Improving Patient Outcomes in Preventing Atrial Fibrillation-related Stroke with Non-Vitamin K Antagonist Oral Anticoagulants

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Abstract

The rising incidence of atrial fibrillation (AF) is increasingly resulting in a substantial worldwide increase in AF-related stroke, particularly in elderly patients and this is creating an increasingly serious healthcare burden. Guidelines recommend the use of AF-related stroke prophylaxis but adherence to these remains poor. Studies conducted in the 1990s showed that warfarin reduced the risk of AF-related stroke by an overall 64% compared with placebo. Subsequently, prophylactic treatment was further improved with the development of non-vitamin K antagonist oral anticoagulants (NOACs). More recently, a meta-analysis of four large clinical trials on NOACs (dabigatran, rivaroxaban, apixaban, and edoxaban) showed there was a relative risk reduction of 0.81 ($p<0.0001$) favouring NOAC treatment over warfarin for stroke or systemic embolic events in patients with AF. The largest trial of NOACs in AF-related stroke, to date, was the ENGAGE AF-TIMI 48 study (n=21,105) which showed that edoxaban was non-inferior to warfarin for ischaemic stroke reduction but significantly reduced bleeding and cardiovascular mortality. A recent subgroup analysis of this study showed that with edoxaban the incidences of intracranial haemorrhage (ICH) subtypes (all ICH, fatal ICH, fatal, subdural and epidural bleed) were significantly lower with 60 mg of edoxaban (p=0.013–<0.001). Edoxaban was also shown to be an effective option in patients with prior stroke. In addition, edoxaban was shown to reduce deaths due to fatal bleeds compared with warfarin. The results of current studies, especially the ENGAGE AF-TIMI 48 subgroup analysis therefore, show that the benefits of anticoagulation therapy in patients with AF substantially outweigh the risks.

Keywords

Atrial fibrillation-related stroke, outcomes, non-vitamin K oral anticoagulants (NOACs)

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In atrial fibrillation (AF), considerable harm can result from the lack of appropriate preventive therapy, and optimal prevention is critical, especially in vulnerable elderly or frail patients. AF markedly increases the risk of stroke and this condition must be monitored and potentially treated wherever it is detected.[1–4] AF is an increasing concern for physicians worldwide as populations age and more people are at risk.[5–7] Although guidelines for stroke prevention in AF that recommend anticoagulation have been established for many years, many at-risk patients receive inadequate anticoagulation or none at all.[8–11] This 'reluctance to treat' stems largely from a fear of inducing intracranial haemorrhage (ICH) and other serious bleeding types that are associated with warfarin and the non–vitamin K antagonist oral anticoagulants (NOACs). This risk, however, is often over-stated and substantially less than the risks that are associated with the lack of stroke prevention treatment in AF. This review discusses the burden of AF-related stroke and evidence that supports current treatments, and considers novel insights on the use of edoxaban as provided by recent subgroup analyses of the ENGAGE AF-TIMI 48 trial results (see end of article for trial name definitions). These topics were presented at a satellite symposium convened at the European Stroke Organisation Annual Meeting in Glasgow, UK, in April 2015. ■

Preventing the Rise of AF-related Stroke– A Call to Action

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Large-scale population-based observational studies have shown AF to be a serious factor increasing the likelihood of strokes and substantially worsening mortality and morbidity after a stroke.[12] Various studies have predicted increasing incidence and prevalence of AF-related stroke and the associated heavy burden this will place on healthcare authorities worldwide. Professor Peter Kelly assessed the history and rising incidence of AF-related stroke. His message constitutes a call to action, encouraging physicians to treat all patients with AF to help stem the burgeoning number of ischaemic strokes and reduce the burden strokes impose on healthcare services.

The incidence and prevalence of atrial fibrillation is increasing worldwide

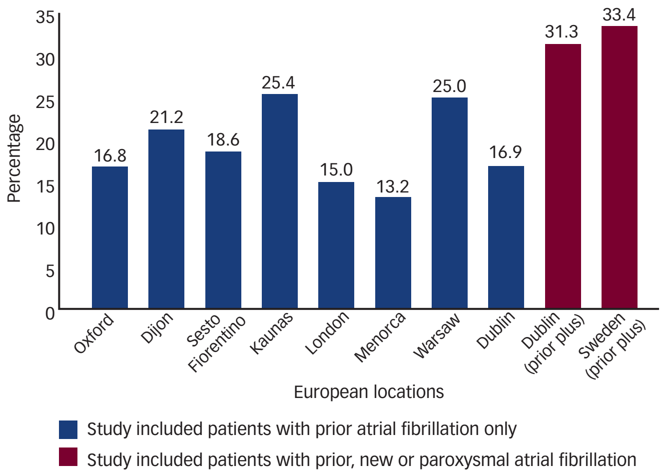
Prior to the 1970s nonrheumatic AF (NRAF) was considered a benign result of ageing.[13,14] In 1972, however, Fisher et al. reported an increased incidence of severe stroke in patients with prior AF and stressed the importance of reducing the risk of embolism by treating these patients with anticoagulants.[15] This observation was later supported by the findings of the extensive, long-term Framingham study showing an approximate five-fold independent increase in risk of stroke associated with NRAF.[16,17] The Global Burden of Disease Investigators carried out a systematic review of population-based studies (n=184) in AF conducted between 1990 and 2010 (71.5% of studies were conducted in Europe or US), defining AF as either chronic or paroxysmal types.[18] The current worldwide prevalence of AF was shown to be 33.5 million in 2010 with nearly five million new cases each year. Over 20 years there was a 3.7% increase in AF prevalence in women and a 4.7% increase in men. In terms of incidence of AF, there was a 36% increase for women and a 28% increase for men. The study also detected large regional variations in prevalence with the highest in North America (700–775 per 100,000) and the lowest in China and Japan (250–400 per 100,000).[18] AF therefore is a very common condition with prevalence up to 8% among Caucasian, 5% among Black and 4% among Hispanic populations.[19]

