Pathophysiology and treatment of adults with arrhythmias in the emergency department, part 1: Atrial arrhythmias

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Purpose: This article, the first in a 2-part review, aims to reinforce current literature on the pathophysiology of cardiac arrhythmias and various evidence-based treatment approaches and clinical considerations in the acute care setting. Part 1 of this series focuses on atrial arrhythmias.

Summary: Arrhythmias are prevalent throughout the world and a common presenting condition in the emergency department (ED) setting. Atrial fibrillation (AF) is the most common arrhythmia worldwide and expected to increase in prevalence. Treatment approaches have evolved over time with advances in catheter-directed ablation. Based on historic trials, heart rate control has been the long-standing accepted outpatient treatment modality for AF, but the use of antiarrhythmics is often still indicated for AF in the acute setting, and ED pharmacists should be prepared and poised to help in AF management. Other atrial arrhythmias include atrial flutter (AFL), atrioventricular nodal reentry tachycardia (AVNRT), and atrioventricular reentrant tachycardia (AVRT), which warrant distinction due to their unique pathophysiology and because each requires a different approach to utilization of antiarrhythmics. Atrial arrhythmias are typically associated with greater hemodynamic stability than ventricular arrhythmias but still require nuanced management according to patient subset and risk factors. Since antiarrhythmics can also be proarrhythmic, they may destabilize the patient due to adverse effects, many of which are the focus of black-box label warnings that can be overreaching and limit treatment options. Electrical cardioversion for atrial arrhythmias is generally successful and, depending on the setting and/or hemodynamics, often indicated.

Conclusion: Atrial arrhythmias arise from a variety of mechanisms, and appropriate treatment depends on various factors. A firm understanding of physiological and pharmacological concepts serves as a foundation for exploring evidence supporting agents, indications, and adverse effects in order to provide appropriate care for patients.

Keywords: amiodarone; anti-arrhythmia agents; arrhythmias, cardiac; atrial fibrillation; tachycardia, supraventricular; tachycardia, atrioventricular nodal reentry

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Authors' note: The terms dysrhythmia *and* arrhythmia *are interchangeable. While we believe that* dysrhythmia *is a more apt academic term,* arrhythmia *is used throughout this article due to its prevalence in the literature.*

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The therapeutic approach to cardiac arrhythmias can seem complex and overwhelming. First, interpretation of an electrocardiogram (ECG) to diagnose arrhythmias may be intimidating. In the acute care setting, appropriate, expeditious therapy is required to control arrhythmias—a daunting task due to the complex overlap in medication classes and rhythm control indications. Finally, there are risks of rhythm degeneration and harm to the patient because antiarrhythmics can also be proarrhythmic. However, participation in arrhythmia workups and pharmacotherapy is a unique intervention

opportunity for acute care clinical pharmacists.

Most true antiarrhythmic medications (Vaughan-Williams class I and III agents) are prescribed less frequently than they were 20 years ago, largely due to multiple landmark trials favoring rate control over rhythm control and advances in procedural interventions such as catheter-directed ablation.[1-3] For many uncomplicated atrial arrhythmias, such procedures are even preferred because they are durable and safe. Although this treatment approach requires hospital admission and cardiac catheterization, patients are often discharged the same day.[4,5] However, antiarrhythmic medications are often still used for initial rate and rhythm control in the acute setting. The presence of pharmacists in the emergency department (ED) setting has increased throughout the US, and it is imperative that ED pharmacists be prepared to appropriately manage new-onset arrhythmias.[6]

Part 1 of this 2-part review focuses on atrial arrhythmias, the most common and relevant being atrial fibrillation (AF), atrial flutter (AFL), atrioventricular nodal reentry tachycardia (AVNRT), and AV reentrant tachycardia (AVRT). These are types of supraventricular tachycardia (SVT), typically narrow-complex tachycardias originating above the bundle of His. It is worth emphasizing that AF and AFL are SVTs. However, the term *paroxysmal SVT* (pSVT) is usually applied broadly to encompass SVT and other tachycardias covered in detail below, such as AVNRT and AVRT.

Figure 1 provides a schematic for categorizing arrhythmias that we will refer to throughout this review. A detailed review of ECGs is beyond the scope of this paper, and we direct readers to a publication by Mar and colleagues[7] for a review of the topic for pharmacists. ECGs are integral to acute patient workups due to their value in ruling out important cardiac etiologies for common presentations (eg, syncope, chest pain) when differential diagnoses are broad.

KEY POINTS

- Atrial arrhythmias resulting in hemodynamic instability require emergency electrical cardioversion regardless of symptom duration.
- Rate or rhythm control may be preferred, depending on patient-specific factors, but recognizing when atrial fibrillation is secondary to another condition (eg, sepsis, toxicological insult, electrolyte imbalance, alcohol withdrawal) is an important step in treating the underlying cause and avoiding harm.
- Pharmacological cardioversion with class I and class III antiarrhythmic agents may be useful in the acute setting for atrial arrhythmias provided that adverse effects and contraindications are considered.

Arrhythmias pertaining to toxicology will not be covered in depth due to the large variability in mechanisms that are beyond the natural pathology of arrhythmias, for which therapeutic approaches are often individualized.

Epidemiology

The burden of cardiovascular disease remains high in the US, and cardiovascular disease is the leading cause of death across the globe, resulting in an estimated 32% of all deaths worldwide.[8] While arrhythmias can be caused by genetic factors such as channelopathies and inherited cardiomyopathies, the prevalence of arrhythmias in the US can be largely attributed to cardiovascular disease.[9]

