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Special Review
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Non-Vitamin K Oral Anticoagulants in Stroke Patients: Practical Issues

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Non-vitamin-K oral anticoagulants (NOACs) represent a major advance in the prevention of stroke in patients with atrial fibrillation (AF), offering a similar, if not superior, efficacy and safety profile and several practical advantages over oral vitamin K antagonists (VKAs). The rapid onset of action of the NOACs, their relatively short half-live, and the availability of specific reversal agents may be advantageous when managing acute ischemic strokes, and in the post-stroke, post-transient ischemic attack, and post-intracranial hemorrhage settings. In this review article, we offer practical guidance on the use of NOACs in these settings, focusing on managing the acute event and on initiating or resuming anticoagulation for secondary prevention. We also assess the use of NOACs to prevent stroke and bleeding in patients with AF who have chronic kidney disease, are elderly, or cognitively impaired, and we offer guidance on optimizing the use of NOACs and VKAs in these patient groups in the absence of evidence-based guidelines.

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Introduction

Patients with atrial fibrillation (AF) have a high risk of stroke. The most important risk factors for stroke are age and a prior transient ischemic attack (TIA) or stroke. The risk of stroke can be dramatically reduced by oral anticoagulation (OAC) with vitamin K antagonists (VKAs).[1,2] However, VKAs have several shortcomings, such as the inconvenience of regular monitoring and increased bleeding risk, which limit their use in some patients. The non-vitamin-K oral anticoagulants (NOACs), which include the factor Xa inhibitors apixaban, edoxaban, and rivaroxaban, and the factor IIa (thrombin) inhibitor dabigatran, have been specifically designed to overcome the limitations of VKAs, and may thus offer a therapeutic alternative to patients with AF. Several large-scale randomized trials have compared NOACs with VKAs for stroke prevention in patients with AF.[3-7] These trials demonstrated that NOACs are similar or superior to warfarin[3-6] and aspirin[7] in terms of therapeutic efficacy and with regard to the incidence of major bleeding.[8] In this review, we will discuss the practical aspects of the use of NOACs in stroke patients. More detailed information is provided by the European Heart Rhythm Association recommendations[9] and two recent review papers.[10,11]

Patients with acute ischemic stroke

Systemic thrombolysis with intravenous recombinant tissue plasminogen activator is the only approved and effective medical therapy for patients with acute ischemic stroke. However, this therapy has a narrow therapeutic window of 4.5 hours from stroke symptom onset. Furthermore, prior anticoagulation with oral anticoagulants is a contraindication for thrombolysis. To date, there are no prospective, randomized trials to define an international normalized ratio (INR) threshold below which recombinant tissue plasminogen activator can be used in patients re-

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ceiving VKA treatment. Two large registry studies from the United States of America[12] and Europe[13] indicate that thrombolysis is not associated with an increased risk of major or intracerebral bleeding if the INR is ≤ 1.7.

For patients receiving NOACs, which have a short half-life, INR is not a suitable measurement of the coagulation status and bleeding risk. Thrombolysis might be considered in patients receiving NOACs if, depending on kidney function, the last dose of anticoagulant was administered at least three half-lives prior to the stroke. For patients with compromised renal function, the therapeutic window is prolonged.

Patients with aphasia are unable to report whether they are anticoagulated and they cannot name the prescribed drug. They are also unable to report the last intake of the anticoagulant. In this situation, coagulation tests are necessary to guide the decision of whether thrombolysis can be performed. To date, there is no point-of-care device available in the emergency room to determine the coagulation status of patients receiving NOACs. A prolonged activated partial thromboplastin time provides a qualitative estimate of the biological activity of dabigatran.[14] A normal activated partial thromboplastin time allows thrombolysis to be performed. The quantitative assessment of dabigatran activity (diluted thrombin time, ecarin clotting time) is too time consuming if a decision has to be made as to whether or not to perform thrombolysis. For the factor Xa inhibitors apixaban, edoxaban, and rivaroxaban, the anti-factor Xa activity has to be determined. In most instances this is also too time consuming. In one small study, the CoaguChek® point-of-care testing (INR) strongly correlated with rivaroxaban concentrations, but did not accurately detect dabigatran or apixaban.[15] The prothrombin time allows for a qualitative assessment of rivaroxaban activity.