Further evidence of increasing AF prevalence was provided by an analysis of 17,947 adult records in the Kaiser Permanente (KP) database in Northern California. This analysis identified individuals with symptomatic episodes of AF and extrapolated these data to determine a prevalence of 2.1 million cases in the entire US in 1995.[5] Based on projected population expansion, this study estimated a 2.5-fold increase in prevalence to more than 5.6 million cases by 2050. This, however, may be an underestimate since not all AF cases may have been symptomatic and may not have been captured in the KP database.[5] A smaller study in Olmsted County, MN among 4,168 adults, estimated a substantially higher future prevalence of AF.[20] Based on a stable increase, the prevalence of AF throughout the US in 2050 was projected to be 12.1 million, which was 2.4-fold higher than in 2000. In this study, however, during the years 1980 to 2000 there was an increased incidence rate of 12.6%. Based on this, the prevalence of AF throughout the US in 2050 was projected to be 15.9 million, a 3.0-fold increase from 2000.[20]

The burden of atrial fibrillation-related stroke is rising

In AF-related stroke there have been few population-based studies and those that have been conducted are not directly comparable due to a lack of methodological standardisation. However, some studies have provided valuable data. For example, the NDPSS, conducted in Ireland (n=750 patients in 294,592 population), reported an incidence of AF-related ischaemic stroke of 42 cases per 100,000 per year.[21]

Figure 1: Pre-stroke risk factors in multiple population studies in Europe using two different definitions of atrial fibrillation



Sources: Rothwell et al., 2004;[23] EROS investigators, 2009;[22] Kelly et al., 2012;[25] Friberg et al., 2014.[24]

The prevalence of first ever stroke in AF has been determined to be 11–25% in various European AF-population studies.[22,23] However, these figures were derived using only prior AF; when the definition was expanded in studies in Ireland and Sweden to include prior, new and paroxysmal AF this prevalence rose to 31–33% (*Figure 1*).[24,25]

AF-related stroke is a very expensive condition in terms of treatment and rehabilitation costs. This was emphasised by a population-based prospective study in Dublin that stratified all costs according to stroke types. In a population of 568 patients with stroke, the total direct and indirect costs (including treatment, nursing care and loss of earnings) amounted to \$33.8 million.[26] In this group, 31% of patients had AF but their costs amounted to 41% of this total cost and 45% of the nursing care costs. Combined inpatient and post-hospital costs (nursing and general practitioner visits) and inpatient-only costs were both significantly higher for patients with AF-related stroke compared with non AF-related stroke ($p<0.001$ for both comparisons).[26]

Compliance with guidelines for atrial fibrillation-related stroke prophylaxis remains poor

There is a well-established gap between guidelines and practice for prophylaxis of individuals with NRAF and a moderate to high risk of stroke. The registry of the Canadian Stroke Network investigated 597 patients who had new ischaemic stroke, known AF, one high-risk or >1 moderate-risk factors.[27] The findings showed that only 10% were receiving therapeutic levels of warfarin, 29% were receiving sub-therapeutic levels of warfarin, 31% were receiving antiplatelet medication but 29% were receiving no antithrombotic treatment at all. This situation was little improved among patients with a previous stroke but admitted to hospital with a subsequent ischaemic event. Of these, only 18% were receiving therapeutic levels of warfarin, 39% were receiving sub-therapeutic levels of warfarin and 15% were still receiving no antithrombotic treatment.[27]

Atrial fibrillation-related stroke – a 'perfect storm' or grounds for optimism?

Ageing populations could have serious implications on the incidence of AF-related stroke. A comparison of data from the Oxfordshire Community Stroke Project for 1981–86 and from the OXVASC project of 2002–12 showed a 1.26% increase in AF-related stroke incidence between these two periods.[28] This rise, however, was entirely due to the increase in those ≥80 years old in the population (RR: 1.52, p=0.001). Based on current incidence, there is a projected 3.2-fold increase in AF-related stroke in those ≥80 years of age in the UK. The total cost of stroke care would be £1.7 billion by 2050, of which £1.4 billion would be for care of the over 80s.

These estimates predict a bleak future in AF-related stroke care as different contributory factors may collectively create a crisis that could be described as a 'perfect storm'. Data from some studies of treated populations with AF, however, give a more optimistic outlook. A study in Minnesota that included 4,117 patients with AF and no previous stroke showed a surprising 3.4% decreased incidence of stroke over the years 1980 to 2000.[29] This was despite an increased incidence of AF over the same period. There was a particular decrease in AF-related stroke during 1995–2000 (p=0.0001 compared with previous five-year durations). This finding was associated with an increased use of warfarin (9% during 1980–84 and 30% during 1995–2000) and decreased hypertension resulting from therapy.[29]

AF, therefore, significantly increases the risk of stroke and worsens the outcomes after strokes have occurred. Ageing populations are substantially increasing the incidence and prevalence or AF-related stroke which is placing a rising burden on medical resources worldwide.[28,30] At current rates of increase, AF-related stroke could become a healthcare crisis in the coming decades. Despite the proven benefits of anticoagulation therapy to reduce stroke incidence as shown in multiple studies and recommendations set out in guidelines, large proportions of patients with AF continue to be untreated or undertreated.[27] This is partly due to physicians' fears of haemorrhage, especially in the elderly and frail.[27,28] Although this picture is gloomy, studies in populations with AF that are appropriately treated with anticoagulants have shown a decline in stroke incidence.[29] These data amount to a call to action; universal adoption of optimal anticoagulant treatment practice by physicians could reverse current trends in AF-related stroke and greatly improve outcomes. ■

Balancing Benefit and Risk of Oral Anticoagulants in Atrial Fibrillation

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In AF, giving warfarin demonstrably decreases the rate of ischaemic stroke and systemic embolic events (SEEs) but increases the rate of various types of haemorrhage so balancing benefit with risk is a key issue.[31] This situation has been improved with the NOACs which have shown comparable efficacy to warfarin with reduced risks.[32] Alternative approaches to balancing benefit and risk in AF are the use of either dual or triple therapy combinations. Carlos Molina considered the evidence supporting these different approaches to anticoagulation in AF-related stroke prevention.

