PACE Pharmaceutical Assistance Contract for the Elderly

Alosa Health
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Getting the beat and rhythm right

Anticoagulation, rate, and rhythm control in atrial fibrillation

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These are general recommendations only; specific clinical decisions should be made by the treating clinician based on an individual patient's clinical condition.

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Anticoagulation, rate, and rhythm control in atrial fibrillation

Activity Start Date: December 9, 2024
Activity Termination Date: December 8, 2027

This activity offers CE credit for:

1. Medicine (AMA)
2. Nurses (ANCC)
3. Other

All other attendees will receive a Certificate of Attendance

Activity Overview:

The goal of this course is to help primary care practitioners manage atrial fibrillation in older adults. The activity provides the most recent evidence on managing atrial fibrillation using rate and rhythm control strategies, assessing need for anticoagulation using a validated tool or an appraisal of co-occurring conditions, and selecting appropriate anticoagulation.

The educational program includes a written evidence report (print monograph) and several non-CME/CE components:

1. Summary document of top 4-5 key messages
2. “Academic detailing” educational sessions in clinicians’ offices with trained outreach educators (pharmacists, nurses, physicians) who present the material interactively
3. Reference cards for easy access to key materials
4. Patient education information (brochure/tear off sheets)

This program synthesizes current clinical information on this topic into accessible, non-commercial, evidence-based educational material, which is taught interactively to providers by specially trained clinical educators.

Learning Objectives:

After completing this activity, participants will be able to:

- Assess the risk of stroke using a validated score.
- Choose the best option for anticoagulation based on patient characteristics.
- Apply appropriate rate control as initial management of atrial fibrillation.
- Identify patients who benefit from early referral to cardiology for rhythm control strategies.
- Recognize the role of specialist procedures and implications for management by the primary care provider.

Financial Support:

There is no commercial support associated with this activity.

Target Audience:

The educational program is designed for physicians, including general internal medicine doctors, family practice physicians, nurse practitioners, physician assistants, nurses, and all other clinicians caring for patients who have atrial fibrillation.

Credit Information:

In support of improving patient care, this activity has been planned and implemented by CME Outfitters, LLC and Alosa Health. CME Outfitters, LLC is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.

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Nurses: This activity is designated for 1.5 nursing contact hours.

California Residents: This continuing nursing education activity was approved by the California Board of Registered Nursing. CME Outfitters LLC's provider number is CEP15510.

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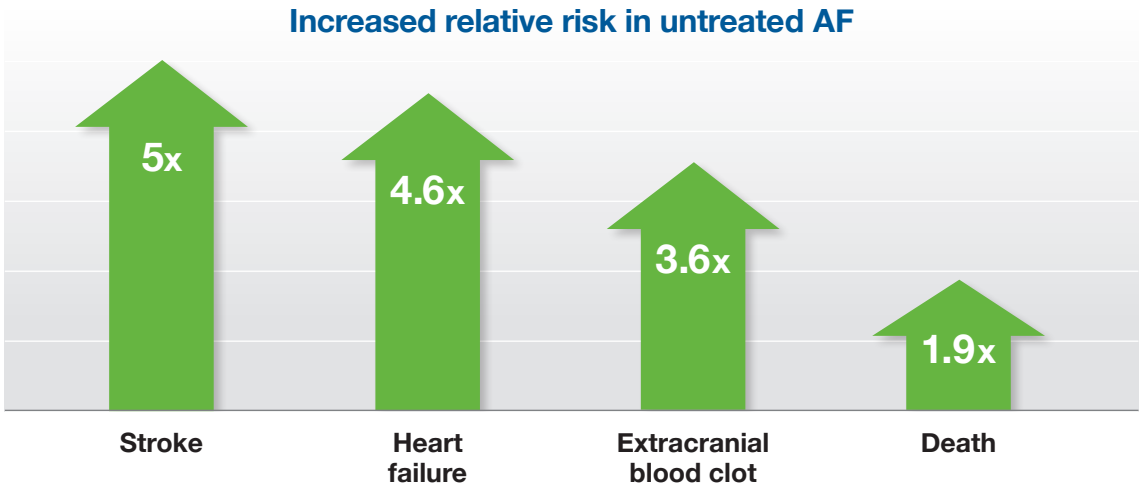
Introduction

Atrial fibrillation (AF) has been described as a "cardiovascular disease epidemic" of the new millennium.[1] AF is the most common sustained cardiac arrhythmia and it substantially increases a patient's risk for stroke, heart failure, hospitalization, and death (Figure 1).[2] About 15% of strokes in the U.S. are caused by AF,[3] and AF contributes to nearly 100,000 deaths in the U.S. every year.[4]

The incidence of AF has been increasing by approximately 3% annually in the past two decades, rising from 4.74 cases per 1000 person years in 2006 to 6.82 cases per 1000 person-years in 2018.[5] AF affects approximately 9 million Americans,[6] and its prevalence is expected to rise to 12.1 million by 2030.[2] This increased prevalence is due not only to increasing numbers of older adults, but also to increased detection and/or increasing prevalence of pre-disposing factors such as obesity and diabetes.[7] AF is associated with substantial healthcare costs. Insurance data show that annual health care costs for patients with AF are approximately $63,000, which is roughly $28,000 more than patients without AF.[8] AF accounted for an estimated $28.4 billion in U.S. health care spending in 2016.[9]

Figure 1: Patients with AF have increased morbidity and mortality compared to patients of the same age without AF[10-13]



In 2023, updated clinical guidelines for the diagnosis and management of AF were published as a report from the American College of Cardiology (ACC)/American Heart Association (AHA) joint committee on clinical practice guidelines[14] and in 2024 similar guidelines were issued by the European Society of Cardiology.[15] This document summarizes the new recommendations as well as the evidence on which these recommendations are based in order to better inform primary care clinicians about current approaches to evaluating and managing older patients with AF.

Definition, epidemiology, pathophysiology

AF is an atrial tachyarrhythmia characterized by uncoordinated atrial activation, which leads to deterioration of atrial mechanical function.[16] Waves of uncontrolled electrical signals travel through the atria, rather than the normal, regulated signals emanating from the sinoatrial (SA) node. These signals often originate in the muscular sleeves of one or more of the pulmonary veins at their insertion into the left atrium.

AF affects approximately 1% of the population younger than age 60, but prevalence increases steeply with age. Men are more likely than women to have AF at every age. A 2023 cohort study in 17,238 adults age ≥65 years found the prevalence of AF rising from 6.4% at 65-69 years to 28.5% at age ≥85 years.[17]

Approximately 88% of AF occurs in patients with a history of cardiac or pulmonary disease.[18] AF is usually associated with anatomical and histological abnormalities in the atria resulting from conditions such as hypertension, coronary artery disease, heart failure, valvular disease, or cardiomyopathy.[19] In addition, specific cardiomyopathies may be more significantly associated with AF. AF may occur in up to 70% of patients with transthyretin cardiac amyloidosis[20] and in at least 25% of patients with hypertrophic cardiomyopathy.[21] Dilation of the atria with fibrosis and inflammation causes a difference in refractory periods within atrial tissue and promotes electrical instability, which can result in AF. The presence of rapidly firing foci, often in the pulmonary veins, may trigger AF.[22] AF may also result as degeneration of other rapid arrhythmias, such as atrial tachycardias and atrial flutter.[4]

Many conditions are associated with AF, some of which may be temporary or reversible (Table 1), and more than half of new diagnoses of AF can be explained by the presence of one or more common risk factors.

Table 1: AF risk factors[10]

Lifestyle • excessive alcohol use • cocaine or amphetamine use • smoking • obesity/overweight	Respiratory • COPD exacerbations • pulmonary embolism • sleep apnea
Infection • pneumonia • urinary tract infection • sepsis	Endocrine • diabetes • hyperthyroidism
Cardiovascular conditions • hypertension • coronary artery disease • heart failure • cardiomyopathy • valvular heart disease • myocarditis • pericarditis • infiltrative disease (amyloidosis) • congenital heart disease	Other • age • cardiothoracic surgery • genetics • environmental (air pollution)

One lifestyle factor that does not appear to be associated with AF is caffeine. No increased risk has been found in population-based studies of AF and caffeine,[23] and a recent observational study in Spain likewise found no significant differences in the rate of AF in those who reported minimal, moderate, or heavy use of coffee.[24]

The disorganized atrial contractions typical of AF can cause blood to pool in the atria, increasing the risk of thrombus formation. Furthermore, paroxysmal AF leads to atrial structural and functional changes that can increase the risk of stroke even when patients are in sinus rhythm.[25] Among AF patients with stroke, two out of three have a cardioembolic stroke, with the left atrial appendage and left atrium the most common sites for thrombus formation.[26] The risk of AF-associated stroke increases significantly with age, with AF accounting for only 1.5% of strokes in adults aged 50-59 years, but 23.5% of strokes in those aged 80-89 years.[27]

New-onset AF during an acute illness (provoked AF) indicates a high risk of recurrent AF even after recovery from the provoking risk factors. For example, among Medicare patients admitted with sepsis, 44% who had new-onset AF during admission received an AF diagnosis within the next year, compared to only 7% of patients without new-onset AF.[28] Similarly, in a longitudinal observation study of ~10,000 individuals with a new diagnosis of AF, 19% were felt to have a provoking factor such as surgery or acute medical illness. Among patients with provoking factors, 41% developed recurrent AF within 5 years compared to 52% who did not have a provoking factor.[29] Thus, the risk of recurrence of provoked atrial fibrillation is high and is similar to the risk of recurrence of AF without an acute provoking factor. AHA guidelines recommend that patients with provoked AF be monitored for recurrence, be assessed for AF triggers, and considered for anticoagulation initiation and rhythm control.[30]

Classification

AF classification is determined by the duration of symptoms (Table 2). Persistent AF may be the first presentation or may be preceded by recurrent episodes of paroxysmal AF. Note that the commonly-used term “permanent AF” does not refer to a duration of AF, but, instead, describes a decision by the patient and clinician to stop further attempts to achieve or maintain sinus rhythm.[4]

The duration of AF is an important clinical consideration since studies have shown significantly increased mortality rates in patient with persistent vs. paroxysmal AF.[31]

Table 2: Classification of AF by duration[14]

Classification	Definition
Paroxysmal	Intermittent and terminates in less than 7 days
Persistent	Continuous, sustained for >7 days, or requires intervention to terminate
Long-standing persistent	Continuous AF lasting more than 12 months

In the 2019 ACC/AHA guidelines, a shift in language away from the distinction of valvular or non-valvular AF was recommended. Valvular AF referred specifically to patients with moderate-to-severe rheumatic mitral stenosis or presence of a mechanical heart valve. These two conditions require anticoagulation with warfarin, and these patients were not included in the pivotal trials of direct oral anticoagulants (DOACs). Patients with other diseases of the heart valves have been included in recent clinical trials and can be managed like any other patient with AF.[14]

About 1 out of 4 patients with paroxysmal AF will progress to persistent AF, and almost 30% of patients with paroxysmal or persistent AF develop long-standing persistent AF over a 30-year period.[32] This is likely related to structural remodeling of the atria due to recurrent episodes of paroxysmal AF.[33] Disease progression can occur even in the absence of new or worsening underlying heart disease. Patients with coexisting cardiopulmonary disease such as hypertension, obstructive sleep apnea, heart failure, and valvular heart disease have a much higher risk for progression of AF.[32]

Related arrhythmias

AF may occur alone or in association with other arrhythmias, most commonly atrial flutter and atrial tachycardias.[16,18] Atrial flutter may degenerate into AF, and AF, in turn, may organize into atrial flutter. Most commonly, this is "typical" atrial flutter, which refers to a macro-reentrant circuit in the right atrium. Typical atrial flutter can usually be distinguished from AF by its saw-tooth pattern on an ECG, most prominent in leads II, III, aVF, and V1.[18] Between 22 and 50% of patients undergoing ablation for typical atrial flutter will develop AF within 5 years.[34] Atrial flutter is associated with a similar level of increased stroke risk as AF, likely due to its association with occult AF.[4] Anticoagulation is recommended according to the same risk stratification used for AF.[4]

Atrial tachycardias are sometimes seen in patients prior to the development of clinical AF. The ECG in atrial tachycardia shows a regular atrial tachycardia with P-wave morphology different from that in sinus tachycardia.[16,18]

BOTTOM LINE: AF is the most common type of cardiac arrhythmia and significantly increases the risks of stroke, heart failure, and mortality. Older patients are at greatest risk for stroke. Common risk factors for AF include hypertension, obesity, diabetes, other cardiovascular diseases, and smoking. AF is classified in relation to duration (paroxysmal, persistent, or long-standing persistent).

Clinical presentation and sequelae

AF can cause or worsen heart failure. Long periods of rapid, uncontrolled heart rate can cause tachycardia-induced cardiomyopathy, with a reduced ejection fraction. And for any patient with a low ejection fraction, AF leads to a loss of coordinated atrial contraction ("atrial kick"), which decreases ventricular filling, reduces cardiac output, and leads to increased left atrial pressures and pulmonary venous congestion (a.k.a. clinical heart failure). AF may also be a *consequence* of structural heart disease – especially those with chronically elevated left atrial pressures.

Many patients with AF are asymptomatic and may be diagnosed incidentally. Symptomatic patients with AF commonly report palpitations and fatigue, although other symptoms may be reported (Table 3). Observational studies comparing symptomatic to asymptomatic AF find no differences in all-cause and cardiovascular morality between groups, nor in the risk of stroke or thromboembolism.[35]

Table 3: Common AF symptoms[36]

Symptom	Paroxysmal AF	Persistent AF
Palpitations	55%	41%
Fatigue	48%	49%
Dyspnea	39%	48%
Dizziness	29%	25%
Chest pain	21%	19%
Heart failure, NYHA class III/IV*	7%	15%
Asymptomatic	21%	23%
* New York Heart Association functional classification system.		

