L/kg $T_{½}$: 13 h, prolonged in CHF and renal dysfunction Metabolism: Hepatic via CYP2D6 Excretion: urine: 30% as unchanged drug	Renal impairment: CrCl < 35: initiate lowest dose and titrate slowly while monitoring QRS duration Hepatic impairment: Consider other agents; if used, monitor drug levels and QRS duration	HFrEF, history of MI, high-degree AV block, baseline prolonged QRS	Dizziness, visual disturbances, dyspnea, tremor, precipitation of CHF exacerbation, 1:1 atrial flutter, VT, worsening AV block	Acute conversion: 80% 3 h after dose NSR at 9 months: 65% [57]	-Patients should be screened for history of MI and HFrEF prior to initiation -Avoid use in patients with a prolonged QRS duration/bundle branch blocks -Combine with an AV nodal blocker (beta-blocker/non-DHP CCB) to reduce the risk of 1:1 atrial flutter -Avoid use in chronic AF due to increased risk of VT/VF
	Propafenone	Oral: IR: 150 mg every 8h, max 300 mg every 8h ER: 225 mg every 12h, max 425 mg every 12h	Bioavailability: 100% Vd: 252 L/kg $T_{½}$: 10 h, highly variable Metabolism: Hepatic via CYP2D6, extensive first pass metabolism Excretion: < 1% in urine as active drug	Renal impairment: No manufacturer recommendations but may accumulate Hepatic impairment: None	HFrEF, CAD, high degree AV block, baseline prolonged QRS, myasthenia gravis	Taste changes, dizziness, nausea, vomiting, angina, precipitation of CHF exacerbation, agranulocytosis, 1:1 atrial flutter, VT, worsening AV block	Acute conversion: 68% 3 h after dose NSR at 6 months: 67% [99]	-Patients should be screened for CAD and HFrEF prior to initiation -Avoid use in patients with a prolonged QRS duration/bundle branch blocks -Combine with an AV nodal blocker (beta-blocker/non-DHP CCB) to reduce the risk of 1:1 atrial flutter

Table 2 (continued)

Class	Drug	Dosing	Pharmacokinetics	Dose adjustments	Contraindications	Adverse effects	Efficacy	Clinical pearls
Class III: potassium channel blockers	Sotalol	Oral: 80 mg every 12h, max 160 mg every 12h	Bioavailability: 95% Vd: 1.2–2.4 L/kg $T_{½}$: 12 h, up to 69 h in renal impairment Metabolism: none Excretion: 100% in urine as unchanged drug	Renal impairment: CrCl > 60 (ABW): 80 mg every 12h CrCl 60–40 (ABW): 80 mg every 24h CrCl < 40 (ABW): Contraindicated Hepatic impairment: No adjustments	Baseline prolonged QTc interval (> 450 ms), severe renal impairment, acute decompensated heart failure, high-degree AV block, severe bradycardia, history of TdP	Bradycardia, fatigue, dizziness, dyspnea, worsening AV block, precipitation of CHF, pulmonary edema, TdP	Acute conversion: 24.2% NSR at 12 months: 53% [100]	-Must initiate while hospitalized for the first 5–6 doses for monitoring of QTc interval -Avoid use in patients with baseline prolonged QTc interval -Antiarrhythmic effects occur at doses 80 mg or higher -75% of serious proarrythmias occur within 7 days intimation -Reduce dose or discontinue if QTc interval is > 500 ms
	Dofetilide	Oral: 500 mcg every q12h, starting dose adjusted based on renal function	Bioavailability: 90–95% Vd: 3 L/kg $T_{½}$: 10 h, prolonged in renal impairment Metabolism: hepatic via CYP 3A4 Excretion: 80% in urine as unchanged drug via active tubular secretion	Renal impairment: CrCl > 60 (ABW): 500 mcg every 12h CrCl 40–60 (ABW): 250 mcg every 12h CrCl 40–20 (ABW): 125 mcg every 12h CrCl < 20 (ABW): Contraindicated Hepatic: Excluded from studies, use cautiously	Baseline prolonged QTc interval (> 440 ms), severe renal impairment, recent ibutilide use, history of TdP	Headache, dizziness, insomnia, angina, TdP	Acute conversion: 30% NSR at 12 months: 49% [60]	-Must initiate while hospitalized for the first 5–6 doses for monitoring of the QTc interval -Avoid use in patients with baseline prolonged QTc interval -Clinically significant drug interactions exist via CYP3A4 and renal tubular secretions, dofetilide use is contraindicated with: cimetidine, hydrochlorothiazide, ketoconazole, megestrol, prochlorperazine, trimethoprim, verapamil and dolutegravir -Reduce dose or discontinue if QTc interval is > 500 ms

Table 2 (continued)

Class	Drug	Dosing	Pharmacokinetics	Dose adjustments	Contraindications	Adverse effects	Efficacy	Clinical pearls
	Amiodarone	Oral: Loading dose: 400 mg every 8h–12h until 6–10 g given Maintenance dose: 200 mg daily IV: 150 mg over 10 min, followed by infusion at 1 mg/min for 6 h, then 0.5 mg/min	Bioavailability: 50% Vd: 66 L/kg $T_{½}$: 40–55 days Metabolism: Hepatic via CYP2C8 and CYP3A4 Excretion: Predominately in the feces, < 1% in urine	Renal impairment: No adjustment Hepatic impairment: Consider dose adjustment if LFTs increase > 2–3 times the upper limit of normal	Younger age, bradycardia	Pulmonary fibrosis, hepatotoxicity, photosensitivity, hypothyroidism and hyperthyroidism, corneal deposition, worsening AV block	NSR at 12 months: 58% [101]	-Useful for acute rate control with IV therapy, chronic PO therapy highly effective for rhythm control -Many long-term toxicities; use should be reserved for patients who cannot tolerate other antiarrhythmic medications -Inhibits CYP3A4, CYP2D6, CYP2C9; many drug-drug interactions exist, including warfarin, digoxin, and colchicine -Required baseline monitoring: thyroid (TSH), liver (AST/ALT), and pulmonary function (chest x-ray, PFT) -Required routine monitoring: LFTs every 3–6 months, chest x-ray every 3–6 months, thyroid function every 3–6 months, annual ophthalmic exam
	Dronedarone	Oral: 400 mg every 12h	Bioavailability: 4–14% Vd: 1400 L $T_{½}$: 13–19 h Metabolism: Hepatic via CYP3A4 to a mildly active metabolite Excretion: Feces: 84%	Renal impairment: No adjustment Hepatic impairment: Contraindicated in severe liver impairment	Symptomatic heart failure, previous liver or lung toxicity with amiodarone, use with strong CYP3A4 inhibitors, baseline QTc > 500, permanent AF	Pulmonary fibrosis, hepatotoxicity, worsening AV block, bradycardia	NSR at 12 months: 32.9% [101]	-Avoid use in patients with baseline prolong QTc interval, history of HFrEF, or in patients with permanent AF -Discontinue if QTc interval is > 500 ms

ABW actual body weight, *AF* atrial fibrillation, *AV* atrioventricular, *BPH* benign prostatic hyperplasia, *CAD* coronary artery disease, *CHF* congestive heart failure, *CR* control release, *CrCl* creatinine clearance (mL/min), *ER* extended release, *HFrEF* heart failure with reduced ejection fraction, *HOCM* hypertrophic obstructive cardiomyopathy, *IBW* ideal body weight, *IR* immediate release, *MI* myocardial infarction, *NAPA N*-acetyl procainamide, *non-DHP CCB* non-dihydropyridine calcium channel blockers, *NSR* normal sinus rhythm, *QTc* corrected QT, $T_{½}$ half-life, *TdP* torsades de pointes, *Vd* volume of distribution, *VT* ventricular tachycardia, *WPW* Wolff-Parkinson-White Syndrome, *NAT2* N-acetyltransferase 2, *CYP* cytochrome protein 450, *LFT* liver function test, *iHD* intermittent hemodialysis, *HF* heart failure, *PO* oral, *AST/ALT* aspartate aminotransferase/alanine aminotransferase, *PFT* pulmonary function test

though rare, is the most serious adverse effect and carries a mortality risk of 20% [38]. A lupus-like syndrome develops in up to 30% of patients receiving prolonged administration of procainamide [38, 43, 47]. A positive antinuclear antibody test and clinical signs of lupus warrant the discontinuation of procainamide and consideration of an alternative antiarrhythmic [47]. Due to these serious safety concerns, oral procainamide was removed from the US market, and the use of the IV formulation is limited to short durations. The IV administration of procainamide is useful in the setting of hemodynamically stable AF with preexcitation.

