Summary of 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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SPECIAL ARTICLE

Summary of 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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ABSTRACT

Objective: To update the 1998 American Academy of Neurology practice parameter on stroke prevention in nonvalvular atrial fibrillation (NVAF). How often do various technologies identify previously undetected NVAF? Which therapies reduce ischemic stroke risk with the least risk of hemorrhage, including intracranial hemorrhage? The complete guideline on which this summary is based is available as an online data supplement to this article.

Methods: Systematic literature review; modified Delphi process recommendation formulation.

Major conclusions: In patients with recent cryptogenic stroke, cardiac rhythm monitoring probably detects occult NVAF. In patients with NVAF, dabigatran, rivaroxaban, and apixaban are probably at least as effective as warfarin in preventing stroke and have a lower risk of intracranial hemorrhage. Triflusal plus acenocoumarol is likely more effective than acenocoumarol alone in reducing stroke risk. Clopidogrel plus aspirin is probably less effective than warfarin in preventing stroke and has a lower risk of intracranial bleeding. Clopidogrel plus aspirin as compared with aspirin alone probably reduces stroke risk but increases the risk of major hemorrhage. Apixaban is likely more effective than aspirin for decreasing stroke risk and has a bleeding risk similar to that of aspirin.

Major recommendations: Clinicians might obtain outpatient cardiac rhythm studies in patients with cryptogenic stroke to identify patients with occult NVAF (Level C) and should routinely offer anticoagulation to patients with NVAF and a history of TIA/stroke (Level B). Specific patient considerations will inform anticoagulant selection in patients with NVAF judged to need anticoagulation. *Neurology*® 2014;82:716–724

GLOSSARY

AAN = American Academy of Neurology; **AF** = atrial fibrillation; **CI** = confidence interval; **CKD** = chronic kidney disease; **CrCl** = creatinine clearance; **GI** = gastrointestinal; **HR** = hazard ratio; **INR** = international normalized ratio; **NVAF** = nonvalvular atrial fibrillation; **RRR** = relative risk reduction; **RR** = relative risk.

The prevalence of atrial fibrillation (AF) in the United States was estimated to be 3.03 million persons in 2005[1] and is strongly associated with increasing age.[1] Because AF is a major risk factor for cardioembolic stroke,[2,3] there is an urgent need to develop strategies for identification of AF and prevention of cardioembolic stroke at all ages.

The ischemic stroke rate among patients with AF averages 5% yearly[2] but varies greatly depending on individual clinical characteristics such as age, sex, race/ethnicity, and associated stroke risk factors. History of stroke or TIA identifies those patients with a high stroke risk, averaging 10% yearly.[3]

This evidence-based guideline updates a 1998 American Academy of Neurology (AAN) practice parameter on stroke prevention in nonvalvular atrial fibrillation (NVAF).[4] The complete guideline on which this summary is based is available as an online data supplement on the *Neurology*® Web site at www.neurology.org. This updated guideline reviews the evidence published since 1998 with regard to the detection of NVAF in patients with stroke and new therapies for the prevention of stroke in patients with NVAF, with a focus on 2 questions: 1) For patients with cryptogenic stroke, how often do various technologies identify previously undetected NVAF? 2) For patients with NVAF, which therapies that include

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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).[5,6] The panel searched MEDLINE, EMBASE, Cochrane, and Web of Science using appropriate search terms to locate relevant articles published between 1998 and March 2013. The search was restricted to peer-reviewed articles on human subjects written in English.

The panel synthesized the evidence and developed conclusions using a modified form of the Grading of Recommendations Assessment, Development and Evaluation process.[7] Evidence synthesis tables are available in appendix e-6 of the complete guideline.

The panel formulated practice recommendations on the basis of the strength of evidence systematically reviewed and other factors, including axiomatic principles of care, the magnitude of anticipated health benefits relative to harms, financial burden, availability of interventions, and patient preferences. The panel assigned levels of obligation (A, B, C, U) to the recommendations using a modified Delphi process.

ANALYSIS OF EVIDENCE **For patients with cryptogenic stroke, how often do various technologies identify previously undetected NVAF?** Two Class II[8,9] and 15 Class III[10–24] studies were identified that address this question. Figure 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.

