AN ONGOING CE PROGRAM
of the University of Connecticut
School of Pharmacy

EDUCATIONAL OBJECTIVES

After completing the continuing education activity, pharmacists will be able to

- Explain the definition, clinical presentation, and types of atrial fibrillation
- Discuss pharmacologic and non-pharmacologic treatment options for atrial fibrillation
- Describe the role of anticoagulation in atrial fibrillation management
- Identify interventions that could improve outcomes in atrial fibrillation patients

After completing this education activity, pharmacy technicians will be able to

- Explain the definition, clinical presentation, and types of atrial fibrillation
- Discuss pharmacological and non-pharmacological treatment options for atrial fibrillation
- Describe the role of anticoagulation in atrial fibrillation management
- Identify programs designed to promote medication adherence in patients with atrial fibrillation

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You Asked for It! CE

Don't Skip a Beat
Taking the Pulse of Atrial Fibrillation

TARGET AUDIENCE: Pharmacists and pharmacy technicians who interact with patients who have atrial fibrillation.

ABSTRACT: Atrial fibrillation (AFib) is a growing problem in the United States and globally. AFib occurs when the electric impulses of the heart's upper chambers become chaotic and irregular. The result is a fast heart rate, pooling of blood in the atria, and erratic pumping of blood by the ventricles. The treatments for AFib include rate-control medications, rhythm-control drugs, anticoagulants, and non-pharmacologic procedures. A standardized scoring system determines the need for anticoagulation, with direct oral anticoagulants preferred over warfarin in most cases. Providers choose rate-control medications like beta-blockers, calcium channel blockers, and digoxin in selected patients; however, they may opt for rhythm-control antiarrhythmics like flecainide, sotalol, and dofetilide for others. Nonpharmacologic options include cardiac ablation, Watchman LLA and AtriClip devices, and electrical cardioversion. Pharmacists are well-positioned to monitor therapy, adjust anticoagulant dosing, and assist in the diagnosis of patients with AFib. Pharmacy technicians can coordinate compliance mechanisms like medication synchronization and refill reminders.

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INTRODUCTION

"My heart feels like it is pounding out of my chest."

Dan Reeves, a 79-year-old white male, makes this statement to the pharmacy technician at the counter while waiting to pick up his prescriptions for flecainide and apixaban. He has his hand over his chest and states he feels tired and short of breath when doing any activity. The pharmacy technician requests help from the pharmacist, who notes that Daniel is showing signs of an arrhythmia. A check

of his records shows that he is two weeks late for his refill of flecainide, a medicine to treat atrial fibrillation (AFib). Upon questioning by the pharmacist, Dan says the doctor has told him how important it is to take the medication properly. However, he admits that he sometimes forgets to take the second dose at bedtime.

AFib is the most common type of sustained heart rhythm disorder, also called an arrhythmia.[1] It occurs when the heart's electrical activity is abnormal or irregular, usually resulting in a fast heart rate.[1] If the rate does not return to normal, it can lead to stroke, heart failure, or other medical problems.[2] AFib is a leading cause of stroke.[1]

An estimated 2.3 million people in the United States have AFib, according to the most recent data available.[3] Given the association between advanced age and AFib occurrence, an estimated 5.6 million will experience AFib by the year 2050.[3] It affects fewer than 1% of people under the age of 60 to 65 but 8% to 10% of those older than 80.[3] It happens more often in males and Caucasians.[1]

Risk factors for developing AFib include the following[1]:

- Advancing age
- Chronic inflammation
- Congenital heart disease
- Endocrine disorders
- Genetic factors
- High blood pressure
- Increased alcohol consumption
- Neurological disorders
- Obstructive sleep apnea
- Underlying heart and lung disease.

Athletes who overtrain in intense cardiovascular sports, like competitive bikers and marathon runners, also are at an increased risk of developing AFib (see the **SIDEBAR** to the right).

AFib occurs when electrical impulses in the heart's upper chambers, called the atria, come from multiple foci, rather than just the sinoatrial (SA) node. The atrial and ventricular depolarization rate becomes rapid and chaotic rather than their normal, consistent firing and propagation (called normal sinus rhythm).[10,11] When different atrial defibrillation waves collide, they cancel each other out meaning no one pacemaker exists. This causes the atrial chambers to quiver, or "fibrillate" instead of contracting in a normal manner from the top of the atria to the bottom. As a result, blood pools in the left atrial appendage (a tissue sack attached to the left atria) which can lead to blood clots. The clots may dislodge from the left atrial appendage, travel to the brain, and cause embolic strokes.[11]

The atrial depolarizations bombard the atrioventricular (AV) node separating the atria from the ventricle with approximately 300 depolarization stimuli per minute. The AV node tries to prevent some of these depolarizations from reaching the ventricles, but the resulting ventricular contractions become faster than normal and irregularly spaced.[11]

SIDEBAR: IS OVERTRAINING TO BLAME FOR AFIB IN ATHLETES?

According to studies, the prevalence of AFib in athletes is about 2 to 10 times higher than in the general population.[4] Most cases occur in endurance athletes, such as marathoners, and may result from overtraining. In one study, a group of middle-aged men who ran marathons had a higher incidence of AFib than their sedentary counterparts.[5] The disease also occurs five times more often in aging cyclists (average age of 66 years old) who continue training.[6] The duration and intensity of exercise correlate to the development of paroxysmal AFib.[4]

Reports cite "irrational" regimens involving overtraining as the primary factors, along with obesity and diabetes.[4] Treatment consists of removing the physical stress and prescribing flecainide or propafenone.[7] Athletes may return to training in four to six weeks but should remain on a beta-blocker to prevent recurrence.[8,9] Providers should consider the cardioselectivity of the beta-blocker and the athlete's sport when choosing a therapy.[4] Prevention and treatment of future episodes may include a "pill-in-pocket" approach or cardiac ablation.[7]

PATHOGENESIS

In a normal heart, electrical impulses travel in a coordinated way through the heart's pacemaker, the SA node, through the atrial tissue, and to the AV node.[13] The AV node slows the impulse before it travels to and depolarizes the ventricles.[14] When the SA node in a normal heart initiates a depolarization wave, it spreads across the atria from top to bottom. Once the cells depolarize, they cannot depolarize again for a while; this is called the effective refractory period. Immediately after the refractory period, the tissue is in a vulnerable period because the electrical charge of the cells is normalized but the amount of sodium in the cell is too high and the potassium inside the cell is too low. If another depolarization stimuli hits tissue in the vulnerable period, fibrillation occurs. But this is rare in normal hearts because it is impossible for the wave of depolarization to circle behind the effective refractory tissue to hit other tissue in the vulnerable period. However, when there is a mixing of electrically active and inactive cells together, the single wave of depolarization becomes fractionated into multiple wavelets in a three-dimensional space and one of the wavelets can emerge and hit tissue in the vulnerable period.