4.1.1.5 Class Ic Sodium Channel Blockers Class Ic sodium channel blockers act primarily on the rapid sodium channel and exert slow dissociation kinetics, leading to a pronounced slowing of the conduction velocity at both fast and slow HRs [48–51]. This causes a pronounced increase in the QRS duration that should be monitored before dose increases occur. These agents also possess negative inotropic effects and should be avoided in patients with HFrEF. An increased risk of mortality noted in the CAST trials due to proarrhythmic potential led to the recommendation that all class Ic sodium channel blockers be avoided in patients with a history of CAD or myocardial infarction [35, 36]. Emerging data from a small retrospective study of 348 patients suggest that flecainide use appears to be safe in patients with stable CAD, with no difference in malignant arrhythmias in patients with no or minimal CAD, nonobstructive CAD, and obstructive CAD. Moreover, there was no difference in mortality after 10 years of follow-up in patients with perfusion defects on myocardial perfusion scans (MPS) compared to those with no perfusion defects [52]. Thus, before initiation, patients should, at a minimum, be screened for LV dysfunction with a transthoracic echocardiogram and not have a history of myocardial infarction, and consideration for evaluation of CAD remains reasonable until larger studies confirm the safety noted in the previously mention trial [39]. If mild QRS widening occurs at rest, exercise treadmill testing while on a class Ic agent may be considered to assess the QRS duration at higher HRs given their use dependence [53, 54]. If the QRS duration prolongs significantly during exercise, discontinuation or dose reduction can be considered. Class Ic agents are used for pharmacological cardioversion of AF ("pill in the pocket" approach) and maintenance of NSR [55]. The class Ic agents, by organizing AF to atrial flutter may allow rapid conduction of impulses over the AV node and cause 1:1 conduction of atrial flutter with rapid ventricular rate response. Hence, these agents should be used concomitantly with a beta-blocker or non-DHP CCB.

4.1.1.6 Flecainide Pharmacologically, flecainide blocks the fast inward sodium channel, resulting in a marked slowing of the conduction velocity through the myocardium, with the largest effect in the His-Purkinje system [48–50, 56]. Flecainide has a mild affinity for potassium channels, which may lead to slight prolongation of repolarization. A prolongation of the QRS duration and potentially a small increase in the QTc interval are expected ECG findings. It is highly effective for acute cardioversion, with an overall success rate of 55–80% of patients after a single dose of 200 mg or 300 mg (if weight > 70 kg) [57]. Flecainide is moderately effective in prolonging time to relapse of AF [39, 57]. Use is contraindicated in patients with CAD, HFrEF, history of a pre-existing second- or third-degree AV block, or right bundle branch block associated with a left hemiblock [56]. Dosing starts at 50 mg twice daily and can be up titrated every 4 days. Monitoring of the ECG at baseline, 3–4 h after the initial dose, and at a steady-state concentration is recommended to assess the QRS duration. If the QRS duration is prolonged by > 25%, dose reduction or cessation of therapy should be considered [56, 57]. Flecainide is also used as a pill-in-the-pocket strategy, wherein the patient takes a dose at the onset of symptoms to attempt pharmacological cardioversion [55]. If this strategy is used, the safety of the effective dose in cardioverting the patient should be established *a priori*, under monitored conditions. If either renal or hepatic dysfunction is present, doses should start at the lowest possible dosage, such as 25–50 mg daily and be uptitrated carefully with ECG monitoring. Flecainide should be avoided with potent cytochrome P450 2D6 (CYP2D6) inhibitors, including amiodarone, propranolol, and fluoxetine, and additionally, flecainide can increase digoxin concentrations [56]. Flecainide, by maintaining NSR, significantly improves quality of life in patients with AF, and is well-tolerated, with the most common side effects being dizziness, visual disturbances, nausea, and headache [57]. Proarrhythmic effects of flecainide include increased premature ventricular contraction (PVC) density, monomorphic or polymorphic ventricular tachycardia, and 1:1 atrial flutter. Combination with an AV nodal blocker, such as a beta-blocker, reduces the risk of proarrhythmia and should be considered in patients prescribed flecainide.

4.1.1.7 Propafenone Pharmacological effects of propafenone are similar to flecainide, with the addition of mild calcium channel blockade and beta-adrenergic receptor blockade, but lesser negative inotropic effects [51, 58]. Major ECG findings can show widening of the QRS duration with higher doses. Propafenone is considered less effective for treating AF and carries additional side effects to flecainide, limiting its use in practice. Propafenone is contraindicated in patients with a history of CAD, HFrEF, Brugada syndrome, and myasthenia gravis [58]. Propafenone is initiated at 150 mg three times daily or 225 mg every 12 h with the sustained-release product. It also may be used in the pill-in-the-pocket strategy [55]. Dose titration should occur no more than every 4 days for

maintenance dosing. Commonly seen adverse effects include dysgeusia, dizziness, nausea, vomiting, and blurred vision. Severe side effects, including a lupus-like rash, worsening of CHF, weakness, and agranulocytosis, may also occur rarely.

4.1.2 Vaughan-Williams Class III: Potassium Channel Blockers

Potassium channel blockers inhibit the efflux of potassium during phases 2 and 3 of the action potential, causing delayed repolarization and prolonging the refractory period. Therefore, the QTc interval must be carefully monitored to reduce the risk of TdP [39]. Potassium channel blockers exhibit reverse-use dependence, meaning they are more effective at lower HRs and thus able to prevent AF recurrence.