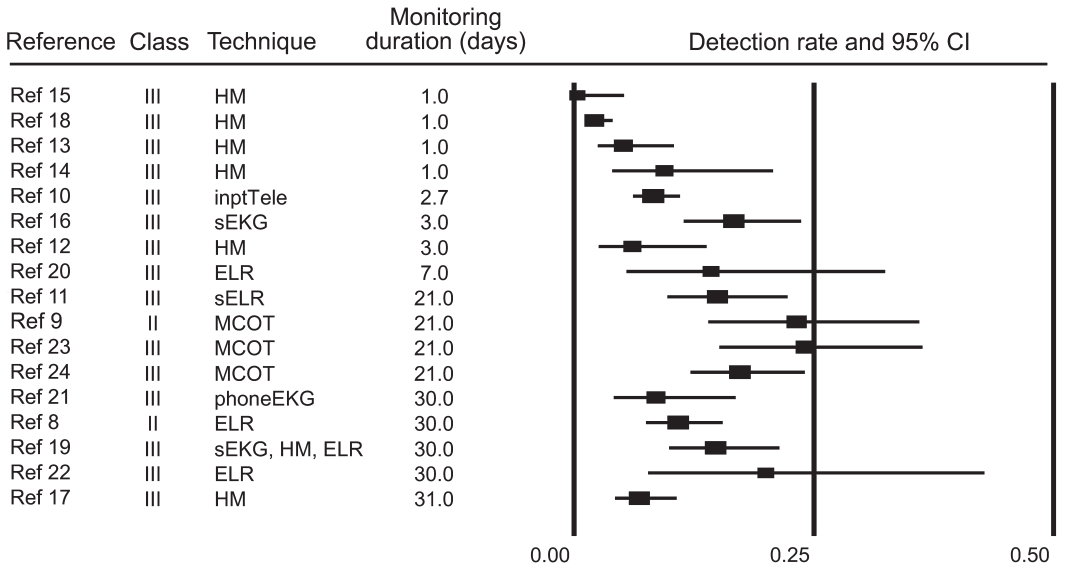
The most common technique used to identify NVAF in these studies was Holter monitoring,[12–19] followed by serial EKG,[8,16,17,19] event loop recorders,[11,19,20,22] inpatient continuous EKG telemetry,[10] outpatient transtelephonic EKG monitoring,[21] and mobile cardiac outpatient telemetry.[9,23,24] Several studies described a stepwise approach for NVAF screening that used serial EKGs and Holter monitoring.[16,17,19] Monitoring duration varied from 24 hours[13–15,18] to 30 days.[8,21,22]

The proportion of patients identified with NVAF (figure 1) ranged from 0%[15] to 23%.[9] Some of these estimates of NVAF incidence include very brief (e.g., <30 seconds) episodes, and the future risk of cardioembolic stroke in this setting is uncertain. The average detection rate of all studies was 10.7% (95% confidence interval [CI] 7.9%–14.3%) (weighted average calculated using a random effects model).

A meta-regression of studies using continuous monitoring techniques[8–15,18–20,22–24] identified a significant increase in NVAF detection 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% to 23% (weighted average of 10.7% [95% CI 7.9%–14.3%]) (2 Class II studies,[8,9] 15 Class III

Figure 1 **Proportion of patients with ischemic stroke identified with nonvalvular atrial fibrillation, by study**



Studies sorted by monitoring duration. CI = confidence interval; ELR = event loop recorder; HM = Holter monitoring; inptTele = continuous inpatient telemetry; MCOT = mobile cardiac outpatient telemetry; phoneEKG = outpatient transtelephonic EKG monitoring; sEKG = serial EKG; sELR = serial event loop recordings.

studies[10–24]). The detection rate is probably related to the duration of monitoring.

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, influence of international normalized ratio level.*** Since the publication of the 1998 practice parameter, 2 Class II studies[25,26] have evaluated the relationship between international normalized ratio (INR) level at the time of stroke presentation and stroke severity and mortality. Both studies demonstrated that an INR of less than 2 as compared with an INR greater than 2 was associated with an increased risk of disabling stroke (odds ratio 1.9 [95% CI 1.1–3.4]) or death (hazard ratio [HR] for death at 30 days 3.4 [95% CI 1.1–10.1]).[25]

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[25,26]).