AFib originates in the pulmonary vein-atrial border 95% of the time because the pulmonary vein contains electrically active atrial cells and inactive pulmonary vein cells that are intermingled.[12] However, in people with longstanding AFib, the stress kills atrial cells, which are replaced by electrically inactive connective tis-

SIDEBAR: ECG Interpretation 101[16,17]

An ECG is a visual representation of the heart's electrical activity. For a 12 lead ECG, six electrodes are placed on the chest and four on the limbs before connecting them to an ECG machine, which produces a readout. A normal ECG consists of a small P-wave, a large and narrow QRS complex, and a T-wave. The P-wave is a small, positive, smooth wave that reflects atrial depolarization, which precedes contraction of the atria. The QRS complex represents depolarization of the ventricles which precedes ventricular contraction. The T-wave follows the QRS complex and reflects rapid repolarization.[17] Abnormal results from an ECG are a sign of potential heart problems like arrhythmias, ischemia or infarction, or even ventricular hypertrophy.

sue, and the anatomic milieu is created to have AFib generated in the body of the atria itself. Patients with AFib may present to healthcare providers with or without symptoms.[1] Patients may experience chest pain, palpitations, a fast heart rate, shortness of breath, nausea, dizziness, sweating, or general fatigue when they have symptoms.[1] The ventricular rate for a patient with AFib is 110 to 140 beats per minute (bpm).[1]

When AFib occurs, the heart can usually quickly abolish it on its own but as periods of AFib continue to occur, subsequent AFib episodes last longer and longer until eventually AFib just continues.

Providers classify AFib into five types[1]:

- Paroxysmal AFib will revert to normal sinus rhythm in less than seven days with no antiarrhythmic medication or electrical cardioversion.
- Persistent AFib occurs and then persists, requiring intervention with antiarrhythmic medication or electrical cardioversion.
- Long-standing persistent AFib exists for longer than 12 months, either due to failure to attempt cardioversion or failure of cardioversion.
- Permanent AFib is unresponsive to antiarrhythmic medication or electrical cardioversion and continues for the rest of the patient's life.
- Non-valvular occurs without rheumatic mitral valve disease, mitral valve repair, or prosthetic heart valves.

AFib can be viewed on an electrocardiogram (ECG), which will show an "irregularly irregular" pattern with no discernable P-waves and irregular RR spacing during rest (see **SIDEBAR** above).[1] Failure to detect paroxysmal AFib on an ECG doesn't preclude having the arrhythmia because normal sinus rhythm can intersperse between the arrhythmic episodes. In that case, a patient may wear a Holter monitor (a small portable ECG machine) continuously for a few days or a patch monitor with 30-day readouts to detect the arrhythmia.[10,15]

TREATMENT OF AFIB

The goals for treating AFib include reducing symptoms, preventing clots, and reducing the risk of heart failure and other cardiac complications.[10] According to the 2023 American Heart Association/American College of Cardiology/American College of Chest Physicians/Heart Rhythm Society (multi-society) guidelines, patient-specific factors direct the choice of antiarrhythmic agent.[2] Among those factors is heart failure, cardiovascular disease, or other health conditions. Treatment also varies based on where providers discovered the AFib: in the inpatient or outpatient setting.[2]

PHARMACOLOGIC AGENTS

The multi-society guidelines divide the agents for treating AFib into rate-control and rhythm-control medications.[2] Rate-control agents control the ventricular rate when patients are in AFib for better symptom management.[18] Rhythm-control medications restore and maintain normal sinus rhythm.[10]

PAUSE AND PONDER: What medications treat AFib symptoms most effectively?

Providers may choose from a wide range of medications, with the treatment choice often determined by the patient's clinical picture and the setting in which the AFib occurs.

RATE CONTROL MEDICATIONS

Rate control medications slow the impulses through the AV node, reducing the rate of contraction of the ventricles.[18] While the number of ventricular contractions per minute decrease (allowing for better ventricular filling with blood during diastole), the RR spacing remains irregular. This irregularity coupled with the loss of atrial contraction in AFib reduces the cardiac output versus normal sinus rhythm. The goal is better symptom control with limited adverse effects. (See **Table 1** on the next page.)[10]

Beta-Blockers

Beta-blockers inhibit the activity of the beta-1 adrenoceptor at the AV node, slowing conduction (negative dromotropic effect).[18] Providers may choose from various options, including atenolol, bisoprolol, carvedilol, metoprolol (succinate and tartrate), and propranolol. Atenolol, bisoprolol, and metoprolol are the cardioselective beta-blockers, which means they less potently block the beta-2 adrenoceptors in the lungs.[19] While all beta-blockers can cause drops in the Forced Expiratory Volume in 1-second (FEV-1) in asthmatic patients, the cardioselective agents do so to a lesser extent. Their effects are readily reversed with standard dosing of inhaled beta-2 agonists. All beta-blockers control the ventricular rate, and the multi-society guidelines consider them first-line therapy.[2]

Non-Dihydropyridine Calcium Channel Blockers

The multi-society guidelines also list non-dihydropyridine calcium channel blockers dilTIAZem and verapamil as first-line for treat-

Table 1. Rate Control Medications in Afib		
Class	**Drugs**	**Notes**
Beta-blockers	Atenolol Bisoprolol Carvedilol Metoprolol Nadolol Pindolol Propranolol	Metoprolol succinate (the XL form) and tartrate (the immediate release form), as well as bisoprolol are beta-1 selective; metoprolol succinate, bisoprolol, and carvedilol are preferred choices for patients with heart failure.
Nondihydropyridine calcium channel blockers	DilTIAZem Verapamil	Dihydropyridine CCBs do not block the AV node.
Cardiac glycosides	Digoxin	Not as effective as beta-blockers or non-DHP CCBs during exercise or stress and has a narrow therapeutic index; may use in combination with other rate-control agents.
Class III antiarrhythmic	Amiodarone	Has antiadrenergic effects similar to beta-blockers and non-DHP CCBs; many drug interactions and adverse effects; good choice in patients with heart failure.
ABBREVIATIONS: CCBs = calcium channel blockers; DHP = dihydropyridine		

ing AFib.[2] They block the L-type calcium channel to produce their negative dromotropic effects and like the beta-blockers have negative chronotropic and inotropic effects, meaning they slow the SA nodal firing rate and decrease the force of muscle contraction, respectively.[18] They provide reasonable rate control and improve AFib-related symptoms compared to beta-blockers.[2] The multi-society guidelines note that dilTIAZem and verapamil are contraindicated in patients with pre-existing heart failure.[18] However, if the signs and symptoms of heart failure are solely due to the AFib and no other underlying diseases, verapamil and dilTIAZem can be used.

