MEETING THE CHALLENGES IN ATRIAL FIBRILLATION MANAGEMENT: THE ROLE OF NEW ANTICOAGULANTS

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MEETING SUMMARY

Prof Gregory Lip opened the symposium with a discussion on determining stroke and bleeding risk in atrial fibrillation (AF) patients and their management. Prof Raffaele De Caterina presented data from the PREFER in AF registry and trends in the management of AF across Europe. Dr Robert Giugliano concluded with a presentation of the latest data from the ENGAGE AF-TIMI 48 trial.

Balancing the Risk of Stroke and Bleeding in the Treatment of Patients with AF

Professor Gregory Lip

The management of AF patients involves a careful balance of the risk of stroke and bleeding. Therefore, it is important that the risk assessment of both these factors is determined as accurately as possible. Traditionally the older CHADS\textsubscript{2} score has been used to assess high-risk patients who would benefit from vitamin K antagonist (VKA) (including warfarin) therapy.\textsuperscript{1} The CHADS\textsubscript{2} score is calculated by adding one point for each of the following conditions: recent congestive heart failure, hypertension, aged \geq 75 years, diabetes mellitus, and two points for stroke or transient ischaemic attack (TIA).\textsuperscript{1} The higher the CHADS\textsubscript{2} score, the greater the risk of stroke. However, there are limitations to the CHADS\textsubscript{2} scoring system as many common risk factors are not accounted for within the CHADS\textsubscript{2} score. This has been demonstrated by several large observational
cohort studies. For example, a Swedish AF cohort study that assessed >182,000 patients showed that age is a very powerful driver of stroke risk, where those aged 65–74 years have nearly a 3-fold increase in the risk of stroke and those aged 75 years and above have a 5-fold increase.\(^2\) Other factors that confer an increased risk of stroke include female gender (HR 1.17; 95% CI 1.11–1.22), prior stroke (HR 2.87; 95% CI 2.74–3.01), hypertension (HR 1.17; 95% CI 1.11–1.22), and diabetes (HR 1.19; 95% CI 1.13–1.26).\(^2\)

The CHA\(_2\)DS\(_2\)-VASc score, which is now the recommended risk score in many guidelines, is more accurate than the CHADS\(_2\) score at determining low-risk patients.\(^3,5\) Olesen et al.\(^5\) showed that patients with a CHADS\(_2\) score of 0 have an annual stroke rate in the region of 1.67% per year. However, based on the CHA\(_2\)DS\(_2\)-VASc score, the ‘low-risk’ patients have a stroke rate of 0.78% per year, which is almost that of the general population.\(^5\) In relation to high-risk patients, the C-statistic gave a value of 0.72 for the CHADS\(_2\) score but a value of 0.85 for the CHA\(_2\)DS\(_2\)-VASc, indicating that the CHA\(_2\)DS\(_2\)-VASc was more discriminating.\(^5\) In addition, a Danish nationwide cohort assessed >17,000 patients with a CHADS\(_2\) score of 0.\(^6\) Applying the CHA\(_2\)DS\(_2\)-VASc score to this population gives a stroke rate ranging from 0.8% per year to as high as 3.2% per year.\(^6\) This shows that a CHADS\(_2\) score of 0 does not guarantee that a patient is at low risk as there may be some patients with a stroke risk as high as 3%, thereby potentially putting patients at risk of experiencing a stroke.

The risk of bleeding in patients can also be estimated by analysing bleeding risk factors in a fashion similar to the assessment of stroke risk. In 2010, the HAS-BLED score was proposed\(^7\) and features in the European guidelines as well as other national guidelines.\(^8\) The HAS-BLED score takes into account hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalised ratio (INR), old age, and drugs/alcohol.\(^7,9\) A high HAS-BLED score corresponds to a high bleeding risk. However, current guidelines recommend that a high HAS-BLED score is not a contraindication to anticoagulant therapy, but rather highlights that a patient may be at potential risk of increased bleeding and require careful review and follow-up. A comparison of the HAS-BLED score with other bleeding risk schemas show that the HAS-BLED score is more accurate than the HEMORRHAGES and ATRIA scores in terms of predicting the risk of serious bleeding.\(^10\) In fact, the HAS-BLED score is the only bleeding risk score that reliably predicts intracranial bleeding.\(^10\)

Can the CHADS\(_2\) or the CHA\(_2\)DS\(_2\)-VASc scores be used to predict bleeding? As the CHADS\(_2\) or the CHA\(_2\)DS\(_2\)-VASc score increases, the bleeding rate also increases, but not significantly so.\(^11\) The C-statistic shows that HAS-BLED outperforms both CHADS\(_2\) and CHA\(_2\)DS\(_2\)-VASc to predict serious bleeding.\(^11\) Thus, the prediction of serious bleeding should be assessed using a specific bleeding score such as HAS-BLED; similarly, stroke risk should be measured using a specific stroke risk score, such as CHA\(_2\)DS\(_2\)-VASc.\(^11\)