Antithrombotics compared with warfarin or its derivatives. Our search strategy identified 6 randomized studies[27–32] (5 Class I studies,[27–31] 1 Class II study[32]) comparing various antithrombotic regimens with warfarin or its derivatives in patients with NVAF. All studies employed masked or adjudicated outcome assessment. Antithrombotic regimens studied were dabigatran,[27] rivaroxaban,[28] apixaban,[29] fluindione plus aspirin,[32] clopidogrel plus aspirin,[30] and triflusal plus acenocoumarol.[31]

Dabigatran is a direct thrombin inhibitor. Rivaroxaban and apixaban are factor Xa inhibitors. Dabigatran, rivaroxaban, and apixaban are administered in fixed doses and do not require regular blood coagulation monitoring. Antithrombotic reversal agents for these drugs are unavailable.

Triflusal is an antiplatelet drug structurally related to aspirin that is used in Europe, Latin America, and Southeast Asia (see appendix e-9 of the complete guideline for the relevant countries).[33,34] Acenocoumarol, a coumarin derivative, is used mostly in European countries. Fluindione is a vitamin K antagonist used in France.

Figure 2 summarizes the effects (relative risk reductions [RRRs]) of these antithrombotic regimens as compared with dose-adjusted warfarin for the outcomes of stroke or systemic embolism, ischemic stroke, major bleeding, intracranial bleeding, and gastrointestinal (GI) bleeding from the Class I studies. The Class II study of fluindione plus aspirin[32] demonstrated that the risk of hemorrhagic complications was increased in the dose-adjusted vitamin K antagonist plus aspirin group as compared with the vitamin K antagonist alone group (risk difference 14.6% [95% CI 5.5%–24.8%]). The study lacked the power to detect important differences in the risk of thromboembolic events.

Conclusions. In patients with NVAF, dabigatran administration is probably more effective for reducing the risk of stroke or systemic embolism (150 mg twice daily, relative risk [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[27]). Dabigatran 150 mg bid was associated with a higher rate of GI bleeding (1.51%/y vs 1.02%/y).

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 risks of major bleeding episodes overall except GI bleeding. However, rivaroxaban is associated with a lesser frequency of intracranial hemorrhage and fatal bleeding as compared with warfarin (RRR 22% [95% CI 5.5%–35.3%]) (single Class I study[28]).

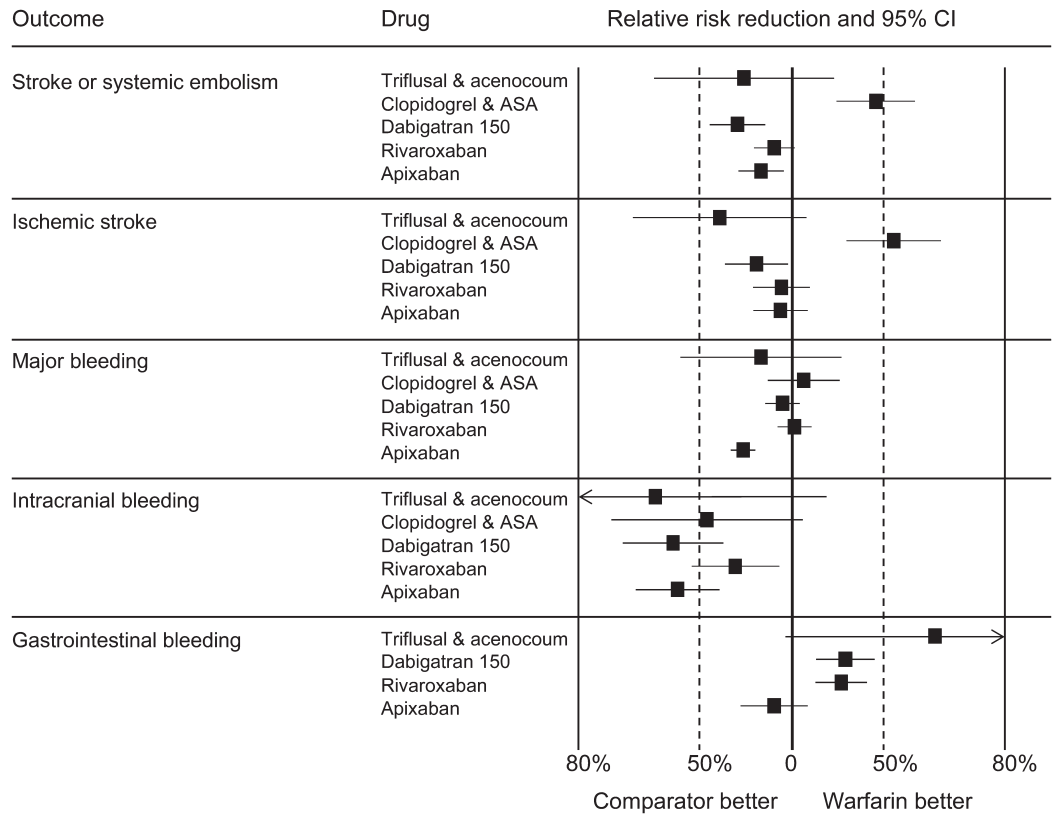
Apixaban 5 mg twice daily is likely more effective than warfarin in patients with NVAF at moderate risk of embolism (RRR 20.3% [95% CI 4.8%–33.3%]). The superiority of apixaban is related to decreased risk of bleeding (including intracranial bleeding) and reduced mortality (1 Class I study[29]), whereas its effect on reduction of risk of cerebral and systemic embolism is not superior to that of warfarin.[29]