The Institute for Safe Medication Practices lists the generic name dilTIAZem on the look-alike sound-alike list due to the potential for confusion with diazePAM.[20] The organization recommends the use of TALLman lettering to distinguish the two drugs.[20]

Digoxin

Digoxin provides a negative dromotropic and chronotropic effects but does not provide a negative inotropic effect. The inotropic effect can be neutral at serum concentration below 1.2 nanograms/mL but can be positive at higher concentrations.[18] Since digoxin slows AV nodal conduction through enhancing the parasympathetic nervous system, it does not work as well in times of higher sympathetic outflow like exercise or stress. The multi-society guidelines indicate providers may use digoxin with other rate-control medications because it will not augment the negative inotropic effects of beta-blockers or non-dihydropyridine calcium channel blockers.[2] The guidelines also recommend digoxin in patients who do not tolerate or have an inadequate response from other rate control agents.[2,18] It is a narrow therapeutic index medication, with the recommended serum digoxin level for AFib being <1.2 nanograms/mL.[2] Providers should use digoxin cautiously with verapamil, since verapamil is a P-glycoprotein inhibitor and the combination may therefore increase digoxin levels (see the **SIDEBAR** on the next page).[18] However, digoxin may be a good initial choice for acute rate control in heart failure patients with AFib since the negative dromotropic effects of beta-blockers and nondihydropyridine calcium channel blockers could induce decompensated heart failure.[2] If patients start with low dose beta-blockers and digoxin in heart failure patients, as the beta-blocker dose is increased to therapeutic levels (doubled every two weeks until therapeutic doses are achieved) the digoxin level can be reduced.

Other Rate-Control Options

The multi-society guidelines recommend amiodarone, dronedarone, and sotalol for rate control, but only in extreme circumstances. Providers sometimes order amiodarone as a last resort in a hospital setting. Still, it should be used sparingly due to its many drug interactions and adverse effect profile.[2] Dronedarone has a chemical structure similar to amiodarone, except that it does not contain iodine, making it safer.[10] However, the guidelines do not recommend its use in patients with heart failure or permanent AFib due to the risk of death.[2,18] Sotalol is both a beta-blocker and a potassium-channel blocker that also exerts rhythm control properties.[18] While it is a negative dromotropic agent, it can also prolong the QTc interval on the ECG, which may lead to a life-threatening arrhythmia called Torsade de Pointes.[18]

In Torsade de Pointes, the ventricles beat in a fast, irregular manner.[29] Torsade de Pointes means “twisting of the points” in

SIDEBAR: DIGOXIN IN AFIB: FRIEND OR FOE?

Digoxin is the oldest medication used today in AFib, with records of its use as early as 1250 AD.[21] Dr. William Withering first described its good and bad effects in 1785.[22] Providers still prescribe it today; however, its use has decreased in the 21st century.[23] In AFib, the multi-society guidelines recommend it as a rate-control agent.[2] The guidelines suggest using it with either beta-blockers or non-dihydropyridine calcium channel blockers or as a standalone medication if the other rate-control options are not tolerated.[2]

Digoxin has a wide variety of adverse effects triggered by toxicity. These include arrhythmias, GI symptoms like anorexia, fatigue, and nausea, and central nervous system issues like mental status changes and visual disturbances.[24] Elevated drug levels cause the most toxic effects, often triggered by drug interactions. Other antiarrhythmics like amiodarone, dronedarone, flecainide, non-dihydropyridine calcium channel blockers, propafenone, and quinidine may block P-glycoprotein and increase digoxin blood levels as a result.[25,26] Antibiotics like macrolides and tetracyclines may have similar effects.[25]

According to reports, toxicity occurs in about 13 to 25 percent of digoxin patients.[25] It happens more often with blood levels greater than 2.0 nanograms/milliliter.[25] While providers may stop digoxin and provide supportive therapy in milder cases, severe cases require digoxin-specific antibody fragments (digoxin-fab).[22] Derived from sheep, digoxin-fab is an intravenous medication that works in 30 to 45 minutes to reverse digoxin toxicity.[27] According to reports, providers use it in about 20% of cases of digoxin toxicity.[28]

French. It refers to a characteristic twisting pattern of QRS complexes around the ECG baseline.[29] QRS complexes are specific waves or deflections on the ECG, representing electrical activation of the ventricles.[14] Symptoms of Torsade de Pointes may include dizziness, fainting, or palpitations, or it may not present with symptoms.[29] The syndrome can be short-lived and self-limiting or life-threatening.[29]

RHYTHM CONTROL MEDICATIONS

The Vaughan Williams classification system divides commonly prescribed rhythm control agents into two classes.[10] Miles Vaughan Williams, a British pharmacologist and fellow at Hertford College in Oxford, created the classification system in 1970.[30] Medications in Class Ic block sodium channels in the heart.[10] Class III medications alter potassium channels.[10] (See **Table 2** on the next page.)