Clinical evaluation

History and physical exam

In cases of suspected AF, the medical history should focus on identifying the presence and nature of AF symptoms, characteristics of AF episodes, and associated conditions.[16,18,19] Important questions to ask:

- Do you have any symptoms?
  - Consider palpitations, fatigue, shortness of breath, dizziness
- When did you have the first episode of symptomatic AF or when were you diagnosed?
- What is the frequency and duration of episodes?
- Are there precipitating factors?
- How do the episodes terminate?
- Are there reversible conditions that we can treat?
  - Is there hyperthyroidism, heavy alcohol use, or obstructive sleep apnea?
- Is there underlying heart disease or other medical conditions that can be treated?
- What risk factors can be controlled?

Physical examination may suggest AF on the basis of a rapid heart rate, irregular pulse, or irregular jugular venous pulsations. The findings are similar in patients with atrial flutter, except that the rhythm may be regular.[18]

A physical exam should also identify conditions that may contribute to AF. Blood pressure should be carefully assessed. Note should be made of the patient's body habitus and neck circumference as risk factors for obstructive sleep apnea. The cardiac exam may reveal murmurs suggestive of heart disease, or clinical signs of heart failure such as elevated jugular venous pressure, pulmonary edema, S3 gallops, abdominal distension, or lower extremity edema. A pulmonary and thyroid exam may reveal underlying lung disease or an enlarged or nodular thyroid, respectively.[19]

Routine ECG or other kinds of electronic screening for AF may detect additional cases, but a systematic review by the U.S. Preventive Services Task Force (USPSTF) concluded that current evidence is insufficient to recommend this as a general practice. The USPSTF notes, however, that pulse palpitation or cardiac auscultation, which can also detect AF by identifying an irregularly irregular heart rhythm, is considered usual care and should be conducted.[37]

The advent of smart watches

Smart watches can detect irregular heart rates. In a study involving 419,297 users of the Apple smartwatch, 0.52% received an alert about irregular heart rates.[38] Of those who were notified and subsequently wore a monitor, 34% were found to have AF. Approximately half of the AF detected with the smart watches lasted >6 hours, which is clinically important since the risk of stroke with AF is highest in paroxysmal AF of longer duration. AF detected by consumer devices should be confirmed by FDA-approved 12-lead ECG. Repeated monitoring periods may be needed to detect rare episodes of paroxysmal AF.

Examine the ECG

When possible, an ECG should be performed during the arrhythmia to confirm a diagnosis of AF. The classic electrocardiographic findings of AF are irregular R-R intervals and the absence of distinct, repeating P waves; there may be no clear evidence of atrial activity, or there may be irregular atrial activity. Patients with suspected AF who are in sinus rhythm at the time of examination may require ambulatory monitoring with a Holter device (24-48 hours), event monitor (weeks to months), mobile continuous outpatient telemetry (weeks to months), or implanted loop record (up to four years).[19]

Get an echocardiogram

All patients with AF should have a transthoracic echocardiogram to assess left atrial and left ventricular size, left ventricular wall thickness and left ventricular systolic and diastolic function, presence of valvular disease, and to exclude pericardial disease and hypertrophic cardiomyopathy.[18,19] Such imaging can guide decisions about anticoagulation, which antiarrhythmic options to pursue, and whether treatment for other pathologies (e.g., cardiac amyloidosis) are required. Transesophageal echocardiography should not be routinely ordered, but is better able to evaluate for the presence of left atrial thrombus compared to transthoracic echo and can be used to guide timing of electrical cardioversion if that treatment is chosen.

Laboratory tests

Thyroid, renal, and hepatic function, serum electrolytes including magnesium, and a complete blood count, should be measured at the first presentation of AF to identify potentially treatable causes of AF, to help establish drug options and doses, and to follow for possible adverse effects.[18,19] Coagulation studies should be ordered if the patient is on an anticoagulant or is being considered for starting an anticoagulant. Cardiac biomarkers (e.g., troponin or B-type natriuretic peptide) are not routinely ordered, but may be useful in patients presenting with signs of heart failure or myocardial ischemia.

Table 4: Routine Laboratory tests for AF[4]

Laboratory Test	Reason
Thyroid studies including TSH and free T4	Patients with hyperthyroidism and subclinical hyperthyroidism have increased risk of AF
Serum electrolytes and renal function	Guidance for initiation of anticoagulation and rate/ rhythm control medications
Complete blood count	Guidance for initiation of anticoagulation
Liver function	Liver dysfunction may be a contraindication for some anticoagulation medications

Additional investigations

Exercise testing (i.e., stress ECG) should not be routinely ordered but may help in specific clinical situations to:

- exclude ischemia prior to initiating certain antiarrhythmic medications
- evaluate rate control during exertion in a symptomatic patient who is rate-controlled at rest

In patients with AF, the ventricular rate may accelerate excessively during exercise even when it is well-controlled at rest. Evaluating the heart rate response to exercise or monitoring the rate over an extended period (e.g., by 24-hour Holter recording) may be helpful in patients with ongoing symptoms despite well-controlled rates at rest.[39]

Obtain a sleep study for patients at risk for obstructive sleep apnea (OSA), since the prevalence of OSA in AF patients ranges from 21% to 87%.[40] AF patients with OSA are less likely to report typical OSA symptoms, and appropriate treatment of OSA reduces the incidence of AF and increases the therapeutic success of AF treatments.[41]

BOTTOM LINE: Perform a thorough history and targeted physical exam. A diagnosis of AF is typically made with an ECG showing irregular R-R intervals and the absence of distinct, repeating P waves. Get an echocardiogram to assess heart function and structure. Blood tests may identify treatable causes of AF and help guide drug therapy.

Principles of management

The management of patients with AF typically involves three general considerations: heart rate/rhythm control, stroke prevention, and optimizing modifiable risk factors. A rate control strategy involves moderating the ventricular rate with no attempt to restore or maintain sinus rhythm. A rhythm control strategy attempts restoration and/or maintenance of sinus rhythm, and also requires attention to rate.[18] Stroke prevention should be considered separately from decisions about rate or rhythm control; that is, a rhythm control strategy does not preclude the need for anticoagulation in a patient with significant stroke risk.

Treatment decisions must take a number of factors into account, including the severity of symptoms, the cause (if known) of AF, the duration of AF, the risk of stroke, co-morbidities (e.g., heart failure), the

potential adverse effects of a particular therapy (e.g., bleeding), and patient preference. Patients presenting with rapid AF and acute symptoms (hypotension, syncope, chest pain, dyspnea, heart failure, or neurological symptoms) require hospitalization for urgent heart rate control and possibly electrical cardioversion.[19]

Key principles for the management of patients with stable AF include:

- Assess for the risk of stroke and mitigate bleeding risk before initiating anticoagulation for stroke prevention.
- Initiate heart rate control for patients who are hemodynamically stable and have few, or tolerable, symptoms.
- Treat underlying risk factors (e.g., hypertension, obstructive sleep apnea).
- Evaluate patients for early referral to cardiology for rhythm control, such as anti-arrhythmic medications and/or cardiac ablation therapy.

Optimize risk factors

As noted above, a number of risk factors have been linked to the development and persistence of AF including obesity, hypertension, diabetes, obstructive sleep apnea, smoking, and alcohol consumption. Emerging research on the effectiveness of changes to reduce these risk factors, individually or collectively, is showing promise.

Weight loss

Obesity or overweight is associated with diastolic dysfunction, a systemic proinflammatory state, autonomic tone abnormalities, and atrial enlargement—changes known to promote arrhythmias.[42] Fat stores have been shown to correlate with incident atrial fibrillation,[43] and obesity is associated with atrial electrical and structural remodeling and subsequent AF.[44] These potential causal mechanisms have spurred research into the effects of weight loss on AF symptoms and the need for drug or device therapies. The 2023 AHA/ACC Guidelines recommend that patients with obesity or overweight lose at least 10% of their weight and reduce other risk factors as part of an effort to control AF.[14]

A 2013 trial randomized 150 patients with symptomatic AF to a weight management program including low-calorie diets and increased physical activity vs. general education.[42] Both groups had intensive management of cardiometabolic risk factors. After 15 months of follow-up, patients in the intervention group had lost a mean of 14.3 kg vs. 3.6 kg in the control group, and AF symptoms and severity improved significantly in the intervention group. Mean AF symptom burden score reduction was 11.8 points in the intervention group vs. 2.6 points in the control group ($P<0.001$), symptom severity score reduction was 8.4 points vs. 1.7 points ($P<0.001$), the reduction in number of AF episodes was 2.5 vs. no change ($P<0.01$), and cumulative duration of AF episodes was a 692 minute decline vs. a 419 minute increase ($P=0.002$).

The ARREST-AF cohort study evaluated 149 patients with a body mass index (BMI) ≥27 kg/m^2 and ≥1 cardiac risk factor who underwent AF ablation.[45] 61 patients opted to enroll in an “aggressive” structured risk factor management (RFM) program that included dietary changes to promote weight loss and reduction in hypertension as well as increases in physical activity (to a goal of 200 minutes of moderate-intensity activity per week) and alcohol reduction. 88 patients who declined the aggressive program (the

control group) were provided information about risk factor management only (in addition to standard medical follow-up). After a mean follow-up of 42 months, AF frequency, duration, symptoms, and symptom severity decreased more in the RFM group than the control group (P<0.001 for all comparisons). It should be noted that the results of this observational study may have been influenced by confounding associated with the opt-in vs. opt-out cohort selection method.[45]

An observational study from Australia followed 355 patients with obesity and AF who attended a dedicated weight loss clinic with a median follow-up of four years.[46] Weight loss was categorized into three groups: ≥10% loss; 3%-9% loss; and <3% loss. Greater weight loss was associated with reduced AF burden and symptoms compared to patients with less weight loss. Patients who lost at least 10% of body weight had a 6-fold increase in arrhythmia-free survival (95% CI: 3.4-fold increase to 10.3-fold increase). Forty-five percent of patients who lost at least 10% of body weight were free from AF symptoms without undergoing ablation or using medications. Twenty-two percent of patients who lost 3-9% of body weight were free from AF symptoms without undergoing ablation or using medications.

Hypertension

ACC/AHA guidelines recommend that patients with AF and hypertension be treated to “optimal BP control” (i.e., <130/80 mm Hg) to reduce AF recurrence and AF-related cardiovascular events.[14]

The benefit of controlling hypertension in patients with AF were demonstrated in a study of 531 patients with AF undergoing catheter ablation therapy.[47] Patients were assigned to three groups: those with uncontrolled hypertension; those with controlled hypertension; and those without hypertension. After mean follow-up of 19 months, 40.6% of those with uncontrolled hypertension had a recurrence of AF compared to 28.1% of those with controlled hypertension and 25.7% of those without hypertension (HR 1.52; 95% CI: 1.01-2.29) for comparison of uncontrolled vs. controlled hypertension).

Evidence based hypertension management may also be effective in primary prevention of atrial fibrillation. In a secondary sub-group analysis of the SPRINT (Systolic Blood Pressure Intervention) Trial individuals with an increased risk of cardiovascular disease and without a history of AF were 26% less likely to develop incident AF when hypertension was intensively controlled (HR 0.74; 95% CI: 0.56–0.98).[48]

Obstructive sleep apnea

Obstructive sleep apnea (OSA) has been reported in roughly 20% of patients with AF.[49] Observational studies have shown that treatment for sleep-disrupted breathing (primarily OSA) is associated with fewer recurrences of AF and reduced AF burden.[14]

A prospective observational cohort study of patients with polysomnography-confirmed OSA undergoing AF catheter ablation compared 32 patients who were treated with continuous positive airway pressure (CPAP) therapy to 30 patients not treated for their OSA.[50] Following ablation, CPAP therapy was associated with higher AF-free survival (71.9% vs. 36.7%; p = 0.01) and AF-free survival off antiarrhythmic drugs or repeat ablation (65.6% vs. 33.3%; p = 0.02). AF recurrence after ablation therapy was substantially higher in the group not treated with CPAP (HR 2.4, p < 0.02).

Tobacco use

Data from observational studies show that cigarette smoking in people with AF is associated with worse cardiovascular outcomes and higher mortality, and that individuals with AF who quit smoking are less likely to develop stroke or die.[14]

A study of 186 AF patients (mean age 63 years) undergoing AF catheter ablation compared AF recurrence in current smokers vs. former smokers or non-smokers.[51] After a mean follow-up of 418 days, recurrence was 34.5% in smokers vs. 14% in former/non-smokers (HR 2.96; 95% CI: 1.32-6.64). Being a former smoker did not increase the risk of AF recurrence compared with patients who never smoked (13.2% vs. 14.6%, p = 0.23).

Alcohol use

Non-drinkers have a lower risk of stroke after a diagnosis of AF compared to current drinkers, and those who stop drinking also lower their risk compared to those who continue to drink.[52] In addition, alcohol use increases the risk of AF recurrence following ablation (81% total AF-free survival for non-drinkers compared to 69% for moderate drinkers and 35% for heavy drinkers) in a study involving 122 patients with symptomatic AF who underwent pulmonary vein isolation.[53]

BOTTOM LINE: Treating modifiable lifestyle risk factors such as obesity/overweight, hypertension, sleep apnea, smoking, and alcohol use has been shown to reduce AF symptoms and burden.