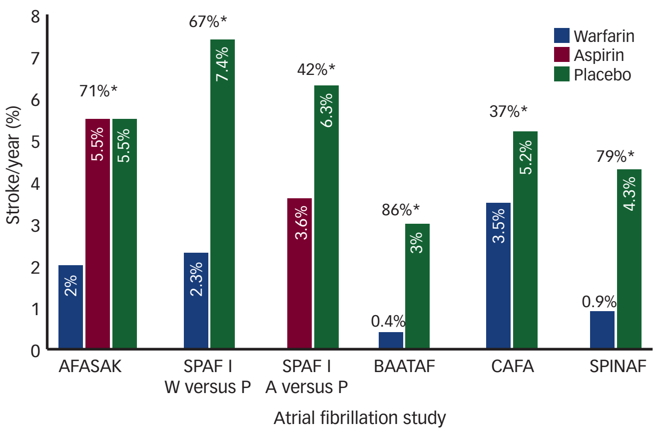
Various factors, especially age, increase the risk of stroke

In Caucasians, up to 20% of strokes are attributable to AF.[19] The prevalence of AF rises from age <55 (0.2% and 0.1% for men and women, respectively) to age ≥85 (11.1% and 9.1%).[30] Both the $CHADS_2$ and the $CHA2DS_2$-VASc scores list congestive heart failure, hypertension, age ≥75 years, diabetes mellitus and previous stroke as factors that increase the risk of stroke in AF.[33,34] The $CHA2DS_2$-VASc score additionally lists vascular disease, age 65–74 years and being female as stroke risk factors, thereby increasing the numbers of patients considered at-risk and/or raising their risk level.[34]

Warfarin anticoagulation – proven to reduce stroke incidence but increases the risk of intracranial haemorrhage

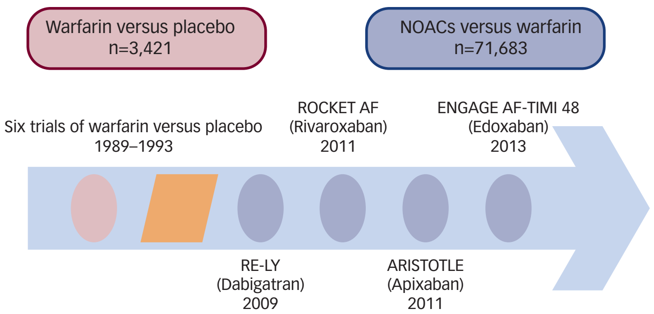
Approximately 20 years ago, stroke prevention initiatives passed an important milestone when randomized clinical trials (RCTs) showed that vitamin K antagonists (VKAs) reduced the risk of stroke in AF (see *Figure 2*).[31,35–40] A meta-analysis of six large RCTs, five of which were conducted during the 1990s, showed that compared with placebo, the overall reduction in AF-related stroke risk was approximately 64% with warfarin compared with placebo. The improvements in patients over 75 years of age, however, were less clear due to haemorrhagic complications.[31] The European Atrial Fibrillation Trial (n=1,007) showed that in patients with a recent stroke, the relative risk of secondary stroke was reduced by 66% with warfarin compared with 14% for aspirin.[40]

Figure 2: A summary of randomised studies of warfarin or aspirin compared with placebo in the prevention of atrial fibrillation and stroke



**% decrease in all events; A = aspirin; AFASAK = Atrial Fibrillation, Aspirin and Anticoagulation Study; BAATAF = Boston Area Anticoagulation Trial for Atrial Fibrillation Study; CAFA = Canadian Atrial Fibrillation Anticoagulation Study; P = placebo; SPAF I = Stroke Prevention in Atrial Fibrillation I Study; SPINAF = Stroke Prevention in Non-Rheumatic Atrial Fibrillation Study; W = warfarin. Sources: Morley et al., 1996;[31] Peterson et al., 1989;[39] SPAF Investigators, 1991;[65] BAATAF Investigators, 1990;[36] Connolly et al., 1991;[37] Ezekowitz et al., 1992.[38]*

Figure 3: Pivotal warfarin–controlled trials of stroke prevention in atrial fibrillation



NOAC = non-vitamin K oral anticoagulant; Sources: RE-LY: Connolly et al., 2009;[45]; ROCKET AF: Patel et al., 2011;[49] ARISTOTLE: Granger et al., 2011;[47] ENGAGE AF-TIMI, 2012, [48] Giugliano et al., 2013;[46] Six trials of warfarin versus placebo: The Stroke Prevention in Atrial Fibrillation Investigators;1990,[35] Boston Area Anticoagulation Trial for AF Investigators; 1990, [36] Connolly et al., 1991;[37] Ezekowitz et al., 1992;[38] Petersen et al., 1989;[39] EAFT Study Group, 1993.[40]

Table 1: Patient characteristics in clinical trials of non-vitamin K oral anticoagulants versus warfarin in the prevention of stroke in atrial fibrillation

