Advances in Atrial Fibrillation-related Stroke Prevention

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Abstract

In patients with atrial fibrillation (AF) the risk of stroke is substantially increased, especially in those who are elderly (over 75 years) or have risk factors such as previous stroke, heart failure or hypertension. Stroke outcomes are also generally much worse in those with AF. Current guidelines indicate that any patient with AF and risk factors for stroke should receive anticoagulant therapy to limit their stroke risk. Despite these established recommendations, only 50 % of patients at risk receive anticoagulation with a vitamin K antagonist (VKA) and only 50 % of those are within the therapeutic range, indicating lack of adherence to the guidelines. Withholding anticoagulant therapy is mainly left to an individual physician's choice, as shown in the ongoing GARFIELD registry of AF stroke prevention practice. Many physicians fear the risk of intracranial haemorrhage (ICH) for which outcomes remain poor. Recent clinical studies have shown that the non-VKA oral anticoagulants (NOACs) (apixaban, rivaroxaban, dabigatran and edoxaban) significantly reduce the risk of ICH and other bleeding events, while having non-inferior stroke prevention to warfarin. Use of these drugs, limiting exposure to aspirin and alcohol and controlling blood pressure have been shown to minimise ICH risk in large clinical trials and meta-analyses. Recent data from the Effective aNticoaGulation with factor xA next GEneration in Atrial Fibrillation (ENGAGE AF)-TIMI 48 study showed that the factor Xa inhibitor edoxaban was non-inferior to well-managed warfarin for reducing all stroke risk, and significantly reduced haemorrhagic stroke, major bleeding, ICH and death. These findings further support the case for using NOAC therapy for stroke prevention in patients with AF and risk factors for stroke.

Keywords

Atrial fibrillation-related stroke, NOACs, prevention, atrial fibrillation treatment guidelines, haemorrhagic stroke, anticoagulant therapy, non-VKA oral anticoagulants

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Atrial fibrillation (AF), the most common type of cardiac arrhythmia, substantially increases the risk and severity of stroke and has a highly negative effect on patient outcomes. AF is associated with a pro-thrombotic state and studies have shown it increases the risk of stroke fivefold.[1,2] This increased risk is particularly great in the elderly aged ≥80 years in whom stroke occurrence is up to 45.8 %.[3] AF is also associated with an increased severity of stroke and the proportion of patients with cardio-embolic stroke is markedly increased with a 30-day mortality of 25 %.[4] Furthermore, the presence of AF with stroke almost doubles the death rate with a 1-year mortality of 50 %. Although these risks are well recognised, too few patients with AF receive preventative and adequate therapy to minimise their stroke risk. As a consequence, there is unnecessary morbidity and mortality. This article reports presentations and discussions from a satellite symposium to discuss the important and timely matter of stroke prevention in AF, which was convened at the 23rd European Stroke Conference held in Nice in May 2014.

Prevention of Atrial Fibrillation-related Stroke – Guidelines and Clinical Reality

Professor Werner Hacke (University of Heidelberg, Germany) considered the current recommendations for treating AF and how well these are being adhered to in Europe and elsewhere.

The Current Recommendations and Stroke Risk Classification

The European guidelines, established for over a decade, have identified the increased stroke risk in AF and set out strategies to minimise it. In the clinical classification scheme for predicting stroke ($CHADS_2$) factors such as congestive heart failure, hypertension, age ≥75 years

and diabetes each score 1 point and a previous stroke or transient ischaemic attack (TIA) scores 2 points.[5] The sum of these points increases with stroke risk: total scores in the range 0 to 6 represent 1.9 to 18.2 strokes/100 patient years (without anticoagulant therapy). The guidelines recommend that any patient with a score ≥2 must be treated with oral anticoagulants (OACs).[6,7] The subsequent revisions to the guidelines in 2011 (CHA_2DS_2-VASc scores) went further and specified that age ≥75 years scored two points, age 64–75 years scored 1 point and that female gender and vascular disease each scored 1 point.[8,9]

