Atrial fibrillation: Anticoagulant therapy to prevent thromboembolism

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INTRODUCTION

Development and subsequent embolization of atrial thrombi can occur with any form (ie, paroxysmal, persistent, or permanent) of atrial fibrillation (AF). (See "Overview of atrial fibrillation", section on 'General classification'.) While ischemic stroke is the most frequent clinical manifestation of embolization associated with AF, embolization to other locations in the systemic and pulmonary circulations also occurs, but is less commonly recognized. (See "Stroke in patients with atrial fibrillation".)

As a result of embolic risk, chronic oral anticoagulation is recommended for most AF patients. However, such therapy is associated with an increased risk of bleeding and recommendations for its use must take both benefit and risk into account.

Anticoagulant therapy for the prevention of embolic events in patients with AF will be reviewed here. Other related topics include:

- (See "Prevention of embolization prior to and after restoration of sinus rhythm in atrial fibrillation".)
- (See "Stroke in patients with atrial fibrillation".)
- (See "Mechanisms of thrombogenesis in atrial fibrillation".)

- (See "Nonpharmacologic therapy to prevent embolization in patients with atrial fibrillation".)
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IMPACT OF ANTICOAGULATION

Many antithrombotic (anticoagulant and antiplatelet) strategies have been evaluated in clinical trials. These trials [1-7] and their meta-analyses [8-10] have demonstrated that among patients with atrial fibrillation (AF) at **moderate to high risk** of thromboembolic events (CHA_2DS_2-VASc risk stratification score ≥2), anticoagulation with warfarin significantly reduces the incidence of clinical stroke with an acceptable risk of bleeding compared with placebo (there have been no randomized trials of non-vitamin K antagonist oral anticoagulants [NOACs; also referred to as direct oral anticoagulants (DOAC)] versus placebo). The benefit-to-risk ratio from oral anticoagulation in patients at **very low risk** (CHA_2DS_2-VASc score of 0) and **low risk** (CHA_2DS_2-VASc score of 1) has not been well studied (table 1). After discussing the benefits and risks with the patient, we anticoagulate some patients with a CHA_2DS_2-VASc score of 1.

Reduction in stroke risk — Anticoagulation reduces the risk of ischemic stroke (and other embolic events) by about two-thirds irrespective of baseline risk. In one contemporary study, the annual risk of ischemic stroke in untreated patients was 0.2, 0.6, and 2.2 percent for those with CHA_2DS_2-VASc scores of 0, 1, and 2 [11].

The Stroke Prevention in Atrial Fibrillation (SPAF) trials SPAF-I, SPAF-II, and SPAF-III; Copenhagen AFASAK; Boston Area Anticoagulation Trial for Atrial Fibrillation (BAATAF); Stroke Prevention In Nonrheumatic Atrial Fibrillation Trial (SPINAF); and Canadian Atrial Fibrillation Anticoagulation Trials (CAFA) randomly assigned more than 4000 patients with nonvalvular AF to warfarin, placebo, or aspirin and demonstrated that anticoagulation with adjusted-dose warfarin significantly reduces clinical stroke risk when compared with placebo (figure 1) [1-6]. Overall, adjusted-dose warfarin reduces the risk of stroke by two-thirds compared with no anticoagulant therapy, with the expected degree of absolute benefit dependent on baseline risk (table 2) [7,8,12].

The warfarin versus placebo or aspirin trials were conducted in the early 1990s, raising concerns that the findings may not be able to be applied to current practice [13-15]. In an observational study (ATRIA), patients in a community-based, clinical practice cohort who were taking warfarin had lower risks in all CHADS2 risk score (table 1) groups (range 0.25 to 4.60 percent per year) [14]. Studies evaluating more contemporary data have found that the absolute risk of stroke in untreated patients has fallen from about 8 to 4 or 5 percent per year, but the relative risk reduction attributable to antithrombotic therapy is in the same range as earlier studies [16,17]. We believe a two-thirds risk reduction at this lower absolute risk is clinically important. (See "Atrial fibrillation: Risk of embolization", section on 'Epidemiology'.)

In addition to the lowering of stroke risk, there is evidence that warfarin, compared with no anticoagulant therapy, leads to less severe stroke episodes and lower 30-day stroke mortality

[8,18].

Increase in bleeding risk — The major safety concern with the use of all antithrombotic agents is the increased risk of bleeding, especially major bleeding, which includes events that require hospitalization, transfusion, surgery, or involves particularly sensitive anatomic locations. Intracranial hemorrhage (ICH) is the most serious bleeding complication since the likelihood of mortality or subsequent major disability is substantially higher than bleeding at other sites [19]. In most contemporary studies, this risk is about 0.2 to 0.4 percent per year, or perhaps slightly higher. While this risk is not trivial, it is substantially lower than the risk of ischemic stroke in the vast majority of AF patients with CHA_2DS_2-VASc >=2 who are not anticoagulated. (See "Risks and prevention of bleeding with oral anticoagulants".)

Overanticoagulation with warfarin (as defined as an international normalized ratio greater than 3), prior stroke, and increasing patient age are three of the most important predictors of major bleeding, including ICH [13,20-22]. The risk of bleeding in contemporary practice was evaluated in a cohort of over 16,000 patients who received a diagnosis of AF between 2005 and 2010. The incidence of major bleeding with current, recent, past, or no warfarin exposure was 3.8, 4.5, 2.7, and 2.9 per 100 patient-years, respectively [17]. However, major bleeding was the sum of ICH, extracranial bleeding, and gastrointestinal bleeding. We think that most patients would want to balance the risk of reduction in ischemic stroke with the increase in ICH, not with a gastrointestinal bleed or other less serious bleeding. Thus, in this study and others, the annual risk of ICH in patients with AF who are not anticoagulated is estimated to be 0.2 percent; that risk approximately doubles with anticoagulation with warfarin [14,17]. Most studies have shown that the risk of ICH with NOACs (both direct thrombin and factor Xa inhibitors) may be less than half of that with warfarin. (See "Risks and prevention of bleeding with oral anticoagulants", section on 'Risk factors related to the anticoagulant'.)

ASSESSING INDIVIDUAL PATIENT RISK

Although tools (eg, risk scores for assessing the benefit from stroke reduction or the increase in bleeding risk with anticoagulation) are available, these instruments do not have a high predictive ability. This is likely due to at least two reasons: The patient risk factors entered into the tools are not equivalent in terms of the event rate associated with them AND the risk associated with many of the risk factors represents a range. For example, in the CHA_2DS_2-VASc risk model (table 1), age 65 to 74 years is one risk factor. However, the risk of a 65-year-old man is lower than that for a 74-year-old, perhaps by a significant amount. The same logic applies to any bleeding risk score. (See 'Estimating bleeding risk' below.)

It is possible that there are other important factors that predict risk not taken into account in the risk models. One such factor might be the duration or frequency of episodes of paroxysmal AF. (See "Atrial fibrillation: Risk of embolization", section on 'Duration and frequency in paroxysmal AF'.)

Estimating embolic risk — Embolic risk in an individual patient is estimated using tools that are imperfect, as discussed directly above. However, we believe the current preferred tool is the CHA_2DS_2-VASc risk model (calculator 1). With this risk model, the individual patient will have a score of 0, 1, or ≥2. (See "Atrial fibrillation: Risk of embolization", section on 'Our approach to risk estimation'.)