4.1.3 Dofetilide

Dofetilide inhibits the rapid component of the delayed rectifying potassium channel (I_{kr}), leading to delayed cardiac repolarization and prolongation of the effective refractory period [39, 59, 60]. The QTc prolongation and efficacy of dofetilide are proportional to its serum concentration [61]. Inpatient hospitalization and ECG monitoring for at least five doses is therefore recommended due to a high risk of QT prolongation and TdP [59]. TdP most often occurs within the first 2–3 days after initiation and is associated with QTc intervals > 500 ms or a change in QTc of > 60 ms from baseline. Contraindications to dofetilide therapy include baseline QTc interval > 440 ms or > 500 ms with ventricular conduction abnormalities, severe renal impairment, recent ibutilide use, history of TdP, or other interacting drug therapy [59]. Initial dofetilide dosing is based on creatinine clearance (CrCl), calculated using actual body weight due to the high degree of renal excretion. Prior to initiation, a baseline ECG showing an acceptable QTc interval (< 440 ms), potassium and magnesium repletion to > 4 mmol/L and > 2 mg/dL, respectively, and CrCl calculation should be confirmed for dose adjustment. An ECG should be performed 2–3 h post-dose for the first five to six doses to assess the QTc interval. The dose of dofetilide should be reduced if the QTc interval is prolonged > 15% from baseline or if the QTc interval is prolonged > 500 ms [59]. Predictors of unsuccessful dofetilide initiation include female sex and increased serum creatinine [62]. Deviation from these QTc interval recommendations has shown a non-significant increased rate of adverse events in a real-world, retrospective study [63]. One small study assessed feasibility of outpatient initiation of dofetilide in low-risk patients who had implanted cardiac electronic devices (CIED), such as implantable loop recorders, permanent pacemakers, and implantable cardioverter-defibrillators (ICD) with close outpatient monitoring [64]. This strategy appeared to be safe, but caution is warranted until further studies are completed. Clinically significant drug interactions, including pharmacodynamic interactions with concomitant QTc-prolonging medications and those mediated by CYP3A4 and renal tubular excretion, can occur. Headaches are the most commonly reported adverse effect. Unlike many other antiarrhythmic drugs, dofetilide is safe and effective in patients with HFrEF and CAD [65, 66]. A recent cohort study showed dofetilide was successfully initiated in 87% of patients, and dofetilide-treated patients had a similar likelihood of experiencing recurrent atrial arrhythmias at 1 year to that of patients treated with amiodarone (37% vs 39%; $p = 0.56$) [62].

4.1.3.1 Sotalol Sotalol is a racemic mixture of d- and l-sotalol. L-sotalol primarily acts as a beta-blocker, while d-sotalol is responsible for the drug's class III antiarrhythmic activity [27, 28, 67]. D-sotalol potently inhibits the rapid component of the I_{kr}, prolonging repolarization in a dose-dependent manner [27, 28, 67]. Due to the reverse-use dependence of class III antiarrhythmic drugs, sotalol exerts synergistic effects by slowing the HR while prolonging repolarization. Generally, total daily doses of sotalol ≥ 160 mg exert potassium channel blockade, while daily doses ≤ 80 mg cause mainly beta-adrenergic receptor blocking effects [39, 67]. Sotalol should be initiated in a hospital setting, and the QTc monitored for at least five doses to minimize the risk of TdP [67]. Risk factors for TdP include female sex, bradycardia, chronic kidney disease, and history of CHF [68]. Approximately 75% of serious arrhythmias occur within the first 7 days of therapy [69]. Use is contraindicated in patients with a baseline QTc interval > 450 ms, severe renal impairment, high degree AV blocks, severe bradycardia (HR < 50 bpm), history of TdP, and acute decompensated heart failure [67]. Prior to initiation, a baseline ECG showing an acceptable QTc interval, potassium and magnesium repletion to > 4 mmol/L and > 2 mg/dL, respectively, and CrCl calculation should be confirmed. ECGs should be monitored 2–3 h post-dose for each of the first five to six doses to assess the QTc interval. The dose of sotalol should be reduced if the QTc interval is prolonged > 15% from baseline or if the QTc interval is prolonged > 500 ms [67, 69]. In patients with normal renal function, sotalol is started at a dosage of 80 mg twice daily and titrated if the QTc interval is not significantly prolonged after 3 days of therapy. Although uncommonly done, an IV loading dose of sotalol may be given over 1 h, followed by two oral doses administered in lieu of the five- to six-dose oral loading regimen [70]. If this strategy is employed, the patient should remain under continuous telemetry. Loading of sotalol in low-risk patients who have CIEDs in an outpatient setting with close monitoring has been evaluated in a small study and appears to be safe with no incidences of

TdP or drug discontinuation due to QTc prolongation [71]. This strategy warrants further investigation. The most common adverse effects of sotalol therapy include fatigue, dizziness, and bradycardia. In patients with left ventricular dysfunction, concomitant use with a guideline-recommended beta-blocker could be considered if HR allows.

4.1.3.2 Ibutilide Ibutilide is a selective potassium channel blocker used intravenously for chemical cardioversion when electrical cardioversion is not desired. Its use should be avoided in patients with a baseline QTc interval > 440 ms or a history of TdP due to the QTc prolongation associated with its use. Prior to administration, magnesium and potassium should be repleted if required [72]. Ibutilide is given as a 10-min IV infusion, and the patient should be monitored for at least 4 h after administration. A second dose of 1 mg may be given 10 min after the completion of the first infusion if the first dose is not successful. Ibutilide can also improve the success of electrical cardioversion. Ibutilide use should be avoided in patients with cardiomyopathies and structural heart disease [73].

4.1.3.3 Amiodarone Amiodarone is a broad-spectrum antiarrhythmic drug that possesses electrochemical properties of each antiarrhythmic drug class. Amiodarone is commonly classified as a class III antiarrhythmic medication because of its effect on repolarization and potassium channel blockade during chronic therapy. Due to the additional properties of sodium channel blocking effects, beta-adrenergic receptor blocking effects, and calcium channel blocking effects, amiodarone is highly effective for the treatment of atrial and ventricular arrhythmias [27, 39]. Unlike other class III antiarrhythmic medications, amiodarone is only rarely associated with TdP despite causing QTc prolongation [39, 74]. Amiodarone distributes widely in the body, including peripheral adipose tissue that acts as a "sink" for amiodarone [27, 74]. Therefore, it requires a large loading dose over a prolonged period to saturate tissues before its full antiarrhythmic effects are noted. Initially, when given intravenously, amiodarone primarily exerts its antiarrhythmic effect via beta-adrenergic receptor blockade and, to a lesser extent, sodium channel blockade. As the loading dose continues, amiodarone begins to exert additional electrochemical effects, particularly potassium channel blockade [74]. Amiodarone is usually given as an oral loading dose over 1–2 weeks at 400 mg two to three times daily. A total amiodarone loading dose is generally 6–8 g for AF. Because of this large volume of distribution, amiodarone has a half-life of 40–55 days. The use of amiodarone is limited by its adverse effect profile, which is driven by its large volume of distribution. Amiodarone is associated with hepatotoxicity, hypo- or hyperthyroidism, pulmonary fibrosis, corneal deposition, hyperpigmentation, and phototoxicity [74]. Most of these toxicities increase in frequency as cumulative amiodarone exposure increases; amiodarone is therefore avoided in younger patients to limit these toxicities with long-term use. For details regarding the required baseline and routine monitoring see Table 2. Unlike other antiarrhythmic medications, it is safe and effective in patients with a variety of cardiac comorbidities, including HFrEF and CAD [39, 74]. Amiodarone is an inhibitor of many CYP isozymes, including CYP3A4, CYP2C9, and CYP2D6, as well as the P-glycoprotein system, resulting in many drug interactions.

4.1.3.4 Dronedarone Dronedarone is structurally similar to but lacks the iodine moieties of amiodarone, a deliberate attempt to minimize toxicities seen with the latter [75]. The two medications share other properties, including pharmacological and electrophysiological profiles. The lack of iodine moiety leads to a decreased incidence of thyroid toxicity, but dronedarone is still associated with pulmonary fibrosis, the most feared toxicity of amiodarone [75, 76]. Dronedarone should be avoided with a QTc interval > 500 ms due to the risk of TdP. Dronedarone increases mortality in patients with HFrEF and is, therefore, contraindicated in this population [37]. Lastly, dronedarone should not be used in permanent AF due to an increased risk of stroke and death within the first 2 weeks of initiation [77]. Dronedarone is, however, safe to use in patients with CAD. One large retrospective cohort study demonstrated patients treated with dronedarone compared to patients treated with other antiarrhythmics had a lower risk of hospitalization for a cardiovascular event (hazard ratio 0.87, 95% CI 0.79–0.96) [78].