	RE-LY (Dabigatran)	ROCKETAF (Rivaroxaban)	ARISTOTLE (Apixaban)	ENGAGE AF-TIMI 48 (Edoxaban)
Randomised, n	18,113	14,264	18,201	21,105
Age, Years [Interquartile Range]*	72 ± 9**	73 [65–78]	70 [63–76]	72 [64–78]
Female,%	37	40	35	38
Mean $CHADS_2$ Score	2.1	3.5	2.1	2.8
Paroxysmal AF,%	33	18	15	25
Prior Stroke/TIA,%	20	55	19	28
VKA Naïve,%	50	38	43	41
Aspirin Use,%	40	37	31	29
Median Follow-up, Years	2.0	1.9	1.8	2.8
Median TTR,%	67	58	66	68
$CHADS_2$ (%)† 0-1	32	0	34	0
2	35	13	36	47
3-6	33	87	30	53

** Mean age for the RE-LY study; other ages are medians; ** ± standard deviation; † $CHADS_2$ (%) data are primarily from drawn Ruff et al., 2014[32] (except the 0 value in the ENGAGE AF-TIMI 48 trial). Study names are defined at the end of the report text. AF = atrial fibrillation; $CHADS_2$ = a stroke risk factor scoring system in which one point is given for history of congestive heart failure, hypertension, age ≥75 years diabetes mellitus and previous stroke; TIA = transient ischemic attack; VKA = vitamin K antagonist. Sources: Connolly et al., 2009;[45] Patel et al., 2011;[49] Granger et al., 2011;[47] Giugliano et al., 2013;[46] Ruff et al., 2014.[32]*

The most feared long-term consequence of anticoagulation is ICH, which is known to be an extremely serious condition with limited treatment options and high rates of death or substantial disability among survivors. In some studies, the terms major bleeding and ICH are essentially synonymous.[41] Determination of the HAS-BLED score assessing bleeding risk is important and helps assess the risk of haemorrhage including major bleeding.[41] This score is derived from uncontrolled hypertension, age >65 years, stroke, bleeding history labile international normalised ratios (INRs), drug or alcohol abuse, abnormal renal or liver function and antiplatelet use.[41] HAS-BLED scores of 6–9 are associated with an up to 12-fold greater risk of haemorrhage than those with a HAS-BLED score of 0.42. To decrease stroke risk in AF, it is necessary to determine bleeding risk and balance INRs in a window of 2.0–3.0. INRs below 2.0 increase the risk of stroke, whereas INRs above 3.0 increase the risk of haemorrhage.[43,44]

Non-vitamin K antagonist oral anticoagulants advance stroke prevention in atrial fibrillation

More recently, a further important milestone was reached when the NOACs were shown in RCTs to reduce the risk of stroke in AF and offered an alternative to warfarin.[45–50] The development programmes of the NOACs included four large clinical trials including a total of 71,638 patients: RE-LY (dabigatran, 2009), ROCKET AF (rivaroxaban, 2011), ARISTOTLE (apixaban, 2011) and ENGAGE AF-TIMI 48 (edoxaban, 2013) (*Figure 3*; *Table 1*).[45–47,49] Although these studies showed similar baseline demographics, they recruited a wide range of patients with differing baseline $CHADS_2$ scores which were highest in the ENGAGE and ROCKET AF studies (mean $CHADS_2$: 2.8 and 3.5, respectively). In addition, 55% of patients in the ROCKET AF study had a prior stroke.

A meta-analysis shows non-vitamin K antagonist oral anticoagulants are more effective than warfarin in AF-stroke prevention with favourable safety profiles

A recent meta-analysis of the RE-LY, ROCKET AF, ARISTOTLE and ENGAGE AF-TIMI 48 studies, found that collectively, there was a relative risk (RR) of 0.81 ($p<0.0001$) favouring NOAC treatment over warfarin in the occurrence of stroke or SEEs in patients with AF.[32] This difference was largely driven by a substantially lower occurrence of haemorrhagic stroke with NOACs (RR: 0.49, $p<0.0001$). There was also a significant reduction in all-cause mortality with NOAC treatment versus warfarin (RR: 0.90, $p=0.0003$). Overall reductions in ischaemic stroke with NOAC treatment were non-significant. The collective reduction in intracranial bleeding was substantially greater with NOACs versus warfarin (RR: 0.48, $p<0.0001$), however, there was an increased risk of gastrointestinal bleeding (RR: 1.25, $p=0.043$). These results indicate a favourable risk–benefit for the NOACs and a favourable safety profile compared with warfarin across a diverse range of patients.[32]

Dual or triple therapy to reduce bleeding risk in AF-associated stroke prevention?

Some clinical studies have addressed the need for antiplatelet therapy in addition to anticoagulation. A notable example was the WOEST study which was an open-label, randomised, controlled trial conducted on patients (mean ages 69–70 years for triple and double therapy, respectively) at centres in Belgium and the Netherlands (n=573). Study participants were all receiving percutaneous coronary intervention (PCI, stent) with oral anticoagulants and were assigned to additionally receive either clopidogrel alone (dual therapy) or clopidogrel plus aspirin (triple therapy). Dual therapy was shown to decrease the risk of bleeding by more than two-fold compared with triple therapy (hazard ratio [HR]: 0.36, $p<0.0001$) with no increase in the rate of thrombotic events.[51] These findings were supported by a registry study in Denmark that included 12,165 patients with AF after myocardial infarction (MI) and/or PCI which showed that dual therapy (oral anticoagulant and clopidogrel) provided equal or better benefits and safety than triple therapy.[52] However, the risk of stent rethrombosis was increased after withdrawing warfarin therapy and switching to clopidogrel or aspirin alone.[53] Physicians therefore face a dilemma in AF – whether to protect the heart or the brain.