A major step forward in NOAC therapy has been the development of the specific reversal agents (antidotes) andexanet alfa for factor Xa inhibitors,[16] and idarucizumab for dabigatran.[17] Theoretically, these reversal agents could be used to normalize the coagulation parameters in patients with an acute ischemic stroke who are receiving NOACs and are in need of systemic thrombolysis. However there are currently no clinical efficacy or safety data for this approach. Therefore, prospective registries are needed to monitor the success and bleeding complications of these antidotes following systemic thrombolysis.

The most effective therapy in acute ischemic stroke is thrombectomy with advanced stent retrievers in patients with distal occlusions of the internal carotid or proximal middle cerebral artery.[18-22] Thrombectomy can be performed in anticoagulated patients, and small case series have shown no increased bleeding risk.[23,24]

Initiation or resumption of anticoagulation with NOACs after TIA or stroke

Continuation of NOACs after an ischemic stroke depends on stroke severity and infarct size.[9] Study data regarding the initiation or resumption of NOACs after TIA or stroke are lacking. Recommendations on the initiation or resumption of NOACs after TIA or ischemic stroke are presently based on consensus opinion (the '1-3-6-12 day rule').[9] For patients with TIA and AF, NOACs can be initiated on day 1, and for those already receiving OACs, treatment can be continued. For patients with mild stroke (National Institutes of Health Stroke Scale [NIHSS] < 8), NOACs can be initiated after 3 days, or after intracranial hemorrhage (ICH) is excluded by imaging (computed tomography or magnetic resonance imaging). For patients with moderate stroke (NIHSS 8-16), anticoagulation can be initiated after 5-7 days, and in severe stroke (NIHSS > 16), after 12-14 days. For both moderate and severe stroke, significant hemorrhagic transformation should be excluded by repeat cerebral imaging.[9] The decision of when to start anticoagulation should be modified by infarct size on imaging, age, and quality of blood pressure control.

NOACs have a fast onset of action. Therefore, bridging with unfractionated heparin or low-molecular-weight heparin is not recommended. Aspirin is given until the initiation of anticoagulation. If patients are treated with NOACs, aspirin treatment is terminated after the first intake of the NOAC. In patients treated with a VKA, aspirin is terminated when an INR of 2 is reached. Secondary stroke prevention in AF patients with aspirin is not superior to placebo.[25] In the AVERROES (Apixaban Versus Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment) trial, treatment with apixaban in patients with previous stroke or TIA reduced the risk of recurrent stroke by 70% without increasing the frequency of major bleeding when compared with aspirin.[26] Therefore, patients with TIA or ischemic stroke should either be anticoagulated or, in the case of clear contraindications, receive no antithrombotic treatment. For these cases, occlusion of the left atrium appendage can be considered.[27]

In patients with AF and symptomatic severe stenosis of the internal carotid artery, carotid endarterectomy should be performed, rather than carotid stenting. This avoids prolonged triple therapy with a high risk of major bleeding in stented patients. In patients undergoing endarterectomy, co-medication with aspirin is only required prior to, and for 10 days after, surgery.[28]

In long-term secondary stroke prevention, anticoagulation should not be combined with antiplatelet therapy. A post-hoc analysis of the SPORTIF (Stroke Prevention using ORal Thrombin

Inhibitor in atrial Fibrillation) trials in which patients with AF were randomized to either ximelagatran or warfarin demonstrated no further benefit of adding aspirin to either anticoagulant in terms of preventing major vascular events.[29] However, the addition of aspirin was associated with an increase in major bleeding complications. Similar observations were made when anticoagulation was combined with antiplatelet therapy in patients with stable coronary heart disease.[11]

Patients with ICH

AF patients treated with VKAs account for 12%-14% of the patients with ICH.[30] The prognosis of anticoagulation-induced intracerebral bleeding is poor, with a mortality rate of around 40%. Mortality is increased in patients with hematoma expansion.[31] The mortality after ICH is similar in patients treated with VKAs or the NOACs dabigatran or rivaroxaban.[32,33] The risk of intracerebral bleeding, however, is reduced in patients treated with NOACs compared with patients treated with warfarin.[8] Mortality is lower in anticoagulated patients with a subdural hematoma or subarachnoid hemorrhage. The coagulation status of patients receiving VKAs or NOACs with ICH needs to be evaluated (see above) and corrected as rapidly as possible. Idarucizumab (2 $\times$ 2.5 g) is recommended in patients treated with dabigatran. If patients are treated with factor Xa inhibitors and their last intake of NOAC is $<$ 6 hours ago, then oral activated charcoal can be given. The efficacy and safety of specific procoagulants, such as prothrombin complex concentrate (PCC), activated PCC, activated factor VII or fresh frozen plasma, in the treatment of ICH associated with VKAs or factor Xa inhibitors are not well documented and therefore need further evaluation in clinical studies.[34,35] PCC, activated PCC, and recombinant factor VII are associated with an increased risk of thromboembolic events.[36]