5 Ablation of Atrial Fibrillation

5.1 Catheter Ablation

Catheter ablation, a non-pharmacological form of rhythm control is performed to induce cellular necrosis and subsequent scarring of atrial tissue around arrhythmogenic areas, such as the pulmonary vein, to limit reentrant circuits that cause AF. Focused energy sources of heat (e.g., radiofrequency ablation) or cold (e.g., cryoablation) are commonly used and have similar safety and efficacy outcomes [79]. Several guidelines endorse the use of catheter ablation for AF across a spectrum of comorbidities for refractory AF [13, 80]. Several studies have examined the safety and efficacy of catheter ablation of AF alone and in comparison to antiarrhythmic medications.

The open-label, randomized AATAC trial compared catheter ablation with amiodarone in 203 patients with persistent AF and a history of HFrEF with prior ICD or cardiac resynchronization therapy with defibrillator (CRT-D) placement.

The primary outcome of procedural success (freedom from atrial arrhythmias > 30 s off antiarrhythmic drugs) at 24 months was significantly higher in patients in the ablation cohort as compared to amiodarone (70% vs 34%; $p < 0.001$). Secondary endpoints of unplanned hospitalization and mortality were lower in the ablation group, although the trial was not powered for these outcomes [81].

The CASTLE-AF study was a multicenter, open-label, randomized controlled trial of 363 patients with either paroxysmal or persistent symptomatic AF, HFrEF, and failure, intolerance, or unwillingness to take antiarrhythmic pharmacotherapy. Patients were randomized to receive pulmonary vein isolation or medications for rate or rhythm control; only 30% of patients received rhythm control medications. In the primary composite outcome of death or worsening of CHF leading to hospitalization, catheter ablation was superior to the medical management cohort at 37 months (hazard ratio 0.62; 95% CI 0.43–0.87) [82].

The CABANA trial was a multicenter, prospective, randomized, open-label trial of 2204 patients of ≥ 65 years of age or < 65 with at least one risk factor for stroke that compared pulmonary vein isolation with pharmacotherapy. No difference in the primary composite endpoint (death, disabling stroke, serious bleeding, or cardiac arrest) was found between catheter ablation and drug therapy (hazard ratio 0.86; 95% CI 0.65–1.15) at a median of 48.5 months. Conversely, the prespecified per-protocol analysis, which excluded patients who did not receive ablation but were assigned to the ablation cohort, showed a significant difference in the primary outcome favoring catheter ablation (hazard ratio 0.67; 95% CI 0.50–0.89) [83]. Recurrent atrial arrhythmias were reduced by 47% in patients that received catheter ablation versus drug therapy alone [84].

With prior studies primarily focusing on patients that have failed pharmacotherapy, catheter ablation has recently been evaluated in several studies as first-line therapy for rhythm control. The STOP-AF First trial randomized patients with paroxysmal AF previously untreated with class I or III antiarrhythmics to either pharmacological rhythm control, predominately with flecainide, or cryoballoon ablation. The efficacy of rhythm control at 12 months was superior in the ablation cohort compared to antiarrhythmic drug therapy (74.6% vs 45%; $p < 0.001$) [85].

Patients in the EARLY-AF trial had previously untreated paroxysmal AF and were randomized to cryoballoon ablation or antiarrhythmic drug therapy. Recurrent atrial arrhythmias, as assessed by an implantable cardiac monitoring device, were lower in patients undergoing ablation than in pharmacological management (42.9% vs 67.8%; hazard ratio 0.48, 95% CI 0.35–0.66) at 1 year [86].

Early recurrence of AF after ablation is common and occurs in up to 50% of patients, but does not necessarily predict long-term treatment failure; this period is known as the blanking phase. Antiarrhythmic medications have been studied in the post-ablation period to prevent AF recurrence. The 5A study was a prospective, open-label study that randomized 110 patients to receive an antiarrhythmic medication or no antiarrhythmic medication following AF ablation. The primary endpoint was a composite of arrhythmia lasting greater than 24 h or requiring antiarrhythmic medication initiation or change, cardioversion or hospitalization for arrhythmia, and adverse events at 6 weeks [87]. The occurrence of the primary endpoint was lower in the antiarrhythmic medication group than the no-antiarrhythmic medication group (19% vs 42%; $p = 0.005$), driven by a reduction in arrhythmias lasting greater than 24 h. A 6-month follow-up study, however, showed that freedom from AF was no different between groups [88]. The 2017 expert consensus on catheter and surgical ablation of AF states that the usefulness of initiation or continuation of antiarrhythmic medications in the post-ablation period to improve long-term outcomes is unclear [80].

5.2 Surgical Ablation

Surgical ablation of AF, including the biatrial Cox-Maze IV procedure, is highly effective and associated with rates of freedom from AF that exceed 90%. Surgical ablation can be performed as concomitant surgery in patients undergoing coronary artery bypass grafting, valve operation, or as a standalone procedure. The Cox-Maze IV procedure has replaced the traditional "cut and sew" technique of the original Cox-Maze operation and uses radiofrequency or cryothermal energy to create ablation lines. Guidelines and an expert consensus document suggest AF surgical ablation offers patients a return to NSR, improved quality of life, reduction in stroke in select patients, as well as improvements in perioperative and long-term mortality [80, 89]. Although limited evidence exists, surgical ablation that includes LAA obliteration may reduce stroke events compared to oral anticoagulation use alone [90].

6 Rate Versus Rhythm Control: Literature Review

A primary goal of treatment of AF is to reduce symptoms, such as palpitations and shortness of breath, with rate control or rhythm control strategy. Patients can be categorized into different classes based on symptom burden as recommended by current guidelines [14, 31]. The optimal strategy, however, is debated, and neither has been definitively shown to reduce mortality compared to the other. Studies comparing the two approaches published in the early 2000s, described below, showed no significant difference in cardiovascular death and resulted in the adoption of an initial rate control

strategy with the addition of antiarrhythmic medications if patients remained symptomatic despite adequate ventricular rate control.

The STAF study was an open-label, controlled trial that randomized 200 patients to rhythm control with cardioversion and antiarrhythmic medications or rate control. No difference was found in the occurrence of the primary composite endpoint of death, stroke or TIA, systemic embolism, and cardiopulmonary resuscitation (rhythm control 5.54%/year vs rate control 6.09%/year; $p = 0.99$) or death (2.5% vs 4.9%) at a mean follow-up of 19.6 months. Patients assigned to the rhythm control group had more hospitalizations for cardiovascular disease (449 days of hospital stay vs 314 days of hospital stay; $p < 0.001$) [91].

The AFFIRM study was an open-label, prospective trial that randomized 4060 patients to rate control with a goal HR of 80–110 bpm or rhythm control with antiarrhythmic medications. No difference was found for the primary endpoint of overall mortality at 5 years (hazard ratio 1.15, 95% CI 0.99–1.34; $p = 0.08$), but patients in the rhythm control group experienced more adverse events and hospitalizations related to antiarrhythmic medications [92].

The RACE study was an open-label, prospective trial that randomized 522 patients with persistent AF to a rhythm control or rate control strategy. The primary endpoint was a composite of cardiovascular death, heart failure, thromboembolic complications, bleeding, need for a pacemaker, or adverse effects of antiarrhythmic drugs. The incidence of the primary outcome was non-inferior for rate control versus rhythm control (rhythm control 22.6% vs rate control 17.2%, 90% CI −11.0 to 0.4) at a mean follow-up of 2.3 years. No difference in the risk of the primary endpoint was found between groups (hazard ratio 0.73, 95% CI 0.53–1.01; $p = 0.11$), but severe adverse events of antiarrhythmic medications were more common in the rhythm control group (rhythm control 4.5% vs rate control 0.8%, 90% CI − 6.0 to − 1.4) [93].