Weigh the benefits and risks of anticoagulation

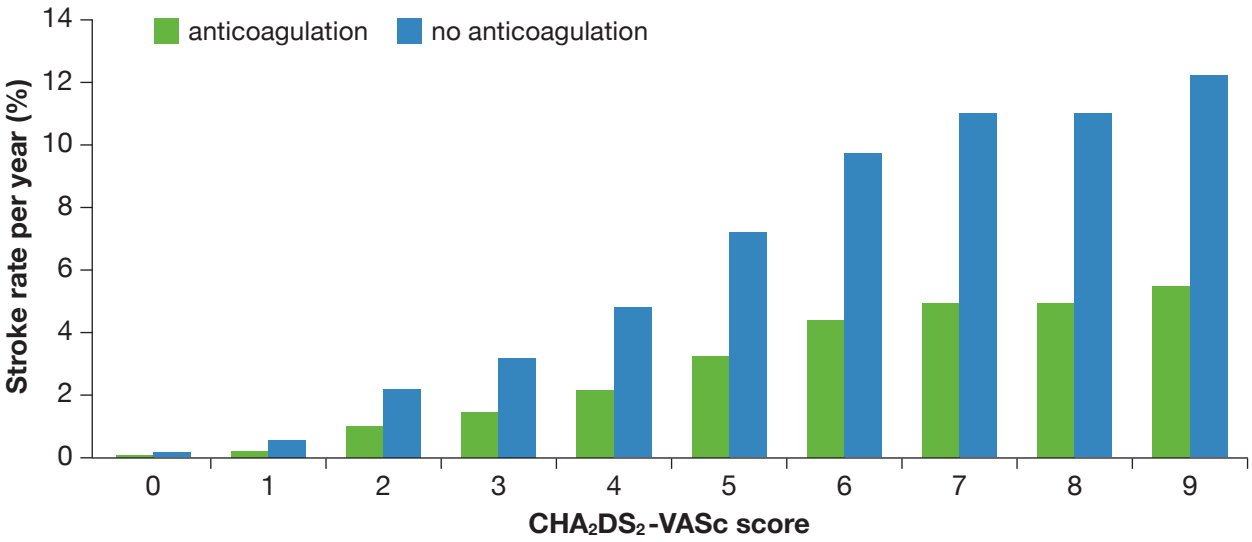
Assess stroke risk

The CHA_2DS_2-VASc scoring system is commonly used to evaluate patient for stroke risk and appropriateness of anticoagulation.[54] Some recent guidelines, however, recommend removing female sex (Sc) from stroke risk assessment. In a Danish population-based study of individuals with AF, female sex was not associated with an increased risk of stroke in patients with no other identifiable risk factors (CHA_2DS_2-VA (sex excluded) score of 0).[55] Thus, female sex is a stroke risk modifier (augmenting stroke risk when additional risk factors are already present), rather than an independent risk factor in otherwise low risk individuals. Given that sex is a weak independent risk factor, the 2024 European Society of Cardiology guidelines recommend using the CHA_2DS_2-VA score (Table 5) —removing female sex as a factor to streamline anticoagulation decisions.[15] Note should be made, however, that in individuals with additional risk factors, female sex is still a significant risk enhancer for stroke.

Table 5: CHA_2DS_2-VA scoring system[15]

Letter	Parameter	Points (if yes)
C	Congestive heart failure*	1
H	Hypertension	1
A	Age ≥75 years	2
D	Diabetes mellitus	1
S	Prior stroke, TIA, thromboembolism	2
V	Vascular disease: prior MI, peripheral artery disease, aortic plaque	1
A	Age 65-74 years	1
		Maximum 8 points
* **Congestive heart failure:** symptomatic HF regardless of EF or asymptomatic HF with LVEF ≤ 40%		

Figure 2: Stroke risk and benefit of anticoagulation both rise with CHA_2DS_2-VASc score[56]

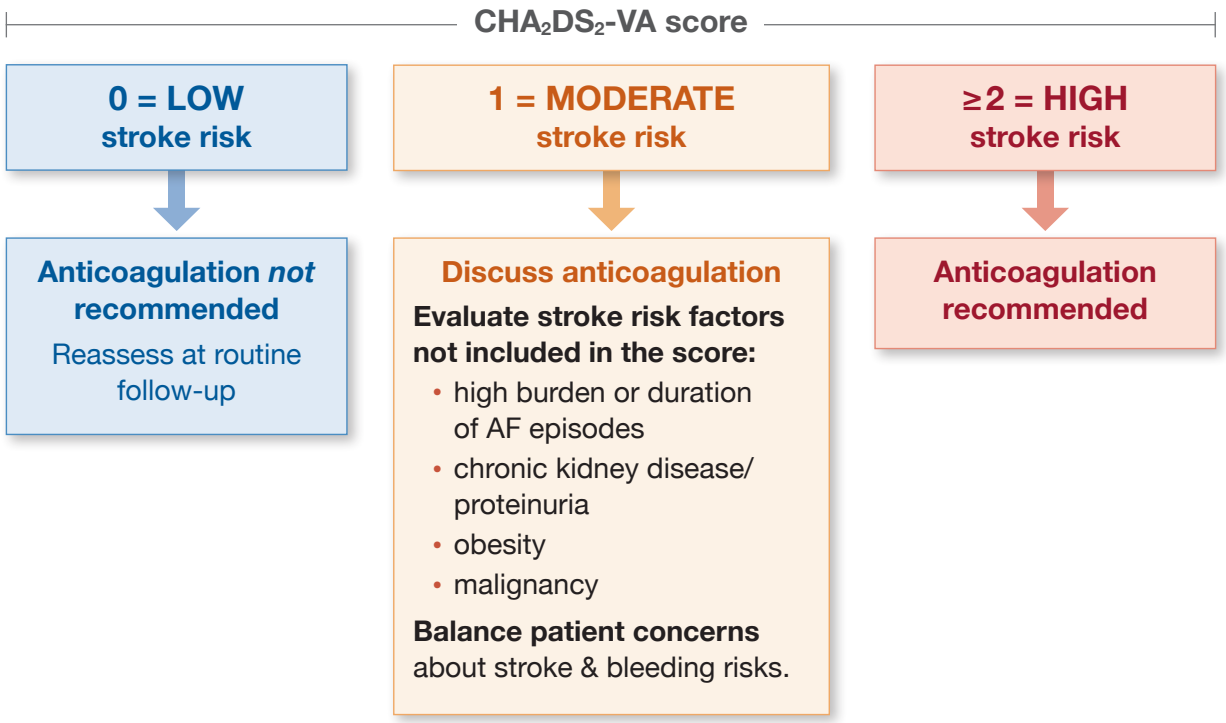


Patients with a CHA_2DS_2-VA score of 0 are at very low risk of stroke (i.e., 0 – 0.2%) and do not need anticoagulation.[54,56] Higher scores need to be carefully interpreted (see management sections that follow) to determine optimal therapy. At every CHA_2DS_2-VA score, anticoagulation reduces the risk of stroke by about half. Note, however, that CHA_2DS_2-VA score does not account for high burden or duration of AF episodes, and it does not include other comorbidities that increase stroke risk, such as chronic kidney disease, obesity, and cancer. In addition, patients with the conditions listed below are at higher thrombotic risk and should be on anticoagulation therapy regardless of CHA_2DS_2-VA score:[14]

- mechanical heart valve
- moderate-severe rheumatic mitral stenosis
- hypertrophic cardiomyopathy
- cardiac amyloidosis

Use the CHA_2DS_2-VA score to decide whether to pursue anticoagulation, as detailed in Figure 3.

Figure 3: Recommend an anticoagulation plan based on CHA_2DS_2-VA score[14]



Evaluate bleeding risk

Current guidelines suggest that bleeding risk scores not be used to assess a patient's candidacy for anticoagulation.[57] Bleeding scores such as HAS-BLED, HEMORR2HAGES, and ATRIA discriminate poorly between low and high bleeding risk. Further, several factors included in these risk scores (e.g., age, hypertension, prior stroke, renal disease) are also associated with increased stroke risk, which limits their utility in assessing risks versus benefits.

Nonetheless, bleeding risk is influenced by some potentially modifiable risk factors, which should be carefully reviewed prior to any treatment with anticoagulants. Potential steps to reduce bleeding risk include controlling hypertension, stopping or reducing alcohol use, stopping other medications that increase bleeding risk (such as NSAIDs), and using a DOAC instead of warfarin to prevent International Normalized Ratio (INR) fluctuations (see section on DOACs below).

The most commonly cited reason among providers for not prescribing anticoagulation to older patients is risk of falls. Data from two studies, however, suggests that the risk-benefit trade off favors anticoagulation. A modeling study from 1999 showed that a patient with AF on warfarin would need to fall approximately 295 times annually before the risk of a subdural hemorrhage outweighed the benefits of stroke prevention.[58] Subsequently, a 2012 prospective study of roughly 500 patients on vitamin K antagonists showed that the risk of major bleeding was not significantly higher among adults with higher fall risk.[59] In isolation, therefore, prior falls or risk of falls should not be considered a contraindication to anticoagulation.

Patients taking anti-platelet agents (e.g., aspirin, clopidogrel, ticagrelor, prasugrel) in addition to anticoagulation are at an increased risk of bleeding. These agents are frequently prescribed for patients with coronary artery disease (CAD). Notably, CAD and AF share common risk factors, and many patients have a diagnosis of both CAD and AF. In the AFIRE trial, an open-label randomized trial among 2,200 patients with coronary artery disease (at least 1 year after revascularization, or without a history of revascularization but with angiographically significant CAD) the addition of anti-platelet agents to oral anticoagulation was associated with a significantly increased risk of bleeding without a reduction in the risk of stroke nor adverse CAD outcomes.[60] Thus, in most patients with AF and chronic coronary disease (e.g., >1 year after revascularization with either percutaneous coronary stenting or coronary artery bypass graft surgery), oral anticoagulation as monotherapy without additional anti-platelet agents is recommended.[14] Note that dual anti-coagulation and anti-platelet therapy is still necessary in the early post-revascularization period to prevent early stent thrombosis (3-12 months after PCI, with duration dependent on severity of clinical presentation and stent location/characteristics), as well as in patients following a myocardial infarction.[61] Treatment decisions on anti-platelet therapy in patients with CAD and AF should be made in an interdisciplinary fashion including the interventional cardiologist - as specific factors (e.g., stent complexity or size) may alter the risk of stent thrombosis.

Long-term anticoagulation, however, is contraindicated in a select group of patients; for such patients, treatment with a left atrial appendage occlusion device may be a reasonable alternative (see separate section below). Patients for whom long-term anticoagulation is contraindicated include those with severe bleeding due to a nonreversible cause, those with spontaneous intracranial/intraspinal bleeding due to a nonreversible cause (such as primary intracranial tumor or cerebral amyloid angiopathy), and those with serious bleeding related to recurrent falls when the cause of falls is not felt to be treatable.

BOTTOM LINE: Use the CHA_2DS_2-VA score to predict stroke risk and guide decisions about anticoagulation. Do not use bleeding risk scores to assess a patient's candidacy for anticoagulation. Address modifiable risks for bleeding whenever possible, particularly for patients at high bleeding risk. Patients with chronic coronary disease and AF can often be managed with anticoagulation alone (without antiplatelet agents).

Stroke prevention options

As new evidence has emerged, a consensus has formed that anticoagulants are more effective and safer than antiplatelet agents in reducing stroke risk in patients with AF and are preferred in most patients. Aspirin and clopidogrel (Plavix) are no longer recommended as alternatives to anticoagulation in patients with AF. Multiple trials comparing anticoagulation to antiplatelet therapy have been stopped early due to superior outcomes with anticoagulation.[62-64]

Although aspirin has been conclusively demonstrated to reduce morbidity and mortality when used for secondary prevention in patients with established atherosclerotic cardiovascular disease (ASCVD),[65] aspirin is no longer recommended for primary prevention of ASCVD, and it is also not recommended for stroke prevention in patients with AF. In a trial that randomized 5,599 patients with AF to either aspirin or the anticoagulant apixaban, those in the aspirin group had similar rates of bleeding but a significantly higher rate of stroke.[62] Even when compared to placebo, aspirin does not prevent stroke and there is a trend toward a higher risk of bleeding in patients with AF.[63,66]

Although no randomized trials have compared clopidogrel alone to placebo in patients with AF, the **ACTIVE A** study evaluated the combination of clopidogrel and aspirin vs. aspirin alone in 7554 AF patients who were not candidates for warfarin, or who did not want to take warfarin, and had at least 1 risk factor for stroke. After 3.6 years follow-up, those in the aspirin + clopidogrel group had significantly fewer strokes and fewer vascular events (stroke, MI, non-CNS emboli, or death), but more episodes of major bleeding (primarily GI).[67] The lack of a safety advantage and the increased bleeding risk with the aspirin and clopidogrel combination has led to recommendations favoring anticoagulants over antiplatelet agents.

