Atrial fibrillation: Anticoagulant therapy to prevent embolization

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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".)

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), warfarin significantly reduces the incidence of clinical stroke at an acceptable risk of bleeding compared to placebo. The benefit to risk ratio from oral anticoagulation in patients at **very low** (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 the latter.

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 SPAF-I, SPAF-II, and SPAF-III trials, and AFASAK, BAATAF, SPINAF, and 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 to placebo (figure 1) [1-6]. Overall, adjusted-dose warfarin reduces the risk of stroke by two-thirds compared to 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 to 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 "Risk of intracerebral bleeding in patients treated with 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 the non-vitamin K oral anticoagulants (NOACs; both direct thrombin and factor Xa inhibitors) may be less than half of that with warfarin. (See "Risk of intracerebral bleeding in patients treated with anticoagulants", section on 'Dabigatran, rivaroxaban, apixaban'.)

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.)

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 "Risk of intracerebral bleeding in patients treated with anticoagulants" and "Management of warfarin-associated bleeding or supratherapeutic INR", section on '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 to cannot. (See "Risk of intracerebral bleeding in patients treated with anticoagulants", section on 'Predictors of risk' and "Risk of intracerebral bleeding in patients treated with anticoagulants", section on 'ICH risk with antithrombotic therapy'.)

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 prefer one of the non-vitamin K antagonist oral anticoagulants (NOAC, sometimes also referred to as direct oral anticoagulants, or DOAC) (eg, dabigatran, rivaroxaban, apixaban, or edoxaban) to 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 one or 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 relatively easy to control with an annual time in the therapeutic range of at least 65 percent. We discuss the option of NOAC with these patients.
- Patients with prosthetic heart valves, those with rheumatic mitral valve disease, 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. (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.

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 disease, 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 (table 7). 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].

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 to** 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) [45].

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 [46].

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 8). 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) [47]. 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 [48]. 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 [49]. 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 [50]. 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 [12,51,52]. 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) [51].

- 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 [53]. 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 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 nonvalvular 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, bioprosthetic valve, or 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 [54]. However, there are few data from randomized trials addressing such patients [55]. For patients who will be started on a non-vitamin K oral anticoagulant (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) [56,57]. 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 [56,57], 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 'Parenteral 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 nonvalvular AF who receive warfarin, an INR between 2 and 3 is recommended [54,58]. 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) [59-63]. 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. This issue is discussed elsewhere. (See "Anticoagulation in older adults".)

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 one of the non-vitamin K oral anticoagulants, 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) [33-35,64-67]. 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. Where available, 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, such as patients older than 75 years. (See 'Impact of anticoagulation' above.)
- In the United States, the 110 mg capsule is not available, and a 75 mg capsule has been marketed. We suggest not using the 75 mg twice daily dose. Consideration should be given to choosing another NOAC.
- 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 [68]. 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 [69,70]. (See "Periprocedural management of antithrombotic therapy in patients receiving long-term oral anticoagulation 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 [71].

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 [72].

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 [73]. 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 [74]. (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 [75]. 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" [72].

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

SPECIFIC PATIENT GROUPS

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. (See "Atrial fibrillation: Risk of embolization", section on 'Duration and frequency in PAF'.)

Similarly, 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 as long as one hour. For patients with episodes of short duration PAF, we suggest that the decision to anticoagulate be influenced on 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.

For example, one of our authors might recommend against anticoagulation for an individual with a CHA_2DS_2-VASc score of 2 or 3 if only a single episode of AF is seen on prolonged monitoring. Conversely, 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. (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 [76,77]. 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 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. One of our experts makes 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 [78-80]. These issues are discussed in detail separately. (See "Antithrombotic therapy after coronary stenting in patients receiving long-term anticoagulation", section on 'Efficacy' and "Chronic anticoagulation after acute coronary syndromes" and "Periprocedural management of antithrombotic therapy in patients receiving long-term oral anticoagulation 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 [81]. 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 [82]. 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 and cardioembolic stroke'):

- Transesophageal echocardiographic (TEE) evidence of dense spontaneous echo contrast and low left atrial appendage ejection velocity [83].

- TEE evidence of complex aortic plaque [83]. TEE-detected thrombi can be related to clinical risk factors [84]. (See "Pathophysiology of ischemic stroke", section on 'Stroke subtypes'.)

- The INR is often subtherapeutic in patients taking warfarin [85] 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) [86], similar for von Willebrand factor [87]. 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 — Many [1-10], but not all [88], of the major clinical trials of antithrombotic therapy and subsequent meta-analyses have excluded patients with mechanical heart valves, those with rheumatic heart disease/mitral stenosis, and those with decompensated valvular heart disease who were likely to require valve replacement in the near future. Based on these studies, the non-vitamin K anticoagulants (NOACs) should not be prescribed for these patients. Anticoagulation in these patients is discussed separately. (See "Antithrombotic therapy for prosthetic heart valves: Indications" and "Medical management and indications for intervention for mitral stenosis", section on 'Prevention of thromboembolism'.)

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 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. Also, we believe it is reasonable to consider using the NOACs in patients with severe valvular heart disease (excluding patients with rheumatic mitral valvular heart disease). The evidence in patients with severe valve disease is significantly less robust compared with the more average AF population represented in the randomized trials.

As an example, in the ARISTOTLE trial (table 5), which compared apixaban to warfarin, about 26 percent of the patients had a history of moderate or severe valvular heart disease or previous valve surgery [89]. 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 to 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 [54,90-92]. 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".)

