

Antithrombotic treatment for secondary prevention of stroke and other thromboembolic events in patients with stroke or TIA and non-valvular atrial fibrillation.

A European Stroke Organisation guideline

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Abstract

Introduction: Patients with ischemic stroke or transient ischemic attack (TIA) and non-valvular atrial fibrillation (AF) have a high risk of recurrent stroke and other vascular events. The aim of this guideline is to provide recommendations on antithrombotic medication for secondary prevention of stroke and other vascular outcomes in these patients.

Methods: The working group identified questions and outcomes, graded evidence, and developed recommendations according to the Grading of Recommendations Assessment, Development, and Evaluation approach and the ESO standard operating procedure for guidelines. The guideline was reviewed and approved by the ESO guideline board and the ESO executive committee.

Results: In patients with AF and previous stroke or TIA, oral anticoagulants (OACs) reduce the risk of recurrence over antiplatelets or no antithrombotic treatment. Non-vitamin K antagonist oral anticoagulants (NOACs) are preferred over vitamin K antagonists because they have a lower risk of major bleeding and death. Recommendations are weak regarding timing of treatment, (re-)starting OACs in patients with previous intracerebral haemorrhage, and treatment in specific patient subgroups of those of older age, with cognitive impairment, renal failure or small vessel disease, because of a lack of strong evidence.

Conclusion: For patients with AF and ischemic stroke or TIA, NOACs are the preferred treatment for secondary prevention of recurrent stroke or thromboembolism. Further research is required to determine the best timing for initiating OACs after an acute ischemic stroke, whether or not OACs should be (re)started in patients with a history of intracerebral haemorrhage, and the best secondary preventive treatment in specific subgroups.

Introduction

In Europe, 1 to 2% of the population has atrial fibrillation (AF).^{1,2} As a result of a steep increase of the prevalence of AF with age and the continuously ageing population,³ the projected number of people with AF in Europe is 17.9 million by the year 2060.⁴ The risk of stroke attributable to AF rises from 1.5% in patients aged 50 to 59 years to 23.5% for those 80 to 89 years.⁵ These proportions are probably underestimated as recent randomized studies have shown that the proportion of patients with stroke and AF increases with more prolonged ECG monitoring, in particular in patients with cryptogenic or embolic stroke of undetermined source.^{6,7} In a recent randomized study of stroke survivors without known AF, longer ECG monitoring consisting of 10-day Holter monitoring at the time of stroke, and at 3 and 6 months' follow up, increased the detection rate of AF to 13.5%, compared with 4.5% in the standard care group (ECG monitoring of 24 hours or longer according to guidelines).⁸ Patients with ischemic stroke or transient ischemic attack (TIA) and AF benefit from oral anticoagulation (OAC) treatment for the prevention of stroke and other thromboembolic events, although many of the studies that demonstrated this benefit, including those investigating non-vitamin K antagonist oral anticoagulants (NOACs), were not restricted to patients with previous ischemic stroke or TIA.

The aim of this guideline is to provide recommendations to guide stroke care providers to reach clinical decisions in practice regarding antithrombotic treatment for secondary prevention of stroke and other vascular outcomes in patients with stroke or TIA and non-valvular AF.

Methods

We followed the ESO guidelines standard operating procedure,⁹ which is based on the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology. In short, the ESO guideline committee invited two chairs (CJMK, MP), who established a working group consisting of five stroke specialists (EB, EK, JK, JP, DJW), two advisors (CD, PK), and one methodologist (AA). The working group was confirmed by the guideline committee. The stroke specialists of the working group discussed and decided by consensus on the PICO (Patient, Intervention, Comparator, Outcome) questions to be addressed and on the outcomes of interest during a face-to-face meeting. Outcomes were rated for

importance by all stroke specialists. PICO questions and outcomes were reviewed by the guideline committee and revised according to its recommendations.

Literature search

We performed searches of the literature in MEDLINE (March 1st 2017), EMBASE (March 7th 2017), CINAHL (March 10th 2017), and the COCHRANE controlled trials register (March 14th 2017) for each of the PICO questions separately (see Online Supplement). Search terms and their corresponding Medical Subject Heading (MeSH) terms used to identify the articles are described in the Online Supplement. For each PICO question, two working group members independently screened titles, abstracts, and subsequently full texts for potentially relevant studies. We based our evidence synthesis on results from randomized controlled trials, systematic reviews and meta-analyses.

Data extraction and risk of bias assessment

We extracted and analyzed tabular data from randomized clinical trials (RCTs) of patients with AF specifically for the population of interest e.g. those patients who had experienced ischemic stroke or TIA. For each PICO question, data were extracted and meta-analyzed by the methodologist (AA) and checked by two or three working group members. The risk of bias of RCTs was assessed using the Cochrane Collaboration's tool. We assessed randomization (random sequence generation), allocation concealment, blinding of participants, outcome assessment, attrition bias (incomplete outcome data), reporting bias (selective reporting) and other biases in each study and summarized findings in evidence profile tables according to the GRADE methodology.

Meta-analysis

Meta-analysis was performed using the Review Manager (RevMan, version 5.3) Cochrane Collaboration software when more than one study reported the outcome and the number of subjects was ≥ 6 in each group. We calculated risk ratios (RR) or odds ratios (OR) and 95% confidence intervals (CI), with a random effects model, for all outcomes. We calculated I^2 statistic to assess heterogeneity of study results. Heterogeneity was classified as moderate ($I^2 \geq 30-49\%$), substantial ($I^2 \geq 50-74\%$), or considerable ($I^2 \geq 75\%$).¹⁰ Where appropriate, we performed subgroup analyses based on category of antithrombotic drug (direct thrombin or factor Xa inhibitors), dose, or severity of comorbidities (e.g. renal failure). Results were summarized in GRADE evidence profiles and summary of findings tables. In addition to

study design, risk of bias, directness, heterogeneity, precision and magnitude of effect, these tables include information on magnitude of effect, confounding, and dose response relationship. Directness refers to the extent by which patient populations, interventions and outcomes are similar to those of interest.

Evidence synthesis and grading, and recommendations

For each of the PICO questions, grading of the evidence and writing of the recommendations were performed by two or three working group members. All drafts were critically revised by all working group members, and discrepancies in grading and recommendations discussed during regular telephone conferences. Quality of evidence was graded as high, moderate, low, and very low as defined in eTable 1, and strengths of recommendations were graded as strong when the desirable effect of an intervention clearly outweighed the undesirable effects or clearly did not, or weak when the trade-off was less certain, either because of low-quality evidence, or because the evidence suggested that desirable and undesirable effects were more closely balanced. Section authors generated a section of 'additional information' based on observational studies and ongoing RCTs if this was deemed to provide additional information beyond the results of any RCTs.

Results

The working group identified five areas for which PICO questions were formulated: i) medical treatment; ii) timing of medical treatment; iii) treatment by means of occlusion of the left atrial appendage; iv) (re-) starting medical treatment in patients with previous intracerebral haemorrhage (ICH); and v) medical treatment in specific patient subgroups (i.e. elderly, patients with cognitive deficits, patients with renal failure, and patients with signs of small-vessel disease on MRI) for a total of 19 PICOs. Study selection for each of the PICO questions is outlined in eFigures 1-5 of the Online Supplement. The risk of bias of included studies is summarized in eFigures 6 and 7. The working group identified seven outcomes of interests, of which the composite of all stroke or thromboembolism was considered the most important (Table 1).

1. Medical treatment in patients with ischemic stroke

1.1 Antiplatelet agents versus control

1.1.1 - In patients with non-valvular AF and previous ischemic stroke or TIA, does single or dual antiplatelet therapy compared to placebo lower the risk of recurrent stroke or thromboembolism and other predefined outcomes?

Aspirin versus placebo

The European Atrial Fibrillation Trial (EAFT) randomized 1,007 patients with minor ischemic stroke or TIA and AF into three arms: warfarin (INR 2.5-4.0), aspirin 300 mg, and placebo.¹¹ The relative risk reduction for all strokes for aspirin versus placebo was 14% (relative risk 0.86, 95% CI 0.64-1.15), which was not statistically significant. In the European Stroke Prevention Study-2 (ESPS-2)¹² and the United Kingdom TIA (UK-TIA) aspirin trial, a total of 260 patients with previous stroke or TIA and AF were randomized to aspirin or placebo (data on patients with previous ischemic stroke or TIA were in part obtained via personal communication with the authors).¹³ A pooled analysis of these three trials showed a risk reduction for stroke or thromboembolism for aspirin versus placebo of 17%, which was not statistically significant (OR 0.83, 95% CI 0.62-1.10; eFigure 8). The risk reduction for stroke and systemic embolism was similar for any dose of aspirin in the different clinical trials. There was no significant difference in the risk of the composite of non-fatal stroke, non-fatal myocardial infarction, or vascular death in patients on aspirin compared to placebo (OR 0.88, 95% CI 0.65-1.18). The risk of ICH was 0.2% in the aspirin group and 0% in the placebo group (OR 2.81, 95% CI 0.11-69.29). The risk of major bleeding was 1.5% in the aspirin group compared to 1.1% in the placebo group (OR 1.41, 95% CI 0.39-5.03; eTable 2).

Aspirin plus dipyridamole or dipyridamole alone versus placebo

In patients with AF included in ESPS-2, patients treated with dipyridamole alone had a stroke or systemic embolism rate of 17.5% compared to 21.5% in the placebo group (OR 0.78, 95% CI 0.40-1.51).¹² The stroke or thromboembolism rate of patients treated with the combination of aspirin and dipyridamole was 13.5% and 21.5% in the placebo group (OR 0.57, 95% CI 0.27-1.18; eFigure 8). Data regarding hemorrhagic outcomes were not reported.

Any antiplatelet agents versus placebo

Pooled data from 4 studies including 1,474 patients randomized to receive antiplatelet agents (aspirin and/or dipyridamole) in patients with AF and previous stroke or TIA did not show a significant risk reduction for stroke or thromboembolism for antiplatelets versus placebo (OR 0.79, 95% CI 0.61-1.01; eFigure 8 in the online data supplement).

1.1.2 - In patients with non-valvular AF and previous ischemic stroke or TIA, does dual antiplatelet therapy compared to single antiplatelet therapy lower the risk of recurrent stroke or thromboembolism, and other predefined outcomes?

Because some patients with AF cannot tolerate vitamin K antagonists (VKAs) and before NOACs were available, there has been considerable interest in the combination of different antiplatelet agents as an alternative therapy to VKAs in hope of better efficacy than single antiplatelet therapy. In the Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events (ACTIVE A) study that compared the combination of aspirin and clopidogrel to aspirin in patients for whom VKAs therapy were deemed unsuitable, 992 patients with AF and prior ischemic stroke or TIA (secondary prevention cohort) had a stroke rate of 4.5% per year when assigned to the combination therapy, compared to 6.3% per year when assigned to aspirin.¹⁴ Data regarding hemorrhagic outcomes were not reported. Considering all the patients included in the study (primary and secondary prevention cohorts), an analysis of major vascular events combined with major hemorrhage showed no difference between the two treatments (RR 0.97, 95% CI 0.89–1.06).

In the ESPS-2, patients with AF treated with dipyridamole alone had a stroke rate of 17.5% compared to 16.3% of patients treated with the combination of aspirin and dipyridamole (OR 0.92; 95% CI 0.45-1.87).¹² Data regarding hemorrhagic outcomes were not reported.

Recommendations

In patients with non-valvular AF and previous ischemic stroke or TIA, we do not recommend antiplatelet agents, either as single or dual therapy, for secondary prevention of all events.