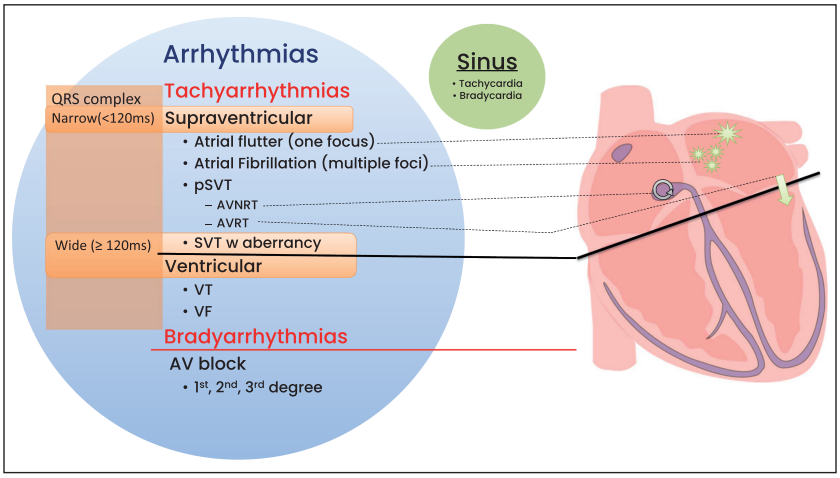
AF is the most commonly occurring arrhythmia, and its prevalence is increasing worldwide because of its association with age as well as modifiable risk factors such as hypertension, obesity, smoking, cardiac disease, and diabetes mellitus.[10] The lifetime risk of AF is currently estimated to be 1 in 3 among White people and 1 in 5 among Black people.[9,10] AF carries its own annual risk of stroke, ranging from 1% to 20% (4.5% on average) if not anticoagulated, with wide variation depending on risk factors and comorbidities. This risk is stratified in practice by the CHA_2DS_2-VASc scoring tool, derived from closely followed cohorts.[9,11] However, due to the asymptomatic nature of most atrial arrhythmia, these risks may be considered an underestimation.[12]

Cardioversion

Cardioversion describes the act of converting an arrhythmia to normal sinus rhythm (NSR) and can be achieved pharmacologically or electrically.[13] Depending on the scenario, electrical cardioversion may provide an opportunity for pharmacist involvement with procedural sedation in the acute setting. If the patient is stable but a poor candidate for sedation, the pharmacist can be involved with decisions regarding pharmacological cardioversion.

Electrical cardioversion, also known as direct current cardioversion (DCCV), consists of primarily 2 modalities: synchronized cardioversion and defibrillation. Modern hospital machines capable of DCCV are termed defibrillators and capable of both of these modalities. In both scenarios 2 pads are placed on the patient, one anteriorly and the other either posteriorly or anterolaterally.[14,15] Synchronized cardioversion is the modality employed when electrically cardioverting arrhythmias that have clearly defined R-wave peaks, such as most atrial arrhythmias, and allows for the electrical impulse to be delivered precisely when the R wave occurs. Synchronization is important to avoid unfavorable depolarization during the T wave, which could precipitate VF. Defibrillation is an unsynchronized shock delivered for unstable ventricular arrhythmias, as

Figure 1. Schematic for categorizing arrhythmias. Arrhythmias can be classified as tachyarrhythmias or bradyarrhythmias. Tachyarrhythmias are often further divided, based on the width of the QRS complex on an electrocardiogram (ECG), as narrow-complex (<120 ms) or wide-complex (≥120 ms); QRS width may suggest where the arrhythmia originates. Narrow-complex tachyarrhythmias are associated with a narrow (ie, normal) QRS duration since there is no pathology along the His-Purkinje system or ventricular myocardium, which generally dictates the QRS duration. AV nodal reentry tachycardia (AVNRT) and AV reentrant tachycardia (AVRT) are similar in name but pathologically unrelated. AVNRT, commonly referred to as paroxysmal supraventricular tachycardia, involves a reentry loop within the AV node. AVRT is an umbrella term for arrhythmias involving a congenital electrical pathway communicating between the atrium and ventricle; Wolff-Parkinson-White syndrome is an example of AVRT wherein a delta wave resulting from early ventricular depolarization may be seen on ECG. Wide-complex tachycardias (WCTs) should elicit concern for ventricular arrhythmias. However, SVT in the presence of a conduction aberrancy such as a bundle branch block (BBB) may appear as a WCT on ECG. Bradyarrhythmias involve AV node dysfunction to varying degrees, which often correlates with severity. Sinus arrhythmias follow normal electrical pathways and can be tachycardia or bradycardia, with a narrow or wide QRS complex, depending on various scenarios such as electrolyte abnormalities or the presence of a BBB.*Optional if onset definitely <24 hours and CHA_2DS_2-VASc = 0_{male} or 1_{female}.[25]



R-wave synchronization is not attainable due to unpredictable QRS timing and morphology.[15] Additionally, little concern for worsening the rhythm exists in this scenario. In general, defibrillation is delivered with a higher energy. Contemporary machines almost exclusively deliver biphasic energy, utilizing energy more efficiently and causing less harm, and are recommended by guidelines.[16] Recommendations for cardioversion and defibrillation energy settings are addressed in detail elsewhere.[15,16]

In stable cases, sedation is important to avoid patient discomfort. The pharmacist can be instrumental in choosing an appropriate agent based on patient-specific characteristics. Short-acting sedatives that have minimal effect on hemodynamics tend to be ideal.[17,18] Because the risks of sedation outweigh the benefits and time is essential, unstable patients should have electrical cardioversion prioritized above sedation.[16]

AF and AFL

Pathophysiology. AF is characterized by an extremely rapid atrial depolarization rate (400-600 beats/min [bpm]) secondary to multiple irritable foci in the atrial tissue, resulting in fibrillating or "quivering." The natural refractory period of the atrioventricular (AV) node limits the number of impulses able to reach the ventricles, most commonly resulting in AF with an irregular rapid ventricular rate/response (RVR). Ineffective atrial contraction leads to thrombus formation, frequently in the left atrial appendage, which subsequently increases the risk of stroke. Notable ECG features include an irregularly irregular rhythm with no discernible P waves.[19] AF can be classified into various levels of duration and permanence; however, the scope of this review will only include AF of acute onset (ie, within 48 hours).[20]

In contrast to AF, AFL is caused by a single reentry circuit (~300 bpm) within the right atrium and is identifiable as a "sawtooth" pattern on ECG.[21] Ventricular rate is dependent on the AV conduction ratio. Ratios of 2:1, 3:1, and 4:1 occur most frequently, resulting in fixed (ie, regular) ventricular rates of 150, 100, and 75 bpm, respectively. 1:1 conduction is rare but if present generally results in rapid clinical deterioration. AF and AFL are generally managed in a similar fashion, with minor exceptions; therefore, the following approach to management may be applied to both arrhythmias.[20]

Initial approach to management. Initial considerations for acute management of AF/AFL with RVR in the ED setting should focus on assessment of hemodynamic stability and whether AF/AFL is the primary cause.