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: Anti-clotting medicines: Warfarin (Coumadin) (The Basics)" and "Patient education: Medicines for atrial fibrillation (The Basics)" and "Patient education: Anti-clotting medicines: Direct oral anticoagulants (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 nonvalvular atrial fibrillation (AF). Anticoagulation with warfarin, dabigatran, rivaroxaban, apixaban, or edoxaban reduces this risk by almost 70 percent, and should be considered for most nonvalvular 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 nonvalvular 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 non-vitamin K antagonist oral anticoagulant (NOAC) agent 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), those with prosthetic heart valves, those with rheumatic mitral valve disease, 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. 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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Topic 1031 Version 96.0

GRAPHICS

Comparison of the CHADS2 and CHA2DS2-VASc risk stratification scores for subjects with nonvalvular AF

Definition and scores for $CHADS_2$ and CHA_2DS_2-VASc	
$CHADS_2$ acronym	**Score**
Congestive HF	1
Hypertension	1
Age ≥75 years	1
Diabetes mellitus	1
Stroke/TIA/TE	2
Maximum score	6
CHA_2DS_2-VASc acronym	**Score**
Congestive HF	1
Hypertension	1
Age ≥75 years	2
Diabetes mellitus	1
Stroke/TIA/TE	2
Vascular disease (prior MI, PAD, or aortic plaque)	1
Age 65 to 74 years	1
Sex category (ie, female sex)	1
Maximum score	9

Stroke risk stratification with the $CHADS_2$ and CHA_2DS_2-VASc scores	
$CHADS_2$ acronym	**Unadjusted ischemic stroke rate (% per year)***
0	0.6%
1	3.0%
2	4.2%
3	7.1%
4	11.1%
5	12.5%
6	13.0%
CHA_2DS_2-VASc acronym	**Unadjusted ischemic stroke rate (% per year)***
0	0.2%
1	0.6%
2	2.2%
3	3.2%
4	4.8%
5	7.2%
6	9.7%
7	11.2%
8	10.8%
9	12.2%

AF: atrial fibrillation; $CHADS_2$: Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, Prior Stroke or TIA or Thromboembolism (doubled); CHA_2DS_2-VASc: Congestive heart failure, Hypertension, Age ≥75 years (doubled), Diabetes mellitus, Prior Stroke or TIA or thromboembolism (doubled), Vascular disease, Age 65-74 years, Sex category; HF: heart failure; LV: left ventricular; MI: myocardial infarction; PAD: peripheral artery disease; TE: thromboembolic; TIA: transient ischemic attack.

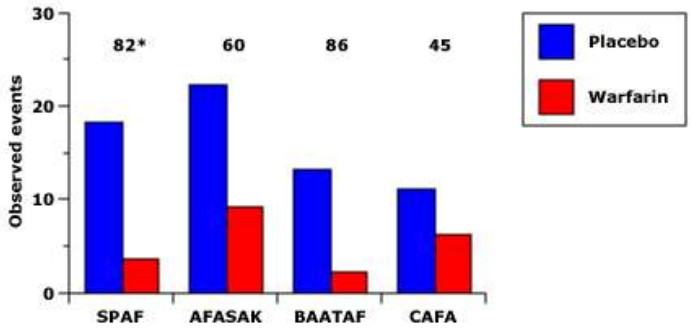
* These unadjusted (not adjusted for possible use of aspirin) stroke rates were published in 2012[1]. Actual rates of stroke in contemporary cohorts might vary from these estimates.

Reference:

1. *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. Eur Heart J 2012; 33:1500.*

Graphic 94752 Version 6.0

Benefit of warfarin in chronic atrial fibrillation



Efficacy of anticoagulation with warfarin to prevent ischemic stroke and other thromboemboli in four major studies. An intention to treat approach was used and transient ischemic attack and hemorrhage were excluded. The numbers at the top represent the risk reduction with warfarin therapy which ranged from 45 to 82 percent.

SPAF: Stroke Prevention in Atrial Fibrillation; AFASAK: Copenhagen AFASAK Study; BAATAF: Boston Area Anticoagulation Trial for Atrial Fibrillation; and CAFA: Canadian Atrial Fibrillation Anticoagulation Study.
* The data in the warfarin group in the SPAK assumes that half of the events were attributable to warfarin toxicity.

Data from Connolly SJ, Laupacis AN, Gent M, et al. J Am Coll Cardiol 1991; 18:349.

Graphic 79839 Version 2.0

Meta-analysis of randomized controlled trials of warfarin and aspirin for primary prevention of stroke in atrial fibrillation

Comparison	Stroke		Major bleeding	
	Odds ratio, 95% CI	p value	Odds ratio, 95 percent CI	p value
Conventional dose warfarin versus placebo	0.31 (0.19 to 0.50)	<0.001	1.88 (0.88 to 4.0)	0.10
Aspirin versus placebo	0.68 (0.46 to 1.02)	0.06	0.82 (0.37 to 1.78)	>0.2
Conventional dose warfarin versus aspirin	0.66 (0.45 to 0.99)	0.04	1.61 (0.75 to 3.44)	>0.2
Conventional dose warfarin versus low dose warfarin	0.52 (0.25 to 1.08)	0.08	2.21 (0.67 to 7.25)	0.19
Conventional dose warfarin versus low dose warfarin plus aspirin	0.44 (0.14 to 1.39)	0.16	1.14 (0.55 to 2.36)	>0.2
Low dose warfarin versus aspirin	1.01 (0.49 to 2.06)	>0.2	1.04 (0.43 to 2.48)	>0.2

NOTE: The data in this table cannot be directly applied to clinical practice (an individual patient) since the decision to use warfarin or aspirin is importantly related to a patient's estimated risk of embolic events.

Adapted from McNamara RL, Tamariz LJ, Segal JB, Bass EB. Ann Intern Med 2004; 139:1018.