Quality of evidence: Moderate

Strength of recommendations: Weak

1.2 Vitamin K antagonists versus control

1.2 - In patients with non-valvular AF and previous ischemic stroke or TIA, do vitamin K antagonists compared to placebo lower the risk of recurrent stroke or thromboembolism and other predefined outcomes?

Data regarding randomized comparison of VKA with placebo in patients with prior ischemic stroke or TIA and AF come from two trials, The European Atrial Fibrillation Trial (EAFT)¹¹ and Veterans Affairs Stroke Prevention in Nonrheumatic Atrial Fibrillation trial.¹⁵ EAFT demonstrated that adjusted-dose warfarin therapy (INR 2.5-4; target 3) reduced the risk of recurrent ischemic stroke and thromboembolism in patients with previous minor ischemic stroke or TIA or from 25.2%, compared to 9.3% in the placebo group (OR 0.31, 95% CI 0.18-0.53).¹¹ The Veterans Affairs Stroke Prevention in Nonrheumatic Atrial Fibrillation study compared low-intensity warfarin (INR 1.2 to 1.5) to placebo. In the small secondary prevention cohort (46 patients), the risk of recurrent ischemic stroke was 9.5% in the warfarin group compared to 16% in the placebo group (OR 0.55, 95% CI 0.09-3.37).¹⁵

A pooled analysis of the results of these trials showed a risk reduction for recurrent ischemic stroke for warfarin versus placebo of 64% (OR 0.36, 95% CI 0.20-0.65). The pooled analysis showed an increase of major bleeding in patients treated with warfarin compared to placebo (OR 4.31, 95% CI 1.21-15.35) without an increase of intracranial hemorrhage (OR 0.32, 95% CI 0.01-7.79; Table 2 and Figure 1).

Recommendations

In patients with non-valvular AF and previous ischemic stroke or TIA we recommend vitamin K Antagonists over no antithrombotic medication for secondary prevention of all events.

Quality of evidence: Moderate

Strength of recommendations: Strong

1.3 Vitamin K antagonists versus antiplatelet agents

1.3 - In patients with non-valvular AF and previous ischemic stroke or TIA, do vitamin K antagonists lead to lower risk of recurrent stroke or thromboembolism and other predefined outcomes than antiplatelet treatment?

Adjusted-dose warfarin versus aspirin

The EAFT demonstrated that OAC therapy (INR 2.5-4; target 3) reduced the risk of recurrent stroke and systemic embolism in patients with AF and TIA or minor ischemic stroke from 23.3% to 9.3% when compared to aspirin (OR 0.34, 95% CI 0.20-0.56).¹¹ The risk of ICH was similar in the groups (OR 0.36, 95% CI 0.02-7.47). The Birmingham Atrial Fibrillation Treatment of the Aged Study (BAFTA) assessed whether warfarin reduced risk of major stroke, arterial embolism, or other intracranial hemorrhage compared with aspirin in elderly patients.¹⁶ For the small secondary prevention cohort (124 patients) data were not

reported regarding ischemic outcomes (ischemic stroke and systemic embolism) while the risk of major bleeding was similar in patients receiving warfarin compared to those treated with aspirin (OR 0.17, 95% CI 0.2-1.54). Pooling EAFT and BAFTA results, the risk of major bleeding was 4.8% in the VKA group compared to 2.4% in the aspirin group (OR 2.39, 95% CI 0.98-5.85; Table 3 and Figure 2).

Adjusted-dose warfarin versus clopidogrel plus aspirin

The Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events (ACTIVE W) compared warfarin with a combination of clopidogrel and aspirin in AF patients with at least one risk factor for stroke.¹⁷ This study was stopped prematurely after 3,371 patients were enrolled because of clear superiority of warfarin (INR 2.0-3.0) over the antiplatelet combination (RR 1.44, 95% CI 1.18-1.76 for clopidogrel and aspirin vs. warfarin). Patients with prior stroke or TIA (510 in the warfarin group and 510 in the clopidogrel plus aspirin group) had a stroke rate of 2.99% per year when assigned to warfarin and 6.22% per year when assigned to clopidogrel plus aspirin (RR 2.13, 95% CI 1.23-3.69). In the secondary prevention cohorts, data regarding hemorrhagic outcomes were not reported.

Adjusted-dose warfarin (INR 2.0-3.0) versus fixed-dose warfarin (INR 1.2-1.5) plus aspirin

In the Stroke Prevention in Atrial Fibrillation III (SPAF III) trial, 1,044 patients with AF and with at least one thromboembolic risk factor were randomly assigned to adjusted-dose warfarin (INR 2.0-3.0) or to a combination of low-intensity, fixed-dose warfarin (INR 1.2-1.5 for initial dose adjustment) and aspirin (325 mg/day).¹⁸ Of the trial arms, 36% of those receiving adjusted-dose warfarin and 40% of those receiving combination therapy had a history of prior thromboembolism. The trial was stopped after a mean follow-up of 1.1 years as an interim analysis showed that the rate of ischemic stroke and thromboembolism in patients given adjusted-dose warfarin (1.9% per year) was significantly lower than in those given combination therapy (7.9% per year), yielding an absolute reduction of 6.0% per year (95% CI 3.4-8.6) by adjusted-dose warfarin. In patients with prior thromboembolism, the rate of ischemic stroke and systemic embolism was 3.4% per year for adjusted-dose warfarin and 11.9% per year for combination therapy. The rates of major bleeding were similar for both regimens (2.1% per year, 95% CI 1.2-3.7 with adjusted-dose warfarin vs. 2.4% per year, 95% CI 1.4-4.1 with combination therapy).

Recommendations

In patients with non-valvular AF and previous ischemic stroke or TIA we recommend vitamin K antagonists (INR 2-3) over antiplatelet therapy (single or dual) for secondary prevention of all events.

Quality of evidence: Moderate

Strength of recommendations: Strong

In patients with non-valvular AF and previous ischemic stroke or TIA, we suggest adjusted-dose vitamin K antagonists (INR 2.0-3.0) over fixed-dose vitamin K antagonists (INR 1.2-1.5) plus aspirin for secondary prevention of all events.

Quality of evidence: Moderate

Strength of recommendations: Weak

Additional information

Regarding the optimal intensity of oral anticoagulation for stroke prevention in patients with AF, an observational study of primary and secondary prevention found that the risk of ischemic stroke rose steeply at INRs below 2.0.¹⁹ In 77 patients with non-rheumatic AF, at an INR of 1.7, the adjusted odds ratio for stroke, as compared with the risk at an INR of 2.0, was 2.0 (95% CI 1.6-2.4); at an INR of 1.5, it was 3.3 (95% CI 2.4-4.6); and at an INR of 1.3, it was 6.0 (95% CI 3.6-9.8). Another study that included 121 patients found that over the entire range of INRs, for each 0.5 increase in INR, the risk for intracranial hemorrhage doubled (OR 2.1, 95% CI 1.4-2.9) and this risk rises even more rapidly at INRs greater than 4 to 5.²⁰

1.4 Non-vitamin K antagonist oral anticoagulants versus vitamin K antagonists

1.4.1 - In patients with non-valvular AF and previous ischemic stroke or TIA, do non-vitamin K antagonists oral anticoagulants compared to vitamin K antagonists lead to lower risks of recurrent stroke or thromboembolism and other predefined outcomes?

We identified four randomized trials comparing NOACs to VKAs in patients with AF providing preplanned subgroup analyses for patients with prior ischemic stroke or TIA.²¹⁻²⁴ One trial investigated the direct thrombin inhibitor dabigatran and three trials factor Xa inhibitors, rivaroxaban, apixaban, and edoxaban. In the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY), 18,113 patients were assigned to 110 mg or 150 mg dabigatran twice daily or warfarin dose-adjusted to INR 2.0 to 3.0.²¹ The regimen was open label, but patients and investigators were not aware of dabigatran dose, and events were adjudicated by investigators blinded to treatment allocation. A total of 2,428 patients with previous ischemic stroke or TIA were randomized and followed for a median of 2.0 years.²¹ In the Rivaroxaban Once-daily, Oral, Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of

Stroke and Embolism Trial in Atrial Fibrillation Patients (ROCKET AF) a total of 14,264 patients were randomly assigned in a double-blind manner to rivaroxaban 20 mg once daily (15 mg if creatinine clearance 30-49 mL/min) or adjusted dose warfarin (INR 2.0-3.0).²² Of these, 7,468 patients had a previous ischemic stroke or TIA and they were followed for a median of 1.85 years. In the double-blind Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE), 18,201 patients were assigned to apixaban 5 mg twice daily (2.5 mg twice daily for patients with 2 or more of the following: age \geq 80 years, bodyweight \leq 60 kg, serum creatinine \geq 133 μ mol/L) or warfarin (INR 2.0-3.0).²³ A total of 3,436 patients had a prior ischemic stroke or TIA and the median duration of follow-up was 1.8 years. In the double-blind Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction 48 (ENGAGE AF-TIMI 48) trial, 21,105 patients were randomized to once-daily edoxaban (60/30 mg in the higher-dose regimen; 30/15 mg in the lower-dose regimen) or warfarin (INR 2.0-3.0). A total of 5,973 patients with previous ischemic stroke or TIA were enrolled and followed for a median of 2.8 years.²⁴ These four trials included a total of 19,305 patients with prior stroke or TIA.

Pooling the results of the four trials, NOACs were associated with a significant reduction of hemorrhagic stroke (RR 0.43, 95% CI 0.29-0.64), and death from any cause (RR 0.87, 95% CI 0.80-0.95; eFigure 9) when compared to adjusted-dose warfarin (Table 4). There was no significant difference in the risk of stroke or thromboembolism (RR 0.91, 95% CI 0.81-1.02; eFigure 10) and ischemic stroke (RR 1.07, 95% CI 0.93-1.22) in patients on NOACs compared to warfarin. There was no significant heterogeneity across the trials in the efficacy outcomes, with the exception of moderate heterogeneity for ICH (I^2 34%).

Analysis of efficacy outcomes using different types and doses of NOACs are summarized in eTable 3 in the online data supplement. Of note, there was a significant reduction of stroke and systemic embolism and of stroke in favor of NOACs when higher dose regimens of dabigatran and edoxaban were included, while the reduction of hemorrhagic stroke remained similar.

Major bleeding was defined according to the International Society on Thrombosis and Hemostasis (ISTH) in all four trials.²⁵ Pooling the results of the four trials, NOACs were associated with a significant reduction of major bleeding (RR 0.79, 95% CI 0.64-0.96; eFigure 11) and, most profoundly, intracranial hemorrhage (RR 0.45, 95% CI 0.45-0.63). Specifically, ICH was only reported in patients with previous ischemic stroke or TIA allocated to rivaroxaban and there was a trend favoring NOACs over warfarin. There was substantial heterogeneity across the trials regarding outcomes major bleeding (I^2 67%) as well as ICH (I^2 74%).

Analysis of safety endpoints are shown in eTables 4-5 in the online data supplement. In these combinations, the key efficacy and safety results were in accordance with the main pooled analysis.

Recommendations

In patients with non-valvular AF and previous ischemic stroke or TIA, we recommend non-vitamin K antagonist oral anticoagulants over vitamin K antagonists for secondary prevention of all events.

Quality of evidence: High

Strength of recommendation: Strong

Additional information

The trials were not uniform with regards to methods of blinding, definitions of co-morbidities and endpoints (for example, definition of hemorrhagic stroke was inconsistent between the trials), baseline co-morbidities, length of follow-up, and time in therapeutic INR range (TTR) in patients allocated to warfarin. Furthermore, we pooled data from trials testing NOACs with two different mechanisms of action, factor Xa inhibition and direct thrombin inhibition, and with varying dosages for some of the drugs. Nevertheless, there was no significant heterogeneity between results for the key efficacy and safety endpoints and data were fairly consistent also when mechanism of action and different dosing regimens were taken into account.