Due to the negative clinical and hemodynamic consequences of AF in patients with HFrEF, restoration and maintenance of NSR are often attempted. The AF-CHF trial randomized 1376 patients with electrocardiographically confirmed AF and CHF with a left ventricular ejection fraction < 35% to rhythm control with preferential use of amiodarone and electrical cardioversion or rate control [94]. At a mean follow-up of 37 months, the primary outcome of cardiovascular mortality did not differ between groups (27% rhythm control vs 25% rate control; hazard ratio 1.06, 95% CI 0.86–1.3; $p = 0.59$), nor did the secondary endpoints of all-cause mortality, stroke, or worsening heart failure. Bradyarrhythmia (6% vs 3%; $p = 0.02$) and hospitalization for AF (14% vs 9%; $p = 0.001$) were more common in the rhythm control group.

The most recent trial comparing rhythm control with rate control, however, showed different results. The EAST-AFNET4 study was an open-label, prospective trial that randomized 2789 patients at high cardiovascular risk with AF of < 12 months to rhythm control or rate control. Rhythm control consisted of antiarrhythmic drugs, catheter ablation, or cardioversion, and anticoagulation was mandated for patients in both arms. The primary endpoint was a composite of cardiovascular death, stroke, or hospitalization; a second primary outcome was the number of nights spent in the hospital per year. The trial was stopped early after a median of 5.1 years of follow-up; patients in the rhythm control group had fewer first-primary-outcome events than those in the rate control group (3.9 per 100 person-years vs 5.0 per 100 person-years; $p = 0.0005$); findings were consistent across subgroups. No difference in nights spent in the hospital was found between groups [95].

Several factors may help explain divergent results of the EAST-AFNET4 trial and prior trials. Advances in rhythm control strategies, including increased use of catheter ablation, the availability of newer antiarrhythmic medications, and closer monitoring of available antiarrhythmic medications, as well as improvement in the overall care of cardiovascular patients and risk factor modification, likely reduces the risk to patients when pursuing this approach. A greater likelihood of maintenance of NSR in recently diagnosed AF, as in EAST-AFNET4, compared with a longer duration seen in the other trials may also contribute to improved clinical outcomes. Furthermore, patients in EAST-AFNET4 were maintained on anticoagulation, and treatment of underlying disease states was emphasized, while previous trials allowed discontinuation of anticoagulation if NSR was achieved. The emphasis on appropriate anticoagulation and appropriate treatment of concomitant cardiovascular disease states in EAST-AFNET4 illustrates the importance of a holistic approach to medical therapy in patients with AF.

In summary, historical trials consistently failed to show a difference in cardiovascular death when comparing rate control and rhythm control. However, a direct comparison of trials is difficult due to differences in baseline patient characteristics, inclusion criteria, treatment approaches, and endpoints. Furthermore, limitations of the trials, including small sample size, high rates of treatment crossover, and variable anticoagulation requirements, may have contributed to the lack of difference in outcomes. Given the adverse events associated with antiarrhythmic medications and lack of definite benefit across a broad patient population, rate control is a reasonable approach in most patients, but the addition of antiarrhythmic medications should be considered if patients remain symptomatic. However, based on more recent evidence, an attempt to restore and maintain NSR is reasonable in patients with recently diagnosed AF before adverse atrial remodeling occurs. Regardless of the

initial treatment strategy, thromboembolic risk and underlying cardiovascular diseases should be assessed and treated accordingly. In addition, control of risk factors for AF and stroke, such as obesity, sleep apnea, and lifestyle changes, with regular exercise, smoking cessation, and avoidance of alcohol are all-important.

7 Gaps in Knowledge

With increased monitoring and safer use of antiarrhythmics and ablative strategies, further studies are warranted to critically reappraise long-term cardiovascular outcomes associated with a rate control versus a rhythm control strategy. Furthermore, class III antiarrhythmics, particularly dofetilide, have largely been underrepresented in trials comparing rate versus rhythm control strategy, despite being highly effective, exhibiting reverse-use dependence properties, and being well-tolerated with low rates of discontinuation. This underrepresentation is likely due to dofetilide being unavailable in European countries, although sotalol use has been consistently low in these trials. Additionally, the optimal timing of initiation of rhythm control remains unclear. Current evidence supports minimizing adverse drug events, utilizing an initial rate control strategy, and subsequent progression to rhythm control based on unacceptable symptoms. Emerging literature suggests that initiation of rhythm control early in the course of AF can reduce the progression of AF and long-term risk of cardiovascular events, possibly by counteracting the adverse pathophysiology associated with long-standing AF. Lastly, the timing of catheter ablation for AF remains unclear; emerging data have suggested that it may be an acceptable first-line therapy in selected patients, supporting its use early in the course of AF.

8 Conclusion

AF is an increasingly common arrhythmia encountered in clinical practice that leads to a substantial increase in healthcare costs and decreased quality of life of patients. Treatment of AF revolves around two tenets: appropriate thromboembolism prophylaxis with oral anticoagulants and a rate or rhythm control strategy to minimize symptoms. Patients with minimal symptoms are often initiated on oral anticoagulation, and rate control medications are titrated to control AV nodal conduction and ventricular rate. Patients who remain symptomatic despite adequate rate control or, as seen in recent studies, patients with a recent diagnosis of AF may benefit from early rhythm control therapy with antiarrhythmic drugs or catheter ablation. As the prevalence of AF continues to increase, future studies should focus on identifying the cardiovascular risk reduction associated with a rate versus rhythm control strategy, in combination with risk factor modulation, and identifying the optimal timing of when to switch to a rhythm control strategy.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40256-022-00529-6.

Declarations

Funding No external funding was used in the preparation of this article.

Conflict of interest Lacoste, Szymanski, Avalon, Kabulski, Kohli, Marrouche, Singla, Balla, and Jahangir declare that they have no potential conflicts of interest that might be relevant to the contents of this article.

Author contributions JLL was involved with conceptualization, writing, editing, reviewing, and administration. TWS was involved with writing, editing, and reviewing. JCA was involved with writing, editing, and reviewing. GK was involved with writing, editing, and reviewing. UK was involved with editing and reviewing. NM was involved with reviewing. AS was involved with reviewing. SB was involved with editing, reviewing, and conceptualization. AJ was involved with editing, reviewing, and conceptualization.

Ethics approval Not applicable.

Consent to participate Not applicable.

Consent for publication Not applicable.

Availability of data and material Not applicable.

Code availability Not applicable.

References

1. Alpert JS, Petersen P, Godtfredsen J. Atrial fibrillation: natural history, complications, and management. Annu Rev Med. 1988;39(1):41–52. https://doi.org/10.1146/annurev.me.39.020188.000353.
2. Petersen P. Thromboembolic complications in atrial fibrillation. Stroke. 1990;21(1):4–13. https://doi.org/10.1161/01.STR.21.1.4.
3. Benjamin EJ. Independent risk factors for atrial fibrillation in a population-based cohort: the Framingham heart study. JAMA. 1994;271(11):840. https://doi.org/10.1001/jama.1994.03510350050036.
4. Dewland TA, Olgin JE, Vittinghoff E, Marcus GM. Incident atrial fibrillation among asians, hispanics, blacks, and whites. Circulation. 2013;128(23):2470–7. https://doi.org/10.1161/CIRCULATIONAHA.113.002449.
5. Go AS, Hylek EM, Phillips KA, et al. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the anticoagulation and risk factors in atrial fibrillation (ATRIA) study. JAMA. 2001;285(18):2370. https://doi.org/10.1001/jama.285.18.2370.
6. Lau DH, Nattel S, Kalman JM, Sanders P. Modifiable risk factors and atrial fibrillation. Circulation. 2017;136(6):583–96. https://doi.org/10.1161/CIRCULATIONAHA.116.023163.