Graphic 66736 Version 2.0

Clinical characteristics comprising the HAS-BLED bleeding risk score

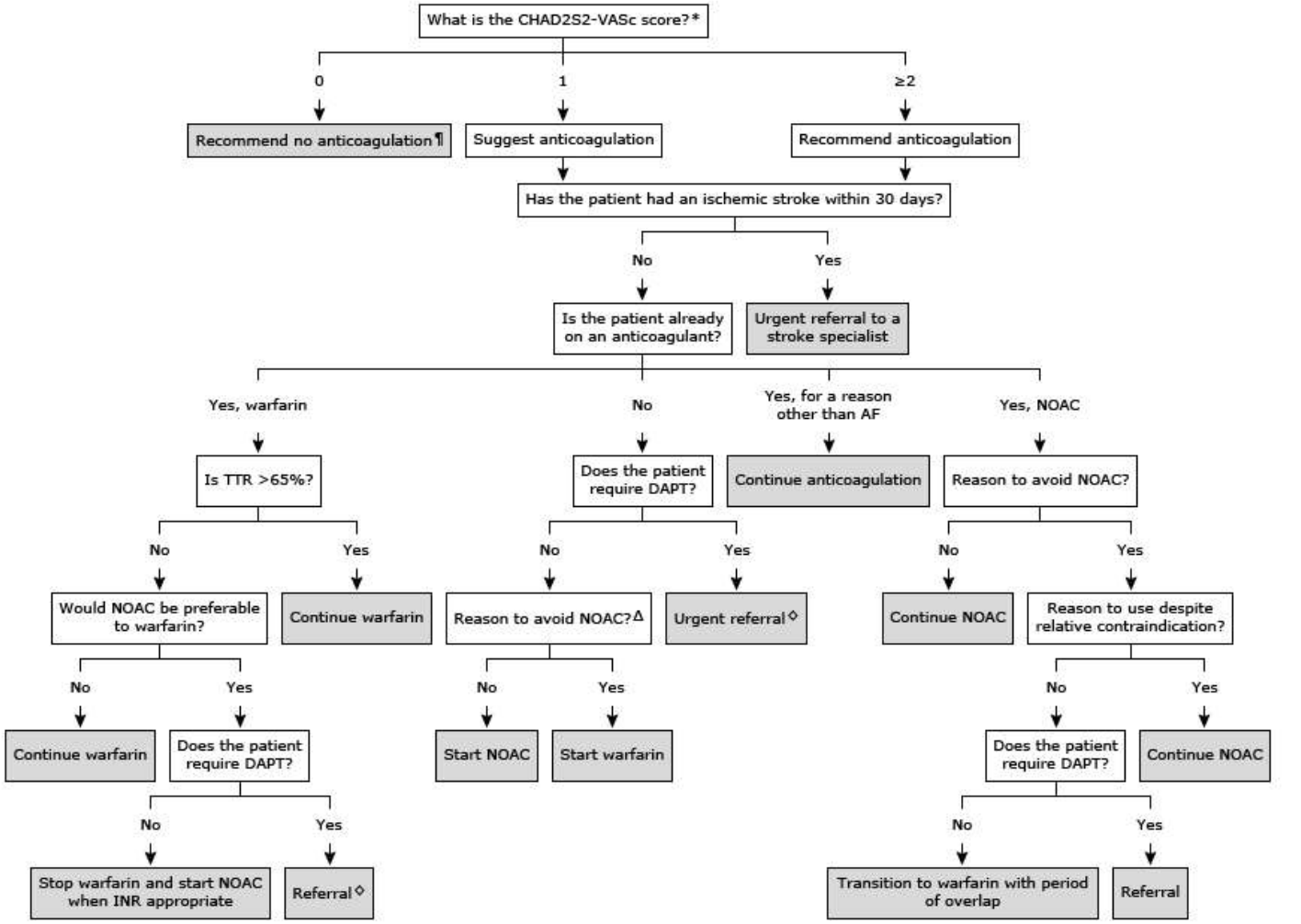
Letter	Clinical characteristic*	Points	HAS-BLED score (total points)	Bleeds per 100 patient-years¶
H	Hypertension (ie, uncontrolled blood pressure)	1	0	1.13
A	Abnormal renal and liver function (1 point each)	1 or 2	1	1.02
S	Stroke	1	2	1.88
B	Bleeding tendency or predisposition	1	3	3.74
L	Labile INRs (for patients taking warfarin)	1	4	8.70
E	Elderly (age greater than 65 years)	1	5 to 9	Insufficient data
D	Drugs (concomittant aspirin or NSAIDs) or excess alcohol use (1 point each)	1 or 2		
		Maximum 9 points		

The HAS-BLED bleeding risk score has only been validated in patients with atrial fibrillation receiving warfarin. Refer to UpToDate topics on anticoagulation in patients with atrial fibrillation and on specific anticoagulants for further information and other bleeding risk scores and their performance relative to clinical judgement.

INR: international normalized ratio; NSAIDs: nonsteroidal anti-inflammatory drugs.
*Hypertension is defined as systolic blood pressure >160 mmHg. Abnormal renal function is defined as the presence of chronic dialysis, renal transplantation, or serum creatinine ≥200 micromol/L. Abnormal liver function is defined as chronic hepatic disease (eg, cirrhosis) or biochemical evidence of significant hepatic derangement (eg, bilirubin more than two times the upper limit of normal, plus one or more of aspartate transaminase, alanine transaminase, and/or alkaline phosphatase more than three times the upper limit normal). Bleeding predisposition includes chronic bleeding disorder or previous bleeding requiring hospitalization or transfusion. Labile INRs for a patient on warfarin includes unstable INRs, excessively high INRs, or <60 percent time in therapeutic range.
¶ Based on initial validation cohort from Pisters, R. 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; 138:1093. Actual rates of bleeding in contemporary cohorts may vary from these estimates.

Graphic 75259 Version 9.0

Atrial fibrillation anticoagulation algorithm



TTR: time in therapeutic range; DAPT: dual antiplatelet therapy.

* The CHAD2S2-VASc score and estimated stroke risk based on the score are meant to provide guidance, but are not substitutes for clinical judgment.

Score 0 recommendation: For a patient with a CHA2DS2-VASc score of 0, the benefit-to-risk ratio generally does not favor anticoagulation. Nevertheless, patients who are not particularly stroke averse may reasonably choose anticoagulation.