Each CHA_2DS_2-VASc score (eg 0, 1, or ≥2) represents a range of risk (table 1), with a mean rate (of stroke) of 0.2, 0.6, and 2.2 percent per year for CHA_2DS_2-VASc scores of 0, 1, and 2. However, the stroke rate can vary with study setting (eg, community versus hospitalized), population studied, etc [23], as well as appropriate methodology [24].

A few studies have examined ischemic stroke rates with a single risk factor (ie, CHA_2DS_2-VASc=1 in males, 2 in females). One study suggested that these patients have an ischemic stroke rate <1 percent per year, which was lower than those previously reported; however, this study excluded patients that had ever used oral anticoagulation; thus, rates may be biased towards low risk [25]. Another study reported that the ischemic stroke rate with a single risk factor was approximately 2.5 to 2.7 percent per year if untreated, with the highest risks evident for age 65 to 74 and diabetes [26]. The Danish nationwide cohort study found ischemic stroke rates with a single stroke risk factor being approximately 1.5 percent per year; of note, mortality was high in such patients, and both stroke and mortality were lowered by use of oral anticoagulation [27]. A net clinical benefit (NCB) analysis in patients with one stroke risk factor clearly shows a positive NCB for warfarin compared to no treatment, or warfarin compared to aspirin [27]. Similar conclusions were reported from the Loire Valley Atrial Fibrillation project, showing that even one non-gender-related stroke risk factor confers a significant risk of stroke and death, with a positive net clinical benefit (NCB) for oral anticoagulation compared with aspirin or no antithrombotic treatment [28,29]. Aspirin use conferred a negative NCB compared with no treatment.

Estimating bleeding risk — Tools to assess bleeding risk in patients taking oral anticoagulants, including the HAS-BLED bleeding risk score (table 3), lead to imprecise estimates in the individual patient. (See "Atrial fibrillation: Risk of embolization", section on 'Options for estimating risk in the individual patient' and "Risks and prevention of bleeding with oral anticoagulants", section on 'Bleeding risk scores' and "Management of warfarin-associated bleeding or supratherapeutic INR", section on 'Mitigating bleeding risk'.)

One problem with the bleeding risk scores is that they were developed from studies that included bleeds of differing severity. While any bleed can lead to death or severe disability, they usually do not. The major exception to this is intracranial hemorrhage (ICH). For the purposes of estimating bleeding risk, we think that most patients care deeply about ICH risk and to a lesser extent about epistaxis or gastrointestinal bleeding requiring hospitalization and possibly transfusion. The former (ICH) can be equated in severity to an ischemic stroke while the latter cannot. (See "Risks and prevention of bleeding with oral anticoagulants", section on 'Intracranial'.)

Multiple observational studies and randomized trials report the risk of ICH attributable to anticoagulant therapy with warfarin to be in the range of 0.2 to 0.4 percent per year. (See 'Increase in bleeding risk' above.) However, for patients with the following clinical problems, the risk is significantly higher:

- Thrombocytopenia or known coagulation defect associated with bleeding
- Active bleeding or recent surgery with a concern for ongoing bleeding
- Prior severe bleeding (including ICH) while on an oral anticoagulant
- Suspected aortic dissection
- Malignant hypertension
- Combined use of anticoagulant and antiplatelet agents

OUR APPROACH TO ANTICOAGULATION

The following questions should be answered sequentially in the process of choosing anticoagulant therapy for an atrial fibrillation (AF) patient (algorithm 1) :

- Should the patient be anticoagulated?
- If yes, which anticoagulant will be used?
- How should the oral anticoagulants be initiated?

Decide on anticoagulation — As discussed directly above, anticoagulant therapy lowers the risk of clinical embolization in all patients with AF, but its use is associated with an increased risk of bleeding. As the benefit generally outweighs the risk, we recommend oral anticoagulant therapy for all but the lowest embolization-risk patients. The benefits and risks of anticoagulation must be carefully discussed with each patient. In order for this discussion to take place, the clinician needs to understand the process of assessing risk, which is discussed directly above. For patients with a CHA_2DS_2-VASc score of 1 and a few patients with a score of 0 (calculator 1), **clinical judgment** is needed when helping the patient decide. (See 'Assessing individual patient risk' above.)

Possible contraindications to anticoagulation are presented in a table (table 4).

CHA2DS2-VASc score greater than or equal to 2 — For non-valvular AF patients with a CHA_2DS_2-VASc score ≥2 (calculator 1), we make a strong recommendation for oral anticoagulation. All studies have concluded that the benefit from anticoagulation significantly exceeds the risks for almost all AF patients with a CHA_2DS_2-VASc score ≥2 [11,13,30,31].

As an example, the ATRIA study evaluated the net clinical benefit (NCB) of warfarin in 13,559 patients with nonvalvular AF identified from an outpatient database in 1996 and 1997 [13]. NCB was defined as the difference between annualized rate of thromboembolic events prevented by warfarin, minus the annualized rate of intracranial hemorrhage (ICH) induced by warfarin, multiplied by a weighting factor. In the base case model, ICH was weighted as 1.5 times the impact

of ischemic stroke, reflecting relative case-fatality rates. Outcomes were evaluated in the warfarin and no-warfarin groups (approximately 50 percent of the latter were on aspirin) over a median follow-up of six years. The NCB became significant at a $CHADS_2$ score of 2 (one event prevented per 100 patient-years) and progressively increased at higher $CHADS_2$ scores (2.2 events prevented per 100 patient-years at a $CHADS_2$ score of 4 to 6). This relationship reflects the much greater absolute reduction in embolic risk compared to increase in ICH risk with higher $CHADS_2$ scores.

CHA2DS2-VASc score of 1 — For patients with a CHA_2DS_2-VASc score of 1 (calculator 1), our authors and section editors have differing approaches, with some recommending no antithrombotic therapy, some recommending oral anticoagulant therapy, and some recommending therapy for selected patients. The particular risk factor present may influence decision making. In particular, older age is the most significant risk factor in these considerations. **Clinical judgment** will play an important role in helping these patients choose between anticoagulation or no anticoagulation.

Our uncertainty regarding the optimal approach in these patients is the result of at least two problems: Few such patients have been enrolled in clinical trials, and the risk of embolization (table 1) attributable to the individual risk factors (that might lead to a score of 1) is not equal. Female sex and vascular disease carry a lower risk than diabetes, hypertension, or age 65 to 74 years. Many of our experts do not anticoagulate women with no other risk factors. The issue of whether vascular disease is an independent predictor of embolic risk is debated. (See "Atrial fibrillation: Risk of embolization", section on 'Clinical predictors'.)

CHA2DS2-VASc score of 0 — For patients with a CHA_2DS_2-VASc score of 0 (calculator 1), we suggest no oral anticoagulation. However, similar to patients with a CHA_2DS_2-VASc score of 1, **clinical judgment** will play an important role in decision making.

