

Evidence-based guideline update: Prevention of stroke in nonvalvular atrial fibrillation

Report of the Guideline Development Subcommittee of the American Academy of Neurology

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ABBREVIATIONS

AAN = American Academy of Neurology

AF = atrial fibrillation

APR = absolute risk ratio

ARR = absolute risk reduction

ASA = acetylsalicylic acid

BAFTA = Birmingham Atrial Fibrillation Treatment of the Aged

CHADS₂ = Congestive heart failure, Hypertension, Age > 75 years, Diabetes

CHA₂DS₂-VASc = Congestive heart failure, Hypertension, Age > 75 years, Diabetes
Stroke/TIA/thromboembolism – Vascular disease

CI = confidence interval

CKD = chronic kidney disease

CrCl = creatinine clearance

EKG = electrocardiogram

EVID = evidence-based conclusions for the systematic review

FDA = Food and Drug Administration

GI = gastrointestinal

HAS-BLED = Hypertension, Abnormal renal and liver function, Stroke, Bleeding, Labile INRs,
Elderly, Drugs or alcohol

HR = hazard ratio

INR = international normalized ratio

MCOT = mobile cardiac outpatient telemetry

MI = myocardial infarction

mRS = modified Rankin score

NVAF = nonvalvular atrial fibrillation

OR = odds ratio

PRIN = (stipulated axiomatic) principles of care

RCT = randomized, controlled trial

RELA = (strong evidence from) related conditions not systematically reviewed

RE-LY = Randomized Evaluation of Long-term anticoagulant therapy

ROCKET AF = Rivaroxaban Once-daily, oral, direct factor Xa inhibition Compared with
vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation

RR = relative risk

RRR = relative risk reduction

TIA = transient ischemic attack

ABSTRACT

Objective.

To update the 1998 American Academy of Neurology practice parameter on stroke prevention in nonvalvular atrial fibrillation (NVAF), we asked 2 questions: 1) For patients with cryptogenic stroke, how often does the use of various technologies, as compared with nonuse of these technologies, identify previously undetected NVAF? and 2) For patients with NVAF, which therapies that include antithrombotic medication, as compared with no therapy or with another therapy, reduce stroke risk and severity with the least risk of hemorrhage?

Methods.

We conducted a systematic review of evidence available in the English-language literature from 1998 to 2012 (updated to March 2013) and followed a modified Delphi process to formulate recommendations.

Results and recommendations.

The panel did not make Level A recommendations. No Level B recommendations were made with regard to identification of patients with occult NVAF.

Level B recommendations.

Selection of patients for antithrombotic therapy.

Clinicians should inform patients with NVAF that these patients have an increased stroke risk and that this risk can potentially be reduced by antithrombotic use. Patients should also be informed that antithrombotic use increases their risk of major bleeding.

Clinicians should counsel all patients with NVAF that the decision to use antithrombotics must be made only after the potential benefit from the stroke risk reduction has been weighed against the potential harm from the increased risk of major bleeding.

Clinicians should also emphasize the important role of judgment and preferences in this decision.

Clinicians should routinely offer anticoagulation to patients with NVAF and a history of transient ischemic attack or stroke, including elderly patients (aged > 75 years) if there is no history of recent unprovoked bleeding or intracranial hemorrhage, to reduce these patients' subsequent risk of ischemic stroke.

To inform their judgments as to which patients with NVAF might benefit more from anticoagulation, clinicians should use a risk stratification scheme to help identify patients with NVAF who are at higher risk for stroke or at no clinically significant risk. However, clinicians should not rigidly interpret anticoagulation thresholds suggested by these tools as being definitive indicators of which patients require anticoagulation.

Selection of a specific oral anticoagulant.

To reduce the risk of stroke or subsequent stroke in patients with NVAF judged to require oral anticoagulants, clinicians should choose 1 of the following options: warfarin, target international normalized ratio (INR) 2.0–3.0; dabigatran 150 mg twice daily (if creatinine clearance [CrCl] > 30 mL/min); rivaroxaban 15 mg/day (if CrCl 30–49 mL/min) or 20 mg/day; apixaban 5 mg twice daily (if serum creatinine < 1.5 mg/dL); triflusal 600 mg plus acenocoumarol, target INR 1.25–2.0 (patients at moderate stroke risk, mostly in developing countries).

Clinicians should administer dabigatran, rivaroxaban, or apixaban to patients who have NVAF requiring anticoagulant medication and are at higher risk of intracranial bleeding.

Other factors affecting administration of new oral anticoagulants.

Clinicians should offer dabigatran, rivaroxaban, or apixaban to patients unwilling or unable to submit to frequent periodic testing of INR levels.

Clinicians should offer apixaban to patients unsuitable for being treated, or unwilling to be treated, with warfarin.

Where triflusal is available and patients are unable or unwilling to take new oral anticoagulants (mostly in developing countries), clinicians should offer acenocoumarol (target INR 1.25–2.0) and triflusal to patients with NVAF who are at moderate stroke risk and higher bleeding risk.

Special populations.

Clinicians should routinely offer oral anticoagulants to elderly patients (aged > 75 years) with NVAF if there is no history of recent unprovoked bleeding or intracranial hemorrhage.

Clinicians might offer oral anticoagulation to patients with NVAF who have dementia or occasional falls. However, clinicians should counsel patients or their families that the risk–benefit ratio of oral anticoagulants is uncertain in patients with NVAF who have moderate to severe dementia or very frequent falls.

Level C recommendations.

Identification of patients with occult NVAF.

Clinicians might obtain outpatient cardiac rhythm studies in patients with cryptogenic stroke without known NVAF, to identify patients with occult NVAF.

Clinicians might obtain cardiac rhythm studies for prolonged periods (e.g., for 1 or more weeks) instead of shorter periods (e.g., 24 hours) in patients with cryptogenic stroke without known NVAF, to increase the yield of identification of patients with occult NVAF.

Selection of patients for antithrombotic therapy.

Clinicians might not offer anticoagulation to patients with NVAF who lack additional risk factors (“lone” NVAF patients).

Clinicians might reasonably offer antithrombotic therapy with aspirin (acetylsalicylic acid, or ASA) to such patients or might not offer antithrombotic therapy at all.

Selection of a specific oral anticoagulant.

Clinicians might recommend that patients taking warfarin whose condition is well controlled continue warfarin treatment rather than switch to treatment with a new oral anticoagulant.

Clinicians might offer apixaban to patients with NVAF and gastrointestinal bleeding risk who require anticoagulant medication.

Other factors affecting administration of new oral anticoagulants.

Where apixaban is unavailable, clinicians might offer dabigatran or rivaroxaban. Where oral anticoagulants are unavailable, clinicians might offer a combination of aspirin and clopidogrel.

The prevalence of atrial fibrillation (AF) in the United States was estimated to be 3.03 million persons in 2005^{e1} and is strongly associated with increasing age, ranging from 1% in patients aged 50–59 years to > 10% in patients over 80 years.^{e1} Because AF is a major risk factor for cardioembolic stroke,^{e2,e3} there is an urgent need to develop strategies for identification of AF and prevention of cardioembolic stroke at all ages.

AF often begins with occasional episodes of fibrillation, called *paroxysmal AF*, which terminate spontaneously. Paroxysmal AF may become more frequent and longer in duration, progressing to persistent AF or permanent AF, also called *chronic AF*.^{e4,e5} Regardless of duration, AF increases cardioembolic stroke risk,^{e6} and therefore this guideline examines both paroxysmal AF and chronic AF. Furthermore, the presence or absence of AF symptoms such as palpitations, shortness of breath, and fatigue do not modify the risk and will not affect the recommendations for stroke prevention.

The ischemic stroke rate among patients with AF averages 5% yearly^{e2} but varies greatly depending on individual clinical characteristics such as age, sex, race/ethnicity, and associated stroke risk factors. History of stroke or transient ischemic attack (TIA) identifies those patients with a high stroke risk averaging 10% yearly.^{e3} AF increases stroke risk by 5-fold and is responsible for approximately 24% of strokes in patients aged 80–89 years.^{e7} Patients with end-stage renal disease and AF have a 1.6- to 4.6-fold increased relative risk (RR) of stroke as compared with those without AF.^{e8,e9} The median age of patients with AF is about 75 years, whereas approximately 70% of patients with AF are aged 65–85 years.^{e10,e11} This guideline does not examine stroke risk prediction schemes, as there are many available, although the Congestive heart failure, Hypertension, Age > 75 years, Diabetes (CHADS₂) and Congestive heart failure, Hypertension, Age > 75 years, Diabetes Stroke/TIA/thromboembolism – Vascular disease (CHA₂DS₂-VASc) are arguably the best known (see tables e-1–e-3).

This evidence-based guideline updates a 1998 American Academy of Neurology (AAN) practice parameter on stroke prevention in nonvalvular atrial fibrillation (NVAF).^{e12} As with the previous practice parameter, this update does not address stroke prevention in patients with NVAF who are known to have a condition that causes major blood flow disturbance (e.g., mitral stenosis, prosthetic mitral valve), because chronic anticoagulation is the accepted practice to reduce thromboembolic risk in these patients. On the basis of an English-language literature search from 1991–1997, the 1998 AAN practice parameter recommends the following:

1. Stratification of patients with NVAF by the presence of additional risk factors for stroke helps select those who are at highest risk and maximizes the potential benefit of warfarin; the document indicates that the issue warranted further study.^{e12}
2. Patients with NVAF should be considered for anticoagulation. With a target international normalized ratio (INR) of 2.5 (range 2.0–3.0), the report states that in patients with NVAF adjusted-dose warfarin reduces stroke risk by about 70% and that aspirin (acetylsalicylic acid, or ASA) reduces stroke risk by about 20%.^{e12}
3. For patients with NVAF unable to receive oral anticoagulant or those at low risk of stroke, aspirin (325 mg/day) is recommended. The report recognizes that aspirin has not

been established as efficacious by clinical trials for these specific subgroups of patients with NVAf.^{e12}

This updated guideline reviews the evidence published since 1998 with regard to the detection of NVAf in patients with stroke or at risk of stroke and recommends therapeutic strategies that are safe and effective, with a focus on two questions: 1) For patients with cryptogenic stroke, how often does use of various technologies, as compared with nonuse of these technologies, identify previously undetected NVAf? and 2) For patients with NVAf, which therapies that include antithrombotic medication, as compared with no therapy or with another therapy, reduce stroke risk and severity with the least risk of hemorrhage?

DESCRIPTION OF THE ANALYTIC PROCESS

This guideline was developed in accordance with the processes described in the AAN guideline development process manuals (2004, 2011).^{e13,e14} After review of potential panel members' conflict of interest statements and curriculum vitae the AAN Guideline Development Subcommittee (see appendices e-1 and e-2) formed a panel of 5 neurologists with special expertise in vascular neurology, including experience in AAN guideline development. The panel engaged a medical librarian to search MEDLINE, EMBASE, Cochrane, and Web of Science for relevant articles published between 1998 and November 2012. The key text words and index words used in the search are "anticoagulation," "antithrombotics," "antiplatelets," "atrial fibrillation," "cardioembolic stroke," "cryptogenic stroke," and "paroxysmal atrial fibrillation." We considered studies that addressed population screening and therapy, including special population groups such as elderly individuals, nursing home residents, people with end-stage renal disease, and people with dementia. Appendix e-3 provides the complete search strategy. The search was restricted to peer-reviewed articles on human subjects written in English. A secondary search of references of selected articles was conducted up to March 2013 to identify any articles missed in the initial search.

The searches yielded 2,450 abstracts, each of which was reviewed for relevance by at least 2 panel members. Of those abstracts, 125 were deemed relevant, and the corresponding articles were obtained for full-text review by 2 panelists working independently. A final selection of 83 relevant articles was made for data extraction. Panel members then rated these articles according to the AAN schemes for classification of diagnostic screening and therapeutic articles (see appendix e-4). Differences in ratings were arbitrated by a third panel member.

Evidence was synthesized and conclusions developed using a modified form of the Grading of Recommendations Assessment, Development and Evaluation process.^{e15} The confidence in evidence was anchored to the studies' risk of bias in accordance with the rules outlined in appendix e-5. The overall confidence in the evidence pertinent to a question could be downgraded by 1 or more levels on the basis of the following factors: consistency, precision, directness, publication bias, or biologic plausibility. In addition, the overall confidence in the evidence pertinent to a question could be downgraded 1 or

more levels or upgraded by 1 level on the basis of the following factors: magnitude of effect, dose response relationship, or direction of bias. Two panel members working together completed an evidence summary table to determine the final confidence in the evidence (see appendix e-6 for the evidence synthesis tables). The confidence in the evidence was indicated by use of modal operators in conclusion statements in the manuscript. “Highly likely” or “highly probable” correspond to high confidence level, “likely” or “probable” correspond to moderate confidence level, and “possibly” corresponds to low confidence level. Very low confidence was indicated by the phrase “insufficient evidence.”

The panel formulated a rationale for recommendations based on the evidence systematically reviewed and stipulated axiomatic principles of care. This rationale is explained in a section which precedes each set of recommendations. From this rationale, corresponding actionable recommendations were inferred. The authors assigned a level of obligation to each recommendation using a modified Delphi process to evaluate the following prespecified domains: the confidence in the evidence systematically reviewed, the acceptability of axiomatic principles of care, the strength of indirect evidence, and the relative magnitude of anticipated health benefits to harms. Additional factors explicitly considered by the panel that could modify the level of obligation include judgments with regard to the importance of outcomes, cost of compliance to the recommendation relative to benefit, the availability of the intervention, and anticipated variations in patient preferences. The prespecified rules for determining the final level of obligation from these domains is indicated in appendix e-7. The level of obligation was indicated using standard modal operators. “Must” corresponds to “Level A,” very strong recommendations; “should” to “Level B,” strong recommendations; and “might” to “Level C,” weak recommendations. The panel members’ judgments supporting the levels of obligation are indicated in the tables in appendix e-8.

ANALYSIS OF EVIDENCE

Diagnostic question: For patients with cryptogenic stroke, how often does use of various technologies, as compared with nonuse of these technologies, identify previously undetected NVAf?

Two Class II^{e16,e17} and 15 Class III^{e18-e32} studies were identified that address this question. Figure e-1 lists these studies and the associated monitoring techniques and durations involved. Studies were downgraded 1 level if they failed to provide data on a cryptogenic stroke cohort, because some of the patients in noncryptogenic cohorts had known NVAf.

Class II studies.

A prospective multicenter Class II cohort study^{e16} of 239 patients with cryptogenic ischemic stroke who underwent 30-day outpatient event loop recorder with the CardioPAL SAVI (Medicomp, Inc, Melbourne, FL) identified paroxysmal NVAf in 11% of patients. Of importance, only 6.1% of detected paroxysmal NVAf events were symptomatic.

A retrospective cohort study (Class II) reviewed 56 patients with cryptogenic stroke who underwent mobile cardiac outpatient telemetry (MCOT; Cardionet, Inc.).^{e17} Paroxysmal NVAf was identified in 23% (13/56) with a median MCOT monitoring duration of 21 days (range 5–21 days). NVAf was first detected after a median of 7 (range 2–19) days of monitoring. Twenty-seven asymptomatic NVAf episodes were detected in the 13 patients; 85% (23/27) of these episodes lasted 30 seconds or less, and the remaining 15% (4/27) were 4–24 hours in duration.

Class III studies.

A retrospective cohort study of 62 patients with cryptogenic stroke and TIA underwent MCOT (Cardionet, Inc.) for up to 30 days (median of 21 days), and 15 (24%) were found to have paroxysmal AF, defined as having a duration lasting more than 30 seconds.^{e31} The vast majority (97%) of the NVAf episodes were clinically asymptomatic.

Another retrospective Class III study of 156 patients with cryptogenic stroke or TIA underwent MCOT (Cardionet, Inc) for up to 30 days (median 21 days) and detected paroxysmal AF in 27 (17.3%). The NVAf duration was < 30 seconds in 18 (66%), > 30 seconds in 7 (26%), and persistent in 2 (7%).^{e32}

A prospective cohort study^{e18} of 496 consecutive patients with acute ischemic stroke identified paroxysmal NVAf in 8.3% of patients. Inpatient continuous telemetry monitoring for a median of 64 hours was more likely to detect paroxysmal NVAf as compared with 24-hour Holter monitoring (65.9% vs 34.1%, $p < 0.001$).

Another Class III prospective cohort study^{e19} followed 127 patients with an acute ischemic stroke and without known NVAf who underwent serial 7-day event loop recorders at 0, 3, and 6 months after their strokes. Overall, NVAf was identified in 15% of patients and was more common in those patients with frequent premature atrial beats detected by a 24-hour Holter monitoring session than in those patients without premature atrial beats (26% vs 6.5%, $p = 0.002$).