Score 1 recommendation: The benefit-to-risk ratio varies depending on the patient's specific risk factor for thromboembolism and bleeding risk, but generally favors anticoagulation. Among those with a risk score of 1, patients between the ages of 65 and 74 years of age are at the highest risk for thromboembolism, followed by patients with heart failure, hypertension, or diabetes. Patients with vascular disease are at lower risk, and patients whose only risk factor is being female are at the lowest risk (but still at increased risk compared with an individual with no risk factors). A decision not to anticoagulant is a reasonable alternative for patients with a score of 1, particularly for patients at lower risk for thromboembolism (eg, women) or at increased risk for major bleeding.

Score 2+ recommendation: The benefit-to-risk ratio generally favors anticoagulation. The rare patient at very high risk of major bleeding, or an informed patient who is particularly averse to bleeding risk, may choose no anticoagulation.

¶ Some particularly stroke averse patients may reasonably choose anticoagulation.

Δ **Reasons to avoid NOAC:** Reasons not to use a non-vitamin K oral anticoagulant (NOAC) include (not an extensive list):

- Creatinine clearance <30 mL/min
- Significant drug interactions, such as rifampin or enzyme-inducing antiepileptic drugs (eg, carbamazepine, phenytoin, some human immunodeficiency virus therapies)
- Patient has risk factors for NOAC accumulation, such as creatinine clearance ≤80 mL/min with low body weight
- Patient belongs to a group in which the use of NOACs has not been adequately studied, such as morbid obesity, weight <60 kg, or age ≥80 years
- NOACs unavailable, not covered by the patient's insurance, or other cost concerns
- Concern about lack of a reversal agent for most of these (a reversal agent is available for dabigatran)
- Patient is pregnant or breast feeding (excretion unknown)

Choice of NOAC: Evidence does not favor one NOAC over another. The choice of NOAC will depend on cost, availability, and clinician experience with the different agents. Edoxaban and rivaroxaban are given once daily and may be preferable in patients who are unlikely to comply with twice daily dosing.

◇ Referral to a clinician experienced in counseling patients in the relative benefits and risks of anticoagulation therapy.

Graphic 106098 Version 3.0

Possible contraindications to anticoagulation

Possible contraindication	Factors to consider
Active, clinically significant bleeding	Site and degree of bleeding (eg, nosebleeds and menses generally are not a contraindication; active intracerebral bleeding is almost always an absolute contraindication); interval since bleeding stopped
Severe bleeding diathesis	Nature, severity, and reversibility of bleeding diathesis
Severe thrombocytopenia (platelet count <50,000/microL)	Absolute platelet count, platelet count trend, and platelet function (eg, some individuals with ITP and a platelet count in the range of 30,000 to 50,000 may tolerate anticoagulation if needed)
Major trauma	Site and extent of trauma, time interval since event (eg, for a patient with a mechanical heart valve it may be appropriate to anticoagulate sooner after trauma than a patient with a lesser indication)
Invasive procedure or obstetric delivery (recent, emergent, or planned)	Type of procedure and associated bleeding risk, interval between procedure and anticoagulation
Previous intracranial hemorrhage	Time interval since hemorrhage and underlying cause (eg, trauma or uncontrolled hypertension)
Intracranial or spinal tumor	Site and type of tumor, other comorbidities
Neuraxial anesthesia	Interval since spinal/epidural puncture or catheter removal, other alternatives for anesthesia. Traumatic procedures are more concerning.
Severe, uncontrolled hypertension	Absolute blood pressure and blood pressure trend

This list does not take the place of clinical judgment in deciding whether or not to administer an anticoagulant. In any patient, the risk of bleeding from an anticoagulant must be weighed against the risk of thrombosis and its consequences. The greater the thromboembolic risk, the greater the tolerance for the possibility of bleeding and for shortening the time interval between an episode of bleeding and anticoagulant initiation. Refer to UpToDate topics on the specific indication for the anticoagulant and the specific possible contraindication for discussions of these risks.

ITP: immune thrombocytopenia.

Graphic 107527 Version 2.0

Trials of warfarin versus newer anticoagulants in AF*¶

	Baseline characteristics				
	Study drug and dose	**Mean $CHADS_2$ score**	**Percent on aspirin**	**Primary outcome**	**Major bleeding definition**
RE-LY	Dabigatran 110 mg twice per day 150 mg twice per day	2.1	40	All stroke and systemic embolism	Reduction in hemoglobin of at least 2 g/dL [20 g/L] or symptomatic bleeding in critical organ
ROCKET-AF	Rivaroxaban 20 mg once per day Δ	3.5	36	All stroke and systemic embolism	Major and non-major clinically relevant bleeding
ARISTOTLE	Apixaban 5 mg twice per day ◇	2.1	31	All stroke and systemic embolism	Overt bleeding plus fall in hemoglobin of at least 2 g/dL [20 g/L] or transfusion of 2 units of packed red blood cells, occurring at a critical site, or resulting in death

		Outcome event rates (percent/yr) (new agent/warfarin)					
		Primary outcome	**Major bleeding**	**Death**	**Stroke (all)**	**Stroke (hemorrhagic)**	**Percent time in INR range**
RE-LY	110 mg	1.53/1.69 (A)	2.71/3.36 (C)	3.75/4.13	1.44/1.57	0.12/0.38 (C)	64
	150 mg	1.11/1.69 (B)	3.11/3.36	3.64/4.13	1.01/1.57 (C)	0.10/0.38 (C)	64
ROCKET-AF	As treated analysis	1.70/2.20 (A)	3.60/3.40	1.90/2.20	2.61/3.12	0.50/0.70 (C)	55
	Intention to treat analysis	2.10/2.40 (A)	---	4.50/4.90	---	---	---
ARISTOTLE		1.27/1.60 (B)	2.13/3.09 (B)	3.52/3.94 (B)	1.19/1.51	0.24/0.47 (C)	62

$CHADS_2$: estimate of stroke risk; (A): statistically significant for noninferiority; (B): statistically significant for superiority; (C): statistically significant.
* Target INR 2.0 to 3.0 in each study.
¶ Mean follow-up of approximately two years in each study.
Δ Dose of rivaroxaban adjusted to 15 mg per day for renal insufficiency (creatinine clearance 30 to 49 mL/minute [0.5 to 0.82 mL/second]).
◇ Dose of apixaban adjusted to 2.5 mg twice per day with two or more of: age ≥80 years, body weight ≤60 kg, or renal insufficiency (serum creatinine level ≥1.5 mg/dL [133 µmol/L]).