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 stroke 1.72). Intracranial bleeding is more common with oral anticoagulation therapy than with clopidogrel plus aspirin (single Class I study[30]).

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 treatment with 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,[31] smaller than recent studies with new oral anticoagulants).

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[32]). 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.

Figure 2 Relative risk reductions of various outcomes in patients with nonvalvular atrial fibrillation receiving various antithrombotic regimens as compared with warfarin or its derivatives



Acenocoum = acenocoumarol; ASA = acetylsalicylic acid; CI = confidence interval.

Antithrombotics compared with aspirin. Our search strategy identified 2 randomized Class I studies[35,36] comparing different antithrombotic regimens with aspirin in patients with NVAF. Antithrombotic regimens studied were apixaban and clopidogrel plus aspirin.

Conclusions. Based on 1 Class I study,[35] 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 are similar for both treatment forms.

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[36]).

Anticoagulants in special populations. One Class I study[37] randomized patients aged ≥75 years with NVAF to warfarin (INR 2.0–3.0) or aspirin 75 mg/d. The RRR for disabling stroke (including intracranial hemorrhage) or systemic embolism favoring warfarin was 52% (95% CI 20%–72%). Extracranial hemorrhage rates were similar in the 2 treatment groups.

In a Class II study,[38] patients aged ≥75 years with NVAF were randomized to a target INR of 1.8 (range 1.5–2.0) or 2.5 (range 2.0–3.0). The composite outcome of thromboembolism and major hemorrhage occurred nonsignificantly less often in the lesser-intensity INR group (HR 0.7 [95% CI 0.4–1.1]).

Among patients with chronic kidney disease (CKD) participating in the Stroke Prevention in Atrial Fibrillation III (Class I) trials,[39] adjusted-dose warfarin (INR target 2.0–3.0) reduced ischemic stroke/systemic embolism in patients with CKD and a high risk of stroke (RRR 76% [95% CI 42%–90%]) as compared with aspirin or low-dose warfarin, with no difference in major hemorrhage rates.

For patients with stage 3 CKD,[40] apixaban as compared with aspirin significantly reduced stroke and systemic embolism event rates (HR 0.32 [95% CI 0.18–0.55], $p < 0.001$) without an increase in major bleeding (absolute rate apixaban 2.5% vs aspirin 2.2%) (1 Class I study).

Conclusion. The benefit of anticoagulation likely extends to elderly patients (1 Class I study[37]) and patients with CKD (2 Class I studies[39,40]). Bleeding risk increases in all patients with CKD taking warfarin.

