PRACTICAL GUIDANCE FOR STROKE PREVENTION IN ATRIAL FIBRILLATION – INTERACTIVE CASE STUDIES

Summary of Presentations from the Boehringer Ingelheim Symposium, ESC Annual Congress 2013, Amsterdam, the Netherlands

Chairpersons

Gregory Y.H. Lip,[1] Michael Brainin[2]

Speakers

Jonas Oldgren,[3] Hans-Christoph Diener,[4] John Eikelboom[5]

1. Professor of Cardiovascular Medicine, University of Birmingham, UK
2. Head, Department of Clinical Neurosciences and Preventive Medicine, Danube-University Krems, Austria
3. Associate Professor of Cardiology, Uppsala University Hospital, Sweden
4. Professor of Neurology, University Hospital of Essen, Germany
5. Associate Professor of Medicine, McMaster University, Canada

Disclosure: For speaker disclosures, see page 76.
Acknowledgements: Writing assistance provided by Dr Jonathan Viney, ApotheCom Scope Medical.
Citation: EMJ Cardiol. 2013;1:72-76.

INTRODUCTION

This Boehringer Ingelheim sponsored satellite symposium was held on 2nd September 2013 as part of the ESC conference, which was hosted this year in Amsterdam, the Netherlands. In light of recent advances within the field of stroke prevention in atrial fibrillation (AF), the scientific programme contained an overview of the updated guidelines, with a subsequent focus on their everyday implementation, through interactive case studies in order to address some of the practical issues that have arisen.

The meeting was co-chaired by Professors Gregory Lip and Michael Brainin, who were supported by a distinguished faculty of Professor Jonas Oldgren, Professor Hans-Christoph Diener and Dr John Eikelboom.

Stroke Prevention in Atrial Fibrillation: From Guidelines to 'Real-World' Practice

Prof Gregory Y.H. Lip

Prof Lip began his presentation by highlighting the importance and risk of developing AF. It was stated that AF is the most commonly occurring cardiac rhythm disorder, and those aged over 40 years have a lifetime risk of 1 in 6, which increases to 1 in 4 in individuals who have suffered a heart attack or heart failure during their lifetime. The field of AF is of particular therapeutic interest owing to the burden it creates due to the increased risk of stroke.

The international normalised ratio (INR) range recommended for patients at risk of stroke was discussed. An INR of >3 leads to an increased risk of bleeding, whereas an INR of <2 leads to a risk of thromboembolism and stroke. It is therefore important to maintain a patient's INR between 2 and 3. The quality of anti-coagulant control is reflected by the time in therapeutic range (TTR), with a TTR of >70% regarded as ideal with respect to favourable stroke and mortality outcomes. Conversely, it has been demonstrated that when

TTR is <50%, these outcomes are in fact worse than in untreated patients thus highlighting the importance of optimal anti-coagulant control.[1] The use of warfarin and vitamin K antagonists is further limited for a variety of reasons, including lack of adherence due to an increased risk of bleeding, as well as the impact of required lifestyle changes, such as regular monitoring and diet modification. As a consequence, warfarin and vitamin K antagonists are associated with suboptimal treatment outcomes, which emphasised the need for the development of alternative and improved strategies.

As a result of this, it was noted that there have been significant changes, which culminated in a focused update to the ESC guidelines in August 2012. These changes reflect the advances within this field, such as the availability of new anti-coagulant therapies beyond warfarin, as well as improved management strategies involving patient risk stratification. An algorithm for the management of AF and assessment of risk of stroke was subsequently delineated. The first stage is to identify AF patients at low risk of stroke, namely those who have a CHA_2DS_2-VASc score of 0 or who are under 65 and have lone AF. These patients are not prescribed anti-coagulant therapy. Patients with a CHA_2DS_2-VASc score of ≥2 are recommended for anti-coagulation therapy and those with a score of 1 for oral therapy. The HAS-BLED score is then used to assess the risk of bleeding, and following this, specific anti-coagulants are chosen. The ESC guidelines state that novel oral anti-coagulants (NOACs) offer improved safety, efficacy and convenience compared to vitamin K antagonists; these NOACs include dabigatran, rivaroxaban and apixaban. Since some of these novel therapies have a degree of renal excretion, it is vital to monitor renal function in patients receiving NOACs.