References:

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3. *Granger CB, Alexander JH, McMurray JJV, et al. Apixaban versus warfarin in patients with atrial fibrillation; N Engl J Med 2011; 365:981.*

Graphic 80932 Version 12.0

Pharmacokinetics and drug interactions of direct oral anticoagulants

Anticoagulant	Bioavailability	Metabolism and clearance*¶	Half-life	Potential for pharmacokinetic drug interactions*¶
Dabigatran (Pradaxa)	▪ 3 to 7% bioavailable ▪ Unaffected by food ▪ Capsule must be taken intact and requires gastric acidity for absorption	▪ Over 80% renally cleared ▪ P-gp substrate*	▪ 12 to 17 hours ▪ Prolonged in renal impairment and older adults	▪ P-gp inhibitors can increase dabigatran effect ▪ P-gp inducers can decrease dabigatran effect ▪ Avoidance of some combinations or dose adjustment may be needed
Apixaban (Eliquis)	▪ 50% bioavailable ▪ Unaffected by food	▪ 27% renally cleared ▪ Metabolized, primarily by CYP3A4¶ ▪ P-gp substrate*	▪ 12 hours ▪ Prolonged in older adults	▪ Strong CYP3A4 inhibitors and/or strong P-gp inhibitors can increase apixaban effect ▪ Strong CYP3A4 inducers and/or strong P-gp inducers can decrease apixaban effect ▪ Avoidance of some combinations or dose adjustment may be needed
Betrixaban (Bevyxxa)	▪ 34% bioavailable ▪ Taken with food at the same time each day. Absorption is increased if taken without food.	▪ Minimal renal clearance (5 to 7%) ▪ Undergoes minimal CYP metabolism ▪ P-gp substrate* ▪ 85% eliminated via hepatobiliary route	▪ 19 to 27 hours (effective half-life); peak-to-trough ratio is low and terminal serum half-life is 37 hours, and betrixaban may persist in the circulation for longer than predicted by the effective half-life	▪ P-gp inhibitors can increase betrixaban effect ▪ P-gp inducers may decrease betrixaban effect ▪ Avoidance of some combinations or dose adjustment may be needed
Edoxaban (Savaysa, Lixiana)	▪ 62% bioavailable ▪ Unaffected by food	▪ 50% renally cleared ▪ Reduced efficacy in patients with NVAF and CrCl >95 mL/minute ▪ Undergoes minimal CYP metabolism¶ ▪ P-gp substrate*	▪ 10 to 14 hours ▪ Prolonged in renal impairment	▪ P-gp inhibitors can increase edoxaban effect ▪ P-gp inducers can decrease edoxaban effect ▪ Avoidance of some combinations or dose adjustment may be needed
Rivaroxaban (Xarelto)	▪ 10 mg dose: • 80 to 100% bioavailable • Unaffected by food ▪ 20 mg dose: • 66% bioavailable if taken when fasting; increased if taken with food	▪ 36% renally cleared ▪ Metabolized, primarily by CYP3A4¶ ▪ P-gp substrate*	▪ 7 to 11 hours ▪ Prolonged in renal impairment and older adults	▪ Strong CYP3A4 inhibitors and/or strong P-gp inhibitors can increase rivaroxaban effect ▪ Strong CYP3A4 inducers and/or strong P-gp inducers can decrease rivaroxaban effect ▪ Avoidance of some combinations or dose adjustment may be needed

Refer to UpToDate for dosing in specific clinical settings, including nonvalvular AF, VTE treatment, and VTE prophylaxis. Data on clearance may help assess the potential for accumulation in patients with renal impairment. Data on metabolism may help assess potential drug interactions through alteration of CYP3A4 metabolism and/or P-gp-mediated drug efflux. Refer to Lexi-Interact, the drug interactions tool included with UpToDate, for specific drug interactions. Tables of P-gp inhibitors and inducers and CYP3A4 inhibitors and inducers are available separately in UpToDate.

P-gp: P-glycoprotein drug efflux pump; CYP3A4: cytochrome p450 3A4 isoform; CrCl: creatinine clearance estimated by the Cockcroft-Gault equation; AF: atrial fibrillation; VTE: venous thromboembolism, includes deep vein thrombosis and pulmonary embolism; DOAC: direct oral anticoagulant.
* Examples of P-gp inhibitors that reduce metabolism of DOACs, leading to increased DOAC levels, include clarithromycin, ombitasvir- or ritonavir-containing combinations, and verapamil. Examples of P-gp inducers that increase DOAC metabolism, leading to lower DOAC levels, include phenytoin, rifampin, and St. John's wort.

¶ Examples of strong CYP3A inhibitors that reduce metabolism of some DOACs, leading to increased DOAC levels, include clarithromycin and ombitasvir- or ritonavir-containing combinations. Examples of strong CYP3A4 inducers that increase metabolism of some DOACs, leading to lower DOAC levels, include carbamazepine, phenytoin, and rifampin.

Δ Blood levels of edoxaban were reduced and a higher rate of ischemic stroke was observed in patients with AF and CrCl >95 mL/minute who were treated with edoxaban compared with those receiving warfarin. Refer to the UpToDate topic on anticoagulation in AF for additional information.

