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Alosa Health
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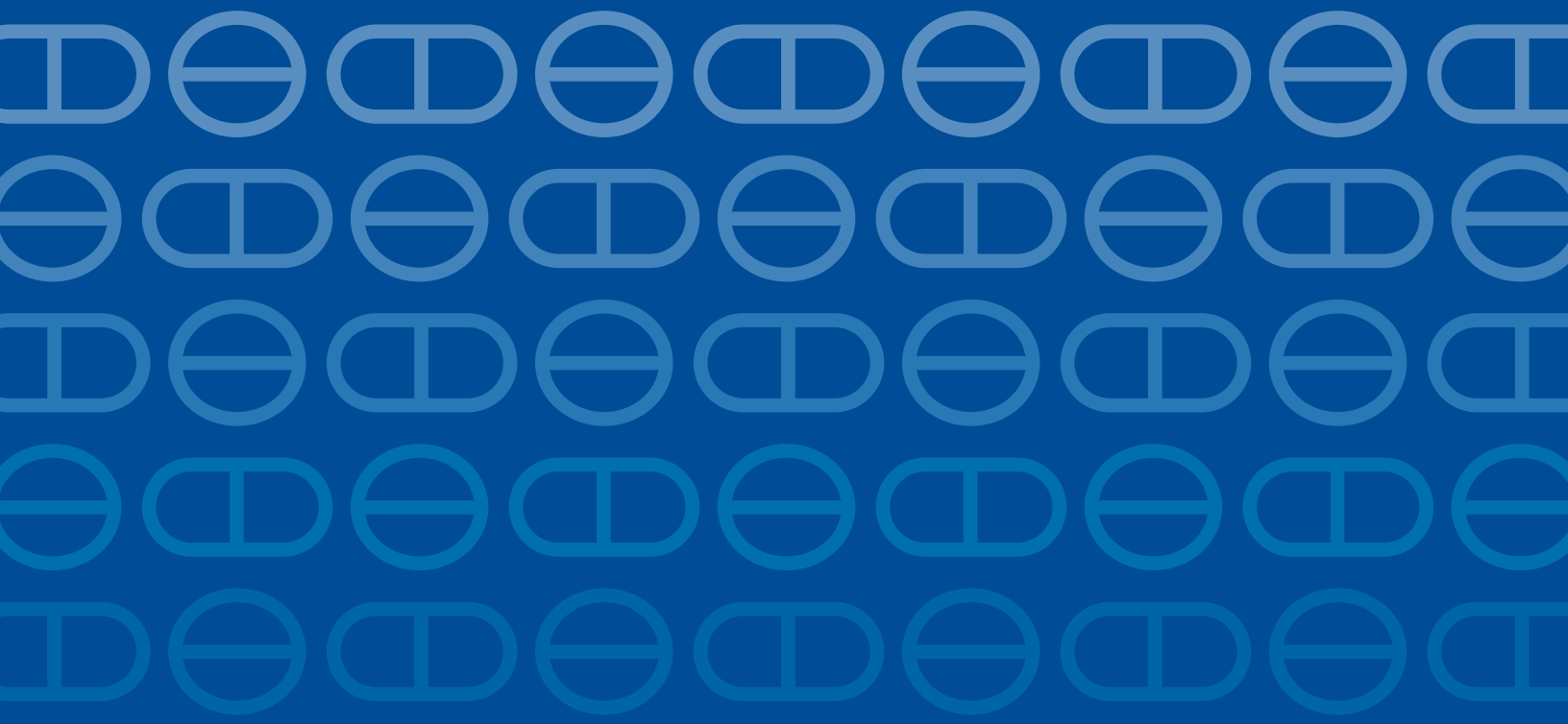
# Caring for patients with atrial fibrillation

## Current evidence on anticoagulants, rate control, and rhythm control



# Caring for patients with atrial fibrillation:

## Current evidence on anticoagulation, rate control, and rhythm control

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The Independent Drug Information Service (IDIS) is supported by the PACE Program of the Department of Aging of the Commonwealth of Pennsylvania.



**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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## Alosa Health

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### Accreditation:

This activity has been planned and implemented in accordance with the accreditation requirements and policies of the Accreditation Council for Continuing Medical Education through the joint providership of Harvard Medical School and Alosa Health. The Harvard Medical School is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

### Credit Designation:

The Harvard Medical School designates this enduring material for a maximum of 1.25 *AMA PRA Category 1 Credits™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

### Activity overview:

The primary 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 or rhythm control, assessing benefits of anticoagulation using a validated tool, assessing and mitigating bleeding risk factors, and selecting appropriate anticoagulation.

The educational program has several components, which include:

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

This program works to synthesize the 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.

### Target Audience:

The educational program is designed for primary care physicians practicing internal medicine, primary care, family practice, and geriatrics, and other health care professionals who deliver primary care.

### Learning Objectives:

Upon completion of this activity, participants will be able to:

- Use a validated score to assess the risk of stroke.
- Assess the clinical evidence regarding the use of direct oral anticoagulants (DOACs) and warfarin for anticoagulation.
- Choose the best option for anticoagulation based on patient characteristics.
- Identify the role of specialist procedures and implications for management by the primary care provider.
- Apply appropriate rate control as initial management of atrial fibrillation.

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Printed educational material.

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The activity will take approximately 1.25 hours to complete.

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Please email any questions to **cme@alosahealth.org** or call **(617) 948-5997.**

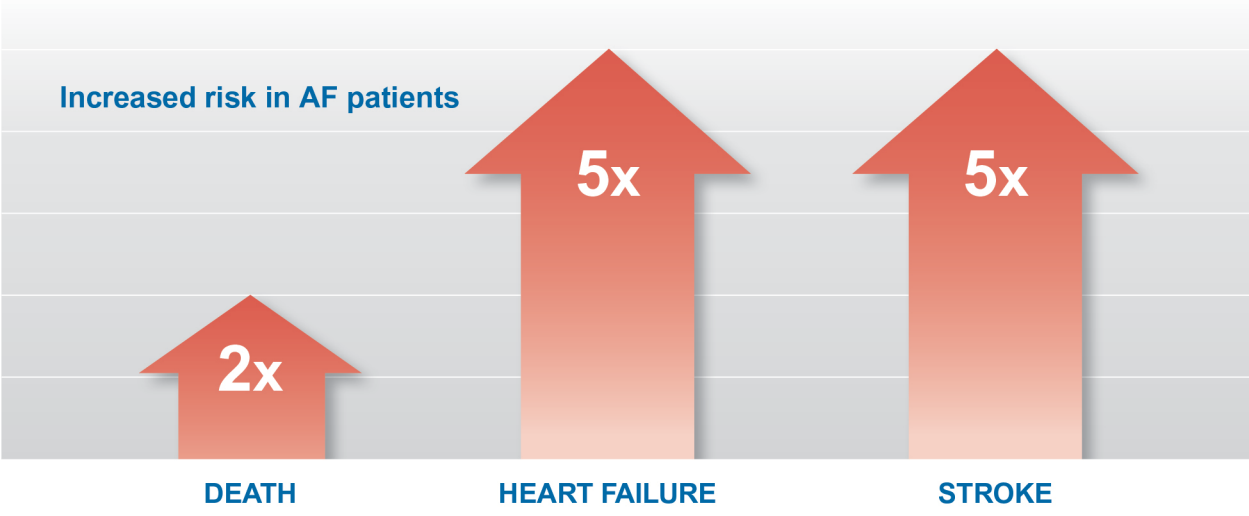
# Table of contents

# Introduction

Atrial fibrillation (AF) has been described as a cardiovascular 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 United States are caused by AF,[3] and AF contributes to nearly 100,000 deaths in the U.S. every year.[4]

AF affects approximately 5.3 million Americans, and its prevalence is expected to rise to 12.1 million in 2030.[2] This increased prevalence is due not only to increasing numbers of older adults, but also to an underlying increase in AF incidence that may be fueled by increased detection and/or increasing prevalence of pre-disposing factors such as obesity and diabetes.[5] AF accounts for approximately a third of hospitalizations for cardiac rhythm disturbances and costs the health system approximately $10,355 per patient per year,[1] with a direct cost burden in the U.S. approaching $6 billion annually and total costs (direct and indirect) of approximately $26 billion annually.[2,6]

**Figure 1: Patients with AF have increased morbidity and mortality compared to patients of the same age without AF[2]**




In 2019, a focused update to the 2014 American Heart Association (AHA), American College of Cardiology (ACC), and Heart Rhythm Society (HRS) AF clinical guidelines was published that included updated information about managing AF (both pharmacologically and with devices), new guidance on managing AF in patients with acute coronary syndromes, and new sections about device detection of AF and weight loss.[7] This document summarizes the new recommendations as well as the evidence on which these recommendations are based in order to better inform primary care physicians about current approaches to evaluating and managing patients with AF.

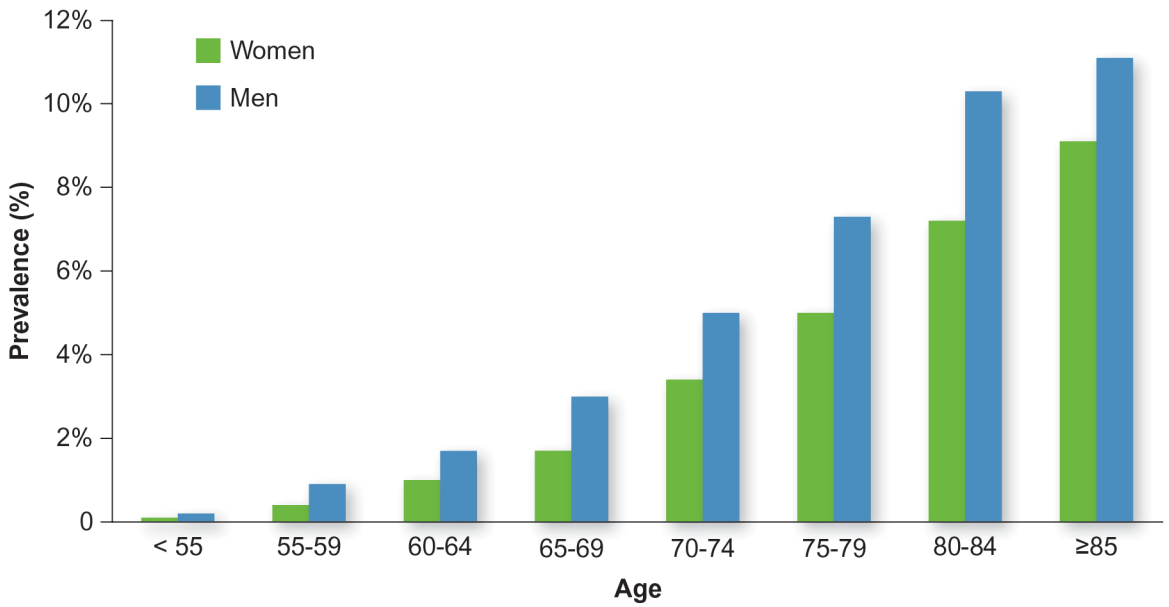
# Definition, epidemiology, pathophysiology

AF is an atrial tachyarrhythmia characterized by uncoordinated atrial activation, which leads to deterioration of atrial mechanical function.[8] 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 (Figure 2). Men are more likely than women to have AF at every age. For poorly-understood, despite higher rates of cardiovascular risk factors (e.g., hypertension), the lifetime risk of developing AF in blacks is about 1 in 5 compared to 1 in 3 among whites.[2]

Approximately 13% of the estimated 5.3 million cases of AF in the U.S. are undiagnosed, and patients with obesity have a 51% higher risk of developing AF compared with non-obese patients.[2]

**Figure 2: AF prevalence with age[9]**




Approximately 88% of AF occurs in patients with a history of cardiac or pulmonary disease.[10] 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.[11] Dilation of the atria with fibrosis and inflammation causes a difference in refractory periods within atrial tissue and promotes electrical re-entry, which can result in AF. The presence of rapidly firing foci, often in the pulmonary veins, may trigger AF.[12] AF may also result as degeneration of other rapid arrhythmias, such as atrial tachycardias and atrial flutter.[4]

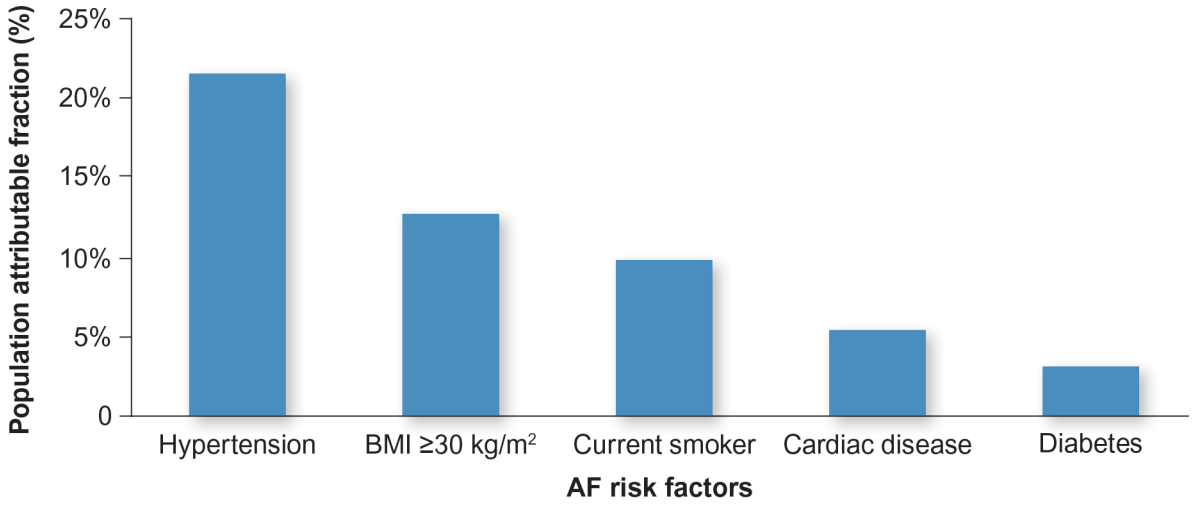
Many conditions are associated with AF, some of which may be temporary or reversible (Table 1).