A third Class III prospective cohort study^{e20} examined 82 consecutive patients with acute ischemic stroke and without documented NVAf. Holter monitoring performed for 72 hours showed that 5 patients (6%) had paroxysmal NVAf. NVAf was identified in 1 patient within the first 24 hours, in 2 patients between 24–48 hours, and in 2 patients between 48–72 hours.

Another Class III cohort study^{e21} of 136 patients with acute ischemic stroke and without NVAf on initial EKG identified paroxysmal NVAf in 7 patients (5.1%) who subsequently underwent 24-hour Holter monitoring.

A Class III retrospective cohort study^{e22} of 53 patients with cryptogenic acute ischemic stroke and without a history of NVAf found paroxysmal NVAf on 24-hour Holter monitoring in 9% of patients. Inpatient telemetry was performed concurrently with the Holter monitoring, but no NVAf was detected.

A Class III retrospective cohort study^{e23} of 149 patients with ischemic stroke reported that 24-hour Holter monitoring detected no additional cases of NVAF beyond the 3 that were previously identified on EKG.

A Class III retrospective cohort study^{e24} of 144 patients with ischemic stroke reported that newly detected NVAF was identified in 16.8% of patients with serial EKG over 72 hours as compared with 7% of patients with a 24-hour Holter monitor.

A Class III prospective cohort study^{e25} performed 24-hour Holter monitoring followed by twice-daily handheld EKG for 30 days on 249 patients with ischemic stroke and without known NVAF. Overall NVAF was identified in 6.8% of patients, and it was more likely to be detected by the handheld EKG than the Holter monitor (6% vs 2%, $p = 0.01$).

A retrospective cohort study (Class III, downgraded for inclusion of patients with noncryptogenic stroke) evaluated the utility of 24-hour Holter monitoring in 425 patients hospitalized with acute ischemic stroke or TIA and found NVAF in 21 patients (4.9%), 9 (2.1%) of whom were previously not known to have NVAF.^{e26} An additional 12 patients (2.8%) had bursts of NVAF lasting up to 20 seconds, and 74 (17.4%) had bursts of NVAF lasting from 5 to 20 beats, but these episodes failed to meet the prespecified criteria for NVAF.

A prospective cohort study (Class III, downgraded for inclusion of patients with noncryptogenic stroke) reported on 149 patients with stroke and without known NVAF who were admitted to a primary care hospital.^{e27} Patients underwent a stepwise NVAF screening consisting of EKG, which was followed first by 24-hour Holter monitoring (if the EKG was negative) and then by a 7-day event loop recorder (if the Holter monitoring studies were negative).^{e27} Overall, NVAF was detected in 22 patients (15%): repeated EKGs identified NVAF in 7% of the cases in the hospital (10/149 patients), whereas Holter monitoring revealed NVAF in an additional 5% of remaining patients with normal EKGs; the event loop recorder detected NVAF in 6% of patients with normal EKG and Holter monitor results.

A prospective cohort study (Class III) of 28 patients with cryptogenic stroke or TIA, including patients with negative EKG and 24-hour Holter monitor results, found NVAF in 4 patients (14%) through use of a 7-day event loop recorder.^{e28}

Another retrospective cohort study (Class III) reported on a group of 98 patients, 82 of whom had cryptogenic ischemic stroke or TIA and had had negative 24-hour Holter monitor results for NVAF in the hospital. These 82 patients subsequently underwent outpatient transtelephonic EKG monitoring daily for 30 days, which resulted in the detection of paroxysmal NVAF in 7 of the 82 patients (8.5%).^{e29}

A retrospective cohort study (Class III) of 36 patients with cryptogenic stroke, 20 of whom underwent 30-day event monitoring, reported that NVAF was detected in 4 patients (20%).^{e30}

A meta-regression of studies utilizing continuous Holter, telemetry, or event loop monitoring identified a significant increase in detection of NVAF with longer monitoring duration ($p < 0.0000$).

Conclusions.

In patients with recent cryptogenic stroke, cardiac rhythm monitoring probably detects previously unidentified NVAF at a rate ranging from 0%–23% (weighted average of 10.7% [95% confidence interval {CI} 7.9%–14.3%]) (2 Class II studies,^{e16,e17} 15 Class III studies^{e18–e30}). The detection rate is probably related to the duration of monitoring (2 Class II studies,^{e16,e17} 15 Class III studies^{e18–e30}).

Treatment question: For patients with NVAF, which therapies that include antithrombotic medication, as compared with no therapy or with another therapy, reduce stroke risk and severity with the least risk of hemorrhage?

Warfarin.

Since the publication of the 1998 practice parameter^{e12} several studies have investigated the efficacy of warfarin for stroke prevention in NVAF. Two Class II studies^{e33,e34} have evaluated the relationship between INR level at the time of stroke presentation and both stroke severity and mortality. The first study^{e33} examined 13,559 subjects with NVAF from an integrated health system who had a combined total of 596 strokes. Patients with an admission INR of < 2.0 as compared with > 2.0 had an increased chance of having a severe stroke, defined as a modified Rankin score (mRS) of ≥ 3 at discharge (odds ratio [OR] 1.9 [95% CI 1.1–3.4]). Thirty-day mortality was 6% with > 2.0 , 16% with < 2.0 , 15% for patients taking aspirin, and 24% for patients on no antithrombotic therapy. An INR of < 2.0 as compared with an INR of > 2 was associated with a hazard ratio (HR) of 3.4 (95% CI 1.1–10.1) for death at 30 days. The second, smaller study of 329 patients with NVAF^{e34} also found a graded relationship between antithrombotic therapy at the time of stroke or TIA and the risk of severe disability (mRS > 3) or death at discharge. The OR for severe disability or death at discharge (relative to warfarin with > 2.0) was 4.1 for no antithrombotic therapy on admission, 2.1 for antiplatelet therapy, and 1.5 for warfarin with < 2.0 .

Warfarin in special population groups.

A multicenter trial in the United Kingdom evaluated the benefits of warfarin as compared with those of aspirin in elderly patients, defined as aged ≥ 75 years (Class I study).^{e35} The Birmingham Atrial Fibrillation Treatment of the Aged Study (BAFTA) enrolled 973 subjects with a mean age of 81.5 years and randomly assigned patients to warfarin (INR 2.0–3.0) or aspirin 75 mg/day, with a mean follow-up of 2.7 years. The annual absolute risk reduction (ARR) for disabling stroke or systemic embolism was 2% (95% CI 0.7%–3.2%) favoring warfarin, with an RR of 0.48 (95% CI 0.28–0.80, $p = 0.003$). Extracranial hemorrhage was comparable in the 2 treatment groups.

In a Class II study^{e36} patients aged ≥ 75 years with NVAF were randomized to receive warfarin to maintain the INR at 1.8 (range 1.5–2.0) ($n=135$) or at a standard target of 2.5 (range 2.0–3.0) ($n=132$). During a mean follow-up lasting 5.1 years, 24 primary-outcome

events (thromboembolism and major hemorrhage) (3.5/100 patient-years) were recorded in the low-intensity group and 35 (5.0/100 patient-years) in the standard-intensity group (HR = 0.7 [95% CI 0.4–1.1], $p = 0.1$). The reduction in the primary endpoint was due to a diminution in major bleeding events (1.9 versus 3.0/100 patient-years; HR = 0.6, 95% CI 0.3–1.2, $p = 0.1$). The median achieved INR values were 1.86 in the low-intensity group and 2.24 in the standard-intensity group ($p < 0.001$).

There is a limited body of literature on warfarin use in patients with NVAF who have dementia or are at high risk of falls. One Class III study^{e37} retrospectively evaluated a geriatrics clinic cohort of 106 patients with NVAF (mean age 82 years), including patients with dementia (19%) and falls history (12%). Eighty-five percent of patients were prescribed warfarin, with the time in therapeutic range (INR 2.0–3.0) being relatively low at 49%. Fifteen percent of patients received aspirin. The 1-year outcomes rate in patients receiving warfarin was stroke 2%, major hemorrhage 6%, and death 20%; patients with falls history or dementia (or both) had a high 1-year mortality rate of 45%.

The prevalence of NVAF in patients with end-stage renal disease is 10- to 20-fold higher, depending on age, than in the general population.^{e38} In a retrospective study by the United States Renal Data System, patients who started hemodialysis in 1996 and were subsequently hospitalized for NVAF had a significantly lower cumulative 3-year, all-cause mortality rate of 33% for those taking warfarin as compared with 56% for those not taking warfarin ($n = 123$).^{e39}

Among patients with NVAF participating in the Stroke Prevention in Atrial Fibrillation III trials,^{e40} stage 3 chronic kidney disease (CKD) was associated with higher rates of ischemic stroke/systemic embolism (Class I study). Adjusted-dose warfarin (INR target 2.0–3.0) markedly reduced ischemic stroke/systemic embolism in patients with NVAF and a high risk of stroke who had stage 3 CKD (76% [95% CI 42%–90%, $p < 0.001$] by adjusted-dose warfarin as compared with aspirin/low-dose warfarin).

In a retrospective observational study of 132,372 patients with NVAF^{e41} (Class II), warfarin treatment was associated with a decreased risk of stroke or systemic thromboembolism among patients with non-end-stage CKD (HR 0.84 [95% CI 0.69–1.01]) and among those whose condition required dialysis (HR 0.44 [95% CI 0.26–0.74]); however, warfarin treatment was associated with an increased bleeding risk (HR 1.36 [95% CI 1.17–1.59] and HR 1.27 [95% CI 0.91–1.77], respectively).

Conclusion.

In patients with NVAF, anticoagulation that results in an INR of 2.0–3.0 likely reduces the frequency and severity of ischemic stroke as compared with anticoagulation resulting in lower INR levels (2 Class II studies).^{e33,e34} This benefit likely extends to elderly patients (1 Class I study).^{e35} The risks of stroke and death from stroke are also reduced in patients with CKD, including patients on hemodialysis. Bleeding risk increases in all patients with CKD taking warfarin.

Dabigatran.

The Randomized Evaluation of Long-term anticoagulant therapy (RE-LY) trial (Class I, randomized, controlled trial [RCT])^{e42} enrolled 18,113 patients and compared 2 doses of dabigatran (150 mg twice daily, available in the United States, and 110 mg twice daily, unavailable in the United States) with warfarin adjusted to an INR of 2.0–3.0. Dabigatran is an oral direct thrombin inhibitor that is administered in a fixed dose without a requirement for regular blood INR monitoring. It does not have meaningful interactions with diet and has many fewer drug interactions relative to warfarin. A dabigatran blood assay is not available in routine clinical practice, and rapid reversal of its antithrombotic effects is limited to emergency dialysis, an impractical procedure, particularly in patients whose condition is unstable. In RE-LY, patients were required to have documented NVAF and additional risk factors for stroke such as being aged > 75 years and having hypertension. Approximately 20% of patients had a history of stroke or TIA. In the trial, treating physicians were nonblinded with respect to administration of warfarin or dabigatran but were blinded to dabigatran dose, and adjudication of endpoints was done blinded to treatment assignment.

The primary endpoint was stroke or systemic embolism, which occurred at rates of 1.69%/year in the warfarin group and 1.11%/year in the dabigatran group (150 mg twice daily) (relative risk reduction [RRR] 34%, RR 0.66 [95% CI 0.53–0.82, $p < 0.001$] for noninferiority). The INR for patients in the warfarin group was in the therapeutic range (2.0–3.0) 64% of the time. Intracranial hemorrhage rate was lower with dabigatran 150 mg bid (0.74%/year with warfarin, 0.30%/year with dabigatran [$p < 0.001$]) (RR 0.40 [95% CI 0.27–0.60]). Overall major-bleeding rates were similar between the 2 agents (3.36%/year with warfarin and 3.11%/year with dabigatran 150 mg bid [$p = 0.32$]). Dabigatran 150 mg bid was associated with a higher rate of dyspepsia (11.3% vs 5.8%) and gastrointestinal (GI) bleeding (1.51%/year vs 1.02%/year) and a higher rate of drug discontinuation by the end of year 2 (21% vs 16.6%).

Although dabigatran doses lower than 110 mg twice daily were not tested in the RE-LY trial, the US Food and Drug Administration (FDA) has recommended a 75-mg dose for patients with end-stage renal disease who are not on hemodialysis and have a creatinine clearance (CrCl) of 15–30 mL/min.^{e43}

Conclusion.

In patients with NVAF, dabigatran administration is probably more effective for reducing the risk of stroke or systemic embolism (150 mg twice daily, RR 0.66; RRR 34%) than is warfarin administration. Hemorrhage risks were similar overall between dabigatran 150 mg administration twice daily and warfarin administration (INR 2.0–3.0), but intracranial hemorrhage was less frequent with administration of dabigatran 150 mg twice daily (dabigatran vs warfarin, RR 0.40 [95% CI 0.27–0.60]) (1 Class I study).^{e42}

Rivaroxaban vs warfarin.

Rivaroxaban is a factor Xa inhibitor available in the United States that was tested in one Class I RCT in comparison with warfarin for efficacy and safety for the prevention of stroke and systemic embolism in patients with NVAF (Rivaroxaban Once-daily, oral, direct factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke

and Embolism Trial in Atrial Fibrillation [ROCKET AF] study).^{e44} A routine clinical blood assay and a specific antidote for rivaroxaban are unavailable. Patients received either rivaroxaban (at a daily dose of 15 mg, if CrCl was 30–49 ml/minute, or 20 mg orally), or warfarin (dose-adjusted), INR target 2.0–3.0. The study was designed as a noninferiority trial, and the enrolled subjects were at moderate to high risk for cerebral or systemic embolism, because they were required to have either history of cerebral/systemic events or at least 2 of the following risk factors: age > 75 years, hypertension, heart failure/ejection fraction < 35%, or diabetes.

The primary outcome was the composite of stroke (ischemic or hemorrhagic) and systemic embolism. Secondary efficacy endpoints included either myocardial infarction (MI) or a composite of stroke, systemic embolism, or death from cardiovascular causes. The primary safety outcome was a composite of major and nonmajor clinically relevant bleeding events.

Stroke and systemic embolism occurred at rates of 1.7%/year in the rivaroxaban group and 2.2%/year in the warfarin group (RRR 22%, HR = 0.79 in favor of rivaroxaban [95% CI 0.66–0.96], $p < 0.001$ for noninferiority). The INR for patients in the warfarin group was in the therapeutic range (2–3) only 55% of the time. Major and nonmajor clinically relevant bleeding occurred at rates of 14.9%/year in the rivaroxaban group and 14.5%/year in the warfarin group, a nonsignificant difference (HR = 1.03 [95% CI 0.96–1.11], $p = 0.44$), but with significant reductions in intracranial hemorrhage (0.5%/year vs 0.7%/year, $p = 0.02$) and fatal bleeding (0.2% vs 0.5%, $p = 0.003$) in the rivaroxaban group. Bleeding from GI sites (including upper-GI, lower-GI, and rectal sites) occurred more frequently in the rivaroxaban group, as did bleeding that led to a drop in the hemoglobin level or that required transfusion (decrease in hemoglobin ≥ 2 g/dl, 2.8%/year in rivaroxaban group vs 2.3%/year in warfarin group).

Among patients in the ROCKET AF study with CKD and CrCl 30–49 mL/min^{e45} the primary endpoint of stroke or systemic embolism occurred in 2.32/100 patient-years with rivaroxaban 15 mg/day vs 2.77/100 patient-years with warfarin (HR 0.84; 95% CI 0.57–1.23) in the per-protocol population (Class I). Rates of the principal safety endpoint (major and clinically relevant nonmajor bleeding: 17.82 vs 18.28/100 patient-years; $p = 0.76$) and intracranial bleeding (0.71 vs 0.88/100 patient-years; $p = 0.54$) were similar in a comparison of rivaroxaban and warfarin. Fatal bleeding (0.28 vs 0.74%/100 patient-years; $p = 0.047$) occurred less often with rivaroxaban.

Conclusion.

In patients with NVAf at high risk of cerebral or systemic embolism, rivaroxaban is probably as effective as warfarin for the prevention of cerebral and systemic embolism, without difference in the risk of major bleeding episodes overall except GI bleeding. However, rivaroxaban is associated with a lesser frequency of intracranial hemorrhage and fatal bleeding (RRR 22% [95% CI 5.5%–35.3%]) (single Class I study).^{e45}

Apixaban vs aspirin.

Apixaban is a factor Xa inhibitor that has been tested for its effectiveness and safety for the prevention of stroke and systemic embolism in patients with NVAF. Routine clinical blood assay and antithrombotic reversal agents for apixaban are unavailable. This agent was compared with aspirin in a double-blind RCT that included 5,599 subjects (2,808 assigned to apixaban, 2,791 to aspirin) who had NVAF and at least 1 stroke risk factor and were at moderately high risk of embolism (Class I study) (Apixaban Versus Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment trial).^{e46} The study was designed as a superiority trial. The enrolled subjects were either unsuitable for or unwilling to receive warfarin for embolism prevention. Patients received apixaban at 5 mg twice daily or aspirin at 81–324 mg/day.