There have been no RCTs on dual therapy with NOACs and antiplatelet therapy in AF so the data on this approach are, as yet, limited. To better investigate dual therapy for the prevention of thrombosis in patients with AF who have had PCI with stent placement, the PIONEER AF-PCI study (NCT01830543, planned n=2,169) is in progress. This is an open-label, randomised, controlled, multicentre study that will evaluate the safety of two different rivaroxaban treatment strategies and one VKA treatment strategy utilising different combinations of dual antiplatelet therapy, low-dose aspirin or clopidogrel (or prasugrel or ticagrelor) over a period of 12 months.[54] A further trial on dual therapy, REDUAL (planned n=8,520) is also in progress. This is designed to compare the efficacy and safety of a dual therapy combination of dabigatran in combination with clopidogrel or ticagrelor versus a triple therapy combination of warfarin with clopidogrel or ticagrelor and aspirin over a period of up to 30 months in patients with AF who have received PCI with stent placement.[55]

The evidence on dual and triple therapy discussed above indicates that if a stented patient with AF has a low bleeding risk, stroke prevention should consist of triple therapy for six months followed by oral coagulation and clopidogrel. If the patient has a moderate bleeding risk, treatment should be oral anticoagulation and clopidogrel. If the patient has a high bleeding risk treatment should be aspirin and clopidogrel for six months followed by NOAC therapy.

In multiple clinical trials warfarin has been shown to reduce the overall risk of AF-related stroke by 64%, but remains underused.[27,31] This treatment, however, necessitates close INR monitoring and increases bleeding risk. In the prevention of stroke or SEE in AF, the NOACs show similar efficacy to warfarin but have a favourable risk–benefit profile showing significant reductions in ICH (including haemorrhagic stroke) and mortality. The NOACs show consistent efficacy and safety in a wide range of patients but are associated with increased gastrointestinal bleeding which requires careful monitoring.[32] ■

Stroke Prevention in AF – What Does the ENGAGE AF-TIMI 48 Trial Add?

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The primary results from the ENGAGE AF-TIMI 48 study[46] clearly indicate the efficacy and safety of the most recently approved NOAC, edoxaban, in the prophylactic treatment of stroke in AF and in patients with AF who had a prior stroke. These results have been used to support the regulatory submission for the drug in this indication. Edoxaban 60 mg has been approved for use in AF in the US by the US Food and Drug Administration (FDA) and across the European Union by the European Medicines Agency (EMA). A recent pre-planned subgroup analysis of the ENGAGE AF-TIMI 48 results has provided valuable insights into the primary findings and helps elaborate the value of the treatment in AF and guides the optimal use of NOACs.[56] Christian T. Ruff discussed the implications of these analyses and what more can be learned from the ENGAGE AF-TIMI 48 study.

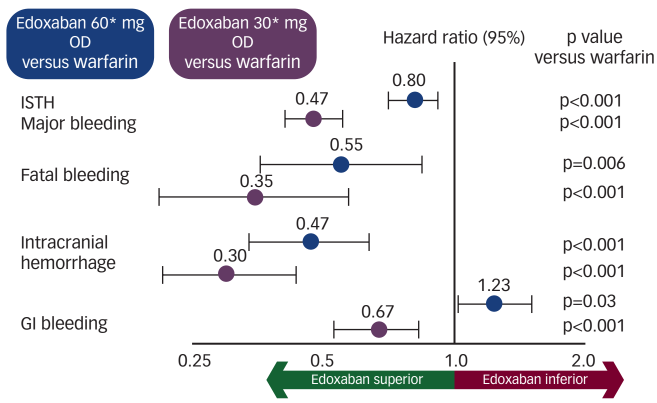
Largest trial of a non-vitamin K antagonist oral anticoagulant in atrial fibrillation with flexible dosing

The ENGAGE AF-TIMI 48 study was the largest Phase 3 trial of the four NOACs developed to date, and overall showed the non-inferiority of edoxaban to warfarin in terms of efficacy but with a significantly improved safety profile including reduced bleeding and cardiovascular mortality.[46] The study recruited 21,105 patients with AF and $CHADS_2 \geq 2$ at 1,393 centres in 46 countries. The patients were randomized in a ratio of 1:1:1 to warfarin [INR 2.0-3.0], edoxaban 60 mg once daily (QD) or edoxaban 30 mg QD. The trial was unique in the fact that edoxaban doses could be reduced by 50% if the creatinine clearance was 30–50 ml/min, body weight ≤ 60 kg or if the patient was receiving strong p-glycoprotein inhibitors, both at randomisation and during the trial.[46] The trial also recruited a large proportion of patients (53%) who were at a higher risk of stroke, having a $CHADS_2$ score ≥3.[32]

Edoxaban – non-inferiority to warfarin in stroke prevention with significant reductions in intracranial haemorrhage and other bleeding events

Among the findings of the ENGAGE AF-TIMI 48 study, the median [interquartile range] proportion of time in therapeutic range (TTR) was 68.4% [56.5–77.4] which was higher than the mean or median TTRs of the other three major NOAC trials.[46] For the primary endpoint, incidence of stroke or SEEs, both the 60 mg and 30 mg doses of edoxaban were non-inferior to warfarin (HR: 0.79 and 1.07, p<0.001 and p=0.005, respectively). The 60 mg edoxaban dose showed some efficacy improvement over warfarin but was not statistically superior in intention-to-treat analysis (HR: 0.87 p=0.08).

