NOVEL ANTICOAGULANTS IN ATRIAL FIBRILLATION

Summary of the Presentations from the Daiichi Sankyo Symposium, AHA Congress 2013, Dallas, Texas, USA

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MEETING SUMMARY

This educational seminar, supported by an independent educational grant from Daiichi Sankyo, was held at the AHA congress in Dallas on 19th November 2013. The meeting provided clinicians with an update on the pharmacokinetics and pharmacodynamics of new anticoagulant drugs. The speakers also discussed how best to use these agents according to the latest evidence.

Anticoagulants in Non-Valvular Atrial Fibrillation

Prof Elaine Hylek

Prof Hylek presented an overview of AF and its treatment. It is estimated that upwards of 9 million people in the USA will have AF by 2020. AF is associated with increased risk of stroke, dementia and heart failure. In addition, overall mortality is increased by 40–90% independent of other risk factors.

Warfarin reduces stroke and systemic embolism by 64% and reduces mortality by 26% compared to placebo. However, maintaining warfarin within the therapeutic range is a challenge and many intracranial haemorrhages, the most feared complication of anticoagulant therapy, apparently occur even when patients' internationalised normalisation ratio (INR) values are between 2 and 3.

Prof Hylek briefly discussed the results of the novel oral anticoagulant (NOAC) clinical trials. The RE-LY trial found that dabigatran 150 mg, given twice-daily, was superior to warfarin for reducing strokes and systemic embolic event (SEE) and was associated with a 50% reduction in intracranial haemorrhage.[1]

The ROCKET-AF trial showed that once-daily rivaroxaban was non-inferior to warfarin in terms of primary stroke and non-central nervous system (CNS) embolic events and also reduced intracranial haemorrhage.[2]

However, there was an increased risk of major haemorrhage from a gastrointestinal site.

The ARISTOTLE trial evaluated apixaban 5 mg twice-daily.[3] The rate of intracranial bleeding was halved. However, the rate of gastrointestinal (GI) haemorrhage was the same as warfarin and Prof Hylek commented that the risk of GI bleeding is one of the main reasons why patients want to stop treatment. Prof Hylek cautioned it was inappropriate to directly compare the results across trials as the patient populations were quite different.

Clinical Pharmacology of Novel Anticoagulants

Prof Jeffrey Weitz

Prof Weitz reviewed the clinical pharmacology of NOACs, with a particular focus on edoxaban. He highlighted the limitations of warfarin treatment, including potential interactions with food and drugs, slow onset and offset of action and its narrow therapeutic window; all of which contribute to the underuse of warfarin for stroke prevention in AF. Warfarin targets multiple steps in the coagulation pathway; in contrast, NOACs target downstream enzymes in the final steps of the coagulation cascade; Factor Xa (rivaroxaban, apixaban and edoxaban) or thrombin (dabigatran).

Prof Weitz compared the pharmacological characteristics of the various NOACs and highlighted the differences in dosing frequency, renal excretion rates and potential for drug–drug interactions. Rivaroxaban (20 mg once-daily) resulted in higher peaks and lower troughs of drug plasma concentration than apixaban (2.5 mg twice-daily). While this may be considered problematic, with either agent there is a marked reduction in intracranial haemorrhage compared to warfarin and at least comparable efficacy. Phase I studies demonstrated that single-dose edoxaban produced a very dose-dependent increase in peak plasma concentrations and that prothrombin times also paralleled drug plasma levels.[4]

Prof Weitz described a Phase II safety study that compared edoxaban at four dose rates (30 mg or 60 mg, once or twice a day) with warfarin.[5] Excess bleeding was observed in both of the edoxaban twice-daily dosing regimens, but not in the once-daily regimen even though the total daily doses were the same. The main predictor of bleeding was the trough concentration of drug (higher in the split dose groups, compared with the once-daily dose), suggesting that the risk of bleeding increased once the trough concentration exceeded a threshold. Single doses of either 30 mg or 60 mg inhibited thrombin generation as effectively as heparin for at least 24 hours.[6]

There are numerous advantages for the use of NOACs over warfarin. These include their rapid onset of action, their predictable dose-response profiles, which eliminate the requirement for monitoring, and having fewer drug–drug interactions than warfarin. Dosing is fixed and simplified at once a day. On the other hand, their short half-lives mean that patient adherence could be critical. The NOACs are eliminated by renal excretion by some degree so creatinine clearance should be monitored and NOACs should not be given to patients with severe renal impairment.