Warfarin

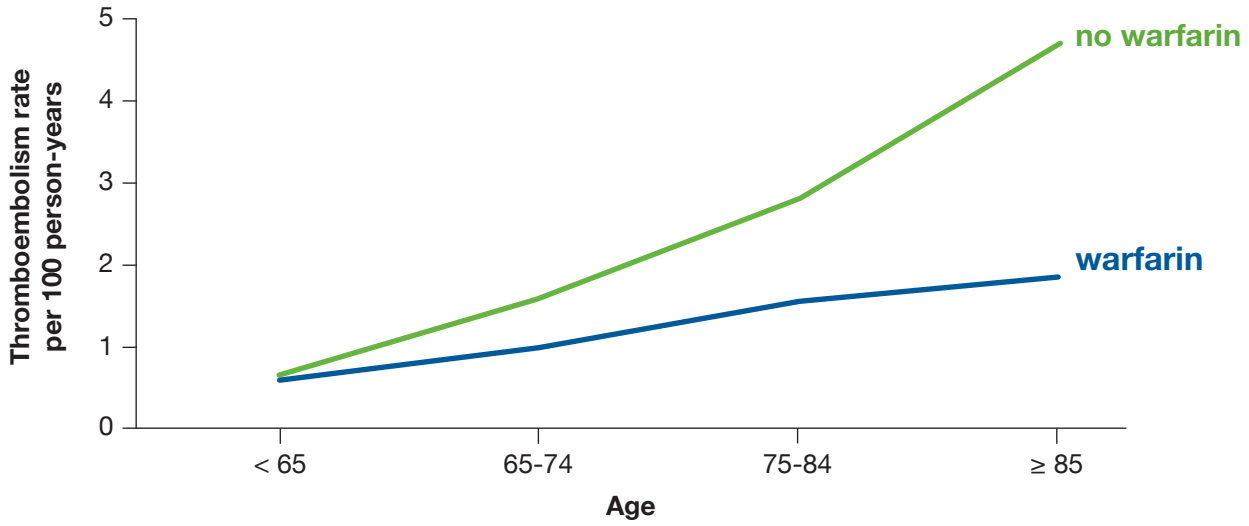
Warfarin has been the most widely prescribed oral anticoagulant in the U.S. since its FDA approval in the 1950's. It works by inhibiting the synthesis of vitamin K-dependent coagulation factors. It also (paradoxically) inhibits proteins C and S, creating a pro-thrombotic effect for the first few days after initiation. Full reduction in the vitamin K-dependent coagulation factors is not achieved until about 5 days after warfarin is started; therefore in patients with a thrombus, warfarin must be combined with heparin (unfractionated or low-molecular weight) for about the first 5 days ("bridging"). In patients without evidence of current thrombus, warfarin can be initiated alone, without bridging (which applies to most patients with AF).

Table 6: Recommended initial warfarin dose[68]

Recommended starting dose	Patient groups
<5 mg /day (min 2 mg)	Renal disease, liver disease, older age, heart failure, poor nutrition, debilitation
5 mg /day	Most patients
>5 mg /day (max 10 mg)	Those with none of the above risk factors and low bleeding risk

A meta-analysis of 29 trials including over 28,000 participants found that warfarin reduced stroke by 64% compared to placebo in patients with atrial fibrillation,[69] although warfarin also increases the risk of bleeding and intracranial hemorrhage.[70] A study of 13,559 patients with AF showed that the clinical benefits of warfarin increase with both patient age and stroke risk scores.[71]

Figure 4: Warfarin benefits increase with patient age[71]



Although warfarin is very effective in reducing stroke in patients with AF, careful monitoring is critical. It is estimated that patients in the U.S. spend only about 60% of time within the optimal therapeutic range, which is problematic because having a sub-therapeutic INR (i.e., <2.0) is associated with a 5-fold increase in stroke risk, while a supra-therapeutic INR (>3.0) is associated with a 3-fold increase in the risk of bleeding events.[72]

Warfarin can interact with many other drugs including those that increase or decrease warfarin metabolism, those that alter the production of vitamin K in the GI tract (e.g., antibiotics), and those that increase the risk of bleeding by other mechanisms (antiplatelets, NSAIDs, or other anticoagulants). Dietary intake of vitamin K can also affect warfarin levels. The recommended daily allowance of vitamin K is 90-120 micrograms per day. A consistent daily amount of vitamin K should be eaten by patients on warfarin to avoid INR variability; the diet can include high vitamin K foods (e.g., kale, collard greens, frozen spinach) as long as intake is consistent (variable intake is not recommended).

Table 7: Medications with potential interactions with warfarin

Effect on warfarin	Interacting medications
Increase effect	Antifungals (fluconazole, miconazole) Antibiotics (most commonly co-trimoxazole, metronidazole, macrolides, and fluoroquinolones) Selective Serotonin Reuptake Inhibitors Amiodarone Acetaminophen Herbal agents (ginkgo biloba, dong qual, fenugreek, chamomile)
Decrease effect	Rifampin St. John's Wort

Warfarin monitoring is required frequently during initiation of therapy (every 1-3 days), but can be reduced to every 2-4 weeks after a stable warfarin dose has been reached. The American College of Chest Physicians recommends an INR goal for atrial fibrillation of 2.5, with a range of 2.0-3.0.[73] Home INR monitoring is at least as good as laboratory-based INR monitoring.[74]

Although warfarin is not considered first-line therapy for most patients, it remains standard of care for a select group of patients (see below).[15] Additionally, for patients on long-term warfarin therapy with acceptable time in the therapeutic range (i.e., >70%) and no bleeding complications it may be appropriate to continue warfarin therapy.[75]

- moderate to severe rheumatic mitral valve stenosis
- mechanical heart valves
- severe liver dysfunction (Child-Pugh Class B and C)
- very elevated body mass index (≥40 kg/m^2)
- breastfeeding

Direct oral anticoagulants (DOACs)

DOACs were developed as an alternative to warfarin and are now first-line therapy for the majority of patients. Four pivotal clinical trials comparing individual DOACs with warfarin showed superiority or non-inferiority to warfarin for prevention of stroke or systemic embolism in patients with AF.[76-79] There are two classes of DOACs: direct thrombin inhibitors, such as dabigatran, and factor Xa inhibitors, such as rivaroxaban, apixaban and edoxaban. Novel therapies directed at factor XI and XIa are in development with two candidate agents currently in phase 2 trials (NCT04218266; NCT04755283), however efficacy and safety remain uncertain. Appropriate drug selection depends on approved indications, patient characteristics, comorbidities, concomitant medications, clinician and patient preference, and cost.[74] Patients taking DOACs do not need INR monitoring. Although this provides increased convenience to many patients, it also means that inexpensive and widely-available coagulation assays cannot be used to identify appropriate levels of anticoagulation and patient adherence.

The management of bleeding events in patients taking a DOAC can be challenging as well, although the advent of reversal agents for dabigatran and factor Xa inhibitors has ameliorated this concern significantly. Patients with minor bleeding may require cessation of a DOAC for a few doses.[74] Patients with GI bleeding may benefit by switching to a DOAC with a better bleeding profile (e.g., apixaban).[74]

Dabigatran

Dabigatran (Pradaxa, generics) is a direct thrombin inhibitor that was evaluated in a randomized trial of >18,000 patients with AF. The Randomized Evaluation of Long-term Anticoagulation Therapy (**RE-LY**) trial enrolled patients who had at least 1 risk factor for stroke (mean $CHADS_2$ score of 2). Participants were given either dabigatran (110 mg or 150 mg twice daily) or warfarin for a median of 2 years.[80] The primary outcome (stroke or systemic embolism) occurred significantly less often in the dabigatran 150 mg group than the warfarin group (Table 8).[80] While dabigatran 110 mg was non-inferior to warfarin, dabigatran 150 mg was superior to warfarin for reducing risk of stroke (RR 0.66; 95% CI: 0.53-0.82). (Note that a dose of 110 mg is approved in Europe but is not available in the U.S.[81])

The stroke prevention benefit of dabigatran occurred independently of the adequacy of INR control in the patients randomized to warfarin, meaning that even if the INR is controlled within the therapeutic range, dabigatran still reduced stroke more effectively than warfarin. The risk of major or clinically relevant

bleeding was slightly lower with dabigatran, but the difference was not statistically significant. The risk of bleeding with dabigatran increased with age.

Table 8: Results of the RE-LY study[80]

	Dabigatran 150mg	Warfarin	Hazard Ratio	P value
Stroke or systemic embolism	1.1%	1.7%	0.66	<0.001
Major or clinically relevant bleed	3.1%	3.4%	0.93	0.31

The anticoagulant property of dabigatran becomes effective within 2 hours. In the U.S., the drug is available in 75 mg and 150 mg tablets, with a recommended dosing of 150 mg orally twice daily. A dose of 75 mg twice daily is approved for patients with creatinine clearance 15-30 mL/min; however, this dose has not been tested in clinical trials. Dabigatran is contraindicated in patients with creatinine clearance <15 mL/min.[82] Dabigatran should not be prescribed with the antibiotic rifampin. The dose of dabigatran should be reduced with dronederone, ketoconazole, and some over-the-counter herbal preparations.[82]

Although dabigatran was associated with a 38% higher risk of MI in RE-LY and a meta-analysis of seven trials also found an increased risk of MI with dabigatran (compared to warfarin), a more recent study of 134,414 patients with AF found no increased risk of MI with dabigatran.[83] There currently is no FDA warning specific to MI for dabigatran.

Idarucizumab is an FDA-approved reversal agent for dabigatran for use in life-threatening bleeding or urgent/emergent surgery.

Rivaroxaban

Rivaroxaban (Xarelto) is a factor Xa inhibitor that has been shown to be non-inferior to warfarin for stroke reduction and to have similar rates of major bleeding as warfarin. Results from the Rivaroxban Once daily oral direct factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation (**ROCKET AF**) study are summarized in Table 9. Note that this trial enrolled patients with a higher risk of stroke than the trials of other DOACs.

Table 9: Rivaroxaban and warfarin[77]

	Rivaroxaban	Warfarin	Hazard Ratio	P value
Stroke or systemic embolism	2.1%	2.4%	0.88	<0.001
Major or clinically relevant bleed	14.9%	14.5%	1.03	0.44

As with dabigatran, the anticoagulant effect of rivaroxaban occurs within 2-4 hours. It has minimal drug or dietary interactions, although it should be avoided with CYP3A4 inhibitors and herbal agents, including rifampin and ritonavir. The recommended dosing is 20 mg daily, or 15 mg daily in the setting of moderate or severe renal dysfunction. The dose should be taken with food, usually with the evening meal since that is often the largest meal of the day. Andexanet alfa is approved for reversal of anticoagulation with rivaroxaban.

There was a significantly higher rate of thromboembolic events in the rivaroxaban arm after the study period, relative to the warfarin group. Subsequent examination of the ROCKET AF data suggests that the risk of thromboembolism upon drug discontinuation was due to these patients being insufficiently anticoagulated, as the INR was allowed to slowly become therapeutic while they were switched to warfarin.[84] Given this observation, there is a "black box" warning on the drug regarding thromboembolic risk at premature drug discontinuation (as well as a warning regarding spinal/epidural risk).

Apixaban

Apixaban (Eliquis) is another factor Xa inhibitor, with an anticoagulant effect occurring within 2-4 hours. Apixaban was superior to warfarin in the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (**ARISTOTLE**) study, a randomized, double-blind trial of 18,201 patients with AF.[78] Stroke and systemic embolism occurred at a rate of 1.25% events per year in the apixaban group and 1.60% per year in the warfarin group (HR 0.79; 95% CI: 0.66-0.95). Note that patients in this study were treated with 2.5 mg apixaban BID (instead of 5 mg BID) if they had 2 or more of the following risk factors: age ≥80 years; body weight ≤60 kg; or a serum creatinine level ≥1.5 mg per deciliter.[78]

Rates of major bleeding events between apixaban and warfarin were similar, but, unlike other DOACs, the rate of GI bleeding was not increased with apixaban relative to warfarin.[78] The reversal agent andexanet alfa is approved for reversal of anticoagulation with apixaban.

In observational studies, apixaban has been shown to be safe and effective in patients with severe kidney disease or on renal replacement therapy—in these patients stroke risk was similar to warfarin, but major bleeding was lower with apixaban.[85] Standard dose-adjustment guidelines (see above) should be followed in this population.

Table 10: Bleeding rates, apixaban v. warfarin[78]

Bleeding rates (% per year)	Apixaban	Warfarin	Hazard Ratio	P value
Major or clinically relevant bleeding	4.1%	6.0%	0.68	<0.001
GI bleeding	0.8%	0.9%	0.89	0.37
Intracranial hemorrhage	0.3%	0.8%	0.42	<0.001

Edoxaban

The Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48 (**ENGAGE AF-TIMI 48**) randomized trial evaluated the factor Xa inhibitor edoxaban (Savaysa) in 21,105 patients. Patients were randomized to 30-60 mg edoxaban daily vs. dose-adjusted warfarin. The study found dose-dependent results for the risk of stroke or systemic embolism (Table 11).[79]

Overall major bleeding rates for edoxaban are lower than warfarin, although the high-dose edoxaban (60 mg/d) had higher rates of GI bleeding than warfarin.[79] Importantly, edoxaban should not be used in patients with normal renal function (creatinine clearance of 95 mL/min or greater), as its efficacy in reducing thromboembolic events appears lower in these patients.

Table 11: Edoxaban vs. warfarin[79]

	Warfarin	High-dose edoxaban	Hazard Ratio (P value)	Low-dose edoxaban	Hazard Ratio (P value)
Stroke or systemic embolism	1.50%	1.18%	0.79 (<0.001)	1.61%	1.07 (0.005)
Major or clinically relevant bleeding	13%	11.1%	0.86 (<0.001)	8.0%	0.62 (<0.001)
GI bleeding	1.2%	1.5%	1.23 (0.03)	0.8%	0.67 (<0.001)
Intracranial bleeding	0.9%	0.4%	0.47 (<0.001)	0.3%	0.30 (<0.001)
Fatal bleeding	0.4%	0.2%	0.55 (<0.006)	0.1%	0.35 (0.001)

Comparing anticoagulants for older patients

Table 12 (next page) summarizes much of the information relevant to deciding which anticoagulant might be most appropriate for an older patient. Further information about efficacy, safety, and other considerations is provided in subsequent sections.