7. Kim MH, Lin J, Hussein M, Kreilick C, Battleman D. Cost of atrial fibrillation in United States managed care organizations. Adv Ther. 2009;26(9):847–57. https://doi.org/10.1007/s12325-009-0066-x.
8. Patel NJ, Deshmukh A, Pant S, et al. Contemporary trends of hospitalization for atrial fibrillation in the United States, 2000 through 2010: implications for healthcare planning. Circulation. 2014;129(23):2371–9. https://doi.org/10.1161/CIRCULATIONAHA.114.008201.
9. 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(5):373–498. https://doi.org/10.1093/eurheartj/ehaa612.
10. Patel P, Dokainish H, Tsai P, Lakkis N. Update on the association of inflammation and atrial fibrillation. J Cardiovasc Electrophysiol. 2010;21(9):1064–70. https://doi.org/10.1111/j.1540-8167.2010.01774.x.
11. Wakili R, Voigt N, Kääb S, Dobrev D, Nattel S. Recent advances in the molecular pathophysiology of atrial fibrillation. J Clin Invest. 2011;121(8):2955–68. https://doi.org/10.1172/JCI46315.
12. Jones J, Stanbury M, Haynes S, et al. Importance and assessment of quality of life in symptomatic permanent atrial fibrillation: patient focus groups from the RATE-AF trial. Cardiology. 2020;145(10):666–75. https://doi.org/10.1159/000511048.
13. January CT, Wann LS, Calkins H, et al. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American college of cardiology/American heart association task force on clinical practice guidelines and the heart rhythm society in collaboration with the society of thoracic surgeons. Circulation. 2019. https://doi.org/10.1161/CIR.0000000000000665.
14. Olesen JB, Lip GYH, Hansen ML, et al. Validation of risk stratification schemes for predicting stroke and thromboembolism in patients with atrial fibrillation: nationwide cohort study. BMJ. 2011;342: d124. https://doi.org/10.1136/bmj.d124.
15. Lip GYH, Nieuwlaat R, Pisters R, Lane DA, Crijns HJGM. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. Chest. 2010;137(2):263–72. https://doi.org/10.1378/chest.09-1584.
16. Ntaios G, Lip GYH, Makaritsis K, et al. $CHADS_2$, CHA_2DS_2-VASc, and long-term stroke outcome in patients without atrial fibrillation. Neurology. 2013;80(11):1009–17. https://doi.org/10.1212/WNL.0b013e318287281b.
17. Friberg L, Rosenqvist M, Lip GYH. Evaluation of risk stratification schemes for ischaemic stroke and bleeding in 182 678 patients with atrial fibrillation: the Swedish Atrial Fibrillation cohort study. Eur Heart J. 2012;33(12):1500–10. https://doi.org/10.1093/eurheartj/ehr488.
18. Edmiston MK, Lewis WR. Bleeding risk scores in atrial fibrillation: helpful or harmful? J Am Heart Assoc. 2018. https://doi.org/10.1161/JAHA.118.010582.
19. January CT, Wann LS, Alpert JS, et al. AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American college of cardiology/American heart association task force on practice guidelines and the heart rhythm society. Circulation. 2014. https://doi.org/10.1161/CIR.0000000000000041.
20. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med. 2009;361(12):1139–51. https://doi.org/10.1056/NEJMoa0905561.
21. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. 2011;365(10):883–91. https://doi.org/10.1056/NEJMoa1009638.
22. Granger CB, Alexander JH, McMurray JJV, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2011;365(11):981–92. https://doi.org/10.1056/NEJMoa1107039.
23. Giugliano RP, Ruff CT, Braunwald E, et al. Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2013;369(22):2093–104. https://doi.org/10.1056/NEJMoa1310907.
24. Hargrove KL, Robinson EE, Lusk KA, Hughes DW, Neff LA, Fowler AL. Comparison of sustained rate control in atrial fibrillation with rapid ventricular rate: metoprolol vs diltiazem. Am J Emerg Med. 2021;40:15–9. https://doi.org/10.1016/j.ajem.2020.11.073.
25. Panchal AR, Bartos JA, Cabañas JG, et al. Part 3: adult basic and advanced life support: 2020 American heart association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. Circulation. 2020. https://doi.org/10.1161/CIR.0000000000000916.
26. Van Gelder IC, Groenveld HF, Crijns HJGM, et al. Lenient versus strict rate control in patients with atrial fibrillation. N Engl J Med. 2010;362(15):1363–73. https://doi.org/10.1056/NEJMoa1001337.
27. Fogoros RN. Antiarrhythmic drugs: a practical guide. 2nd ed. Hoboken: Blackwell Publication; 2007.
28. Podrid PJ, editor. Cardiac arrhythmia: mechanisms, diagnosis, and management. 2nd ed. Philadelphia: Lippincott Williams & Wilkins; 2001.
29. van Gestel YRBM, Hoeks SE, Sin DD, et al. Impact of cardioselective beta-blockers on mortality in patients with chronic obstructive pulmonary disease and atherosclerosis. Am J Respir Crit Care Med. 2008;178(7):695–700. https://doi.org/10.1164/rccm.200803-384OC.
30. Diltiazem [package insert]. Bridgewater, NJ. Valeant Pharmaceuticals 2014.
31. Developed with the special contribution of the European Heart Rhythm Association (EHRA), Endorsed by the European Association for Cardio-Thoracic Surgery (EACTS), Authors/Task Force Members, et al. Guidelines for the management of atrial fibrillation: the task force for the management of atrial fibrillation of the European Society of Cardiology (ESC). European Heart Journal. 2010;31(19):2369-2429. https://doi.org/10.1093/eurheartj/ehq278
32. Digoxin [package insert]. Greenville, NC. GlaxoSmithKline. 2009.
33. Lopes RD, Rordorf R, De Ferrari GM, et al. Digoxin and mortality in patients with atrial fibrillation. J Am Coll Cardiol. 2018;71(10):1063–74. https://doi.org/10.1016/j.jacc.2017.12.060.
34. Pincus M. Management of digoxin toxicity. Aust Prescr. 2016;39(1):18–20. https://doi.org/10.18773/austprescr.2016.006.
35. Echt DS, Liebson PR, Mitchell LB, et al. Mortality and morbidity in patients receiving encainide, flecainide, or placebo: the cardiac arrhythmia suppression trial. N Engl J Med. 1991;324(12):781–8. https://doi.org/10.1056/NEJM199103213241201.
36. Effect of the antiarrhythmic agent moricizine on survival after myocardial infarction. N Engl J Med. 1992;327(4):227–233. https://doi.org/10.1056/NEJM199207233270403
37. Køber L, Torp-Pedersen C, McMurray JJV, et al. Increased mortality after dronedarone therapy for severe heart failure. N Engl J Med. 2008;358(25):2678–87. https://doi.org/10.1056/NEJMoa0800456.
38. Roden DM, Woosley RL. Class I antiarrhythmic agents: quinidine, procainamide and *N*-acetylprocainamide, disopyramide. Pharmacol Ther. 1983;23(2):179–91. https://doi.org/10.1016/0163-7258(83)90012-8.
39. Dan GA, Martinez-Rubio A, Agewall S, et al. Antiarrhythmic drugs–clinical use and clinical decision making: a consensus