The 2012 ESC guidelines for the management of AF emphasise identifying truly low-risk patients, instead of focusing on the identification of high-risk patients.\(^6\) They also include recommendations that male patients with a CHA\(_2\)DS\(_2\)-VASc score of 0, and women with a score of 0 or 1, do not receive any antithrombotic therapy. For those that do receive antithrombotic therapy, the ESC guidelines recommend the use of non-VKA oral anticoagulants (NOACs) compared with VKAs.\(^8\) Similarly, the NICE guidelines clearly state to use the CHA\(_2\)DS\(_2\)-VASc score to predict stroke risk and the HAS-BLED score to predict bleeding risk.\(^12\) Anticoagulation therapy should be offered to patients with AF and additional stroke risk factors. Aspirin monotherapy is not recommended for stroke prevention or people with AF, as evidence indicates that aspirin is virtually ineffective for stroke prevention.\(^8\)

The use of warfarin requires extensive monitoring and effective anticoagulant control. In fact, patients who spend ≥70% of time in therapeutic range (TTR) have been found to have a 79% reduced risk of stroke compared with patients with a TTR of ≤30%.\(^13\) The use of warfarin or VKAs is acceptable providing that TTR remains above 70%, as recommended in the ESC guidelines.\(^8\) However, maintaining patients at this level of TTR is challenging as shown by a national study in the USA that reported an overall mean TTR of 53%.\(^14\)

In order to avoid the limitations of long-term anticoagulation therapy with VKAs, the NOACs were developed and studied in extensive clinical trial programmes. A meta-analysis of Phase III trials compared all four NOACs with warfarin.\(^15\) This analysis showed that the NOACs have a favourable risk–benefit profile and were non-
inferior to warfarin for the prevention of stroke and systemic embolism (Figure 1). The NOACs were also associated with a lower rate of major bleeding (Figure 1).

Patient attitudes towards any chronic treatment are very important. A recent study investigated patient attitudes towards stroke prevention and bleeding and found that the majority of patients would like to avoid a stroke and were willing to sustain approximately four major bleeds rather than endure the potential long-term effects of a stroke episode such as disability, incontinence, and the need to be looked after continuously.

In conclusion, patients with AF are now assessed for both stroke and bleeding risk, and the landscape for stroke prevention in AF is rapidly changing. The HAS-BLED score may be used to identify those at risk of bleeding, whereas the CHA₂DS₂-VASc score may be applied to identify ‘truly low-risk’ patients.

As the landscape in oral anticoagulation for stroke prevention in AF is changing, it is important to understand how treatment guidelines are being implemented in clinical practice. The current ESC guidelines for the management of AF recommend a NOAC for the prevention of thromboembolism in non-valvular AF. Prevention of thromboembolic events - European Registry (PREFER) in AF was a prospective, observational, multicentre study which was designed to determine how patients with AF are currently managed in Europe. The study was conducted in seven European countries (Spain, France, UK, Italy, Germany, Switzerland, and Austria). A total of 7,243 consecutive patients were enrolled from January 2012 to January 2013. Subjects had to be >18 years of age and have a history of AF.

**Figure 1: Efficacy and safety of 4 high-dose NOACs versus warfarin: meta-analysis of Phase III trials. Ruff CT et al.**

GI: gastrointestinal; ICH: intracranial haemorrhage; MI: myocardial infarction; NOAC: new oral anticoagulant; SE: systemic embolism.

Patients were assessed at baseline and at a 1-year follow-up visit. Enrolled patients had similar stroke and bleeding risks at baseline.

In order to assess whether there had been a change in the pattern of the management of AF, the results of the PREFER in AF registry were compared with the EuroHeart survey, a registry that was conducted before the introduction of the ESC 2010 guidelines. The results show that since the introduction of the ESC guidelines, there is an increased use of NOACs as well as VKAs, especially in high-risk patients, which is in accordance with the new guidelines (Figure 2).

The results also showed that with increasing CHA\textsuperscript{2}DS\textsubscript{2}-VASc score, more patients received a VKA or a VKA with an antiplatelet agent. However, a higher HAS-BLED score was associated with fewer patients who received VKAs alone, and an increasing proportion received a VKA with an antiplatelet agent or an antiplatelet agent alone. This analysis showed that physicians may prescribe oral anticoagulants (OACs) less frequently in patients with a very high risk of bleeding.