Studies have shown that increasing CHA_2DS_2-VASc summed scores are also associated with increasing stroke rates. Summed scores in the range 0 to 9 represent a 0.78 % to a 23.64 % 1-year stroke rate.[9] On this scale, a patient with a score of 1 should be considered for adjusted-dose vitamin K antagonists (VKAs), a direct thrombin inhibitor (DTI) (dabigatran) or an oral factor Xa inhibitor (e.g. rivaroxaban or apixaban), based upon an assessment of the risk of bleeding complications and patient preferences (class IIa, level A evidence). It was recommended that patients with scores ≥2 must receive treatment with one of the recommended options above unless it is contraindicated (class I, level A evidence). However, patients with a score of 0 should not receive an OAC to avoid unnecessary treatment (class I level B evidence).[8]

Some commonly used medications are highly effective for stroke prevention in AF. This was emphasised in a pooled analysis of patient data from five prevention trials conducted during the 1980s and 1990s with a total population of 3,691 patients. These studies collectively showed the annual rate of stroke was 4.3 % in patients receiving placebo and 1.4 % for VKAs (e.g. warfarin).[10–12] This relative stroke risk reduction was 68 % for warfarin and 36% for aspirin.[13] The annual rate of major haemorrhage was 1.0% for placebo, 1.0 % for aspirin and 1.3 % for warfarin.[13]

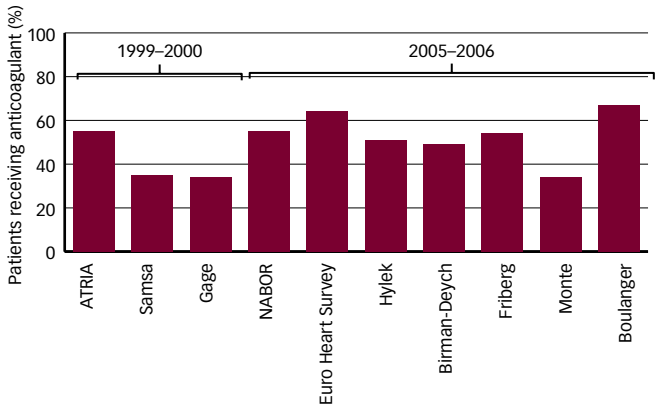
The Guidelines are not Well Adhered to in the Clinic

Despite the development of simple guidelines and the availability of effective treatments, many patients with AF and specified risk factors do not receive appropriate preventative therapy. A series of 10 studies conducted in Europe and the US during the period 1999–2006, involving over 38,000 patients, studied the proportions of patients who were eligible for preventative OAC therapy who were actually receiving it (see *Figure 1*).[14–23] These studies showed that only 34–67 % of patients were receiving OACs with a mean value of 50 %. This situation appears worse when the patient's time in therapeutic range (TTR) is considered. A series of nine retrospective, cohort, observational and population studies conducted at various medical centres in the US on a total population of over 20,000 patients showed TTRs in the range 36–63 % with an average 50 %.[22,24–28] This also indicates that of patients, 50 % are outside the therapeutic range. Taken with the proportion of patients with AF not receiving any preventative medication, this indicates that 75 % are not receiving the adequate measures to reduce their stroke risk.

Reasons for Poor Adherence to Stroke Prevention Guidelines in Atrial Fibrillation

There are a variety of reasons why preventative treatments are not given and include the patient's age especially at or above 80 years, the (by the physician) perceived bleeding risk, the lack of a local monitoring site to maintain target international normalised ratio (INR), the availability of care-givers, cost, patient preference and lifestyle-considerations. In addition, some clinicians are also unwilling to use VKAs due to their narrow therapeutic window, variable dose response, the need for frequent monitoring and long half-life.[29,30]

Figure 1: Underutilisation of Oral Anticoagulation in 10 Studies on Patient Populations with Atrial Fibrillation in Europe and the US



Sources: (ATRIA), Go et al., 1999;[18] Samsa et al., 2000;[22] Gage et al., 2000;[17] (NABOR) Waldo et al., 2005;[23] (Euro Heart Survey) Nieuwlaat et al., 2006;[21] Hylek et al. 2006;[19] Birman-Deych et al. 2006;[14] Friberg et al. 2006;[16] Monte et al., 2006;[20] Boulanger et al., 2006.[15]

Recommended Therapies for Elevated Stroke Risk

The range of drugs available for stroke prevention in AF has expanded in recent years with the approval of factor Xa inhibitors apixaban and rivaroxaban, with edoxaban currently under review for market authorisation, and the DTI dabigatran. These drugs have all shown non-inferiority to warfarin in terms of stroke reduction in large-scale phase III clinical trials versus VKA, and apixaban showed superiority to aspirin.[1,31–33] In addition, the 150 mg dose of dabigatran was superior to warfarin in stroke reduction.[34] With all of these treatments, major bleeding events occurred at a similar or less frequent rate compared with warfarin and there were fewer intracranial bleeds. These drugs are simpler to use than warfarin, require no monitoring and are useful in patients for whom VKA therapy is unsuitable. The availability of such drugs should therefore increase the proportion of patients with AF who receive stroke prevention therapy.