**Table 1: Contributory causes of AF[4]**

| | |
|---|---|
| Lifestyle<br>• Excessive alcohol<br>• Smoking<br>• Obesity | Respiratory<br>• COPD exacerbations<br>• Pulmonary embolism<br>• Sleep apnea |
| Infection<br>• Pneumonia<br>• Urinary tract infection<br>• Sepsis | Endocrine<br>• Diabetes<br>• Hyperthyroidism |
| Cardiovascular conditions<br>• Hypertension<br>• Coronary artery disease<br>• Myocardial infarction<br>• Heart failure<br>• Cardiomyopathy<br>• Valvular heart disease<br>• Myocarditis<br>• Pericarditis<br>• Infiltrative disease (sarcoidosis) | Other<br>• Age<br>• Cardiothoracic surgery<br>• Genetics |

More than half of new diagnoses of AF can be explained by the presence of one or more common risk factors (Figure 3).

**Figure 3: Common atrial fibrillation risk factors[13]**




The disorganized atrial contractions typical of AF can cause blood to pool in the atria, increasing the risk of thrombus formation. 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.[14] 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.[15]

New-onset AF during an acute illness may increase the risk of longer-term AF. For example, among elderly 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 AF.[16] This suggests that patients with new-onset AF during hospitalization who have converted to sinus rhythm at discharge should be closely followed as outpatients to monitor for signs or symptoms of recurrent AF.

## Classification

AF can be classified in relation to valve disease or the duration of symptoms. Valvular AF, as recently clarified in the updated 2019 guidelines, occurs in the context of moderate-to-severe mitral stenosis (potentially requiring surgical intervention) or in the presence of an artificial (mechanical) heart valve, whereas non-valvular AF occurs in the absence of these conditions.[7]

"Lone" or "idiopathic" AF refers to AF occurring in the absence of cardiopulmonary disease or other disease states, especially in patients younger than 60. Current guidelines recommend against such terms because they lack a consistent definition.[4]

AF is also commonly classified 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]

**Table 2: Classification of AF by duration[8]**

| Classification | Definition |
|---|---|
| Paroxysmal | Spontaneous termination or termination with intervention in less than 7 days, usually within 48 hours |
| Persistent | Not self-terminating and lasting >7 days |
| Long-standing persistent | Continuous AF lasting more than 12 months |

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.[17] 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.[17]

## Related arrhythmias

AF may occur alone or in association with other arrhythmias, most commonly atrial flutter and atrial tachycardias.[8,10] 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 with conduction in a counterclockwise fashion. 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.[10] More than 80% of patients undergoing ablation for typical atrial flutter will develop AF within 5 years.[18] Atrial flutter is associated with a similar level of increased stroke risk as AF.[4] Anticoagulation is recommended according to the same risk stratification used for AF.[4]

Atrial tachycardias can also trigger AF. The ECG in atrial tachycardia shows a regular atrial tachycardia with P-wave morphology different from that in sinus tachycardia.[8,10]

**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 can be classified in relation to valvular disease or 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. For patients with severe heart failure, loss of "atrial kick" because of AF can lead to decreased ventricular filling and reduced cardiac output.

AF may also be a *consequence* of a deteriorating condition in patients with underlying heart disease. For example, patients presenting with acute coronary syndrome may have atrial ischemia, leading to AF, and the increased atrial pressures in the context of decompensated heart failure can increase the risk of AF.

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).

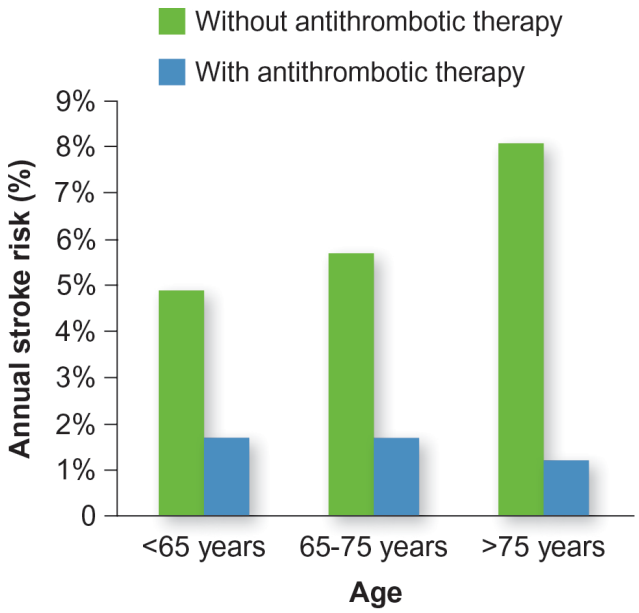
**Table 3: Common AF symptoms[19]**

| 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.

Ischemic stroke is a common consequence of AF with risk increasing with age among patients not receiving antithrombotic therapy and with >1 risk factor (Figure 4).[20] Antithrombotic therapy reduces stroke risk significantly.[20]

**Figure 4: Stroke risk with, and without, antithrombotic therapy[20]**




# Clinical evaluation

## History and physical exam

The medical history should focus on identifying the presence and nature of AF symptoms, characteristics of AF episodes, and associated conditions.[8,10,11] 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?

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.[10]

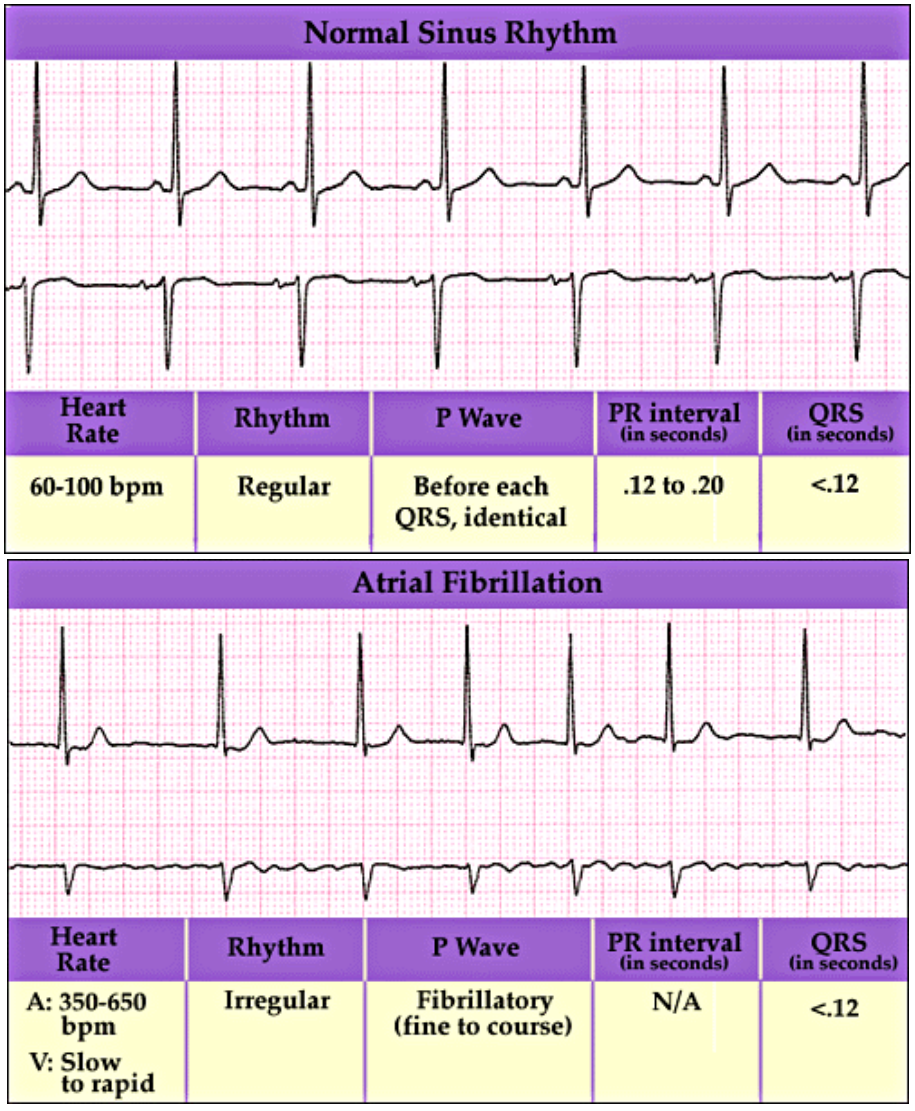
A physical exam should also identify conditions that may contribute to AF. Blood pressure should be carefully assessed. The cardiac exam may reveal murmurs suggestive of heart disease, or clinical signs of heart failure such as elevated jugular venous pressure, pulmonary edema, abdominal distension, or lower

extremity edema. A pulmonary and thyroid exam may reveal underlying lung disease or an enlarged or nodular thyroid, respectively.[11]

## 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), an event monitor (weeks to months) or mobile continuous outpatient telemetry (MCOT) (weeks to months).[11]

**Figure 5: ECGs with normal sinus rhythm and atrial arrhythmias**




ECG traces reproduced with permission from library.med.utah.edu/kw/ecg/ecg_outline/

## Get an echocardiogram

All patients with AF should have 2-dimensional, transthoracic Doppler echocardiography to assess left atrium and left ventricular size, left ventricular wall thickness and function, presence of valvular disease, and to exclude pericardial disease and hypertrophic cardiomyopathy.[10,11] Transesophageal echocardiography should not be routinely ordered, but is better able to evaluate for the presence of cardiac 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.[10,11] 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 rate or 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

A chest X-ray may be appropriate in patients with suspected lung disease. Exercise testing (i.e., stress ECG) should not be routinely ordered but may help in specific clinical situations:

- for diagnosis of exercise-induced AF
- to exclude ischemia prior to initiating certain antiarrhythmic medications
- to 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.[21]

Referral for an electrophysiology study should be considered in patients with pre-excitation (i.e., delta wave on ECG) or in patients with concomitant supraventricular tachycardia.

**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: prevention of thromboembolism, heart rate control, and/or returning patients to sinus rhythm.[10] A rate control strategy involves moderating the ventricular rate with no attempt to restore or maintain sinus rhythm. The rhythm control strategy attempts restoration and/or maintenance of sinus rhythm, and also requires attention to rate.[10] Prevention of thromboembolism should be considered separately from the decision regarding rate versus rhythm control; that is, a rhythm control strategy does not preclude the need for anticoagulation in a patient with significant risk of thromboembolism.

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, 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.[11]

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

- Assess for the risk of stroke and bleeding before initiating any type of antithrombotic therapy.
- Initiate heart rate control and thromboembolism prevention for patients who are hemodynamically stable and have few, or tolerable, symptoms. Focus subsequent long-term management on rate control and/or rhythm control.[11]
- Treat underlying risk factors (especially hypertension).[11]
- If AF persists and is symptomatic despite adequate rate control, refer to cardiology for consideration of rhythm control, including possible electrical cardioversion.

# Lifestyle changes

A number of potentially modifiable risk factors have been linked to the development of AF including obesity, hypertension, diabetes, obstructive sleep apnea, smoking, and alcohol consumption. Research on lifestyle changes to reduce these risk factors, individually or collectively, is relatively sparse, but emerging evidence, particularly for weight loss, suggests lifestyle modifications could play a significant role in AF management.[22]

## Weight loss

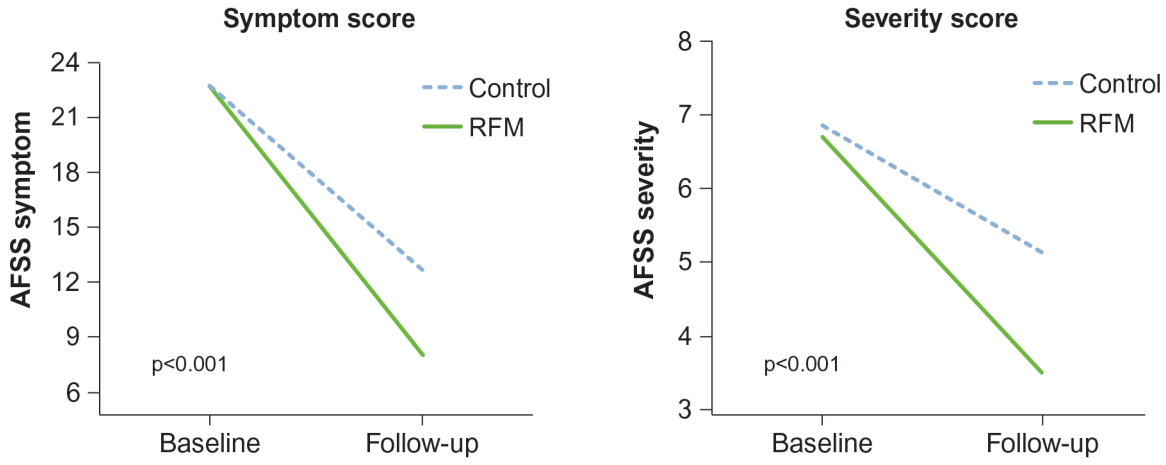
Obesity is associated with diastolic dysfunction, a systemic proinflammatory state, autonomic tone abnormalities, and atrial enlargement—changes known to promote arrhythmogenesis.[23] Fat stores have been shown to correlate with incident atrial fibrillation,[24] and obesity is associated with atrial

electrostructural remodeling and AF.[25] 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 2019 AHA/ACC Guidelines include a new section on weight loss with the recommendation that patients with obesity or overweight be urged to lose weight and reduce other risk factors as part of the effort to control AF.[7]

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.[23] 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. Between the intervention and control groups, mean AF symptom burden score reduction was 11.8 points vs. 2.6 points (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). Patients in the intervention group also showed significant mean reductions in interventricular septal thickness (1.1 mm vs. 0.6 mm) and left atrial area (3.5 $cm^2$ vs. 1.9 $cm^2$) compared to the control group.