The primary outcome was the occurrence of stroke (ischemic or hemorrhagic) or systemic embolism, and the primary safety outcome was the occurrence of major bleeding. Other outcomes of interest included rates of MI, death from vascular causes, and death from any cause, as well as composites of major vascular events.

The primary outcome event (stroke or systemic embolism) occurred significantly less frequently in the apixaban group (1.6%/year; RRR 55.1% [37.8%–67.6%]) than in the aspirin (3.7%/year) group (HR = 0.45; 95% CI 0.32–0.62, $p < 0.001$). Major bleeding and clinically relevant minor bleeding occurred with similar frequency in the 2 groups (1.4%/year for apixaban, 1.2%/year for aspirin, and 3.1%/year for apixaban, 2.7%/year for aspirin, respectively), including instances of intracranial bleeding (11 cases with apixaban, 13 with aspirin). In addition, there was a reduction in hospitalizations for cardiovascular causes with apixaban (12/6%/year) in comparison with aspirin (15.9%/year). The study was terminated prematurely because of demonstrated superiority of apixaban over aspirin for the prevention of stroke and systemic embolism, without a significant increase in the risk of major bleeding, including intracranial bleeding.

For patients with stage 3 CKD^{e47} apixaban 5 mg twice daily (2.5 mg twice daily in selected patients) significantly reduced primary events by 68% (5.6%/year with aspirin vs 1.8%/year with apixaban; HR 0.32; 95% CI 0.18–0.55; $p < 0.001$) without increase in bleeding (major bleeding apixaban 2.5% vs aspirin 2.2%, $p = 0.58$) (Class I).

Conclusion.

Based on 1 Class I study,^{e46} apixaban 5 mg twice daily is likely more effective than aspirin for decreasing risk of stroke or systemic embolism in patients with NVAF who have a moderate risk of embolism and are not candidates for warfarin treatment (RRR 55.1% [95% CI 37.8%–67.6%]). Bleeding risks, including major, clinically relevant minor, and intracranial bleeding, are similar for both treatment forms.

Apixaban vs warfarin.

For the comparison of apixaban with warfarin, 1 Class I study met inclusion criteria (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation study).^{e48} The study was designed as a noninferiority trial, with secondary objectives of testing for superiority with respect to the primary outcome and the rates of major bleeding and deaths from any cause. The 18,201 enrolled subjects were patients

with NVAF and at least 1 additional stroke risk factor. Patients received apixaban at a dose of 5 mg twice daily (N = 9,120) or warfarin (target INR 2.0–3.0) (N = 9,081) if CrCl > 25 mL/minute.

The primary outcome was the occurrence of stroke (ischemic and hemorrhagic), systemic embolism, and major bleeding, whereas secondary outcomes included rates of MI, death from any cause, major bleeding, relevant nonmajor bleeding, and liver function abnormalities. After a median follow-up of 1.8 years, stroke or systemic embolism were found to have occurred significantly less frequently in the apixaban (1.27%/year) group than in the warfarin (1.60%/year) group (HR = 0.79; 95% CI 0.66–0.95; $p < 0.001$ for noninferiority, $p = 0.01$ for superiority; RRR 20.3% [4.8%–33.3%]). The INR for patients in the warfarin group was in the therapeutic range (2.0–3.0) 66% of the time. The major-bleeding rate was lower (2.13%/year) in the apixaban group than in the warfarin (3.09%/year) group (HR = 0.69 [95% CI 0.60–0.80], $p < 0.001$), and the rates of death from any cause were lower in the apixaban group (3.52%/year) than in the warfarin group (3.94%/year) (HR = 0.89 [95% CI 0.80–0.90], $p = 0.047$). The intracranial hemorrhage rate was lower (0.24%/year) in the apixaban group than in the warfarin group (0.47%/year) (RRR 49% [95% CI 25%–65%], HR = 0.51 [95% CI 0.35–0.75], $p < 0.001$).

Conclusion.

Apixaban 5 mg twice daily is likely more effective than warfarin in patients with NVAF at moderate risk of embolism (RRR 20.3% [95% CI 4.8%–33.3%]). The superiority of apixaban is related to decreased risk of bleeding (including intracranial bleeding) and reduced mortality (1 Class I study), whereas its effect on reduction of risk of cerebral and systemic embolism is not superior to that of warfarin.^{e48}

Triflusal plus acenocoumarol vs triflusal alone vs acenocoumarol alone.

Triflusal is an antiplatelet drug structurally related to aspirin that is used in Europe, Latin America, Africa and Southeast Asia^{e49,e50} as a generic product. Acenocoumarol is a coumarin derivative.

A Class I study (National Study for Prevention of Embolism in Atrial Fibrillation study)^{e51} of 1,209 patients investigated 2 groups of patients with NVAF: a moderate-risk group (> 60 years with vascular risk factors but no previous embolism) and a high-risk group (with prior embolism or mitral stenosis). Patients in the former group who had NVAF and were at moderate risk were placed in 1 of 3 therapeutic subgroups: those receiving triflusal (600 mg daily) plus acenocoumarol (INR target, 1.25–2.0), those receiving triflusal (600 mg daily) only, those receiving acenocoumarol (INR target, 2.0–3.0) only. Primary outcomes were vascular death, TIA, and nonfatal stroke or systemic embolism. Secondary outcomes were severe bleeding, MI, nonvascular death, and nonsevere bleeding.

In 714 patients with moderate risk, primary event (vascular death, TIA, and nonfatal stroke or systemic embolism) rates were lower in the triflusal-plus-acenocoumarol group (0.9%/year) than in the acenocoumarol-only group (2.7%/year) [RRR, 67% as compared with the acenocoumarol arm; HR = 0.33 [95% CI 0.12–0.91; $p = 0.02$]) or the triflusal-

only group (RRR, 76%; HR = 0.24 [95% CI 0.09–0.64]; $p = 0.001$). Rates of vascular death, TIA, and nonfatal stroke or systemic embolism plus severe bleeding were lower in the triflusal-plus-acenocoumarol group as compared with the acenocoumarol-only group (RRR 61%; HR = 0.38 [95% CI 0.17–0.87]; $p = 0.02$). Triflusal-plus-acenocoumarol therapy as compared with acenocoumarol-only therapy was associated with decreased rates of stroke, TIA, and systemic embolism by 56% in patients with moderate risk (HR = 0.45 [95% CI 0.11–1.74]). Intracranial bleeding tended to be lower with triflusal-plus-acenocoumarol therapy, but GI bleeding was modestly higher; nonfatal systemic embolism did not occur in this moderate-risk group. Median INR with triflusal-plus-acenocoumarol therapy was 1.93, and median INR with acenocoumarol alone was 2.47.

Conclusion.

In patients who have NVAf and are at moderate stroke risk, treatment with triflusal plus acenocoumarol and moderate-intensity anticoagulation (INR target, 1.25–2.0) is likely more effective than acenocoumarol alone and conventional-intensity anticoagulation (INR target 2.0–3.0) for reducing stroke risk (RRR 61%, vascular death, TIA, nonfatal stroke, systemic embolism plus severe bleeding) (single Class I study, smaller than recent studies with new oral anticoagulants).^{e51}

Dose-adjusted vitamin K antagonists plus aspirin as compared with vitamin K antagonists alone.

Our search identified 1 Class II RCT^{e52} of 157 patients with NVAf that compared the combination treatment of dose-adjusted anticoagulation and the vitamin K antagonist fluindione plus aspirin (100 mg daily) with the combination treatment of dose-adjusted anticoagulation alone (target INR in both groups 2–2.6). The risk of hemorrhagic complications was significantly increased in the fluindione-plus-aspirin group as compared with the fluindione-alone group (risk difference 14.6%, 95% CI 5.5–24.8). The study lacked the statistical precision to exclude an important difference in the risk of thromboembolic events.

Conclusion.

In patients with NVAf, the combination of low-dose aspirin and dose-adjusted vitamin K antagonist therapy probably increases the risk of hemorrhagic complications (1 Class II study).^{e52} There is insufficient evidence to determine whether the combination of aspirin and vitamin K antagonist therapy decreases the risk of ischemic stroke or other thromboembolic events.

Clopidogrel combined with aspirin as compared with aspirin alone.

In patients who have NVAf and 1 or more additional risk factors for stroke and who are unsuitable for or unwilling to receive warfarin, the combination of clopidogrel (75 mg/day) and aspirin (75–100 mg/day) was compared with the combination of aspirin (75–100 mg/day) and placebo in 1 Class I study of 7,554 patients.^{e53} The primary outcome was the composite of stroke, MI, systemic embolism, or death from vascular causes, which is a commonly used primary endpoint. Secondary outcomes were stroke and individual components of the study's composite group.

Stroke occurred in 296 patients receiving clopidogrel (2.4%/year) and 408 patients receiving placebo (3.3%/year) (RR any stroke with clopidogrel, 0.72 [95% CI 0.62–0.83], $p < 0.001$). MI occurred in 90 patients receiving clopidogrel (0.7%/year) and in 115 receiving placebo (0.9%/year) (RR 0.78 [95% CI 0.59–1.03], $p = 0.08$). Major bleeding occurred in 251 patients receiving clopidogrel (2.0%/year) and in 162 patients receiving placebo (1.3%/year) (RR with clopidogrel 1.57 [95% CI 1.29–1.92], $p < 0.001$). Intracranial bleeding was higher in the combination treatment group (RR 1.87 [95% CI 1.19–2.94]).

Conclusion.

In patients with NVAf for whom vitamin K antagonist therapy is unsuitable, the combination of clopidogrel and aspirin (as compared with aspirin alone) reduces the risk of major vascular events, especially stroke (RR 0.72 relative to aspirin) but increases the risk of major hemorrhage (RR 1.57 relative to aspirin), including intracranial bleeding (RR 1.87 [95% CI 1.19–2.94]) (1 Class I study).^{e53}

Clopidogrel combined with aspirin as compared with warfarin.

Another Class I study of 6,706 patients^{e54} assessed whether clopidogrel (75 mg/day) plus aspirin (75–100 mg/day) was noninferior to oral anticoagulation therapy (target INR, 2.0–3.0) for prevention of vascular events in patients with NVAf plus 1 or more stroke risk factors.

The study was stopped early because of clear evidence of the superiority of oral anticoagulation therapy. The annual risk of primary events was 3.9% for patients receiving oral anticoagulation therapy and 5.6% for those receiving combination therapy, with an RR of 1.44 (95% CI 1.18–1.76; $p = 0.0003$) (cumulative RR for stroke 1.72 [95% CI 1.24–2.37], $p = 0.001$). Rates of major hemorrhage were similar in the 2 groups. Intracranial bleeds (including subdural hematoma) were more common with oral anticoagulation therapy than with clopidogrel plus aspirin (21 vs 11; $p = 0.08$). Significantly more minor bleeds occurred with clopidogrel plus aspirin than with oral anticoagulation therapy ($p = 0.0009$). Patients receiving oral anticoagulation therapy who were already receiving anticoagulation at study entry responded differently. They showed a trend toward a greater reduction in vascular events (RR 1.50 [95% CI 1.19–1.80]) and a significantly ($p = 0.03$ for interaction) lower risk of major bleeding with oral anticoagulation therapy (RR 1.30 [95% CI 0.94–1.79]) than patients not receiving this treatment at study entry (RR 1.27 [95% CI 0.85–1.89], and 0.59 [95% CI 0.32–1.08], respectively).

Conclusion.

In patients who have NVAf and are at risk of stroke, oral anticoagulation therapy is likely more effective than clopidogrel plus aspirin for stroke prevention (RR 1.44) (1 Class I study).^{e54} Intracranial bleeding is more common with oral anticoagulation therapy than with clopidogrel plus aspirin (1 Class I study).^{e54}

Figure e-2 summarizes the effects (RRRs) of the new antithrombotic regimens as compared with effects of dose-adjusted warfarin for the outcomes of stroke or systemic embolism, ischemic stroke, major bleeding, intracranial bleeding, and GI bleeding.

RECOMMENDATIONS

Appendix e-8 transparently indicates the panel’s judgment in assigning a level of obligation to each recommendation.

A. Identification of patients with occult NVAF.

Clinical context.

In patients with recent cryptogenic stroke, outpatient cardiac rhythm monitoring performed with nonimplanted devices probably detects unsuspected NVAF at a rate ranging from 0%–23% (weighted average 10.7% [95% CI 7.9%–14.3%]), with longer monitoring periods probably associated with a higher yield (EVID). Many of the NVAF episodes that are detected are clinically asymptomatic (EVID), and thus monitoring devices with continuous recording or automatic detection algorithms, rather than patient-triggered recording, are greatly preferred. The risk of recurrent stroke is uncertain in patients with very brief (e.g., < 30 seconds) or very infrequent episodes of NVAF; however, previous studies have demonstrated that NVAF tends to occur for progressively longer periods, and the stroke risk in patients with paroxysmal NVAF is similar to that in patients with persistent NVAF (RELA).^{e6,e55–e57} In addition, for patients with occult NVAF the risk of recurrent stroke will be importantly reduced with appropriate antithrombotic therapy (PRIN). Thus, we believe the yield of finding a treatable cause of cryptogenic stroke is sufficiently large to justify a search for such a cause when the diagnostic technique has very few adverse effects (PRIN).

Practice recommendations.

A1. Clinicians might obtain outpatient cardiac rhythm studies in patients with cryptogenic stroke without known NVAF, to identify patients with occult NVAF (Level C).

A2. Clinicians might obtain cardiac rhythm studies for prolonged periods (e.g., for 1 or more weeks) instead of shorter periods (e.g., 24 hours) in patients with cryptogenic stroke without known NVAF, to increase the yield of identification of patients with occult NVAF (Level C).

B. Selection of patients for antithrombotic therapy.

Clinical context.

All patients with NVAF are at increased risk of ischemic stroke relative to age-matched patients without NVAF. Within the NVAF population the absolute risk of ischemic stroke varies widely on the basis of the presence of other stroke risk factors.^{e58} Factors that are known to increase stroke risk include a history of previous stroke or TIA,

advanced age, hypertension, and diabetes, and, to a lesser extent, female sex and other symptomatic vascular disease (RELA).^{e58}

The absolute stroke risk is highest among patients with NVAF and a history of stroke and TIA (aggregated absolute risk about 10%/year) (RELA).^{e58} Patients with NVAF who lack any additional risk factors—so-called lone AF patients—have a lower absolute stroke risk ($\leq 2\%$ /year) (RELA).^{e58} Stratification schemes are not accurate enough to identify patients with stroke risk so low that oral anticoagulation is unnecessary, and further investigation of such schemes is needed (RELA).^{e59}

Patients with NVAF who lack a history of stroke or TIA but have other risk factors have an intermediate stroke risk. The absolute stroke risk in this group has been difficult to estimate. As a consequence, although multiple risk stratification tools are available for estimating the absolute stroke risk of patients with NVAF with varying risk factor combinations, the absolute stroke risk estimates generated by these tools vary widely. Thus, although it is clear that patients with NVAF who lack a history of TIA or stroke but have additional risk factors have absolute stroke risks somewhere between those of patients with NVAF and those of patients with NVAF and history of stroke or TIA, it is not possible at present to precisely determine their absolute stroke risks (RELA).^{e60}

Regardless of the absolute stroke risk, the risk for ischemic stroke in all patients with NVAF is reduced by antithrombotic use (RELA).^{e58} The RRR for ischemic stroke from aspirin use is about 20% and that from use of anticoagulation with warfarin is about 65% (RELA).^{e58,e61} The RRR provided by the newer anticoagulants reviewed here is similar to or somewhat greater than that of the RRR from warfarin use (EVID).

The absolute benefit in stroke risk reduction provided by antithrombotics to a given patient with NVAF depends on that individual's absolute stroke risk. A patient with NVAF and a history of stroke or TIA would realize an absolute reduction in stroke risk of about 6.5%/year from anticoagulation ($0.65 * 10\%$ /year) and an ARR of about 2%/year from aspirin ($0.2 * 10\%$ /year). Likewise, patients with NVAF without any risk factors would realize an ARR of ischemic stroke of about 1.3%/year ($0.65 * 2\%$ /year) from anticoagulation and an ARR of about 0.4%/year ($0.2 * 2\%$ /year) from aspirin (PRIN).