As a practical guide, patients with VKA-induced intracerebral hemorrhage should receive PCC or activated PCC in combination with vitamin K. In a retrospective study of 1,547 patients with VKA-induced intracerebral hemorrhage, the combination of PCC and fresh frozen plasma was superior to each treatment alone.[37] Patients treated with anti-factor Xa inhibitors should also be treated with coagulation factors.

Initiation or resumption of anticoagulation with NOACs after ICH

AF patients who are anticoagulated for the prevention of thromboembolic events remain at high risk of a first or recurrent thromboembolic event, regardless of whether or not anticoagulation had to be stopped or interrupted because of an intracerebral bleed. This is particularly so for patients with mechanical heart valves. There is only limited evidence from case series on the safety of starting anticoagulation with VKAs or NOACs after an anticoagulation-related intracerebral bleed, and on the best time to resume anticoagulation. Immobilized patients with AF and intracerebral bleeds are also at risk of deep vein thrombosis, pulmonary embolism,[38] and ischemic stroke.[39] Evidence from case series and stroke registries indicates that administration of low-molecular-weight heparin for prophylaxis of deep vein thrombosis in bedridden patients with intracerebral hemorrhage may not result in hematoma growth.[40,41] Moreover, a small randomized study starting low-dose low-molecular-weight heparin 1 day after intracerebral hemorrhage showed no increased risk of re-bleeding.[42]

Several small observational studies have investigated the effect of resuming OAC after warfarin-related intracerebral hemorrhage. Classen et al.[43] examined the outcome of resuming warfarin therapy following warfarin-related intracerebral hemorrhage. Overall, 52 patients were followed for a mean of 43 months. Of these, 23 resumed warfarin therapy: one patient had a recurrent non-traumatic intracerebral hemorrhage, two had traumatic intracerebral hemorrhages, and two had major extracranial hemorrhages. Of the 25 patients who did not resume warfarin therapy, three had a thromboembolic stroke, one had a pulmonary embolism, and one a distal arterial embolism.

A retrospective study in Germany investigated the long-term effects of resuming OAC in 719 AF patients with intracerebral hemorrhage.[44] OAC was resumed in 172 of 719 survivors (23.9%) and was associated with fewer ischemic complications (5.2% vs. 15.0%) and no significant difference in hemorrhagic complications (8.1% vs. 6.6%) when compared with those patients who did not resume OAC. Long-term mortality was also reduced in patients who resumed OAC compared with those who did not (hazard ratio, 0.258; 95% confidence interval, 0.125–0.534; $P<0.001$).

Different types of intracerebral hemorrhages are associated with different rates of recurrence. For example, the risk of recurrent cerebral hemorrhage is higher in patients with lobar ICH than with deep ICH.[45] Furthermore, patients with AF who have advanced small vessel disease and a large number of microbleeds are also at greater risk of intracerebral bleeding when receiving anticoagulation.[46] However, treatment with NOACs does not appear to increase the incidence of cerebral microbleeds in patients with AF.[47]

To date, no data are available on how many microbleeds constitute an increased risk of a having a second intracerebral bleed when anticoagulation is resumed. Additionally, it is unclear at which time point anticoagulation can safely be resumed after an

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ICH. Expert opinion recommends around 4 weeks in patients with subdural hematoma and around 6-8 weeks in patients with intracerebral bleeds. Additional factors that should be considered when initiating or resuming OAC are advanced age, poorly controlled hypertension, the need for triple therapy after acute coronary syndrome or coronary stenting, and regular alcohol intake. Patients with contraindications for long-term anticoagulation who would be able to tolerate 3-6 months of anticoagulation or dual antiplatelet therapy could be treated with left atrial appendage occlusion.