For efficacy of warfarin it is important that TTR is high (>70%).²⁶ In RE-LY mean TTR was 63%, in ROCKET-AF 57%, in ARISTOTLE 65% and in ENGAGE AF-TIMI 48 68%. With respect to reduction of stroke and systemic embolism, NOACs remain superior to warfarin at TTR levels less than 70%, but this superiority no longer exists at high TTR levels.^{27, 28} However, TTR levels do not appear to similarly modify the superiority of NOACs in safety outcomes.²⁹

Patients with AF may also have symptomatic ischemic heart disease or intra- or extracranial atherosclerosis that can potentially increase the risk of recurrent vascular events warranting antiplatelet therapy. Currently, there are no data to inform us regarding the optimal therapeutic strategy in these patients, the combination of a NOAC and antiplatelet agents, VKAs alone, or VKAs in combination with antiplatelet therapy. Combination therapy of OACs and antiplatelets increases the risk of major bleedings but may be beneficial in some patients, e.g. those with recent ischemic heart disease or in case of recent coronary angioplasty and stenting.³⁰

1.5 Non-vitamin K antagonist oral anticoagulants vs. antiplatelet agents

1.5.1 - In patients with non-valvular AF and previous ischemic stroke or TIA, do non-vitamin K antagonist oral anticoagulants compared to antiplatelets lower the risk of recurrent stroke or thromboembolism and other predefined outcomes?

The Apixaban Versus Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients who have Failed or are Unsuitable for Vitamin K Antagonist Treatment (AVERROES) trial evaluated the efficacy and safety of factor Xa inhibitor apixaban compared with aspirin.³¹ A pre-specified subgroup of patients with previous stroke or TIA was randomly assigned to receive either apixaban (390 patients) 5 mg twice daily, or a reduced dose of 2.5 mg twice daily in patients aged 80 years or older, with bodyweight ≤ 60 kg, or with creatinine concentrations of ≥ 1.5 mg/dL, or to receive 81-324 mg of aspirin (374 patients). Patients and investigators were masked to treatment groups, and all outcomes were adjudicated by a masked committee. The mean duration of follow-up was 1.1 years. No other randomized controlled trials comparing NOACS to antiplatelets were identified.

Apixaban was associated with a significant reduction of stroke and systemic embolism and a significant reduction of stroke. There was no statistically significant difference in deaths from any cause between the apixaban and aspirin groups (Figure 3).

Although there were a few more ICHs in the aspirin group and major bleedings in the apixaban group during follow up period, differences were not significant; the study was terminated prematurely because of a clear benefit in favor of apixaban.

Recommendations

In patients with non-valvular AF and previous ischemic stroke or TIA, we suggest non-vitamin K antagonist oral anticoagulants over aspirin in patients who have failed or are unsuitable for vitamin K antagonist therapy for secondary prevention of all events.

Quality of evidence: Moderate

Strength of recommendations: Weak

Additional information

Although the data favor apixaban compared to aspirin, they are based on a single RCT (AVERROES trial) with only one NOAC and a small number of patients with previous ischemic stroke or TIA. The EAFT study demonstrated that adjusted dose anticoagulation therapy significantly reduced the risk of recurrent

stroke and systemic embolism in patients with AF and TIA or minor stroke compared with aspirin (section 1.3).¹¹ Moreover, the pooled analysis comparing all NOACs vs. VKAs showed that NOACs were associated with a better efficacy and safety without significant heterogeneity (1.4).

2 Timing and bridging of oral anticoagulants

2.1 - In patients with non-valvular AF and previous ischemic stroke or TIA, does “early” compared to “late” initiation of anticoagulant lower the rates of recurrent stroke or thromboembolism, without increasing the risk of intracranial bleeding?

If untreated, the risk of early recurrence of ischemic stroke in patients with AF is between 0.5% and 1.3% per day (1-4).³²⁻³⁵ Although warfarin has been the standard OAC therapy for decades, the optimal timing of its initiation for secondary stroke prevention in AF is based on weak evidence, mainly based on expert opinion. The RAF (Early Recurrence and Cerebral Bleeding in Patients With Acute Ischemic Stroke and Atrial Fibrillation: Effect of Anticoagulation and Its Timing) study was a prospective observational study that included 1,029 ischemic stroke patients with AF, treated with either anticoagulants (alone or in combination with antiplatelets), only antiplatelets, or no treatment.³⁶ The main outcome was a composite of recurrent ischemic cerebrovascular events (stroke or TIA), symptomatic systemic embolisms, symptomatic intracerebral bleedings and major extracerebral bleeding at 90 days. In this non-randomized study, the optimal timing for initiating anticoagulant treatment was between 4 and 14 days. Other recent observational studies reported that, if NOACs are started early (within the first week) after an index event (ischemic stroke or TIA), the risk of intracranial bleeding appears to be low.³⁷⁻⁴⁰

The 5 large NOAC trials (RE-LY,²¹ ROCKET-AF,²² ARISTOTLE,²³ AVERROES,³¹ ENGAGE AF-TIMI 48 trial²⁴) excluded patients with stroke within the previous 7-14 days, and severe disabling stroke within 3-6 months. A recent proof-of-concept open-label trial, Acute Stroke with Xarelto to Reduce Intracranial Hemorrhage, Recurrent Embolic Stroke, and Hospital Stay (Triple AXEL) randomized South-Korean patients with AF-related mild ischemic stroke within the previous 5 days,⁴¹ at a median of 2 days from stroke onset, to rivaroxaban (10 mg/d for 5 days followed by 15 or 20 mg/d) or dose-adjusted warfarin for 4 weeks. The trial used the composite of new ischemic lesion or new intracranial hemorrhage on MRI at 4 weeks as the primary endpoint and length of hospital stay as a key secondary endpoint. Of 195 patients, 183 were included in the analysis. There was no difference in the primary endpoint between the groups (RR 0.91, 95% CI 0.69-1.12), nor any difference in the incidence of new ischemic lesions (RR

0.83, 95% CI 0.54-1.26). New intracranial hemorrhage occurred in 31.6% in the rivaroxaban group and 28.7% in the warfarin group (RR 1.10, 95% CI 0.70-1.71), but all of these were asymptomatic hemorrhagic transformations within or adjacent to the infarction. The duration of hospitalization was significantly shorter with rivaroxaban compared with warfarin. However, this trial was not adequately powered for important clinical outcomes and there was no comparison between early initiation of anticoagulants and late initiation. Therefore, the optimal timing of treatment initiation of NOACs for secondary stroke prevention remains unknown.

Recommendations:

We cannot make recommendations about the optimal time for initiating anticoagulation treatment in patients with acute ischemic stroke based on randomized trials. We encourage inclusion of patients in ongoing randomized controlled trials testing the efficacy and safety of early anticoagulation to answer this question.

Quality of evidence: Low

Strength of recommendation: Weak

Additional information:

Although we found only a single inadequately powered RCT relevant to this PICO question (Triple AXEL trial), some observational evidence suggests an optimal 4-14 day window for anticoagulation post-acute ischemic stroke.³⁶ However, the largest study on this question had limitations, including mixed treatment protocols with low molecular weight heparin (LMWH) and warfarin as well as NOACs, and insufficient statistical power to determine benefit of earlier anticoagulation with NOACs.³⁶ Moreover, index infarct size and severity of stroke may need to be taken into account before making any decision to minimize the risk of hemorrhagic transformation of the infarct or other intracranial bleeding. Although hemorrhagic transformation and infarct size have been associated with poorer outcome^{42, 43} there are no randomized data to confirm that early anticoagulation is more hazardous with potential for net harm in those patients with larger infarcts. Nevertheless, in the absence of definitive data, many expert clinicians currently suggest that stroke severity and infarct size should be considered when deciding on optimal timing for anticoagulation: for example, in patients with mild stroke and small infarcts (<1.5 cm) anticoagulation treatment has been suggested to be appropriate at day three or four from the index stroke; for moderate infarcts, it is suggested that anticoagulation treatment may be started at day seven from index stroke; for large infarcts, anticoagulation treatment might be best delayed for 14 days after

the index stroke.⁴⁴ The European Heart Rhythm Association (EHRA) guidelines suggest that for patients with TIA and AF, VKAs or NOACs can be initiated on day one, and for those already receiving VKAs or NOACs, treatment can be continued because of a low risk of ICH. For patients with mild stroke (National Institutes of Health Stroke Scale [NIHSS] <8), NOACs can be initiated at 3 days, or after ICH has been excluded by imaging (computed tomography or magnetic resonance imaging).⁴⁵ For patients with moderate stroke (NIHSS 8-16), anticoagulation can be initiated at 5-7 days, and in severe stroke (NIHSS >16) at 12-14 days.⁴⁵

The results of two large randomized, non-blinded intervention studies (IST and CAST) indicate that aspirin given within 48 hours of stroke occurrence reduces case fatality and rate of recurrent stroke only minimally.^{34, 46} A meta-analysis showed a reduction in the combined outcome of death or non-fatal recurrent stroke of nine per 1000 patients treated. This benefit was present also in patients with AF. Aspirin may therefore reasonably be given within 48 hours (100–300 mg/day) after acute ischemic stroke or TIA for short-term treatment, pending the introduction of anticoagulation.

RCTs failed to produce any evidence supporting the administration of anticoagulants in patients with acute ischemic stroke within 48 h from stroke onset.³⁵ For this reason, in patients already on VKAs one may consider to stop anticoagulant therapy, repeat a second brain CT scan after 24-72h and decide the time to re-initiate treatment based on the size of the lesion. Thus, pending further evidence, aspirin should be administered in this acute time frame to all patients.

There are several ongoing randomized controlled studies on the best timing of initiation of medical treatment after ischemic stroke: The Timing of oral anticoagulant therapy in acute ischemic stroke with AF (TIMING study; NCT02961348), the Early Versus Late Initiation of Direct Oral Anticoagulants in Post-ischemic Stroke Patients With Atrial fibrillation (ELAN trial; NCT03148457), the Optimal Delay Time to Initiate Anticoagulation After Ischemic Stroke in Atrial Fibrillation Trial (START; NCT03021928), and the OPTimal TIMing of Anticoagulation after AF-associated acute ischemic Stroke (OPTIMAS, Werring, personal communication).

2.2 - In patients with non-valvular AF and previous ischemic stroke or TIA, does bridging with heparin or heparinoids lead to better outcomes than avoiding bridging in the time-window between symptom onset and start of oral anticoagulation?

The risk of early recurrent ischemic stroke occurring within the first 2 weeks, is higher in patients with AF than in patients with stroke resulting from other causes.³²⁻³⁵ In patients with AF and acute ischemic stroke, unfractionated heparin (UFH), low molecular-weight heparin (LMWH), or heparinoids are commonly used in routine clinical practice outside clinical trials while awaiting the commencement or effect of OAC. However, randomized clinical trials indicate that in patients with acute cardioembolic stroke, early anticoagulation with UFH or LMWH is associated with increased intracranial bleeding, a non-significant reduction in recurrence of ischemic stroke, and no substantial reduction in death and disability.³⁵ Furthermore, observational studies reported that patients who had received VKA alone had a significantly lower risk of bleeding events, compared with patients treated with LMWH followed by OAC.⁴⁷⁻⁵⁰

Recommendations:

In patients with non-valvular AF and previous ischemic stroke or TIA, we suggest avoiding routine bridging therapy prior to anticoagulation with vitamin K antagonists or non-vitamin K antagonist oral anticoagulants for secondary prevention of all events.

