

Tailoring the Novel Anticoagulants to the Stroke Patient – One Size Does Not Fit All Novel Anticoagulants in Stroke

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Abstract

Warfarin has been the mainstay of anticoagulation therapy for stroke prophylaxis in patients with non-valvular AF for past decades. Recent times have seen the release of four alternative novel anticoagulants that overcome many of the limitations that plagued patients on warfarin in the past. These agents have gained rapid acceptance and are now considered first line therapies for this indication in international guidelines. The approval of dabigatran, rivaroxaban and apixaban by US and European medication authorities has resulted in widespread uptake of these agents.

In this review, we seek to examine the major trials pertaining to these agents with particular attention to patients that have already suffered a stroke (secondary prevention). Issues relevant to stroke physicians including thrombolysis in patients on these agents, timing of initiation of these agents after an acute stroke, reversibility in the setting of haemorrhage and alternative agents will be addressed. Finally, with an expanding choice of available agents, we offer some pragmatic advice regarding tailoring therapy to an individual patient.

Keywords: Anticoagulation; Dabigatran; Rivaroxaban; Apixaban; Edoxaban; Warfarin; Stroke

Introduction

Stroke is an often devastating syndrome involving neurological dysfunction due to impaired perfusion to areas of the brain. Approximately 85% of these are ischemic in nature whilst the remainder are due to haemorrhage [1]. Whilst many of these ischaemic events are due to in situ thrombosis of cerebral arteries or carotid and vertebral disease, many are due to cardioembolic phenomenon, the majority of which are in the setting of atrial fibrillation (AF). AF predisposes to left atrial stasis and consequential thrombus formation, particularly within the left atrial appendage, which can then dislodge and embolise to the cerebral circulation or other systemic organs. One study [2] showed that 24.6% of patients had AF detected on their index admission for an ischemic stroke. This prevalence increased with age with up to 44.7% of patients aged above 90 years old having AF detected on admission for an ischemic stroke.

A stroke that occurs in the setting of AF results in a worse prognosis and more severe neurological debility than strokes outside of this setting [3]. AF is the most common cardiac arrhythmia with increasing prevalence with age. One study [4] estimated the worldwide prevalence of AF to be 33.5 million people in 2010; the prevalence is expected to increase in the coming decades due to the growth in the elderly population. Whilst AF can result in symptoms due to its cardiovascular and haemodynamic sequelae, its significant long term morbidity and mortality is due to this heightened risk of

cardioembolic stroke; as such thromboprophylaxis is recommended to mitigate this risk.

Recent trials have shown that patients that were deemed to have cryptogenic strokes after standard investigations, were in fact found to have a high rate of atrial fibrillation if followed up with long term cardiac monitoring with either an implantable cardiac monitor (ICM) or external event monitor [5,6]. 30% of patients that were followed up with an ICM were found to have suffered atrial fibrillation at 3 years compared to only 3% of patients who were followed up clinically. With the recent release of a smaller ICM [7] that can be inserted by the bedside, the utility of these devices in these patients is likely to increase leading to significantly greater rates of AF detection and consequential use of anticoagulation in these patients.

Warfarin is highly efficacious; it reduces the risk of ischaemic stroke in the setting of AF by 62% [8], however it is a drug not without its drawbacks. Warfarin has significant interaction with medications and food. There is significant dose variability between patients and a limited therapeutic window requiring frequent monitoring of coagulation parameters. Warfarin has a slow on and offset requiring concomitant therapy with heparin or enoxaparin during initiation or cessation of the drug. These factors have lead to the under prescription of this medication in up to 65% of eligible patients [9].

Currently, there are four novel anticoagulation agents (NOACs) with proven efficacy for stroke prophylaxis in patients with non-valvular AF: this includes the direct thrombin inhibitor, dabigatran, and the Factor-Xa inhibitors, rivaroxaban, apixaban and edoxaban. All four agents have been tested against warfarin in a population of

patients with non-valvular AF in large, Phase III, multi-centre, randomised controlled trials. These medications overcome many of the limitations of warfarin; they involve fixed dosing regimens for most patients, have few significant interactions with medications or food and do not require regular monitoring of coagulation parameters. Edoxaban is still awaiting regulatory approval in the United States of America (USA) [10] and Europe [11] for this indication, whilst dabigatran, rivaroxaban and apixaban have approval from the Federal Drug Administration (FDA) [12-14] and European Medicines Agency (EMA) [15-17] respectively.