Graphic 112756 Version 4.0

Cytochrome P450 3A4 (CYP3A4) inhibitors and inducers*

Strong inhibitors	Moderate inhibitors	Strong inducers	Moderate inducers
Atazanavir	Amiodarone¶	Carbamazepine	Bexarotene
Boceprevir	Aprepitant	Enzalutamide	Bosentan
Ceritinib	Cimetidine¶	Fosphenytoin	Dabrafenib
Clarithromycin	Conivaptan	Lumacaftor	Dexamethasone¶
Cobicistat and cobicistat containing coformulations	Crizotinib	Mitotane	Efavirenz
Darunavir	Cyclosporine¶	Phenobarbital	Eslicarbazepine
Idelalisib	Diltiazem	Phenytoin	Etravirine
Indinavir	Dronedarone	Primidone	Modafinil
Itraconazole	Erythromycin	Rifabutin	Nafcillin
Ketoconazole	Fluconazole	Rifampin (rifampicin)	St. John's wort
Lopinavir	Fosamprenavir	Rifapentine	
Mifepristone	Fosaprepitant¶		
Nefazodone	Grapefruit juice		
Nelfinavir	Imatinib		
Ombitasvir-paritaprevir-ritonavir	Isavuconazole (isavuconazonium sulfate)		
Ombitasvir-paritaprevir-ritonavir plus dasabuvir	Netupitant		
Posaconazole	Nilotinib		
Ritonavir and ritonavir containing coformulations	Ribociclib		
Saquinavir	Schisandra		
Telaprevir	Verapamil		
Telithromycin			
Voriconazole			

Data are for systemic drug forms. Degree of inhibition or induction may be altered by dose, method, and timing of administration. Specific drug interactions and management suggestions may be determined by using Lexi-Interact, the drug interactions program included with UpToDate. Refer to UpToDate topics on specific agents and indications for further details.

* The CYP3A4 inhibitors and inducers listed in this table are relevant for determining potential interactions of drugs that are CYP3A subfamily substrates.
¶ Weak effect on CYP3A4.

Graphic 76992 Version 42.0

Inhibitors and inducers of P-glycoprotein (P-gp) drug efflux pump

Inhibitors of P-gp		Inducers of P-gp
Amiodarone	Lopinavir-ritonavir	Fosphenytoin
Azithromycin (systemic)	Neratinib	Phenobarbital*
Carvedilol	Ombitasvir-paritaprevir-ritonavir (Technivie)¶	Phenytoin
Clarithromycin	Propafenone	Rifampin (rifampicin)
Cobicistat and cobicistat-containing coformulations*	Quinidine	St. John's wort
Cyclosporine (systemic)	Quinine	
Daclatasvir	Ranolazine	
Dronedarone	Ritonavir and ritonavir -containing coformulations¶	
Eliglustat	Rolapitant	
Erythromycin (systemic)	Simeprevir	
Flibanserin	Tacrolimus (systemic)*	
Glecaprevir-pibrentasvir	Tamoxifen*	
Itraconazole	Telaprevir	
Ivacaftor	Ticagrelor*	
Ketoconazole (systemic)	Velpatasvir	
Lapatinib	Vemurafenib	
Ledipasvir	Verapamil	

- Inhibitors of the P-gp drug efflux pump listed above may **increase** serum concentrations of drugs that are substrates of P-gp, whereas inducers of P-gp drug efflux may **decrease** serum concentrations of substrates of P-gp. Examples of drugs that are substrates of P-gp efflux pump include: Apixaban, cyclosporine, dabigatran, digoxin, rivaroxaban, and tacrolimus.
- The degree of effect on P-gp substrate serum concentration may be altered by dose and timing of orally administered P-gp inhibitor or inducer.
- Specific drug interaction effects may be determined by using Lexi-Interact, the drug interactions program included with UpToDate. Refer to UpToDate clinical topics on specific agents and conditions for further details.

* Minor clinical effect or supportive data are limited to in-vitro effects (ie, clinical effect is unknown).

¶ The combination of ombitasvir-paritaprevir-ritonavir plus dasabuvir (Viekira Pak) is not a significant inhibitor of P-gp efflux pump[1].

Reference:

1. *Menon RM, Badri PS, Wang T, et al. Drug-drug interaction profile of the all-oral anti-hepatitis C virus regimen of paritaprevir/ritonavir, ombitasvir, and dasabuvir. J Hepatol 2015; 63:20.*

Graphic 73326 Version 32.0

Suggested protocol for initiating warfarin therapy

Days of warfarin treatment	INR <1.5	INR 1.5 to 1.9	INR 2.0 to 3.0	INR >3.0
Suggested initial dose for days 1 and 2				
Normal adult	5 mg*	n/a	n/a	n/a
Frail adult, malnourished, elderly, liver disease	2.5 mg*	n/a	n/a	n/a
Dosing for day 3 and beyond				
Day 3	5 to 10 mg	2.5 to 5 mg	0 to 2.5 mg	No dose
Day 4	10 mg	5 to 7.5 mg	0 to 5 mg	No dose
Day 5	10 mg	7.5 to 10 mg	0 to 5 mg	No dose
Day 6	7.5 to 12.5 mg	5 to 10 mg	0 to 7.5 mg	No dose