Flecainide

Flecainide, a Class 1c agent, is effective in treating paroxysmal AFib in patients without heart disease.[10] However, it can trigger other arrhythmias; the multi-society guidelines recommend ECG monitoring at initiation and dose changes.[2] Providers should avoid flecainide in patients with structural heart disease or enlarged left ventricles.[10] Given twice daily for chronic use, it also may serve as a "pill-in-pocket" option at a larger, loading dose to convert an AFib episode to normal sinus rhythm.[10]

Providers sometimes give patients "pill-in-pocket" prescriptions, which may be taken at the time of an acute AFib episode to return the heart rate to normal sinus rhythm.[2] Typically, the approach is first tested under the supervision of a provider before the prescription is written for the patient. Providers instruct the patient to carry the dose with them and take it if and when symptoms occur.[2]

Propafenone

Providers use propafenone, another Class 1c agent, in paroxysmal and sustained AFib.[10] It blocks sodium channels and has weak calcium channel-blocking and beta-blocking properties.[10] Like flecainide, it can cause arrhythmias, and the multi-society guidelines recommend ECG monitoring at initiation, dosing changes, and periodically during treatment.[2] Providers prescribe propafenone every 8 to 12 hours as a chronic medication. They may prescribe larger doses in a "pill-in-pocket" approach to convert recent-onset AFib to normal sinus rhythm.[10]

Dofetilide

Dofetilide is a Class III agent that blocks IKr, a key potassium channel in the heart.[10] It limits the maximum frequency of electrical impulses without slowing conduction through the AV node.[10] It can cause dangerous arrhythmias, including Torsade de Pointes.[2] As a result, the multi-society guidelines recommend providers place patients under observation with ECG monitoring for three days when starting this medication.[2] The initial period requires a hospitalization that lasts at least 12 hours after the patient converts to normal sinus rhythm.[2] The guidelines indicate providers should monitor potassium and magnesium blood levels due to the risk of arrhythmia.[2] Providers must dose dofetilide based on kidney function.[10]

Sotalol

Sotalol, another Class III antiarrhythmic, is a beta-1 and beta-2 blocker.[10] It prolongs the length of electrical impulses to control heart rhythm.[10] Like dofetilide, it can cause dangerous arrhythmias, including Torsade de Pointes.[2] The multi-society guidelines recommend three days of inpatient ECG monitoring for patients who start sotalol. The guidelines also suggest regular monitoring of potassium and magnesium levels.[2] Providers must dose sotalol based on renal function.[10]

Amiodarone

While amiodarone is more effective at preventing recurrent AFib episodes than sotalol, dotetilide, and dronedarone, the multi-society guidelines recommend these other options preferably for most patients, although it is a first line option (along with

Table 2. Rhythm Control Medications in Afib			
Agent	**Vaughan Williams Class**	**Dose**	**Notes**
Flecainide	1c	50-150 mg po q12h	Not indicated in patients with structural heart disease* (may cause arrhythmias); pill-in-pocket dose: 300 mg
Propafenone	1c	150-300 mg po q8h or 225-425 mg SR po q12h	Weak calcium channel blocking and beta-blocking properties; not for use in patients with structural heart disease;* pill-in-pocket dose: 600 mg
Amiodarone	III	400-800 mg po daily for 3-4 weeks, then 100-400 mg daily	Also has rate-control action; toxicity and drug interactions a concern; IV dosing: 5-7 mg/kg up to 1500 mg every 24 hours
Sotalol	III	80-240 mg po q12h	Also has beta-blocking action useful for rate control; requires dosing based on kidney function; potential for life-threatening arrhythmias
Dofetilide	III	125-500 mg po BID	Strict dosing based on renal function, body size and age; started with patient in hospital on telemetry for 3 days
Dronedarone	III	400 mg po BID	Contraindicated in patients with permanent AFib or decompensated heart failure
ABBREVIATIONS: AFib = atrial fibrillation; BID = twice daily; IV = intravenous; SR = sustained release *Denotes heart failure, post-myocardial infarction, or left ventricular hypertrophy.			

dofetilide) in heart failure.[2] Amiodarone is a Class III drug that blocks both IKr and IKs potassium channels and exhibits rate-control properties.[10] It blocks sodium and calcium channels and displays antiadrenergic properties as well.[10] The multi-society guidelines note that amiodarone has a long list of adverse effects and drug interactions, making it a poor choice for chronic therapy.[2] The adverse effects include thyroid disorders (see the **SIDEBAR** on the next page), lung toxicity, liver toxicity, photosensitivity, blue-green skin discoloration, corneal microdeposits, peripheral neuropathy, and the potential for Torsade de Pointes.[16] However, the balance of IKr and IKs potassium channel blockade means it is less likely to cause Torsade de Pointes than Class III antiarrhythmics like dofetilide and sotalol.[2] Amiodarone (like dronedarone) blocks many CYP P450 isoenzymes and P-glycoprotein. Notable drug interactions include atorvastatin, calcium-channel blockers, beta-blockers, digoxin, fluoroquinolone and macrolide antibiotics, phenytoin, simvastatin, and warfarin.[35]

Dronedarone

Like amiodarone, dronedarone is a Class III antiarrhythmic that blocks sodium and calcium channels and features beta-blocking properties.[10] It resembles amiodarone in chemical structure but lacks iodine. The absence of iodine makes it safer, removing or reducing thyroid, lung, and liver effects.[10] Dronedarone has shown modest benefits for patients with non-permanent AFib.[10] It is contraindicated in permanent AFib or New York Heart Association Class III to IV heart failure.[2,10,18]

CONSIDERATIONS IN CHOICE OF RATE OR RHYTHM CONTROL

Prescribers sometimes face difficult choices between rate control or rhythm control. Many factors affect the decision, including the patient's clinical picture. How old is the patient? How severe are the symptoms? Does the patient have heart disease?

PAUSE AND PONDER: In what situations would prescribers use rate and rhythm control?

The goals of rate control include treating symptoms, preserving heart function, and improving quality of life.[18] Providers prefer this strategy in older patients (age greater than 80 years) with no or mild symptoms.[18] Rate control also may be the only option if rhythm control fails or the risks of it outweigh the benefits.[18] Finally, rate control is more cost-effective due to the medications' wide availability and low cost.[36]

However, the correct degree of rate control has been debated. Previous sources have recommended a goal ventricular rate of less than 80 bpm at rest in symptomatic patients, but newer recommendations suggest a more lenient approach of less than 110 bpm.[2] A recent study showed no difference in outcomes with the more lenient strategy, which the multi-society guidelines currently favor.[2,37] As a general rule, all AFib patients should have a ventricular rate less than 110 bpm; those who can tolerate lower heart rates should get the opportunity to see if this reduces their hemodynamic symptoms during AFib. Once a patient's ventricular rate is below 80 bpm though, further heart rate reductions