Overview of the Novel Anticoagulants (NOACs)

Dabigatran

Since the withdrawal of ximelagatran, dabigatran remains the only oral direct thrombin inhibitor available for the prevention of stroke in patients with non-valvular AF. The RE-LY trial [18], was a partially open-label, multicentre, randomised, non-inferiority trial of 18,113 patients testing two doses of dabigatran (110 mg twice daily [BD] and 150 mg BD) against dose-adjusted warfarin in patients with non-valvular AF. There was an equal spread of patients across CHADS₂ scores and approximately 20% of patients had suffered a prior stroke or TIA. The primary outcome was a composite of stroke (both ischaemic and haemorrhagic) and systemic embolism. Both doses were found to be non-inferior to warfarin ($p < 0.001$ for non-inferiority) whilst the higher dose was also found to be superior with a 34% relative reduction in stroke or systemic embolic events (hazard ratio [HR] 0.66 [0.53 – 0.82], $p < 0.001$ for superiority). Notably, the higher dose of dabigatran is the only currently available therapy that appears to be more effective than warfarin in preventing ischaemic strokes with a relative risk reduction of 24% (HR 0.76 [0.60 – 0.98], $p = 0.03$). There was a trend towards improved mortality with the higher dose of dabigatran (HR 0.88 [0.77 – 1.00], $p = 0.051$). Both doses were associated with lower rates of haemorrhagic stroke compared to warfarin. Patients on the lower dose had 69% less haemorrhagic strokes (HR 0.31 [0.17 – 0.56], $p < 0.001$) whilst those on the higher dose had 74% less compared to warfarin (HR 0.26 [0.14 – 0.49], $p < 0.001$).

The lower dose of dabigatran was somewhat safer than warfarin with 20% less major bleeding episodes (HR 0.80 [0.69 – 0.93], $p = 0.003$) whilst the higher dose did not show a statistical difference in rates of major bleeding compared to warfarin (HR 0.93 [0.81 – 1.07], $p = 0.31$). Whilst in the original RE-LY trial, rates of intracranial and extracranial bleeding were not statistically different from warfarin with either dose of dabigatran, a subsequent analysis [19] demonstrated an age interaction; in elderly patients (age ≥ 75 years), rates of extracranial bleeding were 20% and 39% higher in patients on the lower and higher doses of dabigatran respectively (110 mg BD: HR 1.20 [0.97 – 1.48], p for interaction = 0.001, 150 mg BD: HR 1.39 [1.13 – 1.70], p for interaction < 0.001). No such interaction was seen with regards to intracranial bleeding. Although approved in patients with chronic renal impairment down to a creatinine clearance (CrCl) of 30 mL/min by Cockcroft Gault, a sub-analysis of RE-LY [20] demonstrated an interaction by degree of renal dysfunction, whereby the reduction in major bleeding compared to warfarin was mainly evident in those with a CrCl of ≥ 80 mL/min (110 mg: HR 0.41 [0.20 – 0.62], $p = 0.0012$, 150 mg BD: HR 0.59 [0.41 – 0.84], $p = 0.005$).

Although major bleeding was not increased in patients on the higher dose of dabigatran, bleeding specifically from the

gastrointestinal tract did occur 50% more frequently in patients on this dose of dabigatran compared to those on warfarin (HR 1.50 [1.19-1.89], $p < 0.001$) an effect that may be related to the direct effect of dabigatran on gastrointestinal mucosa. Warfarin may escape this localised phenomenon due to its requirement for systemic activation with vitamin-K dependent factors in the systemic circulation. Additionally, dyspepsia occurred significantly more often in patients on dabigatran (approximately 11.2 – 11.8%) compared to those on warfarin (5.8%) [$p < 0.001$] resulting in a higher rate of drug discontinuation in patients on dabigatran compared to warfarin (21% vs 17%, $p < 0.001$).