RECOMMENDATIONS **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 that ranges from 0% to 23% (weighted average 10.7% [95% CI 7.9%–14.3%]), with longer monitoring periods probably associated with a greater yield. Many of the NVAF episodes that are detected are clinically asymptomatic, and thus monitoring devices with continuous recording or automatic detection algorithms, rather than patient-triggered recording, are 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.[e1–e4]

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).

Selection of patients for antithrombotic therapy. ***Clinical context.*** Within the NVAF population, the absolute risk of ischemic stroke varies widely on the basis of the presence of other stroke risk factors.[4] The absolute stroke risk is highest among patients with NVAF and a history of stroke and TIA (aggregated absolute risk about 10%/y).[4] Although multiple risk stratification tools are available for estimating the absolute stroke risk of patients with NVAF, the absolute stroke risks estimated by these tools vary widely.[e5]

Because it is difficult to determine with precision the absolute stroke risk in patients with NVAF, 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.

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).

Selection of a specific oral anticoagulant. ***Clinical context.*** Our review indicates that several anticoagulant medications decrease the risk of ischemic stroke in patients with NVAF. In clinical trials, the new oral anticoagulants are noninferior or superior to warfarin for reducing stroke, and in most patients the reduction in ischemic stroke risk outweighs the risk of bleeding complications.[e6]

Practice recommendation.

C1. To reduce the risk of stroke or subsequent stroke in patients with NVAF judged to require oral anticoagulants, clinicians should choose one of the following options (Level B):
- Warfarin, target INR 2.0–3.0
- Dabigatran 150 mg twice daily (if creatinine clearance [CrCl] >30 mL/min)
- Rivaroxaban 15 mg/d (if CrCl 30–49 mL/min) or 20 mg/d
- 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)

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.[25]

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%/y vs 0.74%/y, RR 0.40 [95% CI 0.27–0.60], $p < 0.001$; rivaroxaban 20 mg daily, 0.5%/y vs 0.7%/y, HR 0.67 [95% CI 0.47–0.93], $p = 0.02$; apixaban 5 mg bid, 0.33%/y vs 0.80%/y, HR 0.42 [95% CI 0.30–0.58], $p < 0.001$).

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%/y vs warfarin 1.02%/y). Bleeding from GI 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%/y in rivaroxaban group vs 2.3%/y in warfarin group). GI bleeding was nonsignificantly lesser with apixaban (0.76%/y) relative to that with warfarin (0.86%/y).

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

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 with NVAF who are at risk for stroke and 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%).[e7] 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]).

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%/y vs aspirin group, 3.7%/y), with equal risk of major bleeding, including intracranial hemorrhage.

Practice recommendations.

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).

In patients with NVAF and moderate stroke risk, treatment with triflusal 600 mg/d plus moderate-intensity anticoagulation (INR 1.25–2.0) with acenocoumarol is likely more effective than treatment with 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, a biologic phenomenon consistent with that found in previous studies.[33,34]

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).

Special populations. ***Clinical context.*** Some clinicians are reluctant to use anticoagulants to treat elderly patients with NVAF because of perceived high risk of bleeding.[e8] However, anticoagulation with warfarin is superior to that with aspirin for reducing the risk of ischemic stroke in patients ≥75 years with NVAF, whereas rates of major bleeding are comparable.[37] In one 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.[e9]

Another important subgroup is patients with renal failure. For dabigatran, one of the newer anticoagulants, a lower dose of 75 mg bid is recommended by the US Food and Drug Administration when the CrCl reaches 15–30 mL/min. Apixaban is recommended at 5 mg twice daily, if serum creatinine <1.5 mg/dL, or at 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 at 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.[e1]

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).

AUTHOR CONTRIBUTIONS

Antonio Culebras: study concept and design, acquisition of data, analysis or interpretation of data, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content, study supervision. Steven R. Messé: study concept and design, acquisition of data, analysis or interpretation of data, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content, study supervision. Seemant Chaturvedi: analysis or interpretation of data, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content. Carlos S. Kase: analysis or interpretation of data, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content. Gary Gronseth: study concept and design, analysis or interpretation of data, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content.

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DISCLOSURE

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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 (AAN) 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 3 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.

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