document from the European Heart Rhythm Association (EHRA) and European Society of Cardiology (ESC) Working Group on Cardiovascular Pharmacology, endorsed by the Heart Rhythm Society (HRS), Asia-Pacific Heart Rhythm Society (APHRS) and International Society of Cardiovascular Pharmacotherapy (ISCP). EP Europace. 2018;20(5):731–2. https://doi.org/10.1093/europace/eux373.
40. Disopyramide [package insert]. New York, NY. Pfizer. 2006.
41. Verlinden NJ, Coons JC. Disopyramide for hypertrophic cardiomyopathy: a pragmatic reappraisal of an old drug. Pharmacother J Hum Pharmacol Drug Ther. 2015;35(12):1164–72. https://doi.org/10.1002/phar.1664.
42. Quinidine [package insert]. Philadelphia, PA. Mutual Pharmaceutical Company. 2009.
43. Procainamide [package insert]. Lake Forest, IL. Hospira Inc 2019.
44. Procainamide. Lexi-Comp (Lexi-Drugs) [database online]. Lexi-Comp, Inc; October 26, 2020.
45. Tisdale JE, Rudis MI, Padhi ID, et al. Disposition of procainamide in patients with chronic congestive heart failure receiving medical therapy. J Clin Pharmacol. 1996;36(1):35–41. https://doi.org/10.1002/j.1552-4604.1996.tb04149.x.
46. Stiell IG, Clement CM, Perry JJ, et al. Association of the Ottawa Aggressive Protocol with rapid discharge of emergency department patients with recent-onset atrial fibrillation or flutter. CJEM. 2010;12(3):181–91. https://doi.org/10.1017/s1481803500012227.
47. Sheldon PJ, Williams WR. Procainamide-induced systemic lupus erythematosus. Ann Rheum Dis. 1970;29(3):236–43.
48. Hellestrand KJ, Bexton RS, Nathan AW, Spurrell RA, Camm AJ. Acute electrophysiological effects of flecainide acetate on cardiac conduction and refractoriness in man. Br Heart J. 1982;48(2):140–8.
49. Estes NA, Garan H, Ruskin JN. Electrophysiologic properties of flecainide acetate. Am J Cardiol. 1984;53(5):26B-29B. https://doi.org/10.1016/0002-9149(84)90498-3.
50. Roden DM, Woosley RL. Flecainide. N Engl J Med. 1986;315(1):36–41. https://doi.org/10.1056/NEJM198607033150106.
51. Grant AO. Propafenone: an effective agent for the management of supraventricular arrhythmias. J Cardiovasc Electrophysiol. 1996;7(4):353–64. https://doi.org/10.1111/j.1540-8167.1996.tb00537.x.
52. Ashraf H, Ko NK, Ladia V, et al. Use of flecainide in stable coronary artery disease: an analysis of its safety in both non-obstructive and obstructive coronary artery disease. Am J Cardiovasc Drugs. 2021;21(5):563–72. https://doi.org/10.1007/s40256-021-00483-9.
53. Vallurupalli S, Pothineni NVK, Deshmukh A, Paydak H. Utility of routine exercise testing to detect rate-related QRS widening in patients without structural heart disease on class Ic antiarrhythmic agents (Flecainide and Propafenone). Am J Cardiol. 2015;116(5):730–2. https://doi.org/10.1016/j.amjcard.2015.05.039.
54. Gao X, Guha A, Buck B, et al. Initiation and outcomes with Class Ic antiarrhythmic drug therapy. Indian Pacing Electrophysiol J. 2018;18(2):68–72. https://doi.org/10.1016/j.ipej.2017.12.001.
55. Alboni P, Botto GL, Baldi N, et al. Outpatient treatment of recent-onset atrial fibrillation with the "Pill-in-the-Pocket" approach. N Engl J Med. 2004;351(23):2384–91. https://doi.org/10.1056/NEJMoa041233.
56. Flecainide [package insert]. Columbus, OH. Roxane Laboratories Inc, 2014.
57. Echt DS, Ruskin JN. Use of flecainide for the treatment of atrial fibrillation. Am J Cardiol. 2020;125(7):1123–33. https://doi.org/10.1016/j.amjcard.2019.12.041.
58. Propafenone [package insert]. Research Triangle Park, NC. GlaxoSmithKline. 2013.
59. Tikosyn [package insert]. New York, NY. Pfizer. 2018.
60. Kalus JS, Mauro VF. Dofetilide: a class III-specific antiarrhythmic agent. Ann Pharmacother. 2000;34(1):44–56. https://doi.org/10.1345/aph.19185.
61. Huang HD, Waks JW, Steinhaus DA, Zimetbaum P. Magnitude of increase in QTc interval after initiation of dofetilide in patients with persistent atrial fibrillation is associated with increased rates of pharmacological cardioversion and long-term freedom from recurrent atrial fibrillation. Heart Rhythm. 2016;13(7):1410–7. https://doi.org/10.1016/j.hrthm.2016.02.016.
62. Shantha G, Chugh A, Crawford T, et al. Comparative efficacy of dofetilide versus amiodarone in patients with atrial fibrillation. JACC Clin Electrophysiol. 2021;7(5):642–8. https://doi.org/10.1016/j.jacep.2020.11.027.
63. Dar T, Murtaza G, Yarlagadda B, et al. Dofetilide initiation and implications of deviation from the standard protocol—a real world experience. J Atr Fibrillation. 2019;12(4):2265. https://doi.org/10.4022/jafib.2265.
64. Mascarenhas DAN, Mudumbi PC, Kantharia BK. Outpatient initiation of dofetilide: insights from the complexities of atrial fibrillation management during the COVID-19 lockdown. J Interv Card Electrophysiol. 2022;63(1):21–8. https://doi.org/10.1007/s10840-021-00942-y.
65. Torp-Pedersen C, Møller M, Bloch-Thomsen PE, et al. Dofetilide in patients with congestive heart failure and left ventricular dysfunction. N Engl J Med. 1999;341(12):857–65. https://doi.org/10.1056/NEJM199909163411201.
66. Lars K, Poulerik BT, Mogens M, et al. Effect of dofetilide in patients with recent myocardial infarction and left-ventricular dysfunction: a randomised trial. Lancet. 2000;356(9247):2052–8. https://doi.org/10.1016/s0140-6736(00)03402-4.
67. Sotalol [package insert]. Weston, Florida. Apotex. 2015.
68. Shantsila E, Watson T, Lip GY. Drug-induced QT-interval prolongation and proarrhythmic risk in the treatment of atrial arrhythmias. Europace. 2007;9(Supplement 4):iv37–44. https://doi.org/10.1093/europace/eum169.
69. Benditt DG, Williams JH, Jin J, et al. Maintenance of sinus rhythm with oral d,l-sotalol therapy in patients with symptomatic atrial fibrillation and/or atrial flutter. D,l-Sotalol Atrial Fibrillation/Flutter Study Group. Am J Cardiol. 1999;84(3):270-277. doi: https://doi.org/10.1016/s0002-9149(99)00275-1
70. Somberg JC, Vinks AA, Dong M, Molnar J. Model-informed development of sotalol loading and dose escalation employing an intravenous infusion. Cardiol Res. 2020;11(5):294–304. https://doi.org/10.14740/cr1143.
71. Mascarenhas DAN, Mudumbi PC, Kantharia BK. Outpatient initiation of sotalol in patients with atrial fibrillation: utility of cardiac implantable electronic devices for therapy monitoring. Am J Cardiovasc Drugs. 2021;21(6):693–700. https://doi.org/10.1007/s40256-021-00493-7.
72. Ibutilide [package insert]. New York, NY. Pfizer. 2016.
73. Oral H, Souza JJ, Michaud GF, et al. Facilitating transthoracic cardioversion of atrial fibrillation with ibutilide pretreatment. N Engl J Med. 1999;340(24):1849–54. https://doi.org/10.1056/NEJM199906173402401.
74. Amiodarone [package insert]. Philadelphia, PA. Wyeth Pharmaceuticals. 2018.
75. Multaq [package insert]. Bridgewater, NJ. Sanofi-Aventis 2009.
76. Tave A, Goehring E, Desai V, et al. Risk of interstitial lung disease in patients treated for atrial fibrillation with dronedarone versus other antiarrhythmics. Pharmacoepidemiol Drug Saf. 2021. https://doi.org/10.1002/pds.5233.
77. Connolly SJ, Camm AJ, Halperin JL, et al. Dronedarone in high-risk permanent atrial fibrillation. N Engl J Med.