Patients with renal impairment and on dialysis

Chronic kidney disease is an important risk factor for both stroke and bleeding in anticoagulated patients with AF. All NOACs are eliminated via the kidneys to varying degrees: 80% for dabigatran, 50% for edoxaban, 33% for rivaroxaban, and 27% for apixaban. The relationship between NOAC plasma concentration and kidney function underlies the recommendation to reduce the dose of each NOAC in AF patients with chronic kidney disease.[9]

Dose reductions of NOACs based on creatinine clearance or creatinine plasma levels were important elements of the protocols in three of the four warfarin-comparator trials.[48-50] These studies demonstrated that the benefits of NOACs on stroke and bleeding risks were maintained regardless of renal function.[48-50] Interestingly, in one trial, the effect of NOACs to reduce the risk of major bleeding was greatest in patients with a creatinine clearance of 30-49 mL/min.[48-50] Thus, compared with warfarin, NOACs appear to be a reasonable treatment option for AF patients with moderate renal impairment.

In the AVERROES trial, the benefit of apixaban compared with aspirin was similar in patients with and without stage III chronic kidney disease.[51] In the ARISTOTLE (Apixaban for Reduction In Stroke and Other ThromboembolLic Events in atrial fibrillation) trial, the major bleeding rate in patients with moderate renal impairment was lower with apixaban than with warfarin.[49] Major bleeding was similar with dabigatran (both doses) and warfarin in the RE-LY (Randomized Evaluation of Long-term anticoagulant therapY) trial,[50] and also with rivaroxaban 20 mg daily and warfarin in the ROCKET-AF trial.[52] There was a statistically lower treatment effect for prevention of ischemic stroke in the ENGAGE AF TIMI 48 (Effective aNticoaGulation with factor xA next GEneration in Atrial Fibrillation-Thrombolysis In Myocardial Infarction 48) trial with edoxaban compared with warfarin for patients with a creatinine clearance of >95 mL/min, and a higher stroke rate with edoxaban in this subgroup.[6] Whether this was due to under-dosing of edoxaban, particular effectiveness of warfarin in this subgroup, or a combination of factors is not known.

There are no clinical outcome data regarding the use of NOACs for patients with a creatinine clearance (calculated by the Cockroft–Gault equation) of <30 mL/min. This includes patients on hemodialysis[53] for whom warfarin provides uncertain benefit(s).[54] Compared with dabigatran or rivaroxaban, warfarin can be monitored, and is therefore the preferred anticoagulant for patients with severe chronic kidney disease who are on dialysis.[53]

NOACs and age

The risks of both bleeding and stroke increase with age. Older age is often the reason why anticoagulants are not prescribed for elderly individuals.[55] The BAFTA (Birmingham Atrial Fibrillation Treatment of the Aged Study) trial conclusively showed that individuals aged ≥75 years benefit more from anticoagulation with warfarin than with aspirin.[56] However, the annual risk of extracranial bleeding is not different between these two treatments.

Given the high risk of ischemic stroke, anticoagulant therapy offers net clinical benefit for older adults. Compared with VKAs, all of the NOACs reduce the incidence of ICH.[8] In the RE-LY trial, there was a significant treatment-by-age interaction for major bleeding.[57] Compared with warfarin, the 110 mg twice daily dose of dabigatran was associated with a lower risk of major bleeding among patients aged <75 years, and a similar risk among those aged ≥75 years. The higher dose of dabigatran, 150 mg twice daily, was associated with a lower risk of bleeding in the younger group, but a higher risk in the older group. Therefore, the dose of dabigatran should be reduced to 110 mg twice daily in stroke patients aged >75 years.

In the ARISTOTLE trial, the rate of major bleeding with apixaban 5 mg twice daily compared with warfarin was lower for the older groups of patients (65-74 years, ≥75 years). This dose of apixaban was reduced to 2.5 mg twice daily in patients with two of the following characteristics: age ≥80 years, weight ≤60 kg, and creatinine ≥1.5 mg/dL (133 μmol/L).[58] There was no treatment-by-age interaction for major bleeding among participants enrolled in the ROCKET-AF trial, which found similar rates of bleeding with rivaroxaban and warfarin for each age stratum. However, the dose of rivaroxaban was reduced to 15 mg/day for patients with reduced renal function (creatinine clearance 30-49 mL/min). In the ENGAGE AF TIMI 48 trial, the risk of major bleeding with edoxaban 60 mg daily compared with warfarin was lower among patients aged <75 years and similar among those ≥75 years of age.

As a practical advice, the dose of NOACs should be reduced in patients aged >75 years, particularly those with a body weight of <60 kg.