In the PREFER in AF registry, approximately 10% of patients received combined therapy at baseline, despite combination treatment with an antiplatelet and antithrombotic agent not being recommended in the ESC guidelines, due to the increased risk of bleeding events. Furthermore, in the PREFER trial, out of 660 patients who received an antiplatelet plus OAC, as many as 95.3% were estimated to be inappropriately treated with this combination treatment. Similarly, 63.8% of inappropriate prescribing was found in 105 patients who received triple therapy with an OAC, aspirin, and clopidogrel. These findings indicate that not all physicians currently follow the recommended guidelines which state that vascular disease and AF can be treated with OACs alone in most patients. The reason is that OACs are not only effective at preventing stroke in AF, but also myocardial infarction (MI) and vascular disease.

**Figure 2: EuroHeart and PREFER in AF: Improved anticoagulation by CHADS\textsuperscript{2}/CHA\textsuperscript{2}DS\textsubscript{2}-VASc over time.**

There is evidence that combination treatment can also result in an increased risk of bleeding. The latest analyses from the PREFER in AF registry indicate that combination treatment is prescribed less frequently since the 2012 ESC guidelines. Other trends include a slight decline in the prescription of VKAs and a rise in the prescription of NOACs. It is expected that these trends may continue for several years.

The patterns of prescription of OACs and their management are inconsistent across Europe as different OACs are used in different countries. For example, phenprocoumon is frequently used in Germany, Austria, and Switzerland, fluindione is common in France, acenocoumarol is largely used in Spain, and warfarin is commonly used in the UK and Italy. Importantly, the INR control appears to be better in Western Europe than other parts of the world. Despite this, the perception of physicians towards the quality of anticoagulation treatment does not correspond with recommendations, as it was found in the PREFER in AF study that they have a tendency to overestimate the quality of anticoagulation.

The PREFER in AF registry also assessed quality of life in terms of patient satisfaction with, and convenience of, treatment using the Perception of Anticoagulant Treatment Questionnaire (PACT-Q). In general, treatment satisfaction was reasonably good (63.4±15.9). NOACs were preferred to VKAs for both treatment satisfaction (NOACs versus VKAs; 66.1±16.6% versus 63.2±15.9%) and convenience (NOACs versus VKAs; 81.1 versus 82.1%). There was also very little difference in satisfaction between OACs and antiplatelet agents. Treatment satisfaction and quality of life factors were the main reason for patients to switch from one treatment modality to another.

These results show that treatment guidelines have shaped the way OACs are used to help prevent stroke in AF, with a clear trend towards greater use of OACs in those at higher risk of stroke. NOAC uptake has also increased since 2012, and it is likely that this trend will continue for the next few years.
What does ENGAGE AF-TIMI 48 add to the Management of Patients with AF?

Professor Robert Giugliano

The ENGAGE AF-TIMI 48 trial was conducted in almost 1,400 centres in 46 countries worldwide. The trial was a randomised, double-blind, double-dummy study comparing two once-daily regimens of edoxaban with warfarin in 21,105 patients with AF and a CHADS\textsubscript{2} score of \(\geq 2\). Subjects were randomised to one of three treatment arms; either warfarin, high-dose edoxaban (60 mg once-daily [QD]), or low-dose edoxaban (30 mg QD). Patients in both edoxaban groups were dose reduced by 50\% if they were at risk of overexposure and satisfied one of the following criteria: creatinine clearance of 30–50 mL/min, \(\leq 60\) kg in weight, or taking a strong P-glycoprotein inhibitor. Each edoxaban regimen was tested for non-inferiority to warfarin during the treatment period. The primary efficacy endpoint was stroke or systemic embolism, and composites of ischaemic events were also assessed. The principal safety endpoint was major bleeding as defined by the International Society on Thrombosis and Haemostasis criteria.

Of the patients enrolled, \(99.6\%\) received the study drug with follow-up completed in \(99.5\%\) <9\% of patients per year came off the study drug and <1\% withdrew consent. Median follow-up was 2.8 years. In the warfarin comparator arm, a median TTR of 68.4\% was achieved with one-quarter of the patients achieving a TTR above 77\%, showing that the patients were well controlled on warfarin in this trial. Both doses of edoxaban were shown to be non-inferior to warfarin for the primary endpoint of stroke or systemic embolism (60 mg: \(p<0.001\); 30 mg: \(p=0.005\)). In the superiority analysis, the high-dose regimen of edoxaban had a HR of 0.87 (\(p=0.08\)), whereas the lower-dose regimen had a HR of 1.13 (\(p=0.10\)) (Figure 3).