The original RE-LY trial hinted at the suggestion of higher rates of myocardial infarction (MI) which appeared to reach statistical significance in patients on the higher dose of dabigatran compared to warfarin (HR 1.38 [1.00 – 1.91], $p = 0.048$) although overall event rates were low with only 89 out of 6076 (1.5%) of patients suffering an MI in this group compared to 1.0% in the warfarin group. A subsequent meta-analysis of all clinical trials of dabigatran compared to alternative anticoagulants including warfarin, heparin and low-molecular weight heparin (LMWH) appeared to support this finding [21]. Nonetheless, a re-evaluation of the RE-LY trial which included events missed in the original trial showed that on re-analysis, the increase in MI with dabigatran was not statistically significant [22].

Whilst RE-LY demonstrated significant efficacy and safety benefits of both doses of dabigatran over warfarin, this benefit was most notable in those patients from centres where control of the internationalised normalised ratio (INR) was poor in patients on warfarin. A sub-analysis of RE-LY which examined outcomes by time in therapeutic range (TTR) [23] showed that the reduction in major bleeding in patients on high dose dabigatran was confined to those from centres where TTR was $< 57.1\%$ (the lowest quartile) ($p = 0.03$ for interaction).

Rivaroxaban

Rivaroxaban was the first of the class of oral Factor-Xa inhibitors to reach the market for prevention of stroke in patients with non-valvular AF. The ROCKET AF trial [24] was a multi-centre, randomised controlled trial that tested rivaroxaban against warfarin therapy in 14264 patients of this population. Unlike RE-LY, it was truly double blind with use of double dummy medications. The study utilised a single dosing regimen of 20 mg once daily of rivaroxaban, which was reduced to 15 mg daily in patients with a creatinine clearance of 30 – 49 mL/min. The population of ROCKET AF was higher risk than that of RE-LY with the majority of patients having a CHADS₂ score of at least three. 55% of the patients had already suffered a stroke, systemic embolism or TIA. Rivaroxaban was found to be non-inferior to warfarin in regards to the primary outcome of stroke or systemic embolism (HR 0.88 [0.75 – 1.03], $p < 0.001$ for non-inferiority).

There was no statistical differences in overall rates of clinically relevant bleeding between the two groups (HR 1.03 [0.96 – 1.11], $p = 0.44$). Like with dabigatran, however, there was a higher rate of major gastrointestinal bleeding in the rivaroxaban group (3.15% vs 2.16%, $p < 0.05$). There were also more incidences of epistaxis (10.14% vs 8.55%, $p < 0.01$) and haematuria (4.16% vs 3.40%, $p < 0.05$) in patients on rivaroxaban [25]. However, consistent with the other direct acting anticoagulants, there was a 33% reduction in the rates of intracranial haemorrhage with rivaroxaban (HR 0.67 [0.47 – 0.93], $p = 0.02$).

The ROCKET AF trial gave insights and validation into the short acting nature of these new direct acting agents [26]. Patients allocated to rivaroxaban during this trial were recommended to transition to warfarin at the end of the study. As expected, the median time to achieving a therapeutic INR was much higher in those who were on rivaroxaban (13 days vs 3 days) compared to those already on warfarin. The use of unfractionated heparin or LMWH as bridging therapy until the INR was therapeutic was low (<2% in both groups). Those patients on rivaroxaban had a 3.72 fold increase in rates of stroke or systemic embolism during this period of presumed inadequate anticoagulation compared to those who were already on warfarin (HR 3.72 [1.15 – 9.16], $p = 0.004$) although absolute rates of these events were still low (0.48% vs 0.14% respectively). However, patients who transitioned from warfarin to rivaroxaban had similar outcomes to those patients treated with rivaroxaban de novo [27].

All agents are excreted via the renal route to various degrees. This has led to concerns regarding use of these agents in patients with renal impairment. Reassuringly, a sub analysis of ROCKET AF [28] demonstrated that although patients with moderate renal impairment (CrCl 30 – 49 mL/min) suffered high rates of bleeding, when treated with the reduced dose of rivaroxaban (15 mg), this population yielded similar benefits in regards to stroke and systemic embolism as those patients treated with warfarin. Additionally, bleeding rates with rivaroxaban in this population were not higher than that of patients on warfarin.