Registries Investigating Real-life Treatment Patterns for Stroke Prevention in Atrial Fibrillation

In order to better understand treatment practice in patients with AF at risk of stroke, the Global Anticoagulant Registry in the FIELD (GARFIELD) registry has been established.[35] This initiative is an example of a non-interventional, international registry that aims to describe real-life treatment patterns in newly diagnosed patients with AF and at least one additional risk factor for stroke. Other similar registries include the EURObservational Research Programme (EORP),[36] the Global Registry on Long-Term Oral Anti-thrombotic Treatment In Patients With Atrial Fibrillation (GLORIA – AF)[37] and PREvention oF thromboembolic events – European Registry in Atrial Fibrillation (PREFER in AF) registry.[6] The GARFIELD registry is an ongoing independent academic research initiative that will include 55,000 consecutive patients with non-valvular AF at multiple treatment centres in 34 countries. Recruitment is planned in five sequential cohorts occurring during the period 2009–2015, each with a 24-month follow-up duration. Parameters monitored include the rate of stroke and systemic embolisation, patient outcomes, the incidence of bleeding complications, therapy persistence and fluctuations of INR over time for patients receiving VKA.

Table 1: Why Physicians Withhold Vitamin K Antagonists in Patients with Atrial Fibrillation – Results from the GARFIELD Registry

Reason for Withholding Vitamin K Antagonists	Patients with $CHADS_2$ ≥2 n (%) (n=2,302)
Alcohol misuse	11 (0.5)
Already taking antiplatelet drug for another condition	117 (5.1)
Patient refusal	165 (7.2)
Previous bleeding event	55 (2.4)
Taking medication contraindicated/cautioned for use with vitamin K antagonists	16 (0.7)
Other	239 (10.4)
Unknown	587 (25.5)
Physician choice	1,112 (48.3)
Bleeding risk	170 (7.4)
Concern over patient compliance	121 (5.3)
Guideline recommendation	32 (1.4)
Fall risk	150 (6.5)
Low risk of stroke	95 (4.1)
Other	544 (23.6)

Source: Kakkar et al. 2013.[35]

The GARFIELD Registry – Results from Cohorts 1 and 2

Results from Cohort 1 (n=10,614 in 19 countries) showed that 48 % of occurrences of withholding VKA therapy were down to physician choice resulting from influences such as bleeding risk, concern over compliance and fall risk (see *Table 1*).[35] In patients with a CHA_2DS_2-VASc score of 0, 33 % were found to be receiving OACs, which represented overexposure. Patients with a CHA_2DS_2-VASc score >1 showed no increase in OAC use with increasing risk level, which represented underexposure. The uptake of new OACs (NOACS) does not appear to increase overall OAC use, which demonstrates poor risk stratification. Across the 19 participating countries, there was a wide variation in the proportion of patients receiving anticoagulants (approximately 28–89 %, mainly VKAs) with a global average of 60 %. Cohort 2 (n=10,544 in 30 countries) is currently in progress and the results will be published soon.

Overall, the quality of preventive stroke care in AF remains poor and the situation has not improved over the last 2 decades. Many patients who need anticoagulants do not receive them and some receive them unnecessarily. As the GARFIELD registry progresses it is likely to provide further valuable insights into stroke prevention practice in AF and may provide greater awareness and better targeting of patients at risk.