In terms of the secondary endpoints, haemorrhagic stroke was reduced with the higher-dose regimen and markedly reduced with the lower-dose regimen, compared with warfarin. Protection against ischaemic stroke was the same between the high-dose group and warfarin, whereas the lower-dose group was less effective than warfarin. The rates of all three prespecified secondary composite outcomes were significantly lower with high-dose edoxaban than with warfarin. There was no difference in MI rates between either dose regimen of edoxaban and warfarin. Major bleeding, which was the primary safety outcome, was reduced by 20\% and 50\% in the higher-dose and lower-dose regimen, compared with warfarin, respectively. Similarly, both dose regimens were associated with a reduction in fatal bleeding and intracranial haemorrhage in comparison with warfarin.

Although the lower-dose edoxaban regimen had a lower rate of gastrointestinal bleeding than warfarin, a 23\% relative increase was observed in the high-dose group, compared with warfarin.

An analysis of net clinical outcomes was also conducted, where efficacy and safety were combined with mortality outcomes. The primary net clinical outcome of stroke, systemic embolic event (SEE), death, and major bleeding, was reduced by 11\% and 17\% in comparison to warfarin for the high and low-dose regimen, respectively. Other composites, including disabling stroke, life-threatening bleeding, or death, as well as stroke, SEE, life-threatening bleeds, or all-cause mortality were similarly reduced for both dose regimens of edoxaban.

Since the initial publication of ENGAGE AF-TIMI 48, there have been additional analyses of stroke and intracranial haemorrhage, as well as preliminary findings on the relationship between edoxaban drug concentration, factor Xa levels, and outcomes. With regard to haemorrhagic stroke, there is a marked reduction in risk with both dose regimens of edoxaban in comparison with warfarin. This reduction was observed as quickly as 6 months from treatment initiation, and the reduction in risk was maintained over 3 years. Further analyses also showed that both dose regimens of edoxaban reduced different subtypes of intracranial haemorrhage compared with warfarin. A small number of haemorrhagic transformations and micro-haemorrhages were observed; however, these are less likely to result in death compared with other intracranial haemorrhages.

The rate of ischaemic stroke was similar with high-dose edoxaban and warfarin; however, the lower-dose edoxaban group had a higher rate of ischaemic stroke. Notably, within the first 30 days, during which patients are deemed to be at higher risk, there is no difference between the three treatment arms. Annualised rates of stroke and TIs showed that the higher-dose regimen of edoxaban was non-inferior to warfarin in the prevention of ischaemic stroke plus TIA, and that the lower-dose regimen was less effective.
than warfarin. The same result was found when applying an updated definition of stroke, which incorporated both clinical and tissue criteria.

Additional findings were also available for anti-factor Xa activity and edoxaban drug concentration. Although there were two dosing regimens, four doses of edoxaban were actually studied (15 mg reduced from 30 mg or 30 mg reduced from 60 mg in patients at increased bleeding risk, 30 mg and 60 mg). Anti-factor Xa activity gradually increased from lower to higher doses of edoxaban. The effects of these dose reductions on stroke or SEE and major bleeding were assessed. In the non-dose reduced group, high-dose edoxaban was more effective at preventing stroke or a SEE than warfarin. In contrast, lower-dose edoxaban was less effective than warfarin.

In terms of major bleeding, a stepwise reduction was observed in the non-dose reduced group from warfarin to high-dose to low-dose edoxaban, with the low-dose group exhibiting a significant reduction in major bleeding (p<0.001). The dose-reduced group displayed a higher risk of bleeding overall; the warfarin group showed an increase in major bleeding events from 3.02-4.85% per year. However, both the higher and lower-dose groups displayed a significant protective effect compared with warfarin (high dose versus low dose; 3.05 versus 1.5%).

The results from ENGAGE AF-TIMI 48 showed that in comparison with well-managed warfarin (TTR ≥68%), once-daily edoxaban is non-inferior for the prevention of stroke and systemic embolism. Both edoxaban regimens significantly reduced major bleeding, intracranial haemorrhage, haemorrhagic stroke, and cardiovascular death, with both doses of edoxaban also achieving superior net clinical outcomes.

**Summary**

Treatment of AF patients requires a careful balance between the risk of stroke and bleeding, with guidelines recommending the use of scores to help in assessing the risk–benefit ratio. The updated ESC guidelines also recommend the use of OACs, and increased uptake has been observed across Europe, although VKAs still remain the most commonly used antithrombotic treatment. Recent data from the ENGAGE AF-TIMI 48 trial have also shown both once-daily regimens of edoxaban were non-inferior to warfarin with respect to the prevention of stroke or systemic embolism and were associated with significantly lower rates of bleeding and death from cardiovascular causes.

**REFERENCES**

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