The J-ROCKET AF trial [29] tested rivaroxaban against warfarin in a Japanese population of 1280 patients with non-valvular AF. Due to pharmacokinetic concerns and more conservative established anticoagulation practices in this population, lower doses of rivaroxaban (15 mg daily) and warfarin (target INR 1.6 – 2.5) were compared. The results were consistent with those of the global ROCKET AF trial with a trend towards less stroke and systemic embolism in those patients treated with rivaroxaban (HR 0.49 [0.24 – 1.00], $p = 0.05$).

Apixaban

Apixaban is the third of NOAC to reach the market and the second of the anti-Factor Xa agents after rivaroxaban. It was primarily tested in the ARISTOTLE trial [30] which was a multi-centre, randomised, double blinded trial in 18201 patients in which apixaban was tested against warfarin in patients with non-valvular AF. Like ROCKET AF, ARISTOTLE was a true double-blind trial with double-dummy design. A single dosing regimen of 5 mg twice daily was prescribed, which was dose adjusted to 2.5 mg twice daily in patients with at least two of the three criteria: age ≥ 80 years, body weight ≤ 60 kg, or creatinine level ≥ 133 $\mu\text{mol/L}$. The population of patients in this trial were lower risk than that of ROCKET AF with only approximately 30% of patients having a CHADS2 score of 3 or more. 20% of patients had suffered a prior stroke or TIA.

Patients on apixaban had a 21% reduction in rates of stroke or systemic embolism compared to those on warfarin (HR 0.79 [0.66 – 0.95], $p = 0.01$). However, unlike the higher dose of dabigatran, this was not driven by reduced ischaemic strokes (HR 0.92 [0.74 – 1.13], $p = 0.42$), rather by the 49% reduction in rates of haemorrhagic stroke (HR 0.51 [0.35 – 0.75], $p < 0.001$). In addition to the efficacy benefit, apixaban was also shown to be safer than warfarin with a 31% reduction in major bleeding (HR 0.69 [0.60 – 0.80], $p < 0.001$). Interestingly, patients on apixaban did not have higher rates of gastrointestinal bleeding compared to warfarin (HR 0.89 [0.70 – 1.15],

$p = 0.37$) unlike patients on dabigatran or rivaroxaban in their respective trials. Apixaban was equally well tolerated as warfarin in this study (7.6% vs 8.4% discontinuations respectively). The efficacy and safety benefits of apixaban over warfarin were maintained regardless of the adequacy of INR; in a sub analysis of the ARISTOTLE trial [31], there was no significant interaction between time in therapeutic range of INR and the primary outcome, major bleeding or death, although numerically the safety benefit of bleeding was attenuated in patients from centres with good INR control. Additionally, patients with renal impairment (CrCl ≤ 50 mL/min) not only shared the same efficacy benefit as other patients in ARISTOTLE, the reduction in major bleeding was greatest in this group (HR 0.50 [0.38 – 0.66], $p = 0.03$ for interaction compared to CrCl 50 – 80 mL/min and > 80 mL/min) [32].

Although the efficacy for aspirin as stroke prophylaxis in atrial fibrillation is limited [33], it continues to be utilised in place of anticoagulation, especially in the elderly and those perceived to be at lower risk of stroke [34]. Apixaban is the only direct oral acting anticoagulant that has been directly compared to aspirin in this population of patients. In the AVERROES trial [35], 5599 patients with non-valvular atrial fibrillation who were deemed unsuitable for warfarin, were randomised to apixaban or aspirin. Like ARISTOTLE, the trial was of a double-blind and double dummy design. The dose of apixaban was identical to that of ARISTOTLE, whilst aspirin was prescribed at a dose of 81 to 324 mg daily with the majority (65%) being on the lowest dose. The predominant reasons for not offering warfarin in these patients were concerns regarding the ability to have INRs measured, patient refusal or perceived low stroke risk (CHADS2 score of 1).