Minimising the Risk of Haemorrhagic Stroke During Anticoagulant Therapy for Atrial Fibrillation

The Fear of Intracranial Haemorrhage and Worsening Outcomes

Professor Bo Norrving (Lund University, Sweden) asserted that a major reason for clinicians withholding anticoagulant medication in AF patients at risk of stroke is fear of bleeding events, particularly intracranial haemorrhage (ICH). ICH accounts for half the global burden of stroke and despite progress in other aspects of patient care, prognosis remains extremely poor.[38,39] The high proportion of untreated cases due to physician choice as found in the GARFIELD registry can to some extent be explained by the increasing numbers of anticoagulant-related ICH. This trend was demonstrated in a retrospective study of all patients who were hospitalised with first-ever ICH in greater Cincinnati, US, during 1988, 1993/1994 and 1999.[40] Anticoagulant-associated ICH (AAICH) was defined as ICH in patients receiving warfarin or heparin. The annual incidence of AAICH/100,000 individuals increased significantly (0.8 in 1988, 1.9 in 1993/1994 and 4.4 in 1999 [p<0.001 for trend]). This fivefold increase during the 1990s in the US was mostly explained by increasing warfarin use. A further factor discouraging stroke preventative treatment is that AAICH is associated with larger haematoma volumes, higher rates of haematoma expansion and worse clinical outcomes.[41,42] This poor prognosis remains even after anticoagulation has been reversed. A series of 141 patients given prothrombin complex concentrates for urgent reversal of anticoagulation after ICH showed rapid correction of INR, but despite this their mortality and morbidity rates remained high.[43]

Reducing the Risk of Intracranial Haemorrhage

To reduce the possibility of ICH, associated risk factors should be addressed. Established ICH risk factors include age ≥75 years, hypertension (particularly systolic blood pressure [SBP] ≥160 mmHg), previous cerebrovascular disease and intensity of anticoagulation and concomitant use of aspirin. Possible ICH risk factors include cerebral amyloid angiopathy, Asian or Mexican-American race, tobacco smoking and heavy alcohol consumption. In addition, there are some imaging and genetic markers associated with higher ICH risk including: leucoaraiosis detected by brain computed tomography/magnetic imaging, microbleeds and apolipoprotein E (ApoE) e II or IV genotype.[44] Careful control of warfarin intensity to maintain an INR value ≤3, control of hypertension therapy and avoiding the combination of aspirin and warfarin can substantially reduce the risk of ICH.[44]

The importance of hypertension in ICH risk was demonstrated in a large international multicentre study (PROGRESS) in 6,105 people with a prior history of cerebrovascular events.[45–47] Patients were assigned to perindopril or placebo and followed-up for 3.9 years. In patients treated with perindopril, a mean 9 mmHg reduction in SBP decreased the risk of cerebral haemorrhage by 50 % (95 % confidence interval [CI] 26–67) and a 12 mmHg reduction reduced the risk of cerebral haemorrhage by 76 % (95 % CI 55–87). Furthermore, in patients with AF and ischaemic stroke, adequate control of BP was associated with a 38 % decrease in major vascular events and 34 % decrease in haemorrhagic stroke. Based on these findings, it was suggested that effective BP-lowering therapy should be routinely considered for all patients with a history of cerebrovascular events. The risk of ICH can also be decreased by limiting multiple anticoagulant and antiplatelet therapies. In a trial of patients undergoing percutaneous coronary intervention, the incidence of bleeding episodes was substantially greater in patients receiving clopidogrel and aspirin (44.9 %) compared with clopidogrel alone (19.5%).[48] ICH risk is also greater in individuals whose alcohol intake is high. An analysis of 35 observational studies showed that heavy alcohol consumption (>60 g/day) was associated with a markedly increased risk of both haemorrhagic (relative risk [RR] 2.18 [95 % CI 1.48–3.20]) and ischaemic strokes (RR 1.69 [95 % CI 1.34–2.15]) compared with those who consumed no alcohol.[49] Lower alcohol consumption (12–24 g/day) was associated with a lower risk of ischaemic stroke (RR 0.72 [95 % CI 0.57–0.91]).

Table 2: Major Safety Results from Pivotal Phase III Trials of Non-vitamin K Oral Anticoagulants Dabigatran, Rivaroxaban, Apixaban and Edoxaban