The importance of adhering to guidelines was emphasised through the presentation of improved outcomes in clinical practice following guideline implementation. For example, in the RE-LY trial of warfarin and dabigatran, the use of EU label and ESC guideline-recommended dosages (110 mg and 150 mg) of dabigatran resulted in a reduction in the primary endpoints of stroke and systemic embolism.[2] The successful crossover of this treatment into everyday practice was demonstrated with an analysis of 5,000 patients in Denmark who, after receiving the same doses of dabigatran, had achieved similar results. In addition, reduced mortality, from factors such as myocardial infarction, was also observed when compared to the 9,000 patients receiving warfarin.[3]

Prof Lip concluded his presentation by reiterating that these are new drugs and thus have a lot of questions associated with them. The European Heart Rhythm Association (EHRA) practical guide on the use of NOACs in patients with AF, which also contains follow-up guidance, was therefore strongly recommended.

Initiating and Maintaining Optimal Anticoagulation: Practical Considerations

Prof Jonas Oldgren

Prof Oldgren began his presentation with a case study of a 72-year-old woman with AF, who was a previous smoker and had well-controlled hypertension. She was currently receiving warfarin treatment and wanted to discuss alternative anti-coagulation therapies since these require less monitoring. The audience were asked to state whether they would continue with warfarin or prescribe a new anti-coagulant; a third chose the former option while two-thirds preferred the latter. The range of anti-coagulants that could be considered for treatment was subsequently discussed.

Dabigatran, rivaroxaban and apixaban are three NOACs; the first targets thrombin, while the latter two target factor Xa. Compared to warfarin, the time for these drugs to reach peak concentration is fairly short, and the anti-coagulation effect is rapid onset. In addition, the half-life of these drugs is much shorter than warfarin. However, renal excretion for these drugs is higher, since, unlike warfarin, they are not metabolised.

These NOACs have been compared to warfarin in clinical trials.[4-7] With respect to the primary outcomes of these trials, all three are non-inferior to warfarin. Dabigatran 150 mg twice daily and apixaban 5 mg daily are superior to warfarin.[8] In terms of ischaemic stroke reduction, dabigatran is superior to warfarin whilst rivaroxaban and apixaban are non-inferior.[6,9,10] Each of the three NOACs have comparable safety profiles, with respect to major bleeding events, compared to

warfarin. It was highlighted that, from the results of the RE-LY[4,5] ROCKET[6] and ARISTOTLE[7] trials, the three NOACs demonstrated much improved safety profiles regarding intracranial bleeds, compared to warfarin.

The case of the 72-year-old woman was revisited and the audience were asked whether they would prescribe 110 mg or 150 mg dabigatran taking into consideration that she had normal kidney function and that her INR had dropped to 1.9 after cessation of warfarin treatment. Two-thirds of the audience chose the 150 mg dose, which was the speaker's preferred option since the patient's bleeding risk was low. The hypothetical situation of the patient subsequently developing an irregular heart rhythm, dyspnoea, as well as an elevated heart rate, requiring beta blocker medication and elective cardioversion was presented to the audience, they were then asked to vote whether they would continue dabigatran therapy or switch to warfarin until commencement of cardioversion therapy. Of the two options, 90% chose the former, which was discussed as safe, since the results of the RE-LY trial show that stroke rates were comparable in both dabigatran and warfarin-treated patients after cardioversion. A final question of whether to prescribe long-term dabigatran for this patient was posed to the audience; 93% correctly chose to continue her on anti-coagulation therapy since she had a CHA_2DS_2-VASc score of 3.

Prof Oldgren concluded that NOACs are the preferred option for stroke prevention in patients with AF according to the EHRA Practical Guide and 2012 ESC update,[11] and that patients switching from warfarin may start these drugs if their INR is <2. Available data suggest that elective cardioversion can be safely performed on patients treated with dabigatran.

Shielding the Brain from Ischaemic Stroke: Anticoagulant Strategies for Secondary Stroke Prevention

Prof Hans-Christoph Diener

Prof Diener started his presentation by discussing the effects of AF and stroke from his perspective as a neurologist dealing with prevention of secondary strokes. Due to various factors, 90% of patients admitted to Prof Diener's stroke unit are untreated, undertreated or mistreated for the prevention of secondary strokes. Only 10% of patients were reported to have received warfarin and achieved a recommended INR score of between 2 and 3. In the majority of cases patients are receiving aspirin, sub-optimal doses of warfarin, or no treatment at all, which highlights the major challenge of providing all patients with optimal treatment.