Apixaban demonstrated a 55% reduction in the primary efficacy outcome of stroke and systemic embolism compared to aspirin therapy (HR 0.45 [0.32 – 0.62], $p < 0.001$). This was primarily driven by the 63% reduction in ischaemic strokes (HR 0.37 [0.25 – 0.55], $p < 0.001$). Impressively, this did not come at the cost of increased major bleeding (HR 1.13 [0.74 – 1.75], $p = 0.57$). Apixaban was very well tolerated with less serious adverse events in patients on this agent compared to those on aspirin (22.2% versus 27.2% respectively, $p < 0.001$). A pre-specified analysis of patients who had previously suffered a TIA or stroke (14% of patients) demonstrated the same efficacy benefit of apixaban over aspirin in this subgroup compared to those who had not previously suffered an event ($p = 0.17$ for interaction) [36].

Edoxaban

The final NOAC that has been tested in patients with non-valvular AF is edoxaban. It, like rivaroxaban and apixaban, is an oral Factor-Xa inhibitor. The ENGAGE AF-TIMI 48 trial [37] was a multi-centre, randomised, double blind, double dummy trial of 21,205 patients in which edoxaban was compared to warfarin in this population of patients. Similar to RE-LY, two dosing regimens were utilised both incorporating dose adjustments for patients with renal impairment. Patients assigned to the high dose of edoxaban received 60 mg daily whilst those assigned to the lower dose received 30 mg daily. Patients with at least one of three risk factors (CrCl 30 – 50 mL/min, weight ≤ 60 kg or concomitant use of P-glycoprotein inhibitors or dronedarone) received half the dose in their respective groups (30 mg and 15 mg daily respectively). Patients in this trial were of a higher risk cohort with a minimum CHADS2 score of 2. The majority of patients

(approximately 77%) had a CHADS2 score of 2 or 3. 28% had suffered a prior stroke or TIA.

On a modified intention to treat population in the treatment period, both the high and lower doses of edoxaban were found to be non-inferior to warfarin (HR 0.79 [0.63 – 0.99], $p < 0.001$ for non-inferiority and HR 1.07 [0.87 – 1.31], $p = 0.005$ for non-inferiority respectively). Although the higher dose of edoxaban showed a trend towards superiority, this did not reach statistical significance when analysed in an intention to treat population over the overall study period (HR 0.87 [0.73 – 1.04], $p = 0.08$). Like the other direct acting anticoagulants, both doses of edoxaban demonstrated reductions in haemorrhagic stroke compared to warfarin (HR 0.54 [0.38 – 0.77], $p < 0.001$ and HR 0.33 [0.22 – 0.50], $p < 0.001$ respectively). The lower dose of edoxaban, however, was associated with 41% more ischaemic strokes compared to warfarin (HR 1.41 [1.19 – 1.67], $p < 0.001$).

Both doses of edoxaban were associated with less major bleeding with the magnitude of benefit being particularly strong for the lower dose (HR 0.80 [0.71 – 0.91], $p < 0.001$ and HR 0.47 [0.41 – 0.55], $p < 0.001$ respectively). The higher dose of edoxaban, like high dose dabigatran and rivaroxaban, was associated with a higher rate of gastrointestinal bleeding (HR 1.23 [1.02 – 1.50], $p = 0.03$) although, surprisingly, patients on the lower dose regimen demonstrated a 33% reduction in GI bleeds compared to warfarin (HR 0.67 [0.53 – 0.83], $p < 0.001$). There was a trend towards improved mortality in patients on the higher dose of edoxaban (HR 0.92 [0.83 – 1.01], $p = 0.08$), whilst those on the lower dose regimen had a 13% mortality benefit (HR 0.87 [0.79 – 0.96], $p = 0.006$) presumably due to its safety profile.

Thrombolysis in Patients on NOACs

In appropriate patients who present with an ischaemic stroke, administration of intravenous thrombolysis within four and a half hours of symptom onset has been shown to improve outcomes [38,39]. For patients already on warfarin, there is conflicting data as to whether thrombolysis is appropriate if the internationalised normalised ratio (INR) is subtherapeutic on presentation [40,41]. Nonetheless, the American Heart Association/American Stroke Association guidelines suggest such therapy is reasonable if the INR is less than 1.7 [42]. Experience with thrombolysis in patients with NOACs has been limited to case studies which have mainly involved inadvertent administration of thrombolysis to patients who, at the time of presentation, were taking dabigatran unbeknownst to the treating physicians [43-45].