The risk of major bleeding is increased in all patients with NVAF treated with antithrombotics. The absolute risk of major bleeding from anticoagulation with warfarin is about 3%/year and from anticoagulation with aspirin about 0.5%/year (RELA).^{e58} Bleeding risk from the newer oral anticoagulants is similar to, or somewhat less than, that from warfarin (EVID). Features such as previous intracranial hemorrhage or a history of very frequent falls identify patients at increased risk of bleeding complications from antithrombotics (RELA).^{e62}

In patients with NVAF and a history of TIA and stroke, the benefit from stroke risk reduction from anticoagulation (ARR 6.5%/year) is larger than the harm from the increased risk of major bleeding from anticoagulation (3%/year). The benefit in stroke risk reduction from aspirin (2%/year) is also larger than the bleeding risk from aspirin

(0.4%/year). The benefit in stroke risk reduction from anticoagulation is larger than that provided by aspirin in patients who are at high risk for stroke.

In patients who have NVAF but no risk factors, the absolute risk of major bleeding (3%/year) is larger than the absolute reduction in stroke from anticoagulation (1.3%/year). With aspirin, the magnitude of the risk of major bleeding (0.4%/year) is similar to the magnitude of the stroke risk decrease in this population (0.4%/year) (PRIN).

Because it is difficult to determine with precision the absolute stroke risk in patients with NVAF who lack a history of TIA or stroke but have other risk factors, determining when the benefit from reduced stroke risk outweighs the harm of increased bleeding is likewise difficult. In these circumstances patient preferences and physician judgment become especially important (PRIN).

Practice recommendations.

B1. Clinicians should inform patients with NVAF that these patients have an increased stroke risk and that this risk can potentially be reduced by antithrombotic use. Patients should also be informed that antithrombotic use increases their risk of major bleeding (Level B).

B2. Clinicians should counsel all patients with NVAF that the decision to use antithrombotics must be made only after the potential benefit from the stroke risk reduction has been weighed against the potential harm from the increased risk of major bleeding. Clinicians should also emphasize the important role of judgment and preferences in this decision (Level B).

B3. Clinicians should routinely offer anticoagulation to patients with NVAF and a history of TIA or stroke, to reduce these patients' subsequent risk of ischemic stroke (Level B).

B4. Clinicians might not offer anticoagulation to patients with NVAF who lack additional risk factors ("lone" NVAF patients). Clinicians might reasonably offer antithrombotic therapy with aspirin to such patients or might not offer antithrombotic therapy at all (Level C).

B5. To inform their judgments as to which patients with NVAF might benefit more from anticoagulation, clinicians should use a risk stratification scheme to help identify patients with NVAF who are at higher risk for stroke or at no clinically significant risk. However, clinicians should not rigidly interpret anticoagulation thresholds suggested by these tools as being definitive indicators of which patients require anticoagulation (Level B).

C. Selection of a specific oral anticoagulant.

Clinical context.

Patients with NVAF are at high risk for ischemic stroke, and the risk is highest if patients have suffered a TIA or stroke (RELA).^{e3} Our review indicates that several anticoagulant medications decrease the risk of ischemic stroke or of recurrent ischemic stroke in patients with NVAF (EVID). In clinical trials the new oral anticoagulants are noninferior or superior to warfarin for reducing stroke (EVID), and in most patients the reduction in ischemic stroke risk outweighs the risk of bleeding complications (RELA).^{e59}

Practice recommendation.

C1. To reduce the risk of stroke or subsequent stroke in patients with NVAF judged to require oral anticoagulants, clinicians should choose 1 of the following options (Level B):

- Warfarin, target INR 2.0–3.0
- Dabigatran 150 mg twice daily (if CrCl > 30 mL/min)
- Rivaroxaban 15 mg/day (if CrCl 30–49 mL/min) or 20 mg/day
- Apixaban 5 mg twice daily (if serum creatinine < 1.5 mg/dL) or 2.5 mg twice daily (if serum creatinine > 1.5 and < 2.5 mg/dL, and body weight < 60 kg or age at least 80 years [or both])
- Triflusal 600 mg plus acenocoumarol, target INR 1.25–2.0 (patients at moderate stroke risk, mostly in developing countries) (see appendix e-9 for list of countries)

Patients already taking warfarin.

Duration of warfarin treatment and time in optimal INR therapeutic range (2.0–3.0) are predictors of favorable efficacy and safety (RELA).^{e33}

Practice recommendation.

C2. Clinicians might recommend that patients taking warfarin whose condition is well controlled continue warfarin treatment rather than switch to treatment with a new oral anticoagulant (Level C).

Intracranial bleeding risk.

The new oral anticoagulants have a more favorable intracranial-bleeding profile than warfarin (dabigatran 150 mg bid vs warfarin, 0.3%/year, vs 0.74%/year, RR 0.40 [95% CI 0.27–0.60], $p < 0.001$; rivaroxaban 20 mg daily, 0.5%/year vs 0.7%/year, HR 0.67 [95% CI 0.47–0.93], $p = 0.02$; apixaban 5 mg bid, 0.33%/year vs 0.80%/year, HR 0.42 [95% CI 0.30–0.58], $p < 0.001$) (EVID).

Practice recommendation.

C3. Clinicians should administer dabigatran, rivaroxaban, or apixaban to patients who have NVAF requiring anticoagulant medication and are at higher risk of intracranial bleeding (Level B).

GI bleeding risk.

In patients with NVAF, GI bleeding was greater with dabigatran 150 mg twice daily as compared with warfarin (1.51%/year vs warfarin 1.02%/year). Bleeding from GI sites, including upper, lower, and rectal sites, occurred more frequently in the rivaroxaban group than in the warfarin group, as did bleeding that led to a drop in the hemoglobin level or required transfusion (decrease in hemoglobin ≥ 2 g/dl, 2.8%/year in rivaroxaban group vs 2.3%/year in warfarin group). GI bleeding was nonsignificantly lesser with apixaban (0.76%/year) relative to that with warfarin (0.86%/year) (EVID).

Practice recommendation.

C4. Clinicians might offer apixaban to patients with NVAF and GI bleeding risk who require anticoagulant medication (Level C).

Other factors affecting administration of new oral anticoagulants.

INR monitoring.

INR monitoring is not required for dabigatran, rivaroxaban, and apixaban for maintaining anticoagulation within the therapeutic window (PRIN). Liberation from frequent periodic INR testing may be attractive to patients unwilling or unable to submit to frequent periodic testing (PRIN).

Practice recommendation.

C5. Clinicians should offer dabigatran, rivaroxaban, or apixaban to patients unwilling or unable to submit to frequent periodic testing of INR levels (Level B).

Patients unsuitable for warfarin.

Patients with NVAF who are at risk for stroke and are unsuitable candidates for warfarin treatment are candidates for alternative treatment with aspirin, but the results are poor in view of the substantially lower level of protection conferred by aspirin (22% RRR) relative to that by warfarin (RRR 68%) (RELA).^{e10} The combination of clopidogrel (75 mg) and aspirin (75–100 mg) as compared with aspirin (75–100 mg) alone reduces the risk of any stroke (RR 0.72 [95% CI 0.62–0.83]) but increases the risk of major hemorrhage (RR 1.57 [95% CI 1.25–1.98]), including intracranial bleeding (RR 1.87 [95% CI 1.19–2.94]) (EVID).

Apixaban was compared specifically with aspirin in subjects who were unsuitable for or unwilling to receive warfarin for embolism prevention, and apixaban was shown to be superior to aspirin in preventing cerebral and systemic embolism (apixaban group,

1.6%/year, vs aspirin group, 3.7%/year), with equal risk of major bleeding, including intracranial hemorrhage (EVID).

Practice recommendation.

C6. Clinicians should offer apixaban to patients unsuitable for being treated, or unwilling to be treated, with warfarin (Level B).

C7. Where apixaban is unavailable, clinicians might offer dabigatran or rivaroxaban (Level C).

C8. Where oral anticoagulants are unavailable, clinicians might offer a combination of aspirin and clopidogrel (Level C).

Patients with moderate stroke risk and higher bleeding risk.

In patients with NVAF and moderate stroke risk, treatment with triflusal 600 mg/day plus moderate-intensity anticoagulation (INR 1.25–2.0) with acenocoumarol is likely more effective than acenocoumarol alone (INR 2.0–3.0) for reducing all stroke risk (RRR, 61% in vascular death, TIA, and nonfatal stroke or systemic embolism). The reduction in vascular risk is also related to a reduction in severe bleeding (EVID), a biologic phenomenon consistent with that found in previous studies (RELA).^{e49,e50}

Practice recommendation.

C9. Where triflusal is available and patients are unable or unwilling to take new oral anticoagulants (mostly in developing countries), clinicians should offer acenocoumarol (target INR 1.25–2.0) and triflusal to patients with NVAF who are at moderate stroke risk and higher bleeding risk (Level B).

D. Special populations.

Clinical context.

Elderly patients with NVAF are at greater risk for embolic stroke as compared with younger patients (RELA).^{e7} Some clinicians are reluctant to treat elderly patients with anticoagulation because of perceived high risk of bleeding (RELA).^{e7} However, the BAFTA trial demonstrated that anticoagulation with warfarin was superior to that with aspirin in community-based patients ≥ 75 years for reducing the risk of ischemic stroke, whereas risks of major bleeding were comparable in the 2 study arms (RELA).^{e35} In 1 important subgroup, elderly patients who have frequent falls or advanced dementia, data are insufficient to determine whether anticoagulants are safe or effective. One study that used a decision analysis model estimated that an elderly patient would need to fall 295 times in 1 year to offset the stroke reduction benefits with warfarin (RELA).^{e63}

Another important subgroup is patients with renal failure. For dabigatran, 1 of the newer anticoagulants, a lower dose of 75 mg bid is recommended by the FDA when the CrCl

reaches 15–30 mL/min. Apixaban is recommended at 5 mg twice daily, if serum creatinine < 1.5 mg/dL, or 2.5 mg twice daily, if serum creatinine > 1.5 and < 2.5 mg/dL. Rivaroxaban was tested in patients at 15 mg daily, if CrCl 30–49 mL/min, or 20 mg daily, if CrCl > 50 mL/min, and recommendations are limited to these patient groups. With regard to warfarin, data have shown that warfarin treatment is associated with a decreased risk of stroke or systemic thromboembolism among patients with non-end-stage CKD but that warfarin treatment may be associated with an increased bleeding risk.^{e41}

Practice recommendations.

D1. Clinicians should routinely offer oral anticoagulants to elderly patients (aged > 75 years) with NVAF if there is no history of recent unprovoked bleeding or intracranial hemorrhage (Level B).

D2. Clinicians might offer oral anticoagulation to patients with NVAF who have dementia or occasional falls. However, clinicians should counsel patients or their families that the risk–benefit ratio of oral anticoagulants is uncertain in patients with NVAF who have moderate to severe dementia or very frequent falls (Level B).

D3. Because the risk–benefit ratio of oral anticoagulants in patients with NVAF and end-stage renal disease is unknown, there is insufficient evidence for making practice recommendations (Level U).

RECOMMENDATIONS FOR FUTURE RESEARCH

NVAF detection in cryptogenic stroke.

The results of ongoing trials utilizing implantable cardiac rhythm–monitoring devices are not yet available.^{e64,e65} Further research is required to clarify the implications of detecting only brief NVAF episodes (e.g., < 30 seconds) in patients with otherwise cryptogenic stroke and to establish thresholds for NVAF duration per episode or cumulative burden over a specified monitoring period that would justify long-term anticoagulation.

Stratification risk.

Differences among published schemes designed to stratify stroke risk in patients with NVAF have led to some confusion among clinicians and inconsistent use of oral anticoagulation. The popular CHADS₂ stratification scheme (see tables e-1 and e-2) does not include consideration of end-stage renal disease in the validation of the CHADS₂ score.^{e66} A modified CHA₂DS₂-VASc score (see table e-3) refines stroke risk stratification and increases the proportion of patients selected for anticoagulation^{e67} but is not accurate enough to identify patients with stroke risk so low that oral anticoagulation is unnecessary.^{e68} A novel bleeding risk score (Hypertension, Abnormal renal and liver function, Stroke, Bleeding, Labile INRs, Elderly, Drugs or alcohol, or HAS-BLED)^{e69} (see

tables e-4 and e-5) assesses the individual bleeding risk of patients with NVAF and assists clinical decision making with regard to antithrombotic therapy in patients with NVAF. Future validation and refinement of HAS-BLED, particularly among the elderly NVAF population, and an optimal scheme to predict stroke risk in NVAF are needed. Standardization of recommendations may lead to more uniform selection of patients for administration of oral anticoagulants.^{e60}

Special population groups.

Advanced age, frequent falls, and dementia.

Oral anticoagulant therapy in patients with NVAF who are older than 75 years probably reduces stroke risk,^{e35,e70} but management of elderly patients with NVAF requires that clinicians balance the need for anticoagulation for stroke prevention with the need for protection against the consequent higher risk of hemorrhage from anticoagulation use. Because of this fear, older patients remain more likely to be under-anticoagulated than their younger counterparts.^{e71} More studies are needed to investigate the safety and efficacy of the new oral anticoagulants in the very old (> 85 years). Patients with NVAF at risk of falls are also in danger of having their oral anticoagulation discontinued, with a consequent elevation in stroke risk.^{e63} There are scant data on the efficacy and safety of oral anticoagulants in patients with a high risk of falls or in patients with dementia (or in patients with both). An additional concern in the elderly is the relative high prevalence of cerebral amyloid angiopathy, which is associated with increased intracerebral hemorrhage risk. Further studies are required to assess the risk–benefit ratio in elderly subjects with NVAF who are candidates for anticoagulant treatment for stroke prevention and have imaging features suggestive of cerebral amyloid angiopathy.

End-stage renal disease.

Despite a 1.6-fold higher rate of stroke in patients with end-stage renal disease and NVAF relative to that in patients with end-stage renal disease and without NVAF, there are no large clinical trials that assess the risk–benefit ratio of full-intensity anticoagulation in patients with severe renal impairment.^{e72} It is plausible that possible benefits of oral anticoagulation for stroke prevention may be outweighed by high hemorrhagic risk.^{e73} Severely decreased renal clearance may affect plasma concentrations of the new oral anticoagulants, leading to decreased safety. Low-dose dabigatran (75 mg bid) has been approved by the FDA for administration to patients with end-stage renal disease who are not on dialysis, but there is no clinical evidence to support this dosing strategy. Further research comparing new oral anticoagulants with warfarin in this group of patients is needed.

Therapeutic reversal of new oral anticoagulants.

There is no clinical evidence, because of lack of appropriate studies, that administration of nonspecific procoagulants (such as prothrombin complex concentrate, activated recombinant factor VIIa) is useful in case of bleeding during use of new oral anticoagulants. The new oral anticoagulants have a rapid termination of anticoagulant effect, with a half-life of approximately 12 hours or less (half-life: dabigatran 12–17 hours, rivaroxaban 5–9 hours, apixaban 9–14 hours). Effective reversal strategies in case of bleeding would be a valuable addition to the safety of the new anticoagulants.

Assays in blood of new oral anticoagulants.

Blood assays that accurately reflect the degree of anticoagulation in patients taking the new anticoagulants dabigatran, rivaroxaban, and apixaban are unavailable in routine clinical practice. This may be of high interest in cases of spontaneous bleeding (overdose)^{e74} in therapeutic failures (undertreatment or no treatment). Blood assays may also be necessary if tissue plasminogen activator administration is contemplated in case of an acute stroke.

Silent infarcts.

It is unclear whether silent infarcts should be scored as strokes in the stratification schemes. Routine MRI screening for such infarcts may be helpful in patients who are otherwise considered to be at very low risk for stroke and would not be anticoagulated. Further research is required.

Therapeutic “bridging” with heparin or low-molecular-weight heparins.

Therapeutic bridging with heparin or low-molecular-weight heparins is a relatively common practice that has not been substantiated by systematic research. Future studies are required.

Combination therapy, oral anticoagulants plus aspirin.

The efficacy and safety of the combination of aspirin with new oral anticoagulants in patients with NVAf is unknown. Older studies have shown that the combination of mini-dose warfarin (1.25 mg/day) plus full-dose aspirin (325 mg/day) was associated with minor and major bleeding^{e75} without improvement in efficacy.^{e76,e77} Because of the lack of statistical precision the risk–benefit profile of fluindione plus aspirin could not be assessed.^{e52}

Concerns.

Concerns have been raised about an identified trend toward higher stroke event rates in ROCKET-AF in the rivaroxaban group as patients were transitioned to usual care.^{e78} Per-randomization analysis in ROCKET-AF revealed greater risk of stroke or systemic embolism in the group receiving rivaroxaban with a 5- to 9-hour half-life than in the group receiving warfarin with a 40-hour half-life (31 vs 12 detected events between day 2 and day 7 after discontinuation of randomized treatment). In the per-randomization analysis that captured these events, the RR of stroke or systemic embolism with rivaroxaban was 0.88 (95% CI 0.78–1.03). Optimal strategies for making transitions between oral anticoagulants need to be elucidated.