Figure 4: Main safety results in the ENGAGE AF-TIMI 48 trial of warfarin versus different edoxaban doses in AF-related stroke prevention



Dose reduced by 50% in selected patients GI = gastrointestinal; ISTH = International Society on Thrombosis and Haemostasis; QD = once daily; TTR = time in therapeutic range. Source: Giugliano et al., 2013[46]

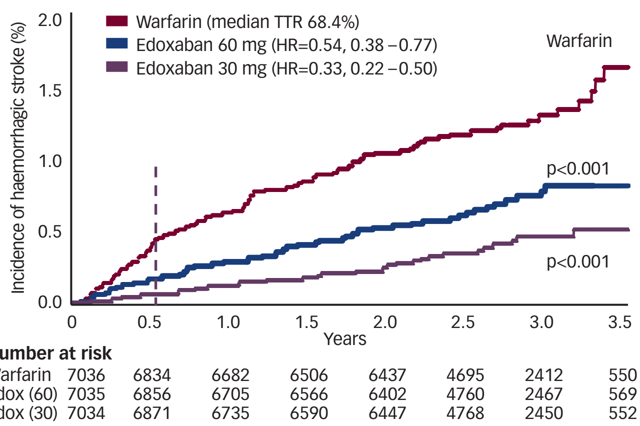
The most notable secondary outcome of the ENGAGE AF-TIMI 48 study was a substantial reduction in risk of haemorrhagic stroke for both edoxaban 60 mg and 30 mg compared with warfarin (HR: 0.54 and 0.33, p<0.001 for both).[46] For these edoxaban doses there were also significant reductions in rates of death or ICH (HR: 0.87 and 0.82, p=0.004 and p<0.001, respectively) and in rates of cardiovascular death (HR: 0.86 and 0.85, p=0.013 and p=0.008, respectively). Among the safety findings for the 60 mg and 30 mg edoxaban doses, there were significant reductions in major bleeding (p<0.001 for both doses), fatal bleeding (p=0.006, p<0.001) and ICH (p<0.001 for both doses)

Table 2: Annualised rates of stroke and transient ischaemic attack in the ENGAGE AF-TIMI 48 trial

Outcome	Warfarin (N=7036)	Edoxaban High Dose (N=7035)	Edoxaban High Dose versus Warfarin HR	p-value	Edoxaban Low Dose (N=7034)	Edoxaban Low Dose versus Warfarin HR	p-value
All stroke	1.69%	1.49%	0.88	0.11	1.91%	1.13	0.12
Haemorrhagic	0.47%	0.26%	0.54	<0.001	0.16%	0.33	<0.001
Ischaemic*	1.25%	1.25%	1.00	0.97	1.77%	1.41	<0.001
Fatal stroke$^{\alpha}$	0.45%	0.42%	0.92	0.61	0.38%	0.84	0.27
Disabling†	0.71%	0.69%	0.97	0.81	0.80%	1.11	0.36
Non-disabling‡	1.01%	0.81%	0.80	0.044	1.13%	1.12	0.26
TIA (Sx <24h)	0.50%	0.56%	1.11	0.45	0.79%	1.56	<0.001
Stroke or TIA	2.17%	2.00%	0.92	0.27	2.62%	1.21	0.005
'New' stroke**	1.77%	1.54%	0.87	0.077	1.99%	1.12	0.13
'New' ischaemic stroke**	1.33%	1.30%	0.98	0.79	1.85%	1.39	<0.001

** Includes stroke with haemorrhagic transformation † Includes Rankin score 3–5 and fatal stroke[56] (Rankin score = 6)[46] ‡ Rankin score 0–2 or alive with no score reported by the investigator (n=231) α Fatal stroke data here are drawn from Giugliano, 2013.[46] The rest of the data in this table are drawn from Giugliano, 2014.[56] ** The 'new' stroke definition reclassified 37 TIAs as ischemic stroke (resolving <24h with infarct on brain imaging, 14 warfarin; 9 edoxaban high dose, 14 edoxaban low dose).[64] High Dose = 60 mg; HR = hazard ratio; Low Dose = 30 mg; Sx = symptoms; TIA = transient ischemic attack.*

Figure 5: Cumulative incidence of haemorrhagic stroke over 3.5 years in patients treated with different edoxaban doses or warfarin in the ENGAGE AF-TIMI 48 study



Edox = edoxaban; HR = hazard ratio (numbers next to HR values are 95% confidence intervals); TTR = time in therapeutic range. Source: Giugliano et al., 2014[56]

parameters as defined by the International Society of Thrombosis and Haemostasis (*Figure 4*).[46] Overall, the ENGAGE trial findings showed a good balance between the proven efficacy and a superior safety profiles of edoxaban 60 mg and were pivotal for EMA approval.

Subgroup analyses of ENGAGE AF-TIMI 48 study emphasises anticoagulation benefits

A positive effect on most stroke types

The recent subgroup analysis of ENGAGE AF-TIMI 48 study results showed that the incidences of multiple ICH subtypes (all ICH, fatal ICH, fatal, subdural and epidural bleed) were significantly lower with both 60 mg (approximately 50% reduction) and 30 mg edoxaban (approximately 70% reduction) doses than with warfarin (p=0.013–<0.001).[56] In addition, the cumulative incidence of haemorrhagic stroke was substantially lower for both edoxaban doses compared to warfarin after only six months and this difference increased over the following three years (p<0.001 for both doses) (*Figure 5*). During 3.5 years of treatment, the cumulative incidence of ischaemic stroke was consistently similar for both 60 mg edoxaban and warfarin (p=0.97) but greater for 30 mg edoxaban (p<0.001). These results were largely reflected in a breakdown of stoke or transient ischaemic attack (TIA) incidence when reported as annualised rates (*Table 2*). There was generally a greater incidence of all strokes with the 30 mg edoxaban dose and lower incidence with the 60 mg dose compared with warfarin.[56] For this reason the lower 30 mg dose was not included in the submission for regulatory approval in Europe or the US.