SIDEBAR: THE TROUBLESOME 'I' IN AMIODARONE

The antiarrhythmic amiodarone comprises 37% iodine (element 'I' on the periodic chart) by weight.[31] The iodine content and the molecule's shape can cause problems for patients prone to thyroid disorders.[31] Depending on the patient's susceptibility, amiodarone may cause low thyroid, called hypothyroidism, or a high thyroid condition, called thyrotoxicosis.[31]

Each 200 mg of amiodarone contains 75 mg of iodine, with 7 mg of free iodine released when enzymes process the medicine.[31] The free iodine is much more than the recommended daily requirement of 0.15 to 0.3 mg, which leads to iodine overload.[31]

Iodine is critical in creating and processing thyroid hormones T3 and T4. Excess iodine in patients may lead to an overproduction of thyroid hormone, especially in the short to moderate term. Thyrotoxicosis may also occur due to direct damage to the thyroid, which is called thyroiditis.[33] The consequences of thyrotoxicosis may be severe, including arrhythmias.[33] Treatment of thyrotoxicosis depends on its subtype but may include methimazole, prednisone, or propylthiouracil.[31,34]

With longer term use of amiodarone, the thyroid produces similar or slightly higher levels of T4 hormone but this T4 is shunted to reverse T3 (rT3) which is biologically inactive, instead of to T3 which is more potent than T4. It is this reduction in T3 that drives signs and symptoms of hypothyroidism in susceptible patients.[31] The treatment of hypothyroidism is the use of levothyroxine, following guidelines for its use in low thyroid conditions.[33] In cases in which providers stop amiodarone, thyroid function may return to normal.[31]

are unlikely to provide additional value and they should consider a rhythm control strategy.

Rhythm control is preferred in most cases, even though it hasn't shown an advantage over rate control in risk of death.[1,10] It prevents stroke and improves quality of life but might increase the risk of hospitalization, especially due to ventricular arrhythmias such as Torsade de Pointes.[38,39] Rhythm control is also the best option in patients with a recent diagnosis and in the case of AFib combined with heart failure.[2] It reduces symptoms and slows disease progress from paroxysmal AFib to more sustained forms of the arrhythmia.[2] Remember that rhythm control medication is overlaid upon rate control medication, one does not replace the other.

ANTICOAGULANTS

To reduce the risk of stroke in patients with AFib, the multi-society guidelines recommend the use of anticoagulation in select cases.[2] Determining the need for anticoagulation involves a risk assessment using a scoring system – the CHA_2DS_2-Vasc (see **Table 3** to the right).[2] In men, a score of 0 indicates low risk, 1 low-moderate risk, and 2 or more is moderate-high risk.[1] In women, a score of 0 or 1 is low risk, a score of 2 is low-moderate risk, and a score of 3 or more is moderate-high risk.[2] Providers should start anticoagulation in patients with moderate-high risk and consider it in patients with low-moderate risk.[1] When uncertain about whether the benefits of anticoagulation are greater than the risk of bleeding, providers may use the HAS-BLED scoring system; however, the multi-society guidelines indicate it should not replace clinical judgment.[2] HAS-BLED considers age, renal and kidney function, stroke history, and other factors to determine the risk of bleeding events with anticoagulation.[40]

Providers prescribe direct oral anticoagulants (DOACs) and warfarin for anticoagulation (see **Table 4** on the next page).[1,2] In patients with AFib and no signs of stroke, providers should start anticoagulation immediately.[2] The standard for patients with a transient ischemic attack or stroke is the "1-3-6-12" rule. Providers should start anticoagulation in 1 day after a transient ischemic attack and 3, 6, and 12 days after mild, moderate, or severe strokes, respectively.[41] This is because there is an increased risk of cerebral bleeding after a stroke for a short period of time and anticoagulation would exacerbate it.

DOACs

In most cases, providers prescribe DOACs, including apixaban, dabigatran, edoxaban, and rivaroxaban.[2] Studies show that each is equal to, if not superior to, warfarin in preventing stroke and has less bleeding.[2] DOACs have fewer drug and food adverse effects, cost more than warfarin, but do not have INR laboratory costs. Dabigatran binds to thrombin (Factor IIa) in the coagulation cascade, and prevents it from activating coagulation factors.[42] Apixaban, edoxaban, and rivaroxaban are Factor Xa inhibitors and prevent the cleavage of prothrombin to thrombin.[43-45]

Warfarin

Warfarin is a Vitamin K antagonist.[2] Researchers believe it competitively inhibits the vitamin K epoxide reductase complex 1 (VKORC1), which is important for activating Vitamin K in the

Table 3. CHA_2DS_2-VASc Scoring Considerations

Condition	Score
Congestive Heart Failure	1
Hypertension	1
Age ≥ 75	2
Diabetes	1
Stroke/TIA	2
Vascular Disease	1
Age 65-74	1
Sex **c**ategory (female sex)	1

body.[46] Without active Vitamin K, Factors VII, IX, X, and II cannot be activated. Warfarin has long been a standard of anticoagulant therapy, although its many drug and food interactions and the need for regular monitoring make its use challenging for clinicians and patients alike.[2] However, providers still use warfarin for the treatment of AFib in patients with mechanical heart valves or mitral stenosis.[2] The goal international normalized ratio (INR) for AFib is 2.0 to 3.0 in most cases, except in the presence of certain mechanical heart valves where the INR is 2.5 to 3.5.[10]

CONSIDERATIONS IN THE SELECTION OF ANTICOAGULANTS

The choice of anticoagulant depends on several factors. Despite their high costs, the multi-society guidelines consider DOACs first-line therapy due to their advantages over warfarin.[2] Compared to warfarin, DOACs have lower bleeding risks, fewer drug and food interactions, no dietary restrictions, and require less therapeutic monitoring.[2] Providers must adjust DOACs based on renal function.[2] However, warfarin is the only anticoagulant indicated for patients with mitral stenosis or mechanical heart valves.[2] Multi-society guidelines do not recommend antiplatelet drugs such as aspirin or P2Y12 inhibitors as a substitute for anticoagulants in treating AFib.[2]

In patients with both AFib and coronary artery disease, the use of an oral anticoagulant can be used alone to treat both. If the patient requires dual antiplatelet therapy (DAPT), after an acute coronary syndrome or the use of a drug eluting stent, but also has AFib, there is a new recommendation. Instead of six to 12 months of DAPT plus an anticoagulant, they recommend a single month of triple therapy, and then 5 months of the P2Y12 inhibitor plus oral anticoagulant followed by the oral anticoagulant alone.