Outcomes versus Warfarin	Dabigatran 110 mg BID	Dabigatran 150 mg BID	Rivaroxaban 20 mg QD	Apixaban 5 mg BID	Edoxaban 30 mg QD	Edoxaban 60 mg QD
▼in stroke/systemic embolism	Non-inferiority	Superiority	Non-inferiority	Superiority	Non-inferiority	Non-inferiority
▼in stroke	No	Yes	No	Yes	No	No
▼in ischaemic/unspecified stroke	No	Yes	No	No	No	No
▼in haemorrhagic stroke	Yes	Yes	Yes	Yes	Yes	Yes
▼in disabling/fatal stroke	No	Yes	No	Yes	No	No
▼in vascular death	No	Yes	No	No	Yes	Yes
▼in all-cause death	No	No	No	Yes	Yes	No
▼in major bleeding	Yes	No	No	Yes	Yes	Yes
▼in intracranial haemorrhage	Yes	Yes	Yes	Yes	Yes	Yes
▲in gastrointestinal bleeding	No	Yes	Yes	No	No	Yes
▼in treatment discontinuation	No	No	No	Yes	No	No

▲: increase ▼: decrease. Source: Connolly et al., 2011,[1] Patel et al., 2011,[33] Granger et al., 2011,[32] Giugliano et al., 2013.[31]

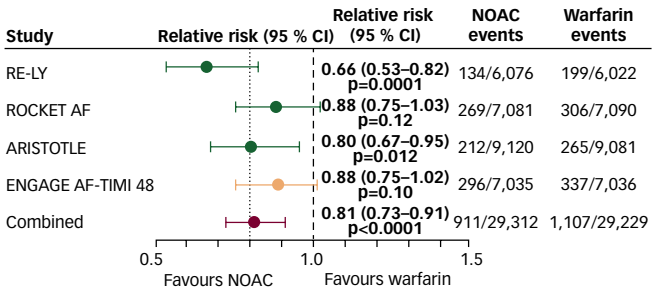
Evidence of Reduced Intracranial Haemorrhage Risk with New Oral Anticoagulants – A Meta-Analysis of Four Large Clinical Trials

The clinical trials RE-LY (dabigatran, n=18,113), ROCKET AF (rivaroxaban, n=14,264), ARISTOTLE (apixaban, n=18,201), ENGAGE AF-TIMI 48 (edoxaban, n=21,105) each compared individual NOAC treatments with warfarin in terms of the effect on stroke and systemic embolism risk in patients with AF.[31–34] A recent meta-analysis of these four trials showed that the NOACs all compared favourably with warfarin and the combined analysis showed a significant reduction in RR of stroke or systemic embolic events (SEEs) (RR 0.81; p<0.0001) (see *Figure 2*).[50] Analysis of safety endpoints showed that the NOACs provided significant reductions in ICH (RR 0.48; p<0.0001), haemorrhagic stroke (RR 0.49; p<0.0001) and all-cause mortality (RR 0.90; p=0.0003) in a wide range of patients (see *Figure 3*). Reductions in ischaemic stroke and myocardial infarction (MI) were non-significant. With the NOACs, there was a general reduction in major bleeds although the pattern was different for each of them. Other bleeds occurred at similar rates to warfarin but there was a general increase in gastrointestinal (GI) bleeding. The overall results of the NOACs compared with warfarin are summarised in *Table 2*.

Further Experience of Bleeding with Anticoagulants and Associated Risk Factors

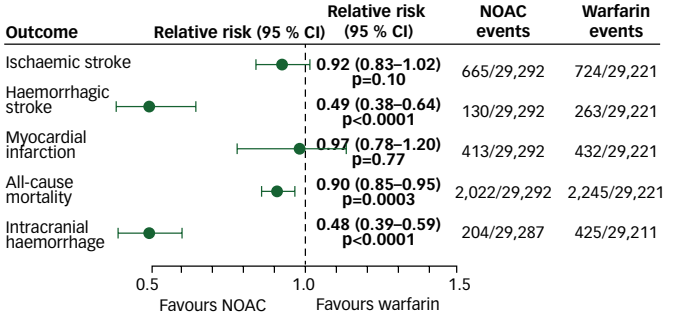
'Real world' experience in Denmark in 4,978 patients with AF treated with dabigatran (150 mg or 110 mg) and 8,936 matched patients treated with warfarin showed that mortality, intracranial bleeding, pulmonary embolism and MI were lower with dabigatran compared with warfarin.[51] GI bleeding, however, was lower for 110 mg dabigatran than warfarin but not for 150 mg. These findings were in line with data from the RE-LY trial that showed significantly lower rates of traumatic (p<0.05) and fatal (p<0.01) ICH than warfarin and that times to spontaneous ICH were greater with dabigatran.[52] The clinical spectrum of haemorrhages in this trial, however, was similar for both dabigatran and warfarin and the most important modifiable independent risk factor for ICH was the concomitant use of aspirin. Further evidence of NOAC benefits in reducing ICH risk was shown in the ROCKET AF study in which patients with AF were treated with either rivaroxaban or warfarin and followed up for 2.5 years.[53] The results showed a greater risk of ICH in Asians, Black Africans, elderly individuals, reduced serum albumin, reduced platelet count and in patients with a previous history of stroke, TIA or increased diastolic BP. There was a reduced risk of ICH in patients receiving rivaroxaban (RR 0.60, 0.44–0.82) compared with warfarin and in those with a history of congestive heart failure (RR 0.65, 0.47–0.89).