Precipitating events such as sepsis, surgery, hemorrhage, MI, pulmonary embolism, and heart failure may be the underlying cause of AF and, if present, should be identified and treated with priority. This should be emphasized since attempts to control heart rate or rhythm in secondary AF may be not only unsuccessful but associated with a nearly 6-fold increased rate of adverse events.[22] Hemodynamic instability exists on a spectrum and is defined as altered mental status, systolic blood pressure of <90 mm Hg, cardiac ischemia, or decompensated heart failure with pulmonary edema.[23] Hemodynamic compromise due to primary AF or AFL is rare but, if suspected, should be managed via emergent synchronized DCCV, which is recommended regardless of AF/AFL duration.[24,25]

Once secondary AF/AFL is excluded, alleviation of symptoms may be accomplished with either a rate control or a rhythm control strategy. Standard teaching and guidelines support rate control as a conservative approach, with rhythm control reserved for patients with an AF/AFL duration of 48 hours or less who are not anticoagulated (referred to as the "48 hour rule") in order to minimize stroke risk.[20,24,26] Due to several factors we address later in this review, rate control has been the predominant strategy in both acute and chronic management of AF/AFL. However, shared decision-making is an important component when the decision is not straightforward.

Rate control. Several randomized controlled trials (RCTs) and meta-analyses have demonstrated no significant difference in the outcomes of all-cause mortality, stroke, embolism, worsening heart failure, and requirement of a pacemaker between rate and rhythm control strategies.[27-30] These trials demonstrated that rhythm control medications carry a higher risk of adverse events, and a preference for a long-term rate control strategy is reflected in current guidelines.[24,31] It is important to note that several of these RCTs, including the landmark AFFIRM trial, were conducted outside of an ED setting and enrolled patients with persistent and long-standing persistent AF. Selection of a rate control agent may be influenced by provider familiarity, institutional pathways, oral AV nodal blocker prescription(s) prior to arrival, and comorbidities or compelling indications. For these reasons, β-blockers and nondihydropyridine calcium channel blockers (non-DHP CCBs) are often considered first-line therapies for initial treatment in the ED setting.

In the acute setting, published data comparing non-DHP CCBs to β-blockers are retrospective, with significant heterogeneity. Two small RCTs have compared the effectiveness of rate control with metoprolol versus diltiazem in adult ED patients with AF/AFL.[32,33] Diltiazem was both more rapid and effective in achieving rate control; however, the dose of metoprolol studied may have been too low for an appropriate comparison. The addition of a second AV nodal blocker successfully achieved an HR of <110 bpm 46% of the time when rate control was not achieved with the first agent.[34]

Retrospective data suggest that use of intravenous (IV) metoprolol and IV diltiazem is associated with similar reductions in blood pressure and hypotension when used for initial management of AF along with RVR in the ED, so either agent is generally acceptable.[35,36] Verapamil is considered to be as effective as diltiazem for AF rate control, with comparable rates of hypotension.[37]

It is important to understand that both β-blockers and non-DHP CCBs have similar negative inotropic and chronotropic properties. In the setting of acute decompensated heart failure (ADHF) or reduced ejection fraction (EF), any negative inotrope should be used with caution and an understanding of pharmacokinetic properties. If a patient has a history of heart failure but adequate EF, either β-blockers or non-DHP CCBs can be used safely in the acute setting.[38] The dogma of heart failure precluding the use of non-DHP CCBs should be thoughtfully examined. Several landmark trials have demonstrated β-blockers provide a long-term survival benefit in heart failure with reduced EF. Therefore, initiating β-blockers in the ED may be done for the sake of long-term continuation to benefit such patients.[39-41] On the other hand, non-DHP CCBs have been largely demerited in heart failure due to findings of the MDPIT trial, published in 1991. However, the study population and outcome measurements should not be extrapolated and applied to treatment of acute AF or perhaps even chronic AF with heart failure.[42] In fact, there has been a renewed focus on using diltiazem for the treatment of AF in the setting of heart failure with reduced EF.[43]

Current guidelines recommend targeting a resting heart rate (HR) of ≤100 to 110 bpm; however, a lower goal (ie, 80 bpm) may be necessary in patients with persistent symptoms despite lenient control.[23-25] Although high-quality data is scarce, strict targets (eg, <80 bpm) were not found to be superior to lenient targets in the prevention of cardiovascular death, stroke, embolism, heart failure hospitalization, bleeding, or life-threatening arrhythmias.[44,45]

When the goal HR is not achieved with a β-blocker or non-DHP CCB, an alternative method of AV nodal blockade may be necessary. Digoxin is not preferred for acute rate control due to its slow initial onset (≥1 hour) and peak effect of approximately 6 hours after IV administration.[23] Furthermore, chronic therapy is associated with an increase in mortality in patients with and without heart failure.[46] One benefit of digoxin is that it is the only AV nodal blocker with positive inotropy and therefore may warrant consideration in patients with acutely decompensated left ventricular EF or pulmonary arterial hypertension.[24,25]

Amiodarone is considered a Vaughan-Williams Class III antiarrhythmic but also slows AV node conduction by antagonizing β-adrenergic receptors and calcium channels.[47] Amiodarone may be useful for rate control in critically ill patients,

but its slow onset and inferior efficacy compared to that of non-DHP CCBs limit its use in acute settings.[23] Polysorbate-80 is commonly added to amiodarone and possesses additive effects that may contribute to hemodynamic instability.

IV magnesium has been evaluated for rate control as an alternative or adjunctive agent, with conflicting results. Magnesium inhibits L-type calcium current in cardiac cells, which results in delayed AV nodal conduction and a prolonged atrial refractory period.[48] Importantly, those effects are seen regardless of magnesium serum levels, and so obtaining serum levels is not necessary to justify administration. In multiple meta-analyses, IV magnesium more than doubled the success of rate control and decreased time to response compared to placebo or antiarrhythmic agents.[49,50] Studied doses of IV magnesium have ranged from 1 to 9 g, but the recent LOMAGHI trial concluded that doses of 4.5 g provided similar rate control, with fewer adverse events, as 9-g doses.[51] Potential adverse effects include mild hypotension and flushing.