Select an anticoagulant — We choose the non-vitamin K antagonist oral anticoagulants (NOAC, also referred to as direct oral anticoagulants, or DOAC) (eg, dabigatran, rivaroxaban, apixaban, or edoxaban) rather than warfarin for most patients in whom oral anticoagulant therapy is chosen. However, without blinded head-to-head trial comparisons between these newer agents, it is difficult to assert that any of the NOAC agents is clearly superior. We suggest that each practitioner become familiar with and comfortable using at least two NOAC agents. (See "Direct oral anticoagulants and parenteral direct thrombin inhibitors: Dosing and adverse effects".)

The following are situations in which it is reasonable or even necessary to prefer warfarin instead of the NOAC agents:

- Patients already on warfarin who are comfortable with periodic international normalized ratio (INR) measurement and whose INR has been well controlled with an annual time in the therapeutic range of greater than 65 percent. We discuss the option of NOAC with these patients.

- Patients with mechanical heart valves, those with moderate or severe mitral stenosis of any origin, or those with other valvular lesions associated with moderate to severe heart failure that might lead to valve replacement in the near future. These patients should not receive NOAC agents. (See 'Patients with valvular heart disease' below.)

- Patients who are not likely to comply with the twice daily dosing of dabigatran or apixaban and who are unable to take rivaroxaban or edoxaban.

- Patients for whom the NOAC agents will lead to an unacceptable increase in cost.

- Patients with chronic severe kidney disease whose estimated glomerular filtration rate is less than 30 mL/min. However, apixaban is approved for use in the United States for patients with end stage renal disease. (See "Management of thromboembolic risk in patients with atrial fibrillation and chronic kidney disease".)

- Patients for whom the NOAC agents are contraindicated, including those on enzyme-inducing antiepileptic drugs (eg, phenytoin) and patients with human immunodeficiency virus infection (HIV) on protease inhibitor-based antiretroviral therapy.

For those who are candidates, anticoagulation with each of these NOACs (dabigatran, rivaroxaban, apixaban, and edoxaban) led to similar or lower rates both of ischemic stroke and major bleeding compared to adjusted dose warfarin (INR of 2.0 to 3.0) in patients with nonvalvular AF in large randomized trials (table 5) [32]. Important additional advantages of the NOAC agents include convenience (no requirement for routine testing of the INR), a high relative but small absolute reduction in the risk of ICH, lack of susceptibility to dietary interactions, and markedly reduced susceptibility to drug interactions [33-36]. Disadvantages include lack of efficacy and safety data in patients with chronic severe kidney disease, lack of easily available monitoring of blood levels and compliance, higher cost, and the potential that unanticipated side effects will subsequently become evident. (See 'Chronic kidney disease' below.)

At least three meta-analyses have pooled the results from the RE-LY (dabigatran) [33,37], ARISTOTLE (apixaban) [35], and ROCKET AF (rivaroxaban) [34] trials and reached similar conclusions [38-40]. The NOAC agents (compared to warfarin) are associated with the following:

- A significant reduction of stroke/systemic embolism (odds ratio [OR] 0.85, 95% confidence interval [CI] 0.74-0.99; absolute risk reduction, 0.7 percent) and major bleeding (OR 0.86, 95% CI 0.75-0.99; absolute risk reduction 0.8 percent) [40].

- A significant and marked relative reduction in hemorrhagic stroke (relative risk [RR] 0.48, 95% CI 0.36-0.62) and a significant reduction in all-cause mortality (RR 0.88, 95% CI 0.82-0.96) [39].

- In these meta-analyses, there was a trend toward reduced major bleeding with the NOAC agents (relative risk 0.86, 95% CI 0.72-1.02 and 0.80, 95% CI 0.63-1.01).

Additional meta-analyses, which included the results from ENGAGE AF-TIMI 48 trial (edoxaban), came to similar conclusions [32,41]. A 2014 Cochrane review compared the factor Xa inhibitors (apixaban, betrixaban, darexaban, edoxaban, idraparinux, and rivaroxaban) to warfarin in patients with AF and found a lower rate of stroke and systemic embolic events with the former (OR 0.81, 95% CI 0.72-0.91; absolute rates 2.5 versus 3.2 patients, respectively), as well a lower rate of death and ICH [41]. A second 2014 Cochrane review evaluated studies that compared direct thrombin inhibitors to warfarin and found no significant difference in the odds of vascular death and ischemic events [42]. Fatal and non-fatal major bleeding events, including hemorrhagic strokes, were less frequent with these agents (odds ratio 0.87, 95% CI 0.78-0.97).

These meta-analyses support the broad concept that NOAC agents (direct thrombin and factor Xa inhibitors) are preferable to warfarin in many cases. They do not directly compare the relative advantages and disadvantages of each agent nor do they demonstrate that the different agents are equivalent in terms of safety and efficacy.

In a 2013 meta-analysis of the RE-LY, ROCKET AF, ARISTOTLE, and ENGAGE AF-TIMI 48 randomized trials (table 5), the NOAC agents had a lower rate of hemorrhagic stroke (RR 0.49, 95% CI 0.38-0.64) [32]. Aggregate ICH (including primarily subdural hemorrhages as well as hemorrhagic stroke) was similarly reduced (RR 0.48, 95% CI 0.39-0.59). This is a crucially important finding since ICH is often fatal.

Observational studies have come to similar conclusions as the randomized trials. In 2014, the United States Food and Drug Administration released a preliminary report of its study of more than 134,000 patients over the age of 65 years treated with dabigatran [43]. Findings were similar to the large randomized trial (RE-LY) with the exception of a comparable risk of myocardial infarction and a higher risk of gastrointestinal bleeding (adjusted hazard ratio 1.28, 95% CI 1.14-1.44).

Further information on the use of these agents, including drug interactions (table 6A-C), dosing in patients with chronic renal insufficiency, and the need to take rivaroxaban with food, is discussed separately. (See "Direct oral anticoagulants and parenteral direct thrombin inhibitors: Dosing and adverse effects".)

Initiate anticoagulant — Protocols for initiating warfarin are available. All patients should have an INR measured before starting therapy. (See "Warfarin and other VKAs: Dosing and adverse effects", section on 'Warfarin administration' and 'Dosing of warfarin' below.)

For patients prescribed one of the NOACs, we suggest that clinicians review dosing recommendations made by regulatory agencies and available in reputable drug information compendia such as Lexi-Comp. Additional comments are made below. (See 'Dosing of non-vitamin K antagonist oral anticoagulants' below.) Additional information on the use of these drugs is available in the 2015 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist anticoagulants in patients with nonvalvular AF [44].

Increasing anticoagulant use — Evidence suggests that despite many years of demonstrated efficacy, many AF patients who meet criteria for anticoagulant therapy are not treated. Patient and/or health care provider factors may play a role. Rates of compliance with treatment recommendations as low as 50 percent have been reported and the problem appears more substantial in middle- and low-income communities/geographies [45,46]. Small studies of the role of educational intervention in stroke prevention have not found strong evidence in support of such an approach [47-49].

The IMPACT-AF trial randomly assigned 2281 patients in five middle-income countries to a customized, multifaceted, and multilevel education intervention on the use of oral anticoagulation or usual care. The intervention included education, regular monitoring, and feedback; and both patients and their health care providers were targeted [50]. Approximately 78 percent of patients were receiving a vitamin K antagonist. At a median follow-up of 12 months, oral anticoagulant use increased in the intervention and control groups (68 percent at baseline to 80 percent and 64 to 67 percent, respectively). The absolute difference in the change between groups was 9.1 percent (95% CI 3.8-14.4). There was a reduction in the secondary outcome of stroke in the intervention group (hazard ratio 0.48, 95% CI 0.23-0.99).