**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.[26] 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 did not opt for 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).[26]

**Figure 6: AF Symptom and severity reductions with risk factor management program[26]**




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.[27] Weight loss was categorized into three groups: ≥10% loss; 3%-9% loss; and <3% loss. Greater weight loss was associated with both

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.

**BOTTOM LINE: Obesity is associated with several mechanisms causally related to AF. Weight loss with dietary restriction and exercise has been shown to reduce AF symptoms and burden.**

# Weigh the benefits and risks of anticoagulation

## Assess stroke risk

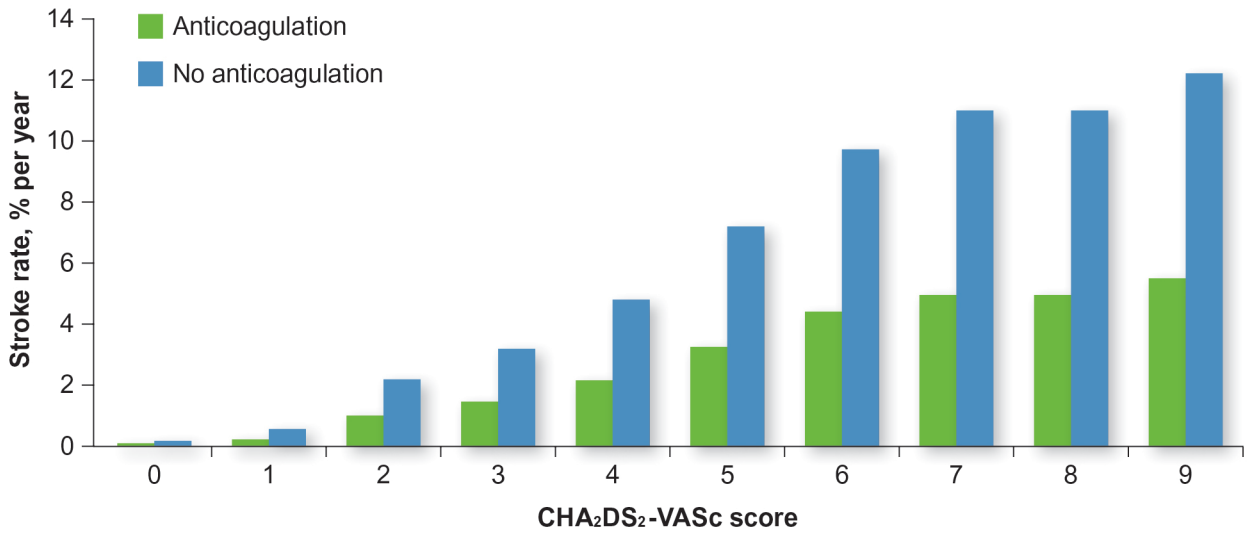
The $CHADS_2$ (Congestive Heart Failure, Hypertension, Age, Diabetes, Stroke [doubled]) risk scoring system, used previously both in clinical practice and in many trials, has been largely replaced by the $CHA_2DS_2$-VASc scoring system, which includes more risk factors, is based on more contemporary patient cohorts, and more accurately identifies patients who are truly low-risk and would not benefit from anticoagulation.[28]

**Table 5: $CHA_2DS_2$-VASc scoring system[28]**

| Letter | Parameter | Points (if yes) |
|---|---|---|
| C | Congestive heart failure* | 1 |
| H | Hypertension | 1 |
| A | Age ≥75 years | 2 |
| D | Diabetes | 1 |
| S | Stroke, TIA, thromboembolism | 2 |
| V | Vascular disease** | 1 |
| A | Age 65-74 years | 1 |
| S | Sex: female | 1 |
| | | Maximum 9 points |

* **Congestive heart failure:** left ventricle ejection fraction ≤ 40
** **Vascular disease:** myocardial infarction, peripheral vascular disease or aortic plaque

**Figure 7: Stroke risk and benefit of anticoagulation both rise with $CHA_2DS_2$-VASc score[29]**




Patients with a $CHA_2DS_2$-VASc score of 0 are at very low risk of stroke (i.e., 0 – 0.2%) and do not need anticoagulation.[28,29] Higher $CHA_2DS_2$-VASc scores need to be carefully interpreted (see management sections that follow) to determine optimal therapy.

## Evaluate bleeding risk

Bleeding risk is influenced by a host of factors, some of them modifiable, which should be carefully reviewed prior to any treatment with anticoagulants. Potential steps to reduce bleeding risk include reducing hypertension, if present, stopping or reducing alcohol use, changing other medications that increase bleeding risk, and using a direct oral anticoagulant (DOAC) instead of warfarin to prevent INR fluctuations (see section on DOACs below). One system for summarizing bleeding risk factors is the HAS-BLED score (Table 6). While the HAS-BLED score can provide a gestalt sense of overall bleeding risk, the score has relatively poor predictive accuracy, and is not felt to have clinical utility in guiding decisions around anticoagulation.[4] The score can nonetheless serve as a good reminder to address modifiable risk factors when possible, particularly in patients with higher bleeding risk.

**Table 6: HAS-BLED scoring system[30]**

| Letter | Parameter | Points (if yes) |
|---|---|---|
| H | Hypertension (>160 mmHg systolic) | 1 |
| A | Abnormal renal and/or liver function (1 point each)* | 1 or 2 |
| S | Stroke | 1 |
| B | Bleeding history | 1 |
| L | Labile INRs** (time in therapeutic range <60%) | 1 |
| E | Elderly (age ≥65 years) | 1 |
| D | Drugs or alcohol*** (1 points each) | 1 or 2 |
| | | Maximum 9 points |

* **Abnormal renal function:** CR >2.26 md/dL, dialysis, or renal transplant. **Abnormal liver function:** cirrhosis or total bilirubin >2x the upper limit of normal, with ALT/AST/AP >3x upper limit of normal
** This score was developed for patients on warfarin, however it can still be used for other anticoagulants.
*** **Drugs:** antiplatelet agents, nonsteroidal anti-inflammatories; **Alcohol:** ≥8 drinks per week

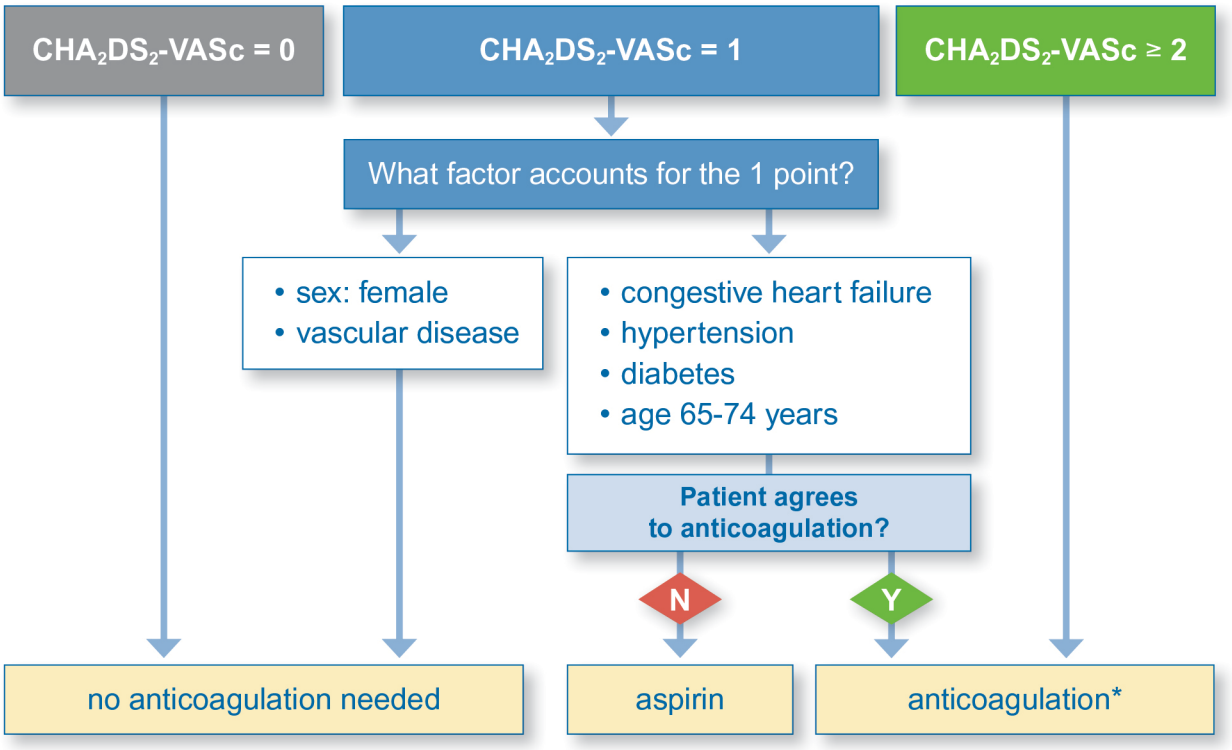
**BOTTOM LINE: Use the $CHA_2DS_2$-VASc score to predict stroke risk. Address modifiable risks for bleeding whenever possible, particularly for patients at high bleeding risk.**

# Stroke prevention options

Both antiplatelet agents and anticoagulants are used to prevent embolic complications in patients with nonvalvular AF. Anticoagulants are more effective than antiplatelet agents in reducing stroke risk and are preferred in most patients.

Anticoagulation is not recommended if a patient has a $CHA_2DS_2$-VASc score of 1 and their only risk factor is being female or having vascular disease (unless anticoagulation is indicated for another reason).[31,32,33]

**Figure 8: Anticoagulation recommendations for nonvalvular AF[4]**




*DOAC preferred over warfarin, unless unaffordable or contraindicated.

## Antiplatelet therapy

### Aspirin

Although aspirin has been conclusively demonstrated to reduce morbidity and mortality when used for general secondary prevention of vascular disease,[34] evidence for aspirin's efficacy in patients with AF is mixed.

In a meta-analysis of seven studies comparing aspirin to no therapy, aspirin reduced the risk of stroke by 19%, however this effect was not statistically significant.[35] Risk reduction was driven primarily by a single trial using a daily dose of 325 mg.[35] Although the trials in the meta-analysis were underpowered to precisely estimate the risk of nonfatal major extracranial bleeding, trials of aspirin for the primary and secondary prevention of cardiovascular disease have conclusively demonstrated that aspirin is associated with an increased risk of major hemorrhage.[36] An individual patient data meta-analysis combining data from six cardiovascular primary prevention trials (95,000 subjects) and a meta-analysis of 60 cardiovascular secondary prevention trials (94,000 subjects) found that aspirin is associated with a 50% to 60% relative increase, respectively, in the risk of major extracranial bleeding.

In addition, the risk of GI bleeding with aspirin can be significant. Low-dose aspirin (81 mg) increases the risk of GI bleeding about 2-fold, while high dose aspirin (≥300 mg) increases the risk 4-fold.[37] Other

adverse events include acute renal failure and heart failure, both of which are very uncommon when aspirin is used at low doses.

### Clopidogrel (Plavix)

Clopidogrel irreversibly blocks the activation of the IIb/IIIa receptor on platelets, reducing their ability to aggregate. It is taken as a 75 mg tablet daily and is not FDA-approved for stroke prevention in atrial fibrillation.

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).[38]

**Table 7: Results of the ACTIVE A study[38]**

| | Aspirin | Aspirin + clopidogrel |
|---|---|---|
| Strokes | 3.3% | 2.4% |
| Vascular events | 7.6% | 6.8% |
| Major bleeding | 1.3% | 2.0% |

P<0.01 for all comparisons

The clinical challenge of interpreting the results from the ACTIVE A trial is balancing the relative risks for stroke reduction and increased risk of bleeding.

As just noted, the combination of aspirin and clopidogrel posed a risk of major bleeding of about 2% per year, which is equivalent to the bleeding risk posed by warfarin therapy.[39] The lack of a safety advantage for bleeding risk with the aspirin and clopidogrel combination limits their role in AF to low- or moderate-risk patients who need to be on dual antiplatelet therapy for other reasons or to patients who have a strong preference to not be on an anticoagulant.

An uncommon, but serious, adverse effect of clopidogrel is thrombotic thrombocytopenic purpura (TTP), which usually occurs within the first few weeks of initiation, and is associated with high morbidity and mortality.