The case of a 70-year-old patient with AF, well-controlled hypertension and well-controlled diabetes, who received sub-optimal warfarin treatment and subsequently suffered a stroke, was described and the audience were asked to choose the best course of further anti-thrombotic therapy. Of the available options, 59% of the audience chose to administer 150 mg dabigatran, which was the correct option since the other options, such as continuing warfarin or switching to aspirin, would not be effective at raising the INR. The audience were subsequently asked how this therapy would be modified if the patient was 78 years old and had a creatinine clearance of 50 ml/min; 50% chose the correct option of prescribing 110 mg dabigatran.

Through presentation of a meta-analysis comparing the three NOACs to warfarin, it was stated that, for secondary stroke prevention, both doses of dabigatran are superior to warfarin.[12] Rivaroxaban was less effective in secondary compared to primary stroke prevention, although this was not statistically significant.[13] Apixaban was superior to warfarin in secondary stroke prevention.[14] Overall, across the three anti-coagulants; the risk reduction was 15% for secondary strokes, 56% for haemorrhagic strokes, and 14% for bleeding complications. In terms of absolute values, the risk reduction in stroke and systemic embolism was 0.7%, and 0.8% for major bleeds.[15]

Prof Diener summarised his presentation by reiterating that AF increases the risk of stroke with an associated 20% mortality rate and 50% permanent disability rate. A major problem with warfarin is intracerebral and intracranial bleeds, which have high mortality rates. This may be one of the main reasons for the high number of patients refusing to take the medication or receiving a sub-optimal dose. It was concluded that the NOACs, 150 mg dabigatran in particular, are superior to warfarin.

Optimising Periprocedural Protection with NOACs

Prof John Eikelboom

In his presentation, Prof Eikelboom discussed the importance of optimal management of patients undergoing procedures. It was stated that as many as 10% of patients every year have their anti-coagulation therapy interrupted in order to undergo a procedure. There is a well-established procedure for interrupting vitamin K antagonist treatment; anti-coagulation is stopped for 5 days, during which heparin is administered to patients deemed to be at a high risk of thromboembolic complications. NOACs have a shorter half-life and more rapid offset compared to warfarin, leaving the question of how they should be managed.

The audience were asked which factors should be considered before a surgical procedure on a patient receiving a NOAC; 90% voted that renal function, type of surgery and bleeding risk should be considered together, since renal function determines drug half-life, and bleeding risk is partly a function of the type of surgery.

The interventions that lead to an increased risk of bleeding were outlined; low-risk interventions included endoscopy with mucosal biopsy, prostate or bladder biopsy, electrophysiological study, angiography, and the insertion of a device. High-risk interventions included complex left-side ablation, spinal or epidural anaesthesia, surgery, liver or kidney biopsy, and transurethral prostate resection.

The timing of when to stop NOACs before interventions was addressed using a case study as an example. The patient in question had AF and was treated with 150 mg dabigatran twice daily. She required a colonoscopy with polypectomy, and the surgery was associated with a standard bleeding risk. She had a creatinine clearance rate of 90 ml/min. The audience were asked to select the appropriate time to stop dabigatran before surgery. From the possible options, 62% of the audience chose the preferred option of ceasing dabigatran 24 hours before surgery, since this is approximately two half-lives of the drug. In cases of reduced creatinine clearance rates, anti-coagulant administration should cease earlier, details are available in the EHRA guidelines.

It was noted that these recommendations on anti-coagulation cessation come from the RE-LY trial; where around 4,500 patients experienced an interruption in their treatment during a two-year period. The rates of thromboembolisms and bleeding in these patients in the 7 days prior to interruption and the 30 days after interruption were analysed. The rates of thromboembolic events for warfarin, 110 mg and 150 mg dabigatran were similar; although it was highlighted that warfarin had comparable bleeding rates to the two doses of dabigatran. In patients who underwent surgery within 24 hours of stopping, bleeding rates for warfarin were significantly higher than for dabigatran. It was further noted that dabigatran is also superior to warfarin in regards to bleeding rates in patients who require urgent interruption.[16]

Regarding the resumption of NOACs following an intervention, it was recommended to use the same principles as the resumption of warfarin; if immediate anti-coagulation is required NOACs can be started the next day, otherwise they can be started the second or third day after the procedure.

Prof Eikelboom concluded that due to their faster offset and shorter half-life, NOACs allow a shorter periprocedural interruption of anti-coagulation than warfarin. In the RE-LY trial, approximately one half of all patients who required an interruption in dabigatran had surgery within 48 hours of stopping; a much higher proportion than those on warfarin. Dabigatran has overall similar rates or perioperative bleeding and thrombotic complications to warfarin, but the former is more favourable for those who require urgent interruption.