POTENTIAL ALTERNATIVES TO ANTICOAGULANT MONOTHERAPY

Anticoagulant monotherapy lowers the risk of thromboembolism significantly compared to aspirin and other combinations of antithrombotic therapy that utilize aspirin. With the availability of the non-vitamin K antagonist oral anticoagulant (NOAC) agents, we do not recommend aspirin as preventative therapy for preventing thromboembolic events in patients with atrial fibrillation (AF).

Aspirin monotherapy — The evidence does not support the use of aspirin as monotherapy for the prevention of thromboembolic events in patients with AF. The issue of whether aspirin could be a reasonable antithrombotic monotherapy in very low-risk patients (CHADS2 = 0) has not been well addressed, as the individual trials enrolled very few such patients [8,10,12]. A 2007 meta-analysis found that aspirin, compared to placebo or no therapy, reduced the risk of stroke by about 20 percent, although this effect was not statistically significant (relative risk reduction 19 percent; 95% CI -1.0 to 35.0) [8]. Further, aspirin had little effect on reducing the risk of disabling stroke.

Additional evidence questioning the benefit from aspirin comes from randomized trials that have shown that it is consistently and substantially less effective in reducing thromboembolic risk **compared with** warfarin in all AF patients with a CHADS2 score ≥1 (table 2) [3,8,9,12]. The magnitude of the difference was illustrated in an individual patient meta-analysis of six prevention trials [9]. Patients treated with warfarin were significantly less likely to experience an ischemic stroke (2.0 versus 4.3 per 100 patient-years, hazard ratio 0.55, 95% CI 0.45-0.71). In this meta-analysis, the absolute rate increase of major bleeding with warfarin compared with aspirin was 0.9 events per 100 patient-years (2.2 versus 1.3 events per 100 patient-years) [9]. The increase in risk,

particularly for intracranial hemorrhage, occurs principally in patients with an international normalized ratio (INR) above 3.0 and the risk is extremely high at an INR above 5.0 (figure 2) [51].

In an observational study (2014) of 49,447 matched pairs of AF patients in the National Swedish Patient register, treatment with aspirin was associated with a higher incidence of stroke and thromboembolism compared to no therapy [52].

Other antiplatelet regimens — Prior to the randomized trials of NOAC agents (see 'Select an anticoagulant' above), alternatives to warfarin (or aspirin) monotherapy using various antiplatelet regimens were studied, including low-dose warfarin plus aspirin, and aspirin plus clopidogrel. We prefer the NOAC agents to each of these:

- Aspirin **plus** clopidogrel – Two large randomized trials have investigated the safety and efficacy of dual antiplatelet therapy in patients with AF. ACTIVE W compared clopidogrel plus aspirin to warfarin and ACTIVE A compared clopidogrel plus aspirin to aspirin alone in patients who were not candidates for anticoagulation with a vitamin K antagonist. All of the patients in the two trials had AF and one or more risk factors for stroke (table 7). The primary end point in both trials was a composite outcome (the first occurrence of stroke, systemic [non-central nervous system] embolization, myocardial infarction, or vascular death).

  The ACTIVE W trial included 6706 patients who were randomly assigned to combined therapy with clopidogrel (75 mg/day) and aspirin (75 to 100 mg/day) or to anticoagulation with a vitamin K antagonist (target INR 2.0 to 3.0) [53]. The primary end point was a composite outcome (the first occurrence of stroke, systemic [non-central nervous system] embolization, myocardial infarction, or vascular death).The trial was stopped at an interim analysis after a median follow-up of 1.3 years because warfarin anticoagulation significantly lowered the annual rate of the primary end point compared to combined antiplatelet therapy (3.9 versus 5.6 percent, relative risk 0.69, 95% CI 0.57-0.85). There was a trend toward a lower risk of major bleeding with warfarin.

  The ACTIVE A trial included 7554 patients with AF who were not candidates for warfarin anticoagulation and were randomly assigned to combined therapy with clopidogrel (75 mg/day) and aspirin (75 to 100 mg/day) or to aspirin alone at the same dose [54]. The reasons that patients were not considered candidates for warfarin included the physician's judgment that such treatment was inappropriate (50 percent), a specific risk for bleeding (23 percent), and strong patient preference (26 percent). Patients were excluded from participation in ACTIVE A if they had documented peptic ulcer disease in the previous six months, significant thrombocytopenia, prior intracranial hemorrhage, or ongoing alcohol abuse. The primary end point, as in ACTIVE W, was the first occurrence of stroke, systemic (non-central nervous system) embolization, myocardial infarction, or vascular death. After a median follow-up period of 3.6 years, patients treated with clopidogrel plus aspirin had a significantly lower annual rate of the primary combined end point (6.8 versus 7.8 percent, relative risk [RR] 0.89, 95% CI

0.81-0.98), which was primarily driven by a reduction in stroke (2.4 versus 3.3 percent, RR 0.72, 95% CI 0.62-0.83). On the other hand, dual antiplatelet therapy had a significantly increased incidence of major bleeding (2.0 versus 1.3 percent per year, RR 1.57, 95% CI 1.29-1.92).

The net clinical benefit of adding clopidogrel to aspirin (compared to aspirin monotherapy) was assessed in an analysis of data from the two ACTIVE trials [55]. There was a small non-significant benefit, defined as ischemic stroke equivalents prevented, to combination therapy (0.57 events per 100 patient-years of treatment; 95% CI -0.12-1.24).

Dual antiplatelet therapy may be a reasonable alternative to therapy with aspirin alone in the occasional high-risk patient with AF who **CANNOT** be treated with anticoagulation [56]. With the availability of the NOAC agents, this situation should be extremely uncommon. It should be kept in mind that dual antiplatelet therapy and oral anticoagulation have similar bleeding risks. Thus, a patient who would not be a candidate for oral anticoagulation because of bleeding risk is also not a candidate for dual antiplatelet therapy.

- Aspirin **plus low-dose** warfarin – In contrast to adjusted-dose warfarin, low-dose warfarin (1.25 mg/day or target INR between 1.2 and 1.5) in combination with aspirin (300 to 325 mg/day) should **not** be used to reduce stroke risk in patients with non-valvular AF [12,57,58]. In the SPAF-III trial of 1044 patients with AF who were at high risk for embolism, low-dose warfarin plus aspirin had a much higher rate of morbidity and mortality than full anticoagulation/adjusted-dose warfarin (figure 3A-B) [57].

- Aspirin **plus full-dose** warfarin – The issue of whether combination of aspirin plus full dose warfarin might have greater efficacy than warfarin alone has not been well studied. In a post-hoc analysis of the SPORTIF trials, which included a high percentage of patients with cardiovascular disease or at high risk, combination therapy with warfarin (or the factor Xa inhibitor, ximelagatran) plus aspirin, in comparison to warfarin alone, did not reduce the rate of stroke or systemic embolism [59]. The potential use of aspirin for indications other than AF is discussed below. (See 'Long-term antiplatelet therapy' below.)