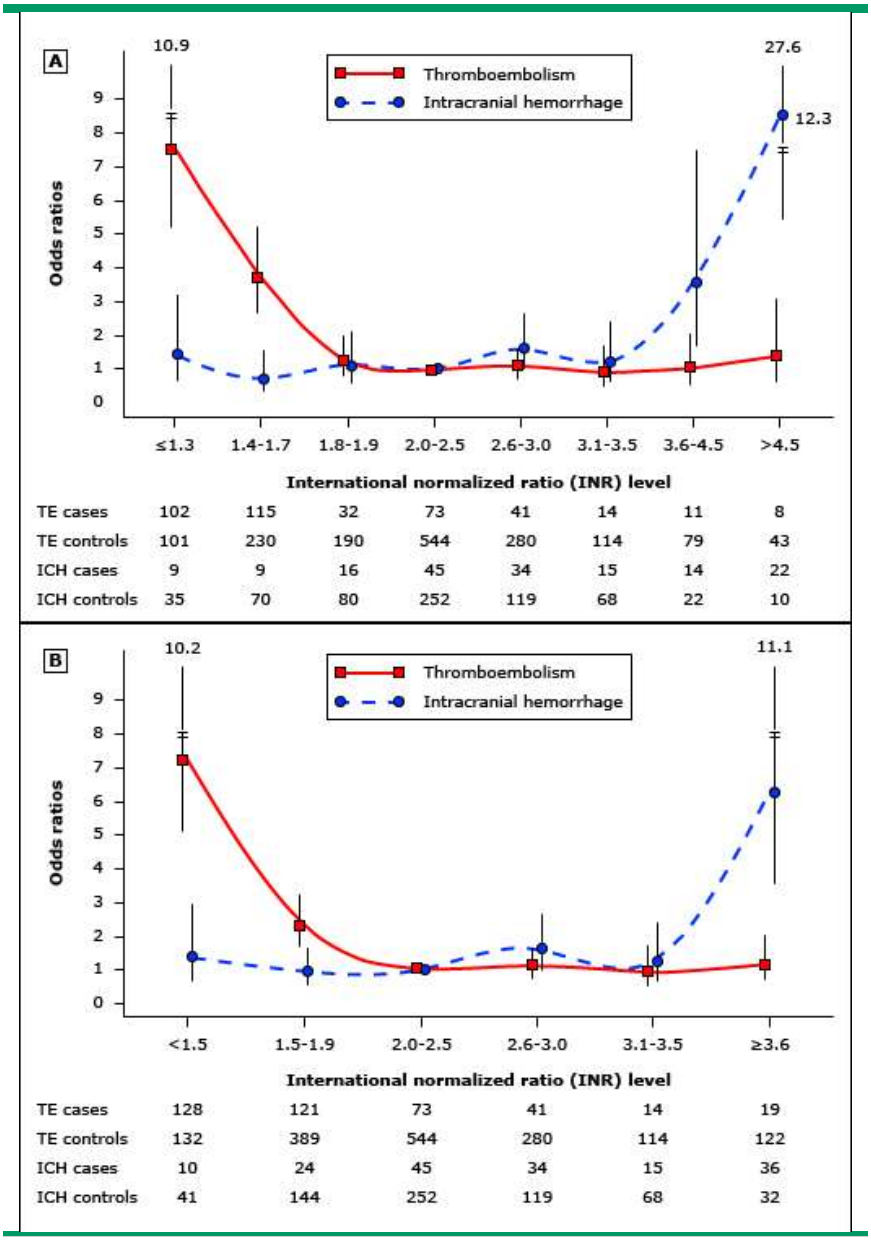
In this protocol, which is provided for guidance only, suggested doses of warfarin after day 2 are given as ranges. The clinician must judge the rapidity and magnitude of INR changes for the individual patient and make dosage adjustments accordingly. An algorithm for monitoring and adjustment of maintenance warfarin is presented separately. Refer to UpToDate topics on use of warfarin and table on suggested protocol for adjustment of maintenance warfarin.

n/a: not applicable.
* This table assumes that the patient has started with an INR in the normal range.

See text for details concerning the source for this protocol and relevant references.

Graphic 71791 Version 8.0

Optimal INR which minimizes both bleeding and thromboembolism in patients with atrial fibrillation



(A) Odds ratios (ORs) for thromboembolism (TE, 396 cases, 1581 controls) and intracranial hemorrhage (ICH, 164 cases, 656 controls) by INR level in adults with nonvalvular atrial fibrillation, with 8 INR categories using INR 2.0 to 2.5 as the referent. Vertical bars indicate 95 percent confidence intervals (CIs). The numbers of cases and controls for each INR category are given below the figure.
(B) ORs for TE (396 cases, 1581 controls) and ICH (164 cases, 656 controls) by INR level in adults with nonvalvular AF, with 6 INR categories using INR 2.0 to 2.5 as the referent. Vertical bars indicate 95 percent CIs. The numbers of cases and controls for each INR category are given below the figure.

Graphic 65373 Version 12.0

CHADS2 score, thromboembolic risk, and effect of warfarin anticoagulation

Clinical parameter	Points
Congestive heart failure (any history)	1
Hypertension (prior history)	1
Age ≥75 years	1
Diabetes mellitus	1
Secondary prevention in patients with a prior ischemic stroke or a transient ischemic attack; most experts also include patients with a systemic embolic event	2

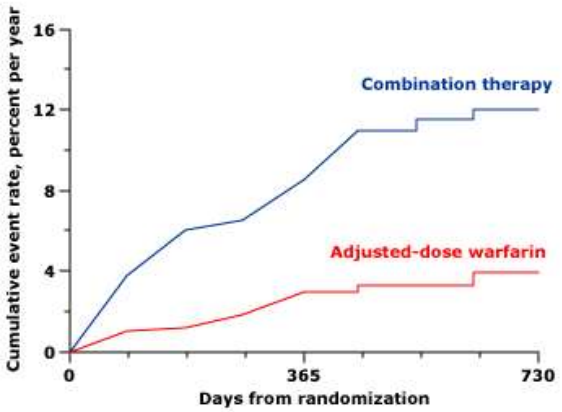
CHADS2 score	Events per 100 person-years*		NNT
	Warfarin	No warfarin	
0	0.25	0.49	417
1	0.72	1.52	125
2	1.27	2.50	81
3	2.20	5.27	33
4	2.35	6.02	27
5 or 6	4.60	6.88	44

NNT: number needed to treat to prevent one stroke per year with warfarin.
* The CHADS2 score estimates the risk of stroke, which is defined as focal neurologic signs or symptoms that persist for more than 24 hours and that cannot be explained by hemorrhage, trauma, or other factors, or peripheral embolization, which is much less common. Transient ischemic attacks are not included. All differences between warfarin and no warfarin groups are statistically significant, except for a trend with a CHADS2 score of 0. Patients are considered to be at low risk with a score of 0, at intermediate risk with a score of 1 or 2, and at high risk with a score ≥3. One exception is that most experts would consider patients with a prior ischemic stroke, transient ischemic attack, or systemic embolic event to be at high risk, even if they had no other risk factors and, therefore, a score of 2. However, the great majority of these patients have some other risk factor and a score of at least 3.