DISCLAIMER

This statement is provided as an educational service of the American Academy of Neurology. It is based on an assessment of current scientific and clinical information. It is not intended to include all possible proper methods of care for a particular neurologic problem or all legitimate criteria for choosing to use a specific procedure. Neither is it intended to exclude any reasonable alternative methodologies. The AAN recognizes that specific patient care decisions are the prerogative of the patient and the physician caring for the patient, based on all of the circumstances involved. The clinical context section is made available in order to place the evidence-based guideline(s) into perspective with current practice habits and challenges. Formal practice recommendations are not intended to replace clinical judgment.

CONFLICT OF INTEREST

The American Academy of Neurology is committed to producing independent, critical and truthful clinical practice guidelines (CPGs). Significant efforts are made to minimize the potential for conflicts of interest to influence the recommendations of this CPG. To the extent possible, the AAN keeps separate those who have a financial stake in the success or failure of the products appraised in the CPGs and the developers of the guidelines. Conflict of interest forms were obtained from all authors and reviewed by an oversight committee prior to project initiation. AAN limits the participation of authors with substantial conflicts of interest. The AAN forbids commercial participation in, or funding of, guideline projects. Drafts of the guideline have been reviewed by at least three AAN committees, a network of neurologists, *Neurology* peer reviewers and representatives from related fields. The AAN Guideline Author Conflict of Interest Policy can be viewed at www.aan.com.

ACKNOWLEDGMENTS

The authors would like to thank Thomas S. D. Getchius, Erin Hagen, and Julie Cox for their extensive support during guideline development.

Table e-1 CHADS₂ score

Risk factor	Score
Congestive heart failure	1 point
Hypertension	1 point
Age >75 years	1 point
Diabetes	1 point
Previous stroke or TIA	2 points

CHADS = Congestive heart failure, Hypertension, Age > 75 years, Diabetes; TIA = transient ischemic attack

Table e-2 CHADS₂ score

CHADS score adjusted stroke rate^{e79}	
0	1.9%
1	2.8%
2	4.0%
3	5.9%
4	8.5%
5	12.5%
6	18.2%

CHADS = Congestive heart failure, Hypertension, Age > 75 years, Diabetes

Table e-3 CHA₂DS₂-VASc score^{e68}

Risk factor	Score
Congestive heart failure	1 point
Hypertension	1 point
Age ≥ 75 years	2 points
Diabetes	1 point
Stroke/TIA/thromboembolism	2 points
Vascular disease^a	1 point
Age 65–74 years	1 point
Sex category (female)	1 point

^aPrior myocardial infarction, peripheral artery disease, or aortic plaque

CHADS = Congestive heart failure, Hypertension, Age > 75 years, Diabetes

Stroke/TIA/thromboembolism – Vascular disease; TIA = transient ischemic attack

Table e-4 HAS-BLED score

Risk factor	Score
H Hypertension	1 point
A Abnormal renal and liver function (1 point each)	1 or 2 points
S Stroke	1 point
B Bleeding	1 point
L Labile INRs	1 point
E Elderly	1 point
D Drugs or alcohol (1 point each)	1 or 2 points

HAS-BLED = Hypertension, Abnormal renal and liver function, Stroke, Bleeding, Labile INRs, Elderly, Drugs or alcohol; INR = international normalized ratio

Note. Table adapted from table 2 published in: Pisters R, Lane DA, Nieuwlaat R, et al.; on behalf of Guideline Development Group for the NICE national clinical guideline for management of atrial fibrillation in primary and secondary care; on behalf of Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation. 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;138:1093–1100. Used with permission.^{e69}

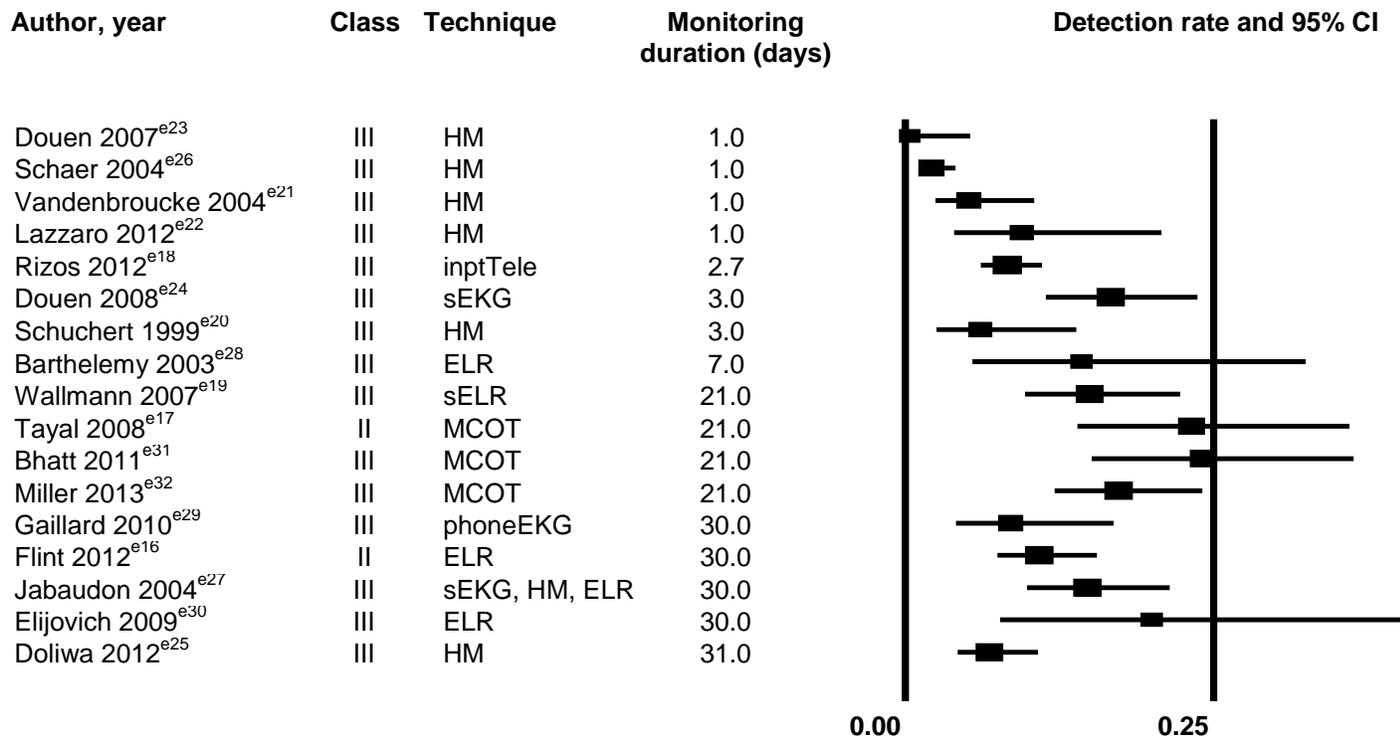
Table e-5 HAS-BLED risk of major bleeding

Risk of major bleeding within 1 year		
Risk factors/score	Number of patients	Number of bleeds per 100 patient-years
0	1,517	1.13
1	1,589	1.02
2	219	1.88
3	41	3.74
4	14	8.70
5	1	12.50

HAS-BLED = Hypertension, Abnormal renal and liver function, Stroke, Bleeding, Labile INRs, Elderly, Drugs or alcohol; INR = international normalized ratio

Note. Table adapted from table 2 published in: Pisters R, Lane DA, Nieuwlaat R, et al.; on behalf of Guideline Development Group for the NICE national clinical guideline for management of atrial fibrillation in primary and secondary care; on behalf of Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation. 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;138:1093–1100. Used with permission.^{e69}

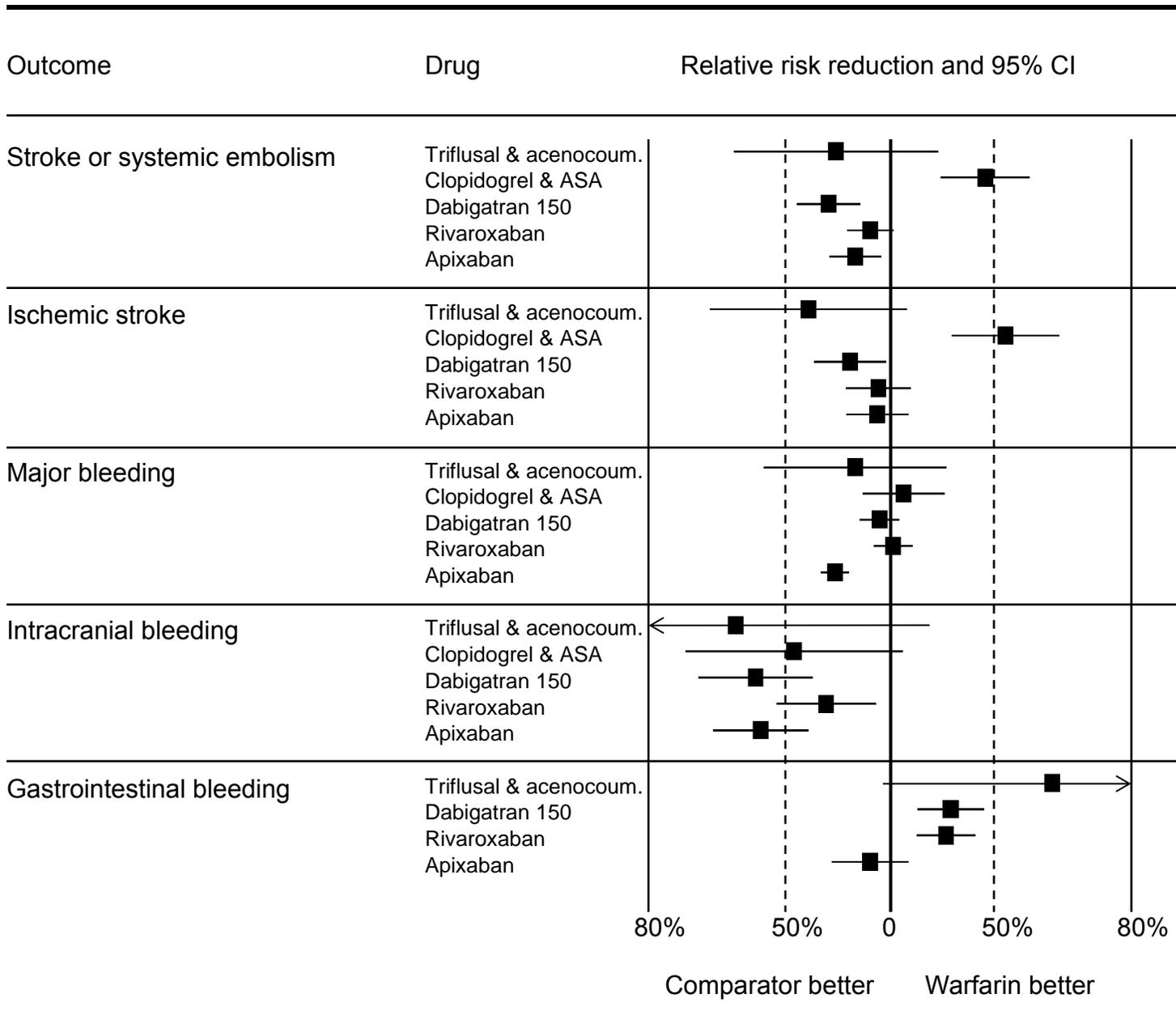
Figure e-1 Proportion of ischemic stroke patients identified with NVAF, by study



Note. Studies sorted by monitoring duration.

CI = confidence interval; ELR = event loop recorder; inptTele = continuous inpatient telemetry; HM = Holter monitoring; sEKG = serial electrocardiograms; MCOT = mobile cardiac outpatient telemetry; NVAF = nonvalvular atrial fibrillation; phoneEKG = outpatient transtelephonic EKG monitoring; sELR = serial event loop recordings.

Figure e-2 Relative risk reductions of various outcomes in patients with NVAf receiving various antithrombotic regimens as compared with warfarin or its derivatives



NVAf = nonvalvular atrial fibrillation; CI = confidence interval; acenocoum. = acenocoumarol; ASA = acetylsalicylic acid.

Appendix e-1: Mission Statement of GDS

The mission of the GDS is to prioritize, develop, and publish evidence-based guidelines related to the diagnosis, treatment, and prognosis of neurological disorders.

The GDS is committed to using the most rigorous methods available within our budget, in collaboration with other available AAN resources, to most efficiently accomplish this mission.

Appendix e-2: 2013–2015 Guideline Development Subcommittee (GDS) members

Cynthia Harden, MD (Chair); Steven R. Messé, MD, FAAN (Vice-Chair); Richard L. Barbano, MD, PhD, FAAN; Jane Chan, MD, FAAN; Diane Donley, MD; Terry Fife, MD, FAAN; Jeffrey Fletcher, MD; Michael Haboubi, MD; John J. Halperin, MD, FAAN; Cheryl Jaigobin, MD; Andres M. Kanner, MD; Jason Lazarou, MD; David Michelson, MD; Pushpa Narayanaswami, MD, MBBS; Maryam Oskoui, MD; Tamara Pringsheim, MD; Alexander Rae-Grant, MD; Kevin Sheth, MD, FAHA; Kelly Sullivan, PhD; Theresa A. Zesiewicz, MD, FAAN; Jonathan P. Hosey, MD, FAAN (Ex-Officio); Stephen Ashwal, MD, FAAN (Ex-Officio); Deborah Hirtz, MD, FAAN (Ex-Officio); Jacqueline French, MD, FAAN (Ex-Officio)

Appendix e-3: Complete search strategy

MEDLINE

Ovid MEDLINE(R) 1950 to June Week 3 2010

Searches Results

1 atrial fibrillation/ep, co, mo, pc 7984

2 exp stroke/ or exp intracranial hemorrhage/ or exp brain ischemia/ or exp "intracranial embolism and thrombosis"/ 145682

3 (cardioembolic* or paroxysmal or cryptogenic*).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] 23198

4 exp stroke/ep, et, pc, mo or exp intracranial hemorrhage/ep, et, pc, mo or exp brain ischemia/ep, et, pc, mo or exp "intracranial embolism and thrombosis"/ep, et, pc, mo 55325

5 1 and (3 or 4) 2459

6 exp anticoagulants/ or exp antifibrinolytics/ or exp platelet aggregation inhibitors/ 240220

7 5 and 6 978

8 ../ 7 hu=y and yr=1995-2010 897

9 limit 8 to (clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or evaluation studies or meta analysis or multicenter study or randomized controlled trial) 233

10 8 and (cohort*.mp. or retrospective studies/ or prospective studies/ or case-controlled study/ or review.pt.) [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] 457

11 9 or 10 578

12 8 and (ec.fs. or quality of life/ or activities of daily living/ or disability evaluation/) 39

13 11 or 12 590

Ovid MEDLINE(R) 1946 to September Week 4 2012 # Searches Results Search Type

1 atrial fibrillation/di, ep, et, pp, co or atrial flutter/di, ep, et, pp, co 21377 Advanced

2 exp brain ischemia/ or exp "intracranial embolism and thrombosis"/ or exp stroke/ 126104 Advanced

3 exp brain ischemia/et, co, pp, pc or exp "intracranial embolism and thrombosis"/et, co, pp, pc or exp stroke/et, co, pp, pc 74261 Advanced

4 exp electrocardiography/ or monitor*.mp. or monitoring, ambulatory/ or recording*.mp. or holter.mp. or telemetry.mp. or "event loop".mp. or elr.mp. or diagnosis, differential/ [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] 1168285 Advanced

5 1 and 3 and 4 416 Advanced

6 predict*.mp. or predictive value of tests/ or "sensitivity and specificity"/ or cohort studies/ or prospective studies/ or retrospective studies/ or risk*.mp. or surviv*.mp. or series.mp. or observation*.mp. or "consecutive patients".mp. [mp=title, abstract, original

title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] 3849095 Advanced
7 *atrial fibrillation/ or *atrial flutter/ or paroxysm*.mp. or intermittent*.mp. or paf.mp. or pxaf.mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] 113652 Advanced
8 5 and 6 335 Advanced
9 5 and comparative study/ 52 Advanced
10 8 or 9 340 Advanced
11 5 and 7 344 Advanced
12 10 or 11 392 Advanced
13 ../ 12 yr=1995-2012 and hu=y 370 Advanced
14 13 not news.pt. 367 Advanced

EMBASE

EMBASE 1988 to 2010 Week 25

Searches Results

1 heart atrium fibrillation/ 31850

2 stroke/dt, ep, et, pc, si [Drug Therapy, Epidemiology, Etiology, Prevention, Side Effect] 27519

3 exp occlusive cerebrovascular disease/co, dt, ep, et, si [Complication, Drug Therapy, Epidemiology, Etiology, Side Effect] 4676