## Warfarin

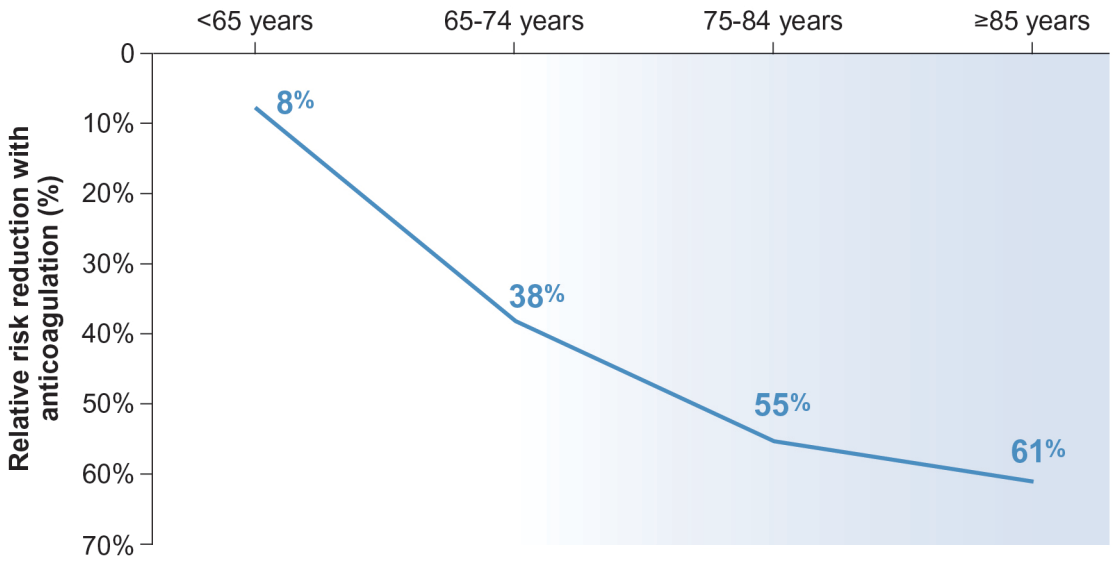
Warfarin has been the most widely-prescribed oral anticoagulant in the US since its FDA approval in the 1950's. It works by inhibiting the synthesis of vitamin K-dependent coagulation factors. It also (paradoxically) inhibits proteins C and S, creating a pro-thrombotic effect for the first few days after 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 8: Recommended initial warfarin dose[40]**

| 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,[35] although warfarin also increases the risk of bleeding and intracranial hemorrhage.[41] A study of 13,559 patients with AF showed that the clinical benefits of warfarin increase with both patient age and $CHADS_2$ scores.[42]

**Figure 9: Warfarin benefits increase with patient age[42]**




The "net clinical benefit" of warfarin was defined in this study as the annual rate of stroke/emboli prevented by warfarin minus the annual rate of intracranial hemorrhage caused by warfarin. It found no net clinical benefit of warfarin for those with $CHADS_2$ scores of 0-1, but an increasing benefit with higher $CHADS_2$ scores, up to 2.2 fewer events of stroke/emboli or intracranial hemorrhage per 100 patients treated for 1 year for those with $CHADS_2$ scores of 4-6. The greatest benefit was found in patients with a history of stroke and age >85.[42]

Although warfarin is very effective in reducing stroke in patients with AF, careful monitoring is critical. It is estimated that patients spend only about 60% of time within the optimal therapeutic range, which is problematic because having a sub-therapeutic International Normalized Ratio (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.[43]

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 9: Medications with potential interactions with warfarin**

| | |
|---|---|
| Increase warfarin effect | Antifungals (fluconazole, miconazole)<br>Antibiotics (most commonly co-trimoxazole, metronidazole, macrolides, and fluoroquinolines)<br>Selective Serotonin Reuptake Inhibitors<br>Amiodarone<br>Acetaminophen<br>Herbal agents (ginkgo biloba, dong qual, fenugreek, chamomile) |
| Decrease warfarin effect | Rifampin<br>St. Johns 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 ACCP recommends an INR goal for atrial fibrillation of 2.5, with a range of 2.0-3.0.[44] Home INR monitoring is at least as good as laboratory-based INR monitoring.[45]

## Direct Oral Anticoagulants (DOACs)

There are 2 classes of DOACs: direct thrombin inhibitors, such as dabigatran, and factor Xa inhibitors, such as rivaroxaban, apixaban and edoxaban. Appropriate drug selection depends on approved indications, patient characteristics, comorbidities, concomitant medications, clinician and patient preference, and cost.[45] Patients taking DOACs do not need INR monitoring. Although this provides increased convenience to many patients, it also means that 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.[45] Patients with GI bleeding may benefit by switching to a DOAC with a better bleeding profile (e.g., apixaban or edoxaban).[45]

### Dabigatran

Dabigatran (Pradaxa) 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.[46] The primary outcome (stroke or systemic embolism) occurred significantly less often in the dabigatran 150 mg group than the warfarin group (Table 10).[46] 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 United States.[47])

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 10: Results of the RE-LY study[46]**

| | 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.[48] 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.[48]

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.[49] 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 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 11. Note that this trial enrolled patients with a higher risk of stroke than the trials of other DOACs.

**Table 11: Rivaroxaban and warfarin[50]**

| | 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. The reversal agent andexanet alfa is approved for use 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.[51] 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 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.[52] 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.[52]

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.[52] The reversal agent andexanet alfa is approved for use with apixaban. In observational studies apixaban at 5 mg doses has been shown to be safe to use in patients with severe kidney disease or on dialysis—in these patients stroke risk was similar to warfarin, but major bleeding was lower with apixaban.[53]

**Table 12: Bleeding rates, apixaban v. warfarin[52]**

| 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 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 13).[54]

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.[54] 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.

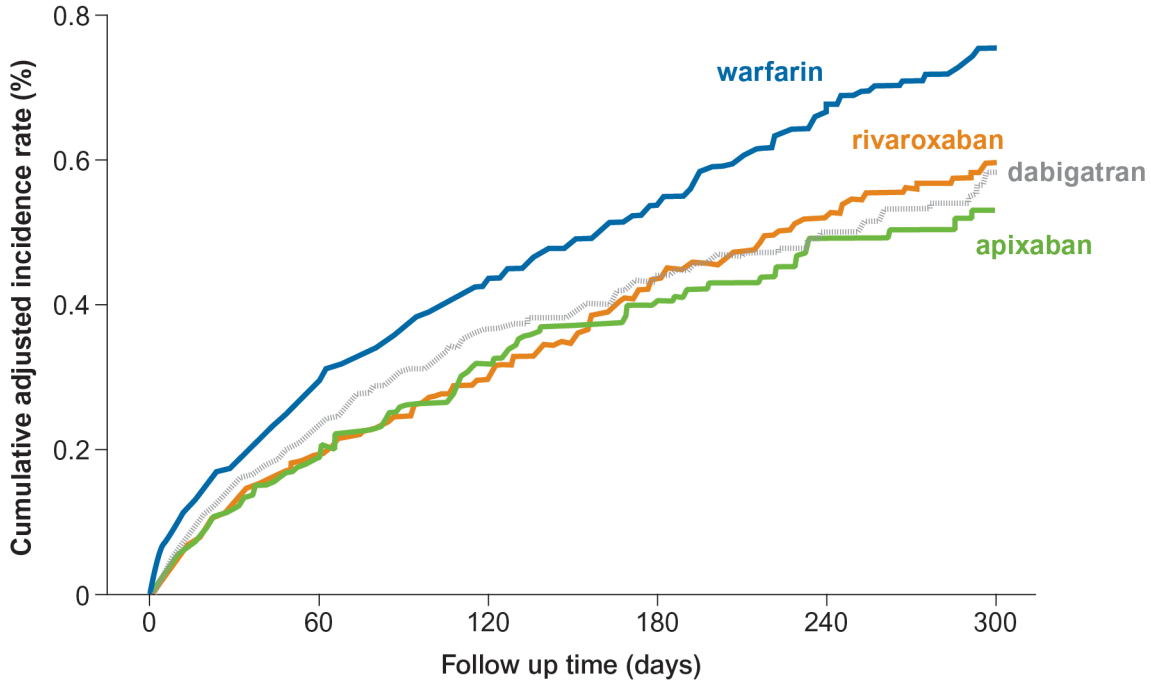
**Table 13: Edoxaban vs. warfarin[54]**

| | 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) |

## Anticoagulation in older patients

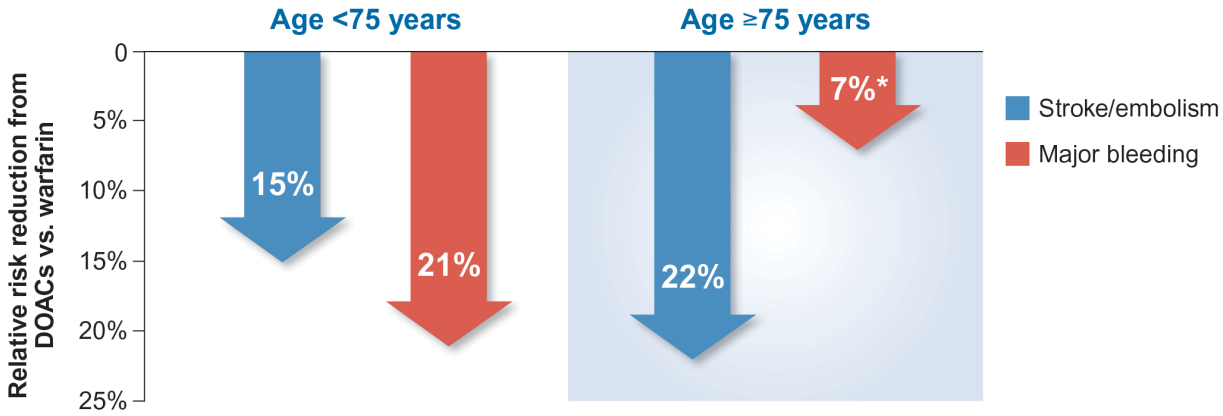
A recent retrospective cohort study evaluated 183,318 older patients with AF enrolled in Medicare and treated with either warfarin or DOACs, which provides data from "real-world" patients (as opposed to those selected for clinical trials).[55] These data show that all DOACs reduce the risk of thromboembolic stroke compared to warfarin, with nonsignificant differences between dabigatran, rivaroxaban, and apixaban (Figure 10). Likewise, all 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.[55]

**Figure 10: All DOACs reduce the risk of stroke compared to warfarin[55]**




In another 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 11: Relative risk reduction for stroke and bleeding risks across 4 major DOAC trials vs. warfarin[56]**




*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.

## Patients with chronic kidney disease (CKD)

The doses of DOACs recommended for patients with severe CKD were approved based on pharmacology studies and were not tested in clinical trials, all of which excluded patients with CrCl <30 mL/min. Patients with mild or moderate CKD can safely take DOACs, in some cases with dose reductions. Warfarin or apixaban are recommended for patients with end-stage renal disease (ESRD),[7] as there is observational cohort data supporting the use of apixaban in this population.[53]

The following table and figures summarize current evidence and information about DOACs.

**Table 14: Anticoagulant characteristics[33]**

| | dabigatran | rivaroxaban | apixaban | edoxaban | warfarin |
|---|---|---|---|---|---|
| **Mechanism** | direct thrombin inhibitor | direct factor Xa inhibitor | direct factor Xa inhibitor | direct factor Xa inhibitor | vitamin K antagonist |
| **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 contraindications** | CrCl <15 | CrCl <15 | none | CrCl <15 or >95 | none |
| **FDA-approved reversal agent** | idarucizumab (Praxbind) | andexanet alfa (Andexxa) | andexanet alfa (Andexxa) | none | vitamin K |
| **Other considerations** | can cause dyspepsia—consider PPI | should be taken with evening meal | safe to use in patients with severe kidney disease or on dialysis[11] | do not use in normal renal function | drug-diet interactions; requires INR monitoring |

*CrCl: creatinine clearance, mL/min
**SCr: serum creatinine, mg/dL
+Dosing reflects FDA labeling, but this dose was not studied in randomized trials.

## Recommendations

In light of the compelling advantages of DOACs over warfarin, the 2019 AHA/ACC guideline recommended DOACs as the first-line choices for DOAC-eligible patients with AF, with the exception of

those with moderate-to-severe mitral stenosis or a mechanical heart valve.[7] Current evidence suggests that, in general, apixaban is the first-choice option based on its favorable risk/benefit balance. 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.

Warfarin, however, is preferred over a DOAC in patients with:

- mechanical heart valves[57]
- moderate to severe mitral stenosis
- active liver disease, including elevated liver enzymes

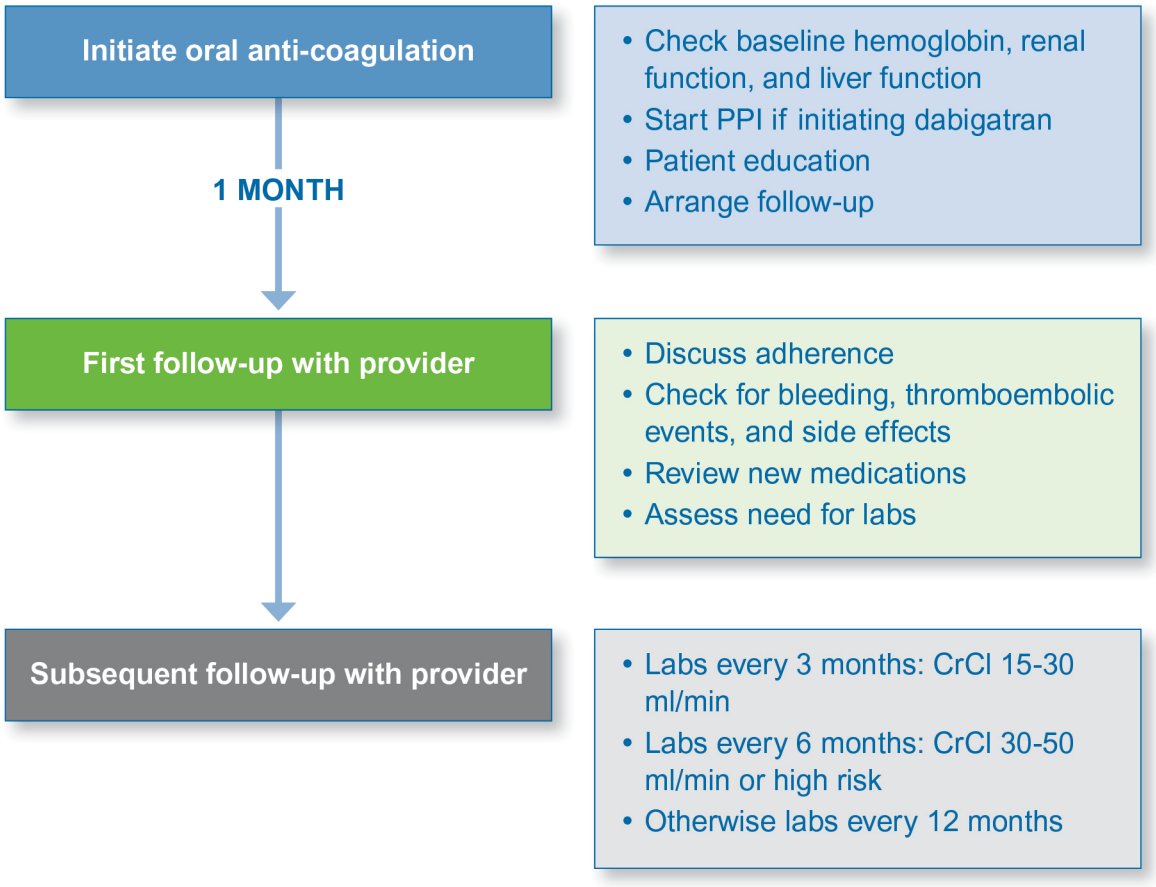
In addition, if a patient is already on warfarin, they should probably continue if they have:

- a contraindication to DOAC therapy
- an inability to pay for a DOAC

Before initiating any anticoagulation, we recommend obtaining baseline laboratory assessment, including hemoglobin/hematocrit, PT/INR, hepatic function, and renal function. Periodic monitoring of renal function is as important as dose adjustment 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.