Rhythm control. Spontaneous conversion has been reported to occur at rates ranging from 9% to 83% and is more likely to occur in AF of short duration (ie, <24 hours).[52] In patients who do not spontaneously convert, the decision to restore NSR in those with recent-onset AF or AFL should be based on patient preference and shared decision-making. Cardioversion can be achieved either electrically or pharmacologically. DCCV is highly efficacious (≥90%) and reduces ED length of stay compared to a pharmacological approach but requires procedural sedation and an increased level of resource utilization.[53] The efficacy of pharmacological cardioversion ranges widely by agent and setting. In settings with limited resources, it is reasonable to attempt pharmacological cardioversion initially, which may circumvent the need for DCCV.[54]

In contrast to the AFFIRM trial, the recent EAST-AFNET 4 study, an international RCT that enrolled older patients with newly diagnosed AF (<12 months) and a CHA_2DS_2-VASc score of ≥2, concluded that early rhythm control was superior to usual care in reducing cardiovascular death and stroke (hazard ratio, 0.79; 95% CI, 0.66-0.94).[55] This study will impact future long-term AF management as it highlights the idea that AF begets AF and that restoration of NSR is ultimately beneficial, even in older patients with comorbidities. Of note, this study was performed in Europe and early rhythm control with antiarrhythmic agents, most commonly flecainide, was employed in 87% of patients. At 2 years, 65% of patients were still receiving an antiarrhythmic agent and 30% had catheter ablations performed.[55] Whereas the EAST-AFNET study is an important addition to the literature as it augments evidence from the older AFFIRM and RACE trials, few published studies are available to guide clinicians in determining the appropriate course of action in the acute setting. In such settings, it is paramount to first exclude secondary etiologies of AF and prudent to consider an immediate rhythm control modality according to time frame and CHA_2DS_2-VASc score, as discussed below.[24,31]

Procainamide is a class IA sodium channel blocker used for both atrial and ventricular arrhythmias. Cardioversion of atrial arrhythmias with procainamide is more likely to be successful in patients with recent-onset AF (50%-60% effectiveness) versus AFL (28.1% effectiveness).[54,56] Procainamide was shown to be safe and effective in the ED setting for cardioversion of atrial arrhythmias with use of the Ottawa Aggressive Protocol, which provides a reasonable option for management of select patients presenting within 48 hours from symptom onset.[56] Hepatic acetylation of procainamide produces a renally eliminated major active metabolite, *N*-acetylprocainamanide (NAPA), which has potent potassium channel blocking properties and may prolong QT interval duration.[57] Patients should be observed for widening of the QRS complex, and the infusion should be stopped when an increase of 50% above baseline is noted or the arrhythmia is controlled. Hypotension is the most common adverse event associated with procainamide use (occurring at a rate of 5%-10%) and can be resolved with administration of a 250- to 500-mL crystalloid bolus in addition to temporarily pausing or slowing the infusion rate.[58,59]

Flecainide and propafenone are class IC sodium channel blockers and are only available orally in the US. Unlike many other antiarrhythmics, they do not alter the effective refractory period but, rather, slow depolarization. Therefore, any QT prolongation is a result of QRS widening.[60,61] For paroxysmal AF, an outpatient dose administered when symptoms develop (eg, a "pill-in-the-pocket" strategy) is a reasonable approach if deemed safe after an initial trial in a monitored setting. Class IC agents are contraindicated in structural heart disease (SHD) as a result of the CAST trial. The clinical utility of IC agents has since been traditionally limited to treatment of AF/AFL in younger patients without comorbidities since SHD widely involves a variety of conditions, including ischemic heart disease, valvular pathologies, and heart failure.[60-64] However, it should be noted that US black-box warnings for class IC agents were based on results of the CAST trial, which studied ventricular tachycardia (VT) suppression after MI rather than patients with AF and any SHD. Recently, in Europe, where IC agents are more liberally utilized and labeling is more nuanced with regard to contraindications, Kirchhof and colleagues[55] demonstrated successful treatment of AF with an early rhythm control approach in patients who averaged 70 years of age and had an average CHA_2DS_2-VASc score of 3. Most patients were treated with propafenone or flecainide.

Ibutilide is a class III selective potassium channel antagonist administered intravenously. Cardioversion with ibutilide is more likely to be successful in AFL (50%-75% effectiveness) vs AF (30%-55% effectiveness) and should occur within 30 to 60 minutes.[65-71] Prolongation of the HR-corrected

QT interval (QTc) with ibutilide use is dose dependent. The ibutilide product labeling cites an incidence of nonsustained VT (usually in the form of torsades de pointes [TdP]) of up to 3%, but occurrence of TdP was driven by patients with a history of heart failure or electrolyte derangements.[72] Otherwise, the risk of TdP is 0.8% or perhaps lower, according to an analysis of observational data.[71] Nevertheless, serum potassium and magnesium levels should be obtained and repleted prior to ibutilide administration. Prophylactic magnesium (at doses of ≥4 g) has been shown to improve conversion rates and decrease the risk of TdP associated with ibutilide.[73-75] Ibutilide should not be administered to patients with a prolonged QTc (ie, >440 milliseconds), reduced LVEF, or concern for MI.[23,24] Dofetilide, an oral class III agent, may be used for long-term maintenance of sinus rhythm but is not routinely used in the ED setting for acute cardioversion. Initiation of dofetilide requires hospital admission with continuous ECG monitoring to minimize the risk of QT prolongation and ventricular arrhythmias.[76]