4 1 and (2 or 3) 3038

5 exp anticoagulant agent/ 253589

6 exp antithrombotic agent/ 145604

7 4 and (5 or 6) 2412

8 ../ 7 hu=y and yr=1995-2010 2192

9 exp case control study/ or exp case study/ or exp clinical trial/ or exp intervention study/ or exp major clinical study/ or exp prospective study/ or exp retrospective study/ 1722024

10 8 and 9 1465

11 8 and (systematic review/ or meta-analysis/ or cohort*.mp. or population*.mp.) [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] 570

12 10 or 11 1565

13 *heart atrium fibrillation/ or *stroke/dt, ep, et, pc, si or exp *occlusive cerebrovascular disease/co, dt, ep, et, si 31244

14 12 and 13 1095

15 *stroke/dt, ep, et, pc, si and 14 687

16 exp brain hemorrhage/ 38262

17 12 and 16 335

18 17 not 15 161

EBM Reviews - Cochrane Central Register of Controlled Trials/ Cochrane DB SYS Rev
- 2nd Quarter 2010

Searches Results

- 1 atrial fibrillation.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] 2685
- 2 1 and (stroke* or cerebrovascular or cryptogenic* or cardioembol* or paroxysm*).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] 911
- 3 2 and (prevent* or prophyla*).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] 386
- 4 (anticoagula* or antiplatelet* or antifibrinoly* or antithrombo*).mp. or platelet aggregation inhibitors/ [mp=title, original title, abstract, mesh headings, heading words, keyword] 7228
- 5 3 and 4 159

Embase 1988 to 2012 Week 40 # Searches Results Search Type

- 1 exp brain ischemia/ or exp "intracranial embolism and thrombosis"/ or exp stroke/ 395139 Advanced
- 2 exp electrocardiography/ or monitor*.mp. or monitoring, ambulatory/ or recording*.mp. or holter.mp. or telemetry.mp. or "event loop".mp. or elr.mp. or diagnosis, differential/ [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] 1045842 Advanced
- 3 predict*.mp. or predictive value of tests/ or "sensitivity and specificity"/ or cohort studies/ or prospective studies/ or retrospective studies/ or risk*.mp. or surviv*.mp. or series.mp. or observation*.mp. or "consecutive patients".mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] 4258192 Advanced
- 4 *atrial fibrillation/ or *atrial flutter/ or paroxysm*.mp. or intermittent*.mp. or paf.mp. or pxaf.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] 120986 Advanced
- 5 1 and 4 and 2 1972 Advanced
- 6 exp case control study/ or exp case study/ or exp clinical trial/ or exp intervention study/ or exp longitudinal study/ or exp major clinical study/ or exp prospective study/ or exp retrospective study/ 2500323 Advanced
- 7 exp brain infarction/di, ep, et, co, pc, si or exp brain ischemia/di, ep, et, co, pc, si or exp cerebrovascular accident/di, ep, et, co, pc, si or exp occlusive cerebrovascular disease/di, ep, et, co, pc, si or exp stroke/di, ep, et, co, pc, si 95291 Advanced
- 8 7 and 2 and 4 749 Advanced
- 9 8 and (3 or 6) 624 Advanced
- 10 ../ 9 yr=1995-2012 603 Advanced
- 11 limit 10 to human 598 Advanced
- 12 limit 11 to embase 514 Advanced
- 13 exp heart atrium arrhythmia/co, di, dm, ep, et, pc, si [Complication, Diagnosis, Disease Management, Epidemiology, Etiology, Prevention, Side Effect] 27855 Advanced
- 14 12 and 13 191 Advanced
- 15 electrocardiography monitoring/ or ambulatory monitoring/ or Holter monitoring/ 20045 Advanced

16 telemedicine/ or telephone/ or 15 48913 Advanced
17 12 and 16 69 Advanced
18 14 or 17 218

Web of Science/Current Contents

6 464 #4 AND #2

Refined by: Document Type=(ARTICLE OR REVIEW OR PROCEEDINGS PAPER)
Databases=SCI-EXPANDED Timespan=1995-2009

5 514 #4 AND #2

Databases=SCI-EXPANDED Timespan=1995-2009

4 >100,000 TI=(stroke* OR intracranial or cerebral or cerebrovascular OR
cardioembol* OR brain)

Databases=SCI-EXPANDED Timespan=1995-2009

3 602 Topic=(atrial fibrillation AND stroke* AND (prophyla* OR prevent* OR "risk
assessment")) AND Topic=((anticoagul* OR antithromb* or anti OR antifibrinoly* OR
antiplatelet* OR warfarin OR aspirin OR heparin*)) AND Topic=(cohort* OR
population* OR series OR "case control" OR trial*)

Refined by: Topic=(intracranial* OR hemorrhag* OR bleed* OR cardioemboli* or
paroxysmal or cryptogenic*)

Databases=SCI-EXPANDED Timespan=1995-2009

2 1,229 Topic=(atrial fibrillation AND stroke* AND (prophyla* OR prevent* OR "risk
assessment")) AND Topic=((anticoagul* OR antithromb* or anti OR antifibrinoly* OR
antiplatelet* OR warfarin OR aspirin OR heparin*)) AND Topic=(cohort* OR
population* OR series OR "case control" OR trial*)

Databases=SCI-EXPANDED Timespan=1995-2009

Topic((((paf or pxaf or paroxysm* or intermittent) SAME "atrial fibrillation") OR
"premature beats" OR palpitation*) AND Topic=(stroke* OR ((brain OR cerebral OR
cerebrovascular OR intracranial) AND (cryptogenic* OR occult OR silent OR
asymptomatic* OR unknown* OR undetect*)) OR cardioembol* OR "transient
isch?emic") AND Topic=(ecg OR ekg OR electrocard* OR monitor* OR holter* OR
telemet* OR "event loop" OR ELR OR record* OR screen*) AND Topic=(detect* OR
predict* OR risk* or trial* OR incidence or surviv* or value OR effective* or sensitiv*
OR specific*) 245

Appendix e-4: AAN rules for classification of evidence for risk of bias

For questions related to therapeutic intervention

Class I

- The study is a randomized clinical trial.
- All relevant baseline characteristics are presented and substantially equivalent between treatment groups or there is appropriate statistical adjustment for differences.
- Outcome measurement is objective or determined without knowledge of treatment status.
- The following also are required:
 - a. The primary outcome(s) is/are defined.
 - b. The inclusion criteria are defined.
 - c. There is accounting of dropouts and crossovers (with at least 80% of enrolled subjects completing the study).
 - d. There is concealed allocation.
 - e. For noninferiority or equivalence trials claiming to prove efficacy for one or both drugs, the following are also required*:
 1. The authors explicitly state the clinically meaningful difference to be excluded by defining the threshold for equivalence or noninferiority.
 2. The standard treatment used in the study is substantially similar to that used in previous studies establishing efficacy of the standard treatment (e.g., for a drug, the mode of administration, dose, and dosage adjustments are similar to those previously shown to be effective).
 3. The inclusion and exclusion criteria for patient selection and the outcomes of patients on the standard treatment are comparable with those of previous studies establishing efficacy of the standard treatment.
 4. The interpretation of the results of the study is based on a per-protocol analysis that takes into account dropouts or crossovers.

Class II

- The study is a cohort study meeting criteria a–c above or is a randomized, controlled trial that lacks one or two criteria a–d.¹
- All relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.
- There is masked or objective outcome assessment.

Class III

- The study is a controlled study (including well-defined natural history controls or patients serving as their own controls).
- The study includes a description of major confounding differences between treatment groups that could affect outcome.

- Outcome assessment is masked, objective, or performed by someone who is not a member of the treatment team.

Class IV

- The study does not include patients with the disease.
- The study does not include patients receiving different interventions.
- The study uses undefined or unaccepted interventions or outcome measures.
- No measures of effectiveness or statistical precision are presented or calculable.

For questions related to screening (yield)

Class I

A statistical,^a population-based^b sample of patients studied at a uniform point in time (usually early) during the course of the condition. All patients undergo the intervention of interest. The outcome, if not objective,^c is determined in an evaluation that is masked to the patients' clinical presentations.

Class II

A statistical,^b non-referral-clinic-based^d sample of patients studied at a uniform point in time (usually early) during the course of the condition. Most (>80%) patients undergo the intervention of interest. The outcome, if not objective,^c is determined in an evaluation that is masked to the patients' clinical presentations.

Class III

A sample of patients studied during the course of the condition. Some patients undergo the intervention of interest. The outcome, if not objective,^c is determined in an evaluation by someone other than the treating physician.

Class IV

The data are derived from expert opinion, case reports, or any study not meeting criteria for Class I to III.

Notes

- Statistical sample: The study uses a complete (consecutive), random, or systematic (e.g., every third patient) sample of the available population with the disease.
- Population based: The available population for the study consists of all patients within a defined geographic region.
- Objective: The objective consists of an outcome measure that is very unlikely to be affected by an observer's expectations (e.g., determination of death, the presence of a mass on head CT, serum B12 assays).
- Non-referral-clinic based: The available population for the study consists of all patients presenting to a primary care setting with the condition. For referral-clinic-

based studies, the available population consists of all patients referred to a tertiary care or specialty setting. These patients may have been selected for more severe or unusual forms of the condition and thus may be less representative.

Appendix e-5: Rules for determining confidence in evidence

- Modal modifiers used to indicate the final confidence in evidence in the conclusions
 - High confidence: highly likely or highly probable
 - Moderate confidence: likely or probable
 - Low confidence: possibly
 - Very low confidence: insufficient evidence
- Initial rating of confidence in the evidence for each intervention outcome pair
 - High: requires two or more Class I studies
 - Moderate: requires one Class I study or two or more Class II studies
 - Low: requires one Class II study or two or more Class III studies
 - Very low: requires only one Class III study or one or more Class IV studies
- Factors that could result in downgrading confidence by one or more levels
 - Consistency
 - Precision
 - Directness
 - Publication bias
 - Biologic plausibility
- Factors that could result in downgrading confidence by one or more levels or upgrading confidence by one level
 - Magnitude of effect
 - Dose response relationship
 - Direction of bias

Summary evidence table template

Therapy	Outcome(s)	Number & Class of Studies	Effect	Precision	Consistent	Directness	Plausible	Reporting Bias	Magnitude of Effect	Dose Response	Direction of Bias	Comment	Confidence in Evidence

Appendix e-6. Evidence synthesis tables

Population screening

Patient population: For patients with cryptogenic stroke Intervention: How often do various technologies Inpatient telemetry Holter monitor											
Intervention	Outcomes	Number & Class of Studies	Effect (yield)	Precision	Consistent	Directness	Plausible	Magnitude of Effect	Dose Response	Comment	Confidence in Evidence
Atrial fibrillation screening	Incidence of atrial fibrillation	2 Class II and 13 Class III	Overall, among patients with cryptogenic stroke, occult atrial fibrillation was identified	-	-	-	-	-	U	Overall, it appears that screening for atrial fibrillation after hospitalization yields a meaningful incidence of atrial fibrillation and the yield is related to the duration of monitoring	Moderate

Therapies

Patient population: For patient with nonvalvular atrial fibrillation

Including these special populations:

Patients with intracranial hemorrhages (spontaneous transformation, posttraumatic, hypertensive,

***Patients with intracranial or intraspinal (vascular malformations)

***Patients s/p CABG

Other special populations: Elderly, nursing home residents, end-stage renal disease, dementia

Intervention: What therapies

Apixaban vs aspirin

Intervention	Outcome	Number & Class of Studies	Effect	Precision	Consistent	Directness	Plausibility	Magnitude of Effect	Dose Response	Comment	Confidence in Evidence
APIXABAN 5 mg bid vs.	The primary efficacy outcome was the occurrence of stroke (ischemic or hemorrhagic) or systemic embolism.	ONE STUDY	U					U		The study was terminated prematurely.	MODERATE
ASPIRIN 81-324 mg/day	The primary safety outcome was the occurrence of major bleeding,	CLASS I								In patients with atrial fibrillation for whom vitamin K antagonist therapy was unsuitable, apixaban reduced the risk of stroke or systemic embolism without significantly increasing the risk of major bleeding or intracranial hemorrhage.	
	Other outcomes of interest included the rates of myocardial infarction, death from vascular causes, and death from any cause, as well as composites of major vascular events										

Apixaban vs warfarin

Intervention	Outcome	Number & Class of Studies	Effect	Precision	Consistent	Directness	Plausibility	Magnitude of Effect	Dose Response	Comment	Confidence in Evidence
APIXABAN 5 mg bid VS	The primary objective was to determine whether apixaban was noninferior to warfarin in reducing the rate of stroke (ischemic or hemorrhagic) or systemic embolism among patients with atrial fibrillation and at least one other risk factor for stroke. The primary safety outcome was major bleeding	ONE STUDY	U					U	D		MODERATE
WARFARIN INR 2-3	secondary objectives were to determine whether apixaban was superior to warfarin with respect to the primary outcome and to the rates of major bleeding and death from any cause.	CLASS I								In patients with atrial fibrillation, apixaban was superior to warfarin in preventing stroke or systemic embolism, caused less bleeding, and resulted in lower mortality.	

Clopidogrel plus aspirin vs aspirin

Intervention	Outcome	Number & Class of Studies	Effect	Precision	Consistent	Directness	Plausible	Magnitude of Effect	Dose Response	Comment	Confidence in Evidence
CLOPIDOGREL ADDED TO ASA VS ASA AND PLACEBO	Primary outcome was the composite of stroke, myocardial infarction, systemic embolism, or death from vascular causes Secondary outcome was stroke and individual components of the composite group.	ONE STUDY CLASS I	U	—	—	—	—	U	U	In patients with atrial fibrillation for whom vitamin K-antagonist therapy was unsuitable, the addition of clopidogrel to aspirin reduced the risk of major vascular events, especially stroke, and increased the risk of major hemorrhage. The combination is not suitable as a recommendation for therapy of atrial fibrillation.	HIGH

Dabigatran vs warfarin

Intervention	Outcome	Number & Class of Studies	Effect	Precision	Consistent	Directness	Plausible	Magnitude of Effect	Dose Response	Comment	Confidence in Evidence
DABIGATRAN VS WARFARIN	Primary outcomes: Stroke and systemic embolism. Secondary outcomes: Major hemorrhage, Stroke, systemic embolism, and death. Other outcomes were myocardial infarction, pulmonary embolism, transient ischemic attack, and hospitalization.	ONE STUDY CLASS I	U	—	—	—	—	—	U	In patients with atrial fibrillation, dabigatran given at a dose of 110 mg was associated with rates of stroke and systemic embolism that were similar to those associated with warfarin, as well as lower rates of major hemorrhage. Dabigatran administered at a dose of 150 mg, as compared with warfarin, was associated with lower rates of stroke and systemic embolism but similar rates of major hemorrhage.	MODERATE

Warfarin one INR range vs warfarin different INR

Intervention	Outcome (complication)	Number & Class of Studies	Effect	Precision	Consistent	Directness	Plausibility	Magnitude of Effect	Dose Response	Comment	Confidence in Evidence
Warfarin INR target 1.5-2.0 vs. Warfarin INR target 2-3	Thromboembolism and major hemorrhages	One, Class I	Lower event rate with INR 1.5-2.0 in patients >age 75 p=0.1	D	D	-	-	-	-	Study severely underpowered	Low
Warfarin INR target 2-3 vs. Aspirin 75 mg per day	fatal or disabling stroke, major hemorrhage, systemic embolism	One, Class I	relative risk 0.48 with warfarin relative to ASA p=0.003 Absolute risk reduction 2% per year	-	D	-	-	U	-	Open label with blinded adjudication of endpoints. At odds with study above but this was a much larger RCT	High
Warfarin INR >2 vs. Warfarin INR <2 vs. ASA vs. No therapy	severe disability mRS >3 or death at discharge	Two, Class II	Odds ratio 4.1, 2.1, and 1.5 for no therapy, ASA, or warfarin INR <2 for endpoint of severe disability or death compared to warfarin >2	-	-	-	-	-	-	therapeutic INR on admission associated with lower stroke severity	moderate
			Odds ratio 1.9 for severe stroke if INR <2 on admission; hazard ratio 3.4 for death within 30 days if INR <2 on admission							therapeutic INR on admission associated with lower stroke severity and lower mortality at 30 days	
Warfarin INR	stroke, major hemorrhage, death	One, Class II	Observational study of geriatrics clinic pts followed for one year 2% risk of stroke, 6% risk of major hemorrhage, 20% mortality	-	-	-	-	-	-	Patients with history of falls and/or dementia had a high mortality rate (45%) compared to the overall group (20%)	low

Rivaroxaban vs warfarin

Intervention	OUTCOME	Number & Class of Studies	Effect	Precision	Consistent	Directness	Plausible	Magnitude of Effect	Dose Response	Comment	Confidence in Evidence
RIVAROXABAN	The primary efficacy end point was the composite	ONE STUDY	U	-	N/A	-	-	U	-	In patients with atrial fibrillation, Rivaroxaban was	MODERATE
VS. WARFARIN	of stroke (ischemic or hemorrhagic) and systemic embolism.	CLASS I								noninferior to Warfarin for the prevention of stroke or systemic embolism. There was no significant between-group difference in the risk of major bleeding, although intracranial and fatal bleeding occurred less frequently in the Rivaroxaban group.	