Quality of evidence: Low

Strength of recommendation: Weak

Additional information:

Although we did not find any RCTs relevant to this PICO question, results of some observational studies indicate that bridging therapy should be avoided. Several studies found that patients who had received OACs alone had a significantly lower risk of bleeding events than patients treated with full-dose LMWH followed by OAC.⁴⁷⁻⁵⁰ The results of these studies should not be applied in a generalized manner because patients who received LMWH were more likely to have dysphagia and perhaps be at inherently greater risk of adverse outcomes.

3 Left atrial appendage occlusion versus oral anticoagulants

3.1 - In patients with non-valvular AF and previous ischemic stroke or TIA, does left atrial appendage closure reduce risk of recurrent stroke or thromboembolism and other predefined outcomes compared to oral anticoagulant treatment?

Because in patients with non-valvular AF the majority of thrombi leading to ischemic stroke originate from blood stasis in the left atrial appendage (LAA), endovascular LAA occlusion (LAAO) provides a potential treatment to reduce the risk of ischemic stroke.⁵¹ Two RCTs have tested LAAO in comparison to dose-adjusted warfarin but the majority of patients did not have a prior ischemic stroke or TIA (PROTECT-AF and PREVAIL).^{52,53} For the primary outcome of stroke (ischemic or hemorrhagic) and thromboembolism, both these trials showed non-inferiority to dose-adjusted warfarin. PROTECT AF randomized 707 patients with non-valvular AF and an additional stroke risk factor (19% with previous ischemic stroke or TIA) to dose-adjusted warfarin or LAA closure in a 2:1 ratio.⁵³ The primary outcome of stroke, thromboembolism, or cardiovascular or unexplained death occurred in 3% in the WATCHMAN group versus 4.9% in the warfarin group (RR 0.62, 95% CI 0.35-1.25). In PREVAIL (Evaluation of the WATCHMAN LAA Closure Device in Patients With Atrial Fibrillation Versus Long Term Warfarin Therapy), 407 patients (with a mean CHADS2 score of 2.6; 28% with previous ischemic stroke or TIA) were randomized 2:1 to LAAO or warfarin. LAAO was non-inferior to warfarin for the primary outcome of stroke or thromboembolism >7 days post-randomization.⁵² Observational data from 1,047 patients using another device, the AMPLATZER cardiac plug, showed an annual stroke risk of 2.3%.⁵⁴ However, the procedure of LAAO device implantation carries a procedural risk of complications including device embolization, arteriovenous fistula, cardiac perforation, and pericardial effusion with cardiac tamponade. The rate of procedural complications was 8.7% in PROTECT-AF and 4.2% in PREVAIL.

Recommendations

For patients with non-valvular AF and previous ischemic stroke or TIA, we cannot make any recommendation on whether left atrial appendage occlusion should be preferred over long-term vitamin K antagonists for secondary prevention of all events.

Quality of evidence: low

Strength of recommendation: weak

Additional information

For clinicians and patients, a major attraction of LAAO is that patients do not need to take long term oral anticoagulants. This makes LAAO potentially beneficial for patients deemed to be at high risk of bleeding complications.^{55,56} No data from randomized studies exist on the optimal duration of antiplatelet therapy after LAAO. The benefit of LAAO in comparison to OACs or no medical treatment in patients with

previous ICH is now being tested in RCTs (A3ICH, NCT03243175; and STROKECLOSE, NCT 02830152; see also under 4).

4 Oral anticoagulants versus no oral anticoagulants in patients with intracerebral hemorrhage

4.1 - In patients with non-valvular AF who have experienced intracerebral hemorrhage, does starting or restarting oral anticoagulants reduce the risk of recurrent stroke or systemic embolism and other predefined outcomes in comparison to not (re-)starting oral anticoagulants?

Around 15-25% of patients presenting with ICH use OAC,⁵⁷⁻⁵⁹ in the majority because of AF.⁵⁷ This proportion rises to >30% in patients 65 years and older,⁵⁷ and has increased over time.⁵⁹ So far, most patients in studies on OAC associated ICH were treated with VKA.⁵⁷⁻⁵⁹ Adoption of NOACs for secondary prevention in AF might result in a decreasing incidence of OAC associated ICH in the coming years, at least in high-income countries, but increased uptake of OAC in older people might counteract this trend. In a recent Cochrane review no randomized controlled trials could be identified that analyzed efficacy and safety of administration of OAC or antiplatelet drugs after ICH.⁶⁰ As a result, there is large variation in clinical practice, as illustrated in a cohort study providing observational data from four different countries, in which the proportion of patients who restarted antithrombotic drugs varied between 11% and 45%.⁶¹ In a recent systematic review and meta-analysis specifically addressing patients with AF (7 studies; 2,452 patients), survivors of intracranial hemorrhage who restarted OAC had a lower risk of ischemic stroke in comparison to those in whom anticoagulants were not recommenced (pooled RR 0.46, 95% CI 0.29-0.72), whereas the risk of recurrent ICH was comparable (pooled RR 1.23, 95% CI 0.80-1.87).⁶² A recent study of 1,012 patients with ICH and AF, that was not included in the previous meta-analysis, found that both in patients with lobar ICH (379 patients; OAC restarted in 23%) and in patients with non-lobar ICH (633 patients; OAC restarted in 28%), OAC resumption was associated with a decreased risk of death (adjusted [a] HR 0.29, 95% CI 0.17-0.45 for lobar and aHR 0.25, 95% CI 0.14-0.44 for non-lobar ICH), and with a decreased risk of ischemic stroke (aHR 0.48, 95%-CI 0.25-0.75 for lobar and aHR 0.39, 95%-CI 0.21-0.74 for non-lobar ICH).⁶³ Restarting OAC was not associated with an increase in the risk of ICH recurrence for both lobar (aHR, 1.26, 95% CI, 0.88-1.71) and non-lobar (aHR, 1.17, 95% CI, 0.89-1.54) ICH patients.⁶³ In 190 patients who fulfilled the modified Boston criteria for cerebral amyloid angiopathy (CAA),⁶⁴ OAC resumption was associated with decreased risk of death both in those with possible CAA (aHR, 0.27, 95% CI 0.08-0.86; 136 patients) and in those with probable CAA (aHR 0.30, 95% CI 0.10-0.92; 54 patients); moreover, the presence of ≥ 2 cerebral microbleeds or cortical superficial

siderosis did not modify these associations.⁶³ In these previous studies, OAC consisted predominantly or exclusively of VKA and no information is available yet on the safety and efficacy of the use of NOACs in patients who have experienced ICH.

The results of these observational studies should be interpreted with caution as they are prone to selection biases and confounding by indication. Several randomized controlled trials are now addressing the clinical dilemma of whether or not to restart OACs in patients with AF who have had an ICH, APACHE-AF (NCT02565693),⁶⁵ NASPAF-ICH (NCT02998905), SoSTART (NCT03153150), A3ICH (NCT03243175), and STATICH (NCT03186729), STROKECLOSE (NCT 02830152), PRESTIGE-AF, and ASPIRE, with most of them testing the use of NOACs against other strategies, including no OAC.⁶⁶

Recommendations

In patients with AF who have experienced an intracerebral hemorrhage, we cannot make recommendations regarding whether or not oral anticoagulation should be (re-)started or not.

Quality of evidence: Low

Strength of recommendation: Weak

5 Medical treatment in subgroups of patients with ischemic stroke

5.1 Elderly patients

5.1.1 - In elderly patients with non-valvular AF and previous ischemic stroke or TIA, does oral anticoagulant treatment reduce the risk of recurrent stroke or systemic embolism and other predefined outcomes compared to antiplatelet treatment or no anticoagulant treatment?

We found no data to suggest that the benefit-risk ratio is different in elderly patients with ischemic stroke or TIA receiving OAC treatment for AF. The absolute risk of intracranial hemorrhage is increased, as indicated by the HAS-BLED score, but so is also the absolute risk of ischemic events, as indicated by the CHA₂DS₂Vasc score. In the trials of anticoagulant treatment vs. no OAC treatment (EAFT,¹¹ Veterans Affairs Stroke Prevention in Nonrheumatic Atrial Fibrillation trial¹⁵) and in the trials of OAC vs. antiplatelet treatment (EAFT,¹¹ BAFTA,¹⁶ ACTIVE-W,¹⁷ AVERROES³¹) there was no evidence of effect modification by age. Since there are no direct comparisons in elderly patients with previous ischemic stroke or TIA, the quality of evidence is low and the strength of the recommendation is weak.

Recommendations

In elderly patients with non-valvular AF and a history of ischemic stroke or TIA, we suggest oral anticoagulant treatment over antiplatelet treatment or no oral anticoagulant treatment for secondary prevention of all events.

Quality of evidence: Low

Strength of recommendation: Weak

5.1.2 - In elderly patients with non-valvular AF and previous ischemic stroke or TIA, does non-vitamin K antagonist oral anticoagulants reduce the risk of recurrent stroke or systemic embolism and other predefined outcomes compared to vitamin K antagonists?

In the trials of NOACs vs. VKAs (RE-LY,²¹ ROCKET-AF,²² ARISTOTLE,²³ ENGAGE AF-TIMI 48 trial²⁴), analyses of the subgroups of elderly patients showed no evidence of any different effect in elderly patients.⁶⁷ Since there are no direct comparisons in elderly patients with previous ischemic stroke or TIA, the quality of evidence is moderate and the strength of the recommendation is weak.

Recommendation

In elderly patients with non-valvular AF and previous ischemic stroke or TIA, we suggest non-vitamin K antagonist oral anticoagulants treatment over vitamin K antagonist treatment for secondary prevention of all events.

Quality of evidence: Low

Strength of recommendation: Weak

5.2 Patients with cognitive deficits

5.2.1 - In patients with cognitive deficits, non-valvular AF and previous ischemic stroke, does anticoagulant treatment reduce the risk of recurrent stroke or systemic embolism and other predefined outcomes compared to antiplatelet treatment or no anticoagulant treatment?

In the trials of OAC vs. no OAC treatment (EAFT,¹¹ Veterans Affairs Stroke Prevention in Nonrheumatic Atrial Fibrillation trial¹⁵) and in the trials of anticoagulant vs. antiplatelet treatment (EAFT,¹¹ BAFTA,¹⁶ ACTIVE-W¹⁷) there were no subgroup analyses of patients with cognitive deficits. Analyses of the

subgroups of elderly patients and patients with previous ischemic stroke showed no evidence of any different effect in those patients, and this can perhaps be used as indirect evidence. In addition, many considerations must be made when offering long-term anticoagulant treatment to patients with cognitive decline, such as reduced capacity to consent, reduced life expectancy and quality of life, poorer adherence to treatment, and increased risk of bleeding, so we believe that the strength of the recommendation should be “weak”.

Recommendation

In patients with cognitive deficits, non-valvular AF and previous ischemic stroke or TIA, we suggest oral anticoagulant treatment over antiplatelet treatment or no oral anticoagulant treatment for secondary prevention of all events.

Quality of evidence: Low

Strength of recommendation: Weak

5.2.2 - In patients with cognitive deficits, non-valvular AF atrial fibrillation and previous ischemic stroke or TIA, does non-vitamin K antagonist oral anticoagulants reduce the risk of recurrent stroke or systemic embolism and other predefined outcomes compared to vitamin K antagonists?