2011;365(24):2268–76. https://doi.org/10.1056/NEJMoa1109867.
78. Goehring EL, Bohn RL, Pezzullo J, et al. Outcomes associated with dronedarone use in patients with atrial fibrillation. Am J Cardiol. 2020;135:77–83. https://doi.org/10.1016/j.amjcard.2020.08.026.
79. Kuck KH, Brugada J, Fürnkranz A, et al. Cryoballoon or radiofrequency ablation for paroxysmal atrial fibrillation. N Engl J Med. 2016;374(23):2235–45. https://doi.org/10.1056/NEJMoa1602014.
80. 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. EP Europace. 2018;20(1):e1–160. https://doi.org/10.1093/europace/eux274.
81. Di Biase L, Mohanty P, Mohanty S, et al. Ablation versus amiodarone for treatment of persistent atrial fibrillation in patients with congestive heart failure and an implanted device: results from the AATAC multicenter randomized trial. Circulation. 2016;133(17):1637–44. https://doi.org/10.1161/CIRCULATIONAHA.115.019406.
82. Marrouche NF, Brachmann J, on behalf of the CASTLE-AF Steering Committee. Catheter Ablation versus Standard Conventional Treatment in Patients with Left Ventricular Dysfunction and Atrial Fibrillation (CASTLE-AF)—Study Design: CASTLE-AF STUDY DESIGN. Pac Clin Electrophysiol. 2009;32(8):987-994. doi:https://doi.org/10.1111/j.1540-8159.2009.02428.x
83. Packer DL, Mark DB, Robb RA, et al. Effect of catheter ablation vs antiarrhythmic drug therapy on mortality, stroke, bleeding, and cardiac arrest among patients with atrial fibrillation: the CABANA randomized clinical trial. JAMA. 2019;321(13):1261. https://doi.org/10.1001/jama.2019.0693.
84. Poole JE, Bahnson TD, Monahan KH, et al. Recurrence of atrial fibrillation after catheter ablation or antiarrhythmic drug therapy in the CABANA trial. J Am Coll Cardiol. 2020;75(25):3105–18. https://doi.org/10.1016/j.jacc.2020.04.065.
85. Wazni OM, Dandamudi G, Sood N, et al. Cryoballoon Ablation as Initial Therapy for Atrial Fibrillation. N Engl J Med. 2021;384(4):316–24. https://doi.org/10.1056/NEJMoa2029554.
86. Andrade JG, Wells GA, Deyell MW, et al. Cryoablation or drug therapy for initial treatment of atrial fibrillation. N Engl J Med. 2021;384(4):305–15. https://doi.org/10.1056/NEJMoa2029980.
87. Roux JF, Zado E, Callans DJ, et al. Antiarrhythmics After Ablation of Atrial Fibrillation (5A Study). Circulation. 2009;120(12):1036–40. https://doi.org/10.1161/CIRCULATIONAHA.108.839639.
88. Leong-Sit P, Roux JF, Zado E, et al. Antiarrhythmics after ablation of atrial fibrillation (5A Study): six-month follow-up study. Circ Arrhythm Electrophysiol. 2011;4(1):11–4. https://doi.org/10.1161/CIRCEP.110.955393.
89. Ad N, Damiano RJ, Badhwar V, et al. Expert consensus guidelines: Examining surgical ablation for atrial fibrillation. J Thorac Cardiovasc Surg. 2017;153(6):1330-1354.e1. https://doi.org/10.1016/j.jtcvs.2017.02.027.
90. Whitlock RP, Belley-Cote EP, Paparella D, et al. Left atrial appendage occlusion during cardiac surgery to prevent stroke. N Engl J Med. 2021;384(22):2081–91. https://doi.org/10.1056/NEJMoa2101897.
91. Carlsson J, Miketic S, Windeler J, et al. Randomized trial of rate-control versus rhythm-control in persistent atrial fibrillation: the Strategies of Treatment of Atrial Fibrillation (STAF) study. J Am Coll Cardiol. 2003;41(10):1690–6. https://doi.org/10.1016/s0735-1097(03)00332-2.
92. Wyse DG, Waldo AL, DiMarco JP, et al. A comparison of rate control and rhythm control in patients with atrial fibrillation. N Engl J Med. 2002;347(23):1825–33. https://doi.org/10.1056/NEJMoa021328.
93. Van Gelder IC, Hagens VE, Bosker HA, et al. A comparison of rate control and rhythm control in patients with recurrent persistent atrial fibrillation. N Engl J Med. 2002;347(23):1834–40. https://doi.org/10.1056/NEJMoa021375.
94. Roy D, Talajic M, Nattel S, et al. Rhythm control versus rate control for atrial fibrillation and heart failure. N Engl J Med. 2008;358(25):2667–77. https://doi.org/10.1056/NEJMoa0708789.
95. Kirchhof P, Camm AJ, Goette A, et al. Early rhythm-control therapy in patients with atrial fibrillation. N Engl J Med. 2020;383(14):1305–16. https://doi.org/10.1056/NEJMoa2019422.
96. Crijns HJGM, Gosselink ATM, Lie KJ. Propafenone versus disopyramide for maintenance of sinus rhythm after electrical cardioversion of chronic atrial fibrillation: a randomized, double-blind study. Cardiovasc Drug Ther. 1996;10(2):145–52. https://doi.org/10.1007/BF00823592.
97. Coplen SE, Antman EM, Berlin JA, Hewitt P, Chalmers TC. Efficacy and safety of quinidine therapy for maintenance of sinus rhythm after cardioversion. A meta-analysis of randomized control trials. Circulation. 1990;82(4):1106–16. https://doi.org/10.1161/01.CIR.82.4.1106.
98. Stiell IG, Clement CM, Symington C, Perry JJ, Vaillancourt C, Wells GA. Emergency department use of intravenous procainamide for patients with acute atrial fibrillation or flutter. Acad Emerg Med. 2007;14(12):1158–64. https://doi.org/10.1197/j.aem.2007.07.016.
99. Stroobandt R, Stiels B, Hoebrechts R. Propafenone for conversion and prophylaxis of atrial fibrillation. Am J Cardiol. 1997;79(4):418–23. https://doi.org/10.1016/S0002-9149(96)00779-5.
100. Alt E, Ammer R, Lehmann G, et al. Patient characteristics and underlying heart disease as predictors of recurrent atrial fibrillation after internal and external cardioversion in patients treated with oral sotalol. Am Heart J. 1997;134(3):419–25. https://doi.org/10.1016/S0002-8703(97)70076-0.
101. Le Heuzey JY, De Ferrari GM, Radzik D, Santini M, Zhu J, Davy JM. A Short-term, randomized, double-blind, parallel-group study to evaluate the efficacy and safety of dronedarone versus amiodarone in patients with persistent atrial fibrillation: the DIONYSOS study. J Cardiovasc Electrophysiol. 2010;21(6):597–605. https://doi.org/10.1111/j.1540-8167.2010.01764.x.