Standard tests of anticoagulation such as the activated partial thromboplastin time (APTT) or prothrombin time (PT)/INR cannot be reliably used to quantify the anticoagulant effect of the NOACs. A normal thrombin time (TT) or Hemoclot thrombin inhibitor assay would suggest minimal anticoagulant activity from dabigatran [46]. For the Factor-Xa inhibitors, specific Factor Xa inhibition assays for each individual drug are likely to be required [47]. The limiting factor for these more specific tests of coagulation is their availability in general hospital laboratories; a crucial factor given the time-dependent nature of thrombolysis for ischaemic stroke.

This limited availability of timely and accurate assessment of anticoagulant effect of the NOACs, will limit the eligibility of patients who present with an ischemic stroke on these agents for thrombolysis. Nonetheless, in certain scenarios it can be considered after careful assessment of relevant factors including the timing and certainty of the last NOAC dose, the patient's renal function, the perceived potential

benefit of thrombolysis and, if available, the more specific coagulation assays. Early involvement of the haematology service would be prudent. Endovascular interventions may be considered in patients on NOACs who are ineligible for thrombolysis, though evidence supporting this practice is limited to case studies [48].

Timing of NOACs Post-Stroke

The NOACs have proven efficacy for the secondary prevention of strokes in patients with AF who have previously suffered an stroke or TIA. Approximately 20% of patients in RE-LY and ARISTOTLE, 28% of patients in ENGAGE AF-TIMI 48 and 55% of patients in ROCKET-AF had suffered a previous stroke or TIA. However, patients were excluded if they had suffered an acute stroke within 7 days (ARISTOTLE), 14 days (ROCKET-AF) or 30 days (ENGAGE AF-TIMI 48 and RE-LY).

The superior efficacy of anticoagulation with warfarin or a NOAC over aspirin needs to be balanced against the risk of precipitating a haemorrhagic transformation of the stroke lesion if therapy is commenced too early. Current guidelines recommended commencing anticoagulation within 2 weeks of a cardioembolic stroke unless it is particularly severe or large [49]. It would be reasonable to use similar clinical judgement when determining when to switch from aspirin to a NOAC, with the caveat that one must account for the immediate effect of NOACs versus the delayed therapeutic effect of warfarin. Apixaban may prove to be a useful option in this setting, as it was demonstrated in AVERROES to have far greater efficacy than aspirin in preventing ischemic strokes with no significant difference in rates of major bleeding or haemorrhagic stroke.

Reversal of NOACs in the Setting of Bleeding

A remaining concern of the anticoagulants is the current lack of a reversal agent. Whilst in situations of major or life threatening haemorrhage, the effects of warfarin can be reversed with vitamin K, fresh frozen plasma or prothrombin complex concentrate, the anticoagulant effect of the novel anticoagulants cannot be directly reversed at this time. A number of practical guidelines have been published addressing this issue [50,51]. Generalised haemostatic measures whilst awaiting the anticoagulant effect of NOACs to wear off comprise the current strategy in managing bleeding in these patients. In the event of severe bleeding, therapies such as prothrombin complex concentrates (PCC) or activated Factor VIIa can be considered; one must consider that whilst these therapies are unproven in regards to their haemostatic effect in the presence of NOACs, there is a real risk of a pro-thrombotic effect. For patients on dabigatran (but not the Factor Xa inhibitors), haemodialysis can be considered for uncontrolled bleeding.

Despite the lack of reversal agents, studies have demonstrated that patients that bleed on dabigatran or rivaroxaban do not have worse outcomes compared to those that bleed on warfarin [52,53]. The perceived benefit of warfarin's reversibility may be false reassurance and is unlikely to offset the benefit of the universal reduction in haemorrhagic strokes evident across all NOACs when compared to warfarin. The short half-life of these agents mean the main 'reversal agent' in most cases of bleeding will be time. Nonetheless, direct acting reversal agents are currently undergoing Phase III trials; idarucizumab, a monoclonal antibody is being tested in subjects on dabigatran [54] and andexanet alfa, a recombinant decoy Factor Xa molecule, is being tested in subjects on rivaroxaban and apixaban [55,56].