Prior stroke worsens patient status but does not reduce preventive treatment efficacy

The ENGAGE AF-TIMI 48 study subgroup analysis examined data from the subgroup of 5,973 patients (28.3% of the study population) with prior stroke and showed that 67% had $CHADS_2$ >3 and 36% were aged ≥75 years. Cerebrovascular event rates differed significantly between those with previous stroke versus those with no previous stroke (p<0.001 for ischaemic stroke and ICH), and between those with previous stroke receiving edoxaban versus warfarin.[57] Among those receiving warfarin, the annualised rates of haemorrhagic stroke and ischaemic stroke were 0.59% and 2.13%, respectively, for those with prior stroke and 0.43% and 0.92%, respectively, for those with no prior stroke. For those receiving edoxaban 60 mg, the annualised rates of haemorrhagic stroke and ischaemic stroke were 0.31% and 2.04%, respectively, for those with prior stroke and 0.24% and 0.95%, respectively, for those with no prior stroke.[57] Patients receiving warfarin and a prior stroke had a 1.07% annualised event rate for ICH compared with 0.73% for those with no prior stroke. Patients receiving edoxaban 60 mg and a prior stroke had a 0.62% annualised event rate for ICH compared with 0.30% for those with no prior stroke. These findings indicate that patients with a prior stroke are at high risk of recurrent ischaemic or haemorrhagic events but edoxaban is a suitable option for their treatment.

Dose reduction reduces bleeding risk without markedly increasing stroke risk

Patients with impaired renal function or low body weight are likely to accumulate the drugs used in AF prevention so dose reduction is a valid precaution to avoid bleeding. In the ENGAGE AF-TIMI 48 study subgroup analyses, reducing doses (to 30 mg or 15 mg due to renal impairment or low body weight) was shown to correspondingly reduce plasma concentrations and anti-factor Xa activity.[58] The HRs for edoxaban doses versus warfarin for annualised stroke or SEEs in those with or without dose reduction were the same or similar in both dose groups (60 mg dose: 0.78 versus reduced dose: 0.81; 30 mg dose: 1.07 versus reduced dose: 1.07; for interactions, p=0.85 and p=0.99, respectively). So, reducing the dose of edoxaban did not confer any reduction in stroke protection. For major bleeding events, the HRs for edoxaban 60 mg or 30 mg versus warfarin were lower after dose reduction (60 mg dose: 0.88 versus reduced dose: 0.63; 30 mg dose: 0.55 versus reduced dose: 0.31; p=0.023 and 0.002, respectively for the interaction). Reducing the edoxaban dose by 50% therefore, further decreased bleeding. This finding can be explained by the steeper effect of increasing trough concentrations on major bleeding compared with a less pronounced effect on stroke and a largely flat effect on ICH incidence, as shown in *Figure 6*.[58] For this reason tailoring the edoxaban dose in patients with AF who need dose reduction can provide optimal efficacy with improved safety profiles.

Edoxaban markedly reduces death rates mainly as a result of reductions in fatal or non-fatal bleeds

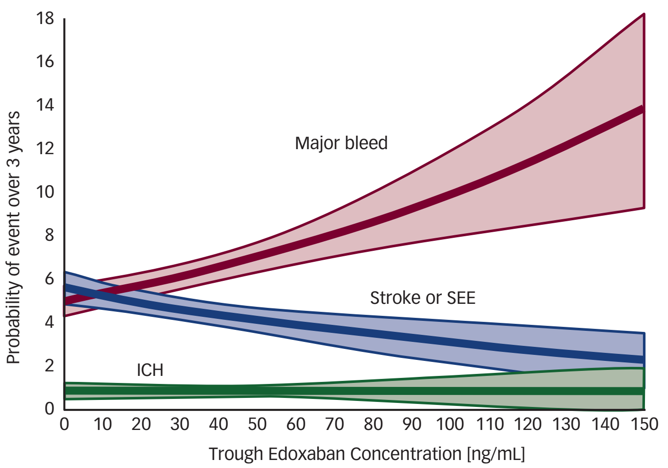
The subgroup analysis of the ENGAGE AF-TIMI 48 study investigated the various causes of death and showed that patients receiving edoxaban show generally lower rates of death than those receiving warfarin. In addition, the analyses showed that 45% and 40% of the additional deaths in patients receiving warfarin compared with 60 mg and 30 mg edoxaban, respectively, were due to fatal bleeds.[59] The cumulative total of fatal bleeding, bleeding that contributed to death and deaths following a non-fatal major bleed constituted 89% and 86% of the additional deaths observed in patients receiving warfarin compared with those receiving the 60 mg and 30 mg edoxaban regimens, respectively. This showed that most of the reduction in all-cause mortality observed with edoxaban in the ENGAGE AF-TIMI 48 trial resulted from lower rates of fatal or non-fatal major bleeding with edoxaban compared with warfarin.

The benefits of anticoagulation therapy outweigh the risks

The findings from the ENGAGE AF-TIMI 48 study and sub-analyses add to the substantial body of evidence emphasising the importance of oral anticoagulation in AF. Other such evidence comes from a variety of studies including an analysis of a very large hospital discharge registry in Sweden that included 182,678 patients with AF.[60] Despite variable elevated CHA2DS$_2$-VASc and HAS-BLED scores, in almost all patients over four years of follow-up the risk of ischaemic stroke without anticoagulant treatment was greater than the risk of intracranial bleeding with anticoagulant treatment.[60]

The overall clinical study evidence also emphasises that in elderly patients with AF who are at high risk of stroke and bleeding, anticoagulation therapy should be given because the risk of stroke substantially outweighs the risk of bleeding.[60] Elevated HAS-BLED scores should not be used as a reason to withhold anticoagulation.