CLINICAL USE OF ANTICOAGULANTS

Initiation of therapy — For most patients in whom anticoagulant therapy will be started, we do not recommend bridging with an intravenous heparin, particularly if a non-vitamin K oral anticoagulant (NOAC; also referred to as direct oral anticoagulants [DOAC]) is used.

The choice of whether to start oral anticoagulant alone or in combination with unfractionated heparin or low-molecular-weight heparin (ie, bridging) is based on a comparison of the risk of a thrombus developing within the next several days compared with the risk of bleeding complications. (See "Heparin and LMW heparin: Dosing and adverse effects".)

In patients with atrial fibrillation (AF) **without a prior history of thromboembolism**, the risk of a thromboembolic event during the several days typically required to achieve therapeutic anticoagulation with warfarin is very low. Thus, it is reasonable for outpatients to initiate warfarin without bridging. For patients deemed to be at high risk of thromboembolism (eg, **prior** cerebrovascular event/transient ischemic attack or intracardiac thrombus, mechanical heart valve, or moderate/severe mitral stenosis) and low risk of intracranial hemorrhage, initiation of warfarin with a heparin bridging regimen is reasonable. This approach is in general agreement with the 2012 American College of Chest Physicians guidelines [60]. However, there are few data from randomized trials addressing such patients [61]. For patients who will be started on a NOAC agent, we do not recommend heparin bridging, as the time to full anticoagulation is relatively short.

Patients with nonvalvular AF who present **with acute stroke** have a relatively high risk of recurrent embolism and/or progressive ischemia (approximately 5 percent during the first two weeks) [62,63]. Although early use of heparin reduces the rate of recurrent embolism and/or progressive ischemia in some trials, this is balanced by an increased incidence of transformation to hemorrhagic stroke, especially in patients with large strokes. The conclusion from these data are that there is no overall benefit to early heparin therapy [62,63], and we generally do not recommend heparin bridging in patients with acute stroke. Though unproven, it may be reasonable if the stroke is small and/or there is residual left atrial appendage thrombus identified on transesophageal echocardiogram (if performed). This issue is discussed elsewhere. (See "Antithrombotic treatment of acute ischemic stroke and transient ischemic attack", section on 'Anticoagulation'.)

Other issues surrounding the initiation of warfarin are found elsewhere. (See "Warfarin and other VKAs: Dosing and adverse effects", section on 'Initial dosing'.)

Dosing of warfarin — Warfarin dosing is guided by use of the international normalized ratio (INR). For patients with AF who receive warfarin, an INR between 2 and 3 is recommended [60,64]. This is based upon the increased risk of stroke observed with INR values significantly below 2 (four- to sixfold at an INR of 1.3 compared with an INR of 2 or above) and the increased risk of bleeding associated with INR above 3.0 (figure 2) [65-69]. The dosing of warfarin is discussed in detail elsewhere. (See "Warfarin and other VKAs: Dosing and adverse effects", section on 'Warfarin administration'.)

Advanced age (over 74 years) is an independent risk factor for bleeding during anticoagulation as well as a risk factor for stroke. However, we recommend an INR between 2 and 3 for these patients as well.

Dosing of non-vitamin K antagonist oral anticoagulants — The principal discussion of the dosing of the NOAC agents (dabigatran, apixaban, rivaroxaban, and edoxaban) is found elsewhere. (See "Direct oral anticoagulants and parenteral direct thrombin inhibitors: Dosing and adverse effects".)

For patients prescribed a NOAC, we suggest that clinicians review dosing recommendations made by regulatory agencies and available in reputable drug information compendia such as Lexicomp.

Dosing recommendations for these drugs are largely derived from the doses tested in the randomized clinical trials (table 5) [33-35,70-72]. The following specific points apply to dabigatran and edoxaban (see "Direct oral anticoagulants and parenteral direct thrombin inhibitors: Dosing and adverse effects", section on 'Direct factor Xa inhibitors' and "Direct oral anticoagulants and parenteral direct thrombin inhibitors: Dosing and adverse effects", section on 'Direct thrombin inhibitors'):

- For patients prescribed dabigatran, we suggest the 150 mg twice daily dose, as opposed to the 110 mg dose, for most patients. The 110 mg twice daily dose may be preferred in those who are particularly concerned about the risk of bleeding or in those assessed to be at increased risk of bleeding. (See 'Impact of anticoagulation' above.)

- The use of dabigatran in patients with an estimated glomerular filtration rate of less than 30 mL/min/1.73m^2 is discussed elsewhere. (See "Management of thromboembolic risk in patients with atrial fibrillation and chronic kidney disease", section on 'Summary and recommendations'.)

- Edoxaban should be prescribed at 60 mg once daily in patients with an estimated glomerular filtration rate of 50 to 95 mL/min. It should not be used in those with an estimated glomerular filtration rate of greater than 95 mL/min, as estimated by the Cockcroft-Gault equation due to a higher rate of ischemic stroke in this group. For patients with an estimated glomerular filtration rate of 30 to 50 mL/min, the dose is 30 mg once daily.

Temporary interruption of anticoagulation — Temporary interruption of oral anticoagulation for reasons of bleeding or urgent/elective surgery/invasive procedure results in an increased risk of thromboembolism after the period of effective anticoagulation has ended [73]. The optimal approach to such patients is unclear and likely depends on issues such as baseline thromboembolic risk, duration of anticoagulant, and bleeding risk. These issues are discussed in detail elsewhere. (See "Perioperative management of patients receiving anticoagulants" and "Management of anticoagulants in patients undergoing endoscopic procedures" and "Use of anticoagulants during pregnancy and postpartum" and "Management of warfarin-associated bleeding or supratherapeutic INR", section on 'Urgent surgery/procedure'.)

The discussion of the management of anticoagulant therapy in the patient undergoing percutaneous coronary intervention is found elsewhere [74,75]. (See "Periprocedural management of antithrombotic therapy in patients receiving long-term oral anticoagulation and undergoing percutaneous coronary intervention", section on 'Elective patients'.)

Reversal of anticoagulant effect — The reversal of the anticoagulant effect of warfarin and NOAC agents is discussed separately. (See "Management of warfarin-associated bleeding or

supratherapeutic INR" and "Management of bleeding in patients receiving direct oral anticoagulants", section on 'Anticoagulant reversal'.)

Transition from NOAC to warfarin — Some patients may need to be switched from a NOAC agent to warfarin or between NOAC agents for reasons such as cost, availability, or intolerance. The United States Food and Drug Administration has required the manufacturers of apixaban, rivaroxaban, dabigatran, and edoxaban to include information about transitioning patients to warfarin. As these NOAC agents have a relatively short period of clinical efficacy compared to warfarin, there is a concern that patients might not be adequately anticoagulated unless there is a period of drug overlap. This concern was supported by the observation of an increased risk of stroke in the ARISTOTLE and ROCKET AF trials when patients were transitioned from apixaban and rivaroxaban, respectively, to warfarin at the end of the trials [76].

While there are no data to inform us as to the optimal method of transition, we believe that consideration should be given to co-administration of each of the NOAC agents with warfarin for at least two days prior to stopping the NOAC agents. In some cases, consideration can also be given to discontinuing the NOAC and starting a parenteral anticoagulant and warfarin at the time the next dose of a newer agent would have been taken; the parenteral anticoagulant can be discontinued when the INR reaches an acceptable range.