Figure 2: Relative Risk of Stroke or Systemic Embolic Events in Patients with Atrial Fibrillation Treated with Non-vitamin K Oral Anticoagulants for Stroke Prevention Compared with Warfarin in an Analysis of Four Large Clinical Trials



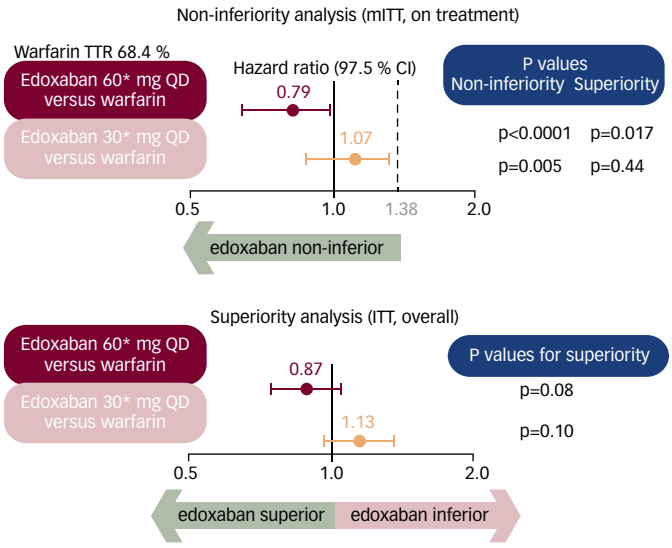
CI = confidence interval; NOAC = non-oral anticoagulants. Source: Ruff et al., 2014.[50]

Figure 3: Main Safety Advantages of Non-Vitamin K Oral Anticoagulants versus Warfarin in Patients with Atrial Fibrillation Treated with Non-vitamin K Oral Anticoagulants for Stroke Prevention in an Analysis of Four Large Clinical Trials – Lower Risk of ICH



Data are n/N, unless otherwise indicated. Heterogeneity: ischaemic stroke I^2 = 32 %; p=0.22; haemorrhagic stroke I^2 = 34 %; p=0.21; myocardial infarction I^2 = 48 %; p=0.13; all-cause mortality I^2 = 0 %; p=0.81; intracranial haemorrhage I^2 = 32 %; p=0.22. Dabigatran 150 mg BID; rivaroxaban 20 mg QD; apixaban 5 mg BID; edoxaban 60 mg QD. Source: Ruff et al., 2014.[50] CI = confidence interval; NOAC = non-oral anticoagulants.

Figure 4: Comparison of Stroke and Systemic Embolic Events in Patients with Atrial Fibrillation Treated with Edoxaban or Warfarin Over a Median 2.8 Years Follow-up Period in the ENGAGE AF-TIMI 48 Trial



**Dose reduced by 50 % in selected patients. ENGAGE AF-TIMI 48: Effective aNticoaGulation with factor xA next GEneration in Atrial Fibrillation study. Source: Giugliano et al. 2013.[31] CI = confidence interval; mITT = modified intention to treat; TTR = time in therapeutic range.*

Fear of Intracranial Haemorrhage is a Deterrent to Anticoagulant Use but the Risk can be Minimised

ICH is the most serious and most feared complication of anticoagulant therapy. This and the possibility of other bleeds therefore can deter many clinicians from prescribing anticoagulant therapy in patients with AF and risk factors for stroke. This is an understandable response that requires the benefits of such treatment to be carefully considered against possible complications. The risk of ICH during anticoagulant therapy, however, may be reduced by BP lowering/BP control, the cautious use of combinations with antiplatelet therapy and a limited consumption of alcohol. Clinical trial and 'real world' data show that the NOACs reduce the risk of ICH by about half, which is a major benefit.