PAUSE AND PONDER: What are the recommendations for reversing anticoagulation with warfarin and DOACs?

Providers must also consider reversal of anticoagulation in the case of bleeding. Removal of the offending drug works in some cases, but providers have options in life-threatening instances. They may reverse warfarin by administering Vitamin K and 4-factor proprotein complex concentrate (PCC) in an acute setting.[2] Reversal of DOACs occurs in only 2% to 4% of cases.[2] Providers reverse dabigatran using idarucizumab.[2] Andexanet-α reverses apixaban, edoxaban, and rivaroxaban.[2] Providers administer PCC, idarucizumab, and andexanet-α intravenously.

NONPHARMACOLOGIC INTERVENTIONS

Electrical Cardioversion

Providers may attempt electrical cardioversion in emergencies or when medications fail to treat AFib adequately.[2] The procedure is completed in an outpatient facility. Providers place electrode pads on the patient's chest and back and connect them to a cardioversion machine.[47] The patient receives anesthesia, and providers administer a high-voltage shock. The shock resets the heart to its normal sinus rhythm. Providers monitor patients for several hours and then patients may go home if they experience no complications.[47]

The multi-society guidelines recommend anticoagulation therapy three weeks before and four weeks after electrical cardioversion if AFib has been present for more than 48 hours (or an unknown period).[2] The anticoagulant reduces the risk that a clot may be formed during or after the procedure that can be dislodged and cause medical problems.[48] Even after the AFib is shocked to normal sinus rhythm, it takes a few weeks for the atria to fully start contracting normally again.

Catheter Ablation

Catheter ablation involves the insertion of small tubes directed through the veins to the heart. The ends of the tubes contain electrodes that damage the diseased heart tissue that is causing

Table 4. Anticoagulants

Class	Agents	Dosing	Notes
Vitamin K antagonists	Warfarin	Dependent on INR	Frequent monitoring and dosing changes; drug and food interactions; required anticoagulant if patient has mitral stenosis or mechanical valves
Direct oral anticoagulants (DOACs)	Apixaban	5 mg po BID	Renal dosing: 2.5 mg po BID in patients with ≥ 2 of the following: age > 80 yr, body weight ≤ 60 kg, creatinine level ≥ 1.5 mg/dL
	Dabigatran	150 mg po BID	Renal dosing: 75 mg po BID in patients with CrCl of 15-30 mL/min
	Edoxaban	60 mg po daily	Renal dosing: 30 mg po daily in patients with CrCl of 15-50 mL/min
	Rivaroxaban	20 mg po daily	Take with food; renal dosing: 15 mg po daily in patients with CrCl of 15-50 mL/min

ABBREVIATIONS: BID = twice daily; CrCl = creatinine clearance; INR = international normalized ratio

abnormal electrical pulses.[49] Heat (radiofrequency ablation) or cold (cryoablation) from the electrodes destroy the tissue.[50] As a result, ectopic foci or re-entry circuits are eliminated, and normal electrical conduction resumes. Young, healthy patients are good candidates for catheter ablation and the procedure is much more effective in patients with paroxysmal AFib.[10] The multi-society guidelines recommend catheter abation when antiarrhythmic therapy is ineffective, not tolerated, or non-preferred.[2] Catheter ablation can be curative of AFib in 70% of cases but may take as many as three attempts to fully resolve the arrhythmia.[10] Providers should continue anticoagulation during and after the procedure unless it is clear that the procedure was curative months down the line.[2]

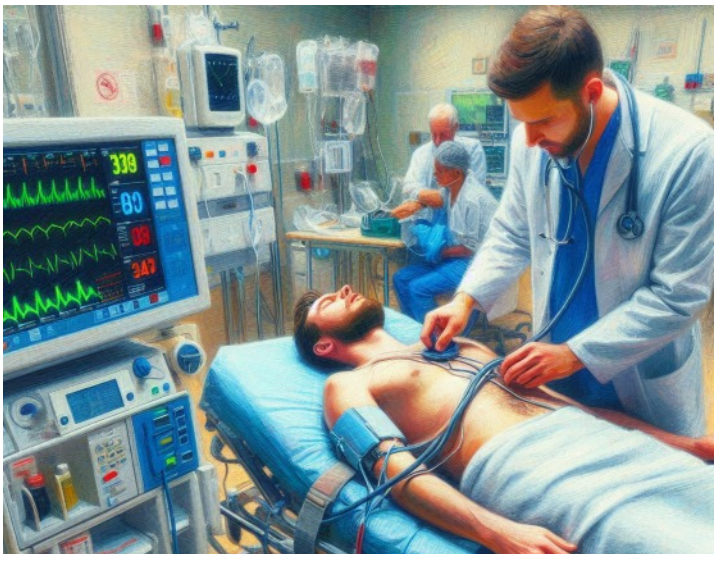
Watchman LAA Device and AtriClip

In patients who require anticoagulation, but the risk of bleeding outpaces the potential benefits, there are devices that occlude the left atrial appendage (LAA, the pouch on the left atria where most of the clots form in AFib). The Watchman LAA device is placed inside the atria and then opens like an umbrella to block off the LAA. The AtriClip is a clamp that is applied to close off the LAA from the outside of the heart during open heart surgery. In this case, the clots still form in the LAA but cannot get out in the circulation. If a patient is having nonadherence to oral anticoagulation due to bleeding, this is a potential option that a pharmacist could recommend a patient discuss with their cardiologist.