In the trials of NOACs vs. VKAs (RE-LY,²¹ ROCKET-AF,²² ARISTOTLE,²³ ENGAGE AF-TIMI 48 trial²⁴), there was no analyses of subgroups of patients with cognitive deficits. Analyses of the subgroups of elderly patients and patients with previous stroke showed no evidence of any different effect in those patients, which can perhaps be used as indirect evidence. In addition, many factors should be taken into account when prescribing long-term OACs to patients with cognitive decline, including reduced capacity to consent, reduced life expectancy and quality of life, poor adherence to treatment, and increased risk of bleeding. Therefore, the strength of the recommendation should be “weak”.

Recommendation

In patients with cognitive decline, non-valvular AF and previous ischemic stroke or TIA, we suggest non-vitamin K antagonist oral anticoagulants treatment over -vitamin K antagonist treatment for secondary prevention of all events.

Quality of evidence: Low

Strength of recommendation: Weak

5.3 Patients with renal impairment

5.3.1 - In patients with renal impairment, non-valvular AF, previous ischemic stroke or TIA, do non-vitamin K antagonist oral anticoagulants compared to vitamin K antagonists reduce the risk of recurrent stroke or systemic embolism and other predefined outcomes?

Impaired renal function is associated with a higher prevalence of AF and with an increased risk of ischemic stroke and systemic embolism.⁶⁸⁻⁷¹ About 15-20% of AF patients also have chronic kidney disease (CKD).⁷² Renal impairment confers a substantially increased risk of major bleeding and often contributes to underuse of OAC in patients with AF.^{71, 73} No RCT has directly investigated the efficacy and safety of NOACs compared to VKAs in AF patients with a prior stroke or TIA and impaired renal function. Available data focusing on renal function derive from pre-specified subgroup analyses of all four completed phase 3 clinical trials comparing NOACs with dose-adjusted warfarin in patients with AF.⁷⁴⁻⁷⁸ Considering that patients with prior ischemic stroke or TIA represent a substantial proportion in those studies, ranging from 20%-63%, results may also be considered to be informative for patients with a previous stroke or TIA and renal impairment.

In all sub-group analyses renal function was estimated using the Cockcroft-Gault method.⁷⁹ Renal dysfunction was defined according to the original trials based on the European Medicines Agency classification as moderate when creatinine clearance (CrCl) ranged between 30 and 50 ml/min, and as mild in the case of CrCl between 50 and 80 ml/min. Definitions of renal impairment varied across trials. In ENGAGE TIMI (HDER) mild renal impairment was defined as CrCl of 50-95 ml/min and in ENGAGE TIMI (LDER) and ROCKET AF it was defined as CrCl >50 ml/min.

The RELY trial tested the long-term efficacy and safety of two different doses (110 mg and 150 mg BID) of the direct thrombin inhibitor dabigatran and dose-adjusted warfarin. Renal elimination with dabigatran is approximately 80%. According to the Cockcroft-Gault equation a total of 8,553 patients (47.6%) had CrCl 50-<80 ml/min, and 3,554 (19.8%) had CrCl <50 ml/min. The proportion of patients with a history of previous stroke or TIA in each group was 19.4% and 20.1%, respectively.⁷⁸ ROCKET-AF compared fixed-dose rivaroxaban 20 mg daily or 15 mg daily with dose-adjusted warfarin. Of the 14,264 patients with AF, 2,950 had moderate renal insufficiency defined as CrCl 30-49 ml/min at baseline. In patients with CrCl <50 ml/min, representing 20.7% of the trial cohort, the dose of rivaroxaban was reduced from 20 to 15

mg daily. Approximately, one third of rivaroxaban is excreted via the kidneys. Almost 50% of patients with CrCl<50 ml/min and 56% of patients with preserved renal function had a history of a previous ischemic stroke/TIA.⁷⁵

In the ARISTOTLE trial, apixaban was administered at 5 mg twice daily or 2.5 mg twice daily for a subgroup of patients with two or more of the following criteria: age ≥80 years, body weight ≤60 kg, serum creatinine ≥1.5 mg/dL (133 mmol/L). Renal elimination of apixaban is approximately 25%. According to the Cockcroft-Gault equation 7,587 patients had a CrCl 50-80 ml/min and 3,017 had severe renal impairment with CrCl ≤50 ml/min. The proportion of patients with a history of a previous stroke/TIA in each group was 21.6% and 25.1%, respectively.⁷⁶

The Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction 48 (ENGAGE AF-TIMI 48) trial evaluated the long-term efficacy and safety of two dosing regimens (60 mg and 30 mg) of edoxaban and adjusted- dose warfarin in patients with AF.⁷⁴ Because of the significant renal clearance of edoxaban (50%), patients with moderate renal dysfunction (CrCl 30-50 ml/min) and low body weight (≤60 kg,) or concomitant use of a phosphorylated glycoprotein inhibitor received a dose of edoxaban reduced by 50% (30 mg and 15 mg, respectively). Of 14,071 patients in the warfarin and high dose edoxaban arms, 2,740 patients (19.5%) had a CrCl ≤50 ml/min, and 8,208 (58.3%) had a CrCl 50-95 ml/min at the time of randomization. Of the 14,070 patients in the warfarin and Low Dose Edoxaban Regimen (LDER) arm of the study, 2,695 patients had a CrCl ≤ 50 ml/min and 11,375 had a CrCl >50 ml/min. Among patients with moderate renal failure randomized to high dose edoxaban, 30% had previous ischemic stroke or TIA.⁷⁴

Patients with moderate renal failure (Creatinine clearance <50ml/min)

We pooled a total of 13,880 patients with moderate renal impairment from five RCTs (8,258 patients were assigned to NOAC and 5,622 were assigned to warfarin). The reduction in risk of stroke or systemic embolism in patients with moderate renal failure did not differ significantly in patients receiving NOAC compared to those receiving warfarin (RR 0.87, 95% CI 0.74-1.04; eTable 6 and eFigure 15). Notably, there was a significant reduction of stroke or systemic embolism with the high dose of dabigatran, without however a significant reduction in major bleeding at the same dose. There was little heterogeneity across the trials (I^2 13%).

Major bleeding was defined according to the ISTH criteria in all included trials.²⁵ Pooling the results of four trials corresponding to a total population of 13,574 patients (8,101 assigned to NOAC and 5,473

patients to warfarin), use of NOACs was associated with a significant reduction of major bleeding by 27% (RR 0.73, 95% CI 0.54-0.99; eFigure 16). The most significant reduction of major bleeding events was observed with apixaban and the lower dose of edoxaban, which was consistent with the main pooled analysis, whereas rivaroxaban, the higher dose of edoxaban as well as the lower and higher dose of dabigatran did not significantly reduce the rate of major bleeding compared to dose-adjusted warfarin in patients with moderate renal impairment. Heterogeneity among trials was high (I^2 83%).

Three of the trials assessed the effect on all-cause death,^{74, 76, 78} whereas, two trials assessed vascular death.^{75, 77} Pooling the results on all-cause death from three trials corresponding to 9,299 patients (5,302 assigned to NOAC group and 3,997 assigned to warfarin) death was not significantly reduced with NOACs compared to warfarin (RR 0.93, 95%CI 0.80-1.07; eFigure 17). The main pooled results were consistent across all trials with the exception of the higher dose of edoxaban, which showed a significant reduction in death (RR 0.83, 95%CI 0.71-0.96). Heterogeneity was substantial (I^2 50%) across the trials.

Recommendations

In patients with non-valvular AF and previous stroke or TIA, and moderate renal impairment, we suggest non-vitamin K antagonist oral anticoagulants over vitamin K antagonists for secondary prevention of all events.

Quality of evidence: Low

Strength of recommendation: Weak

Outcomes in patients with mild renal failure (CrCl 50-80 ml/min)

Analysis of pooled data deriving from subgroup analyses of three RCTs (RE-LY,^{21, 78} ARISTOTLE,^{23, 76} ENGAGE AF-TIMI 48 trial low dose,^{24, 74} corresponding to a population of 17,130 patients (9,968 assigned to NOAC group and 7,162 assigned to warfarin), showed that NOACs significantly reduced the risk of stroke or systemic embolism compared to warfarin in patients with mild renal failure (RR 0.73, 95% CI 0.56-0.97; eFigure 15). Heterogeneity among studies was moderate (I^2 48%).

Major bleeding was defined according to the ISTH²⁵ in all included trials. Pooling results from RELY and ARISTOTLE showed a significant reduction of major bleeding with NOAC compared to warfarin (RR 0.82, 95% CI: 0.72-0.93; eFigure 16). No heterogeneity was observed among studies (I^2 0%).

Pooled results from RE-LY and ARISTOTLE showed a significant reduction in death from all causes with NOAC compared to dose-adjusted warfarin (RR 0.85%, 95% CI 0.73-0.99; eFigure 17). Heterogeneity among studies was moderate (I^2 42%).

Recommendations

In patients with mild renal impairment, non-valvular AF, and previous ischemic stroke or TIA, we suggest non-vitamin K antagonists oral anticoagulants over vitamin K antagonists for secondary prevention of all events.

Quality of evidence: Low

Strength of recommendation: Weak

Additional information:

Extrapolation of results from pre-defined subgroup analyses on all AF patients with impaired renal function to AF patients with a previous ischemic stroke or TIA and renal impairment may be inadequate. Although patients with moderate renal insufficiency represent a substantial population within the RCTs, the pre-defined subgroup analyses on patients with renal dysfunction were not powered to demonstrate superiority or non-inferiority for the comparisons of NOAC over warfarin. Moreover, we pooled data from trials testing NOACs with different metabolism and pharmacokinetics: renal elimination is approximately 80% using dabigatran, 35% using rivaroxaban, 25% using apixaban and 50% using edoxaban. In addition patients with impaired renal function across all trials were older and had higher event rates irrespective of study treatment. RCTs testing dabigatran, rivaroxaban and edoxaban excluded patients with CrCl <30 ml/min, while trials of apixaban excluded those with CrCl <25 mL/min. Furthermore, patients were recruited according to the baseline GFR with no dose adjustments post-baseline for alterations in creatinine levels. The risk of drug accumulation and bleeding may have been amplified by several drug-drug interactions as well.

Anticoagulation constitutes the treatment of choice also for AF patients with moderate-to-severe renal dysfunction who have been excluded from RCTs testing NOACs over warfarin. Results from two large RCTs showed that OAC are effective and safe for AF patient with severely impaired renal function. SPAF III trial reported favorable efficacy and safety profile of adjusted dose warfarin (target INR 2.0-3.0) compared to aspirin in high-risk AF patients with stage 3 chronic kidney disease (CKD).⁷⁰ A subgroup analysis of AVERROES trial also showed that among patients with stage III CKD, apixaban significantly reduced ischemic stroke compared to aspirin without a significant increase in major bleeding.⁸⁰ Chronic kidney disease is most prevalent in older people and OAC should be prescribed with caution.

Nevertheless, even in this patient group anticoagulation seems to be of benefit associated with lower rate of all-cause death, despite an increased rate of ischemic stroke and hemorrhage.⁸¹

Finally, there are no data on the efficacy and safety of NOAC in patients on hemodialysis and VKAs remain the OAC of choice in those patients. Multiple trials are investigating different treatment options in AF patients with end-stage renal disease and a history of stroke or at increased risk of stroke or embolism (RENAL-AF, NCT02942407, apixaban vs. warfarin AXADIA, NCT02933697, apixaban vs. phenprocoumon; STOP-HARM, NCT02885545, LAAO vs. continuation of prescribed OAC (VKA or apixaban or rivaroxaban); AVKDIAL, NCT02886962, no OAC vs. VKA).

5.4 Patients with cerebral small vessel disease

5.4.1 - In patients non-valvular AF, previous ischemic stroke or TIA and small vessel disease, does oral anticoagulant treatment reduce the risk of recurrent stroke or thromboembolism and other predefined outcomes compared to antiplatelet treatment or no anticoagulant treatment?