Table 12: Anticoagulant characteristics[86]

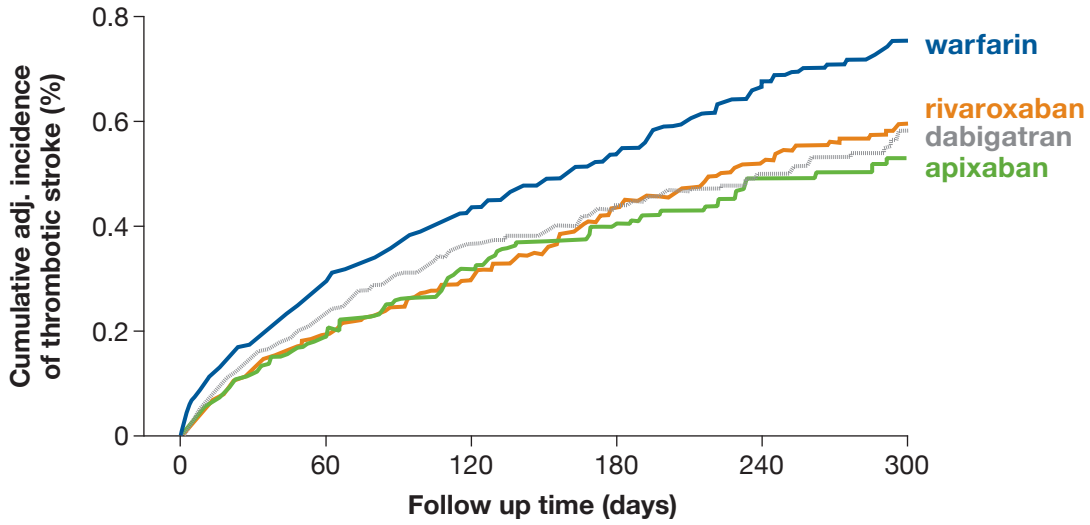
	dabigatran	rivaroxaban	apixaban	edoxaban	warfarin
Dosing frequency	twice daily	once daily	twice daily	once daily	once daily
Standard dose	150 mg	20 mg	5 mg	60 mg	based on INR
Dose adjustment	CrCl 15-30: 75 mg*	CrCl 15-49: 15 mg	**Two of:** age ≥ 80, weight ≤ 60 kg, or SCr ≥ 1.5: 2.5 mg	CrCl 15-49: 30 mg	based on INR
Renal contra-indications	CrCl < 15	CrCl < 15	none	CrCl < 15 or > 95	none
FDA-approved reversal agent	idarucizumab (Praxbind)	andexanet alfa (Andexxa)	andexanet alfa (Andexxa)	none	4-factor PCC
Other considerations	can cause dyspepsia—consider PPI	should be taken with the largest meal	safe to use in patients with severe kidney disease or on dialysis[3]	do not use in normal renal function	drug-diet interactions; requires INR monitoring
Use in older adults (≥ 65)**	!	!!	✓	✓	✓

CrCl = creatinine clearance, mL/min; PCC = prothrombin complex concentrate; SCr = serum creatinine, mg/dL. *Dosing reflects FDA labeling, but this dose was not studied in randomized trials. **Based on American Geriatric Society Beers Criteria.

Efficacy

A retrospective cohort study evaluated 183,318 older patients with AF enrolled in Medicare and treated with either warfarin or DOACs, which provides data from "real-world" patients (as opposed to those selected for clinical trials).[87] These data show that selected DOACs reduce the risk of thromboembolic stroke compared to warfarin, with nonsignificant differences between dabigatran, rivaroxaban, and apixaban (Figure 5). Likewise, in this study, DOACs showed lower bleeding risks compared to warfarin, with dabigatran posing the lowest risk for intracranial hemorrhage and apixaban posing the lowest risk for major extracranial bleeding.[87]

Figure 5: DOACs reduce the risk of stroke compared to warfarin[87]

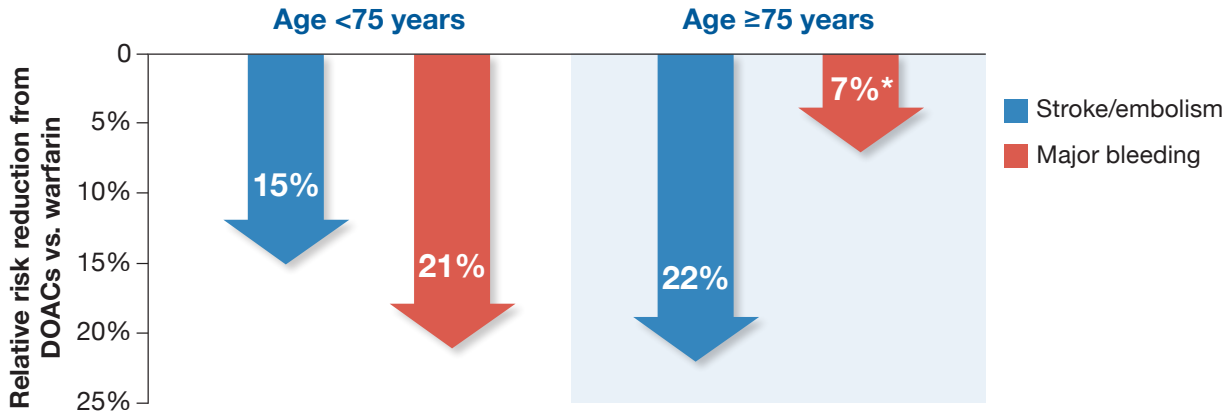


A multinational population-based cohort study in 527,226 patients newly diagnosed with AF who received a DOAC prescription found no significant differences in the rates of ischemic stroke, systemic embolism, intracranial hemorrhage, and all-cause mortality between apixaban, dabigatran, edoxaban, and rivaroxaban.[88] The results were consistent for patients aged 80 years or older.

Safety

In a study evaluating data across four major DOAC trials, in which 38% of enrolled patients were ≥ 75 years old, the risks of stroke or systemic embolism were lower with DOACs compared to warfarin and the risk of major bleeding was similar to warfarin (Figure 6 next page).[89] In the multinational study just cited above, apixaban was associated with lower risk for GI bleeding compared to dabigatran (HR 0.81; 95% CI: 0.70-0.94), edoxaban (HR 0.77; 95% CI: 0.66-0.91), or rivaroxaban (HR 0.72; 95% CI: 0.66-0.79).[88]

Figure 6: Relative risk reduction for stroke and bleeding risks across 4 major DOAC trials vs. warfarin[89]



*The reduced bleeding risk with DOACs compared to warfarin was significant in patients <75, but not in those ≥75. In some trials, older patients at higher risk received lower DOAC doses.

In a study assessing the risks of DOACs vs. warfarin in older adults with frailty, apixaban was associated with a 32% relative reduction in the hazard of a composite endpoint of death, ischemic stroke, or major bleeding compared to warfarin (HR 0.68; 95% CI: 0.65-0.72).[90] The DOACs dabigatran and rivaroxaban were not associated with a lower hazard compared to warfarin among frail older adults.

Co-occurring kidney disease

The doses of DOACs recommended for patients with severe chronic kidney disease (CKD) were approved based on pharmacology studies and were not tested in clinical trials, all of which excluded patients with creatinine clearance (CrCl) <30 mL/min. Patients with mild or moderate CKD can safely take DOACs, in some cases with dose reductions. Apixaban is recommended for patients with end-stage renal disease (ESRD) including those on renal replacement therapy,[91] as observational cohort data show it is safe and effective in this population.[85]

Drug interactions

Warfarin and individual DOACs interact with other medications in sometimes unique ways, which are summarized in Table 13 and should be considered when choosing an anticoagulant.

Table 13: Common and major drug interactions with anticoagulants[15]

Vitamin K antagonist oral anticoagulants	Direct oral anticoagulants			
	Apixaban	Dabigatran	Edoxaban	Rivaroxaban
Avoid where possible NSAIDs Fluconazole Voriconazole Fluoxetine	**Avoid where possible** Carbamazepine Phenytoin Phenobarbital Rifampicin Ritonavir Itraconazole Ketoconazole	**Avoid where possible** Dronedarone Carbamazepine Phenytoin Rifampicin Ritonavir Itraconazole Ketoconazole Cyclosporin Glecaprevir/pibrentasvir Tacrolimus	**Avoid where possible** Carbamazepine Phenytoin Phenobarbital Rifampicin Ritonavir	**Avoid where possible** Dronedarone Carbamazepine Phenytoin Phenobarbital Itraconazole Ketoconazole Posaconazole Voriconazole Rifampicin Ritonavir
Reduce warfarin dose Amiodarone Metronidazole Sulphonamides Allopurinol Fluvastatin Gemfibrozil Fluorouracil	**Avoid or reduce apixaban dose if another interacting drug therapy** Posaconazole Voriconazole Protease inhibitors Apalutamide Enzalutamide Tyrosine kinase inhibitors	**Delay timing of drugs and/or adjust dose** Amiodarone Ticagrelor Verapamil Quinidine Clarithromycin Posaconazole	**Avoid or reduce edoxaban dose** Dronedarone **Avoid or reduce edoxaban dose if another interacting drug therapy** Cyclosporin Itraconazole Ketoconazole Erythromycin	**Avoid if another interacting drug therapy** Protease inhibitors Tyrosine kinase inhibitors **Caution if renal function impaired** Verapamil Cyclosporin Clarithromycin Erythromycin Fluconazole
Increase warfarin dose Carbamazepine				
Monitor INR carefully Dronedarone Statins Penicillin antibiotics Macrolide antibiotics Quinolone antibiotics Rifampicin Methotrexate Ritonavir Phenytoin Sodium valproate Tamoxifen Chemotherapies	**Limit consumption** Grapefruit juice St John's wort	**Limit consumption** Grapefruit juice St John's wort	**Limit consumption** Grapefruit juice St John's wort	**Limit consumption** Grapefruit juice St John's wort
Limit consumption Alcohol Grapefruit/cranberry juice St John's wort				

Note: the above list is not all inclusive. Please consult the package insert or your local prescribing resource for more information.

Recommendations for anticoagulation in older adults

Ultimately, the best anticoagulant is the one the patient will take, which means that obtaining patient buy-in with treatment (and carefully considering any hesitations they may have) is a critical component of the overall approach. That said, in light of the compelling advantages of DOACs over warfarin, DOACs are first-line choices for eligible patients with AF, with the exception of those with moderate-to-severe mitral stenosis or a mechanical heart valve.[91] Current evidence suggests that, in general, apixaban is the first-choice option in older adults based on its favorable risk/benefit balance.[88,92]

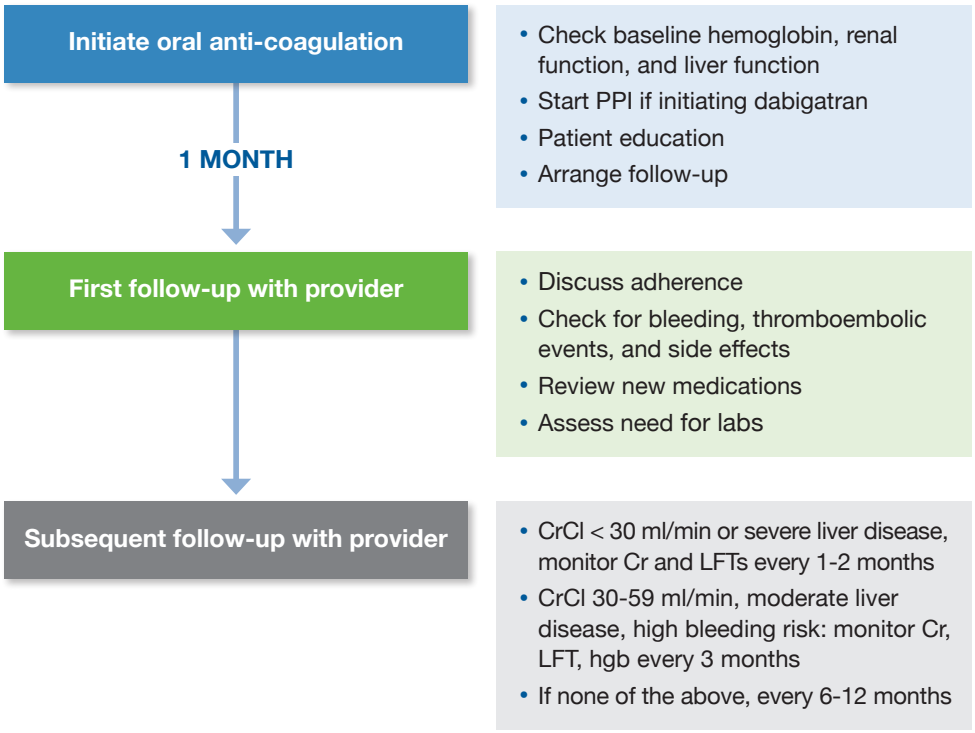
The 2023 American Geriatrics Society Beers Criteria recommend avoiding rivaroxaban in older adults and using caution with dabigatran based on observational and meta-analysis data showing higher rates of major and GI bleeding in older adults compared to apixaban, although guidelines acknowledge that rivaroxaban or edoxaban (assuming appropriate with renal function) may be preferable when a patient cannot adhere to twice daily dosing.[93]

The different DOACs, however, offer advantages and disadvantages that must be weighed in light of each patient's condition, medication regimen, preferences, dietary restrictions, and risk factors.

Before initiating any anticoagulation, we recommend obtaining a baseline laboratory assessment, including hemoglobin/hematocrit, PT/INR, hepatic function, and renal function. Periodic monitoring of renal function and dose adjustment are important in patients with impaired renal function. DOACs are contraindicated in patients with end-stage renal dysfunction (CrCl <15 mL/min) with the exception of apixaban as previously noted, and in those with severe hepatic dysfunction.