Prof Weitz concluded that NOACs are just as effective but more convenient than warfarin, safer for the brain and many are safer in terms of major bleeding.

The ENGAGE AF – TIMI 48 Trial[7]

Prof Robert Giugliano

Prof Giugliano detailed the recently published results from the ENGAGE AF – TIMI 48 trial. The main objective of this trial was to determine whether two dose regimens of edoxaban were non-inferior to warfarin in preventing ischaemic and haemorrhagic strokes and SEE in patients with non-valvular AF. This double-blinded, double-dummy study involved 21,105 patients with moderate to high-risk AF with a clinical prediction risk score ($CHADS_2$) of at least 2 (mean of 2.8). Patients were randomised into one of three treatment arms: warfarin (dose adjusted to an INR of 2–3), high-dose edoxaban (60 mg once-daily) or low-dose edoxaban (30 mg once-daily). Where necessary, patients in the edoxaban groups were also dose adjusted (reduced by 50%) before and during the study, for example if they had renal impairment.

The primary endpoint was a composite of stroke or SEE. The secondary efficacy endpoint was a composite of stroke, SEE, or cardiovascular

mortality, and the principal safety outcome was major bleeding. It was a particularly rigorous trial, with a high rate of follow-up (99.1%), low discontinuation of treatment (<9% per year) and a median follow-up of 2.8 years. Both the low and high-dose edoxaban groups were shown to be non-inferior to warfarin for the primary endpoint (incidence of 1.6% and 1.1%, respectively, versus 1.5% for warfarin [p=0.005]). Haemorrhagic stroke was dramatically reduced with both dose rates of edoxaban compared to warfarin. There was no difference in ischaemic stroke between high-dose edoxaban and warfarin; however, there was a significant increase in ischaemic stroke with low-dose edoxaban compared with warfarin with a hazard ratio of 1.41. Cardiovascular mortality was significantly reduced for both dose regimens of edoxaban (reduction of 14–15% and 8–13%, for 60 mg and 30 mg, respectively). Net clinical outcomes were also assessed. Disabling stroke, life-threatening bleeding and death were all reduced significantly with both dose regimens of edoxaban (12% for 60 mg, 17% for 30 mg).

International Society on Thrombosis and Haemostasis (ISTH) major bleedings were reduced by 20% overall. There was a 20% reduction in major bleeding in the high-dose edoxaban group compared to warfarin, and a 53% reduction in the low-dose group. A significant reduction in fatal bleeding and intracranial haemorrhage was also observed in the edoxaban groups. GI bleeding was more common in the high-dose group compared to warfarin (p=0.03). However, the low-dose group had 33% less GI bleeding than the warfarin group. Patients receiving edoxaban demonstrated significantly better compliance and there were no differences in serious adverse events compared to warfarin.

Prof Giugliano summarised that in comparison to well-managed warfarin (median time in the therapeutic range [TTR] was 68.4%), once-daily edoxaban was non-inferior for stroke or SEE at both high and low doses. There was a trend towards reduced stroke and SEE observed in the high-dose edoxaban regimen treatment arm. Both dose regimens significantly reduced major bleeding, i.e. haemorrhagic stroke, and cardiovascular death. Both dose regimens of edoxaban achieved superior net clinical outcomes.

Meta-Analysis of 72,000 Patients with AF Treated with Novel Anticoagulants

Dr Christian Ruff

Dr Ruff presented the results of a meta-analysis of the four warfarin-controlled, landmark trials investigating the efficacy of NOACs for preventing stroke in AF: RE-LY,[1] ROCKET-AF,[2] ARISTOTLE,[3] and ENGAGE AF – TIMI 48.[7] The data for NOACs used at their highest dose were pooled to create a sample size of almost 72,000 patients. A separate analysis was carried out for dabigatran and edoxaban used at a lower dose rate.