Patients with cognitive impairment

AF patients with dementia or severe cognitive impairment were excluded from the randomized trials comparing NOACs with warfarin. Ambulatory patients with dementia and AF have a right to be saved from the devastating consequences of a severe cardioembolic stroke. As long as compliance with medication intake is provided by a caregiver, these patients should be anticoagulated. The situation is different for patients with dementia who are bedridden.

Patients at risk of falls

A frequent reason to withhold anticoagulation in elderly patients with AF is the fear of severe or frequent falls.[59] Gage et al.[60] observed a relationship between falls and bleeding risk: the rate of ICH was 2.8 per 100 patient-years in 1,245 anticoagulated patients at high risk of falls, compared with 1.1 per 100 patient-years in >18,261 controls. In patients with a high $CHADS_2$ score, the benefit of anticoagulation in terms of prevention of ischemic stroke was greater than the risk of ICH. Overall, the decision to indicate anticoagulation in the elderly should be assessed on an individual basis.

Anticoagulation is not usually contraindicated for patients with normal pressure hydrocephalus or Parkinson's disease as the risk of serious injury due to a fall is not usually high; however, it is contraindicated for patients with supranuclear palsy or grand mal seizures as these populations are at high risk of serious injury due to a fall.

Conclusions

The development of NOACs has provided a novel alternative therapy to conventional VKAs. In randomized clinical trials, NOACs have demonstrated similar or superior efficacy to VKAs in preventing stroke and systemic embolism in AF, with a lower incidence of major bleeding and mortality. To date, treatment recommendations are based on limited available data from case series or registries, and, in some cases, on expert opinion. Importantly, treatment with NOACs in patients with, or at risk of, AF should be based on the assessment of the risks and benefits, taking patient-related factors, such as renal function, age, cognition, and risk of falls into consideration. Ongoing large prospective registries such as GARFIELD (Global Antico-agulant Registry in the FIELD)[61,62] and GLORIA-AF[63,64] are essential to further define the rational use of these agents in patients who have had a neurological event and in those at increased risk.

Conflicts of Interest

HCD received honoraria for participation in clinical trials, contribution to advisory boards or oral presentations from: Abbott, Allergan, AstraZeneca, Bayer Vital, BMS, Boehringer Ingelheim, CoAxia, Corimmun, Covidien, Daiichi-Sankyo, D-Pharm, Fresenius, GlaxoSmithKline, Janssen-Cilag, Johnson & Johnson, Knoll, Lilly, MSD, Medtronic, MindFrame, Neurobiological Technologies, Novartis, Novo-Nordisk, Paion, Parke-Davis, Pfizer, Sanofi-Aventis, Schering-Plough, Servier, Solvay, St. Jude, Syngis, Talecris, Thrombogenics, WebMD Global, Wyeth and Yamanouchi. Financial support for research projects was provided by AstraZeneca, GSK, Boehringer Ingelheim, Lundbeck, Novartis, Janssen-Cilag, Sanofi-Aventis, Syngis and Talecris. The Department of Neurology at the University Duisburg-Essen received research grants from the German Research Council (DFG), German Ministry of Education and Research (BMBF), European Union, NIH, Bertelsmann Foundation and Heinz-Nixdorf Foundation. HCD has no ownership interest and does not own stocks of any pharmaceutical company.

Within the past year HCD served as editor of Aktuelle Neurologie, Arzneimitteltherapie, Kopfschmerznews, Stroke News and the Treatment Guidelines of the German Neurological Society, as co-editor of Cephalalgia and on the editorial board of Lancet Neurology, Stroke, European Neurology and Cerebrovascular Disorders.

CK received honoraria for participation in clinical trials, contribution to advisory boards or oral presentations from: Bayer Vital, BMS, Biotronik, Boehringer Ingelheim, Biogen, Daiichi-Sankyo, Eisai, Ever Pharma, Genzyme, Merck Serono, Novartis, Pfizer, Sanofi-Aventis, Roche, Siemens, Stago, Teva. Financial support for research projects was provided by Bayer Vital, Biogen, Ever Pharma, Genzyme, Merck Serono, Teva, the German Research Council (DFG), the German Ministry of Education and Research (BMBF), the Else-Kröner Fresenius Foundation, the Schilling Foundation, the German Neurology Foundation (DSN) and the European Union. CK does not own stocks of any pharmaceutical company.

Within the past year CK served as editor of Experimental and Translational Stroke Medicine, Frontiers in Cellular Neuroscience, Journal of Cerebral Blood Flow & Metabolism, PLoS One and Stroke.

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