Monitoring and long-term use

Figure 7: Recommended schedule for assessment and testing following DOAC initiation[94]



Switching between anticoagulants

Transition carefully between anticoagulant agents, since discontinuing a DOAC prematurely may be associated with an increased risk of thromboembolism.[95] Monitor a patient's INR when transitioning from warfarin to a DOAC to avoid over-anticoagulation, and delay DOAC initiation until the patient's INR drops below 2.[74] If a patient is being switched from a DOAC to warfarin, bridging with a short-acting parenteral agent (e.g., enoxaparin) or a lower dose of the DOAC may be needed.[74] INR monitoring should be done at least twice weekly, and the warfarin dose should be adjusted until the INR reaches 2.0 to avoid excess bleeding or thrombotic events.[74]

Anticoagulation interruption

An anticoagulant may need to be temporarily stopped if a patient is expecting to undergo a procedure with a high risk of bleeding. Warfarin, for example, is usually halted five days before a procedure with an INR check before the surgery itself. Warfarin may be continued in patients expecting a procedure with a low risk of bleeding, although it is best to check with the surgeon/proceduralist. Use of short-acting anticoagulation (e.g., with heparin or enoxaparin) may be necessary during a period of warfarin interruption for patients at very high risk for thromboembolic events (e.g., patients with some mechanical heart valves, prior stroke, cardiac thrombus, or a recent venous thromboembolism).

In patients on DOAC therapy, the length of interruption depends upon the expected bleeding risk of the procedure although, again, it is best to check with the surgeon or institution prior to changing the regimen. Deciding when to resume DOAC therapy after a procedure depends on the risk of post-procedure bleeding, since maximal anticoagulation effects of DOACs are achieved within two hours of ingestion. For procedures with no increased bleeding risk, the dose may be resumed within 6-8 hours, whereas for procedures with increased bleeding risk the dose may be resumed after 48-72 hours.

Table 14: Plan for DOACs prior to a procedure based on bleeding risk[96]

Bleeding risk	Procedure (examples)	Anticoagulation plan
No important increased bleeding risk	Dental extractions, glaucoma surgery, endoscopy	Perform at trough level (12 or 24 hours after last dose)
Low bleeding risk	Biopsy or angiography	Hold DOAC for 24 hours prior, longer if impaired renal function
High bleeding risk	Abdominal surgery or spinal anesthesia	Hold DOAC for 48 hours prior, longer if impaired renal function

Medication Costs

DOACs are currently considerably more expensive than warfarin, although DOAC patents will be expiring in coming years, which may result in more affordable generic formulations. Cost can be an important consideration for some patients and must always be considered when choosing anticoagulant treatment. Some DOACs may have co-payment reduction benefits provided by the drug manufacturer, however these tend to only include patients with commercial insurance. See Appendix I for 30-day cash prices.

Left atrial appendage occlusion devices

The left atrial appendage (LAA) has been identified as a primary source of stroke-causing blood clots in patients with AF. LAA occlusion devices block thrombi that may form there from entering systemic

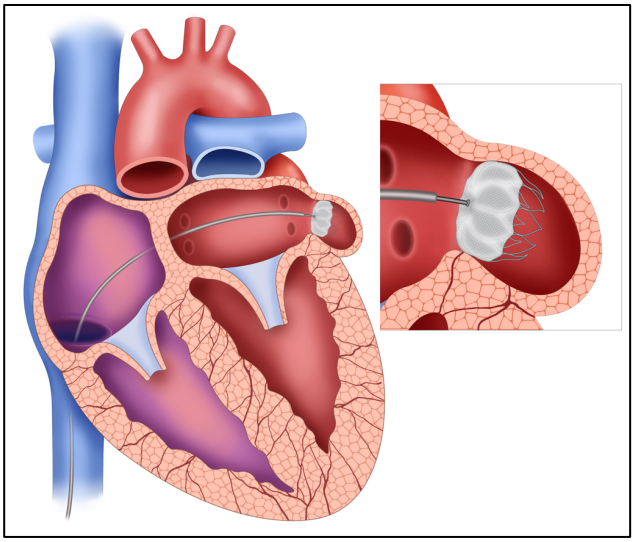
circulation. These devices may be an option for patients who cannot receive long-term anticoagulation, although anticoagulation is still recommended with these devices for up to 6 months post-placement.[97] The periprocedural risks of pericardial effusion, device related thrombosis, and device embolization must be carefully weighed in the decision. The 2023 ACC/AHA guidelines say that for patients with moderate-to-high stroke risk and contraindications to anticoagulants, percutaneous LAA occlusion is "reasonable" based on patient preference - with considerations of the procedural risks and with the understanding that the evidence base for anticoagulants is more extensive at this time.[14] The guidelines note the following situations where long-term anticoagulation is contraindicated and, thus, where LAA occlusion may be reasonable:

- severe bleeding due to a nonreversible cause involving the GI, pulmonary, or genitourinary systems
- spontaneous intracranial/intraspinal bleeding due to a nonreversible cause
- serious bleeding related to recurrent falls when cause of falls is not felt to be treatable

Three LAA occlusion devices are currently FDA-approved: the Watchman FLX (based on original design approved in 2015); Watchman FLX Pro (includes polymer coating and wider range of sizes); and the Amplatzer Amulet. The Lariat, which is still under investigation, uses an alternative approach of tying off the LAA from the rest of the atrium.

The original Watchman device was evaluated in the **PREVAIL**[98] and **PROTECT AF**[99] trials, which randomized a total of 1,114 patients to the Watchman device vs. warfarin. A meta-analysis of 5-year data from both trials found no statistically significant difference between groups in the composite outcome of stroke, systemic embolism or CV/unexplained death (2.8% in the device group vs. 3.4% in warfarin group, P=0.27).[100] The rate of ischemic stroke/systemic embolism was actually higher in the device group, although the difference was not statistically significant (1.6% vs. 0.95%; P=0.08). Rates of hemorrhagic stroke (0.17% vs. 0.87%), disabling stroke (0.44% vs. 1%), CV/unexplained death (1.3% vs. 2.2%), and major non-procedure-related bleeding (1.7% vs. 3.6%) were all significantly lower with the device.

Figure 8: Left atrial appendage closure



BOTTOM LINE: DOACs are recommended for first-line anticoagulation treatment for stroke prevention in newly diagnosed AF, in most patients without a contraindication. Apixaban has the most favorable efficacy and safety profile, particularly in older adults and those with chronic kidney disease or who are on dialysis. Reversal agents are now available for most DOACs (with the exception of edoxaban). Warfarin is the preferred treatment for patients with contraindications to DOACs (e.g., mechanical heart valves, moderate-severe rheumatic mitral stenosis, severe liver disease), or when DOACs are unaffordable for patients. Left atrial appendage closure devices have not been shown to be superior to anticoagulation for reducing ischemic stroke risk, however they are a reasonable option for patients with contraindications to anticoagulation.

Rate and rhythm control

Good heart rate control, whether achieved by rate or rhythm control, improves symptoms, reduces morbidity, and decreases the risk of developing heart failure.[4] The goal of a rate control strategy is to improve symptoms by keeping the heart rate within a physiologic range; it does not involve an attempt to convert the patient into sinus rhythm (SR). The goal of rhythm control is to convert AF into a stable SR and keep the patient in SR, although rate control and anticoagulation are still crucial even when rhythm control strategies are actively pursued

Decisions about rate and rhythm control strategies are patient-specific. Primary care providers (PCPs) can play a key role in treating AF with early initiation of anticoagulation, controlling rate, managing patient comorbidities, and selecting patients appropriately for early referral to cardiology for rhythm control. Although PCPs normally prescribe and monitor rate control medications, rhythm control methods are generally initiated by cardiologists. Early referral to cardiology (i.e., <1 year after diagnosis of AF) for rhythm control may lead to improved outcomes, as illustrated by a 2020 study showing a 21% relative risk reduction when rhythm control is initiated early.[101]

Table 15: Guidance for deciding whether to pursue rate control or refer for rhythm control[14]

		Favors rate control	Favors rhythm control
Patient factors	Patient choice	Prefers rate control	Prefers rhythm control
	Age	“Older”	“Younger”
	Antecedent history of AF	Longer history of AF	Shorter history of AF
	Symptom burden	Fewer symptoms	More symptoms
Physical examination / anatomy	Heart rate (HR) control in AF	Easily controlled HR	Difficult to control HR
	Left atrial (LA) size	Larger LA	Smaller LA
	Left ventricle (LV) function in AF	Less AV regurgitation	More AV regurgitation
	Aortic valve (AV) regurgitation in AF		

Rate Control

Rate control is an important component of management for all patients with AF.[18] Evidence suggests that the appropriate goal for asymptomatic patients and those with preserved LV systolic function is a resting heart rate ≤110 beats per minute (bpm), while a more aggressive goal of ≤80 bpm is recommended for symptomatic AF patients or those with systolic dysfunction, hypertrophic cardiomyopathy, or valve disease.[102]

The Rate Control Efficacy in Permanent Atrial Fibrillation (**RACE II**) trial randomized patients to a lenient (resting heart rate <110 bpm) or a strict (resting heart rate <80 bpm) rate control strategy. The study’s primary outcome, a composite of death from CV causes, hospitalization for heart failure, stroke, systemic embolism, bleeding, and life-threatening arrhythmias, favored the lenient-control strategy, although the 86

bpm mean achieved heart rate in the lenient group was close to the target rate in the strict control group (Table 16).[103]

Table 16: Results of the RACE II trial[104]

	Strict heart rate control	Lenient heart rate control
Goal heart rate (HR)	HR <80 bpm at rest and <110 bpm with exercise	HR <110 at rest
Achieved heart rate	75 bpm	86 bpm
Symptoms of AF	46%	46%
Combined primary endpoint*	15%	13%

* A composite of death from CV causes, hospitalization for heart failure, stroke, systemic embolism, bleeding, and life-threatening arrhythmias.

The absolute difference in the primary outcome between the lenient-control group and the strict-control group was -2.0% (90% CI: -7.6 to 3.5; p <0.001 for the prespecified non-inferiority margin). In addition, the lenient group was significantly more likely to achieve their target heart rate (98% vs. 67%) and were much more likely to be on either 0 or 1 drug (65% vs. 28%) compared to the strict control group. Thus, a heart rate goal of <110 bpm was considered to be non-inferior to a strict heart rate goal and requires fewer medications and fewer follow up visits.

Table 17 lists the most common drugs used for controlling heart rate, including those that can be used in patients with concomitant heart failure. These drugs act by reducing conduction velocity through the AV node, thus slowing ventricular rates.

Table 17: Medications for rate control in AF

Medication	Use in concomitant heart failure
Beta-blockers (e.g., atenolol, metoprolol, carvediolol, bisprolol)	Avoid in decompensated heart failure. Recommended in hemodynamically stable systolic heart failure. Beta-1 receptor blockers (e.g., atenolol, metoprolol) are preferred in COPD.
Non-dihydropyridine calcium channel blockers (diltiazem, verapamil)	Use with caution in decompensated heart failure, LV systolic dysfunction, pre-excitation syndrome (e.g., Wolff-Parkinson-White syndrome). NOTE: dihydropyridine CCBs (e.g., amlodipine) do *not* lower heart rate as they do not act on the AV node.
Digoxin	Not first-line therapy for rate control and not appropriate for single-agent therapy, but can be combined with beta-blockers and/or calcium channel blockers (CCBs). Reduces HR at rest but not with exercise. Recommended in decompensated heart failure. Monitoring of serum levels required. Use caution in renal dysfunction, the elderly, or with medications that reduce clearance (e.g., amiodarone, CCBs).

Commonly used doses and routes of administration of medications used for rate control in AF are provided in Table 18.

Table 18: Typical doses used for rate control.[1]

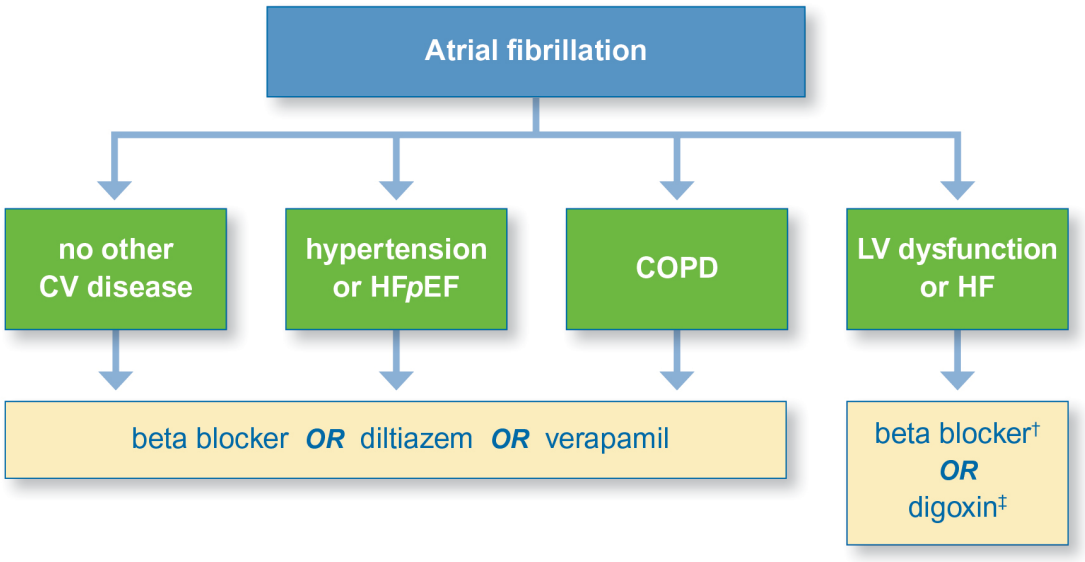
Beta-blockers	Range of oral dosing*
Metoprolol tartrate	25-100 mg BID
Metoprolol succinate	50-200 mg daily
Atenolol	25-100 mg daily
Propranolol	10-40 mg TID
Nadolol	10-240 mg daily
Carvedilol	3.125-25 mg BID
Bisoprolol	2.5-10 mg daily
Calcium channel antagonists	
Verapamil	40 mg TID to 360 mg (ER) daily
Diltiazem	60 mg TID to 360 mg (ER) daily
Other	
Digoxin	0.125-0.25 mg daily

* Starting doses may be lower for elderly patients.