This satellite symposium provided a platform for discussion on the updated guidelines as well as an opportunity for the esteemed faculty to present their translation into real-life practice. Following a stimulating and interactive session, there were several questions posed by the audience, which continued the theme of the use of these new treatments and associated guidelines in a real-world setting.

REFERENCES

1. Gallagher AM et al. Risks of stroke and mortality associated with suboptimal anticoagulation in atrial fibrillation patients. Thromb Haemost. 2011;106:968–77.

2. Lip GYH et al. Guidance adherent dabigatran etexilate treatment versus warfarin in the RE-LY population: an analysis onthe basis of the European label recommendations for dabigatran etexilate Poster presented at ESC, August 31–September 4 2013, Amsterdam, the Netherlands. Poster P4278.

3. Larsen TB et al. Efficacy and safety of dabigatran etexilate and warfarin in "real-world" patients with atrial fibrillation: a prospective nationwide cohort study. J Am Coll Cardiol. 2013;61:2264–73.

4. Connolly SJ et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med. 2009;361:1139–51.

5. Connolly SJ et al. Newly identified events in the RE-LY trial. N Engl J Med. 2010;363:1875–6.

6. Patel MR et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. 2011;365:883–91.

7. Granger CB et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2011;365:981–92.

8. De Caterina R et al. New oral anticoagulants in atrial fibrillation and acute coronary syndromes: ESC Working Group on Thrombosis-Task Force on Anticoagulants in Heart Disease position paper. J Am Coll Cardiol. 2012;59:1413–25.

9. European Medicines Agency. Pradaxa Summary of Product Characteristics 2012.

10. Lopes RD et al. Efficacy and safety of apixaban compared with warfarin according to patient risk of stroke and of bleeding in atrial fibrillation: a secondary analysis of a randomised controlled trial. Lancet. 2012;380:1749–58.

11. Heidbuchel H et al. EHRA practical guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation: executive summary. Eur Heart J. 2013;34:2094–106.

12. Diener HC et al. Dabigatran compared with warfarin in patients with atrial fibrillation and previous transient ischaemic attack or stroke: a subgroup analysis of the RE-LY trial. Lancet Neurol. 2010;9:1157–63.

13. Hankey GJ et al. Rivaroxaban compared with warfarin in patients with atrial fibrillation and previous stroke or transient ischaemic attack: a subgroup analysis of ROCKET AF. Lancet Neurol. 2012;11:315–22.

14. Easton JD et al. Apixaban compared with warfarin in patients with atrial fibrillation and previous stroke or transient ischaemic attack: a subgroup analysis of the ARISTOTLE trial. Lancet Neurol. 2012;11:503–11.

15. Ntaios G et al. Nonvitamin-K-antagonist oral anticoagulants in patients with atrial fibrillation and previous stroke or transient ischemic attack: a systematic review and meta-analysis of randomized controlled trials. Stroke. 2012;43:3298–304.

16. Healey JS et al. Periprocedural bleeding and thromboembolic events with dabigatran compared with warfarin: results from the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) randomized trial. Circulation. 2012;126:343–8.

Disclosure

GL is a consultant for Bayer, Astellas, Merck, Sanofi, BMS/Pfizer, Daiichi Sankyo, Biotronik, Portola, and Boehringer Ingelheim; and a member of the speakers bureau for Bayer, BMS/Pfizer, Boehringer Ingelheim, and Sanofi Aventis.

JO received an institutional research grant from Boehringer-Ingelheim and consulting and speaker fees from Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, and Pfizer.

H-CD has received financial support from the following bodies or companies: German Research Council, German Ministry of Health, German Ministry of Science and Technology, European Union, Bertelsmann Foundation, Heinz-Nixdorf Foundation, Yamanouchi, Novo Nordisk, Novartis, Neurobiological Technologies, MindFrame, Fresenius, CoAxia, Abbott, Schering, Janssen-Cilag, Sanofi, MSD, AstraZeneca, GlaxoSmithKline, Pfizer, Paion, Solvay, Schering Plough, Medtronic, Lundbeck, Syngis, Tacrelis, Boehringer Ingelheim, D-Pharm, BMS, Bayer, Wyeth, Knoll, Servier, EV3, and J&J.

JE served as an advisor or consultant for: AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Corgenix, Daiichi Sankyo, Eisai, Eli Lilly, GlaxoSmithKline, Haemonetics, Johnson & Johnson Pharmaceutical Research & Development, Ortho-McNeil-Janssen, and Sanofi; and received grants for clinical research from: Accumetrics, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Corgenix, GlaxoSmithKline, Sanofi, and Siemens Healthcare Diagnostics.