Data from: 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; 290:2685; and CHADS2 score from Gage BF, Waterman AD, Shannon W, et al. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. JAMA 2001; 285:2864.

Graphic 61615 Version 7.0

Low-dose warfarin plus aspirin is not optimal in high risk AF

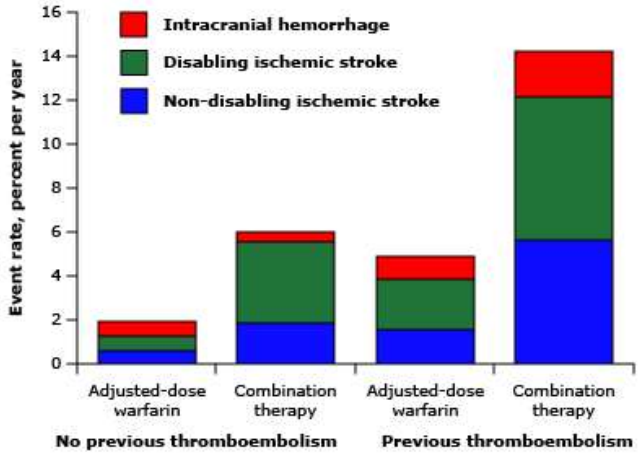


Cumulative event rate of patients with atrial fibrillation (AF) at high risk for thromboembolism in the SPAF III trial. High risk was defined as the presence of at least one of the following: previous thromboembolism, female older than 75 years of age, heart failure or severe left ventricular systolic dysfunction, and systolic pressure >160 mmHg. There was a much lower incidence of events with standard adjusted-dose warfarin therapy (INR 2 to 3) compared to treatment with aspirin and low-dose warfarin (INR 1.2 to 1.5) ($p < 0.0001$).

Data from Stroke Prevention in Atrial Fibrillation Investigators. Lancet 1996; 348:633.

Graphic 72790 Version 2.0

Increased stroke risk with low dose warfarin plus aspirin in AF



Results from the SPAF III trial of high-risk patients showing significantly higher event rates for intracranial hemorrhage and ischemic stroke in patients treated with fixed low dose warfarin plus aspirin compared with standard adjusted-dose warfarin. The risk was greater in those with a previous thromboembolic event.

Data from Stroke Prevention in Atrial Fibrillation Investigators. Lancet 1996; 348:633.

Graphic 62833 Version 1.0

Contributor Disclosures

Warren J Manning, MD Patent Holder: Samsung Electronics [MRI]. Equity Ownership/Stock Options: Pfizer [Anticoagulants]. Equity Ownership/Stock Options (Spouse): General Electric [Cardiac imaging]. **Daniel E Singer, MD** Grant/Research/Clinical Trial Support: Bristol-Myers Squibb [Atrial fibrillation and stroke (Apixaban)]; Boehringer Ingelheim [Atrial fibrillation and stroke (Dabigatran)]; Medtronic [Stroke rise and atrial fibrillation (Implantable cardiac and heart rhythm devices)]. Consultant/Advisory Boards: Boehringer Ingelheim [Preventing stroke in atrial fibrillation using anticoagulants (Dabigatran)]; Bristol-Myers Squibb [Atrial fibrillation and stroke (Apixaban)]; Johnson and Johnson [Atrial fibrillation and stroke (Rivaroxaban)]; Merck [Atrial fibrillation and stroke (Antithrombotics)]; Pfizer [Atrial fibrillation and stroke (Apixaban)]; CVS Health [Atrial fibrillation and stroke (Pharmacy benefits manager)]; Medtronic [Stroke rise and atrial fibrillation (Implantable cardiac and heart rhythm devices)]. **Gregory YH Lip, MD, FRCPE, FESC, FACC** Speaker's Bureau: Bayer [Atrial fibrillation and thrombosis (rivaroxaban)]; BMS/Pfizer [Atrial fibrillation and thrombosis (apixaban)]; Boehringer Ingelheim [Atrial fibrillation and thrombosis (dabigatran)]; Daiichi-Sankyo [Atrial fibrillation and thrombosis (edoxaban)]; Medtronic [Atrial fibrillation and thrombosis]; Sanofi Aventis [Atrial fibrillation and thrombosis]. Consultant/Advisory Boards: Bayer/Janssen [Atrial fibrillation and thrombosis (rivaroxaban)]; BMS/Pfizer [Atrial fibrillation and thrombosis (apixaban)]; Boehringer Ingelheim [Atrial fibrillation and thrombosis (dabigatran)]; Daiichi-Sankyo [Atrial fibrillation and thrombosis (edoxaban)]; Medtronic [Atrial fibrillation and thrombosis]. **Peter J Zimetbaum, MD** Consultant/Advisory Boards: Medtronic [Atrial fibrillation (Linq)]. **Scott E Kasner, MD** Grant/Research/Clinical Trial Support: WL Gore and Associates [Stroke (PFO closure)]; Acorda [Stroke (dalfampridine)]; AstraZeneca [Stroke (ticagrelor)]; Bayer [Stroke (rivaroxaban)]; Bristol Meyers Squibb [Stroke]. Consultant/Advisory Boards: Bayer [Stroke]; BMS [Stroke]; Novartis [Stroke]; Merck [Stroke]; Daiichi Sankyo [Stroke]; Boehringer Ingelheim [Stroke]; Abbvie [stroke]; J&J [stroke]. **Gordon M Saperia, MD, FACC** Nothing to disclose

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