A systematic review of randomized trials found that calcium channel blockers (verapamil and diltiazem), beta-blockers, digoxin, or a combination of these drugs are all more effective than placebo in slowing tachycardia associated with AF.[105] Digoxin was less effective at controlling heart rate during exercise than beta-blockers or diltiazem (mean difference 15 to 30 bpm higher with digoxin).[105] In the AFFIRM trial, beta-blockers were the most effective drugs for slowing heart rate, but combinations with other drugs were often needed to achieve adequate rate control.[106]

Figure 9 summarizes the recommended approach to using a rate control strategy in patients with AF.

Figure 9: Rate control in AF[4]



†Beta blockers should be instituted following stabilization of patients with decompensated HF. The choice of beta blocker (e.g., cardioselective) depends on the patient's clinical condition.
‡Digoxin is not usually first-line therapy. It may be combined with a beta blocker and/or a nondihydropyridine calcium channel blocker when ventricular rate control is insufficient and may be useful in patients with HF.

Atrioventricular (AV) node ablation with pacemaker

Rate control with medications may be ineffective or poorly tolerated in some patients. Sick sinus syndrome may lead to conversion pauses, for example, leading to lightheadedness, pre-syncope or syncope. Rate control medications may also lead to bradycardia or heart block when in sinus rhythm, and patients with advanced heart failure may not tolerate rate control.[18]

AV nodal catheter ablation with permanent ventricular pacing can be used for controlling ventricular rate in patients with symptomatic AF refractory to medical treatment. A meta-analysis found that this technique significantly improved quality of life, ventricular function, and exercise duration, and reduced healthcare use.[107] The main limitations are a small risk of sudden death during the first few months after ablation (which appears to be related to the abrupt change in heart rate and can be largely avoided by initially pacing the patient at a faster-than-normal rate and gradually reducing the set rate), the need for lifelong use of a pacemaker, and continued need for anticoagulant treatment.[19,107]

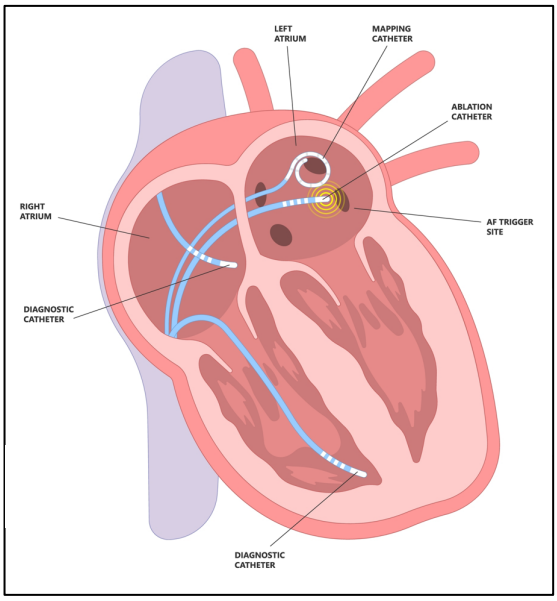
BOTTOM LINE: Rate control with a lenient goal of ≤110 bpm is a reasonable initial therapy for most patients with AF. Beta blockers or non-dihydropyridine calcium channel antagonists are first-line options, although digoxin can be considered in patients with LV dysfunction. AV node ablation is a procedural option to be considered in patients who are not candidates for rhythm control, and who have symptomatic AF refractory to medical attempts at rate control.

Rhythm control

While medications remain an option for rhythm control, procedural therapies (catheter ablation, also called pulmonary vein isolation) for AF have become safer and more effective to reduce the burden of disease.

Referral for rhythm control should not be delayed—and should occur, ideally, within one year of diagnosis. Rhythm control is usually managed by a cardiologist or electrophysiologist, with the role of the PCP limited to identifying appropriate patients for referral. This section summarizes aspects of rhythm control that may be helpful for PCPs to know in order to better co-manage patients selected for a rhythm control strategy.

Figure 10: AF catheter ablation



AF catheter ablation

Antiarrhythmic drugs (AADs) for AF are non-invasive but generally require long-term use,[36] and their effectiveness is inconsistent. The likelihood of AF recurrence within 6 to 12 months approaches 50% with most drugs, and they often cause cumulative adverse effects over time.[108] In contrast, minimally invasive procedures such as catheter ablation may prevent the

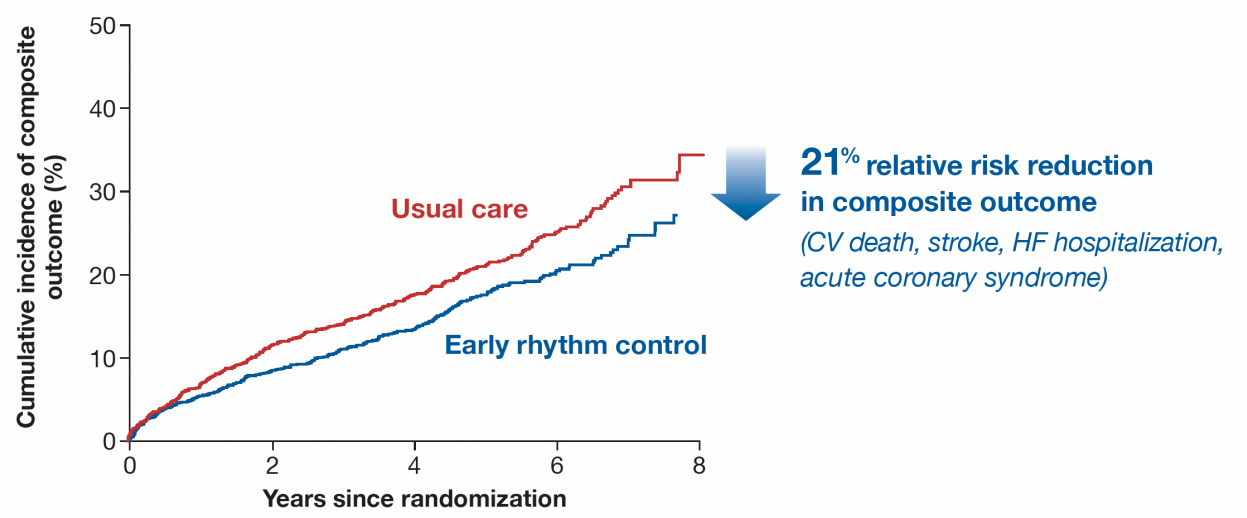
need for long-term use of these medications.[36] AF commonly originates from muscle fibers in the left atrium around the pulmonary veins, hence ablating these foci can reduce AF recurrence and AF burden.

Although early studies of rate and rhythm control led to recommendations favoring rate control, these studies have been criticized for low enrollment of patients with recent onset AF, use of older rhythm control drugs, and for being conducted prior to the development of effective catheter ablation techniques. The results from the 2020 **EAST-AFNET trial** have led to a reconsideration of the value of rhythm approaches, particularly for selected patient populations.[101] In that trial, 2789 patients with AF diagnosed within the past year and with risk factors for cardiovascular disease were randomized to either rhythm control (medications, ablation, or combination) or usual care (primarily rate control medications), with a median follow-up of 5.1 years. In this study, 'cardiovascular risk factors' included kidney disease, hypertension, diabetes, coronary artery disease, or heart failure. Most patients in the rhythm control arm (~87%) were treated with anti-arrhythmic medications. The primary composite outcome of death from cardiovascular causes, stroke, or hospitalization for heart failure or myocardial infarction occurred in 249 patients in the rhythm control group vs. 316 in the rate control group (HR 0.79; 95% CI: 0.66-0.94). Serious adverse events in the rhythm control group occurred in 4.9% of patients compared to 1.4% of patients in the rate control group (difference not statistically significant).

Age appears to modify the benefits of rhythm control, with younger patients benefiting more. A US-based observational study found no significant benefit to rhythm control in patients ≥75 years of age.[109] Similarly, a retrospective population cohort study in Korea with 31,220 patients with AF found clear benefits of a rhythm control strategy compared to rate control in patients under age 75, but no significant differences among patients aged 75 and older.[110] In addition, the effectiveness of rhythm control strategies appears to decrease as time from diagnosis increases,[111] suggesting that referral to cardiology for rhythm control should be done within a year of diagnosis.

In summary, for patients ≤ 75 years of age with risk factors for cardiovascular disease, early rhythm control is effective in reducing adverse cardiac events. These recent findings led to an update in the 2023 ACC/AHA guideline stating that "in patients with a recent diagnosis of AF (<1 year), rhythm control can be useful to reduce hospitalizations, stroke, and mortality."

Figure 11: Early rhythm control reduced composite cardiovascular outcomes in high-risk AF patients compared to usual care (primarily rate control only)[101]



AF catheter ablation

Most AF ablation strategies electrically isolate the pulmonary veins from the rest of the left atrium.[112,113] Several randomized trials and systematic reviews have shown that in both paroxysmal and persistent AF, catheter ablation (also called pulmonary vein isolation (PVI) or circumferential pulmonary vein ablation) is significantly better than antiarrhythmic medications at preventing recurrences of AF, and also better for improving symptoms, exercise capacity, and quality of life.[19,114,115]

A recent double-blind, sham-controlled trial of catheter ablation (n=64 with cryoablation, n=62 with sham procedure) in patients with paroxysmal AF found a mean AF burden reduction of 60% in the ablation group vs. 35% in the sham group at 6 month follow-up.[116] While most contemporary AF ablation procedures use radiofrequency ablation or cryoablation, non-thermal, electroporation ablation methods known as pulsed field ablation have recently been shown to be efficacious with a significantly lower risk of major procedural complications compared to traditional ablations.[117]

The **CABANA trial** randomized 2,204 patients (37% female) with symptomatic AF of any type to pulmonary vein isolation vs. drug therapy (either rate or rhythm control).[118] After a median follow-up of 48.5 months there was no significant difference in the rate of the composite primary outcome of death, disabling stroke, serious bleeding, or cardiac arrest (8% in the ablation group vs. 9.2% in the drug group, P=0.3). Adverse events rates with ablation were low and similar to those seen in the RAAFT-2 trial (e.g., 3.9% related to catheter insertion, 0.8% cardiac tamponade with perforation, 1.1% severe pericardial chest pain). Ablation was associated with lower rates of recurrent AF (50% vs. 69.5% at 3 years, P<0.001), lower rates of CV hospitalization (50% vs. 55%, no P-value reported), greater time to first AF recurrence (adjusted HR 0.52; 95% CI: 0.45-0.6), and better quality-of-life scores at 1 year.

The 2023 ACC/AHA guidelines state that catheter ablation is useful as first-line rhythm control therapy in selected patients (generally younger with few comorbidities) who have symptomatic paroxysmal AF and who desire rhythm control.[14] Catheter ablation is also recommended for patients in whom anti-arrhythmic drugs have been ineffective, contraindicated, not tolerated, or not preferred. The guidelines also recommend that oral anticoagulation be continued after catheter ablation for at least 3 months, with a longer duration determined by underlying stroke risk.

Patients with heart failure

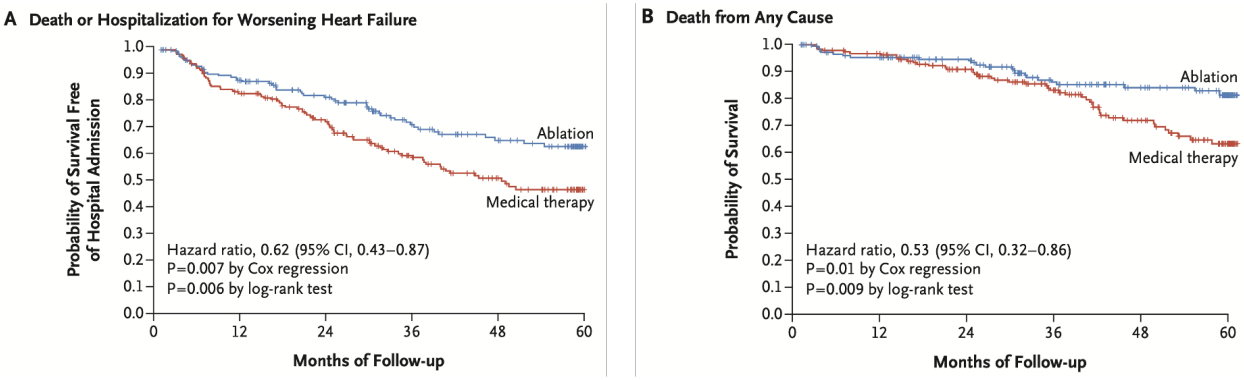
The 2008 **AF-CHF trial** of patients with AF and heart failure with an EF < 35% found no significant difference between rate and rhythm control for a range of clinical outcomes, including death from CV causes, death from any cause, stroke, worsening heart failure, and a composite of several of these outcomes.[119] Rhythm control was achieved using anti arrhythmic medications only. The role of procedures such as catheter ablation remained unclear.