Practitioners should also be aware that the NOAC agents can alter the INR, limiting the usefulness of initial INR measurements during overlap for determining the maintenance dose of warfarin and causing uncertainty as to when the patient is properly anticoagulated with warfarin. Licensing information available from the European Medicines Agency includes the following text regarding apixaban: After two days of co-administration of apixaban with warfarin therapy, obtain an INR prior to the next scheduled dose of apixaban. Continue co-administration of apixaban and warfarin therapy until the INR is ≥2.0 [77]. Specific instructions for transition from each NOAC to warfarin are provided in the individual drug monographs included within UpToDate.

Transition from edoxaban was evaluated in the ENGAGE AF-TIMI 48 trial [78]. (See 'Dosing of non-vitamin K antagonist oral anticoagulants' above.) Patients in the edoxaban (60 or 30 mg) and warfarin arms were transitioned to long-term warfarin or NOAC agent. The end-of-trial transition plan included four components: selection of the long-term oral anticoagulant, a 14-day transition kit of modified-dose edoxaban, early and frequent INR testing, and a warfarin titration algorithm. The transition kit was continued until the INR was ≥2 or until day 14. With this protocol, there was no difference in the rate of stroke or major bleeding among the three groups. This protocol may be a model for transitioning patients taking dabigatran, apixaban, or rivaroxaban.

Transition to NOAC from warfarin — There have been no studies that have evaluated the optimal method of switching patients from warfarin to either apixaban or dabigatran. Until such studies are performed, we suggest following instructions contained in the approved prescribing information for each of these anticoagulants. Dabigatran or apixaban may be started after warfarin

discontinuation when the INR is <2.0. Specific instructions for transition to each NOAC are provided in the individual drug monographs included within UpToDate.

The issue of the optimal method of switching patients from warfarin to rivaroxaban was addressed in a prespecified subgroup analysis of ROCKET AF [79]. Approximately 55 percent of patients were taking warfarin for at least six weeks at the time of randomization and of these about 48 percent had an INR of 2.0 to 3.0. The approach to transitioning patients from warfarin to rivaroxaban in the protocol required that rivaroxaban be started only when the INR was <3.0. Among those assigned to rivaroxaban, there was no significant difference in the primary efficacy and safety outcomes between those who were warfarin “naïve” and those who were taking warfarin. Based on these results, we suggest starting rivaroxaban (and stopping warfarin) when the INR is <3.0.

Transition from one NOAC to another — We suggest following instructions contained in the approved prescribing information for each of these anticoagulants. For example, United States labeling (6/16/2015) states that when transitioning from apixaban (Eliquis) to anticoagulants other than warfarin, "Discontinue ELIQUIS and begin taking the new anticoagulant other than warfarin at the usual time of the next dose of ELIQUIS" and when transitioning from another NOAC to apixaban, "Discontinue the anticoagulant other than warfarin and begin taking ELIQUIS at the usual time of the next dose of the anticoagulant other than warfarin."

Transition from parenteral anticoagulants — Recommendations for transitioning between NOACs and parenteral anticoagulants, including unfractionated heparin and low molecular weight heparin, are available in the individual drug monographs for each NOAC.

Drug interactions — The individual NOACs are in varying degrees eliminated by CYP3A4 metabolism or are substrates of P-glycoprotein (P-gp) efflux pump and subject to pharmacokinetic drug interactions, although fewer in number than warfarin interactions. Drugs that inhibit CYP3A4 metabolism or P-gp efflux can increase NOAC levels (ie, greater anticoagulant effect and bleeding), whereas drugs that are inducers can decrease NOAC effect which can lead to therapeutic failure.

A detailed review of the different drug interactions can be found in tables (table 6A-C) and the Lexicomp drug interaction program within UpToDate. Additional related content is found elsewhere. (See "Direct oral anticoagulants and parenteral direct thrombin inhibitors: Dosing and adverse effects".)

SPECIFIC PATIENT GROUPS

Elderly — The risk of intracranial hemorrhage (ICH) and mechanical falls leading to subdural hematomas is increased in elderly patients taking oral anticoagulants (see "Risks and prevention of bleeding with oral anticoagulants", section on 'Age, race, and sex'). Thus, concern about

increased risks of falls with resultant intracranial hemorrhage leads to reduced use of oral anticoagulant (OAC) in elderly patients. We carefully assess the relative benefits and risks of OAC in the elderly. In many such patients, we do recommend OAC.

For most older patients, including those over the age of 75 years, we prefer non-vitamin K oral anticoagulants (NOACs) to warfarin. Since there are no head-to-head randomized trials comparing NOACs in this patient group, we do not have a preference for a specific NOAC. Dose adjustment should be made only if the patient meets relevant criteria such as weight or renal function for the NOAC. (See 'Dosing of non-vitamin K antagonist oral anticoagulants' above.)

In a Taiwanese database study of 11,064 elderly (≥90 years of age) patients with and 14,568 elderly patients without AF, the following observations were made [80]:

- Patients with AF had an increased risk of ischemic stroke (hazard ratio [HR] 1.93, 95% CI 1.74-2.14) and a similar risk of ICH (HR 0.85, 95% CI 0.66-1.09).
- Among patients with AF, warfarin use was associated with a lower stoke risk (3.83 versus 5.75; HR 0.69, 95% CI 0.439-0.96) with no difference in ICH risk.
- Compared with warfarin, NOACs were associated with a lower risk of ICH (0.42 versus 1.63 percent per year; HR 0.32, 95% CI 0.10-0.97).

Short duration atrial fibrillation — Some patients with paroxysmal atrial fibrillation (PAF) have episodes lasting as short as 30 seconds; these may be clinically significant or silent. It is not known whether such patients are at the same level of risk as those with longer or more frequent episodes at the same CHA_2DS_2-VASc risk score. This issue is discussed in detail in a 2018 scientific statement form the American Heart Association [81]. (See "Atrial fibrillation: Risk of embolization", section on 'Duration and frequency in paroxysmal AF'.)

There are no good data to establish a threshold of duration of AF for the initiation of anticoagulant therapy. Some of our experts recommend a single threshold as short as 30 seconds and others use a threshold as long as six hours. Those experts who do not routinely anticoagulate patients with shorter duration AF believe that the benefit is small and potentially outweighed by the bleeding risk.

For patients with episodes of short duration PAF, we suggest that the decision to anticoagulate be influenced by an individual's CHA_2DS_2-VASc risk score (calculator 1), similar to the broad population of patients with AF. However, for an occasional patient, the duration of AF may influence our recommendation. Our inclination to recommend anticoagulation for a patient with a CHA_2DS_2-VASc score of at least 2 increases as the duration of AF increases despite the absence of evidence to suggest that this approach leads to better outcomes. In particular, we would anticoagulate a patient with short duration AF and an embolic stroke despite the uncertainties outlined here. (See 'CHA2DS2-VASc score of 1' above.)

Chronic kidney disease — While not included in the CHA_2DS_2-VASc or CHADS2 risk prediction models, chronic kidney disease (estimated glomerular filtration rate of less than 60 mL/min/1.73m^2) is a powerful predictor of thromboembolic risk, as well as bleeding, in patients with AF. This issue is discussed in detail elsewhere. (See "Management of thromboembolic risk in patients with atrial fibrillation and chronic kidney disease".)