Role for Warfarin or Anti-platelet Agents

Despite the improved efficacy, safety and convenience profiles that the NOACs offer over warfarin, there remain clinical scenarios in which warfarin remains the anticoagulant of choice for stroke prevention in AF. All four agents undergo partial renal excretion to various degrees; as such patients with severe renal impairment (CrCl < 30 mL/hr for dabigatran, rivaroxaban or edoxaban and CrCl < 25 mL/hr for apixaban) should be offered warfarin as these patients were excluded from the clinical trials.

Patients with ‘valvular AF’ as defined by severe mitral stenosis or mechanical prosthetic valves should be offered warfarin; higher doses of dabigatran have been compared to warfarin in patients with mechanical cardiac valves in the Phase II RE-ALIGN trial which demonstrated that patients on dabigatran had not only increased thromboembolic events but also more bleeding events than those on warfarin [57]. The pathophysiology of thrombus formation on mechanical valves likely differs to that due to atrial stasis; the selective action of the NOACs may be insufficient for this scenario. Factor Xa inhibitors have not been tested in this setting.

Patients with other concomitant indication for warfarin such as the presence of a left ventricular thrombus, severe aortic arch atheroma or a medically managed patent foramen ovale (PFO) which is thought to be directly responsible for an embolic stroke may be best served by warfarin as there is little data regarding the efficacy of NOACs in these settings. Finally, there are scenarios where the physician or patient may feel more comfortable with warfarin. If compliance is questionable, the ability to monitor INRs and an anticoagulation profile that is more forgiving of a missed dose makes warfarin a reasonable choice. Some patients may prefer warfarin as they feel more comfortable with a “tried and tested” medication.

Aspirin has, at best, shown marginal benefit in preventing ischaemic events in patients with AF [33]. International guidelines are moving away from recommending aspirin [58,59]. Given the AVERROES trial showed vastly superior efficacy of apixaban compared to aspirin in preventing strokes with no significant bleeding penalty, there is little reason to consider aspirin monotherapy even in low risk patients. Additionally, any patient who has already suffered a stroke has a minimum CHADSVASc score of 2 and therefore justifies oral anticoagulation.

The combination regimen of aspirin and clopidogrel were tested in the ACTIVE trials. The ACTIVE A trial [60] showed that adding clopidogrel to aspirin reduced vascular events by a relative risk of 11% (HR 0.89, [0.81 – 0.98], p = 0.01) at the expected cost of increased major bleeding (HR 1.57 [1.29 – 1.92], p < 0.001). However the ACTIVE W trial [61] demonstrated that dual antiplatelet therapy with aspirin and clopidogrel was inferior to warfarin in preventing vascular events (HR 1.44 [1.18 – 1.76], p = 0.0003) with no difference in major bleeding (p = 0.53) and, in fact, 21% more total bleeding in the patients on antiplatelet therapy (HR 1.21 [1.03 – 1.35], p = 0.001). There is, therefore, no role in antiplatelet therapy in patients deemed unsuitable for anticoagulation based on bleeding risk alone.

Individualising the Choice of NOAC to the Patient

With three agents currently on the market, and the fourth pending approval, physicians must choose which anticoagulant they wish to offer their patients if he or she is deemed appropriate for a NOAC. One must be cautious in making direct comparisons, as these agents

have not been directly cross compared in a randomised trial. Nonetheless, the nuances of each individual drug evident within their respective clinical trials make some particularly well or less suited in certain patients. Factors to assist in deciding on individualisation of NOAC therapy in patients with AF are outlined in Tables 1-6. Appropriate dosing regimens for each agent are outlined in Table 7.

Dabigatran (high dose)	
Strengths	Weaknesses
stroke and systemic embolism than warfarin	extracranial bleeding than warfarin in the elderly (age > 75 years)
ischaemic stroke than warfarin	GI bleeding than warfarin
	tolerability compared to warfarin (dyspepsia)
	Twice daily dosing

Table 1: Risk:Benefit Assessment of High Dose Dabigatran

Dabigatran (low dose)	
Strengths	Weaknesses
↓ major bleeding than warfarin	↑ extracranial bleeding than warfarin in the elderly (age > 75 years)
	↓ tolerability compared to warfarin (dyspepsia)
	Twice daily dosing