TREATMENT IN THE ACUTE SETTING

Providers in an acute setting order beta-blockers or non-dihydropyridine calcium channel blockers as the first-line treatment.[2] If ineffective, digoxin is the next choice. Amiodarone is also an option, but only if the previous treatments fail. Providers should not use dilTIAZem and verapamil in patients with poor left ventricular function or heart failure.[2]

Providers may attempt electrical or pharmacologic cardioversion in the acute setting, especially in unstable patients.[2] Providers use one of three intravenous medications in pharmacologic conversion. The multi-society guidelines recommend ordering ibutilide if patients do not have reduced ventricular function or risk for Torsade de Pointes.[2] Ibutilide is a Class III antiarrhythmic available only in an intravenous form that quickly restores normal sinus rhythm.[10] Providers may also order amiodarone; however, converting to sinus rhythm takes longer than other antiarrhythmics (8 to 12 hours).[2] The multi-society guidelines suggest procainamide as another option.[2] It is a Class 1a antiarrhythmic that quickly restores normal sinus rhythm; however, the multi-society guidelines discourage its long-term use due to its many adverse effects.[2,10] Procainamide may cause low blood pressure, nausea, vomiting, and a Lupus-like syndrome.[10] Providers should avoid using it in patients with heart failure, and it can prolong the QTc interval, potentially leading to Torsade de Pointes.[10]



LIFESTYLE MODIFICATIONS

The multi-society guidelines recommend lifestyle modifications for patients with factors that may influence the disease course.[2] Providers should recommend weight loss in overweight and obese patients and moderate to vigorous exercise for all AFib patients. The guidelines also recommend screening for sleep apnea with appropriate treatment if it is found. Finally, providers should counsel patients to reduce or eliminate alcohol and tobacco use.[2]

AFIB AND HEART FAILURE

Several factors complicate the management of AFib in the presence of heart failure.[2] Providers should consider the degree of left ventricular dysfunction, which determines the type of heart failure and limits the choice of antiarrhythmic.[2,51]

The multi-society guidelines recommend rhythm control over rate control in AFib with heart failure.[2] However, the multi-society guidelines recommend against certain rhythm control agents—namely, flecainide, dronedarone, and propafenone—in patients with heart failure.[2] Digoxin may be an appropriate choice for rate control, as it has a role in treating both diseases while non-dihydropyridine calcium channel blockers should not be used.[2] Beta-blockers can be used, and actually provide enhanced survival in heart failure patients, but need to be started with low doses and then slowly titrated up to therapeutic doses.

Besides treating AFib, an evaluation of the patient should reveal whether their profile meets guideline-directed medical therapy for heart failure.[2] In the case of heart failure with reduced ejection fraction, this includes one of three approved beta-blockers: bisoprolol, metoprolol, or carvedilol.[51] It also includes mineralocorticoid antagonists like spironolactone, a sodium-glucose cotransporter-2 inhibitor, and either an angiotensin-converting enzyme (ACE) inhibitor, angiotensin II receptor blocker, or sacubitril/valsartan.[51]

DIGITAL HEALTH AND AFIB

Smartphones, smartwatches, and handheld devices show promise for uncovering asymptomatic AFib.[52] In approximately one-quarter of patients with asymptomatic disease, providers do not discover AFib until patients suffer a stroke.[53] In recent years, smart devices have provided a solution – ECG monitors. The devices use a technology called photoplethysmography (PPG) sensor technology.[52] Reflected light from the device measures changes in blood flow from the irregular heart rate.[52]

Specific versions of the Apple Watch, the Garmin Venu, and the Samsung Galaxy all use PPG technology to look for irregular heart rhythms.[52] Fitbit also has PPG capabilities in its Charge and Sense models.[52] A meta-analysis showed that smartphones detect AFib with a sensitivity of 94% and a specificity of 96%.[54] Sensitivity means that if a patient is having AFib, the device will detect it 94% of the time. Specificity means that in 4% of cases, when AFib is found, it is due to something other than AFib. PPG technology is equally as effective at detecting AFib as a single-lead ECG.[54] Another meta-analysis confirmed that smartwatches were not inferior to medical-grade devices.[55]

Some limitations of using smart devices in ECG monitoring include the potential for false positives, disparities in access, and the possibility patients will overload providers with consumer data. ECG monitors may incorrectly indicate positives, especially for young, healthy patients.[53] AFib patients older than 65 with a low educational and socioeconomic status often do not own smart devices.[56] Experts also worry about the possibility of consumer data overwhelming the overworked healthcare system.[52]

Investigators are examining the possibility that mobile ECG monitoring can reduce stroke risk.[52] A large initial trial of 75-year-old patients using a Zenicor-ECG device twice daily for two weeks revealed a small but significant reduction in endpoints, which included strokes, at a five-year follow-up.[57]

Application stores feature digital apps to help manage AFib.[58] The apps allow patients to record appointments, feelings, symptoms, and questions for their doctors, among other things. App quality varies, and providers should advise patients to check ratings and reviews and provide recommendations.[58]

PHARMACY TEAM IMPACT ON AFIB MANAGEMENT

Nearly 90% of Americans live within five miles of a community pharmacy.[59] That fact makes pharmacists one of the most accessible healthcare providers.[60] Pharmacists and technicians can leverage their familiarity with their customers in several ways.

For pharmacists, managing and monitoring anticoagulation is the most obvious intervention that can improve outcomes. Providers and administrators often ask pharmacists to dose INRs for warfarin patients in clinics, hospitals, and outpatient settings. Pharmacists may monitor for bleeding complications, both with warfarin and DOACs.

Pharmacist medication review activities may catch meaningful drug-drug and drug-food interactions in AFib patients. Pharmacists can also monitor for the toxic effects of medications like digoxin and amiodarone and report any observations to providers. Even common agents like beta-blockers and calcium channel blockers may cause troublesome interactions in patients with complicated clinical pictures. Pharmacists may catch these problems and intervene with the prescriber.

Pharmacists can collaborate with pharmacy technicians to improve patient adherence to medications. While technicians may coordinate the adherence programs, pharmacists counsel patients on the importance of following providers' medication orders and communicate nonadherence to the prescriber.

Pharmacists also may counsel patients on lifestyle modifications. If a pharmacy has a smoking cessation program, for example, the pharmacist may refer AFib patients to it. The pharmacist may also counsel on the need for weight loss or exercise and help the patient set goals.

Finally, the advent of portable ECG monitors allows pharmacists to set up screening programs for asymptomatic or suspected AFib. The AliveCor KardiaMobile is a single-lead ECG that connects through a smartphone. Pharmacists may use it to collect ECGs and triage patients. A cardiologist then confirms any positive result and refers the patient for treatment.[61]

Pharmacy technicians may also help manage AFib. Technicians often coordinate medication adherence programs, such as automated refill reminders, medication synchronization, and compliance packaging. Pharmacy technicians can then inform the pharmacist of cases of nonadherence.