Amiodarone is recommended as a second-line agent for acute AF rhythm management due to a delay in sinus conversion (up to 8 hours) compared to ibutilide.[23,24,77] A meta-analysis including 1,174 patients demonstrated amiodarone is similar to placebo at 2 hours, inferior to IC agents up to 8 hours, and similar to class 1C agents at 24 hours from a cardioversion standpoint.[78] In a propensity score matching study, the median time for cardioversion was 420 minutes in the amiodarone group and 55 minutes in the group treated with class IC agents, with similar rates of adverse effects.[79] Amiodarone is recommended as a safe alternative to other agents when treating AF in the setting of SHD or an LVEF of <40%.[20] Amiodarone is also considered an effective broad-spectrum antiarrhythmic and suitable for many patients with AF being admitted to the hospital because it offers the option of transition to oral therapy. Several landmark trials support use of amiodarone as an effective maintenance therapy for patients with cardiac comorbidities despite adverse effects that affect multiple organs and are associated with the cumulative amiodarone dose.[80-82] Phlebitis, hypotension, and bradycardia are the most common adverse medication reactions observed with IV administration of amiodarone. Although QT interval prolongation may occur, the rate of TdP with amiodarone is low; explanations for this are elusive and controversial, but the leading theories involve QT dispersion (ie, smaller differences in interlead QT intervals correlate with lower rates of TdP) with amiodarone use and the fact that amiodarone has elements of other Vaughan-Williams class effects that may be protective against the early after-depolarizations thought to provoke TdP.[83]

Rhythm control can be an important consideration in appropriately selected patients. Although the historical literature reports unimpressive rates of sinus rhythm maintenance at 1 year (40%-60%) with both electrical and pharmacologic maintenance therapy, advances in practice such as catheter ablation have undoubtedly improved care.[81,84-86] Dosing, pharmacokinetics, and selected clinical pearls regarding rate and rhythm agents are described in Table 1.

Anticoagulation. The duration of AF/AFL must be determined prior to cardioversion (pharmacological or electrical) in the stable patient. Patient history can be unreliable given the frequency of asymptomatic AF, but smartwatches and other monitoring devices may become a reliable safeguard in the future.[112] When cardioversion occurs in the acute setting, the 48-hour rule has historically been used to determine the risk of cardioembolic stroke in non-anticoagulated patients. However, this rule is now in question after a large retrospective study provided evidence of a more distinct time frame for risk stratification.[113] When compared to a time frame of less than 12 hours, a time to cardioversion of 12 to 24 hours independently predicted a higher 30-day rate of cardioembolism (odds ratio, 4.0 [95% CI, 1.7-9.1]). The rate of cardioembolic complications was 0.3% in the less-than-12-hour group, compared to 1.1% in the 12- to 24-hour group (P = 0.004). However, within all time frames, higher-risk groups (eg, patients with a CHA_2DS_2-$VASc_2$ score of >1) had higher rates of stroke.[114] This finding highlights how scoring tools can be utilized in the acute setting along with duration of AF. Patients with a higher stroke risk should be managed with rate control and anticoagulation until further workup and shared decision-making can form a long-term treatment plan.[113,114]

A pooled analysis of 10 trials including over 3,500 cardioversions for AF with a time from symptom onset of greater than 48 hours demonstrated a 30-day thromboembolic rate of 2.39% in patients who were not anticoagulated.[115] The traditional recommended approach involves oral anticoagulation (OAC) for 3 weeks or transesophageal echocardiogram (TEE) to rule out intracardiac thrombi prior to cardioversion, followed by continued OAC for a minimum of 4 weeks after cardioversion for all patients with AF or AFL of greater than 48 hours' duration (or unknown duration), regardless of $CHADS_2$-VASc score.[116] A pathway for anticoagulation in the pericardioversion setting is depicted in Figure 2.

Other types of SVT

AVNRT. Excluding AF and AFL, AVNRT (50%-60% of cases), and AVRT (30% of cases) comprise the rest of the SVTs.[117] While the term *supraventricular tachycardia* is often used to describe AVNRT, it is an umbrella term encompassing all of the aforementioned atrial arrhythmias. *Atrioventricular nodal reentry tachycardia* is a more specific and academic term that also reinforces understanding of pathology and mechanism. AVNRT consists of an electrical reentry loop that has developed within the AV node, resulting in a narrow-complex

Table 1. Medications Used in Management of Atrial Arrhythmias

Medication	Indication(s)	Dosage	Onset[a]	Duration[a]	Clinical pearls and considerations
β-blockers					
Metoprolol	AF, AFL, AVNRT	IV: 5 mg by IV push over 2 min; may repeat every 5 min up to 15 mg in total[19] (guideline dosing)[31] IV: 0.15 mg/kg (max 10 mg) diluted in 50 mL of fluid over 30-60 min (alternate dosing)[87]	10-20 min[34]	2-4 h	• Frequently used for rate control in AF although not FDA approved for indication[87] • As rate control is achieved, simultaneous initiation of oral metoprolol (25-50 mg immediate release) may provide seamless transition to outpatient therapy in selected patients • Convert to oral using 1:2.5 (IV:oral) ratio • Extensive hepatic metabolism via CYP2D6
Esmolol[88]	AF, AFL, AVNRT	IV: 500 μg/kg bolus over 1 min, followed by 50-300 μg/kg/min	2-10 min	Minutes after infusion stopped (half-life of 9 min)	• Consider re-bolus with each up-titration of infusion • Maximum FDA-approved dose for SVT is 200 μg/kg/min; while 300 μg/kg/min has been studied, additional benefit is not clear • May be used cautiously for rate control in ADHF or septic shock due to short half-life upon discontinuation if unexpected clinical worsening occurs • Ultrashort half-life of 9 min • Metabolized by plasma esterase to a metabolite with 1/1,500 β-blocking activity that is renally eliminated but may accumulate significantly in ESRD
Non-DHP CCBs					
Diltiazem[89]	AF, AFL, AVNRT	0.25 mg/kg by IV push; may repeat at dose of 0.35 mg/kg after 15 min (FDA-approved dose) Fixed-dose strategy (eg, 10 mg by IV push) has been shown to be effective[90,91] Continuous infusion: initiate at 5 mg/h and increase to 15 mg/h	3 min	Varies: <7 hours after infusion discontinued	• Studies suggest more rapid and durable IV rate control compared to metoprolol[92] • As rate control is achieved with IV dosing, simultaneous initiation of oral diltiazem (30-60 mg) may provide seamless transition to outpatient therapy in selected patients • Consider IBW for weight-based dosing[93] • IV infusion for >24 h not recommended[89]
Verapamil	AF, AFL, AVNRT	5-10 mg by by slow IV push (≥2 min); continuous infusion of 5-20 mg/h; may repeat at dose of 10 mg 30 min after first dose[94]	3-5 min	0.5-6.0 h	• Greater concern for hypotension than with diltiazem[39] • IV calcium pretreatment may prevent hypotension[95]