Acute stroke — Recommendations for the prevention of secondary embolism in AF patients with an acute stroke and for the antithrombotic management of patients with an acute embolic stroke are presented separately. AF patients for whom anticoagulant therapy is being considered and who have had an ischemic stroke within 30 days should be referred to a neurologist or other practitioner who is experienced in managing antithrombotic care in such patients. (See "Stroke in patients with atrial fibrillation".)

Rhythm control — Patients treated with pharmacologic rhythm control have rates of thromboembolic events similar to those with rate control, as was shown in the RACE and AFFIRM trials [82,83]. Anticoagulant therapy is used in a manner similar to the broad population of patients with AF. (See "Rhythm control versus rate control in atrial fibrillation", section on 'Comparative studies'.)

Hyperthyroidism — The role of anticoagulant therapy is less well defined in patients in whom the underlying disease associated with AF can be corrected, as in hyperthyroidism. (See "Epidemiology of and risk factors for atrial fibrillation" and "Cardiovascular effects of hyperthyroidism", section on 'Atrial fibrillation'.)

For patients with AF attributable to hyperthyroidism, we recommend starting antithrombotic therapy similar to the broad population. After successful treatment of the disorder, and after documentation that AF has not been present for at least three months, most of our experts suggest discontinuing anticoagulant treatment with periodic reassessment of the patient for recurrence of AF. We consider the absence of symptoms or signs of AF, one electrocardiogram demonstrating sinus rhythm, and 24-hour continuous monitoring showing no AF as adequate documentation. Some experts prefer additional documentation. However, two of our experts make a decision about continuing anticoagulant therapy based on the CHA_2DS_2-VASc score.

AF after cardiac surgery — The approach to the patient at risk of AF after cardiac surgery is discussed separately. (See "Atrial fibrillation and flutter after cardiac surgery".)

Long-term antiplatelet therapy — Combined therapy with either aspirin or aspirin plus a $P2Y_{12}$ inhibitor and an anticoagulant may be reasonable in selected AF patients with coronary artery disease, especially those with recent acute coronary syndromes or those who have received coronary stents or coronary artery bypass surgery, for whom the potential benefits may outweigh the increased risk of hemorrhage [84-86]. These issues are discussed in detail separately. (See "Coronary artery disease patients requiring combined anticoagulant and antiplatelet therapy",

section on 'Efficacy and safety studies' and "Chronic anticoagulation after acute coronary syndromes" and "Periprocedural management of antithrombotic therapy in patients receiving long-term oral anticoagulation and undergoing percutaneous coronary intervention", section on 'Elective patients'.)

The issue of whether aspirin is necessary for secondary prevention of cardiovascular disease in patients treated with anticoagulant for AF is discussed in detail elsewhere. (See "Aspirin for the secondary prevention of atherosclerotic cardiovascular disease".)

As discussed above, neither aspirin alone nor in combination with clopidogrel is as effective as warfarin in preventing stroke. However, the combination of antiplatelet with anticoagulant increases the risk of bleeding compared to either alone [87]. Thus, for patients with indications for both therapies, any potential benefit must take into account an increased risk of bleeding with concomitant antiplatelet and anticoagulant therapy. (See 'Aspirin monotherapy' above and 'Potential alternatives to anticoagulant monotherapy' above.)

The impact of antiplatelet therapy on bleeding (and efficacy) outcomes in patients taking either warfarin or dabigatran was evaluated in a post-hoc, subgroup analysis of the RE-LY trial (see 'Select an anticoagulant' above) in which about 40 percent of patients were taking concomitant aspirin or clopidogrel at some point during the study [88]. Very few patients were taking two antiplatelet agents and individuals taking prasugrel or ticagrelor were not enrolled. The following findings were noted:

- In the comparison of dabigatran 110 mg twice daily to warfarin for the prevention of ischemic events, antiplatelet therapy did not significantly change the relative risk (dabigatran non-inferior to warfarin) of the primary outcome. With regard to the outcome of major bleeding, the relative risk did not change significantly, but the crude rates of bleeding were higher in those receiving antiplatelet therapy (2.22 versus 2.81 and 3.84 versus 4.81 percent, comparing dabigatran 110 mg to warfarin in the no antiplatelet and antiplatelet groups, respectively).

- In the comparison of dabigatran 150 mg twice daily to warfarin for safety end point of ischemic events, there was a non-significant decrease in the relative superiority of dabigatran compared to warfarin with the use of antiplatelet therapy (hazard ratios [HR] 0.52, 95% CI 0.38-0.72 and 0.80, 95% CI 0.59-1.08, comparing dabigatran to warfarin in the no antiplatelet and antiplatelet groups, respectively). With regard to the outcome of major bleeding, the relative risk did not change significantly, but the crude rates of bleeding were higher in those receiving antiplatelet therapy (2.65 versus 2.81 for dabigatran 150 mg twice daily and 4.41 versus 4.81 percent for warfarin (international normalized ratio [INR] 2.0 to 3.0), comparing the no antiplatelet and antiplatelet groups, respectively).

- Concomitant use of a single antiplatelet agent significantly increased the risk of major bleeding (HR 1.60) while dual antiplatelet therapy further increased this risk (HR 2.31).

This subgroup analysis from RE-LY raises the possibility that in AF patients treated with both oral anticoagulant and antiplatelet therapy, dabigatran might be preferred to warfarin to reduce the absolute risk of major bleeding.

Anticoagulant failure — Thromboembolic events occur despite adequate anticoagulation in patients with AF. Predictors of these events include (see "Antithrombotic treatment of acute ischemic stroke and transient ischemic attack", section on 'Atrial fibrillation'):

- Transesophageal echocardiographic (TEE) evidence of dense spontaneous echo contrast and low left atrial appendage ejection velocity [89].
- TEE evidence of complex aortic plaque [89]. TEE-detected thrombi can be related to clinical risk factors [90]. (See "Pathophysiology of ischemic stroke", section on 'Stroke subtypes'.)
- The INR is often subtherapeutic in patients taking warfarin [91] and patients may be non-compliant with NOAC agents.
- Elevated D-dimer levels. In a single center, prospective, observational study of 269 patients, D-dimer levels were elevated (at least 0.5 mcg/mL) in 23 percent and elevated levels were significantly associated with a higher rate of thromboembolism (HR 15.8, 95% CI 3.33 to 75.5) [92], similar for von Willebrand factor [93]. However, we do not recommend D-dimer or von Willebrand factor testing, as it has not been shown that changing the antithrombotic regimen alters outcome in this setting.

There are no studies of the optimal anticoagulation strategy for those experiencing a thromboembolic event. For those patients with a subtherapeutic INR at the time of the event, an attempt should be made to identify the cause (compliance, drug/food interaction) and to consider switching to a NOAC if the annual time in the therapeutic range has been less than 65 percent. For those on a twice-a-day NOAC, consideration of a once-a-day NOAC should be made if non-compliance is an issue. For those on a once-a-day NOAC, consideration of a different once-daily agent may be considered. Though reasonable, at this time, none of these approaches is of proven benefit.