The ENGAGE AF-TIMI 48 Trial – What Does it Add to our Knowledge of the New Oral Anticoagulants?

Evidence continues to emerge indicating that the NOAC therapies are valuable alternatives to warfarin for stroke prevention in patients with AF. The latest NOAC being investigated in a large phase III trial is the factor Xa inhibitor edoxaban. The recent evidence supporting the use of this drug in AF was discussed by Dr Natalia Rost (Harvard Medical School, Boston, MA, USA)

Edoxaban has been submitted for approval in the US and Europe for prevention of stroke in patients with AF and treatment and secondary prevention of venous thromboembolism. Edoxaban is an effective anticoagulant that is metabolised by cytochromes proteins but is a substrate of the P-glycoprotein drug transporter and a substantial proportion is excreted unchanged into the urine and faeces.[54] Edoxaban reaches peak plasma concentrations in 1.5 hours, has a half-life of 10–14 hours, a relatively high bioavailability of 62 % and exhibits highly selective, competitive, concentration-dependent inhibition of human factor Xa.[4,55]

The ENGAGE AF-TIMI 48 Trial – Evidence for Edoxaban in Stroke Prevention in a Large Population with Atrial Fibrillation

The benefits of edoxaban in the prevention of stroke were recently demonstrated in the Effective aNticoaGulation with factor xA next GEneration in Atrial Fibrillation (ENGAGE AF)-TIMI 48 study, which evaluated two doses of the drug compared with warfarin (INR 2.0–3.0) in a large population of patients with AF ($CHADS_2$ ≥2, n=21,105 at 1,393 sites in 46 countries), who were followed-up for a median period of 2.8 years.[31] The population in the study were 38 % female, the median age was 72 years (inter-quartile range: 64–78 years), the mean $CHADS_2$ score at baseline was 2.8 (standard deviation: ±1), 53 % were $CHADS_2$ ≥3 and 23 % were $CHADS_2$ ≥4. Among the patients, 94 % had hypertension 36 % had diabetes and 28 % had a prior stroke or TIA.

Edoxaban and Stroke Prevention

The study design was double-blind, double-dummy and patients were randomised 1:1:1 to edoxaban 30 mg QD, edoxaban 60 mg QD or warfarin. At the end of the trial, after 2.8 years of follow-up, patients were transitioned to another OAC or VKA treatment. Of the recruited patients, 99.6 % received treatment and 99.5 % had complete follow-up. The median time in therapeutic range was 68.4 %. For the primary endpoint, in the modified intention to treat (mITT) analysis set, over 2.8 years, edoxaban 30 mg and 60 mg showed non-inferiority to warfarin in terms of stroke and SEE risk (HR 1.07; p=0.005 and HR 0.79; p<0.0001, respectively). In the ITT analysis there was a trend for edoxaban 60 mg towards superiority over warfarin in reducing stroke and SEE risk (p=0.08). In the on-treatment mITT analysis, the edoxaban 30 mg dose did not show superiority, but the 60 mg dose did show superiority for stroke and SEE risk over warfarin (p= 0.44 and 0.017, respectively) (see *Figure 4*).

Edoxaban, Bleeding Events and Other Outcomes

Edoxaban produced a significant reduction in bleeding events. Among secondary endpoints, the 30 mg and 60 mg edoxaban doses significantly reduced the rate of haemorrhagic stroke (HR 0.33; p<0.001 and HR 0.54; p<0.001, respectively) and cardiovascular death (HR 0.85; p=0.013 and HR 0.86; p=0.008). Ischaemic stroke was increased with edoxaban 30 mg versus warfarin (HR 1.41; p<0.001) but unchanged for the 60 mg dose (HR 1.00; p=0.97). Analysis of the Safety Cohort showed that in patients treated with 30 mg and 60 mg edoxaban, respectively, the following events were reduced compared with warfarin: major bleeding (HR 0.47; p<0.001 and HR 0.80; p<0.001), ICH (HR 0.30; p<0.001 and HR 0.47; p<0.001), fatal bleed (HR 0.35; p=0.001 and HR 0.55; p=0.006). All-cause mortality was significantly lowered by edoxaban 30 mg (HR 0.87; p=0.006), but not significantly by edoxaban 60 mg (HR 0.92, p=0.08). GI bleeds were reduced with 30 mg edoxaban (HR 0.67, p<0.001) but were significantly increased edoxaban 60 mg (HR 1.23, p=0.03) compared with warfarin. For net clinical outcomes both edoxaban doses provided significant reductions in risk of stroke, SEE, death, major bleeding and in disabling stroke and life-threatening bleeding (HR 0.83–0.89; p<0.001–0.008).