## Follow-up schedules

**Figure 12: Recommended schedule for assessment and testing following DOAC initiation[58]**




## Switching between anticoagulants

Transition carefully between anticoagulant agents since discontinuing a DOAC prematurely may be associated with an increased risk of thromboembolism.[59] Monitor a patient's INR when transitioning from warfarin to a DOAC to avoid over-anticoagulation.[45] 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.[45] 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. When transitioning from warfarin to a DOAC, delay DOAC initiation until the patient's INR drops below 2.[45]

## 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 the 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. 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).

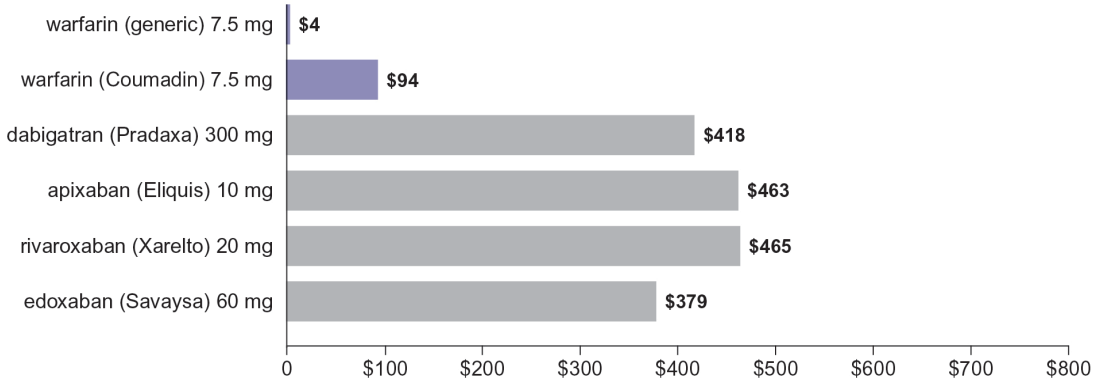
In patients on DOAC therapy, the length of interruption depends upon the expected bleeding risk of the procedure although, again, it is best to check with the surgeon or institution prior to changing the regimen. Deciding when to resume DOAC therapy depends on the risk of post-operative bleeding since 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 15: Plan for DOACs prior to a procedure based on bleeding risk**

| 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 |

## Cost

**Figure 13: 30-day costs of anticoagulants**



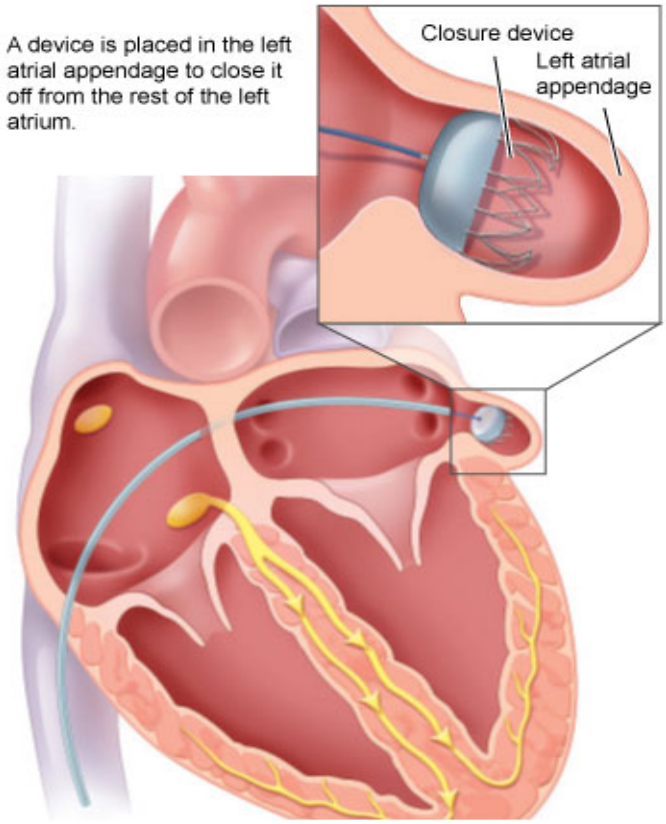

## Triple therapy

When treating patients with AF who need anticoagulation and antiplatelet therapy (e.g., patients having percutaneous intervention), assess ischemic risk using validated tools such as $CHA_2DS_2$-VASc and keep triple therapy (i.e., an oral anticoagulant with clopidogrel plus aspirin) as short as possible.[60] Clopidogrel is the $P2Y_{12}$ inhibitor of choice, and if aspirin is used, use low-dose aspirin only. Proton pump inhibitors should be used in patients with a history of GI bleeding. For more detailed information on antiplatelet therapy see AlosaHealth.org/Antiplatelet.

## Left atrial appendage occlusion devices

Cardiac plugs are placed in the left atrial appendage (LAA) to block thrombi that may form there from entering systemic circulation. Cardiac plugs 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.[61] The periprocedural risks of pericardial effusion, air embolism, and device embolization must be carefully weighed in the decision. The Watchman LAA occlusion device was approved by the FDA in 2015, with the Amplatzer device still under investigation. The Lariat, which is also still under investigation, uses an alternative approach of tying off the LAA from the rest of the atrium.

**Figure 14: Left atrial appendage closure**




The Watchman device was evaluated in the **PREVAIL**[62] and **PROTECT AF**[63] 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).[64] 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.

**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. Reversal agents are now available for DOACs. Warfarin is the preferred treatment for patients with contraindications to DOACS (e.g., mechanical heart valves, active liver disease), or with financial concerns. Left atrial appendage closure devices have not been shown to be superior to warfarin for reducing ischemic stroke risk.**

# Rate vs. 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 patients in SR.

A number of randomized trials and a meta-analysis have compared rate vs. rhythm control in patients with AF (Table 16). The rhythm control arm in all these studies included pharmacologic therapy with the option of electrical cardioversion. No study found statistically significant differences between the two strategies in mortality, major cardiovascular events, or stroke (the AFFIRM trial found that rate control was non-inferior to rhythm control). However, rate control was better than rhythm control for some secondary outcomes, including fewer adverse effects and hospital admissions. There was a non-significant trend towards lower mortality with rate control in some of the studies.

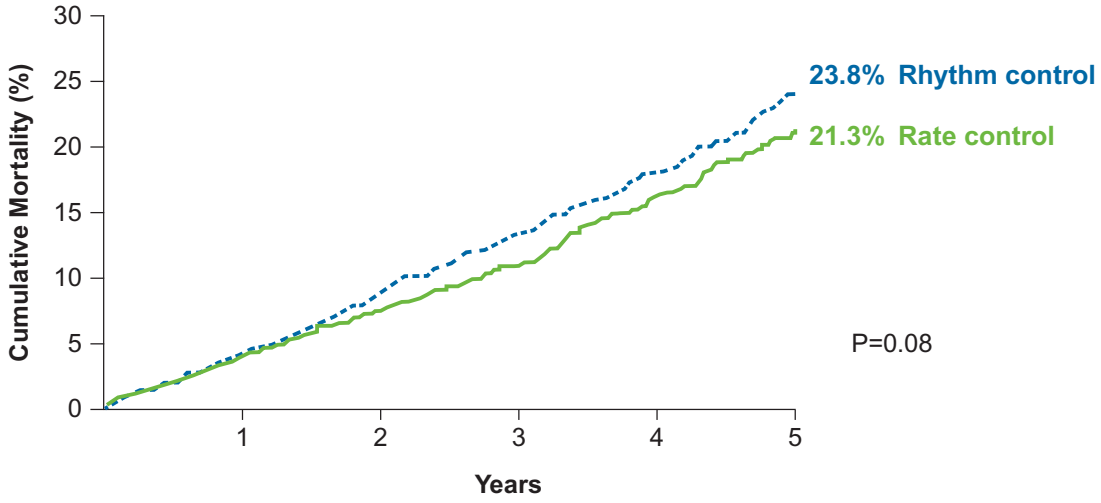
Decisions about rate vs. rhythm control strategies are patient-specific and driven by symptoms and expected sequelae, although, as a general rule, rate control is the default choice with a rhythm control strategy chosen only after justification for the need for such an approach (simply having AF is an inadequate reason).

**Table 16: Studies of rate vs. rhythm control for AF**

| Study | Target group/follow-up | Main results |
|---|---|---|
| Atrial Fibrillation Follow-up Investigation of Rhythm Management (**AFFIRM**)[65] | 4,060 patients with AF and a high risk of stroke or death. Follow-up for 5 years. | Mortality: no significant difference (see figure below) |
| How to Treat Chronic Atrial Fibrillation (**HOT-CAFÉ**)[66] | 205 patients with persistent AF. Mean follow-up 1.7 years. | Composite endpoint: no significant difference (all-cause mortality, number of thromboembolic events, or major bleeding)<br>Hospital admissions: lower in the rate group (12% vs. 74%; P<0.001). |
| Pharmacological Intervention in Atrial Fibrillation (**PIAF**)[37] | 252 patients with AF of between 1 week and 1 year. Follow-up for 1 year. | QOL: no significant difference<br>Hospital admission: lower in the rate group (24% vs. 69%; P<0.0001).<br>Adverse drug effects leading to change in therapy: lower in the rate group (14% vs. 25%, P=0.036).<br>Exercise tolerance: higher in rhythm group. |
| Rate Control Versus Electrical Cardioversion for Persistent Atrial Fibrillation (**RACE**)[67] | 522 patients with recurrent persistent AF. Mean follow-up 2.3 years. | No significant difference (non-inferiority) for a composite endpoint of death from cardiovascular causes, heart failure, thromboembolic complications, bleeding, implantation of a pacemaker, or severe adverse drug effect. |
| Strategies of Treatment of Atrial Fibrillation (**STAF**)[68] | 200 patients with persistent AF. Mean follow-up 20 months. | No significant difference in a composite endpoint of death, cardiopulmonary resuscitation, cerebrovascular event, or systemic embolism. |
| Atrial Fibrillation and Congestive Heart Failure Investigation (**AF-CHF**)[69] | 1376 patients with AF and heart failure. Mean follow-up 37 months. | CV death: no significant difference<br>No significant difference in secondary outcomes of death from any cause, stroke, worsening heart failure, or a composite outcome of death from cardiovascular causes, stroke, or worsening heart failure. |

A meta-analysis of 5,239 patients with persistent or recurrent AF found no significant difference in all-cause mortality between the rate and the rhythm control groups (13% vs. 15%; OR 0.87; 95% CI: 0.74-1.02).[70]

**Figure 15: Mortality rates in the AFFIRM study[65]**




Patient characteristics such as age and presence of heart failure may influence the outcomes of rhythm vs. rate control therapy. The AFFIRM study found that older patients (≥65 years of age) and patients without heart failure had significantly lower mortality with rate control.[71] The **CAFÉ-II** study found patients with heart failure had better LV function and quality of life with rhythm control.[72]

**BOTTOM LINE: Overall, patients treated with rate control, compared to rhythm control, have similar survival rates, lower rates of hospitalization and other arrhythmias, and have similar quality of life. However, some patients may have better outcomes with a rhythm control strategy.**

# Rate Control

Rate control is a reasonable initial therapy for most patients with AF.[10] Evidence suggests that the appropriate goal for asymptomatic patients and preserved LV systolic function is a resting heart rate ≤110 beats per minute (bpm), while a more aggressive goal of ≤80 bmp is recommended for symptomatic AF patients.[4]

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 17).[73]

**Table 17: Results of the RACE II trial[67]**

| | 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 was considered to be non-inferior to a strict heart rate goal and requires fewer medications and fewer follow up visits.

Table 18 (next page) lists the most common drugs used for controlling heart rate, including those that can be used in patients with concomitant heart failure.