PATIENTS WITH VALVULAR HEART DISEASE

The approach to anticoagulation in patients with AF and one or more prosthetic valves (ie, mechanical, surgical bioprosthetic, or transcatheter bioprosthetic) or mitral stenosis is discussed separately. (See "Antithrombotic therapy for prosthetic heart valves: Indications" and "Overview of the management of mitral stenosis", section on 'Prevention of thromboembolism' and "Transcatheter aortic valve implantation: Periprocedural and postprocedural management", section on 'Antithrombotic therapy'.)

Some patients with valvular lesions (without heart failure) such as mitral valve prolapse, non-rheumatic moderate mitral regurgitation, mitral valve repair (except for the first three to six months postoperatively), or moderate or less aortic valvular conditions have been enrolled in the clinical trials of the non-vitamin K oral anticoagulants (NOACs). These trials also included a few patients (with or without heart failure) with severe native valvular conditions who were not scheduled to undergo valve replacement. We believe it is reasonable to consider using the NOACs in patients with severe valvular heart disease (excluding patients with moderate to severe mitral stenosis).

The evidence in patients with severe native valve disease is significantly less robust compared with the more typical AF population represented in the randomized trials. As an example, in the ARISTOTLE trial (table 5), which compared apixaban with warfarin, about 26 percent of the patients had a history of moderate or severe valvular heart disease or previous valve surgery [94]. While these patients had higher rates of stroke and systemic embolism than those without, the benefits of a lower rate of stroke/systemic embolism and major bleeding with apixaban (compared with warfarin) were similar to those without valvular heart disease.

There a few data with which recommendations can be made for the use of NOAC in patients with mitral rings. We think a NOAC is a reasonable choice as long as there is no significant gradient across the ring. If the gradient is increased, the patient has functional mitral stenosis.

RECOMMENDATIONS OF OTHERS

Recommendations for the use of antithrombotic agents in patients with atrial fibrillation are available from the American Heart Association/American College of Cardiology/Heart Rhythm Society, the European Society of Cardiology, and the American College of Chest Physicians [60,95-98]. In general, we agree with relevant recommendations made in these guidelines.

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Atrial fibrillation" and "Society guideline links: Arrhythmias in adults" and "Society guideline links: Anticoagulation".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, “The Basics” and “Beyond the Basics.” The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and

more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on “patient info” and the keyword(s) of interest.)

- Basics topics (see "Patient education: Atrial fibrillation (The Basics)" and "Patient education: Medicines for atrial fibrillation (The Basics)" and "Patient education: Choosing an oral medicine to prevent or treat blood clots (The Basics)" and "Patient education: Staying safe while taking an oral medicine to prevent or treat blood clots (The Basics)")

- Beyond the Basics topics (see "Patient education: Atrial fibrillation (Beyond the Basics)" and "Patient education: Warfarin (Coumadin) (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

Indications — Anticoagulant therapy is effective in reducing the risk of systemic embolization in patients with atrial fibrillation (AF). Anticoagulation with warfarin, dabigatran, rivaroxaban, apixaban, or edoxaban reduces this risk by almost 70 percent, and should be considered for most AF patients. However, the use of anticoagulant therapy is also associated with an increased risk of major bleeding. While the benefit outweighs the risk in most patients, careful consideration of the risk-to-benefit ratio is necessary in those at relatively very low (CHA_2DS_2-VASc score of 0) and low risk (CHA_2DS_2-VASc score of 1). (See 'Decide on anticoagulation' above.)

Our recommendations for anticoagulant therapy in patients with nonvalvular AF are as follows (see 'Decide on anticoagulation' above):

- For patients with a CHA_2DS_2-VASc score ≥2 (calculator 1), we recommend chronic anticoagulation (**Grade 1A**).

- For male patients with a CHA_2DS_2-VASc score of 1 (calculator 1), our authors and reviewers have differing approaches, with some recommending no antithrombotic therapy and some recommending oral anticoagulant therapy. The risk factor present may influence decision making. Age 65 to 74 years is a stronger risk factor than the other features conferring a CHA_2DS_2-VASc score of 1.

- For patients with a CHA_2DS_2-VASc of 0 (calculator 1) or 1 in females, we suggest no anticoagulant therapy (**Grade 2C**). Patients who are particularly stroke averse and who are at low bleeding risk may reasonably choose anticoagulation.

Choice of agent — For those patients who receive antithrombotic therapy, we almost always choose an oral anticoagulant rather than aspirin (or any other antiplatelet regimen). For most

patients, we have no confidence that the use of aspirin alone is associated with net clinical benefit. (See 'Decide on anticoagulation' above.)

- In patients with AF for whom anticoagulant therapy is chosen, we suggest an oral direct thrombin inhibitor or a factor Xa inhibitor rather than warfarin (**Grade 2B**). The evidence does not allow for us to prefer one of these non-vitamin K antagonist oral anticoagulant (NOAC) agents (also referred to as direct oral anticoagulants or DOAC [eg, dabigatran, rivaroxaban, apixaban, or edoxaban]) rather than warfarin for most patients in whom oral anticoagulant therapy is chosen to another. Thus, we suggest that practitioners become familiar with and comfortable using at least one NOAC agent.

  Warfarin is a reasonable choice in the following circumstances:

  - Patients already on warfarin who are comfortable with periodic international normalized ratio (INR) measurement and whose INR has been relatively easy to control, with an annual time in therapeutic range of at least 65 percent.
  - Patients who are not likely to comply with the twice daily dosing of dabigatran and apixaban, and for whom once-a-day rivaroxaban or edoxaban is not available.
  - Patients for whom the cost of the non-vitamin k oral antagonist anticoagulants is an important concern.
  - Patients with chronic severe kidney disease, whose estimated glomerular filtration rate is less than 30 mL/min/1.73m^2 (less than 25 mL/min/1.73m^2 for apixaban). (See "Management of thromboembolic risk in patients with atrial fibrillation and chronic kidney disease", section on 'Benefits and risks of oral antithrombotic therapy'.)
  - Patients for whom NOACs are contraindicated, including those on enzyme-inducing antiepileptic drugs (eg, phenytoin) and patients with human immunodeficiency virus infection (HIV) on protease inhibitor-based antiretroviral therapy.

- For the rare patient who cannot take anticoagulant therapy for reasons other than bleeding risk, we suggest aspirin 75 to 100 mg daily plus clopidogrel 75 mg daily, rather than aspirin alone (**Grade 2B**). (See 'Other antiplatelet regimens' above.)

- Dabigatran, rivaroxaban, apixaban, and edoxaban should not be used in patients with severely impaired renal function (estimated glomerular filtration rate less than 30 mL/min/1.73m^2 for dabigatran and rivaroxaban; less than 25 mL/min/1.73m^2 for apixaban). Edoxaban should also not be prescribed for patients with an estimated glomerular filtration rate of greater than 95 mL/min.

Dosing

- Our approach to starting warfarin is presented separately (see "Warfarin and other VKAs: Dosing and adverse effects", section on 'Initial dosing')

- For patients prescribed warfarin, we recommend a target INR between 2.0 and 3.0, as opposed to values below or above this range (**Grade 1B**). (See 'Dosing of warfarin' above.)

- For patients prescribed one of the NOACs, we suggest that clinicians review dosing recommendations made by regulatory agencies and available in reputable drug information compendia such as Lexi-Comp. (See 'Initiate anticoagulant' above.)

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