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Medication	Indication(s)	Dosage	Onset[a]	Duration[a]	Clinical pearls and considerations
Sodium channel blockers (class I)					
Procainamide (1A)	AF, AFL, AVRT, VF	IV: 1,000 mg over 60 min (Ottawa Protocol)[56]; 15 mg/kg (max 1,500 mg) over 30 min (RAFF-2)[54] IV: 100 mg over 5 min every 10 min (max 17 mg/kg)[59] Maintenance infusion: 2-6 mg/min[59]	Varies with administration time (rapid); median 23-55 min[54,56]		• Commonly administered as fixed dose of 1 g infused IV over 60 min • Hepatic metabolite *N*-acetylprocainamide is a known potassium channel blocker[59] • Parent compound and metabolite are renally excreted; dose adjustment required for maintenance infusion in renal insufficiency; consider monitoring procainamide and *N*-acetylprocainamide levels if available[59] • Avoid in Brugada syndrome
Class IC agents					• Contraindicated in patients with structural heart disease[c] • Guideline-endorsed as pill-in-pocket approach to managing paroxysmal AF/AFL[96] • Since IC agents do not possess AV-nodal blocking activity, a β-blocker or non-DHP CCB is recommended 30 min prior to the class IC drug to avoid precipitation of RVR[23]
Flecainide[60]	AF, AFL	Oral: if weight <70 kg, 200 mg once; if weight ≥70 kg, 300 mg once	30-60 min	8-12 h	• Metabolized by CYP2D6 • Decrease dose and monitor in renal dysfunction (CL_{cr} <35 mL/min)
Propafenone[61]	AF, AFL	Oral: if weight <70 kg, 450 mg once; if weight ≥70 kg, 600 mg once	30-60 min	8-12 h	• Metabolized by CYP2D6, CYP3A4, and CYP1A2 • Active metabolites renally excreted; monitor in renal dysfunction
Potassium channel blockers (class III)					
Amiodarone[96]	AF, AFL	IV: 150 mg once, then 1 mg/min over 6 h, followed by 0.5 mg/min for 18 h (FDA-approved VT/VF dosing regimen) AF guideline option: 300 mg IV over 1 h, then 10-50 mg/h over 24 h[97]	Up to 8 h for cardioversion after bolus	24 h after single bolus dose[98]; half-life of >15 d after C_{ss} reached[96]	• Frequently used but not FDA approved for AF • AF/AFL conversion is slower than with other agents (up to 8 h) • Some commercially available products use polysorbate-80 as a solvent, which may contribute to hypotension; polysorbate-80 has also been demonstrated to lower heart rate, inhibit AV node conduction, and lengthen atrial and ventricular refractory periods[99] • Rapid IV push administration should be avoided in patients with a pulse to reduce the risk of hypotension

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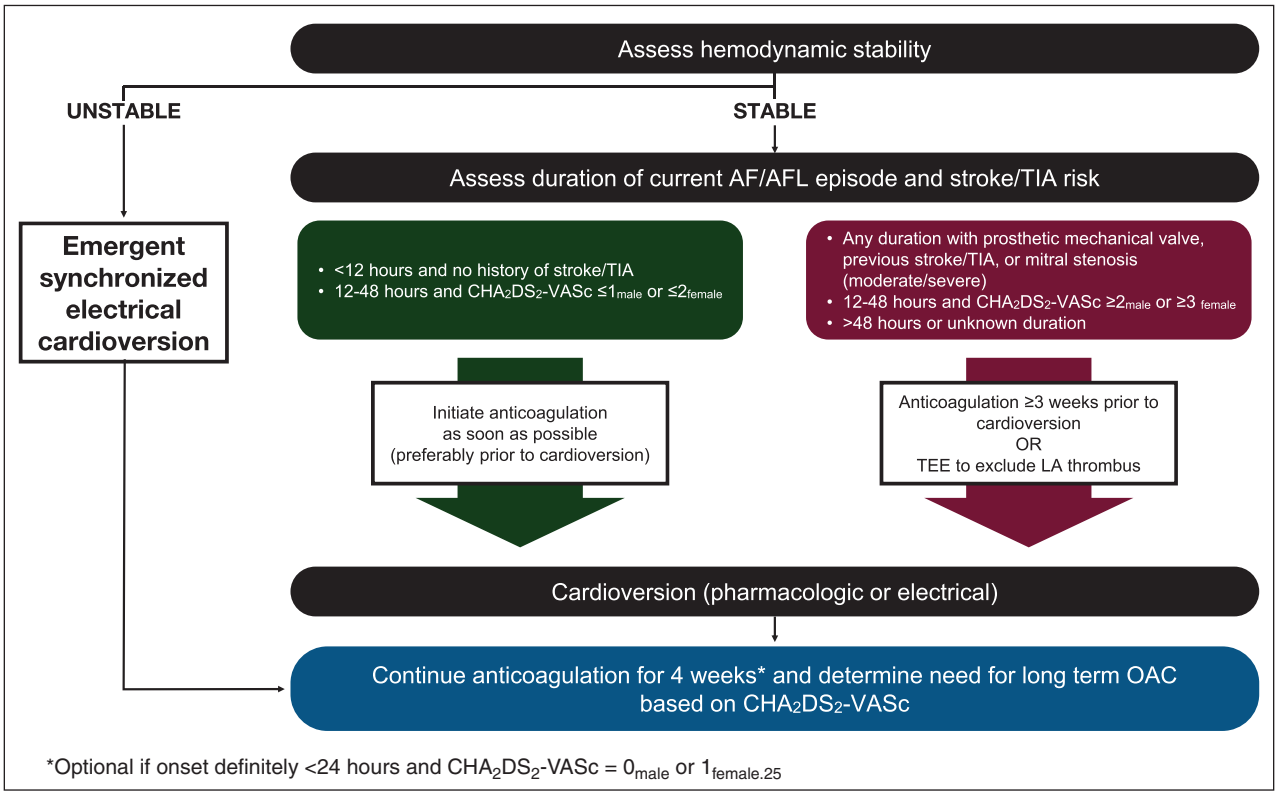
Table 1. Medications Used in Management of Atrial Arrhythmias