This evidence gap was addressed in the 2018 Catheter Ablation vs. Standard Conventional Treatment in Patients With LV Dysfunction and AF (**CASTLE-AF**) trial, which enrolled patients with heart failure with reduced ejection fraction (HFrEF) who also had paroxysmal or persistent AF and who did not respond to, or could not take, antiarrhythmic drugs.[120] Patients were randomized to receive AF catheter ablation (n=179) vs. medical therapy (rate or rhythm control) (n=184) in addition to guideline-directed management and therapy for HFrEF. Patients in the AF catheter ablation group had significantly reduced overall mortality rate (HR 0.62; 95% CI: 0.43-0.87), reduced rates of hospitalization for worsening HF (HR 0.53; 95% CI: 0.32-0.86), and improved LV ejection fraction compared with the medical therapy group,

and according to device interrogation, more patients in the AF catheter ablation group were in sinus rhythm. (013)

These results extend to patients with advanced heart failure. In the subsequent CASTLE-HTX trial, catheter ablation was also found to benefit patients with end-stage heart failure (among patients who had been referred for cardiac transplant) compared to routine care.[121]

Figure 12: Rhythm control with ablation superior to rate control in patients with AF and heart failure[120]



Antiarrhythmic drugs

Maintaining sinus rhythm with the use of antiarrhythmic drugs is challenging, because many of these drugs have limited efficacy and pose safety risks, particularly in patients with kidney disease, bradycardia, coronary artery disease or congestive heart failure.[122] Overall, the benefit-to-risk ratio of antiarrhythmic drugs is low and they should generally be prescribed only by experienced specialists.[19] Nonetheless, for selected patients, achieving and maintaining sinus rhythm with medications may improve quality of life. The **SAFE-T trial** randomized 624 patients with persistent AF to amiodarone, sotalol, or placebo. Those not achieving sinus rhythm at day 28 were electrically cardioverted. After 1 year, patients who achieved sinus rhythm were significantly more likely to report improved QOL, reduced burden of AF symptoms, and improved exercise capacity.[123]

AF is likely to recur in patients on antiarrhythmic medications, however. The **Canadian Trial of Atrial Fibrillation study** comparing amiodarone to either sotalol or propafenone found that between 25% and 50% of patients on the antiarrhythmic medications experienced AF recurrence within a mean follow-up of 16 months.[124]

Limitations of a pharmacological rhythm control strategy include:

- high rate of AF recurrence
- increased risk of dangerous arrhythmias

Table 19 summarizes the classes of antiarrhythmic medications.

Table 19: Antiarrhythmic medications used for AF

Class	Mechanism	Medications
Class IA	Sodium channel blocker Lengthens action potential	quinidine procainamide (IV) disopyramide
Class IC	Sodium channel blocker No effect on action potential	flecainide propafenone
Class III	Potassium channel blocker Some agents have beta blocker action	amiodarone dronedarone dofetilide sotalol

Note: Class IA drugs are rarely used for atrial fibrillation, except in specific populations (e.g., disopyramide in patients with hypertrophic cardiomyopathy and AF)

A prospective trial in 403 patients found that amiodarone is more effective than propafenone or sotalol in converting and maintaining sinus rhythm,[124] however this drug is associated with many side effects (e.g., itching, hives, skin rash, nausea, vomiting, headache) and toxicities as well as posing potentially hazardous interactions with multiple medications, including warfarin.

Table 20: Recommended monitoring for patients taking amiodarone[14]

Adverse effect	Baseline testing	Initial follow-up testing	Additional follow-up testing
Hypo- or hyperthyroidism	TSH (T4 and T3, if TSH abnormal)	3 – 6 months	Every 6 months
Hepatotoxicity	AST, ALT	3 – 6 months	Every 6 months
QT interval prolongation	ECG	Annually	-
Interstitial lung disease	Chest x-ray: recommended CT chest: not recommended	Chest x-ray: unexplained cough or dyspnea or other signs/symptoms suspicious for interstitial lung disease	CT chest: as indicated to follow-up ongoing symptoms or chest x-ray findings
Corneal microdeposits (epithelial keratopathy)	Not recommended	Development of visual abnormalities, with may indicate optic neuropathy	-
Dermatologic (blue-gray skin discoloration), photosensitivity	Not recommended	Physical exam annually	Development of skin discoloration, severe sunburn
Neurological	Not recommended	Physical exam annually	Development of peripheral neuropathy or other neurological abnormalities

Table 21: Clinical considerations with other antiarrhythmics for AF[14]

Antiarrhythmic	Monitoring	Cautions or warnings	Notes
Dofetilide	Serial lab monitoring to detect CKD + ECG for QT (every 3-6 months) Initiated in inpatient settings for continuous monitoring and serial ECGs for QTc monitoring	Avoid in patients with CKD, prolonged QTc or use of other QTc-prolonging medications	Can be used in patients with CAD and HF
Dronedarone	Check baseline LFT + 1x check after 3-6 months.	Contraindicated in patients with decompensated HF; Discontinue in patients with permanent AF	
Flecainide Propafenone	May require CAD screening in high-risk patients.	Avoid in patients with CAD, HFrEF, bradycardia, atrial flutter, prolonged QTc or who are on other QTc-prolonging medications	Always give with a nodal agent May exacerbate underlying conduction disease
Sotalol	Serial lab monitoring to detect CKD + ECG for QT (every 3-6 months.) Initiated in inpatient settings for continuous monitoring and serial ECGs for QTc monitoring	Avoid in patients with HFrEF,[125] CKD, prolonged QTc or use of other QTc-prolonging medications	

CAD: coronary artery disease; CKD: chronic kidney disease; ECG: electrocardiogram; HRrEF: heart failure with reduced ejection fraction; LFT: liver function test

Cardioversion

Cardioversion may be performed electively, but it may be needed in patients with hemodynamic instability (angina, hypotension, acute heart failure, myocardial infarction, shock, or pulmonary edema). This strategy carries a risk of thromboembolism – a risk which is greatest when AF has been present for more than 48 hours.[18]

Cardioversion can be performed either with medication (pharmacological cardioversion) or by direct current shocks (electrical cardioversion). Electrical cardioversion generally requires a short-acting

anesthetic.[126] Restoration of sinus rhythm with electrical cardioversion is less likely in patients whose AF has been present for over a year, compared to those with AF of shorter duration, with initial success rates varying from about 50% to more than 80% depending on the population.[18] Even if cardioversion is initially successful, the recurrence of AF is high.[127] Most recurrences occur within the first month after cardioversion.[18] Repeat cardioversion may be required if the patient spontaneously reverts to AF.

Starting an antiarrhythmic drug and establishing adequate plasma drug concentrations before cardioversion increases the likelihood of success and reduces the rate of recurrent AF.[18] Given the potential for chemical cardioversion with these drugs, if transesophageal echocardiography (TEE) is indicated prior to cardioversion, it should be performed prior to drug initiation. Pre-medication is of most benefit in patients who either fail to respond to DC cardioversion or who relapse soon after.

Although electrical cardioversion followed by long-term maintenance therapy with an anti-arrhythmic medication is often used to achieve sinus rhythm, some cardiologists will consider a trial of cardioversion without anti-arrhythmic medications as a “trial of sinus rhythm” to identify patients who respond with improvements in their AF symptoms.

BOTTOM LINE: AF catheter ablation is a first-line rhythm control option for younger patients with paroxysmal AF or for those in whom anti-arrhythmic drugs are ineffective, contraindicated, not tolerated, or not preferred. Rhythm control with medications or ablation can improve outcomes in selected patients with recent onset of AF and in those with LV systolic dysfunction. Oral anticoagulation should be continued after catheter ablation for at least 3 months, with a longer duration determined by underlying stroke risk. Antiarrhythmic drugs to maintain sinus rhythm cause significant adverse effects and some are associated with increased mortality. Antiarrhythmic drugs are usually administered with the help of a cardiac specialist. Both electrical and pharmacological cardioversion can restore sinus rhythm, although the rate of recurrent AF is high.

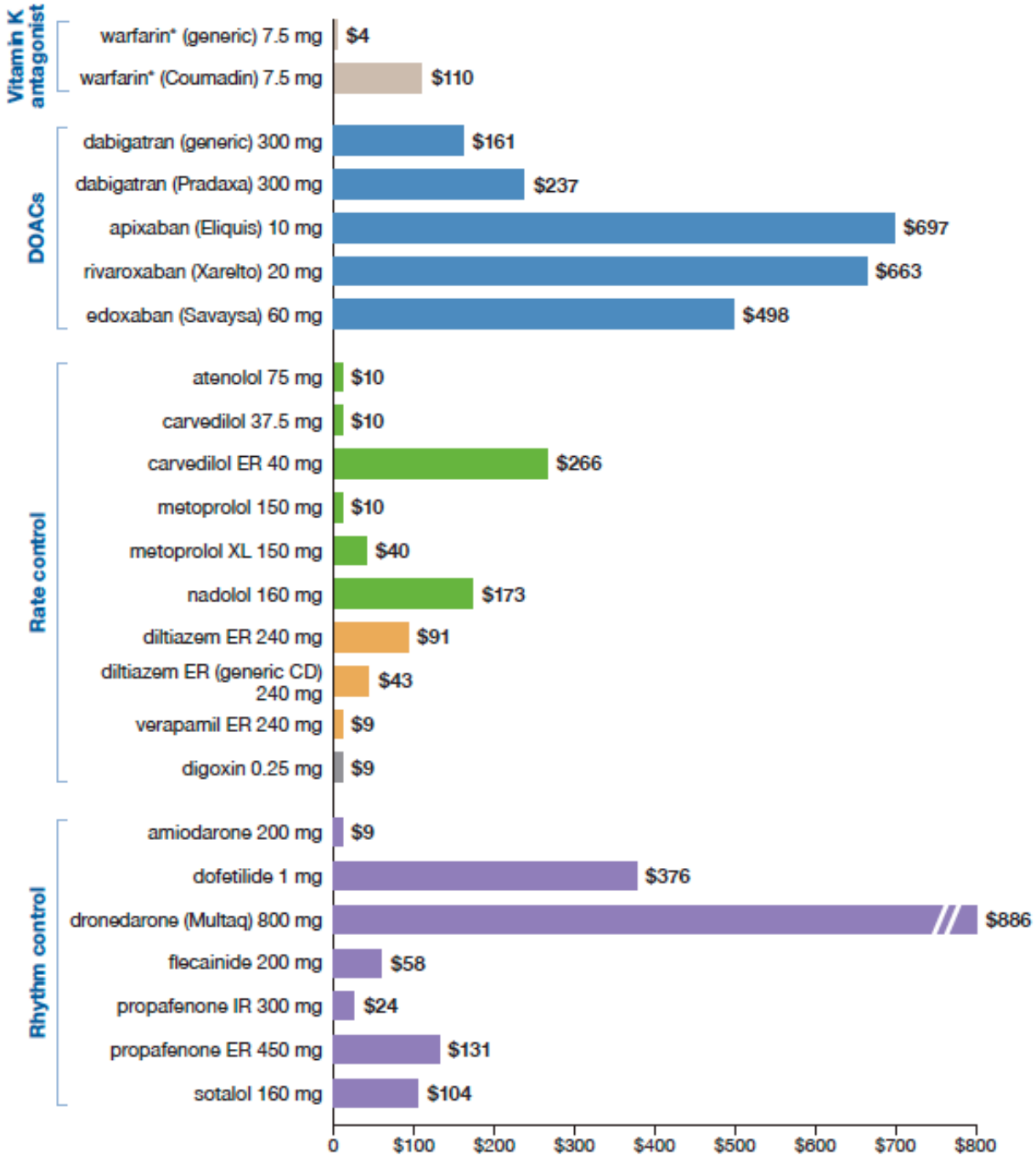
Putting it all together

Atrial fibrillation can be challenging to manage because of the range of possible etiologies, the variations in the type and pattern of the arrhythmia itself, the significant differences that comorbidities can make in treatment decisions, and the wide range of potential therapeutic options available. The evidence presented in this document can be distilled to these key points:

1. AF sharply increases the risk of stroke, but this risk is markedly reduced by anticoagulation.
2. Older patients with AF are at the greatest risk of stroke and benefit the most from anticoagulation.
3. Use the CHA_2DS_2-VA score to predict stroke risk and guide prescribing anticoagulation.
4. Address modifiable risks for bleeding.
5. Initiate a DOAC for most patients requiring anticoagulation, reserving warfarin for selected patients.
6. Patients taking warfarin can be switched to a DOAC unless there are contraindications or financial concerns that prevent the change.
7. Selected patients should be referred for rhythm control as soon as possible after AF diagnosis, with catheter ablation being increasingly used as a first-line strategy.
8. For patients where rate control is the preferred strategy, use medications to target a heart rate of <110 bpm. Patients with continued symptoms may require a target rate of <80 bpm.
9. Anticoagulation is critical regardless of whether rate or rhythm control is used.

Appendix I: Cost of medications

Figure 13: price of a 30-day supply of medications for anticoagulation, rate control, or rhythm control



*Price of warfarin does not include INR monitoring costs. ER / XL / CD = extended release; IR = immediate release

Prices from goodrx.com, September 2024. Listed doses are based on Defined Daily Doses by the World Health Organization, when available, or package inserts; they should not be used for dosing in all patients. All doses shown are generics when available, unless otherwise noted. These prices are a guide; patient costs will be subject to copays, rebates, and other incentives.

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These are general recommendations only; specific clinical decisions should be made by the treating clinician based on an individual patient's clinical condition.

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