During transition to another NOAC or VKA, INR was frequently monitored but there was no difference between edoxaban doses and warfarin in terms of stroke/SEE incidence over 30 days and major bleeds over 14 days. Tolerability and adverse event findings showed little difference between the edoxaban doses and warfarin in terms of

severe adverse events (18.4 %, 18.3 % and 17.3 % for warfarin, 30 mg and 60 mg edoxaban, respectively) and elevations in liver enzymes (alanine aminotransferase and aspartate aminotransferase, 2.1 %, 2.1 % and 2.2 %, respectively) (differences were non-significant). There was, however, a significantly greater proportion of patients who had never had treatment interruptions during edoxaban treatment than warfarin (p<0.001 for both comparisons).

Long-term Reduction in Haemorrhagic Stroke Risk

A more recent secondary analysis of stroke and ICH events in the ENGAGE-AF TIMI 48 study showed that over 3.5 years, the annualised risk of haemorrhagic stroke was significantly reduced by both edoxaban 30 mg and 60 mg doses (HR 0.33; p<0.001 and HR 0.54; p<0.001, respectively).[7] In addition, the risk of TIA was significantly reduced for the 30 mg edoxaban dose (HR 1.56; p<0.001) over this time period. There were no significant differences in rates of fatal, disabling or non-disabling stroke types between edoxaban and warfarin. Cumulative results showed there was a significantly higher incidence of ischaemic stroke with edoxaban 30 mg (p<0.001) than with edoxaban 60 mg or warfarin. Importantly, over 3.5 years, both the 30 mg and 60 mg doses of edoxaban were shown to reduce the incidence of haemorrhagic stroke to a greater extent than warfarin (p<0.001 for both comparisons).

The ENGAGE AF-TIMI 48 Trial – Edoxaban is Non-inferior to Warfarin in Reduction of Stroke Risk and Significantly Reduced Intracranial Haemorrhage

In the ENGAGE AF trial, therefore, edoxaban QD was non-inferior to well-managed warfarin in the prevention of all types of strokes in patients with AF. Both dose levels of edoxaban (30 mg and 60 mg) reduced the incidence of ICH subtypes to a similar extent and were associated with lower rates of cardiovascular death, non-fatal stroke and non-fatal ICH than warfarin. The higher dose of edoxaban (60 mg) and warfarin produced similar rates of ischaemic stroke and TIA, but the lower dose of edoxaban (30 mg) was less effective in preventing ischaemic cerebrovascular events. Although the 30 mg dose may appear less effective, the choice of edoxaban dose is dependent on individual patient criteria, in particular, renal function as determined by creatinine clearance. Edoxaban has a short half-life but the QD dosing schedule has proved to be an appropriate and convenient therapy in edoxaban's extensive phase II programme. Overall, the ENGAGE AF results indicate that edoxaban shows marked net benefits over warfarin in stroke prevention in a very large and varied population with AF.

Summary and Concluding Remarks

The risk of stroke in patients with AF and risk factors is significantly higher than the rest of the population and strokes that occur in this group are likely to be more serious or fatal. Preventative therapy is therefore a critical need in patients with AF but the risk of major bleeds, particularly ICH, still deters clinicians from treating many patients, especially those they consider vulnerable to haemorrhage, such as patients with hypertension or who are over 75 years or have a history of ICH. The NOACs are easier to administer than warfarin and bring several benefits. Careful selection of patients, avoidance of concomitant aspirin, lowering BP and monitoring INR will enable these drugs to be used safely in a wider population with AF without increasing the risk of ICH and other major bleeds. The large-scale clinical trials evaluating the use of NOACs in AF have provided convincing evidence of benefits in reducing stroke, but also significantly limit the incidence of ICH and haemorrhagic stroke compared with the previous standard of care, i.e. warfarin. With such a substantial body of evidence supporting their use, the administration of NOACs in patients with AF is likely to increase in the future to ensure that many more patients are protected from strokes without compromising their safety. ■

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