Medication	Indication(s)	Dosage	Onset[a]	Duration[a]	Clinical pearls and considerations
Ibutilide[72]	AF, AFL, AVRT	IV: if weight <60 kg, 0.01 mg/kg IV over 10 min; if weight ≥60 kg, 1 mg over 10 min[b] Repeat dose may be administered 10 min after completion of first infusion (per product labeling)		4 hours	• Risk of TdP is low in the absence of HF or electrolyte derangements[72] • Consider prophylactic magnesium regardless of serum levels • Avoid different antiarrhythmic agent for 4 h post infusion[72]
Miscellaneous					
Adenosine	AVNRT	IV: initial dose of 6 mg; if necessary, may give 12 mg and repeat with additional 12 mg	Seconds	<20 s	• Consider initial dose of 12-mg in healthy, larger adults or those with increased caffeine intake[100] • Administration technique is important for effectiveness; for peripheral IV, consider raising patient arm after administration to increase venous return • In post–heart transplant patients, consider initial dose of 1.5 mg (if weight ≥60 kg)[101] • If multiple failed attempts at adenosine therapy, consider pathology other than AVNRT (ie, AF, AFL, or VT) before escalating to higher doses (18 or 24 mg), which have been reported[102] • Safe in pregnancy[103,104]
Digoxin[105-107]	AF, AFL	IV: 0.5 mg bolus followed by 0.25 mg every 6 hours for a total of 1 to 1.5 mg over 24 hours. Renal adjustment (if CL_{cr} ≤20 mL/min): loading dose of 0.25 mg every 6 h for 2 doses, followed by 0.125 mg daily[105]	1 h; peak in 2-6 h	8-12 h after single dose; days in C_{ss}	• Various loading or "digitalizing" regimens exist due to large Vd (6.7-16.3 L/kg) and half-life (36-44 h) • Loading dose not recommended in HF
Magnesium	AF, AFL	IV: 2-6 g over 2 h as adjunct to other rate or rhythm control[49] Note: dose of ≥4.5 g shown in RCT to enhance rate and rhythm control[51]	< 1 hour	Indeterminate (rapidly excreted renally if kidney function is normal)	• Low serum levels associated with increased risk of AF[108] • Empiric use may be beneficial in atrial arrhythmias regardless of serum magnesium levels[49] • Antiarrhythmic mechanisms proposed via effects on L-type calcium, potassium, and sodium channels[109-111]

Abbreviations: ADHF, acute decompensated heart failure; AF, atrial fibrillation; AFL, atrial flutter; AVNRT, AV-nodal reentry tachycardia; C_{ss}, clearance at steady state; CCB, calcium channel blocker; CL_{cr}, creatinine clearance; CYP, cytochrome P450 isozyme; DHP, dihydropyridine; ESRD, end-stage renal disease; FDA, Food and Drug Administration; IV, intravenous; LV, left ventricular; LVEF, left ventricular ejection fraction; RCT, randomized controlled trial; SVT, supraventricular tachycardia; TdP, torsades de pointes; Vd, volume of distribution; VF, ventricular fibrillation; VT, ventricular tachycardia;
[a]For typical doses described in table.
[b]May be stopped upon conversion to sinus rhythm.
[c]Structural heart disease includes LV hypertrophy, LV dysfunction with LVEF of ≤40%, valvular pathologies, ischemic coronary artery disease, and second- or third-degree AV block.

Figure 2. Pathway for anticoagulation in the pericardioversion setting. AF indicates atrial fibrillation; AFL, atrial flutter; LA, left atrial; OAC, oral anticoagulation; TIA, transient ischemic attack; TEE, transesophageal echocardiography.



tachycardia with heart rates that typically range between 150 and 200 bpm but can be over 250 bpm in some patients (Figure 1).[117] A hallmark characteristic of this rhythm is its faster rate and regularity relative to AF. AVNRTs develop due to an off-timed atrial contraction when part of the AV node is between action potentials, often under the circumstance of abnormal sympathetic or vagal tone. While palpitations from AVNRT may cause significant discomfort to patients, this rhythm is rarely indicative of underlying heart disease when compared to other arrhythmias.[118] AVNRT is twice as common in females as in males and is the most common arrhythmia encountered during pregnancy, with up to 44% of patients with known AVNRT experiencing symptoms during pregnancy.[119,120]

Various nonpharmacologic therapies are effective for AVNRT. Vagal maneuvers are aimed at stimulating the vagus nerve to release acetylcholine and increase refractoriness on the AV node. While several techniques exist, the most common are the Valsalva and modified Valsalva maneuvers. These maneuvers have been shown to be only 28% to 50% effective but are recommended as first-line modalities due to a low risk of harm.[16,121,122]

Several efficacious pharmacologic options may be employed to terminate AVNRT. Adenosine is the first-line pharmacological approach to AVNRT because of its efficacy and extremely short half-life. Adenosine renders the AV node refractory, temporarily inducing a complete heart block. This may cause significant patient discomfort, including flushing and chest pain, but has been shown to be 90% effective, and adenosine is the preferred agent according to recent American Heart Association (AHA) guidelines.[16]

Several considerations should be given when selecting an adenosine dose. The AHA guidelines recommend 6 mg, followed by 12 mg if necessary, which may be repeated.[123] Caffeine consumption causes dysregulation of adenosine receptors and can result in adenosine resistance, which may be a reason to choose 12 mg as the initial dose.[124] Adenosine should be given through a peripheral IV line for AVNRT, but reducing the dose to 3 mg is recommended if only a central line is available since prolonged bradycardia and asystole causing patient and provider discomfort have been reported.[125] Carbamazepine itself has been associated with heart block, and therefore adenosine may evoke an exaggerated response in patients chronically taking carbamazepine.[126-128] Finally, in the circumstance that adenosine is given to post–heart transplant patients, the dose should be reduced to account for receptor dysregulation after vagal denervation in heart transplantation (Table 1).[129,130]

In addition to chest discomfort and flushing, there is a concern for bronchospasm in patients with

preexisting asthma. Hypotension is cited as a concern with higher doses of adenosine, which is transient and likely due to a decrease in cardiac output.[131]