Table 2: Risk:Benefit Assessment of Low Dose Dabigatran

Rivaroxaban	
Strengths	Weaknesses
Once daily dosing	↑ GI bleeding, haematuria and epistaxis than warfarin

Table 3: Risk:Benefit Assessment of Rivaroxaban

Apixaban	
Strengths	Weaknesses
↓ stroke and systemic embolism than warfarin and aspirin	Twice daily dosing
↓ major bleeding than warfarin	
↓ mortality compared to warfarin	
Similar bleeding profile to aspirin	
↑ tolerability compared to aspirin	

Table 4: Risk:Benefit Assessment of Apixaban

Edoxaban (high dose)	
Strengths	Weaknesses
↓ major bleeding than warfarin	↑ GI bleeding than warfarin

Once daily dosing	
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Table 5: Risk:Benefit Assessment of High Dose Edoxaban

Edoxaban (low dose)	
Strengths	Weaknesses

↓ major bleeding than warfarin	↑ ischaemic strokes than warfarin
↓ mortality compared to warfarin	
Once daily dosing	

Table 6: Risk:Benefit Assessment of Low Dose Edoxaban

Dosing in Non-Valvular AF	
Dabigatran (high dose)	150 mg twice daily Contraindicated if CrCl < 30 mL/hr
Dabigatran (low dose)	110 mg twice daily Contraindicated if CrCl < 30 mL/hr
Rivaroxaban	20 mg daily if CrCl ≥50 mL/hr 15 mg daily if CrCl 30 – 50 mL/hr Contraindicated if CrCl < 30 mL/hr
Apixaban	5 mg twice daily 2.5 mg twice daily if at least 2 of the 3: - Age ≥80 years - Weight < 60 kg - Creatinine Contraindicated if CrCl < 25 mL/hr
Edoxaban (high dose)	60 mg daily 30 mg daily if at least 1 of the 3: CrCl 30 – 50 mL/hr Weight < 60 kg Concomitant P-glycoprotein inhibitor or dronedarone use Contraindicated if CrCl < 30 mL/hr
Edoxaban (low dose)	30 mg daily 15 mg daily if at least 1 of the 3: CrCl 30- 50 mL/hr Weight < 60 kg Concomitant P-glycoprotein inhibitor or dronedarone use Contraindicated if CrCl < 30 mL/hr

Table 7: NOAC Dosing Regimens in Patients with Non-Valvular AF

Patients who already have suffered or are at particularly high risk of an ischaemic stroke may best consider the high dose of dabigatran as this is the only regime to result in reduced ischaemic strokes compared to warfarin; conversely low dose dabigatran is probably inadequate in this scenario. Patients that have previously suffered a bleeding event may consider apixaban, either dose of edoxaban or low dose dabigatran (if young) as these regimens have an improved bleeding profile compared to warfarin.

Patients with prior GI bleeding should consider apixaban or low dose edoxaban as these are the only regimens that did not result in higher rates of GI bleeding than warfarin. Patients with a prior history of significant haematuria or epistaxis should consider avoiding rivaroxaban.

Patients at relatively lower risk of stroke but who still require anticoagulation may consider apixaban or low dose edoxaban as these

regimens maintain efficacy whilst markedly reducing haemorrhagic risk; this overall balance results in improved mortality compared to warfarin therapy.

Finally, patients may prefer the convenience of once daily dosing, particularly if they have been used to warfarin therapy in the past. Rivaroxaban or one of the edoxaban regimens are reasonable in this circumstance.

Conclusion

The availability of the NOACs have ushered in a new era of ischaemic stroke prophylaxis in patients with non-valvular AF. International guidelines support the use of these NOACs as first line therapies for stroke prophylaxis in patients with non-valvular AF [58,59]. All four agents offer at least equivalent efficacy in preventing

stroke compared to warfarin, a reduction in risk of haemorrhagic stroke, increased convenience and in some cases improved mortality. Although further research is required to determine the suitability of thrombolysis in patients on these agents, the appropriate timing of initiation of NOACs after an ischaemic stroke and in regards to reversal agents in the setting of catastrophic bleeds, the availability of these agents has dramatically improved the therapeutic options available to stroke physicians and cardiologists.

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