Acenocoumarol plus triflusal vs acenocoumarol

Intervention	Outcome	Number & Class of Studies	Effect	Precision	Consistent	Directness	Plausible	Magnitude of Effect	Dose Response	Comment	Confidence in Evidence
Triflusal plus acenocoumarol	Primary outcomes: Vascular death, TIA, and nonfatal	One study Class I	U	-	-	-	-	-	U	The combined antiplatelet plus moderate-intensity anticoagulation therapy significantly	MODERATE
compared to triflusal and acenocoumarol	stroke or systemic embolism									decreased vascular events compared with anticoagulation alone and proved to be safe in atrial fibrillation patients. Primary outcome plus severe bleeding was lower with combined therapy in the intermediate-risk group. Median follow-up: 2.76 years.	
in patients with afib	Secondary outcomes : Severe bleeding, MI, nonvascular death, and non-severe									Median INR on acenocoumarol, 2.47	
and moderate risk										Median INR on combined therapy, 1.93 Time within range: acenocoumarol, 65% (SD=22); combination therapy, 66% (SD=25).	
										Triflusal is an antiplatelet drug structurally related to acetylsalicylic acid that is widely used in Europe, Latin America and South East Asia. Acenocoumarol is a coumarin derivative mostly used in European countries.	

Appendix e-7: Steps and rules for formulating recommendations

Constructing the recommendation and its rationale

Rationale for recommendation summarized in the Clinical Context includes three categories of premises

- Evidence-based conclusions for the systematic review
- Stipulated axiomatic principles of care
- Strong evidence from related conditions not systematically reviewed

Actionable recommendations include the following mandatory elements

- The patient population that is the subject of the recommendation
- The person performing the action of the recommendation statement
- The specific action to be performed
- The expected outcome to be attained

Assigning a level of obligation

Modal modifiers used to indicate the final level of obligation (LOO)

- Level A: “Must”
- Level B: “Should”
- Level C: “Might”
- Level U: No recommendation supported

LOO assigned by eliciting panel members’ judgments regarding multiple domains, using a modified Delphi process. Goal is to attain consensus after a maximum of three rounds of voting. Consensus is defined by:

- $\geq 80\%$ agreement on dichotomous judgments
- $\geq 80\%$ agreement, within one point for ordinal judgments
- If consensus obtained, LOO assigned at the median. If not obtained, LOO assigned at the 10th percentile

Three steps used to assign final LOO

1. Initial LOO determined by the cogency of the deductive inference supporting the recommendation on the basis of ratings within four domains. Initial LOO anchored to lowest LOO supported by any domain.
 - Confidence in evidence. LOO anchored to confidence in evidence determined by modified form of the Grading of Recommendations Assessment, Development and Evaluation process¹⁵
 - Level A: High confidence
 - Level B: Moderate confidence
 - Level C: Low confidence
 - Level U: Very low confidence
 - Soundness of inference assuming all premises are true. LOO anchored to proportion of panel members convinced of soundness of the inference
 - Level A: 100%
 - Level B: $\geq 80\%$ to $< 100\%$
 - Level C: $\geq 50\%$ to $< 80\%$
 - Level U or R: $< 50\%$

- Acceptance of axiomatic principles: LOO anchored to proportion of panel members who accept principles
 - Level A: 100%
 - Level B: $\geq 80\%$ to $< 100\%$
 - Level C: $\geq 50\%$ to $< 80\%$
 - Level U or R: $< 50\%$
 - Belief that evidence cited from related conditions is strong: LOO anchored to proportion of panel members who believe the related evidence is strong
 - Level B: $\geq 80\%$ to 100% (recommendations dependent on inferences from nonsystematically reviewed evidence cannot be anchored to a Level A LOO)
 - Level C: $\geq 50\%$ to $< 80\%$
 - Level U or R: $< 50\%$
- 2. LOO is modified mandatorily on the basis of the judged magnitude of benefit relative to harm expected to be derived from complying with the recommendation
 - Magnitude relative to harm rated on 4-point ordinal scale
 - Large benefit relative to harm: benefit judged large, harm judged none
 - Moderate benefit relative to harm: benefit judged large, harm judged minimal; or benefit judged moderate, harm judged none
 - Small benefit relative to harm: benefit judged large, harm judged moderate; or benefit judged moderate, harm judged minimal; or benefit judged small, harm judged none
 - Benefit to harm judged too close to call: benefit and harm judged to be substantially similar
 - Regardless of cogency of the recommendation the LOO can be no higher than that supported by the rating of the magnitude of benefit relative to harm
 - Level A: large benefit relative to harm
 - Level B: moderate benefit relative to harm
 - Level C: small benefit relative to harm
 - Level U: too close to call
 - LOO can be increased by one grade if LOO corresponding to benefit relative to harm greater than LOO corresponding to the cogency of the recommendation
- 3. LOO optionally downgraded on the basis of the following domains
 - Importance of the outcome: critical, important, mildly important, not important
 - Expected variation in patient preferences: none, minimal, moderate, large
 - Financial burden relative to benefit expected: none, minimal, moderate, large
 - Availability of intervention: universal, usually, sometimes, limited

The Clinical Contextual Profiles shown in appendix e-8 summarize the results of panel ratings for each domain described above. The profiles also indicate the corresponding assigned LOOs. The last column in each indicates whether consensus was obtained for that domain.

Appendix e-8: Clinical contextual profiles

A1. Clinicians might obtain outpatient cardiac rhythm studies in patients with cryptogenic stroke without known NVAF, to identify patients with occult NVAF (Level C).

	R	C	B	A	Consensus
Level of obligation	None	May	Should	Must	
Availability	Limited 0	Sometimes 0	Usually 4	Universal 1	Yes
Financial burden	Prohibitive 0	Moderate 2	Minimal 3	None 0	Yes
Variation in preferences	Large 0	Moderate 0	Small 4	Minimal 1	Yes
Importance of outcomes	Not important	Mildly Important	Important	Critical	Yes
Benefit relative to Harm	Too close to call	Small	Moderate	Large	
Magnitude of Harm	Large 0	Moderate 0	Modest 3	Minimal 2	Yes
Magnitude of Benefit	Minimal 0	Modest 0	Moderate 3	Large 2	Yes
Cogency of recommendation	Very wkly Cogent	Weakly Cogent	Modtly Cogent	Strngly Cogent	
Strong evidence other cond	<50%	≥50% to < 80%	≥80% to 100%	X	Yes
Confidence in evidence	Very low 0	Low 2	Moderate 1	High 2	No
Acceptance of Principles	<50%	≥50% to < 80%	≥80% to < 100%	100%	Yes
Sound inference	<50%	≥50% to < 80%	≥ 80% to < 100%	100%	Yes

A2. Clinicians might obtain cardiac rhythm studies for prolonged periods (e.g., for 1 or more weeks) instead of shorter periods (e.g., 24 hours) in patients with cryptogenic stroke without known NVAF, to increase the yield of identification of patients with occult NVAF (Level C).

	R	C	B	A	Consensus
Level of obligation	None	May	Should	Must	
Availability	Limited 0	Sometimes 0	Usually 5	Universal 0	Yes
Financial burden	Prohibitive 0	Moderate 4	Minimal 1	None 0	Yes
Variation in preferences	Large 0	Moderate 1	Small 4	Minimal 0	Yes
Importance of outcomes	Not important	Mildly Important	Important	Critical	Yes
Benefit relative to Harm	Too close to call	Small	Moderate	Large	
Magnitude of Harm	Large 0	Moderate 0	Modest 1	Minimal 4	Yes
Magnitude of Benefit	Minimal 0	Modest 0	Moderate 3	Large 2	Yes
Cogency of recommendation	Very wkly Cogent	Weakly Cogent	Modtly Cogent	Strngly Cogent	
Strong evidence other cond	<50%	≥50% to < 80%	≥80% to 100%	X	Yes
Confidence in evidence	Very low 0	Low 1	Moderate 4	High 0	Yes
Acceptance of Principles	<50%	≥50% to < 80%	≥80% to < 100%	100%	Yes
Sound inference	<50%	≥50% to < 80%	≥ 80% to < 100%	100%	Yes

B1. Clinicians should inform patients with NVAF that these patients have an increased stroke risk and that this risk can potentially be reduced by antithrombotic use. Patients should also be informed that antithrombotic use increases their risk of major bleeding (Level B).

	R	C	B	A	Consensus
Level of obligation	None	May	Should	Must	
Availability	Limited 0	Sometimes 0	Usually 0	Universal 5	Yes
Financial burden	Prohibitive 0	Moderate 0	Minimal 1	None 4	Yes
Variation in preferences	Large 0	Moderate 0	Small 3	Minimal 2	Yes
Importance of outcomes	Not important	Mildly Important	Important	Critical	Yes
Benefit relative to Harm	Too close to call	Small	Moderate	Large	
Magnitude of Harm	Large 0	Moderate 0	Modest 0	Minimal 5	Yes
Magnitude of Benefit	Minimal 0	Modest 0	Moderate 0	Large 5	Yes
Cogency of recommendation	Very wkly Cogent	Weakly Cogent	Modtly Cogent	Strngly Cogent	
Strong evidence other cond	<50%	≥50% to < 80%	≥80% to 100%	X	Yes
Confidence in evidence	Very low 0	Low 0	Moderate 2	High 3	Yes
Acceptance of Principles	<50%	≥50% to < 80%	≥80% to < 100%	100%	Yes
Sound inference	<50%	≥50% to < 80%	≥ 80% to < 100%	100%	Yes

B2. Clinicians should counsel all patients with NVAF that the decision to use antithrombotics must be made only after the potential benefit from the stroke risk reduction has been weighed against the potential harm from the increased risk of major bleeding. Clinicians should also emphasize the important role of judgment and preferences in this decision (Level B not downgraded to C for preferences).

	R	C	B	A	Consensus
Level of obligation	None	May	Should	Must	
Availability	Limited 0	Sometimes 0	Usually 1	Universal 4	Yes
Financial burden	Prohibitive 0	Moderate 1	Minimal 1	None 3	No
Variation in preferences	Large 0	Moderate 2	Small 0	Minimal 3	No
Importance of outcomes	Not important	Mildly Important	Important	Critical	Yes
Benefit relative to Harm	Too close to call	Small	Moderate	Large	
Magnitude of Harm	Large 0	Moderate 0	Modest 2	Minimal 3	Yes
Magnitude of Benefit	Minimal 0	Modest 0	Moderate 1	Large 4	Yes
Cogency of recommendation	Very wkly Cogent	Weakly Cogent	Modtly Cogent	Strngly Cogent	
Strong evidence other cond	<50%	≥50% to < 80%	≥80% to 100%	X	Yes
Confidence in evidence	Very low 0	Low 0	Moderate 1	High 3	Yes
Acceptance of Principles	<50%	≥50% to < 80%	≥80% to < 100%	100%	Yes
Sound inference	<50%	≥50% to < 80%	≥ 80% to < 100%	100%	Yes

B3. Clinicians should routinely offer anticoagulation to patients with NVAF and a history of TIA or stroke, to reduce these patients' subsequent risk of ischemic stroke (Level B not downgraded to C for cost or preferences).

	R	C	B	A	Consensus
Level of obligation	None	May	Should	Must	
Availability	Limited 0	Sometimes 0	Usually 5	Universal 0	Yes
Financial burden	Prohibitive 0	Moderate 4	Minimal 1	None 0	Yes
Variation in preferences	Large 0	Moderate 4	Small 1	Minimal 0	Yes
Importance of outcomes	Not important	Mildly Important	Important	Critical	Yes
Benefit relative to Harm	Too close to call	Small	Moderate	Large	
Magnitude of Harm	Large 0	Moderate 1	Modest 4	Minimal 0	Yes
Magnitude of Benefit	Minimal 0	Modest 0	Moderate 0	Large 5	Yes
Cogency of recommendation	Very wkly Cogent	Weakly Cogent	Modtly Cogent	Strngly Cogent	
Strong evidence other cond	<50%	≥50% to < 80%	≥80% to 100%	X	Yes
Confidence in evidence	Very low 0	Low 0	Moderate 2	High 3	Yes
Acceptance of Principles	<50%	≥50% to < 80%	≥80% to < 100%	100%	Yes
Sound inference	<50%	≥50% to < 80%	≥ 80% to < 100%	100%	Yes

B4. Clinicians might not offer anticoagulation to patients with NVAF who lack additional risk factors (“lone” NVAF patients). Clinicians might reasonably offer antithrombotic therapy with aspirin to such patients or might not offer antithrombotic therapy at all (Level C).

Level of obligation	R None	C May	B Should	A Must	Consensus
Availability	Limited 0	Sometimes 0	Usually 0	Universal 5	Yes
Financial burden	Prohibitive 0	Moderate 0	Minimal 4	None 1	Yes
Variation in preferences	Large 0	Moderate 1	Small 3	Minimal 1	No
Importance of outcomes	Not important	Mildly Important	Important	Critical	Yes
Benefit relative to Harm	Too close to call	Small	Moderate	Large	
Magnitude of Harm	Large 0	Moderate 0	Modest 3	Minimal 2	Yes
Magnitude of Benefit	Minimal 0	Modest 2	Moderate 3	Large 0	Yes
Cogency of recommendation	Very wkly Cogent	Weakly Cogent	Modtly Cogent	Strngly Cogent	
Strong evidence other cond	<50%	≥50% to < 80%	≥80% to 100%	x	Yes
Confidence in evidence	Very low 0	Low 0	Moderate 4	High 1	Yes
Acceptance of Principles	<50%	≥50% to < 80%	≥80% to < 100%	100%	Yes
Sound inference	<50%	≥50% to < 80%	≥ 80% to < 100%	100%	Yes

B5. To inform their judgments as to which patients with NVAF might benefit more from anticoagulation, clinicians should use a risk stratification scheme to help identify patients with NVAF who are at higher risk for stroke or at no clinically significant risk. However, clinicians should not rigidly interpret anticoagulation thresholds suggested by these tools as being definitive indicators of which patients require anticoagulation (Level B).

Level of obligation	R None	C May	B Should	A Must	Consensus
Availability	Limited 0	Sometimes 0	Usually 0	Universal 5	Yes
Financial burden	Prohibitive 0	Moderate 0	Minimal 0	None 5	Yes
Variation in preferences	Large 0	Moderate 0	Small 3	Minimal 2	Yes
Importance of outcomes	Not important	Mildly Important	Important	Critical	Yes
Benefit relative to Harm	Too close to call	Small	Moderate	Large	
Magnitude of Harm	Large 0	Moderate 0	Modest 1	Minimal 4	Yes
Magnitude of Benefit	Minimal 0	Modest 0	Moderate 4	Large 1	Yes
Cogency of recommendation	Very wkly Cogent	Weakly Cogent	Modtly Cogent	Strngly Cogent	
Strong evidence other cond	<50%	≥50% to < 80%	≥80% to 100%	x	Yes
Confidence in evidence	Very low 0	Low 0	Moderate 5	High 0	Yes
Acceptance of Principles	<50%	≥50% to < 80%	≥80% to < 100%	100%	Yes
Sound inference	<50%	≥50% to < 80%	≥ 80% to < 100%	100%	Yes

C1. To reduce the risk of stroke or subsequent stroke in patients with NVAF judged to require oral anticoagulants, clinicians should choose 1 of the following options (Level B not downgraded to C for preferences or cost):

- Warfarin, target INR 2.0–3.0
- Dabigatran 150 mg twice daily (if CrCl > 30 mL/min)
- Rivaroxaban 15 mg/day (if CrCl 30–49 mL/min) or 20 mg/day

- Apixaban 5 mg twice daily (if serum creatinine < 1.5 mg/dL) or 2.5 mg twice daily (if serum creatinine > 1.5 and < 2.5 mg/dL, and body weight < 60 kg or age at least 80 years [or both])
- Triflusal 600 mg plus acenocoumarol, target INR 1.25–2.0 (patients at moderate stroke risk, mostly in developing countries)

	R	C	B	A	Consensus
Level of obligation	None	May	Should	Must	
Availability	Limited 0	Sometimes 0	Usually 4	Universal 1	Yes
Financial burden	Prohibitive 0	Moderate 3	Minimal 2	None 0	Yes
Variation in preferences	Large 0	Moderate 5	Small 0	Minimal 0	Yes
Importance of outcomes	Not important	Mildly Important	Important	Critical	Yes
Benefit relative to Harm	Too close to call	Small	Moderate	Large	
Magnitude of Harm	Large 0	Moderate 2	Modest 3	Minimal 0	Yes
Magnitude of Benefit	Minimal 0	Modest 0	Moderate 0	Large 5	Yes
Cogency of recommendation	Very wkly Cogent	Weakly Cogent	Modtly Cogent	Strngly Cogent	
Strong evidence other cond	<50%	≥50% to < 80%	≥80% to 100%	X	Yes
Confidence in evidence	Very low 0	Low 0	Moderate 1	High 4	Yes
Acceptance of Principles	<50%	≥50% to < 80%	≥80% to < 100%	100%	Yes
Sound inference	<50%	≥50% to < 80%	≥ 80% to < 100%	100%	Yes

C2. Clinicians might recommend that patients taking warfarin whose condition is well controlled continue warfarin treatment rather than switch to treatment with a new oral anticoagulant (Level C).