The term “cerebral small vessel disease” (SVD) describes pathological processes affecting the small arteries, arterioles, venules, and capillaries of the brain.⁸² Small vessel disease causes about 25% of ischemic stroke (through small artery occlusion)⁸² and about 80% of ICH (through small artery rupture).⁸³ The radiological lesions caused by SVD include lacunes (the commonest type of silent brain infarct), white matter hyperintensities (WMH), cerebral microbleeds (CMB), cortical superficial siderosis and perivascular spaces, as defined by the STRIVE (STandards for Reporting Vascular changes on nEuroimaging) consensus group.⁸⁴ SVD is of interest in patients with stroke or TIA and AF, because it might affect the risk of both future ischemic stroke and ICH (and different markers might differentially affect these outcomes), potentially affecting the risk-balance of antithrombotic treatment decisions. Of these imaging markers, the most widely studied in cohorts relevant for secondary stroke prevention for AF are WMH and CMBs; these are common in populations of patients with AF with previous stroke (WMH prevalence 19-23%, CMBs prevalence 7-32%), and can lead to clinical uncertainty regarding optimal antithrombotic therapy.⁸⁵

5.4.2 - In patients with non-valvular AF, previous ischemic stroke or TIA, and small vessel disease does antiplatelet treatment compared to no antithrombotic treatment reduce the risk of recurrent stroke or thromboembolism and other predefined outcomes compared?

We found no randomized controlled trials investigating the efficacy and safety of antiplatelet therapy compared to no antithrombotic treatment for secondary stroke prevention in patients with non-valvular AF and small vessel disease (WMH, CMBs).

Recommendations:

In patients with non-valvular AF, previous ischemic stroke or TIA and small vessel disease we cannot make recommendations on whether antiplatelet therapy should be preferred over no antithrombotic treatment for secondary prevention of all events.

Quality of evidence: Low

Strength of recommendation: Weak

Additional information

In the PERFORM study 748 patients with athero-thrombotic disorders and recent ischemic stroke or TIA (excluding those with cardiac causes requiring long term OAC) were randomized to aspirin or tetrutroban (an oral selective antagonist of thromboxane-prostaglandin receptors in platelets and in the vessel wall). There was progression of fluid-attenuated inversion recovery (FLAIR) vascular lesions, and of CMB, but with no difference between patients treated by terutroban and those treated by aspirin.⁸⁶

In a meta-analysis including 5,068 patients with ischemic stroke or TIA from 15 studies (most without AF, treated with antiplatelet agents), CMBs were associated with increased stroke risk after ischemic stroke or TIA, with a greater relative risk for ICH than ischemic stroke (for ischemic stroke, pooled RR 1.8 for CMBs vs no CMBs, 95% CI 1.4-2.5); for ICH, pooled RR 6.3 for CMBs vs no CMBs, 95% CI 3.5-11.4). With increasing CMB burden (compared to no CMBs), the risk of ICH increased more steeply than that of ischemic stroke. However, the ischemic stroke absolute event rate (115/1,284 (9.6%)) was higher than the ICH absolute event rate (212/3,781 (5.6%)) across all CMB burden categories.⁸⁷

5.4.3 - In patients with small vessel disease, non-valvular AF and previous ischemic stroke or TIA, do vitamin K antagonists reduce the risk of recurrent stroke or systemic embolism and other predefined outcomes compared to antiplatelet treatment?

We found no randomized controlled trial investigating the efficacy and safety of VKA therapy compared to antiplatelet therapy for secondary stroke prevention in patients with AF and small vessel disease (WMH, CMBs).

Recommendations:

In patients with non-valvular AF, previous ischemic stroke or TIA and small vessel disease, we cannot make recommendations about whether vitamin K antagonists should be preferred over antiplatelet therapy for secondary prevention of all events.

Quality of evidence: Low

Strength of recommendation: Weak

Additional information

A post-hoc retrospective aggregate data meta-analysis of cohort studies including 1,552 patients with prior ischemic stroke or TIA and AF treated with VKA found (CMBs prevalence 30%, 7% with ≥ 5 CMBs) found that the pooled annual ICH incidence increased from 0.30% (95% CI 0.04-0.55) among CMB-negative patients to 0.81% (95% CI 0.17-1.45) in CMB-positive patients ($p = 0.01$) and 2.48% (95% CI 1.2-6.2) in patients with ≥ 5 CMBs ($p = 0.001$). There was no association between CMBs and recurrent ischemic stroke.⁸⁸ This study had important methodological limitations, including being dominated by a single cohort of 550 patients from Asia (Korea), and having variable completeness and duration of follow-up.

Limited observational data suggest that SVD biomarkers detected on brain imaging, particularly if hemorrhagic (e.g. CMBs, cortical superficial siderosis) or severe, might increase the risk of ICH to a greater extent than that of recurrent ischemic stroke in patients with AF and prior ischemic stroke or TIA treated with VKA. Since conventional clinical risk scores for ICH in AF patients have limited predictive performance for ICH, the use of SVD neuroimaging biomarkers in risk scores might allow clinicians to make better informed predictions of ICH risk to personalized treatment. Prospective observational cohort studies are awaited:(CROMIS-2 (NCT02513316)⁸⁹ and HERO (HemorrhageNCT02238470)) and should inform this question. A large-scale international collaborative individual patient data met-analysis on CMBs and future stroke risk in patients with prior ischemic stroke or TIA is also underway (the Microbleeds International Collaborative Network),⁹⁰ which should help develop more accurate ICH risk prediction scores, determine patients who might be at net harm from OAC, assess the potential benefits of NOACs in populations with severe SVD, and potentially inform the design of future RCTs.

5.4.4 - In patients with small vessel disease, non-valvular AF and previous ischemic stroke or TIA, do non-vitamin K antagonist oral anticoagulants reduce the risk of recurrent stroke or systemic embolism and other predefined outcomes compared to vitamin K antagonists?

We found no randomized controlled trials or high quality observational studies investigating the efficacy and safety of NOACs compared to VKAs for secondary stroke prevention in patients with AF and small vessel disease.

Recommendations:

In patients with non-valvular AF, previous ischemic stroke or TIA and small vessel disease we cannot make recommendations about whether non-vitamin K antagonist oral anticoagulants should be preferred over vitamin K antagonists for reducing recurrent stroke or thromboembolism

Quality of evidence: Low

Strength of recommendation: Weak

Additional information

In the AVERROES trial, participants with AF deemed unsuitable for long term oral VKA were randomized to apixaban or aspirin. An MRI sub-study followed up 931 participants (of 1,180 patients with MRI at baseline) reported no significant difference in mean change (baseline to follow-up) in periventricular white matter hyperintensity score in patients treated with apixaban compared to those treated with aspirin.⁹¹ The rate of new infarction detected on MRI was 2.5% in the apixaban group and 2.2% in the aspirin group (HR 1.09, 95% CI 0.47-2.52), but new infarcts were smaller in the apixaban group (p =0.03). There was no difference in proportion with new CMBs on follow-up MRI (HR 0.92, 95% CI 0.53-1.60) between treatment groups. Only a minority of participants in this study were stroke survivors (17.8 in the apixaban group, 15.4 in the aspirin group) and the observation period was short.

Prospective cohort studies of patients with SVD have mainly included those treated with VKA.

Theoretically, NOACs might be preferable to VKA in patients with severe SVD, but there are no current data to support this hypothesis. Future studies including patients treated with NOACs are awaited (CROMIS 2, NCT02513316; and HERO, NCT02238470).

All recommendations are summarized in Table 5.

Discussion

Our analyses on currently available evidence shows that in patients with non-valvular AF and previous stroke or TIA, OACs reduce the risk of recurrence over antiplatelets or no treatment. Of OACs, NOACs are the preferred treatment for secondary prevention of stroke or thromboembolism because they have a similar benefit to VKAs with regard to the prevention of stroke or thromboembolism or ischemic complications but a lower risk of major bleeding and death. Furthermore, other than for safety, NOACs offer a significant advantage over VKAs because INR measurement, dose adjustment, and dietary restrictions are not required for patients who receive NOACs. The choice of a specific agent may be individualized taking into account unique individual characteristics, comorbidities (e.g. renal function, gastrointestinal bleeding risk), and concomitant medications, as well as patients expressed values and preferences. Antiplatelet agents, either as single or dual therapy, should not be used even in patients with contraindications to OAC because they have a significantly smaller effect in patients with non-valvular AF and stroke or TIA. In patients who have had ischemic stroke while treated with VKA, or are unsuitable for VKAs, we identified moderate quality of evidence to recommend NOACs over aspirin.

For the questions regarding timing of antithrombotic treatment, treatment by means of LAAO, (re-) starting OACs in patients with previous ICH, and medical treatment in the specific patient subgroups of those of older age, with cognitive impairment, with renal failure, and those with small vessel disease on brain imaging, we can only make weak recommendations.

Ongoing RCTs like ELAN, START, TIMING, OPTIMAS will clarify the optimal timing of treatment with NOACs after ischemic stroke. In a recent prospective study, patients with acute ischemic stroke and non-valvular AF who were treated with NOACs had a 90-day rate of 2.8% for recurrent ischemic stroke or TIA and 1.6% for symptomatic ICH. The large majority of patients in this study received NOACs within 15 days.⁹² Another prospective cohort study reported that, despite the early start of NOACs (65% of the 155 included patients received therapy within 7 days), no ICH occurred and 4 patients had recurrent ischemic stroke during follow-up of at least 3 months.³⁹

RCTs are also ongoing that test whether or not OACs should be restarted in patients with AF who have experienced ICH. A recent meta-analysis⁶² of observational studies has suggested that restarting OACs (in these studies all VKAs) may in fact be more safe and effective than previously thought, and might improve outcome. Even in patients with lobar ICH who have a relatively high risk of recurrent ICH restarting OACs might be effective.⁶³ However, as the observational studies were affected by selection by

indication RCTs are needed to provide evidence on the optimal secondary preventive treatment in patient with AF after ICH.

Available data focusing on renal function derived from pre-specified subgroup analyses of all four completed phase 3 RCTs that compared NOACs with dose-adjusted warfarin in patients with non-valvular AF. Considering that patients with previous ischemic stroke or TIA represent a substantial proportion in those studies, we have considered the pooled results from these trials to be informative for patients with a previous stroke or TIA and renal impairment. For this reason, we have suggested that in patients with non-valvular AF and previous ischemic stroke or TIA, NOACs are the preferred treatment.

Evidence is increasing that there is a modifying effect of presence of neuroimaging biomarkers of SVD on the risk of ischemic stroke and ICH, and on the risk-benefit ratio of antithrombotic treatment. However, in the absence of RCTs or large high quality observational cohort data specifically addressing patients with SVD neuroimaging biomarkers, we cannot make firm recommendations on the optimal treatment for secondary prevention in this subgroup. The results of the AVERROES MRI study were reassuring with respect to their finding that there was no difference in proportion of patients with new CMBs on follow-up MRI after on average one year between patients treated with apixaban and those treated with aspirin.⁹¹

For all patients, the above information should result in an individualized choice for a specific (N)OAC taking into account unique individual characteristics, co-morbidities (e.g. renal function, gastrointestinal bleeding risk), and concomitant medications, as well as patients expressed values and preferences.

The strengths of this guideline include its systematic approach to searching the literature and guidance by the GRADE recommendations, including predefining outcome events and grading their importance. Furthermore, we have addressed several subgroups of patients for whom clinical practice raises additional questions regarding the secondary prevention medical therapy.

Our guideline also has limitations. First, the GRADE approach only allows for the strength of recommendations to be strong or weak. For some PICO questions, we found evidence that could have resulted in an intermediate strengths of the recommendation, e.g. in case of availability of one RCT.