As a class of drugs, NOACs significantly reduce stroke and SEE by 19% compared to warfarin. Although they are comparable to warfarin in reducing ischaemic stroke, they reduce haemorrhagic stroke by 51%, which is reflected in the reduction in intracranial haemorrhage of 52%. NOACs significantly reduce all-cause mortality by 10%, indicating that this class of drug does help patients live longer. Dr Ruff also highlighted that NOACs in general tend to reduce major bleeding. Even in the whole range of patient subgroups, those with and without adequate TTR on warfarin, the benefits of NOACs in reducing stroke and systolic embolic events are consistent. Indeed there was an even greater reduction in bleeding in patients who could not achieve an INR between 2 and 3 for 66% of the time. In terms of safety, Dr Ruff noted there was an excess of GI bleeding by approximately 25% with NOAC use, but there was heterogeneity between the different trials.

In the lower dose meta-analysis, the NOACs were similar to warfarin in terms of stroke reduction and SEE. As expected with a lower dose of anticoagulant, there tended to be more ischaemic stroke (a 28% excess), but in contrast there was an even greater reduction in haemorrhagic stroke than with the higher dose (67% compared to 51%). There was less bleeding (35% reduction) and less intracranial haemorrhage (69% reduction) associated with low-dose NOAC use.

Dr Ruff explained that there is a trade-off between the increased risk of ischaemic stroke and reduced risk of haemorrhagic stroke when using a lower dose of NOAC. He also noted that lower doses of NOACs produced a similar reduction in all-causes mortality (11%) to the higher doses.

Dr Ruff concluded that NOACs offer an effective and safe therapeutic alternative to warfarin. In comparison to warfarin, NOACs significantly reduced all-cause stroke by 19%, primarily due to a 51% reduction in haemorrhagic stroke. NOACs significantly reduced all-cause mortality by about 10%, and in addition there was a trend towards less bleeding, although there was an increase in GI bleeding.

The Future of Antithrombotic Therapy for Atrial Fibrillation

Prof John Camm

Prof Camm summarised the preceding presentations and discussed the way forward in anticoagulant therapy in AF patients, with a particular focus on edoxaban.

Most physicians have concerns that the risk of haemorrhage may outweigh the antithrombotic benefits of warfarin, which may result in underuse. He said it was important to remember that warfarin treatment is associated with a 26% reduction in mortality compared to placebo. Although there are problems keeping warfarin within the therapeutic range, patient self-testing can significantly improve dose management.[8] The major difficulty with warfarin therapy is that intracranial haemorrhage occurs even when the dosage is properly controlled.[9] Prof Camm commented that there is still a role for warfarin use. NOACs need to be used with care in patients with renal impairment and are contraindicated in patients with mechanical heart valves. There are currently no data for their use in children or adolescents, while some patients may be intolerant of NOACs.

Edoxaban has been evaluated in the largest and longest clinical trial of NOACs, in a moderate-to-high risk population with excellent warfarin control. Edoxaban treatment reduced all-cause mortality at the low dose and tended towards a reduction in all-cause mortality at the higher dose compared to warfarin. Most of the bleeding complications were reduced and there was a marked 50% reduction in intracranial haemorrhage. However, the low dose of edoxaban was associated with an increase in ischaemic stroke.

Prof Camm discussed the PINNACLE registry. The data from this study revealed that only 12% of patients are currently being treated with a NOAC. The European Society of Cardiologists guidelines point out that aspirin is not necessary for the majority of patients with AF and that when there is a thromboembolic risk and an anticoagulant can be used, then a NOAC should be the preferred treatment option. Prof Camm raised the issue of the cost of NOACs, which are approximately £5,000 per quality-adjusted life year. When this figure is taken into account, NOACs are a cost-effective therapy option in the UK. However, the overall cost of implementing a switch to NOACs for all patients currently on warfarin would be considerable. Nevertheless, Prof Camm concluded by intimating that NOACs will hopefully be gradually but fully implemented in the not too distant future.

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