	R	C	B	A	Consensus
Level of obligation	None	May	Should	Must	
Availability	Limited 0	Sometimes 0	Usually 1	Universal 4	Yes
Financial burden	Prohibitive 0	Moderate 1	Minimal 1	None 3	No
Variation in preferences	Large 0	Moderate 4	Small 1	Minimal 0	Yes
Importance of outcomes	Not important	Mildly Important	Important	Critical	Yes
Benefit relative to Harm	Too close to call	Small	Moderate	Large	
Magnitude of Harm	Large 0	Moderate 0	Modest 3	Minimal 2	Yes
Magnitude of Benefit	Minimal 0	Modest 1	Moderate 0	Large 4	No
Cogency of recommendation	Very wkly Cogent	Weakly Cogent	Modtly Cogent	Strngly Cogent	
Strong evidence other cond	<50%	≥50% to < 80%	≥80% to 100%	X	Yes
Confidence in evidence	Very low 0	Low 0	Moderate 2	High 3	Yes
Acceptance of Principles	<50%	≥50% to < 80%	≥80% to < 100%	100%	Yes
Sound inference	<50%	≥50% to < 80%	≥ 80% to < 100%	100%	Yes

C3. Clinicians should administer dabigatran, rivaroxaban, or apixaban to patients who have NVAf requiring anticoagulant medication and are at higher risk of intracranial bleeding (Level B not downgraded to C for preferences of cost).

	R	C	B	A	Consensus
Level of obligation	None	May	Should	Must	
Availability	Limited 0	Sometimes 0	Usually 5	Universal 0	Yes
Financial burden	Prohibitive 0	Moderate 4	Minimal 1	None 0	Yes
Variation in preferences	Large 0	Moderate 4	Small 1	Minimal 0	Yes
Importance of outcomes	Not important	Mildly Important	Important	Critical	Yes
Benefit relative to Harm	Too close to call	Small	Moderate	Large	
Magnitude of Harm	Large 0	Moderate 0	Modest 4	Minimal 1	Yes
Magnitude of Benefit	Minimal 0	Modest 0	Moderate 2	Large 3	Yes
Cogency of recommendation	Very wkly Cogent	Weakly Cogent	Modtly Cogent	Strngly Cogent	
Strong evidence other cond	<50%	≥50% to < 80%	≥80% to 100%	X	Yes
Confidence in evidence	Very low 0	Low 0	Moderate 2	High 3	Yes
Acceptance of Principles	<50%	≥50% to < 80%	≥80% to < 100%	100%	Yes
Sound inference	<50%	≥50% to < 80%	≥ 80% to < 100%	100%	Yes

C4. Clinicians might offer apixaban to patients with NVAf and GI bleeding risk who require anticoagulant medication (Level C).

	R	C	B	A	Consensus
Level of obligation	None	May	Should	Must	
Availability	Limited 0	Sometimes 3	Usually 2	Universal 0	Yes
Financial burden	Prohibitive 0	Moderate 2	Minimal 3	None 0	Yes
Variation in preferences	Large 0	Moderate 3	Small 2	Minimal 0	Yes
Importance of outcomes	Not important	Mildly Important	Important	Critical	Yes
Benefit relative to Harm	Too close to call	Small	Moderate	Large	
Magnitude of Harm	Large 0	Moderate 0	Modest 2	Minimal 3	Yes
Magnitude of Benefit	Minimal 1	Modest 0	Moderate 2	Large 2	No
Cogency of recommendation	Very wkly Cogent	Weakly Cogent	Modtly Cogent	Strngly Cogent	
Strong evidence other cond	<50%	≥50% to < 80%	≥80% to 100%	X	No
Confidence in evidence	Very low 0	Low 0	Moderate 1	High 4	Yes
Acceptance of Principles	<50%	≥50% to < 80%	≥80% to < 100%	100%	Yes
Sound inference	<50%	≥50% to < 80%	≥ 80% to < 100%	100%	Yes

C5. Clinicians should offer dabigatran, rivaroxaban, or apixaban to patients unwilling or unable to submit to frequent periodic testing of INR levels (Level B not downgraded to C for cost or preferences).

	R	C	B	A	Consensus
Level of obligation	None	May	Should	Must	
Availability	Limited 0	Sometimes 0	Usually 5	Universal 0	Yes
Financial burden	Prohibitive 0	Moderate 4	Minimal 1	None 0	Yes
Variation in preferences	Large 0	Moderate 4	Small 1	Minimal 0	Yes
Importance of outcomes	Not important	Mildly Important	Important	Critical	Yes
Benefit relative to Harm	Too close to call	Small	Moderate	Large	
Magnitude of Harm	Large 0	Moderate 0	Modest 5	Minimal 0	Yes
Magnitude of Benefit	Minimal 0	Modest 0	Moderate 2	Large 3	Yes
Cogency of recommendation	Very wkly Cogent	Weakly Cogent	Modtly Cogent	Strngly Cogent	
Strong evidence other cond	<50%	≥50% to < 80%	≥80% to 100%	X	Yes
Confidence in evidence	Very low 0	Low 0	Moderate 1	High 3	Yes
Acceptance of Principles	<50%	≥50% to < 80%	≥80% to < 100%	100%	Yes
Sound inference	<50%	≥50% to < 80%	≥ 80% to < 100%	100%	Yes

C6. Clinicians should offer apixaban to patients unsuitable for being treated, or unwilling to be treated, with warfarin (Level B not downgraded to C for preferences).

	R	C	B	A	Consensus
Level of obligation	None	May	Should	Must	
Availability	Limited 0	Sometimes 2	Usually 3	Universal 0	Yes
Financial burden	Prohibitive 0	Moderate 2	Minimal 3	None 0	Yes
Variation in preferences	Large 0	Moderate 3	Small 2	Minimal 0	Yes
Importance of outcomes	Not important	Mildly Important	Important	Critical	Yes
Benefit relative to Harm	Too close to call	Small	Moderate	Large	
Magnitude of Harm	Large 0	Moderate 0	Modest 2	Minimal 3	Yes
Magnitude of Benefit	Minimal 0	Modest 0	Moderate 2	Large 3	Yes
Cogency of recommendation	Very wkly Cogent	Weakly Cogent	Modtly Cogent	Strngly Cogent	
Strong evidence other cond	<50%	≥50% to < 80%	≥80% to 100%	X	Yes
Confidence in evidence	Very low 0	Low 0	Moderate 2	High 3	Yes
Acceptance of Principles	<50%	≥50% to < 80%	≥80% to < 100%	100%	Yes
Sound inference	<50%	≥50% to < 80%	≥ 80% to < 100%	100%	Yes

C7. Where apixaban is unavailable, clinicians might offer dabigatran or rivaroxaban (Level C).

	R	C	B	A	Consensus
Level of obligation	None	May	Should	Must	
Availability	Limited 0	Sometimes 0	Usually 5	Universal 0	Yes
Financial burden	Prohibitive 0	Moderate 2	Minimal 2	None 1	No
Variation in preferences	Large 0	Moderate 3	Small 1	Minimal 1	No
Importance of outcomes	Not important	Mildly Important	Important	Critical	Yes
Benefit relative to Harm	Too close to call	Small	Moderate	Large	
Magnitude of Harm	Large 0	Moderate 0	Modest 4	Minimal 1	Yes
Magnitude of Benefit	Minimal 0	Modest 0	Moderate 2	Large 3	Yes
Cogency of recommendation	Very wkly Cogent	Weakly Cogent	Modtly Cogent	Strngly Cogent	
Strong evidence other cond	<50%	≥50% to < 80%	≥80% to 100%	X	Yes
Confidence in evidence	Very low 0	Low 0	Moderate 5	High 0	Yes
Acceptance of Principles	<50%	≥50% to < 80%	≥80% to < 100%	100%	Yes
Sound inference	<50%	≥50% to < 80%	≥ 80% to < 100%	100%	Yes

C8. Where oral anticoagulants are unavailable, clinicians might offer a combination of aspirin and clopidogrel (Level C).

	R	C	B	A	Consensus
Level of obligation	None	May	Should	Must	
Availability	Limited 0	Sometimes 0	Usually 1	Universal 4	Yes
Financial burden	Prohibitive 0	Moderate 1	Minimal 4	None 0	Yes
Variation in preferences	Large 0	Moderate 2	Small 2	Minimal 1	No
Importance of outcomes	Not important	Mildly Important	Important	Critical	Yes
Benefit relative to Harm	Too close to call	Small	Moderate	Large	
Magnitude of Harm	Large 0	Moderate 0	Modest 4	Minimal 1	Yes
Magnitude of Benefit	Minimal 0	Modest 1	Moderate 4	Large 0	Yes
Cogency of recommendation	Very wkly Cogent	Weakly Cogent	Modtly Cogent	Strngly Cogent	
Strong evidence other cond	<50%	≥50% to < 80%	≥80% to 100%	X	Yes
Confidence in evidence	Very low 0	Low 0	Moderate 2	High 3	Yes
Acceptance of Principles	<50%	≥50% to < 80%	≥80% to < 100%	100%	Yes
Sound inference	<50%	≥50% to < 80%	≥ 80% to < 100%	100%	Yes

C9. Where triflusal is available and patients are unable or unwilling to take new oral anticoagulants (mostly in developing countries), clinicians should offer acenocoumarol (target INR 1.25–2.0) and triflusal to patients with NVAf who are

at moderate stroke risk and higher bleeding risk (Level B not downgraded to C for availability, cost or preferences).

Level of obligation	R None	C May	B Should	A Must	Consensus
Availability	Limited 0	Sometimes 4	Usually 1	Universal 0	Yes
Financial burden	Prohibitive 0	Moderate 3	Minimal 2	None 0	Yes
Variation in preferences	Large 0	Moderate 4	Small 1	Minimal 0	Yes
Importance of outcomes	Not important	Mildly Important	Important	Critical	Yes
Benefit relative to Harm	Too close to call	Small	Moderate	Large	
Magnitude of Harm	Large 0	Moderate 0	Modest 2	Minimal 3	Yes
Magnitude of Benefit	Minimal 0	Modest 0	Moderate 5	Large 0	Yes
Cogency of recommendation	Very wkly Cogent	Weakly Cogent	Modtly Cogent	Strngly Cogent	
Strong evidence other cond	<50%	≥50% to < 80%	≥80% to 100%	X	Yes
Confidence in evidence	Very low 0	Low 0	Moderate 5	High 0	Yes
Acceptance of Principles	<50%	≥50% to < 80%	≥80% to < 100%	100%	Yes
Sound inference	<50%	≥50% to < 80%	≥ 80% to < 100%	100%	Yes

D1. Clinicians should routinely offer oral anticoagulants to elderly patients (aged > 75 years) with NVAF if there is no history of recent unprovoked bleeding or intracranial hemorrhage (Level B not downgraded to C for preferences).

Level of obligation	R None	C May	B Should	A Must	Consensus
Availability	Limited 0	Sometimes 0	Usually 5	Universal 0	Yes
Financial burden	Prohibitive 0	Moderate 2	Minimal 3	None 0	Yes
Variation in preferences	Large 0	Moderate 4	Small 1	Minimal 0	Yes
Importance of outcomes	Not important	Mildly Important	Important	Critical	Yes
Benefit relative to Harm	Too close to call	Small	Moderate	Large	
Magnitude of Harm	Large 0	Moderate 0	Modest 5	Minimal 0	Yes
Magnitude of Benefit	Minimal 0	Modest 0	Moderate 2	Large 3	Yes
Cogency of recommendation	Very wkly Cogent	Weakly Cogent	Modtly Cogent	Strngly Cogent	
Strong evidence other cond	<50%	≥50% to < 80%	≥80% to 100%	X	Yes
Confidence in evidence	Very low 0	Low 0	Moderate 5	High 0	Yes
Acceptance of Principles	<50%	≥50% to < 80%	≥80% to < 100%	100%	Yes
Sound inference	<50%	≥50% to < 80%	≥ 80% to < 100%	100%	Yes

D2. Clinicians might offer oral anticoagulation to patients with NVAF who have dementia or occasional falls. However, clinicians should counsel patients or their families that the risk–benefit ratio of oral anticoagulants is uncertain in patients with NVAF who have moderate to severe dementia or very frequent falls (Level B not downgraded to C for preferences).

	R	C	B	A	Consensus
Level of obligation	None	May	Should	Must	
Availability	Limited 0	Sometimes 0	Usually 0	Universal 5	Yes
Financial burden	Prohibitive 0	Moderate 0	Minimal 0	None 5	Yes
Variation in preferences	Large 0	Moderate 2	Small 0	Minimal 3	No
Importance of outcomes	Not important	Mildly Important	Important	Critical	Yes
Benefit relative to Harm	Too close to call	Small	Moderate	Large	
Magnitude of Harm	Large 0	Moderate 0	Modest 0	Minimal 5	Yes
Magnitude of Benefit	Minimal 0	Modest 0	Moderate 4	Large 1	Yes
Cogency of recommendation	Very wkly Cogent	Weakly Cogent	Modtly Cogent	Strngly Cogent	
Strong evidence other cond	<50%	≥50% to < 80%	≥80% to 100%	X	Yes
Confidence in evidence	Very low 0	Low 2	Moderate 3	High 0	Yes
Acceptance of Principles	<50%	≥50% to < 80%	≥80% to < 100%	100%	Yes
Sound inference	<50%	≥50% to < 80%	≥ 80% to < 100%	100%	Yes

D3. Because the risk–benefit ratio of oral anticoagulants in patients with NVAF and end-stage renal disease is unknown, there is insufficient evidence for making practice recommendations (Level U).

	R	C	B	A	Consensus
Level of obligation	None	May	Should	Must	
Availability	Limited 0	Sometimes 0	Usually 4	Universal 1	Yes
Financial burden	Prohibitive 0	Moderate 2	Minimal 2	None 1	No
Variation in preferences	Large 0	Moderate 5	Small 0	Minimal 0	Yes
Importance of outcomes	Not important	Mildly Important	Important	Critical	Yes
Benefit relative to Harm	Too close to call	Small	Moderate	Large	
Magnitude of Harm	Large 0	Moderate 0	Modest 5	Minimal 0	Yes
Magnitude of Benefit	Minimal 0	Modest 3	Moderate 2	Large 0	Yes
Cogency of recommendation	Very wkly Cogent	Weakly Cogent	Modtly Cogent	Strngly Cogent	
Strong evidence other cond	<50%	≥50% to < 80%	≥80% to 100%	X	Yes
Confidence in evidence	Very low 0	Low 5	Moderate 0	High 0	Yes
Acceptance of Principles	<50%	≥50% to < 80%	≥80% to < 100%	100%	Yes
Sound inference	<50%	≥50% to < 80%	≥ 80% to < 100%	100%	Yes

Appendix e-9: List of countries where triflusal available

List of countries (35) where triflusal is marketed and is available

The Americas

Argentina
Belize
Brazil
Costa Rica
Dominican Republic
El Salvador
Guatemala
Honduras
Mexico
Nicaragua
Panama
Uruguay

Africa

Angola
Mozambique

Asia

Armenia
Azerbaijan
Georgia
Indonesia
Kuwait
Lebanon
Malaysia
Mongolia
Philippines
South Korea
Thailand
Turkmenistan
Uzbekistan
Vietnam

Europe

Albania
Greece
Italy
Portugal
Romania
Spain
Ukraine

List of countries (20) where triflusal is in the process of registration and will be available soon

Africa

Benin
Cameroon
Chad
Ethiopia
Gabon
Ghana
Guinea-Conakry
Ivory Coast
Kenya
Mali
Mauritania
Mauritius
Rwanda
Senegal
South Africa
Tanzania
Togo
Uganda

Asia

Kyrgyztan

Europe

Moldova

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