Technicians may also coordinate filling pill-in-pocket prescriptions for medications like flecainide or propafenone. They can also use TALLman lettering for sound-alike look-alike medications and place dosing labels on shelving for narrow therapeutic index medications like warfarin or digoxin.[20]

Finally, technicians can inform pharmacists when AFib patients try to purchase inappropriate over-the-counter or herbal medications. Decongestants like pseudoephedrine can increase heart rate, and herbals like St. John's wort and hawthorn can interact with antiarrhythmics.[62,63] Medications like non-steroidal anti-inflammatory medications, aspirin, and herbals like vitamin E supplements, ginseng, and ginkgo biloba may interfere with anticoagulation.[62,63]

Finally, pharmacies can foster knowledge and understanding of the disease by hosting community events in coordination with local healthcare providers. For example, a pharmacy could hold an event during AFib awareness month in September. Pharmacy staff could invite representatives from local clinics and cardiologists' offices.

CONCLUSION

AFib is the most common type of heart rhythm disorder or arrhythmia, and its incidence and prevalence continue to grow as the population ages. Goals for AFib patients include prevention of stroke, control of heart failure symptoms, and improvement in quality of life. Rate and rhythm control antiarrhythmics can treat AFib. The rate control strategies help with symptoms by controlling the ventricular rate. Rhythm control medications restore the normal sinus rhythm, but providers must carefully choose and monitor them due to their side effects and contraindications. Providers prefer rhythm control agents in many patients due to their ability to reduce the risk of stroke and improve quality of life. Anticoagulation is indicated in cases of higher stroke risk; providers should choose DOACs over warfarin in most cases, except for patients with mitral stenosis or mechanical heart valves.

Beta-blockers and calcium channel blockers are the first choices in the acute setting, followed by digoxin. Providers have limited options in both rate and rhythm control in patients with heart failure. Beta-blockers, digoxin, dofetilide, sotalol, and amiodarone provide options. Pharmacists can play essential roles in managing and monitoring anticoagulation, performing drug use reviews and adherence monitoring, and screening patients for asymptomatic cases. Pharmacy technicians can aid pharmacists by coordinating adherence mechanisms, filling pill-in-pocket refills, and notifying the pharmacist of patients' improper OTC or herbal selections.

Now let's return to our patient case. Dan's uncontrolled AFib requires a quick call to his cardiologist, who suggests he go to a local emergency room for examination. The pharmacy staff offers to put his apixaban, flecainide, and other medications on a medication synchronization program with refill reminders. They also suggest that he invest in a digital device that monitors ECG. He promises to go straight to the emergency room. **Figure 1** summarizes some key points about AF.

Figure 1. Differentiating and Advising about Atrial Fibrillation

Best

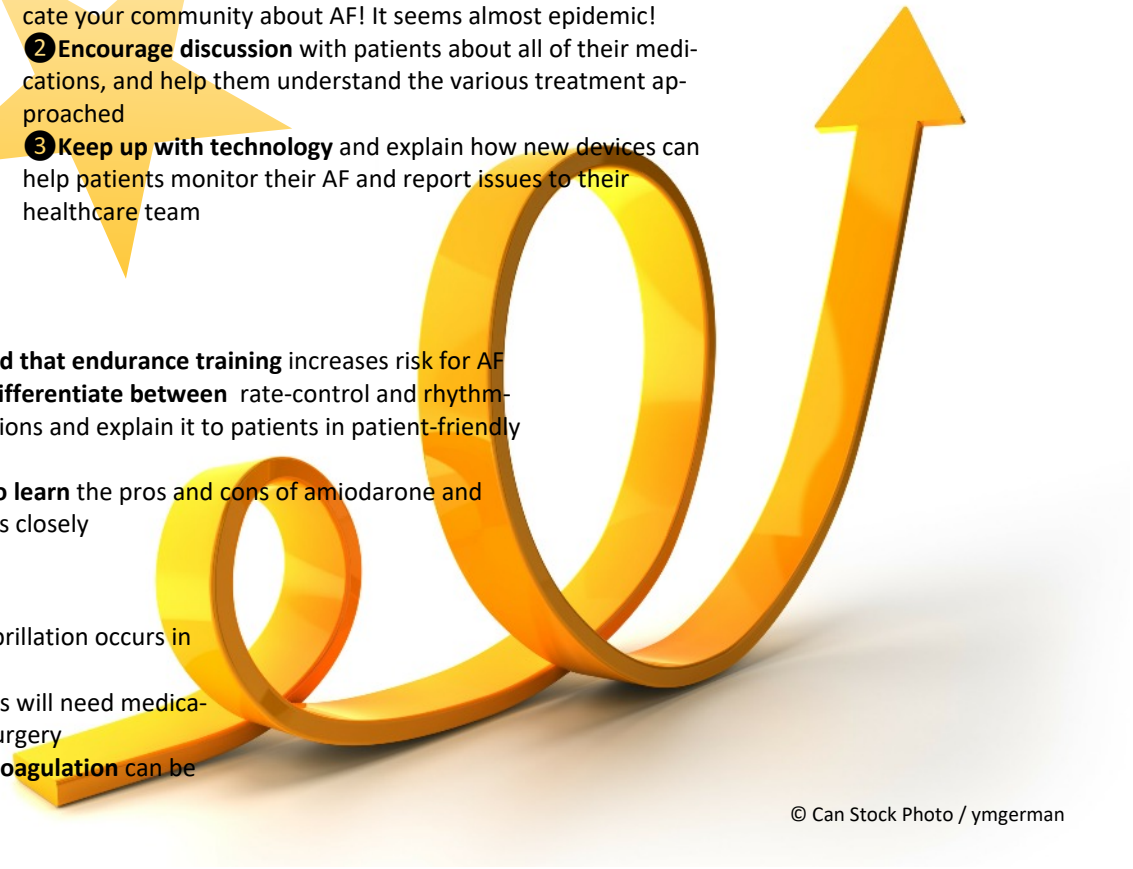
❶ **Be COMMUNITY CHAMPIONS** and whenever possible, educate your community about AF! It seems almost epidemic!
❷ **Encourage discussion** with patients about all of their medications, and help them understand the various treatment approached
❸ **Keep up with technology** and explain how new devices can help patients monitor their AF and report issues to their healthcare team

Better

❶ **Keep in mind that endurance training** increases risk for AF
❷ Be able to **differentiate between** rate-control and rhythm-control medications and explain it to patients in patient-friendly language
❸ **Take time to learn** the pros and cons of amiodarone and monitor patients closely

Good

❶ **Remember** that atrial fibrillation occurs in various presentations
❷ **Know** that many patients will need medication, and some may need surgery
❸ **Keep in mind that anticoagulation** can be life-saving!



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