Figure 6: Effect of edoxaban trough plasma concentrations on the incidence of major bleed, stroke or systemic embolic events or intracranial haemorrhage in the ENGAGE AF-TIMI 48 study



ICH = intracranial haemorrhage; SEE = systemic embolic event. Source: Ruff et al., 2015[58]

Reducing contributory factors to a high HAS-BLED score such as hypertension, poor liver or kidney function, labile INR and alcohol or drug abuse can mitigate the risks associated with such treatment.[9]

Falling in the elderly and other risks should not deter anticoagulant treatment

The findings of the ENGAGE AF-TIMI 48 study and multiple other clinical studies make an overwhelming case for the use of anticoagulation in AF. Despite this, anticoagulation is still underused mainly due to contraindications, patient unwillingness, patient frailty, old age and the risk of falls.[1,27] Most of these reasons, especially the risk of falls, should not prevent the use of anticoagulation. This was emphasised by a study in Canada which found that patients must fall 295 times in one year for warfarin not to be their optimal therapy in AF-associated stroke prevention.[61] A study in the US showed that the time to first bleeding among 515 patients who were receiving anticoagulants was similar for those at high risk to those at low risk of falling (p=0.65).[62] Fall risk should therefore not deter anticoagulant therapy despite concerns among many physicians.

After a stroke – restart anticoagulation quickly

The European Heart Rhythm Association Practical Guide on the use of new oral anticoagulants in AF recommends that patients with AF should be restarted on anticoagulant therapy as soon as possible after a stroke, depending on the size of the infarct. After a stroke, NOAC treatment should be restarted after one day for a TIA, three days for small non-disabling infarct, six days for moderate infarct and 12 days or more for large infarct involving large sections of arteries.[11] Failure to restart treatment exposes the patient to a substantially higher risk of stroke and poorer outcomes. ■

Discussion and Conclusion

The incidence, prevalence and economic data outlined above are a call to action. They indicate that AF is an increasingly serious burden to healthcare systems worldwide, which is likely to increase in the coming decades as populations age. Disabilities caused by AF-related strokes are more serious than in non-AF-related strokes and consequent treatment and rehabilitation costs are high.[18,26,28] The outlook for physicians treating AF appears bleak but there might be some grounds for optimism. The results from the study in Minnesota that spanned 1980–2000,[29] were encouraging and showed a long-term decrease in AF-related stroke despite a generally increasing incidence of AF in the US and elsewhere. This can be attributed to greater use of anticoagulation and better management of risk factors such as hypertension.[29] This suggests that better awareness of AF and increased willingness to treat it may help reduce its impact in the future. Guidelines strongly recommend the use of anticoagulants in AF[9] but despite this various studies including an analysis of the Canadian Stroke Network[27] and OXVASC[28] report that the proportions of patients with AF who receive anticoagulation therapy are low, even among those with a previous stroke.

The evidence supporting the use of warfarin in AF-related stroke prevention is convincing, being drawn from experience in extensive patient populations. Warfarin, however, increases the risk of ICH and this deters many physicians from using this drug or other anticoagulants in vulnerable patients.[28,63] In recent years reluctance to use anticoagulation could have been diminished by the introduction of the NOACs which have shown improved AF-related stroke prevention, reduced the risk of intracranial bleeding and haemorrhagic stroke and reduced mortality in studies that collectively included >70,000 patients.[32] In addition, dual or triple therapy with warfarin and agents such as clopidogrel or rivaroxaban and aspirin in patients with stents have also shown improved efficacy against stroke but can increase bleeding risk. As a result, the risk of bleeding with dual and triple therapy including a NOAC, such as dabigatran or rivaroxaban, is being investigated in larger trials.[54,55]

The main results of the ENGAGE AF-TIMI 48 trial showed that in a population of 21,105 patients, edoxaban 60 mg and 30 mg doses were non-inferior to warfarin in terms of AF-related stroke reduction and showed significant reductions in haemorrhagic stroke and death due to ICH or cardiovascular causes.[46] The recent subgroup analysis of the ENGAGE AF-TIMI 48 study results provided valuable insights and emphasised the benefits of edoxaban treatment.[56] The finding that almost all types of ICH were less frequent with edoxaban than warfarin emphasised the safety of the treatment.[56] In addition, the analysis of patients with prior strokes who are at greater risk of ischaemic and haemorrhagic strokes showed similar efficacy of edoxaban to those without prior stroke.[57] Furthermore, reducing the edoxaban dose in patients with renal insufficiency or low body weight did not diminish efficacy and indicated that the dose can be tailored to suit the individual where necessary.[56] The ENGAGE AF-TIMI 48 study subgroup analyses also showed that the reduced death rates with edoxaban were largely due to reductions in fatal bleeds or bleeds contributing to death.[59] The efficacy of edoxaban across different patient subgroups therefore indicates that it is an attractive treatment option even in the most vulnerable groups.

These new insights into the ENGAGE AF-TIMI 48 study results support existing evidence that patients with AF who are at risk of stroke should receive appropriate anticoagulant therapy. The benefits of this treatment substantially outweigh the risks. In the event of an AF-associated stroke, the patient should be restarted on anticoagulant therapy as quickly as possible, subject to infarct size, to mitigate the greater risk of a further stroke.[11] The use of NOACs has certainly improved the efficacy and safety of anticoagulation therapy in AF.[48,50] Greater awareness of their benefits and the imperative of reducing stroke risk in AF are likely to contribute to their use across a diverse range of patients and consequently improve outcomes in this frequently lethal and increasingly common condition.■

ARISTOTLE = Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation
ENGAGE AF-TIMI 48 = Effective aNticoaGulation with factor xA next GEneration in Atrial Fibrillation–Thrombolysis In Myocardial Infarction study 48
OXVASC = The Oxford Vascular Study
PIONEER AF-PCI = Study Exploring Two Strategies of Rivaroxaban and One of Oral Vitamin K Antagonist in Patients With Atrial Fibrillation Who Undergo Percutaneous Coronary Intervention
RE-LY= Randomized Evaluation of Long-Term Anticoagulant Therapy
ROCKET AF = Rivaroxaban Once-daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation
WOEST = What is the Optimal antiplatElet and anticoagulant therapy in patients with oral anticoagulation and coronary StenTing

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