**Table 18: Medications for rate control in AF**

| Medication | Use in concomitant heart failure |
|---|---|
| Beta-blockers (e.g., atenolol, metoprolol, nadolol, propranolol) | Avoid in decompensated heart failure. Recommended in hemodynamically stable systolic heart failure.<br>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).<br>NOTE: dihydropyridine CCBs (e.g., amlodipine) do *not* lower heart rate. |
| Digoxin | Not first-line therapy for rate control and not appropriate for single-agent therapy, but can be combined with beta-blockers and CCBs.<br>Reduces HR at rest but not with exercise.<br>Recommended in decompensated heart failure.<br>Monitoring of serum levels required.<br>Use caution in renal dysfunction, the elderly, or with medications that reduce clearance (e.g., amiodarone, CCBs). |

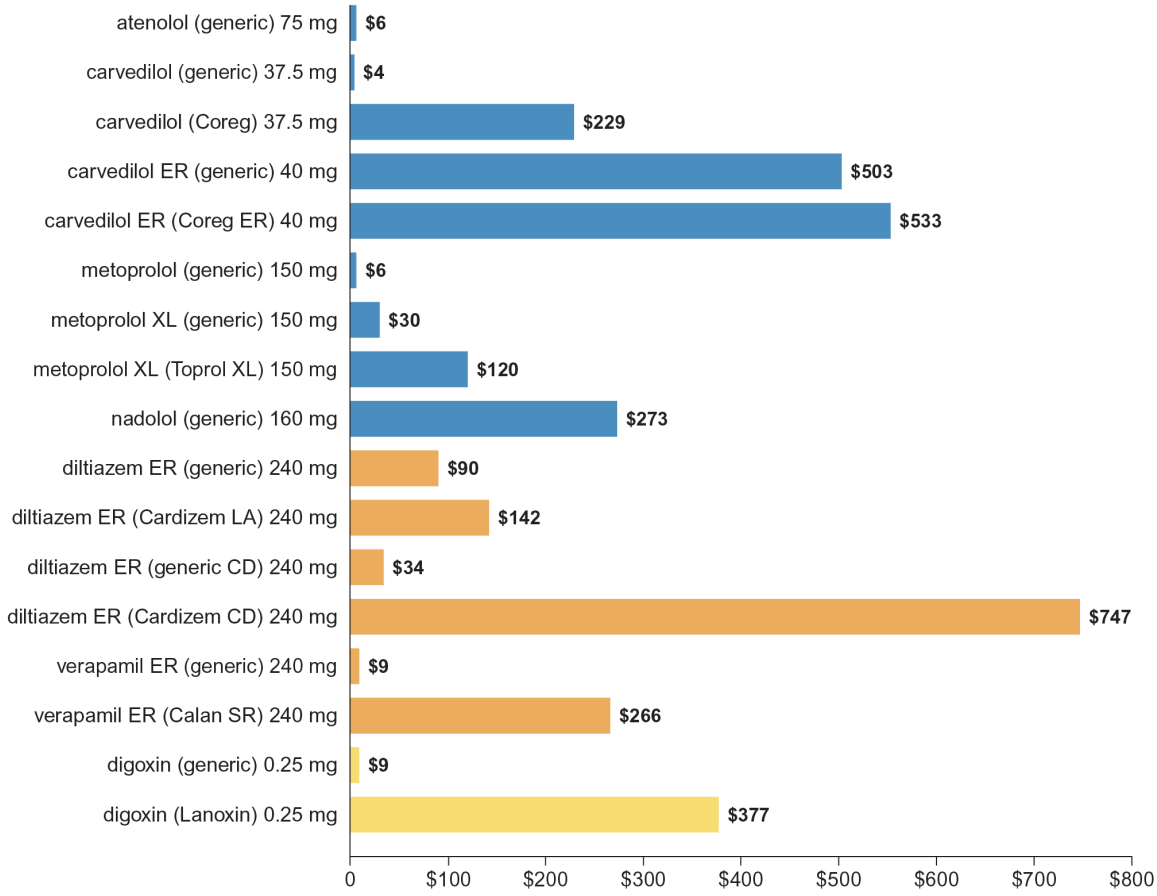
Commonly-used doses and routes of administration of diltiazem, verapamil, and digoxin for AF are provided in Table 19. Doses of beta-blockers vary with the individual agent used.

**Table 19: 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 QD |
| 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.[74] Digoxin was less effective at controlling heart rate during exercise than beta-blockers or diltiazem (mean difference 15 to 30 bpm higher with digoxin).[74] 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.[65]

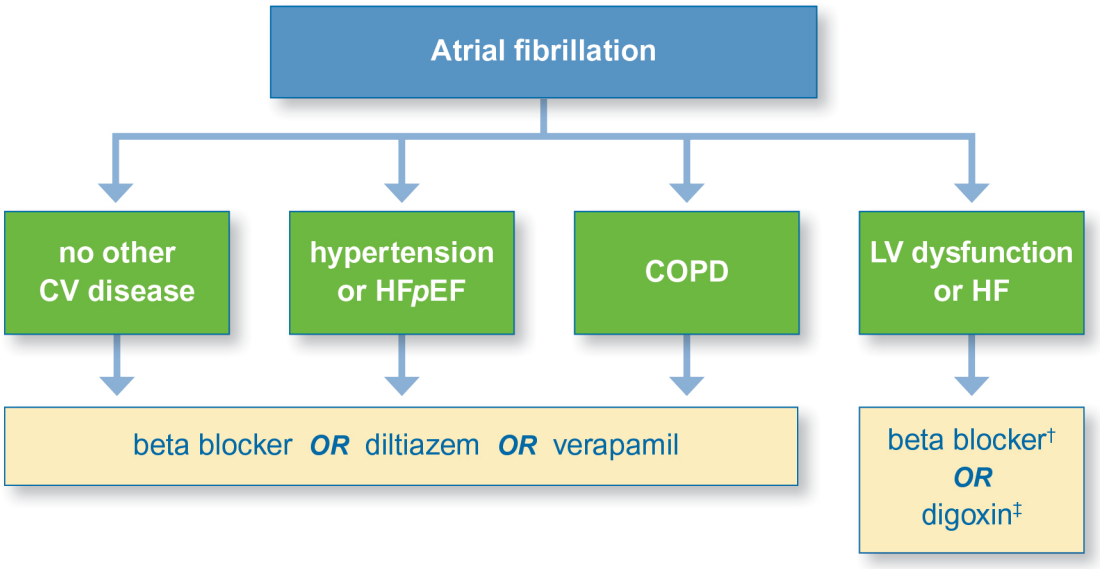
**Figure 16: Cost of rate control medications**




If rate control offers inadequate symptomatic relief, restoration of sinus rhythm should be considered.[10]

Figure 17 summarizes the recommended approach to using a rate control strategy in patients with AF.

**Figure 17: 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

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 (compared to these measures before the intervention).[75] The main limitations are a small risk of sudden death during the 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.[11,75]

**BOTTOM LINE: Rate control with a lenient goal of ≤110 bpm is a reasonable initial therapy for most patients with AF, while a more aggressive goal of ≤80 bmp is recommended for symptomatic AF patients.**

# Rhythm control

Acute restoration and maintenance of sinus rhythm should generally be reserved for patients who cannot be adequately rate controlled or who continue to have symptoms despite adequate rate control.

Rhythm control may be the preferred strategy in patients with:[10,11]

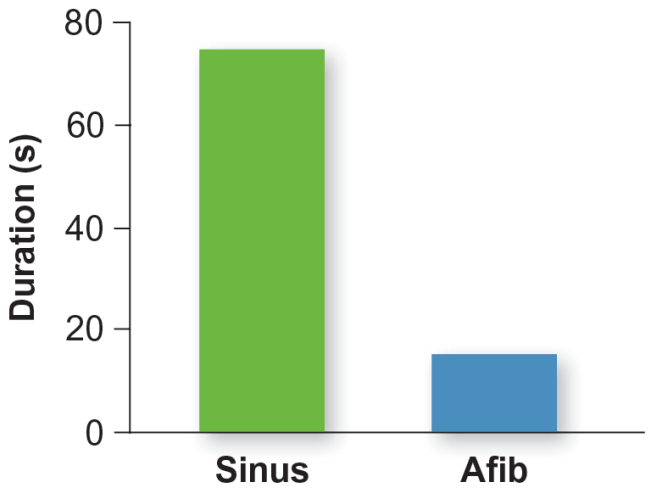
- younger age
- inability to achieve adequate rate control
- persistent symptoms despite adequate rate control
- hypertrophic cardiomyopathy

Although rhythm control has historically been recommended for patients with heart failure, the **AF-CHF trial** of patients with AF and systolic heart failure 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.[69] The two groups of heart failure patients who may do better with a rhythm control strategy are those with hypertrophic cardiomyopathy or tachycardia-induced cardiomyopathy with a poorly controlled rate.

## 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 coronary artery disease or congestive heart failure.[76] Overall, the benefit-to-risk ratio of antiarrhythmic drugs is low and they should generally be prescribed by experienced specialists.[11] Nonetheless, for selected patients, achieving and maintaining sinus rhythm may improve quality of life. The **SAFE-T trial** of 624 patients randomized to either rate or rhythm control found that, after 1 year, patients on rhythm control were significantly more likely to report improved QOL, reduced burden of AF symptoms, and improved exercise capacity (Figure 18).[77]

**Figure 18: Exercise duration at 12 months[77]**



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.[78]

Limitations of a rhythm control strategy include:

- high rate of AF recurrence
- increased risk of dangerous arrhythmias
- stroke risk stratification and anticoagulation still needed

Table 20 summarizes the classes of antiarrhythmic medications. (Class II [beta-blockers] and Class IV [calcium channel blockers] are used as rate control agents and were discussed previously.)

**Table 20: Antiarrhythmic medications used for AF**

| Class | Mechanism | Medications |
|---|---|---|
| Class I | Sodium channel blocker | |
| Class IA | Lengthens action potential | Quinidine<br>Procainamide (IV)<br>Disopyramide |
| Class IC | No effect on action potential | Flecainide<br>Propafenone |
| Class III | Potassium channel blocker<br>Some agents have BB action | Amiodarone<br>Dronedarone<br>Dofetilide<br>Sotalol |

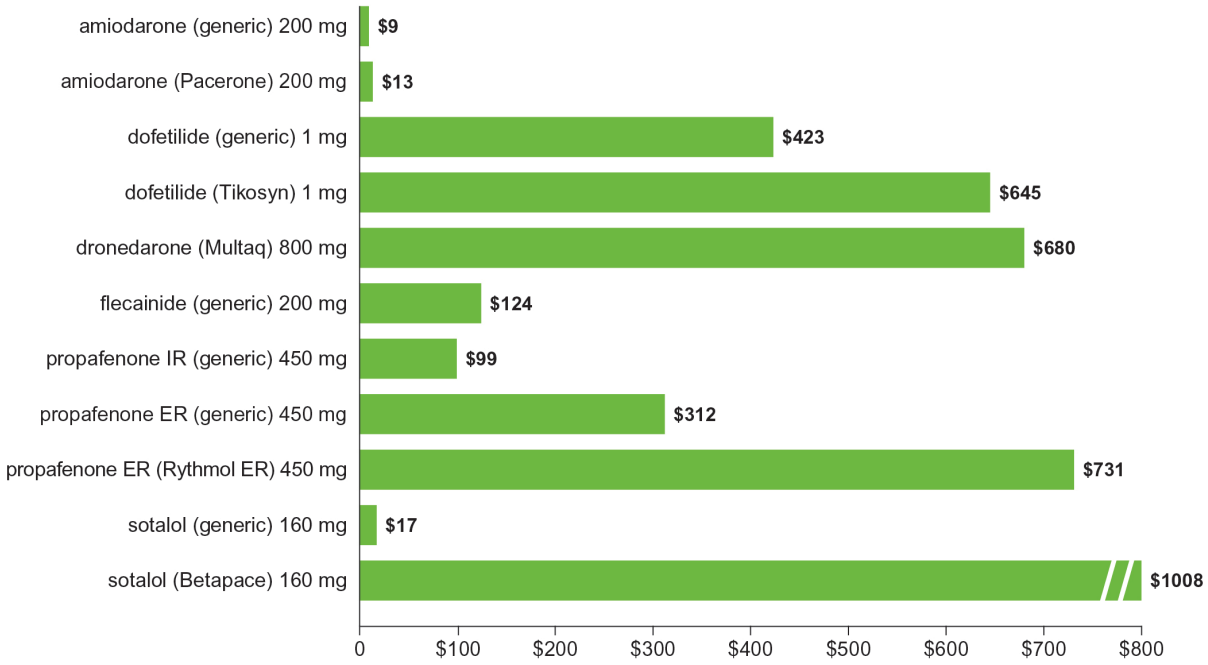
Note the following medication-specific cautions:

- Class IA drugs are rarely used for atrial fibrillation, except in specific populations (e.g., disopyramide in patients with hypertrophic cardiomyopathy and AF)
- Flecainide and propafenone should always be given with a nodal agent because they can paradoxically increase ventricular rate due to slowing of atrial arrhythmias, and these drugs may exacerbate underlying conduction disease. These drugs should be avoided in patients with:
  - coronary disease or systolic heart failure
  - prolonged QTc or who are on other QTc-prolonging medications
  - atrial flutter
- Sotalol is generally not effective in converting AF to sinus rhythm but can help maintain sinus rhythm after cardioversion. Dofetilide can chemically convert patients, and can help maintain sinus rhythm.[79] Both drugs:
  - prolong QTc and are pro-arrhythmic. Given this they should be initiated in inpatient settings with continuous monitoring and serial electrocardiograms for QTc monitoring
  - should be avoided in patients with CKD, patients with prolonged QTc or who are on other QTc-prolonging medications
  - require serial lab monitoring
- Sotalol should be avoided in patients with systolic heart failure
- Dofetilide can be used in patients with CAD or HF

- Dronedarone is contraindicated in patients with decompensated heart failure, and should be discontinued in patients with permanent AF (i.e., should not be used as a rate control agent)
- Amiodarone requires both baseline testing (liver function, thyroid function, pulmonary function) and periodic lab monitoring

A prospective trial in 403 patients found that amiodarone is more effective than propafenone or sotalol in converting and maintaining sinus rhythm,[78] 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.