Second, our guideline is restricted by the limited amount of evidence available for some of the PICO questions.

In conclusion, among patients with non-valvular AF and ischemic stroke or TIA, NOACs are the preferred medical treatment for secondary preventions of recurrent stroke or thromboembolism because of a lower risk of major bleeding and death compared to VKAs. Further research is required to test the best timing for initiating OACs after an acute ischemic stroke and whether or not OACs should be (re-)started in patients with who have experienced an ICH. Future RCTs should include pre-specified subgroup analyses for patients of older age, those with cognitive deficits, and renal failure, and should consider MRI biomarkers, which modify the effect of OACs after stroke or TIA.

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Table 1. Outcomes of interest and judgement of their importance

Outcomes	Ranking
Stroke (all) or thromboembolism	9
Ischemic stroke	8
Intracerebral hemorrhage	8
Major bleeding complications	8
Non-fatal stroke, non-fatal myocardial infarction, and vascular death	7
Death	7
Venous thromboembolism	4

Table 2. Effect of Vitamin K antagonist compared to placebo in patients with previous ischemic stroke or TIA and AF

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vitamin K antagonist	Placebo	Relative (95% CI)	Absolute (95% CI)		
Stroke or thromboembolism												
1	randomized trials	not serious	not serious	not serious	not serious	publication bias strongly suspected ^a	21/225 (9.3%)	54/214 (25.2%)	OR 0.31 (0.18 to 0.53)	158 fewer per 1,000 (from 101 fewer to 195 fewer)	⊕⊕⊕ MODERATE	CRITICAL
Ischemic stroke												
2	randomized trials	not serious	not serious	not serious	not serious	publication bias strongly suspected ^b	18/246 (7.3%)	43/239 (18.0%)	OR 0.36 (0.20 to 0.65)	107 fewer per 1,000 (from 55 fewer to 138 fewer)	⊕⊕⊕ MODERATE	CRITICAL
Intracerebral hemorrhage												
2	randomized trials	not serious	not serious	not serious	serious ^c	publication bias strongly suspected ^b	0/246 (0.0%)	1/239 (0.4%)	OR 0.32 (0.01 to 7.79)	3 fewer per 1,000 (from 4 fewer to 28 more)	⊕⊕ LOW	CRITICAL
Major bleeding complications												
2	randomized trials	not serious	not serious	not serious	serious ^c	publication bias strongly suspected ^b	13/246 (5.3%)	3/239 (1.3%)	OR 4.31 (1.21 to 15.35)	39 more per 1,000 (from 3 more to 151 more)	⊕⊕ LOW	CRITICAL
Death												
2	randomized trials	not serious	not serious	not serious	not serious	publication bias strongly suspected ^b	46/246 (18.7%)	48/239 (20.1%)	OR 0.91 (0.58 to 1.44)	15 fewer per 1,000 (from 65 more to 74 fewer)	⊕⊕⊕ MODERATE	CRITICAL

CI: Confidence interval; OR: Odds ratio

Explanations

- a. Single study
- b. Two studies to report this outcome
- c. Wide confidence intervals

Table 3. Effect of Vitamin K antagonist compared to aspirin in patients with previous ischemic stroke or TIA and AF

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vitamin K antagonist	Aspirin	Relative (95% CI)	Absolute (95% CI)		
Stroke or thromboembolism												
1	randomized trials	serious ^a	not serious	not serious	not serious	publication bias strongly suspected strong association ^b	21/225 (9.3%)	94/404 (23.3%)	OR 0.34 (0.20 to 0.56)	139 fewer per 1,000 (from 88 fewer to 175 fewer)	⊕⊕⊕ MODERATE	CRITICAL
Ischemic stroke												
1	randomized trials	serious ^a	not serious	not serious	not serious	publication bias strongly suspected strong association ^b	16/225 (7.1%)	64/404 (15.8%)	OR 0.41 (0.23 to 0.72)	87 fewer per 1,000 (from 39 fewer to 117 fewer)	⊕⊕⊕ MODERATE	CRITICAL
Intracerebral hemorrhage												
1	randomized trials	serious ^a	not serious	not serious	serious ^c	publication bias strongly suspected ^b	0/225 (0.0%)	2/404 (0.5%)	OR 0.36 (0.02 to 7.47)	3 fewer per 1,000 (from 5 fewer to 31 more)	⊕ VERY LOW	CRITICAL
Major bleeding complications												
2	randomized trials	serious ^a	serious ^d	not serious	not serious	publication bias strongly suspected strong association ^e	14/289 (4.8%)	11/464 (2.4%)	OR 2.39 (0.98 to 5.85)	31 more per 1,000 (from 0 fewer to 101 more)	⊕⊕ LOW	CRITICAL
Death												
1	randomized trials	serious ^a	not serious	not serious	not serious	publication bias strongly suspected ^b	41/225 (18.2%)	102/404 (25.2%)	OR 0.66 (0.44 to 0.99)	70 fewer per 1,000 (from 2 fewer to 123 fewer)	⊕⊕ LOW	CRITICAL

CI: Confidence interval; OR: Odds ratio

Explanations

- a. Data not randomized between intervention and comparator
- b. Single study
- c. Wide confidence intervals
- d. Significant heterogeneity
- e. Two studies to report this outcome

Table 4. Effect of non-vitamin K antagonist compared to vitamin K antagonist in patients with previous ischemic stroke or TIA and AF

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NOAC	VKA	Relative (95% CI)	Absolute (95% CI)		
Stroke or thromboembolism												
4	randomized trials	not serious	not serious	not serious	not serious	none	648/11858 (5.5%)	495/8642 (5.7%)	RR 0.91 (0.81 to 1.02)	5 fewer per 1,000 (from 1 more to 11 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
Ischemic stroke												
4	randomized trials	not serious	not serious	not serious	not serious	none	557/11858 (4.7%)	362/8642 (4.2%)	RR 1.07 (0.93 to 1.22)	3 more per 1,000 (from 3 fewer to 9 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Intracerebral hemorrhage												
1	randomized trials	not serious	not serious	not serious	not serious	publication bias strongly suspected ^a	26/3754 (0.7%)	31/3714 (0.8%)	RR 0.83 (0.49 to 1.39)	1 fewer per 1,000 (from 3 more to 4 fewer)	⊕⊕⊕ MODERATE	CRITICAL
Major bleeding complications												
4	randomized trials	not serious	serious ^b	not serious	not serious	none	649/11858 (5.5%)	551/8642 (6.4%)	RR 0.79 (0.64 to 0.96)	13 fewer per 1,000 (from 3 fewer to 23 fewer)	⊕⊕⊕ MODERATE	CRITICAL
Death												
4	randomized trials	not serious	not serious	not serious	not serious	none	1048/11858 (8.8%)	827/8642 (9.6%)	RR 0.87 (0.80 to 0.95)	12 fewer per 1,000 (from 5 fewer to 19 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL

CI: Confidence interval; RR: Risk ratio

Explanations

a. Single study. Intracranial hemorrhage however showed large effect on pooling of 4 studies

b. Significant, I² = 67%. Subgroup analysis however did not show any publication bias for Apixaban, Rivaroxaban, Edoxaban 60 mg, Dabigatran

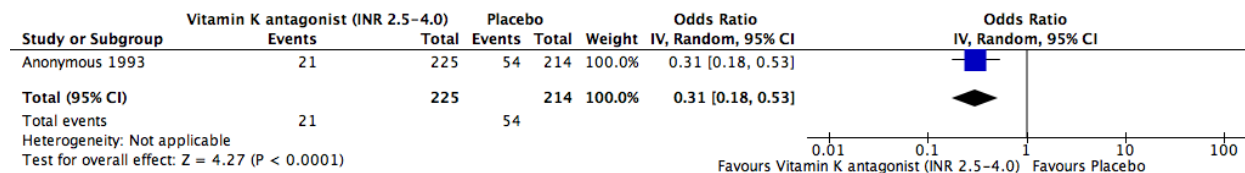
Table 5. Summary of recommendations for secondary prevention of recurrent stroke or systemic embolism and other vascular outcomes in patients with non-valvular AF and stroke or TIA

	Quality of evidence	Strength of recommendation
1 Medical treatment		
1.1 We do not recommend antiplatelet agents (single or dual), over no antiplatelet therapy	Moderate	Weak
1.2 We recommend VKA therapy over no antithrombotic medication	Moderate	Strong
1.3 We recommend VKAs (INR 2-3) over antiplatelet therapy	Moderate	Strong
1.4 We recommend NOACs over VKAs	High	Strong
1.5 We suggest NOACs over aspirin in patients who have failed or are unsuitable for VKA therapy.	Moderate	Weak
2 Timing and bridging of medical treatment		
2.1 We cannot make recommendations about the optimal time for initiating anticoagulation treatment in patients with acute ischemic stroke.	Low	Weak
2.2 We suggest that bridging therapy should be avoided prior to anticoagulation with VKAs or NOACs	Low	Weak
3 Left atrial appendage occlusion		
We cannot make recommendation on whether LAAO is an acceptable alternative to long-term anticoagulation with either VKAs or NOACs.	Low	Weak
4 (Re-) starting treatment in patients with previous intracerebral hemorrhage		
We cannot make recommendations on whether or not oral anticoagulation should be restarted in patients who have experienced intracerebral hemorrhage	Low	Weak
5 Medical treatment in specific patient subgroups		
<i>5.1 Elderly patients</i>		
5.1.1 In elderly patients we suggest anticoagulant treatment over no anticoagulant treatment and over antiplatelets	Low	Weak
5.1.2 In elderly patients with non-valvular AF and a history of ischemic stroke or TIA, we suggest NOACs over VKAs	Low	Weak
<i>5.2 Patients with cognitive deficits</i>		

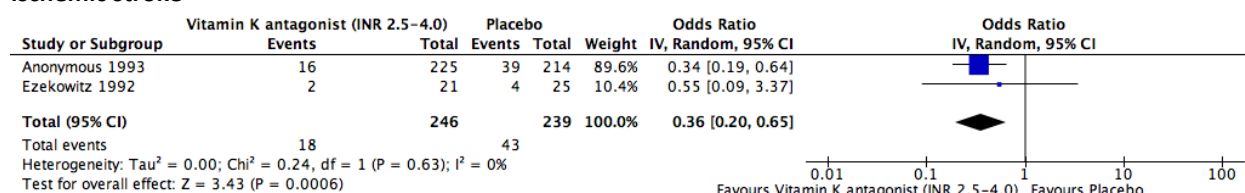
5.2.1 In patients with cognitive decline we suggest anticoagulant treatment over no anticoagulant treatment and over antiplatelets	Low	Weak
5.2.2 In patients with cognitive decline we suggest NOACs over VKAs	Low	Weak
<i>5.3 Patients with renal impairment</i>		
In patients with mild (CrCl 50-80 mL/min) or moderate (<50 mL/min) renal impairment we suggest NOACs over VKAs	Low	Weak
<i>5.4 Patients with small vessel disease</i>		
In patients with small vessel disease, we cannot make recommendations regarding medical secondary prevention for reducing recurrent stroke or thromboembolism	Low	Weak

Figure 1: Effect of Vitamin K antagonists compared to placebo in patients with previous ischemic stroke or TIA and AF