Due to the short half-life of adenosine, administration strategy is a key component of ensuring good response. Various techniques for adenosine administration have been published and countless others proposed at bedside based on anecdotes. Evidence supports a single-syringe method as simpler and as effective as multiple syringes and a 3 way stopcock.[132,133] This method, which involves dilution of adenosine in about 20 mL of 0.9% sodium chloride injection, avoids unnecessary or unstocked equipment and delivers the maximum drug amount to the patient, which is especially important for pediatric populations.[134]

Adenosine is an overwhelmingly popular approach to AVNRT; however, other equally effective pharmacological approaches exist. Both non-DHP CCBs and β-blockers are reasonable approaches to treating AVNRT, but the prolonged duration of these agents and the higher potential for hypotension relative to adenosine therapy warrant consideration. In a 2017 Cochrane review analyzing 7 RCTs involving 622 patients, non-DHP CCBs were shown to achieve the same conversion rates as adenosine, roughly 90%, but conversion to sinus rhythm was significantly faster with adenosine than with non-DHP CCBs (mean, 44 seconds vs 394 seconds), with similar rates of hypotension.[135] Various dosing regimens were used, but notably all of the RCTs studied only verapamil, with the exception of one trial that also contained a diltiazem arm consisting of 59 patients.[135] One of the key studies featured in the Cochrane review, showing the evidence on CCBs to be equivocal, involved slow infusion of diltiazem (2.5 mg/min up to 50 mg) and verapamil (1 mg/min up to 10 mg), and slow infusion may be a reason for the observed longer time to conversion and lower rates of hypotension. IV verapamil is used less in the US now than it was decades ago, as it was historically thought to provide more potent AV node blocking, but IV verapamil is also associated with a higher rate of hypotension when compared to IV diltiazem.[136,137]

Another treatment option for AVNRT is IV β-blockers, but there is less evidence to support their use. Only esmolol has been formally evaluated; it was shown to be significantly less effective at rhythm conversion than diltiazem in a small RCT that was terminated early.[138] If pharmacological interventions fail or if the patient is hemodynamically unstable, DCCV is safe and recommended.[16] Ultimately, if AVNRT is recurrent and bothersome, ablation is recommended. Of note, AVNRT is a common cause for ablation across all age groups over 20 years old.[120]

AVRT. AVRT is the other major form of pSVT and involves substantially different pathology than AVNRT. It is also referred to as pre-excitation, of which there are many variants, one of the most common being Wolff-Parkinson-White (WPW) syndrome. In these cases, a typically congenital, excitable area of tissue exists between the atrial and ventricular myocardium; this area is called an AV bypass tract (Figure 1). This AVRT mechanism is termed pre-excitation since a portion of the ventricular myocardium prematurely depolarizes. Accordingly, WPW syndrome is diagnosed by a short PR interval, with a delta wave on ECG, indicating retrograde ventricular pre-excitation.[139] Conversely, if AV conduction is antegrade (ie, from ventricle to atria) then a delta wave will not appear, which occurs in roughly 10% of cases. AVRT is the most common arrhythmia in the first 2 decades of life and can often be repaired with ablation.[117] It is important to note that WPW syndrome is frequently an incidental ECG finding and not necessarily dangerous alone. Patients with WPW syndrome can safely be given AV-nodal blockers such as adenosine, non-DHP CCBs, and β-blockers. However, considerable anxiety surrounding this approach exists due to theoretical concerns that the rhythm may degenerate to a ventricular arrhythmia. This is only relevant when AF develops in the presence of WPW syndrome, which will appear on ECG as a wide complex tachycardia (WCT) with an irregular rate. If there is a concern for WPW syndrome and AF, avoiding any AV-nodal blocker is prudent since shunting of electrical impulses to the ventricle without the protection of the AV node's refractory period sets the stage for the "R-on-T" phenomenon (ie, superimposition of an ectopic beat on the T wave of a preceding beat), early after-depolarizations, and subsequent ventricular arrhythmia.[117] AF in the presence of WPW is rare and only encountered in 1% of patients with WPW syndrome.[140,141] Furthermore, sudden cardiac death is seen in only 0.15% of patients with WPW syndrome overall.[142] If WPW syndrome with AF is likely and the patient is stable, an approach using a pure antiarrhythmic medication such as procainamide or ibutilide is recommended.[18] Amiodarone is traditionally avoided as it possesses AV-nodal blocking properties, and case reports confirm some risk of harm.[141,143-145] However, in a recent retrospective study of 27 patients with AF and WPW, amiodarone did not cause ventricular arrhythmia but resulted in a 60% rate of cardioversion (median time, 8.1 hours).[145] As with any hemodynamically unstable arrhythmia, electrical cardioversion is the preferred approach.

The term *aberrant conduction* describes any abnormal conduction pathway but is most commonly used to describe a left or right bundle branch block (BBB) reflecting a pathological malfunction in the nerve bundle as a result of cardiac disease and myocardial scarring in the area.[146] Because ventricular conduction is then discordant and slightly delayed in one ventricle, a BBB results in a widened QRS complex on ECG and is not typically consequential in itself. However, if an SVT occurs in the presence of this BBB, it will appear as a WCT but can be more accurately described as an SVT

with aberrancy.[7] This resultant WCT may be regular (in the case of pSVT with a BBB) or irregular (in the case of AF with RVR), but definitive diagnosis based on ECG alone is complex and, if the patient is clinically unstable, the rhythm should always be assumed to be VT and addressed promptly with DCCV.

Conclusion

Atrial arrhythmias confer high morbidity and mortality in the US and worldwide. AF is the most prevalent arrhythmia and not expected to decline in prevalence, because of its association with age and several metabolic comorbidities. AVNRT and AVRT are important to distinguish physiologically and are treated differently. Approaches to treatment for all atrial arrhythmias can overlap in the acute setting and may include reducing heart rate and cardioversion. Such approaches are nuanced, and therapy depends on a wide variety of factors, including hemodynamic stability, recent duration of arrhythmia, and even provider preference and shared decision-making with the patient.

While antiarrhythmic medications are less frequently utilized in the acute setting for cardioversion, pharmacists can play a vital role in endorsement or avoidance of medications depending on the indication or expected adverse effect.

Disclosures

The authors have declared no potential conflicts of interest.

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