**Figure 19: Price of 30-day supply of antiarrhythmics**




## Cardioversion

Cardioversion may be performed electively, but its emergent use 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.[10]

Cardioversion can be performed either with medication (pharmacological cardioversion) or by direct current shocks (electrical cardioversion). Many of the drugs used for cardioversion are also used to maintain sinus rhythm (e.g., IV ibutilide and PO flecainide or propafenone). Electrical cardioversion generally requires a short-acting anesthetic.[80] 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

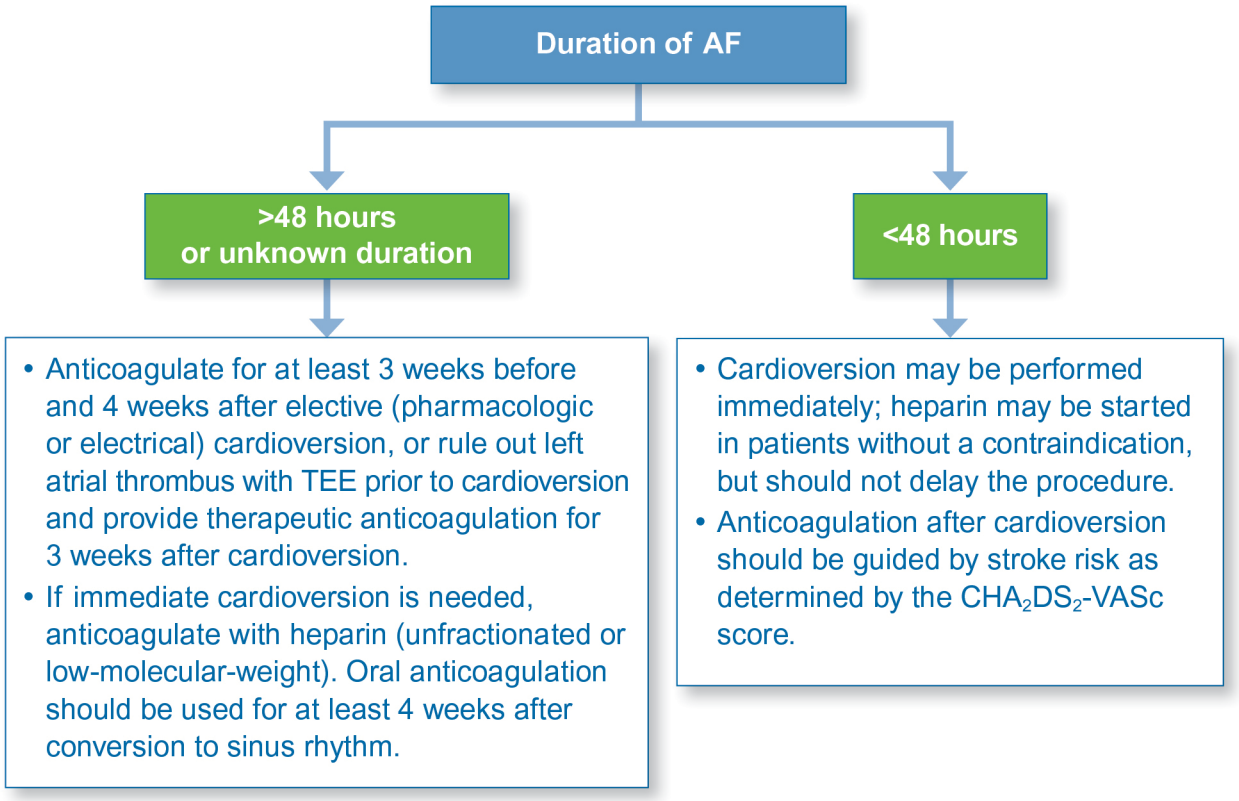
population.[10] Even if cardioversion is initially successful, the recurrence of AF is high.[81] Repeat cardioversion may be required if the patient spontaneously reverts to AF.

Sinus rhythm can be restored in a substantial proportion of patients by DC cardioversion, but the rate of relapse is high without coordinated drug therapy.[10] Most recurrences of AF occur within the first month after DC cardioversion.[10] Starting an antiarrhythmic drug and establishing adequate plasma drug concentrations before cardioversion increases the likelihood of success and reduces the rate of recurrent AF.[10] 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.

## Prevention of thromboembolism in cardioversion

The risk of thromboembolism rises after cardioversion, hence steps must be taken to reduce this risk (with either warfarin or a DOAC).

**Figure 20: Algorithm for anticoagulation therapy for patients with non-emergent AF undergoing cardioversion[7,29]**



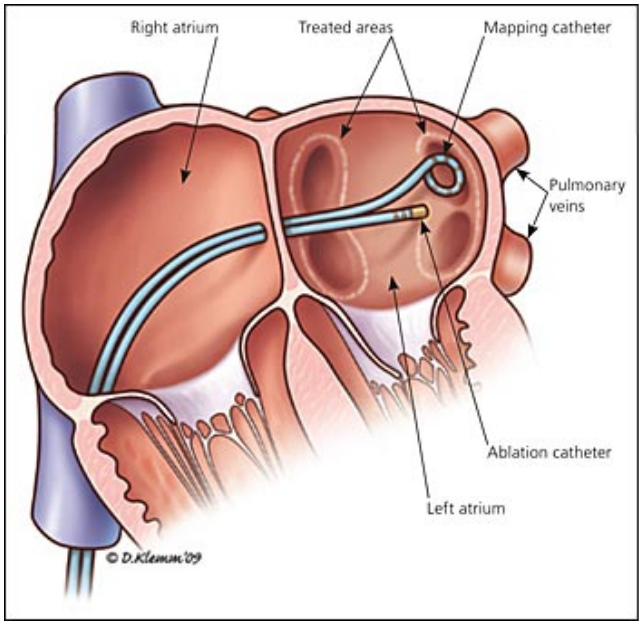
**BOTTOM LINE: Although many patients need antiarrhythmic drugs to maintain sinus rhythm, these medications cause significant adverse effects and some are associated with increased mortality. Antiarrhythmic drugs are usually administered with the help of a cardiac specialist. Both electrical and pharmacological cardioversion can restore sinus rhythm, although the rate of recurrent AF is high. Either a DOAC or warfarin may be used for prophylactic anticoagulation in the context of cardioversion.**

## AF catheter ablation

Antiarrhythmic drugs (AADs) for AF are non-invasive but generally require chronic use,[19] 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.[82] In contrast, minimally invasive procedures such as catheter ablation may prevent the need for long-term use of these medications in patients requiring a rhythm control strategy.[19]

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. The **RAAFT-2 trial** of 127 patients with paroxysmal AF randomized to AAD vs. catheter ablation found that AF recurrence was common at 2 years but occurred less frequently in the catheter ablation group: 72% in the AAD group vs. 55% in catheter ablation group.[83] No difference was found in quality of life scores between the two treatments.

**Figure 21: AF catheter ablation**




The more recent, and larger, **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).[84] 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 reduced 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 Catheter Ablation vs. Standard Conventional Treatment in Patients With LV Dysfunction and AF (**CASTLE-AF**) trial, enrolled patients with heart failure with reduced ejection fraction (HFrEF) who also had paroxysmal or persistent AF and an implanted cardioverter-defibrillator or a cardiac resynchronization therapy defibrillator device who did not respond to, or could not take, antiarrhythmic drugs.[85] 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, reduced rates of hospitalization for worsening HF, 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.

Catheter ablation for AF is recommended for patients with paroxysmal AF without structural heart disease who have "failed" at least one AAD, and can be considered as a first-line therapy (prior to attempting any antiarrhythmics).[4] Some providers discontinue anticoagulation if the patient remains in sinus rhythm ≥3 months after ablation, although evidence for this approach is lacking and not recommended in patients at high risk of stroke.

Most AF ablation strategies electrically isolate the pulmonary veins from the rest of the left atrium.[86,87] Several randomized trials and systematic reviews have shown that in both paroxysmal and persistent AF, catheter ablation (pulmonary vein isolation [PVI] and circumferential pulmonary vein ablation) is significantly better than antiarrhythmic medications at preventing recurrences of AF, and in improving symptoms, exercise capacity, and quality of life.[11,88,89]

**BOTTOM LINE: AF catheter ablation is an option for patients with persistent symptomatic AF, but is limited by procedural complications and relatively high rates of atrial arrhythmia recurrence. The role of continued anticoagulation in patients after a successful ablation is debated, but patients with significant stroke risk likely should continue anticoagulation.**

# 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 fibrillation itself, the significant differences that comorbidities can make in treatment decisions, and the wide range of potential therapeutic options available to treat the condition. The evidence presented in this document can be distilled to six key points:

1. Atrial fibrillation 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 most from anticoagulation.
3. Use the $CHA_2DS_2$-VASc score to predict stroke risk and guide prescribing.
4. Address modifiable risks for bleeding.
5. Direct oral anticoagulants (DOACs) reduce both stroke and bleeding risk compared to warfarin in most patients.
6. Patients taking warfarin can be switched to a DOAC unless there are contraindications or financial concerns that prevent the change.
7. Rate control is preferred over rhythm control for most patients, targeting a heart rate of <110 bpm. Patients with continued symptoms may require a target rate of <80 bpm.

# References


1. Braunwald E. Shattuck lecture--cardiovascular medicine at the turn of the millennium: triumphs, concerns, and opportunities. *N Engl J Med.* 1997;337(19):1360-1369.
2. Benjamin EJ, Muntner P, Alonso A, et al. Heart Disease and Stroke Statistics-2019 Update: A Report From the American Heart Association. *Circulation.* 2019;139(10):e56-e528.
3. Saffitz JE. Connexins, conduction, and atrial fibrillation. *N Engl J Med.* 2006;354(25):2712-2714.
4. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol.* 2014;64(21):e1-76.
5. Colilla S, Crow A, Petkun W, Singer DE, Simon T, Liu X. Estimates of current and future incidence and prevalence of atrial fibrillation in the U.S. adult population. *Am J Cardiol.* 2013;112(8):1142-1147.
6. Kim MH, Johnston SS, Chu BC, Dalal MR, Schulman KL. Estimation of total incremental health care costs in patients with atrial fibrillation in the United States. *Circulation Cardiovascular quality and outcomes.* 2011;4(3):313-320.
7. January CT, Wann LS, Calkins H, et al. 2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society in Collaboration With the Society of Thoracic Surgeons. *Circulation.* 2019;140(2):e125-e151.
8. Levy S, Camm AJ, Saksena S, et al. International consensus on nomenclature and classification of atrial fibrillation: A collaborative project of the Working Group on Arrhythmias and the Working Group of Cardiac Pacing of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. *J Cardiovasc Electrophysiol.* 2003;14(4):443-445.
9. Go AS, Hylek EM, Phillips KA, et al. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. *JAMA.* 2001;285(18):2370-2375.
10. Fuster V, Ryden LE, Cannom DS, et al. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation--executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation). *J Am Coll Cardiol.* 2006;48(4):854-906.
11. Lafuente-Lafuente C, Mahe I, Extramiana F. Management of atrial fibrillation. *BMJ.* 2009;340:40-45.
12. Haissaguerre M, Jais P, Shah DC, et al. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. *N Engl J Med.* 1998;339(10):659-666.
13. Huxley RR, Lopez FL, Folsom AR, et al. Absolute and attributable risks of atrial fibrillation in relation to optimal and borderline risk factors: the Atherosclerosis Risk in Communities (ARIC) study. *Circulation.* 2011;123(14):1501-1508.
14. Feng D, Edwards WD, Oh JK, et al. Intracardiac thrombosis and embolism in patients with cardiac amyloidosis. *Circulation.* 2007;116(21):2420-2426.
15. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke.* 1991;22(8):983-988.
16. Walkey AJ, Hammill BG, Curtis LH, Benjamin EJ. Long-term outcomes following development of new-onset atrial fibrillation during sepsis. *Chest.* 2014;146(5):1187-1195.
17. Bunch TJ, Gersh BJ. Rhythm Control Strategies and the Role of Antiarrhythmic Drugs in the Management of Atrial Fibrillation: Focus on Clinical Outcomes. *J Gen Intern Med.* 2011;26(5):531-537.
18. Ellis K, Wazni O, Marrouche N, et al. Incidence of atrial fibrillation post-cavotricuspid isthmus ablation in patients with typical atrial flutter: left-atrial size as an independent predictor of atrial fibrillation recurrence. *J Cardiovasc Electrophysiol.* 2007;18(8):799-802.