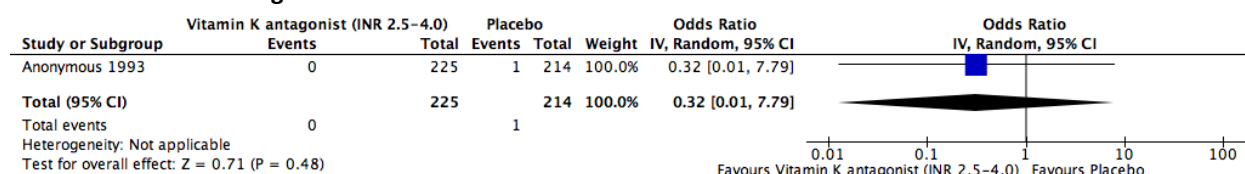
Stroke or thromboembolism



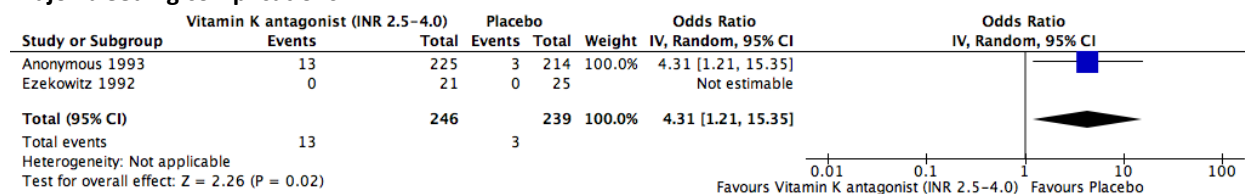
Ischemic stroke



Intracerebral hemorrhage



Major bleeding complications



Death

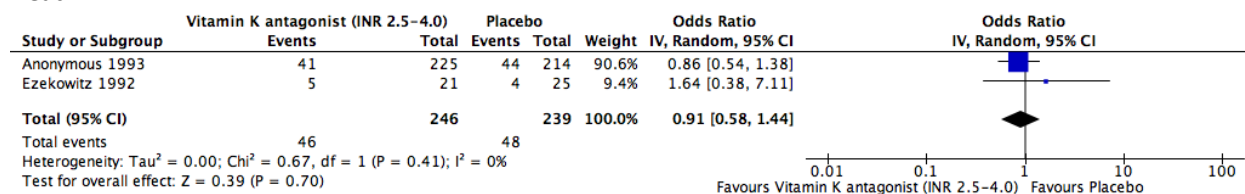
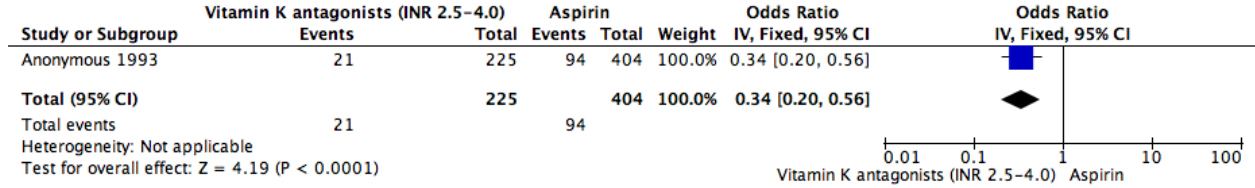
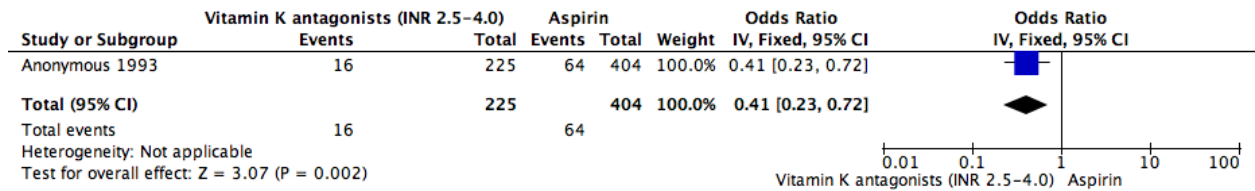


Figure 2: Effect of vitamin K antagonists compared to aspirin in patients with previous ischemic stroke or TIA and AF

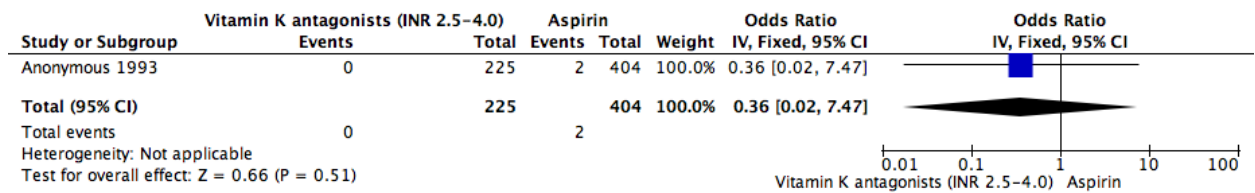
Stroke or thromboembolism



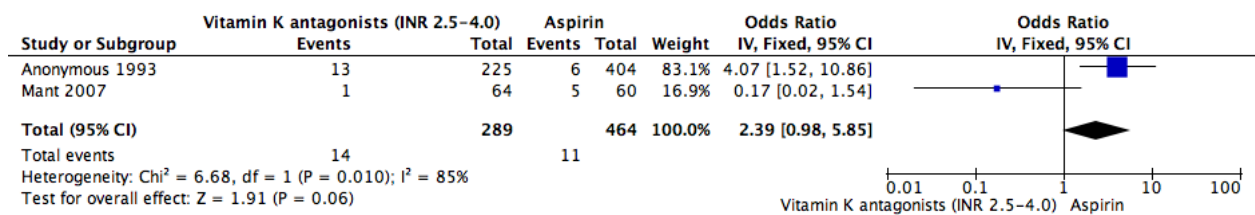
Ischemic stroke



Intracerebral hemorrhage



Major bleeding complications



Death

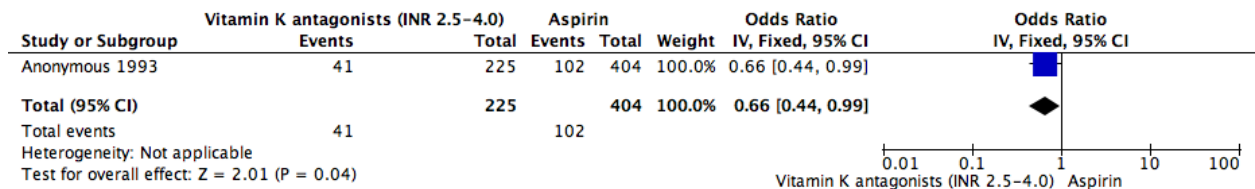
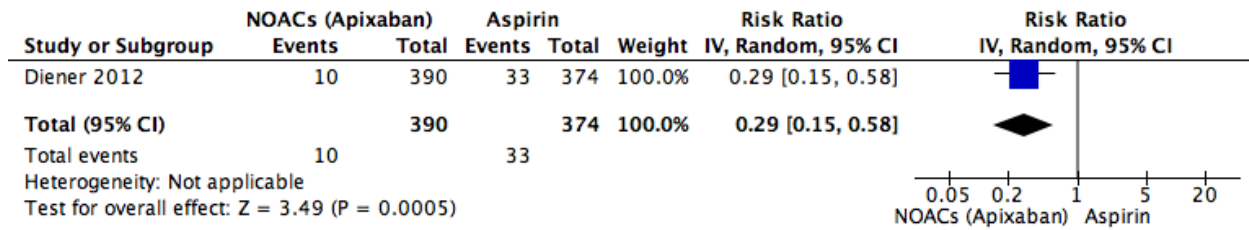
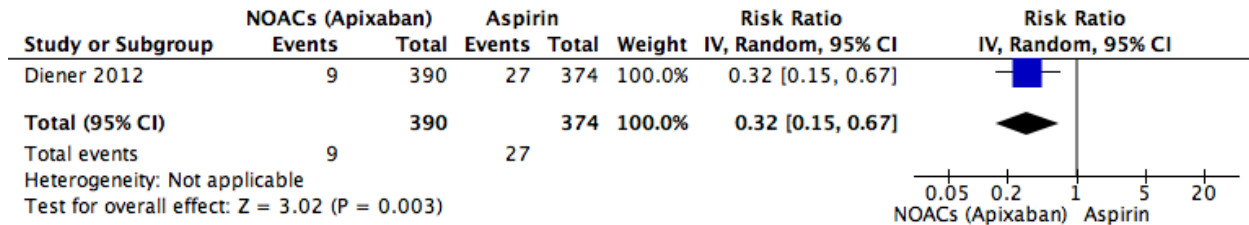


Figure 3: Effect of NOACs versus aspirin in patients with previous stroke or TIA and AF

Stroke or thromboembolism

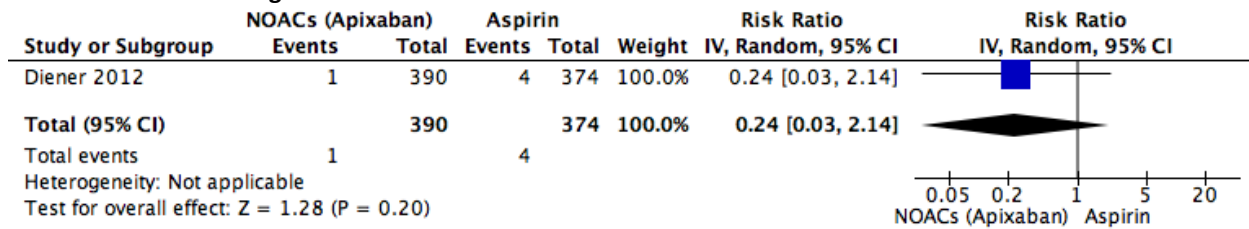


Ischemic stroke*

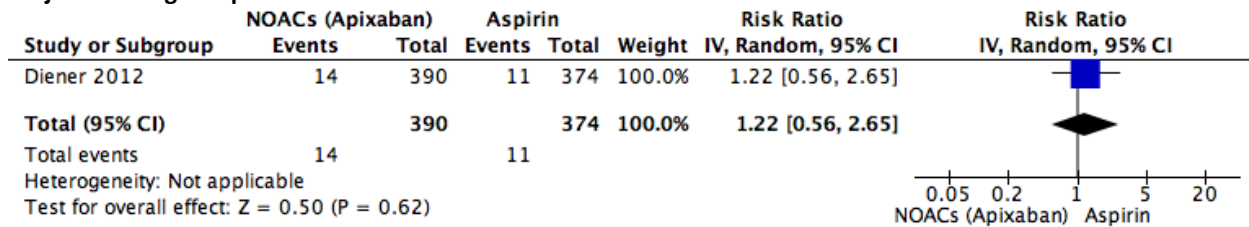


*Included patients with ischemic and undefined stroke

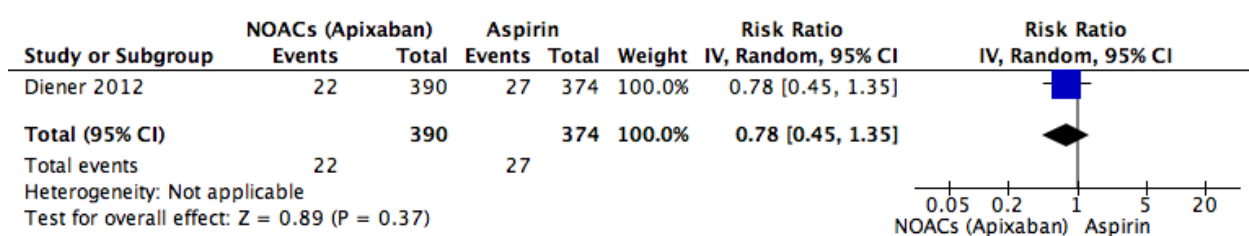
Intracerebral hemorrhage



Major bleeding complications



Death



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