19. Nabauer M, Gerth A, Limbourg T, et al. The Registry of the German Competence NETwork on Atrial Fibrillation: patient characteristics and initial management. *Europace.* 2009;11(4):423-434.
20. Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation. Analysis of pooled data from five randomized controlled trials. *Arch Intern Med.* 1994;154(13):1449-1457.
21. Wann L, Curtis A, January C, et al. 2011 ACCF/AHA/HRS Focused Update on the Management of Patients With Atrial Fibrillation (Updating the 2006 Guideline): A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation 2011;123:104-123. 2011.
22. Kottkamp H. Catheter ablation of atrial fibrillation: on the pathophysiology of the arrhythmia and the impact of cardiac risk factor management. *J Am Coll Cardiol.* 2014;64(21):2232-2234.
23. Abed HS, Wittert GA, Leong DP, et al. Effect of weight reduction and cardiometabolic risk factor management on symptom burden and severity in patients with atrial fibrillation: a randomized clinical trial. *JAMA.* 2013;310(19):2050-2060.
24. Wong CX, Abed HS, Molaee P, et al. Pericardial fat is associated with atrial fibrillation severity and ablation outcome. *J Am Coll Cardiol.* 2011;57(17):1745-1751.
25. Abed HS, Samuel CS, Lau DH, et al. Obesity results in progressive atrial structural and electrical remodeling: implications for atrial fibrillation. *Heart Rhythm.* 2013;10(1):90-100.
26. Pathak RK, Middeldorp ME, Lau DH, et al. Aggressive risk factor reduction study for atrial fibrillation and implications for the outcome of ablation: the ARREST-AF cohort study. *J Am Coll Cardiol.* 2014;64(21):2222-2231.
27. Pathak RK, Middeldorp ME, Meredith M, et al. Long-Term Effect of Goal-Directed Weight Management in an Atrial Fibrillation Cohort: A Long-Term Follow-Up Study (LEGACY). *J Am Coll Cardiol.* 2015;65(20):2159-2169.
28. Lip GY, Tse HF, Lane DA. Atrial fibrillation. *Lancet.* 2012;379(9816):648-661.
29. Friberg L, Rosenqvist M, Lip GY. Evaluation of risk stratification schemes for ischaemic stroke and bleeding in 182 678 patients with atrial fibrillation: the Swedish Atrial Fibrillation cohort study. *European heart journal.* 2012;33(12):1500-1510.
30. Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJ, Lip GY. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. *Chest.* 2010;138(5):1093-1100.
31. Friberg L, Benson L, Rosenqvist M, Lip GY. Assessment of female sex as a risk factor in atrial fibrillation in Sweden: nationwide retrospective cohort study. *BMJ.* 2012;344:e3522.
32. Lip GY, Skjoth F, Rasmussen LH, Larsen TB. Oral Anticoagulation, Aspirin, or No Therapy in Patients With Nonvalvular AF With 0 or 1 Stroke Risk Factor Based on the CHA2DS2-VASc Score. *J Am Coll Cardiol.* 2015;65(14):1385-1394.
33. Camm AJ, Lip GY, De Caterina R, et al. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation. Developed with the special contribution of the European Heart Rhythm Association. *European heart journal.* 2012;33(21):2719-2747.
34. Antithrombotic Trialists C. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ.* 2002;324(7329):71-86.
35. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Ann Intern Med.* 2007;146(12):857-867.
36. Antithrombotic Trialists C, Baigent C, Blackwell L, et al. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. *Lancet.* 2009;373(9678):1849-1860.
37. Hohnloser SH, Kuck KH, Lilienthal J. Rhythm or rate control in atrial fibrillation--Pharmacological Intervention in Atrial Fibrillation (PIAF): a randomised trial. *Lancet.* 2000;356(9244):1789-1794.
38. Connolly SJ, Pogue J, Hart RG, et al. Effect of clopidogrel added to aspirin in patients with atrial fibrillation. *N Engl J Med.* 2009;360(20):2066-2078.
39. Connolly S, Pogue J, Hart R, et al. Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomised controlled trial. *Lancet.* 2006;367(9526):1903-1912.

40. Gage BF, Fihn SD, White RH. Management and dosing of warfarin therapy. *The American journal of medicine.* 2000;109(6):481-488.
41. Go AS, Hylek EM, Chang Y, et al. Anticoagulation therapy for stroke prevention in atrial fibrillation: how well do randomized trials translate into clinical practice? *JAMA.* 2003;290(20):2685-2692.
42. Singer DE, Chang Y, Fang MC, et al. The net clinical benefit of warfarin anticoagulation in atrial fibrillation. *Ann Intern Med.* 2009;151(5):297-305.
43. Reynolds MW, Fahrbach K, Hauch O, et al. Warfarin anticoagulation and outcomes in patients with atrial fibrillation: a systematic review and metaanalysis. *Chest.* 2004;126(6):1938-1945.
44. Singer DE, Albers GW, Dalen JE, et al. Antithrombotic therapy in atrial fibrillation: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest.* 2008;133(6 Suppl):546S-592S.
45. Kovacs RJ, Flaker GC, Saxonhouse SJ, et al. Practical Management of Anticoagulation in Patients With Atrial Fibrillation. *J Am Coll Cardiol.* 2015;65(13):1340-1360.
46. Wallentin L, Yusuf S, Ezekowitz MD, et al. Efficacy and safety of dabigatran compared with warfarin at different levels of international normalised ratio control for stroke prevention in atrial fibrillation: an analysis of the RE-LY trial. *Lancet.* 2010;376(9745):975-983.
47. Beasley BN, Unger EF, Temple R. Anticoagulant options--why the FDA approved a higher but not a lower dose of dabigatran. *N Engl J Med.* 2011;364(19):1788-1790.
48. Stangier J, Rathgen K, Stahle H, Gansser D, Roth W. The pharmacokinetics, pharmacodynamics and tolerability of dabigatran etexilate, a new oral direct thrombin inhibitor, in healthy male subjects. *British journal of clinical pharmacology.* 2007;64(3):292-303.
49. Graham DJ, Reichman ME, Wernecke M, et al. Cardiovascular, bleeding, and mortality risks in elderly Medicare patients treated with dabigatran or warfarin for nonvalvular atrial fibrillation. *Circulation.* 2015;131(2):157-164.
50. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med.* 2011;365(10):883-891.
51. Patel MR, Hellkamp AS, Lokhnygina Y, et al. Outcomes of discontinuing rivaroxaban compared with warfarin in patients with nonvalvular atrial fibrillation: analysis from the ROCKET AF trial (Rivaroxaban Once-Daily, Oral, Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation). *J Am Coll Cardiol.* 2013;61(6):651-658.
52. Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med.* 2011;365(11):981-992.
53. Siontis KC, Zhang X, Eckard A, et al. Outcomes Associated With Apixaban Use in Patients With End-Stage Kidney Disease and Atrial Fibrillation in the United States. *Circulation.* 2018;138(15):1519-1529.
54. Giugliano RP, Ruff CT, Braunwald E, et al. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med.* 2013;369(22):2093-2104.
55. Graham DJ, Baro E, Zhang R, et al. Comparative Stroke, Bleeding, and Mortality Risks in Older Medicare Patients Treated with Oral Anticoagulants for Nonvalvular Atrial Fibrillation. *The American journal of medicine.* 2019;132(5):596-604 e511.
56. Ruff CT, Giugliano RP, Braunwald E, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. *Lancet.* 2014;383(9921):955-962.
57. Van de Werf F, Brueckmann M, Connolly SJ, et al. A comparison of dabigatran etexilate with warfarin in patients with mechanical heart valves: THE Randomized, phase II study to evaluate the safety and pharmacokinetics of oral dabigatran etexilate in patients after heart valve replacement (RE-ALIGN). *Am Heart J.* 2012;163(6):931-937 e931.
58. Heidbuchel H, Verhamme P, Alings M, et al. EHRA practical guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation: executive summary. *European heart journal.* 2013;34(27):2094-2106.
59. Pearson TA, Laurora I, Chu H, Kafonek S. The lipid treatment assessment project (L-TAP): a multicenter survey to evaluate the percentages of dyslipidemic patients receiving lipid-lowering therapy and achieving low-density lipoprotein cholesterol goals. *Arch Intern Med.* 2000;160(4):459-467.

60. Levine GN, Bates ER, Bittl JA, et al. 2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol.* 2016;68(10):1082-1115.
61. Food and Drug Administration. WATCHMAN left atrial appendage closure device, Patient Information Guide. https://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=12&cad=rja&uact=8&ved=2ahUKEwilhp3e8aXlAhWRdd8KHVYLCgwQFjALegQIBBAC&url=https%3A%2F%2Fwww.accessdata.fda.gov%2Fcdrh_docs%2Fpdf13%2FP130013c.pdf&usg=AOvVaw3lRopXVl0Vtt7Gnu4muqGB. Accessed October 18 2019.
62. Holmes DR, Jr., Kar S, Price MJ, et al. Prospective randomized evaluation of the Watchman Left Atrial Appendage Closure device in patients with atrial fibrillation versus long-term warfarin therapy: the PREVAIL trial. *J Am Coll Cardiol.* 2014;64(1):1-12.
63. Reddy VY, Doshi SK, Sievert H, et al. Percutaneous left atrial appendage closure for stroke prophylaxis in patients with atrial fibrillation: 2.3-Year Follow-up of the PROTECT AF (Watchman Left Atrial Appendage System for Embolic Protection in Patients with Atrial Fibrillation) Trial. *Circulation.* 2013;127(6):720-729.
64. Reddy VY, Doshi SK, Kar S, et al. 5-Year Outcomes After Left Atrial Appendage Closure: From the PREVAIL and PROTECT AF Trials. *J Am Coll Cardiol.* 2017;70(24):2964-2975.
65. Wyse DG, Waldo AL, DiMarco JP, et al. A comparison of rate control and rhythm control in patients with atrial fibrillation. *N Engl J Med.* 2002;347(23):1825-1833.
66. Opolski G, Torbicki A, Kosior DA, et al. Rate control vs rhythm control in patients with nonvalvular persistent atrial fibrillation: the results of the Polish How to Treat Chronic Atrial Fibrillation (HOT CAFE) Study. *Chest.* 2004;126(2):476-486.
67. Van Gelder IC, Hagens VE, Bosker HA, et al. A comparison of rate control and rhythm control in patients with recurrent persistent atrial fibrillation. *N Engl J Med.* 2002;347(23):1834-1840.
68. Carlsson J, Miketic S, Windeler J, et al. Randomized trial of rate-control versus rhythm-control in persistent atrial fibrillation: the Strategies of Treatment of Atrial Fibrillation (STAF) study. *J Am Coll Cardiol.* 2003;41(10):1690-1696.
69. Roy D, Talajic M, Nattel S, et al. Rhythm control versus rate control for atrial fibrillation and heart failure. *N Engl J Med.* 2008;358(25):2667-2677.
70. de Denus S, Sanoski CA, Carlsson J, Opolski G, Spinler SA. Rate vs rhythm control in patients with atrial fibrillation: a meta-analysis. *Arch Intern Med.* 2005;165(3):258-262.
71. Curtis AB, Gersh BJ, Corley SD, et al. Clinical factors that influence response to treatment strategies in atrial fibrillation: the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study. *Am Heart J.* 2005;149(4):645-649.
72. Shelton RJ, Clark AL, Goode K, et al. A randomised, controlled study of rate versus rhythm control in patients with chronic atrial fibrillation and heart failure: (CAFE-II Study). *Heart.* 2009;95(11):924-930.
73. Van Gelder IC, Groenveld HF, Crijns HJ, et al. Lenient versus strict rate control in patients with atrial fibrillation. *N Engl J Med.* 2010;362(15):1363-1373.
74. Segal JB, McNamara RL, Miller MR, et al. The evidence regarding the drugs used for ventricular rate control. *J Fam Pract.* 2000;49(1):47-59.
75. Wood MA, Brown-Mahoney C, Kay GN, Ellenbogen KA. Clinical outcomes after ablation and pacing therapy for atrial fibrillation : a meta-analysis. *Circulation.* 2000;101(10):1138-1144.
76. Hsu LF, Jais P, Sanders P, et al. Catheter ablation for atrial fibrillation in congestive heart failure. *N Engl J Med.* 2004;351(23):2373-2383.
77. Singh SN, Tang XC, Singh BN, et al. Quality of life and exercise performance in patients in sinus rhythm versus persistent atrial fibrillation: a Veterans Affairs Cooperative Studies Program Substudy. *J Am Coll Cardiol.* 2006;48(4):721-730.
78. Roy D, Talajic M, Dorian P, et al. Amiodarone to prevent recurrence of atrial fibrillation. Canadian Trial of Atrial Fibrillation Investigators. *N Engl J Med.* 2000;342(13):913-920.
79. Grines CL. Safety and effectiveness of dofetilide for conversion of atrial fibrillation and nesiritide for acute decompensation of heart failure: a report from the cardiovascular and renal advisory panel of the Food and Drug Administration. *Circulation.* 2000;101(21):E200-201.

80. Mead GE, Elder AT, Flapan AD, Kelman A. Electrical cardioversion for atrial fibrillation and flutter. *Cochrane Database Syst Rev.* 2005(3):CD002903.
81. Lafuente-Lafuente C, Mouly S, Longas-Tejero MA, Bergmann JF. Antiarrhythmics for maintaining sinus rhythm after cardioversion of atrial fibrillation. *Cochrane Database Syst Rev.* 2007(4):CD005049.
82. Wilber DJ, Pappone C, Neuzil P, et al. Comparison of antiarrhythmic drug therapy and radiofrequency catheter ablation in patients with paroxysmal atrial fibrillation: a randomized controlled trial. *JAMA.*303(4):333-340.
83. Morillo CA, Verma A, Connolly SJ, et al. Radiofrequency ablation vs antiarrhythmic drugs as first-line treatment of paroxysmal atrial fibrillation (RAAFT-2): a randomized trial. *JAMA.* 2014;311(7):692-700.
84. Packer DL, Mark DB, Robb RA, et al. Effect of Catheter Ablation vs Antiarrhythmic Drug Therapy on Mortality, Stroke, Bleeding, and Cardiac Arrest Among Patients With Atrial Fibrillation: The CABANA Randomized Clinical Trial. *JAMA.* 2019;321(13):1261-1274.
85. Marrouche NF, Brachmann J, Andresen D, et al. Catheter Ablation for Atrial Fibrillation with Heart Failure. *N Engl J Med.* 2018;378(5):417-427.
86. Calkins H, Brugada J, Packer DL, et al. HRS/EHRA/ECAS expert Consensus Statement on catheter and surgical ablation of atrial fibrillation: recommendations for personnel, policy, procedures and follow-up. A report of the Heart Rhythm Society (HRS) Task Force on catheter and surgical ablation of atrial fibrillation. *Heart Rhythm.* 2007;4(6):816-861.
87. Terasawa T, Balk EM, Chung M, et al. Systematic review: comparative effectiveness of radiofrequency catheter ablation for atrial fibrillation. *Ann Intern Med.* 2009;151(3):191-202.
88. Jais P, Cauchemez B, Macle L, et al. Catheter ablation versus antiarrhythmic drugs for atrial fibrillation: the A4 study. *Circulation.* 2008;118(24):2498-2505.
89. Noheria A, Kumar A, Wylie JV, Jr., Josephson ME. Catheter ablation vs antiarrhythmic drug therapy for atrial fibrillation: a systematic review. *Arch Intern Med.* 2008;168(6):581-586.

## About this publication

**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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